Autoregulation Versus Other Vasoconstrictors in Hypertension
A Critical Review
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SUMMARY Hypertension is a disease of relatively normal blood flow and increased vascular resistance. The search for neural and humoral vasoconstrictors to explain this pattern has not produced convincing evidence in most cases. Autoregulatory vasoconstriction is an alternative explanation supported by Borst, Ledingham and others; the validity of this idea is strengthened by frequent observations of relatively normal cardiac output and blood flow distribution in hypertension. Autoregulatory vasoconstriction has been combined with concepts of renal excretory function to form the following theory: Renal excretion is determined by arterial pressure — pressure must be high enough to maintain salt and water balance — and autoregulation provides the hemodynamic pattern of vasoconstriction with normal flow. Several different types of experiments point to the kidney as the long-term controller of blood pressure. However, data relevant to the autoregulatory part of the theory are conflicting. In some experiments, autoregulation is suggested by changes in flow that precede changes in resistance. In other experiments, no change in flow has been observed. In some experiments, volume expansion appears to be an intermediary between kidney dysfunction and the autoregulatory response. In other instances, volumes are normal or low. Flow relative to metabolic needs, venous capacity, and the abruptness of the hypertension-producing perturbation become important considerations in understanding these results. The argument that autoregulation supplies vasoconstriction in most cases of hypertension is based on interpretation of many different observations that are unfortunately relatively indirect. Controversy over vasoconstrictor mechanisms in hypertension is fostered by a lack of direct experimental results either supporting or refuting the various possibilities. (Hypertension 1: 324-330, 1979)

KEY WORDS • hypertension • autoregulation • cardiac output • total peripheral resistance • vasoconstriction • arterial blood pressure • renal excretion

HYPERTENSION is generally characterized by increased arterial pressure and increased vascular resistance. The search for a vasoconstrictor mechanism to explain the increased total peripheral resistance has focused on humoral factors such as renin, and on overactivity of the autonomic nervous system. But in many instances, changes in these suspected variables are small in relation to the increases in resistance observed, and additional phenomena, such as subtle effects, cumulative effects, or supersensitivity, have been postulated. None of these explanations has been entirely satisfactory and further examination of the relationships between arterial pressure, blood flow, and vascular resistance in hypertension seems warranted. This paper reviews autoregulatory phenomena and the possibility that autoregulation is responsible for the vasoconstriction seen in hypertension.

Total and Regional Blood Flow in Hypertension
In hypertension, measurements of cardiac output and regional blood flow in a wide variety of instances have shown values within the normal range for these variables. Measurement of cardiac output sometimes shows values that are outside of the normal range but these observations can often be explained in terms of accepted pathophysiological mechanisms. For instance, elevated cardiac output in young hypertensive patients appears to be a response to increased...

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metabolism and oxygen consumption. Elevated cardiac output in end-stage renal disease seems to be due to the underlying anemia, the increased flow is an appropriate response to decreased red cell mass. In some instances, such as in very severe hypertension, inappropriately low blood flows are observed. Figure 1 shows a sampling of cardiac indices from nine hypertensive patients on chronic hemodialysis. In these patients, subnormal cardiac indices correlated with very high plasma renin levels; our interpretation is that angiotensin-induced vasoconstriction dominates the control of blood flow in this situation and reduces flow to levels that are below those that would normally be mediated by metabolic demands. The data points shown in the left half of figure 1 are in the normal range and are typical of the vast majority of instances in which cardiac output is observed to be normal in hypertension.

A variety of techniques have been used to estimate regional blood flow in hypertension. Brod et al. found elevated total peripheral resistance and normal cardiac output along with vasoconstriction in skin and kidneys in patients with essential hypertension. He did note, however, that skeletal muscle in the arm was not vasoconstricted. In experimental animals, microspheres have been used to measure blood flow and it appears that in most instances the tissues all receive a normal blood flow. Therefore, although there are some exceptions, hypertension can in general be characterized by a vasoconstriction that occurs in all organs. It should be noted that both angiotensin and autonomic nerves do not affect all vascular beds equally and therefore produce a redistribution of vascular resistance and blood flow.

Vasoconstriction, at least in benign cases of hypertension, does not represent a fixed resistance. For instance, the values of increased cardiac output and decreased total peripheral resistance observed in exercising hypertensive patients are nearly the same as in exercising normotensive subjects. Lowenstein et al. observed a renal vasodilatation during saline loading in essential hypertensive patients that was actually greater than that seen in normotensive subjects. Therefore, the vasoconstriction appears to be functional in these instances and vasodilatory stimuli can acutely lower total peripheral resistance in the face of a chronic vasoconstriction.

**Autoregulation as a Vasoconstrictor in Hypertension**

An explanation that is consistent with a generalized elevation in peripheral resistance and normal tissue perfusion is that increased resistance in hypertension is due to autoregulation of blood flow. Autoregulation in this case means that an individual tissue can intrinsically regulate its own blood flow via changes in vascular resistance. Borst and Borst-de Geus and Ledingham and Cohen were among the first to apply this concept in detail to the genesis of hypertension. Borst and Borst-de Geus were analyzing the hypertensjon that accompanies overindulgence in licorice and were trying to connect increased arterial pressure and vasoconstriction with expanded body sodium. They suggested that because of autoregulation, fluid retention will cause "an increase in cardiac performance ... [that will] ... ultimately be reflected in a rise in arterial pressure only; cardiac output will remain normal." Ledingham and Cohen replied that if this were the case than "a phase of increased cardiac output [would] be demonstrated during the development of hypertension." Ledingham and Cohen had already shown that a transient phase of decreased cardiac output preceded vasodilation in the reversal of renal hypertension after unclipping the renal artery. Guyton and colleagues used mathematical methods to analyze the possible temporal relationships in an autoregulatory response. Their analysis predicted that temporary derangements in flow and volume could occur at the onset of hypertension; the magnitude and time course of these changes would depend on the severity of the stimulus and the responsiveness of the circulatory system. However, almost every aspect of these changes was transient in this analysis and little derangement was predicted for established hypertension.

A similar hemodynamic pattern was observed in Guyton's laboratories in a series of experiments in dogs. Langston et al. showed that subtotal nephrectomy plus saline produced a hypertension that was reversible when the saline administration was discontinued. Douglas et al. showed that increases in blood volume, exchangeable sodium, and interstitial fluid pressure temporarily accompanied the onset of hypertension in this model. In the same preparation, Coleman and Guyton further showed that right atrial pressure and cardiac output were elevated at the
onset of hypertension. Figure 2 shows the arterial pressure, cardiac output, and total peripheral resistance relationships observed during the first 13 days of isotonic saline infusion into a group of six subtotally nephrectomized dogs. Increased cardiac output preceded the increase in total peripheral resistance. These results are consistent with the idea that the individual tissues adjust their resistance, and subsequently their flow, according to the local metabolic needs rather than in response to external signals. If autoregulation controls flow via resistance changes in hypertension, we would expect hypertension to be characterized by increased resistance and normal flow; if humoral or nervous vasoconstrictors adjusted resistance independent of the metabolic needs of the tissues, we would expect flow derangement to often be a part of the overall hemodynamic description of hypertension.

The Kidney, Fluid Volumes and Vasoconstriction

Autoregulation in this analysis is only part of the total explanation of arterial hypertension. The concept that has been widely reviewed and discussed is that renal dysfunction is the initiating event in hypertension. The idea is built around the concepts of long-term salt and water balance and the kidneys' excretory capacity. Many factors influence renal excretion: physical composition of the blood, nervous influences, aldosterone, antiuretic hormone, angiotensin, blood pressure, and possibly many other yet undiscovered factors. Normally, salt and water balance can readily be maintained by some combination of these factors working in concert to precisely adjust excretion in response to the body's needs and in response to capricious intake. However, in cases such as renal disease, hyperaldosteronism, or pheochromocytoma, the normal balance of influences is upset. Furthermore, most of these factors have a limited capacity to alter salt and water excretion. At very low blood pressure, for instance, excretion is impaired even though all of the factors may be attempting to facilitate excretion. The renal dysfunction-autoregulation theory postulates that when other regulatory factors are upset or are not powerful enough to maintain fluid balance, then increased blood pressure is required as a last resort to maintain salt and water balance.

Several different experimental approaches have produced data that support the notion that renal dysfunction is the most important factor in the initiation of hypertension. These include perfusion of isolated kidneys, measurement of blood pressure and sodium excretion in the intact animal at different levels of excretion and in different experimental models, and cross transplantation of kidneys. The results in general support the theory outlined above. For instance, Thompson and Dickinson found that greater than normal blood pressures were needed to produce normal excretion in perfused kidneys from renal hypertensive rabbits. In a similar protocol, Tobian et al. found a depressed excretory function in perfused kidneys from the Dahl strain of spontaneously hypertensive rats; that is, normal excretion could only be achieved at high perfusion pressure. Norman et al. found an altered blood pressure-excretion relationship in intact spontaneously hypertensive rats and renal hypertensive rats. Cross-transplantation studies have shown the kidney to be a fundamental component of hypertension in the Milan strain and the Dahl strain of spontaneously hypertensive rats. Although not universally proven, and still very controversial in the case of essential hypertension, the data generally support the concept that decreased excretory capacity is important in the maintenance and probably in the cause of many different forms of hypertension.

Difficulties arise in trying to connect observations of renal dysfunction with subsequent vasoconstriction. The simplest explanation is that decreased excretion leads to fluid retention and that the fraction of the
retained fluid that remains in the circulation causes increased blood flow that, in turn, triggers the autoregulatory vasoconstriction. The final result would be increased pressure and increased resistance with normal flow. If the autoregulatory response is very powerful, little residual disturbance in volume and flow would be necessary to maintain the vasoconstriction. There is evidence both in support of and in conflict with this simple explanation, and there are also more complex explanations built upon the basic principle of autoregulation of blood flow. Some of these details are discussed below.

**Detailed Considerations of Autoregulation in Hypertension**

**Circulating Vasoconstrictors**

Autoregulatory vasoconstriction is definitely not required to explain resistance increases in situations where high levels of circulating vasoconstrictors are present. Hyperreninemia with advanced renal disease and increased catecholamine concentrations in pheochromocytoma are two examples in humans as is the hypertension produced by I.V. angiotensin infusion in animals. These cases account for only a small percentage of the total incidence of hypertension, however.

**Hemodynamic Transients**

With regard to autoregulatory transients, some experimental results have shown a temporal hemodynamic relationship wherein changes in flow precede changes in resistance. Some results have not shown this. The response of the salt-loaded, subtotally nephrectomized dogs described above show the temporal pattern of increased flow preceding increased resistance. Bianchi et al. and Ledingham and Cohen saw early elevations in cardiac output in renal hypertension in rats. Ferrario saw increased cardiac output in perinephritic hypertension and in Goldblatt hypertension in dogs. But, the observed transients in the latter study seem to be much too prolonged to be ascribed totally to autoregulation. In contrast, Fletcher et al. saw a gradual decrease in cardiac output with increasing blood pressure after wrapping rabbit kidneys with cellophane. Terris et al. did not see any increase in cardiac output when pigs given deoxytocosterone acetate (DOCA) became hypertensive, but Conway and Hatton saw small, temporary increases in cardiac output in unilaterally nephrectomized dogs given DOCA plus saline. We observed a transient increase in the cardiac output of anephric patients that accumulated excess salt and water during hemodialysis. Onesti et al. saw no change in cardiac output as hypertension developed in similar circumstances.

**Tissue Metabolism**

Consideration of the metabolic needs of the tissues is essential in interpreting flow changes during the onset of hypertension. Elevated flow during anemia or at high altitude is probably the final result of autoregulation rather than flow perturbations that are in the transient phase of an autoregulatory response. Similarly, the high cardiac output seen in many young essential hypertensive patients might be considered an appropriate response to changing metabolic needs and the increased oxygen consumption in these circumstances. Therefore, changes in flow over the long term probably represent a normal physiological response to changing metabolic demands. In contrast, acute changes of flow might be at variance with the metabolic needs of the tissues and might be a signal that an autoregulatory change in resistance is about to occur or is in progress.

Several studies with beta-adrenergic receptor blockade have been used to address the question of autoregulation in hypertension. Drugs, such as propranolol, have been shown to lower cardiac output and increase oxygen extraction without appreciably changing oxygen consumption and metabolic rate. Spontaneous hypertension in rats and DOCA plus saline hypertension in dogs both occur just as readily after beta-blockade as before. Cardiac output in these instances has been observed to not rise at all during the onset of hypertension or to remain below the pretreatment level. Therefore, increased blood pressure and vasoconstriction occurred with a blood flow that was less than normal. This response has been interpreted as evidence against the role of autoregulation in the genesis of hypertension. However, autoregulation may function perfectly adequately in beta-blockade; for instance, marked vasodilation is seen during exercise after beta-blockade. It might be then that autoregulatory vasoconstriction is a part of the genesis of hypertension during beta-blockade, although the normal or reference level of autoregulated blood has been changed by the receptor blockade. Growth rate was normal in the beta-blocked spontaneously hypertensive rats of Pfeffer et al., indicating that the total metabolic needs were being satisfied in these animals at the decreased blood flow rates observed. Detailed interpretation of these studies is difficult since the exact metabolic needs of the tissues are not known, the mechanism of action of beta-adrenergic blockers has not been fully delineated, and the detailed mechanisms responsible for autoregulation remain unclear.

**The Abruptness of the Hypertension-Producing Stimulus**

Another important point involves the methods used to produce experimental hypertension. If we assume that autoregulation is a rapidly responding and very powerful mechanism, then transients in blood flow would occur only infrequently and only very briefly. This point is explored theoretically in figure 3. With the same concept of autoregulation used in each of two cases, only an abrupt, severe stimulus (fig. 3, left panel) caused obvious flow disturbance. Focal renal artery constriction might be a good example. A more insidious disturbance (fig. 3, right panel) produced an autoregulatory vasoconstriction in this hypothetical
example without any overt (or experimentally measurable) change in blood flow. Slowly progressing renal disease might be a suitable example. Therefore, according to this concept of autoregulation, changes in flow over the long term probably represent the appropriate responses to metabolic needs or, in rare instances, represent the effects of severe disease. Transient flow changes that herald subsequent autoregulatory changes in resistance can be expected only in protocols that use an abrupt stimulus.

Vascular Compliance

The connection between renal dysfunction and autoregulatory vasoconstriction appears in the first analysis to require sodium retention. But, evidence of sodium retention and volume expansion is not always found. Most notably, many measurements in subjects with essential hypertension have shown normal or low blood volumes. However, the hemodynamic response to volume changes involves both the absolute value of blood volume and the vascular compliance of the circulatory system. Situations might exist where there is relative or functional vascular overhydration but normal or low measured values for total blood volume. Such situations would be caused by decreased vascular compliance. Therefore, a decreased vascular compliance can theoretically be just as effective as an increased absolute volume in promoting increases in cardiac output.

There is some evidence for decreased venous compliance in human and experimental hypertension. But also, estimates of venous pressure or mean circulatory filling pressure might help to show the combined contribution of volume and compliance in these situations. Micropuncture studies in the spontaneously hypertensive rat have shown elevated venous pressures and several different estimates of mean circulatory filling pressure have shown increased values for this pressure in hypertension. Therefore, in exploring the connection between renal dysfunction and vasoconstriction, neither absolute increases or decreases in volume can be fully interpreted without additional information about the compliances and pressures within the circulation.

Acute and Long-Term Autoregulation

Much of what we know about autoregulation comes from studies outside of hypertension research. The observation that body weight and blood flow increase in direct proportion during growth could be interpreted as a manifestation of autoregulation. Short-term studies show that active vasoconstriction occurs in individual organs with increases in pressure and flow; the responses might be related to metabolic or myogenic factors or to other special properties of the individual organs. To date, autoregulation of blood flow has been observed in every organ studied including the brain, gut, coronary arteries, skeletal muscle and kidneys.

The autoregulatory response in individual organs has been observed to be very rapid. It is not clear if
these changes might persist indefinitely in hypertension or if there might be further development of vasoconstriction and a gradual substitution of long-term mechanisms. There is some evidence in support of a gradual change in mechanisms. For instance, in hypertension, thickening of the media of the blood vessel wall and a decrease in the minimum resistance that can be obtained with maximum dilation signal a change in vasoconstrictor mechanisms. Studies using arterial ligation in the dog's leg have shown a very rich and varied pattern of events following a decrease in femoral artery blood flow due to arterial ligation. Initially, the distal vasculature dilates and oxygen extraction increases. At the same time, collateral vessels open around the main arterial ligation and blood flow increases even more. As time passes, further development of collateral vessels around the ligation tends to re-establish normal perfusion. These responses are shown schematically in figure 4. The net result is that a spectrum of processes and a spectrum of time constants within these processes are all involved in maintaining normal tissue perfusion. Over the short term, arteriolar dilation and increased oxygen extraction can make large contributions, along with the opening of existing collateral pathways. Over the long term, oxygen delivery and oxygen extraction are maintained at normal values by a change in the number and structure of blood vessels.

It would appear then that the proper level of blood flow to the tissues is maintained by resistance changes that involve this variety of mechanisms as one of the highest physiological priorities of the intact organism. If an unusual pressure level is needed to maintain salt and water balance, then we would expect, according to this theory, to get increased resistance in proportion to the increase in pressure required without any obvious disruption in total blood flow distribution. Transient flow disruption might be seen in instances where abrupt transitions in arterial pressure are taking place, but abnormal flow would not be seen with more gradual pressure changes.

Conclusion

There is evidence that autoregulation of blood flow is a very powerful mechanism that can increase or decrease vascular resistance as necessary. A role for autoregulation of blood flow in hypertension comes from a variety of indirect observations and from the general observation that blood flow is normal in most cases of hypertension. To our knowledge, experiments to clearly substantiate or refute the concept that autoregulation is the predominant source of vasoconstriction in hypertension have not yet been undertaken. Similarly, experiments to clearly validate or invalidate other putative vasoconstrictor mechanisms are also missing. Protocols to critically evaluate the role of autoregulation in hypertension might involve attempting to produce hypertension in common experimental models with and without autoregulation operative and then measuring the hemodynamic consequences. Such experiments are difficult if not impossible with the experimental tools available at this time. Therefore, until the time that direct scientific evidence becomes available, interpretation of many different and less direct experimental results serves as a forum for debate.

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