SUMMARY  Autoregulation of tissue blood flow is a mechanism by which tissues control their own blood supply. The mechanism is dependent on an intrinsic capacity of tissues to vary their arteriolar resistance in relation to their needs. One view of the nature of the increased peripheral resistance in essential hypertension is that it represents autoregulatory vasoconstriction functioning to hold in check a cardiac output that would otherwise be excessive; in this situation autoregulation would be functioning normally. An alternative view is that the increased peripheral resistance represents the effect of a direct-acting vasoconstrictor substance; in this situation autoregulation would be rendered defective in its vasodilator capacity. A study of autoregulatory vasodilatation in eight subjects with essential hypertension supported an autoregulatory mechanism as the cause of the increased peripheral resistance. (Hypertension 7: 1003–1007, 1985)

KEY WORDS  •  forearm perfusion pressure  •  forearm blood flow  •  plethysmography  •  autoregulation  •  hypertension

ESSENTIAL hypertension is a disorder of unknown etiology and ill-understood pathophysiology. Study of the condition would be greatly facilitated by an appropriate animal model, and it is commonly thought that rats with spontaneous hypertension most nearly fulfill this role.1-3

There appears to be a developing consensus that essential hypertension is due basically to an inherited deficiency in the capacity of the kidneys to excrete sodium. The evidence for this is based on epidemiological,4 clinical,5 and experimental6-8 work in humans and on experimental studies in the hypertensive rat.3,9-12 The defect is exemplified as a shift in the pressure-natriuresis relationship so that at any given blood pressure there is a reduced capacity to excrete sodium. This is thought to initiate a sequence of hemodynamic changes ultimately leading to hypertension, but there is no clear consensus as to the intermediate steps in the process. The present study examined this particular problem.

There are two main views on the problem. On the one hand, sodium retention is believed to increase the peripheral vascular resistance by initiating a process culminating in the direct action of a vasoconstrictor substance on the peripheral arterioles.13 Unanimity would not necessarily exist as to the details of the process. On the other hand, it is maintained that the initial effect of the excess sodium is an increase in blood volume, which tends to augment the cardiac output by the Starling mechanism. Hand in hand with the increasing cardiac output, and restraining its full development, the peripheral vascular resistance is increased through the action of total body blood flow autoregulation. Autoregulation is the mechanism that has been evolved to maintain control of tissue blood flow. It is dependent on an intrinsic capacity of tissues to vary the tissue arteriolar resistance in direct proportion to the arterial perfusion pressure. It is independent of the nervous system. Guyton14 and his group have been the main proponents in recent times of this view. They have demonstrated convincingly its feasibility in a long series of studies, and in 1979 they wrote, "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. . . . Such experiments are difficult if not impossible with the experimental tools available at this time."15 This study is an attempt to provide such an experiment.

The implications of these two separate views of the pathophysiology of the hemodynamics of essential hypertension require further elaboration to provide the rationale for the present study.
A primary increase in peripheral vascular resistance, whether due directly to sodium retention or some other mechanism, would, in the absence of any change in myocardial contractility, increase the blood pressure and reduce the cardiac output. A reduction in cardiac output is equivalent to a reduction in tissue blood flow, and this can occur only if autoregulation, which functions to maintain tissue blood flow, is counteracted. Since the cardiac output is generally normal in essential hypertension, this would at first sight argue against the thesis that the primary hemodynamic alteration in essential hypertension is an increase in peripheral vascular resistance. However, if myocardial contractility were subsequently to increase through some such mechanism as muscle hypertrophy, the cardiac output might thus be maintained at or close to the normal level. The price to be paid for such an adjustment would be a further increase in blood pressure. If, in that particular situation, the blood pressure perfusing any given tissue were reduced experimentally by mechanical means to the level that prevailed before the increase in myocardial contractility (to be referred to as the basal level), then the blood flow to that tissue would decrease to its previous, reduced level, and autoregulation would be incapable of functioning to prevent this reduction. The reduction would be all the more pronounced if the perfusion pressure were reduced to a normal blood pressure level, which by definition is lower than the basal level.

On the other hand, if, as Guyton and his group propose, the mechanism by which salt retention produced essential hypertension were primarily a thrust toward an augmented cardiac output, then this would not immediately interfere with the autoregulatory mechanism either in its vasodilator or vasoconstrictor capacity. Freely functioning autoregulation would in fact be the cause of the increased vascular resistance. In this situation, a reduction in the perfusion pressure of a particular tissue to a normal blood pressure level would elicit an appropriate autoregulatory reaction unhampered by interference from a peripheral vasoconstrictor agent.

Therefore, the present study attempted to check the integrity of autoregulatory vasodilatation in subjects with essential hypertension by lowering the perfusion pressure of some representative tissue to a normal blood pressure level and noting if this action elicited a normal degree of autoregulatory vasodilatation.

### Subjects and Methods

The main experimental problem was how to reduce the perfusion pressure of a given tissue without having to use vasodilators, which might interfere with the autoregulatory mechanism, and without lowering the general body blood pressure, which would elicit a response from baroreceptors, again possibly modifying the normal functioning of autoregulation. The chosen solution was to study the forearm circulation, reducing the forearm perfusion pressure at the level of the brachial artery by mechanical means. The forearm is composed predominantly of muscle, and in essential hypertension the arterioles of voluntary muscle partake in the general elevation of vascular resistance.

Initially, an attempt was made to reduce the forearm perfusion pressure by localized external compression, either manually or instrumentally, of the brachial artery. This method proved unsuccessful. Compression was difficult to maintain at a constant level for the requisite period and inevitably obstructed the venae comitantes, thus interfering with the plethysmographic technique used to measure blood flow. The only feasible technique entailed the use of an intra-arterial catheter with an inflatable balloon at the tip and a more proximal opening to monitor the perfusion pressure. A 4F Berman angiograph catheter (Critikon Inc., Tampa, FL, USA), proved satisfactory for the purpose.

Forearm blood flow was measured by venous occlusion plethysmography using a water-filled plethysmograph that was modified to include a copper heating coil with which to maintain the water jacket at a constant 37°C. The hand circulation was excluded to minimize the involvement of skin blood flow.

Pressures were measured by Hewlett-Packard pressure transducers (Model HP 1280; Palo Alto, CA, USA) and displayed on a four-channel Hewlett-Packard amplifier recorder (Model HP 7754A). In all instances arterial pressures are given as mean pressures in millimeters of mercury, recorded electronically.

Seventeen hypertensive subjects, aged 29 to 65 years, and three normal subjects, aged 21 to 24 years, were enrolled for study. The three normal subjects were studied to establish, for purposes of comparison, the normal degree of autoregulation within subjects. They were studied at all ages to confirm that the main experimental problem was due to the hypertensive condition and not due to an intrinsic problem in the aging process. Sixteen of the 17 subjects had a family history of hypertension. There were no signs of cardiac failure or other complications. Within the limits of these criteria, the choice of subjects was random. All gave informed consent.

In seven hypertensive subjects the study could not be performed for technical reasons (inability to catheterize the brachial artery in two, balloon rupture in two, and in three a persistent ooze from the arterial puncture site that could be controlled only by withdrawing the catheter). In the remaining 10 hypertensive subjects the catheter was introduced percutaneously into the brachial artery at the elbow and advanced until the tip was high up in the artery above the likely origin of any branch arteries to the forearm. Two to 30 minutes was then allowed for stabilization of the circulation before the forearm blood flow was measured. The result of this first measurement was recorded as flow 1. The balloon was then inflated with normal saline with the initial objective of reducing the forearm blood pressure by successive steps.
down to a normal mean level of 100 to 110 mm Hg. This goal proved impossible. The balloon tended to inflate and deflate in an all-or-none fashion. It was possible to reduce the forearm perfusion pressure in one step to a stable mean level of 100 to 105 mm Hg in 8 of the 10 hypertensive subjects, while in the remaining 2 subjects only a stable mean level of 75 mm Hg could be achieved. Since this was below the normal blood pressure level and thus too low for the purpose of the study, these subjects were excluded from further consideration. In the normotensive subjects the forearm perfusion pressure was reduced to a stable mean of 75 to 85 mm Hg, which is within the autoregulatory range.

Once the perfusion pressure had been reduced to the target level, the forearm blood flow was again measured and recorded as flow 2. Over the subsequent 3 to 4 minutes the process of autoregulation was monitored by continuous measurement of the forearm blood flow until a new stable flow was established. This final blood flow was recorded as flow 3.

### Results

Mean blood pressures are given to the nearest 5 mm Hg and are shown for all subjects in Tables 1 and 2. Forearm blood flows are given as milliliters per 100 ml of tissue per minute. In the eight hypertensive subjects, the average blood pressure at the start of the study was 142.5 mm Hg and the average forearm blood flow (flow 1) was 4.95 ml/100 ml tissue/min. With reduction of the perfusion pressure to an average of 102 mm Hg, the flow rate (flow 2) in seven of these subjects dropped immediately to an average of 2.3 ml/100 ml tissue/min, which represented 47% of flow 1. (In one hypertensive subject it was not possible to obtain a measure of flow 2 for technical reasons, but the more important flow 3 was obtained.) In the course of the next 3 to 4 minutes the flow autoregulated upward by means of vasodilatation to a stable level (flow 3) of 3.7 ml/100 ml tissue/min, which was equivalent to 75% of flow 1. The increase from 2.3 ml/100 ml tissue/min to 3.7 ml/100 ml tissue/min is a measure of the degree of autoregulation. Autoregulation was manifest in all hypertensive subjects; the degree is represented for each subject in Table 1 as the difference between flow 3 and flow 2, and the efficiency of the process is represented as the closeness of flow 3 to flow 1.

In the three normal subjects the perfusion pressure was reduced from an average of 100 mm Hg to 78 mm Hg, which gave a flow 1 value of 4.3 ml/100 ml tissue/min, a flow 2 value of 1.3 ml/100 ml tissue/min, which represented 30% of flow 1, and a flow 3 value of 3.8 ml/100 ml tissue/min, which represented 88% of flow 1 (Table 2). The data for each normal subject are given in Table 2.

There were no complications other than a small subcutaneous hematoma in two instances. These resolved over a period of some days and had no long-term complications.

### Table 1. Forearm Blood Flow in Relation to Perfusion Pressure in Eight Hypertensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>38 38 40 48 64 38 52 31 44</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>160 130 130 140 160 135 125 160 142.5</td>
</tr>
<tr>
<td>Reduced perfusion pressure (mm Hg)</td>
<td>100 100 100 105 100 100 105 105 102</td>
</tr>
<tr>
<td>Flow 1 (ml/100 ml tissue/min)</td>
<td>2.5 4.5 2.3 4.2 5.5 4.3 7.3 9.0 4.95</td>
</tr>
<tr>
<td>Flow 2 (ml/100 ml tissue/min)</td>
<td>1.8(72%) 2.4(53%) 1.2(52%) 1.5(36%) — 1.1(26%) 4.3(59%) 4.1(46%) 2.3(47%)</td>
</tr>
<tr>
<td>Flow 3 (ml/100 ml tissue/min)</td>
<td>2.3(92%) 3.3(73%) 1.8(78%) 2.9(69%) 5.0(91%) 2.6(60%) 6.0(82%) 5.6(62%) 3.7(75%)</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent flow 2 and flow 3 as a percentage of flow 1.

### Table 2. Forearm Blood Flow in Relation to Perfusion Pressure in Three Normal Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>24 21 22 22</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>95 100 105 100</td>
</tr>
<tr>
<td>Reduced perfusion pressure (mm Hg)</td>
<td>75 75 85 78</td>
</tr>
<tr>
<td>Flow 1 (ml/100 ml tissue/min)</td>
<td>6.8 3.0 3.1 4.3</td>
</tr>
<tr>
<td>Flow 2 (ml/100 ml tissue/min)</td>
<td>1.9(28%) 1.3(43%) 0.8(25%) 1.3(30%)</td>
</tr>
<tr>
<td>Flow 3 (ml/100 ml tissue/min)</td>
<td>6.3(93%) 2.6(87%) 2.6(84%) 3.8(88%)</td>
</tr>
</tbody>
</table>

Numbers in parentheses represent flow 2 and flow 3 as a percentage of flow 1.
Discussion

When the perfusion pressure to a tissue is suddenly reduced the arterioles to that tissue behave as inert elastic tubes for a few brief seconds before autoregulation comes into operation. The reduction in distending pressure causes an elastic recoil of the vessel wall so that the vascular resistance increases. Thus, there is an abrupt reduction in blood flow, due in part to the lower perfusion pressure and in part to the increased vascular resistance. This process explains the reduction in blood flow from flow 1 to flow 2 found in this study. It has been shown that a reduction of perfusion pressure from 150 mm Hg to 100 mm Hg produces approximately a 50% increase in vascular resistance, and the incremental effect is much greater at lower arterial pressures. The changes found in this study were in a similar range. As autoregulation comes into play, arteriolar resistance is actively reduced and tissue flow returns toward normal, as shown in this study by the change from flow 2 to flow 3.

The crucial result in the hypertensive subjects is the degree to which autoregulation returned the blood flow toward normal following reduction of the perfusion pressure. The average flow recovered from a nadir of 47% of normal back up to 75%. The interpretation of this figure is the central issue. The three normal subjects were studied to establish some measure of the range of short-term autoregulation in the normal human forearm with reduction of perfusion pressure within the autoregulatory range. With an average pressure reduction of 22 mm Hg, the three normal subjects autoregulated back up to 84%, 87%, and 93% of normal. Although this response is not much greater than that achieved by the hypertensive subjects as a whole, the only hypertensive subjects who can be said with certainty to have preserved full autoregulation at normal perfusion pressure were those who autoregulated as fully as the normal subjects. On this basis, two of the eight hypertensive subjects autoregulated normally (91%, 92%), and two came very close (78%, 82%).

The fact that the other four did not reach this level must be viewed in the light of the following points. First, since the normal subjects were younger than the hypertensive subjects (mean of 22 yr vs 44 yr), their peripheral vessels would be expected to respond more readily to the stimulus of autoregulatory vasodilatation. Second, in the normal subjects the perfusion pressure was reduced on average by only 22 mm Hg, while in the hypertensive subjects the reduction was 40.5 mm Hg. Since autoregulation is a slightly imperfect, graded response, the larger reduction clearly puts a greater demand on autoregulation. Third, Folkow and his group have convincingly demonstrated that just as the left ventricle hypertrophies when exposed for a time to increased wall tension, so does the muscular layer of human forearm arterioles when exposed to the stress of an elevated blood pressure. The increased vessel wall thickness augments arteriolar resistance at all levels of transmural pressure and also at maximal dilatation. Even if autoregulation in hypertensive subjects were initially complete at normal blood pressure it might, in time, become incomplete if the whole autoregulation curve were progressively shifted upward to a higher pressure range by the organic vascular changes. This shift has in fact been shown in the cerebral circulation of hypertensive animals and humans. The gradual nature of the downward gradation in the percentage of autoregulation found in our hypertensive subjects (92%, 91%, 82%, 78%, 73%, 69%, 62%, 60%) would favor such a secondary type of shift from an initially high level.

Finally, for these results to support an autoregulatory mechanism for the increased peripheral resistance, it would only have been necessary to show a normal degree of autoregulation with reduction of the perfusion pressure to basal level. Since there was no way of calculating the basal level, the perfusion pressure was reduced instead to a normal blood pressure level. As this level is lower than the basal level, it created an unnecessarily stringent test of autoregulation. It could well be, for instance, that a hypertensive subject would demonstrate a normal degree of autoregulation at basal level though not at normal blood pressure level.

It thus appears that in two of the eight subjects with essential hypertension the elevated blood pressure could not have been due to a vasoconstrictor substance acting directly on the peripheral resistance but to an autoregulatory increase in the peripheral resistance arising in response to a thrust toward an excessive cardiac output. Furthermore, the weight of evidence strongly favors the view that a similar pathophysiology holds for the remaining six hypertensive subjects. Clearly, it must be so if the premise is accepted that all cases of essential hypertension possess a common pathophysiology, at least as far as hemodynamics are concerned. This is the working premise of many researchers in the field.

It may be objected that the behavior of muscle circulation is not representative of the circulation as a whole. There is no evidence to support this objection, and it is noteworthy that muscle circulation, even under basal conditions, composes as much as 15% of the total circulation. Furthermore, Arendshorst and Beierwaltes have shown precisely similar behavior for the renal circulation of the spontaneously hypertensive rat, and Johansson et al. reported studies suggesting the same for human cerebral circulation. In the rat it was found that on reducing the renal pressure to normal by locally applied mechanical means the renal blood flow autoregulated back to normal. Since young rats were used, with a relatively brief duration of hypertension, autoregulation was complete. In the case of the human cerebral circulation, evidence was presented that hypertensive encephalopathy was due to excessive blood pressure breaking through maximal autoregulatory vasoconstriction and causing capillary flooding and edema. This finding suggests a high vis a tergo pressure rather than a primary increase in peripheral resistance as the cause of the hypertension. If the primary hemodynamic abnormality were an increase in peripheral vascular resistance, then an exac-
erbation of that condition could only lead to diminished cerebral blood flow, whereas if the primary abnormality were a thrust toward an increased flow, which was being held in check by autoregulatory vasoconstriction, then an exacerbation of that thrust might well break through autoregulation and lead to tissue flooding.

If the pathophysiology of the increased vascular resistance in muscle, kidney, and brain conforms to Guyton's autoregulation concept, then it seems reasonable to assume that this concept is correct for the circulation in general.

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