A Vascular Abnormality in Hypertension

A Study of Blood Flow in the Forearm

By James Conway, M.D., Ph.D.

The increased peripheral resistance associated with hypertension has been demonstrated for the circulation as a whole by measurements of blood pressure and cardiac output. The site of this resistance has not been precisely identified but it is believed to reside in the smallest arteries and arterioles. Since the activity of the smooth muscle in these vessels is readily affected by humoral and neurogenic stimuli, it has been assumed that there is an increased level of vasoconstrictor tone in this disease, but no evidence has yet been obtained for this assumption. On the other hand, there is considerable evidence in man affected by hypertension that the blood vessels themselves show exaggerated responses to vasoconstrictor drugs, although this may not be readily demonstrated when these drugs are given intravenously. Paradoxically, however, Folkow and associates have shown that under the influence of the powerful vasodilator stimuli of heat and reactive hyperemia the blood vessels maintain a greater level of resistance in hypertensive than in normal subjects. These facts suggest that whatever abnormal vasoconstrictor stimuli may be operative in hypertension, the function of the blood vessels themselves may also be abnormal.

A study has, therefore, been undertaken to determine the presence of a vascular abnormality of the blood vessels in hypertension and to relate it to the severity of the disease in a large group of patients.

Methods and Materials

Apparatus

Measurements of blood flow by plethysmography have been made in the vascular bed of the upper half of the forearm. This was dictated in part by the suitability of this region for the apparatus to be used and in part because this vascular bed is not dominated by skin vessels, with their numerous arteriovenous anastomoses, which are so much affected by neurogenic stimuli and are therefore unsuitable for studies of vascular resistance under vasodilator stimuli. The tissue composition of the upper forearm is reported as 63.6 per cent muscle and 8.6 per cent skin.

Venous occlusion plethysmography has been employed to measure blood flow with use of the mercury-in-rubber strain-gage plethysmograph described by Whitney. This instrument is convenient to use and has been shown to give values for blood flow that are comparable with those obtained by the water-filled plethysmograph.

Plethysmographic Measurements

Subjects were studied in the recumbent position, covered with blankets, in a quiet room in which temperature ranged from 68 to 78° F. The subject's arm was elevated by pillows to approximately 20° from horizontal, to raise it above the heart level. A 5-cm. pneumatic cuff was placed at the wrist and a collecting cuff 12 cm. wide was positioned above the elbow. In all cases the circulation was occluded at the wrist before a measurement of blood flow was made. The venous collecting pressure was approximately 40 to 50 mm. Hg for normal and 40 to 70 mm. Hg for hypertensive subjects. This pressure was delivered from an air pressure reservoir and the time of rise in pressure, which was less than one second, was recorded for each blood flow. Records were made with the Gilson multichannel polygraph.

Blood pressure measurements were obtained by the auscultatory method in the opposite arm immediately before each group of blood flow recordings was made. Disappearance of the Korotkoff sounds was used to indicate the diastolic level, and for each pressure reading, the mean of three measurements was taken.

Experimental Routine

On each occasion the subject relaxed for 15 to 20 minutes in the recumbent position after which 4 to 6 measurements of resting flow in the forearm were made at approximately 1-minute intervals. Thereafter, the circulation was occluded for a period of 8 or 10 minutes during which the subject exercised the forearm muscles by squeezing a sphygmomanometer bulb 20 times. At the end of the period of occlusion, blood pressure was measured in the opposite arm and im-
Maximal blood flow obtained with an \textit{intra-arterial} infusion of adenosinetriphosphate and \textit{reactive} hyperemia. Blood pressure was simultaneously recorded from catheters inserted in the brachial artery and a forearm vein.
Figure 2

Relationship between blood pressure and the minimal resistance obtained with reactive hyperemia. The regression line relates blood pressure and resistance in hypertensive subjects and does not include data from the patients with renovascular disease and aldosteronism.

of norepinephrine (four cases) or angiotensin (two cases). A patient with a pheochromocytoma, in whom elevation of pressure could be readily produced by movement, also volunteered for this study.

Material

Fifty normal subjects and 131 untreated hypertensive patients, who were being evaluated in the Hypertension Unit of the University Hospital, have been studied. In the hypertensive patient particular emphasis was placed upon the estimation of the duration of the disease or the presence of arteriosclerotic complications. No patients with demonstrable cardiac failure or with marked renal failure were included. The limit of nitrogen retention was a blood urea nitrogen of 35 mg. per cent. Ninety-one patients were believed to have essential hypertension. This number includes 10 patients regarded as labile hypertensives in whom occasional pressure readings in the normal range were found. Eleven patients with renal hypertension (on the basis of either chronic glomerulonephritis or pyelonephritis) were also included in this figure. There were, in addition, 21 patients with renovascular disease verified at operation and eight with primary aldosteronism.

Blood flow measurements were made on 362 occasions in the entire group of 181 subjects. The blood pressure values reported for the normal and the hypertensive groups have been taken from the average of the readings obtained with the subjects recumbent when resting blood flows were being recorded.

The mean blood flow data are recorded in milliliters per 100 ml. of tissue per minute, and the resistance in units was obtained by dividing the mean pressure (diastolic + 1/3 pulse pressure) by the blood flow. All averages are given ± the standard error.

Animal Experiments

The data obtained with human subjects were supplemented by direct blood flow measurements from the denervated hind limb of six dogs. Blood flow was measured by the Shipley-Wilson rotameter inserted into the divided femoral vein; arterial pressure and venous pressure were recorded simultaneously on a Grass polygraph. To obstruct collateral flow a constricting tourniquet was applied to the leg below the inguinal ligament beneath the exposed artery and vein; another was applied below the knee to eliminate the paw circulation. Pressure flow curves were obtained by partially constricting the femoral artery while the change in perfusion pressure was observed. The effect of vasoconstrictor and dilator drugs infused intra-arterially on the pressure flow curve was then determined.

Results

Normal Subjects

In the normal subjects, with an average blood pressure of 120/65 mm. Hg, the average blood flow in the forearm at rest was 3.4 ± 0.2 ml. and the resistance was 31.3 ± 2.1 units. These values are of the same order as those found for the forearm by others, using the conventional technic or the strain-gage plethysmograph. After arterial occlusion for 8 or 10 minutes, the average flow increased to 45.8 ± 2.0 ml. and resistance fell to 2.0 ± 0.07 units. This resistance was not related to the initial blood pressure, and no trend was noted with respect to age in the resting or in the reactive hyperemia flows.

Hypertensive Subjects

In the hypertensive patients, with an average blood pressure of 176/103 mm. Hg, the mean resting flow of 3.9 ± 0.27 ml. did not differ significantly from that of the normal, but the calculated resistance of 40.1 ± 2.1
units was significantly greater than normal ($p < 0.001$). The resistance during reactive hyperemia, $3.1 \pm 0.1$ units, showed a more marked difference from normal ($p < 0.001$). The level of this resistance was related to the severity of the disease as indicated by the level of the resting blood pressure, $r = 0.4$ (fig. 2). Clinical manifestations of the severity of the disease were in keeping with this finding, since 25 patients with retinopathy of grades III and IV had an average reactive hyperemia resistance of $3.3 \pm 0.12$ units at a mean blood pressure of 140 mm. Hg. By contrast, 17 patients with evidence of arteriosclerotic complications, as indicated by cardiographic signs of coronary thrombosis, angina, peripheral vascular disease, or x-ray evidence of dilatation of the aorta, did not demonstrate an unusually high reactive hyperemia resistance ($2.9 \pm 0.15$ units) at a mean pressure of 138 mm. Hg. The known duration of the disease was not related to the level of the reactive hyperemia resistance (fig. 3) and, as in the normal subjects, age was not related to the level of resting flow or the reactive hyperemia resistance.

To determine possible interrelationships between the high reactive hyperemia resistance and other characteristics of the disease, the hypertensive patients were subdivided into two groups: those with a resistance below 3.0 units and those with resistance of 3.0 units or more (table 1). In the mild group the resting resistance was normal, since both blood flow and pressure were found to be increased proportionately. During reactive hyperemia, flow was also greater than normal but the resistance at this time was significantly greater ($2.5 \pm 0.09$ units) than the normal ($2.0 \pm 0.07$ units) ($p < 0.01$). On the other hand, the patients with the more severe disease not only had a higher resting resistance ($47.4 \pm 2.8$ units) than normal ($p < 0.001$) but during reactive hyperemia the blood flow itself ($39.2 \pm 1.1$ ml.) was lower than normal ($45.8 \pm 0.2$ ml.) (table 1). Thus the very high reactive hyperemia resistance was the result of a limitation of blood flow in addition to the higher perfusion pressure.

**Renovascular Disease and Primary Aldosteronism**

The patients with the more unusual forms of hypertension did not show distinct differences in their blood flow data from the pa-
tients with other forms of the disease. In the 21 renovascular patients the average resting resistance was $36.3 \pm 2.6$ units, and the average reactive hyperemia resistance was $2.9 \pm 0.51$ units. The relationship between the reactive hyperemia resistance and the resting blood pressure was similar to that found in patients with other types of hypertension (fig. 2). The patients with primary aldosteronism provided similar findings, with an average resting and reactive hyperemia resistance of $39.0 \pm 5.8$ and $2.7 \pm 0.21$ units respectively (table 1) (fig. 2).

**Plethysmography at High Flow Rates**

Since the most prominent finding related to blood flow was the increased resistance during reactive hyperemia, the possibility that some defect in the method might be causing a falsely low recording of blood flow in hypertensive patients was considered. The following possible sources of error were investigated:

1. At high rates of blood flow the venous pressure might be approaching the occluding pressure so rapidly that blood escapes under the cuff.

2. Arterial pressure in the limbs might fall excessively during reactive hyperemia, giving an undue reduction in blood flow.

3. The rate of blood flow in patients with very high pressures might be limited by turbulence or some other factor which would make it impossible to develop the high flow rates required to give a normal resistance.

Simultaneous recording of brachial arterial and venous pressures in eight patients with high reactive hyperemia resistance showed (fig. 1) that although the venous pressure rose steeply when the blood flow was high, the linear portion of the blood flow curve occurred when it was below the pressure in the occluding cuff. Arterial pressure, as indicated by others\(^23\) does not rise to its full value immediately after the release of the arterial occlusion but achieved this within the ensuing 15 to 30 seconds. For this reason, the maximal flow was rarely recorded at the first period of venous occlusion after release of pressure, but at the time of the recorded maximal flow the average fall in pressure was only $12/8$ mm. Hg. Application of the venous occlusion cuff at the pressure of $70$ mm. Hg in hypertensive patients did not influence arterial inflow.

In the routine blood flow studies, the average time elapsing between the release of the arterial occlusion and the attainment of maximal flow was the same in the normal subjects ($22.2 \pm 1.04$ seconds) and hypertensive patients ($16.8 \pm 0.5$ seconds) ($p < 0.1$), suggesting that arterial obstruction was not preventing the attainment of maximal flow.

The third possibility seems unlikely, since

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control</th>
<th>After pentolinium</th>
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<td></td>
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</table>

**Table 2**

*Effect of Acute Reduction in Blood Pressure on Maximal Reactive Hyperemia Blood Flow*
Table 3

Comparison of the Maximal Blood Flow Produced by Reactive Hyperemia and Intra-Arterial Infusions of Adenosinetriphosphate

<table>
<thead>
<tr>
<th>Subject</th>
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</table>

the blood flow data show that reactive hyperemia in the severe cases was accompanied by smaller maximal flow than in the normal. The possibility was investigated, however, in 10 patients in whom an acute change in blood pressure was produced by ganglionic blockade between recordings of reactive hyperemia. The average mean pressure falling from 151 mm. Hg to 122 mm. Hg produced parallel changes in blood flow from 45.4 ± 2.0 to 36.4 ± 3.6 ml., which gave a mean reactive hyperemia resistance of 3.3 and 3.4 units respectively (table 2).

Full Relaxation of Blood Vessels

Although these experiments demonstrate the adequacy of the methods for measurement of blood flow, the possibility remained that the degree of vasodilatation produced by ischemia had not approached its asymptote during the circulatory arrest.

Variation in the duration of the arterial occlusion was used to indicate whether the vasodilator stimulus was below the maximal level. In all groups the average resistance value for the 8-minute occlusion was nearly identical with the value for the 10-minute occlusion, the mean of the former, 8-minute occlusion, being 2.50, and of the latter, 2.84 units. In seven patients intra-arterial infusion of adenosinetriphosphate was undertaken to achieve maximal dilatation. This was used, since it has been shown to effect the same degree of dilatation as maximal doses of acetylcholine without the coincident discomfort produced by the latter.24 The infusion was maintained for several minutes and arterial occlusion was applied for periods of 0.5 to 2 minutes in order to achieve the maximal flow for each subject. The maximal blood flow resulting from the infusion of adenosinetriphosphate (43.1 ± 3.0 ml.) did not differ from that obtained with reactive hyperemia (42.8 ± 4.3 ml.) (table 3, fig. 1).

Reactive hyperemia was also able to overcome the effects of intravenously administered vasoconstrictor drugs. In seven subjects the elevation in mean pressure from 77 to 115 mm. Hg resulted in an increase in blood flow from 40.9 ± 2.9 ml. to 52.3 ± 2.8 ml. without change in resistance (table 4).

The animal experiments confirmed these findings. Figure 4 shows a typical pressure flow curve in the denervated limb which is convex to the pressure axis, and this is reduced by an intravenous infusion of angiotensin. In these experiments the resistance at 80 mm. Hg in the denervated limb varied from 5.1 to 13.7 units, and during the infusion of acetylcholine intra-arterially it fell to 1.3 to
Pressure flow curve obtained from denervated hind limb of the dog (with the paw excluded). Each point refers to one measurement of blood flow at the corresponding perfusion pressure produced by temporary occlusion of the femoral artery.

Discussion

There have been several studies of reactive hyperemia flow in hypertension, and all have shown that the increase in flow after ischemia is approximately the same in normal subjects as in hypertensive patients. It was concluded, therefore, that the blood vessels in hypertension are not sclerotic and are capable of considerable dilatation. Stead and Kunkel and later Folkow and associates drew attention to the resistance to blood flow and noted that it could not be reduced to normal levels by maximal vasodilator stimuli. The present study confirms their findings, and further shows that the abnormality is related to the level of resting arterial pressure. Patients with high reactive hyperemia resistance have also an increased resistance to blood flow in the resting state. These studies have been made in the forearm but similar results have been reported in the hand, foot, and brain, and it has been shown that blocking the sympathetic nerves to the hand or the foot does not reduce resistance to the same degree in hypertensive as in normal subjects. Microangiographic studies have also demonstrated a diffuse narrowing of the submucosal vessels in hypertensive patients.

The precise mechanism by which reactive hyperemia results in vasodilatation is unknown, but it has been shown to be capable of overcoming the vasoconstrictive action of many drugs; this has been confirmed by the infusion experiments of this study. Furthermore, the dilator effect of ischemia closely corresponds to that of the intra-arterial infusion of adenosinetriphosphate in man and acetylbolamine in the hind limb preparation in dogs—both drugs being infused in supra-

Table 4

<table>
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<tr>
<th>Subject</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Maximum flow (ml/100 ml/min)</th>
<th>Mean blood pressure (mm Hg)</th>
<th>Maximum flow (ml/100 ml/min)</th>
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<td>2.9</td>
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</table>

Circulation, Volume XXVII, April 1963
maximal doses. The linear pressure flow curve obtained with acetylcholine in the dog further suggests that the distensibility of the blood vessels is then limited, as would be expected when the vascular smooth muscle is fully relaxed.

If reactive hyperemia were capable of overcoming the increased resistance of hypertension, the higher perfusion pressure should result in a greater rate of blood flow than in normal subjects. This can be demonstrated in normal subjects after the pressure is elevated acutely by the intravenous infusion of noradrenaline or angiotensin. It must be concluded, therefore, that in the hypertensive state an element of resistance exists that is not related to the activity of vascular smooth muscle as we know it. This resistance could result from hypertrophy of the muscular or intimal layers of the vessels, or from their swelling, as suggested by Tobian. Likewise, a change in the relaxed state of the muscle fibers or increased stiffness of the vessel wall could lead to an increased resistance.

The presence of a vascular abnormality suggests that the means by which vascular resistance is maintained in hypertension may be more complex than we appreciate at present. The observation that renovascular disease and primary aldosteronism possess the same vascular abnormality as the more common types of the disease raises the hope that these conditions share a common underlying mechanism.

The vascular abnormality detected in this study becomes evident upon relaxation of the blood vessels. The vessels maintain their ability to constrict and relax under the normal variations of vasoconstrictor and dilator stimuli and thus can respond adequately to antihypertensive therapy. Indeed, Folkow’s group has suggested that if the inability to dilate fully were due to hypertrophy of the inner layers of the vessel wall it would lead to an increased responsiveness to vasoconstrictor and dilator drugs.

In conclusion, therefore, the fact that the resistance in blood vessels in hypertensive disease cannot be reduced to the minimal level achieved in normal subjects suggests that there is a mechanism outside the normal activity of vascular smooth muscle participating in the increased peripheral resistance in this condition. Although this may be the result of hypertension and not causal, such an assumption should be viewed in the light of the fact that the increased residual resistance is not related to the duration of the disease but only to its severity.

**Summary**

Forearm blood flow measurements have been made at rest and after 8 to 10 minutes arterial occlusion in 50 normal and 131 untreated hypertensive subjects. The latter group comprised 91 with essential hypertension; 11 with chronic renal disease (nephritis or pyelonephritis); 21 with renovascular disease; and eight with primary aldosteronism.

The resting blood flow increased with the rising pressure in patients with mild hypertension but there was a significant increase in the resting resistance in the more severe cases. The average minimal resistance obtained during reactive hyperemia was greater in hypertensive (3.1 SE 1.0 units) than in normal subjects (2.0 SE 0.07 units). This abnormality was related to the level of blood pressure but not to the duration of the disease.

Patients with renovascular disease or aldosteronism presented the same vascular fault as the more common causes of hypertension.

Evidence is presented to show that the reactive hyperemia produced maximal dilatation of the forearm vasculature, and acute elevation in pressure in normotensive or acute depression of pressure in hypertensive subjects did not influence the level of resistance achieved by reactive hyperemia.

It is concluded that the blood vessels themselves are abnormal in hypertension and that this abnormality may not be related to the activity of vascular smooth muscle.

**Acknowledgment**

The author gratefully acknowledges the technical assistance of Barbara Mudge and Gladys Knoll in the performance of blood flow tests.
References


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Circulation, Volume XXVII, April 1963


Effect of Electricity on Muscular Motion

This morning in our Hospital of Sajnt Ursula, in which the Professor of Surgery is the learned and my most distinguished colleague Doctor Gaspar Gentili, excellent master of surgery, I tested, with my customary devices, an amputated leg and arm, immediately after the operation, in the presence of the aforesaid professor and other physicians and men of learning, and the flexor muscles of the thumb and of the adjacent digits were seen to contract, both of the hand and of the foot, and in consequence the aforesaid digits to move.

The device which I employed was to place a good part of the leg and of the foot, denuded of their integuments, immediately in warm water, and then to armature the corresponding nerves of the indicated muscles with tin-foil close to their entrance into the same; then I applied a little conducting metal cap, and singularly of silver, and I applied it in such a way that with one part it touched the edge of the tin-foil, and with another the portion of nerve uncovered or some contiguous part, so that there was, as I suppose, an arc composed partly of the aforesaid metals, partly of extrinsic moisture, which brought back to the external surface of the indicated muscles the natural electricity of the internal surface, which had ascended to the place of contact of the nerve, and from that had gone out through the force of the same contact.

The same nerves were then invested with wax or with some other insulating body, or else the same bodies were superimposed on the first armature, and no further contraction then was obtained. Therefore the existence of animal electricity seems proved, and its law in man also proposed.—LUIGI GALVANI. Commentary on the Effect of Electricity on Muscular Motion. Translated by ROBERT MONTRAVILLE GREEN, M.D. Cambridge, Massachusetts, Elizabeth Licht, Publisher, 1953, p. 96.
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Circulation. 1963;27:520-529
doi: 10.1161/01.CIR.27.4.520
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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