Vascular Reactivity in Hypertension

By A. E. DOYLE, M.D., AND J. R. E. FRASER, M.D.

In established human hypertension, there has never been any real doubt that the baroreceptor mechanisms remain active but regulate the arterial pressure to a new high level. The upward setting of these baroreceptors occurs not only in essential hypertension but also in hypertension secondary to renal disease of various sorts. There is also evidence from the effects of ganglion blocking drugs that, in most hypertensive patients, a substantial part of the elevated blood pressure is maintained by the sympathetic nervous system and that blocking sympathetic ganglia leads to a larger fall of blood pressure in hypertensive than in normal subjects. In most patients with established hypertension, however, catecholamine excretion is within normal limits so that, if the neurogenically maintained part of the blood pressure is increased in hypertension, it probably results from an increased effect of sympathetic nervous activity rather than from an increase in the activity itself. One possible way in which this could occur is by an increase in sensitivity of the blood vessels to the endogenous nor-epinephrine produced by sympathetic nerve endings. An alternative explanation would be that blood vessels already constricted by other means respond more vigorously to nervous stimulation.

There have been numerous efforts to elucidate this problem in man. Most have involved the systemic administration of pressor amines, with assessment of the effect in terms of change in blood pressure or peripheral resistance. It is known, however, that in hypertension, as in health, stimuli that tend to alter blood pressure are opposed by homeostatic mechanisms, so that the changes in blood flow or in peripheral resistance that follow the systemic administration of pressor substances represent the resultant of the effects of the pressor stimulation and its modification by the baroreceptors. Moreover, the differences in starting levels of blood pressure and total peripheral resistance also complicate these experiments.

We have studied this problem by administering pressor substances intra-arterially in amounts that, although active locally, are too small to affect the general circulation. The fall in forearm blood flow obtained by the infusion of norepinephrine into the brachial artery (fig. 1) is expressed as a per cent fall of the average of the preceding and subsequent control periods.

We found that hypertensive patients had a significantly greater response to norepinephrine than normal subjects, although there was a considerable overlap between the two groups (fig. 2). By using different concentrations of norepinephrine, it was possible to construct dose response curves that confirmed the fact that hypertensive patients required about half as much norepinephrine as normal subjects to obtain a given fall in forearm blood flow (fig. 3).

Although the dose response curves were significantly separated, the slopes of the lines were the same. In attempting to interpret this finding, we could not decide whether it represented a difference in the threshold of response in the two groups, or whether it reflected a greater initial constriction of blood vessels in hypertensive patients than in normal subjects.

The average initial forearm blood flow was 3.6 ml./100 ml./min. in the hypertensive group and 3.3 ml./100 ml./min. in the normal group. The average mean blood pressure of the hypertensive group was 168 mm. Hg as compared to 103 mm. Hg for the normotensive group. Thus, the average initial vascular re-
Plethysmograph illustrating the effect of norepinephrine. The upper record was taken during the infusion of saline into the left arm; the lower record was taken during the infusion of norepinephrine (0.4 µg./min.) into the left arm. In both records, the lower tracing is from the left arm. (From Doyle et al.)

Figure 1

Histogram showing the responses of 50 hypertensives and 48 normal subjects to the infusion of norepinephrine (0.4 µg./min.). The normal subjects are indicated by continuous lines, the hypertensives by interrupted lines.

Figure 2

The relationship between the rate of infusion of norepinephrine and the percentage fall in blood flow. The solid circles represent the mean responses for 10 hypertensive subjects; the open circles refer to the mean responses of 10 normal subjects. (From Doyle et al.)

Figure 3

The relationship between initial forearm resistance and the rise in forearm resistance caused by the intra-arterial infusion of 0.4 µg. of norepinephrine per minute.

Figure 4

Resistance of the forearm was greater in the hypertensive patients than in the normotensive controls. Because of the great variation in forearm blood flow, however, many hypertensive subjects had a rather low vascular resistance, whereas in many normal patients it was quite high, thus providing an overlap of initial resistance in the forearm. It is evident (fig. 4) in both groups that, as the initial resistance in the forearm increases, so the change in resistance induced by norepineph-

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The relationship between responses in individual subjects to norepinephrine and angiotonin. (From Doyle et al.)

It is equally evident that for comparable initial resistances the hypertensive patients experienced a much larger change in resistance than did the normal subjects. The conclusions can be drawn that the forearm vessels of hypertensive patients react more strongly to norepinephrine, whether they are initially constricted or not, and, when the initial resistance is high, the difference between the two groups is accentuated still further.

Thus, there appears to be conclusive evidence of vascular hypersensitivity to norepinephrine in patients with high blood pressure. It seemed important to know whether this is specific for norepinephrine or whether there is an altered sensitivity to pressor agents in general. Figures 5 and 6 demonstrate the relationship in individual hypertensive and normal subjects between the response to norepinephrine and the response to angiotensin and 5-hydroxytryptamine respectively. It is apparent that, in general, marked vascular response to one pressor substance is associated with a similar response to the others.

There are a number of possible relationships between increased vascular reactivity and high blood pressure. An important preliminary to elucidating the significance of the altered vascular sensitivity is to determine whether it represents a metabolic or a struc-
atural vascular abnormality, which causes high blood pressure, or whether it is one of the ways in which a rise in blood pressure, initiated by some other mechanism, becomes an established change. The evidence that increased vascular reactivity follows the induction of experimental hypertension favors the second possibility but does not deny in any way the existence of the first.

We are studying this problem currently and are comparing the pressor sensitivity of a group of normotensive medical students whose parents have normal blood pressure with a group of normotensive children whose parents are attending the hypertension clinic. The groups are matched for age and all are males; the children of the hypertensive patients were selected because of an unequivocal family history of high blood pressure.

Our results to date are summarized in fig. 7. It appears that there is a distinct difference in the distribution of the response of the two groups of subjects. The mean responses of the children of hypertensive families are slightly greater than those of children from normal families. Although the difference in mean response is small and not statistically significant, examination of the distribution curves shows that many of the children of hypertensive parents respond more vigorously than do those from normotensive families. Thus the modal points differ, the distribution curve of the hypertensive families showing a shift to the right. Such a difference between apparently normal individuals who differ only in family history suggests very strongly that a tendency to vascular hypersensitivity precedes the onset of high blood pressure and that this tendency is genetically determined. If further observations confirm our preliminary results, there seems no reason to doubt that such a tendency of the blood vessels to respond more vigorously to pressor stimuli could be at least as significant a factor as the magnitude of pressor stimulation in determining the height to which blood pressure might rise in response to physiological and pathological stimuli. Such an observation would be consistent with the fact that high blood pressure, whether essential or secondary, is more common in some families than in others.

References
Discussion

Dr. Baldwin: We have performed studies quite similar to those of Dr. Doyle, but our interest has centered around the reactivity of the renal circulation. We have determined the response of the renal circulation to intravenously administered norepinephrine in patients with essential hypertension and in normotensive subjects. We recognize, as does Dr. Doyle, that the initial constriction is greater in hypertensive than in normotensive patients, a fact that makes the interpretation of our results even more difficult. Our observations show that the reactivity of the renal circulation is considerably greater in normotensive than in hypertensive individuals, both by percent increase in renal resistance and decrease in renal plasma flow. Also, we performed these studies in the same individuals after severe sodium restriction and found that the difference was exaggerated. In normotensive patients, renal circulatory resistance was enhanced by sodium restriction but in hypertensives it was somewhat diminished.

Dr. Hoobler: I should like to congratulate Dr. Doyle not only on the general tenor of his paper but also on the imagination shown in studying the offspring of hypertensive parents. I think important leads may be found in the prehypertensive subject that might remain undiscovered in those with the established form of the disease.

I should like to ask two questions and comment on some of our own studies. We can confirm that the cold pressor reactivity is unaltered in the normal person and in the patient with established or fixed hypertension. Also, we could not identify the patient with labile hypertension by the cold pressor test. I wonder whether you have tested individuals with labile blood pressure during the normotensive phase and, if so, whether they had an exaggerated response? It seems to me that such people may represent a more ideal test object than patients with fixed hypertension in whom the hyperreactivity may have disappeared. Also, may I ask whether you have seen any changes in initial resistance to forearm blood flow after two weeks' treatment with chlorothiazide?

Dr. Doyle: In reply to Dr. Baldwin: I am sorry that you used the intravenous route. The difficulty in giving drugs intravenously is that you produce a rise in blood pressure and very often, I think, vasodilatation at the same time. This makes assessment of the vascular response to intravenous injection extraordinarily difficult. There is a good deal of evidence that intravenous norepinephrine produces a rise in forearm blood flow, whereas intra-arterial injection produces a fall. It may well be that your results could be modified by baroreceptor responses. Although injection into the renal artery is difficult, we are trying to do this at the present time.

In answer to Dr. Hoobler: We were unable to distinguish the response of labile hypertensives in any way. We were able to get some calmed down so that their blood pressure was fairly normal before we put them into water, but they did not seem to be more hyperreactive than normal subjects. There was no alteration in initial resistance after a fortnight's treatment with chlorothiazide. There was often a fall in both cardiac output and plasma volume and in the response to intravenously administered norepinephrine, although not to intra-arterial norepinephrine.

Dr. Rodbard: Familial relationships always raise the question of whether a genetic or an aggregational phenomenon is in operation. Dr. Winkelstein in our laboratory has recently examined the question of familial hypertension on an epidemiological basis. His analysis demonstrated that the wives of hypertensive individuals tended to have higher blood pressure than the wives of normotensive persons. Wives may generally be expected to have different genetic patterns than their husbands. Can Dr. Doyle tell us if his data would support the belief that a familial hypertensive tendency may be based on aggregation rather than on heredity?

Dr. Doyle: No, Dr. Rodbard, it wouldn't, nor would it refute it. I think it possible that
people who live with hypertensives are likely to have elevated blood pressure too. I understand from Dr. Stokes in Boston that the serum cholesterol level of wives tends to rise in parallel with that of their husbands. It is obvious that environmental factors must be involved. In some of the children in our group of patients, both parents had strong histories of hypertension but in the great majority one parent had hypertension and the other normal blood pressure.

Dr. Mendlowitz: I think Dr. Doyle, in characteristic British fashion, has understated his case. I say this because resistance, as you all know, represents a flow-pressure ratio that is really an index of caliber. In the hypertensive person, a rise in resistance seems to mean that a caliber change has taken place against an increased blood pressure. If this factor were taken into account, I think the differences would be even more striking than those that have been presented. We have used the intravenous route in the digit and have found results very similar to Dr. Doyle's. We have also found that chlorothiazide decreases reactivity in the hypertensive but either has little effect or increases reactivity in the normotensive. Steroids seem to increase reactivity in the normotensive but have no effect in the hypertensive. What all this means I do not know, except that it suggests we may be dealing with a chemical factor.

Dr. Doyle: On the whole I agree with what Dr. Mendlowitz has said. I am quite convinced that there is no change in vascular response when one uses chlorothiazide in the usual dosage. We have done some work on patients who were treated with chlorothiazide, sodium restriction, and ion exchange resins, and although the blood pressure fell very markedly, we were unable to demonstrate a convincing change in vascular response.

The possibility that hypertension may result from some metabolic disorder is pure speculation—an attractive hypothesis. The findings presented this morning do give some support to the thought that hypertension may be related to the metabolism of norepinephrine, but it is obviously a local thing, something in the blood vessels themselves; that problem is more for those experts we heard this morning than for clinicians such as Dr. Mendlowitz and myself.

Dr. Thomas: I, too, was interested in the familial aspects of Dr. Doyle's fine presentation. That the comparison between the two groups of offspring—those with and those without hypertensive parents—did not show so great a contrast as that between hypertensive patients and normotensive subjects is not surprising. We have found that no more than 25 per cent of middle-aged offspring of two hypertensive parents have hypertension themselves and that the proportion of offspring who have hypertension, when only one parent is affected, is even smaller. Accordingly, in any population of offspring of hypertensive parents, the "prehypertensive" group is greatly outnumbered by the group that, in all probability, may never develop hypertension. One would therefore expect that the distribution curve arising from this mixed population would fall somewhere between the curves for hypertensive and nonhypertensive groups, as was the case here.

Dr. Finnerty: We have repeated some of Lars Werko's work and found that cardiac output after exercise does not rise much in the patient with hypertension. When chlorothiazide is given and the experiment is repeated, the greater cardiac output occurring after exercise closely approaches the normal response. One may postulate that the only way this can happen is through decreased peripheral resistance. Could the reason for this be removal of sodium from the walls of large vessels?

We have been most interested in trying to distinguish patients with, from those without, arteriosclerosis. The patients with the most sensitive blood-pressure response to infusion of norepinephrine are those with glomerular disease and toxemia of pregnancy; they are much more sensitive than patients with essential hypertension. Can this be explained solely by the fact that they are young people with pliable vessels? I should like to hear someone comment on this.
**Dr. Doyle:** Toxemia of pregnancy is certainly humoral in nature, because ganglion blockers do not reduce blood pressure even though cardiac output falls. It is often difficult to shift the blood pressure of these patients. I suggest that, in toxemia of pregnancy, the baroreceptors are already strained from the elevated blood pressure and cannot modify the vascular response to norepinephrine.

**Dr. Ogden:** When Dr. Doyle suggested that hypersensitivity might occur before the elevation of blood pressure in essential hypertension, I recalled some work which Page, Brown, and I did some years ago that made us think it might happen in Goldblatt hypertension too. We used intravenous injections; and, because we weren't prepared to measure cardiac output, we tried to skitter around such changes by using a variety of pressor agents, including vasopressin, which we thought would not much increase cardiac output. We came to the conclusion that increased vascular sensitivity, as reflected by the greater rise of blood pressure in response to Pitressin and other substances, occurred before the development of the hypertension that follows the application of Goldblatt clamps. It should have been as obvious to us while writing it, as it was to people who read it, that using the Grant capsule method for measuring blood pressure necessitated warming the rabbit to get enough blood flow through the ear. Thus we probably never knew when our rabbits became hypertensive; we only knew when they became so hypertensive that warming them wouldn't lower their blood pressure to normal. Under those conditions however, there was no question that vasopressin, epinephrine, noises, and smoke blown into their faces—anything that might stir them up—produced increased pressor responses a few days after the application of the clamp, although stable, measurable hypertension did not appear for a couple of weeks. If these two things tie together, it broadens this concept—the suggested hypothesis that this feature of essential hypertension may be a metabolic disturbance—because it may apply to the Goldblatt type of hypertension, which most of us, I believe, have been inclined to think is different from essential hypertension.

**Dr. Gillow:** This question of which comes first, the increased reactivity or the hypertension can be resolved, I think, by the patient with pheochromocytoma. Such an individual may have hypertension for many years, certainly ample time to develop the hypertrophied wall about which Dr. Doyle is concerned, yet will show decreased vascular reactivity to norepinephrine. This has been shown by Corn and other workers on many different blood vessels. It would seem to me that the hypertrophied wall has very little if anything to do with this, so it obviously must be something else.

**Dr. Preis:** Dr. Doyle, do you agree with that?

**Dr. Doyle:** No, not particularly. Pheochromocytoma is one situation in which this might be but, if so, it is, I believe, a special example. Much experimental evidence suggests that hypertension induced in animals is associated with a demonstrable increase in vascular reactivity. I don't think one can say that those animals were predestined to become hypertensive. They had never before had hypertension.
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