Peripheral Venous and Arteriolar Responses to Infusions of Angiotensin in Normal and Hypertensive Subjects

By J. Edwin Wood, M.D.

Few studies of peripheral vascular physiology in essential hypertension have been devoted to the veins. Methods for the study of these vessels have not been entirely satisfactory and, in addition, the precapillary resistive vessels of the circulation command primary attention in this disease. The apparent absence of participation of the veins in the otherwise extensive vasoconstriction observed in essential hypertension seemed deserving of detailed investigation. The peripheral veins are active participants in vascular responses to a wide variety of vasoconstrictor stimuli. Naturally occurring humoral substances, such as norepinephrine and epinephrine, or stimuli that result in activity of the sympathetic nervous system, such as a cool environment, cause constriction of the veins as well as constriction of the arterioles. The pattern of arteriolar constriction without venoconstriction is physiologically unusual. Thus, the proposal of an etiology of essential hypertension would be strengthened if the agent in question produced constriction of the arterioles without affecting the veins. It is the purpose of this communication to describe experiments that: (a) determine whether or not the peripheral veins are constricted in patients with essential hypertension as compared with normal individuals, (b) determine whether or not peripheral veins of patients with essential hypertension respond to stimuli that result in a sympathetic discharge, and (c) record the venomotor responses of normal and hypertensive patients to infusions of angiotensin and norepinephrine.

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Methods

General

Subjects were studied one hour after the noon meal while comfortably warm in a constant temperature room of 72 F. An intravenous infusion of saline was started at the beginning of each experiment in which angiotensin* or norepinephrine were to be given. Both drugs were diluted in saline. The apparatus was arranged so that the patient could not determine when the infusion of a drug was initiated. Ordinary intravenous drip sets were used for the infusions. The drug was given for 30 minutes. The first 10 to 15 minutes were devoted to adjusting the dose so that the diastolic pressure was raised by about 30 mm. Hg. Arterial pressure was measured by the auscultatory method. Venous pressure was measured directly with a saline manometer. Blood flow and venous distensibility were measured plethysmographically on the calf or forearm.

Studies of Posture

The effect of the upright position was investigated with one arm in the plethysmograph. The subject rested in a bed that was placed in the 60-degree head-up position. Control studies were obtained while pneumatic leggings were inflated, thus preventing pooling of blood in the veins of the legs. Then, pressure in the leggings was released, and the legs were congested for a period of 30 to 45 minutes while studies of the forearm vessels were repeated.

Plethysmographic Methods

A water plethysmograph that consisted of two chambers was utilized in these experiments. It was constructed so that water could be added to a height that produced sufficient local external pressure on the extremity to counterbalance the local venous pressure. The net result of this procedure was to reduce the transmural or effective venous pressure to a level of 1 mm. Hg. A pneumatic cuff was placed on the wrist or ankle and inflated to suprasystolic pressure during all measurements. A pneumatic cuff on the thigh or upper arm was inflated so that the effective venous pressure was raised from the 1 mm. Hg starting pressure by 5 mm. Hg increments to a level of

*Supplied as Synthetic Hypertensin II by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.
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30 mm. Hg. Thus the veins within the plethysmograph were exposed to stepwise increases of effective venous pressure. This resulted in stepwise increases in their recorded volume. Data so obtained allowed plotting of the relationship between pressure change and volume change of the veins, referred to hereafter as the venous pressure-volume curve (fig. 1). Thus, both the pressure range to which the vessels were exposed and the starting pressure are defined. Previous experiments have indicated that the total volume of blood in the extremity with an effective venous pressure of 1 mm. Hg is relatively small as compared with the volume of blood in the extremity at higher venous pressures. It is important to recognize that, when the effective venous pressure is 1 mm. Hg, a stimulus that produces constriction of the veins, such as an infusion of norepinephrine, does not alter the volume of the extremity importantly. This indicates that, though the veins are less distensible when inflated, their starting volume in either the constricted or dilated state is approximately the same. A relatively lower pressure-volume curve would indicate venoconstriction. The volume of the veins at an effective venous pressure of 30 mm. Hg reflects the relative position of the venous pressure-volume curve so that, for convenience, the observations reported are for this point on the curve and are referred to as "venous volume (30)" (fig. 1).

Patients

All subjects for these experiments were normal males or hospitalized patients who had received no hypotensive or diuretic agents for at least one month prior to the studies. All patients with hypertension were considered to be of the essential type.

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Results

Ten male patients with untreated essential hypertension were studied. Their blood pressures averaged 165/109 (range 138-208/92-136) mm. Hg. They were studied on 20 occasions with three venous pressure-volume curves in each experiment. Their venous volume (30) averaged 3.5 (range 2.4 to 4.4) ml. per 100 ml. of forearm tissue. Blood flow and blood pressure were simultaneously measured nine times in each experiment. The values were used to calculate peripheral resistance in arbitrary units. Peripheral resistance averaged 38 (range 17 to 108) units. Fourteen normotensive male subjects were studied in the same manner on 28 occasions. Their forearm venous volume (30) averaged 3.3 (range 2.4 to 5.4) ml. per 100 ml. of forearm tissue. Peripheral resistance averaged 25 (range 13 to 42) units (fig. 2).

The effect of congestion of the legs, the patient being in the upright position, was studied in 18 normotensive subjects, with a resultant significant decrease in venous volume (30) of the forearm during the period of leg congestion. Venous volume (30) averaged 3.1 per 100 ml. of forearm tissue prior to, and 2.5 ml. during, leg congestion. Eleven male subjects with untreated essential hypertension were subjected to this procedure and there was no significant change in venous volume (30) during the leg congestion period as compared with the control period (fig. 3).

Eight male patients without evidence of cardiovascular disease received infusions of angiotensin for 30 minutes. The dosage re-
Venous pressure rose during the infusions of angiotensin in normal individuals by an average of 9 (range 4 to 15) cm. of water. In hypertensive patients the infusions resulted in an average rise of venous pressure of 2 (range 0 to 3) cm. of water.

Infusion of angiotensin at these relatively rapid rates usually caused headache, dyspnea, chest discomfort, nausea, or abdominal cramps in normotensive subjects. Patients with essential hypertension suffered none of these symptoms despite the fact that they received essentially the same dose of this material.

Six of the patients with essential hypertension received infusions of norepinephrine that consistently resulted in venoconstriction with an average venous volume (30) of 4.1 and 3.2 ml. per 100 ml. of leg before and during the infusion respectively.

**Discussion**

The results of these experiments are not consonant with the hypothesis that essential hypertension is caused by overactivity of the sympathetic nervous system. Stimuli that ordinarily result in discharge of the sympathetic nervous system, such as a cool environment, the upright posture, or exercise, all cause peripheral arteriolar constriction associated with constriction of the peripheral veins. The peripheral veins of patients with essential hypertension are not constricted relative to those of normal individuals. If the sympathetic nervous system were responsible for the constriction of the peripheral resistive elements of the circulation without participation of the peripheral veins, this would represent a degree of selectivity of action not ordinarily observed.

The effect of the upright posture on hypertensive subjects suggests, if anything, that the responsiveness of the sympathetic nervous system is less than that observed in normotensive individuals. Whether or not this represents a decrease of sympathetic nervous activity in the face of an independent pressor stimulus is an important question. Alternately the question arises of whether or not this relative inactivity of the peripheral veins is
somehow primarily responsible for the presence of hypertension. It has been suggested that peripheral veins, in responding poorly to postural stimuli, would reduce filling pressure of the heart, thus inducing counterbalancing reflexes that resulted in overactivity of the arterioles. The fact that peripheral veins of hypertensive subjects respond normally to infusions of norepinephrine leaves this postulate in the unlikely position that sympathetic nervous activity to the arteries would be excessive and sympathetic nervous activity to veins diminished.

The most obvious independent mechanism for production of elevated arterial pressure that might apply to the patient with essential hypertension is the renin-angiotensin system. The hypertensive patient presents an unusual pattern of peripheral arteriolar constriction without peripheral venous constriction. Thus, the effect of synthetic angiotensin upon the peripheral blood vessels would seem to be of interest. Infusions of angiotensin produced constriction of the veins as well as constriction of the arterioles in normal individuals. In addition, as has been observed by others, venous pressure was elevated to abnormal levels. Finally, normal subjects receiving this drug suffered acutely from abdominal cramps as well as from a peculiar oppressive feeling in the chest that was associated with dyspnea. All of these findings lead to the conclusion that the hypertension induced in the normotensive individual by angiotensin infusion is not akin to essential hypertension as it occurs naturally, although such a conclusion must be tempered by a realization of the acute nature of the experiments.

The question arose of whether or not the hypertensive patient would differ in his responses to infusions of angiotensin. Here the situation was entirely different, in that constriction of the veins did not occur despite the rises in arterial pressure and peripheral resistance induced by the infusions of angiotensin. A rise of venous pressure was not observed, and the symptoms in the chest and abdomen did not occur.

It has been suggested that the dyspnea experienced by normal subjects receiving angiotensin is due to a rise in pulmonary-artery pressure induced by a shift of blood centrally from the peripheral veins, in that pulmonary vascular resistance is unaltered. The results of these experiments indicate that such may be the case in the normotensive patient. Peripheral vasoconstriction was present, the venous pressure rose, and the subject suffered dyspnea; whereas hypertensive patients did not have peripheral venoconstriction, with a rise in venous pressure, and did not suffer dyspnea. It has been demonstrated that angiotensin will cause the smooth muscle of the gut to contract and, should this occur in the human in response to this material, he might experience abdominal cramps. The absence of this response to angiotensin in the hypertensive suggests that the smooth-muscle response of the gut was not so intense. Since the smooth muscle of the veins of the hypertensive subject responds normally to norepinephrine infusion, the lack of responsiveness to angiotensin in such subjects seems somewhat specific. The results of these studies suggest that the responses of smooth muscle in patients with hypertension are modified. This could occur with exposure to some material at least similar to angiotensin that is not present in the circulation of normotensive individuals, or the responses of these vessels might be altered for some more obscure reason. The finding of venoconstriction, elevated venous pressure, elevated pulmonary-
artery pressure, and probably gastrointestinal smooth-muscle stimulation on infusion of angiotensin in a normotensive subject, and the absence of these responses in patients with essential hypertension receiving exogenous angiotensin do not rule out angiotensin as an agent of etiological importance in this disease.

**Summary**

The distensibility of the peripheral veins of the hypertensive subject is normal, that is, there is no evidence of peripheral venoconstriction, despite the excessive arteriolar constriction. The forearm veins of hypertensive patients respond to pooling of blood in the upright position to a lesser degree than do veins of normotensive individuals, indicating a lesser degree of sympathetic nervous activity in response to this stimulus. The peripheral veins of hypertensive subjects constrict normally in response to an infusion of norepinephrine, indicating that failure of venoconstriction in any circumstance cannot be attributed to failure of the smooth muscle of the veins.

Infusions of angiotensin produce constriction of the veins as well as the arterioles in normotensive individuals thus failing to mimic the naturally occurring state of essential hypertension. Infusions of angiotensin in hypertensive patients result in further arteriolar constriction and hypertension without concomitant venoconstriction. The results of these experiments suggest that peripheral venous responses of hypertensive subjects to angiotensin infusions may have been modified by previous exposure of these vessels to a material at least similar to angiotensin.

**References**


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Discussion

Dr. Boyle: I wonder if it is possible that the hypertensive subject's previous experience with high blood pressure has an effect in some nonspecific way. In 1941 Dr. Bradley reported some effects of angiotensin in normal people; I think he found that venous pressure rose quite sharply, the heart dilated, and lung fields developed an appearance suggesting congestive failure. If this situation did occur in these normal individuals, it would be reasonable to expect that cardiac output had fallen, whereas it might not have done so in hypertensive persons. I think this could account for the venous constriction.

Dr. Wood: I think that is a distinct possibility. We attempted to attack this question by using hypertensives whose blood pressures had fallen in the hospital, but we don't really have enough data to discuss this point extensively. We have several patients with essential hypertension of the labile variety who respond in the same way as patients with established hypertension, so that prolonged hypertension is not necessary to establish this difference in the two groups. The venous pressure rise has been described by Dr. Bradley.

Dr. Bradley: I must rise to say that Dr. Robert Wilkins was the first to observe the rise in venous pressure in response to angiotensin. We found that right atrial pressure rises too. Since cardiac output decreases, the response somewhat resembles heart failure, but I am sure that neither Dr. Wilkins nor I would call it "failure." S-Methyl isothiourea induces the same response. What happens to venous volume under these circumstances is another problem. We haven't been able to make measurements of the blood volume in the splanchnic bed with these drugs.

We do have clinical evidence that tends to support Dr. Wood's contention. Hypertensives, as a group, appear to be more susceptible to situations that tend to interfere with the return of the blood to the heart. Thus, they seem to suffer orthostatic hypotension more readily and more quickly when tilted into the upright position than a group of "normotensives" who appear equally well. We have found that putting an abdominal pressure cuff on a group of hypertensives not infrequently results in a fall of blood pressure that we seldom, if ever, see in a group of normal persons. Hypertensives differ from normal also in showing a tendency for the blood pressure to fall strikingly during the pyrogenic reaction. In hypertensives the cardiac output does not seem to rise so effectively to maintain arterial pressure as in the normal person. One might argue that here again venous return is inadequate, perhaps because venules if you wish, that capillary pressures are forced to rise locally.

Dr. Finnerty: Sometime ago we compared the hemodynamic effects of infusions of angiotensin with those of norepinephrine and found, strangely enough, that the effect of norepinephrine on the venous pressure was four times that of angiotensin in normotensive subjects. In hypertensive subjects, however, both substances affected venous pressure to the same extent. What is the reason for the peculiar kind of swelling that is frequently seen when a hypertensive patient is infused with angiotensin for a two- to three-hour period? The swelling may remain for 24 hours after discontinuation of infusion. Did you experience this?

Dr. Wood: Our infusions were limited to 30 minutes. We didn't see the edema. I think Dr. Haddy's ideas might well apply to this situation as well as to other forms of peculiar local edema. Perhaps there is increased resistance to flow on the venous side, in the venules if you wish, so that capillary pressures are forced to rise locally.

Dr. Blaquier: I wonder if your method actually measures venous constriction only. In the dog, infusion of angiotensin increases central venous pressure, as well as peripheral venous pressure, together with an increase in central blood volume that we do not interpret.
as venous constriction. Have you measured central venous pressure?

\textit{Dr. Wood:} The venous pressures that we measured were peripheral. Others have measured central venous pressure and found that it goes up in normotensive subjects when angiotensin is infused. It seems likely that the dyspnea suffered by these patients is due to an increased volume centrally; further than that I cannot say.

\textit{Dr. Blaquier:} Do you mean that the venous pressure rise in the periphery might be the result of central venous pressure rise?

\textit{Dr. Wood:} These experiments are not dependent on what happens to the central venous pressure. The starting venous pressure for each curve is exactly the same for all experiments regardless of what is going on centrally. The failure to observe a peripheral venous pressure rise in hypertensives means to me that central venous pressure rise did not occur. This is not to say that higher doses of angiotensin would not have caused an increase in these pressures. Rather, the same dose of this material gave very different responses in these two groups of subjects.

\textit{Dr. Freis:} Your pressures are obtained by a congesting cuff around the arm that raises the pressure so that you are actually cutting off the central venous pressure?

\textit{Dr. Wood:} Yes.
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