Effect of Angiotensin II on the Intact Forearm Veins of Man

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Studies on animals other than man have demonstrated that angiotensin II has little venoconstrictor action.\(^1,2\) Recently the digital vascular responses to angiotensin II in man have been shown to consist primarily of constriction of precapillary blood vessels with little or no constriction of the postcapillary vessels or the arteriovenous anastomoses.\(^3\) The digital vascular response to angiotensin II differed from that of norepinephrine which constricts the postcapillary vessels and the arteriovenous anastomoses as well as the precapillary vessels.\(^4\) The present study was performed to learn the effect of angiotensin II on the intact superficial veins of the forearm of normal man.

**Methods**

The experimental preparation consisted of a venous segment\(^5,6\) approximately 2.0 cm in length and 0.2 to 0.4 cm in diameter free of tributaries and valves located on the volar aspect of the human forearm. The venous segment was cannulated with two 25-gauge needles. One needle was connected by means of polyethylene tubing to a Statham strain-gauge transducer (no. P23D). The other needle was connected to a specially constructed microsyringe which made it possible to inject and withdraw small quantities of fluid.\(^7\) Each complete turn of the volume control knob of the microsyringe produced a volume change of exactly 0.016 cc (fig. 1).

After the venous segment was cannulated with the two needles the segment was isolated from the remainder of the circulation by means of two brass wedges in a manner previously described.\(^5,6\) In such a preparation, because blood flow is no longer a factor, variations in pressure within the isolated venous segment directly reflect changes in tone of the smooth muscle in the wall of the vein.

Two groups of experiments were performed.

**Group I Experiments**

**Experimental Procedure.** The effect of angiotensin II on an isolated venous segment was studied in 18 normal subjects ranging in age from 18 to 62 years (mean 38 years). Fifteen subjects were male and three were female.

The experiments were performed in the following manner: While recording the pressure continuously in the isolated venous segment, a known volume of blood was withdrawn from the segment. After the pressure within the segment became stable, the same fluid volume (blood mixed with isotonic saline) as had been withdrawn previously was injected into the segment. The experiment was then repeated in exactly the same manner except that this time angiotensin II diluted with isotonic saline was used to restore the fluid volume of the venous segment. In some instances the order of the experiment was reversed with angiotensin II being injected into the segment before the control saline injections. In five subjects norepinephrine was injected into the venous segment following the injections of saline and of angiotensin II.

The concentration of angiotensin II used in these experiments was 500 \(\mu g/cc\). The total amount of angiotensin II injected into the venous segment depended upon the volume of fluid withdrawn from the segment. Since each turn of the volume control knob of the microsyringe represented 0.016 cc of fluid, approximately 8.0 \(\mu g\) of angiotensin II were delivered to the segment during most of the experiments. Some experiments were repeated by withdrawing either 0.032 cc or 0.064 cc of fluid from the segment and then injecting an equal volume of the solution of angiotensin II, representing an injection of 16 \(\mu g\) and 32 \(\mu g\), respectively, of the drug.
STUDY OF PRESSURE-VOLUME RELATIONSHIP IN INTACT VENOUS SEGMENT OF MAN

Results. In no instance did the injection of angiotensin II into the isolated venous segment result in a rise in pressure in the venous segment. Figure 2 shows a representative experiment in which first saline and then angiotensin II was used to replace fluid withdrawn from the isolated venous segment. There was no evidence that angiotensin II produced a change in segmental venous tone.

Thirty-two micrograms of angiotensin II injected into the isolated venous segment of one subject did not produce an increase in segmental venous pressure, but did produce a marked increase in systemic arterial blood pressure after the isolating wedges were removed, releasing the content of the segment into the general circulation.

In several experiments 0.02 cc of saline was injected directly into a venous segment without previous withdrawal of blood from the segment (fig. 3). After observing the response to the saline, 0.02 cc of blood was removed from the segment. After the pressure within the segment became stable, 0.02 cc (10 μg) angiotensin II was injected directly into the venous segment. This was followed by a slight rise in segmental venous pressure which was of the same magnitude as that produced by an equal volume of isotonic saline (fig. 3). On the other hand the injection of norepinephrine into an isolated venous segment was associated with a marked rise in segmental venous pressure (fig. 3).

Comments. The injection of angiotensin II directly into an isolated venous segment produced no change in tone of the venous segment. This finding would indicate that there are no receptors for angiotensin in the segment of the vein studied. Another possibility is that the receptors were present but the angiotensin II did not reach them or some type of inhibitors or inactivators of angiotensin exist in the walls of the veins studied. Although there is no way to disprove the latter possibilities, it is obvious that norepinephrine reached suitable receptors to produce a marked constriction of the same venous segment. Structurally angiotensin II is an octa-

**Figure 1**

Diagram of technique used for studying pressure-volume relationships in an intact venous segment of the forearm of man. One complete turn of the volume control of the microsyringe either withdraws or injects 0.016 cc of fluid. Pressure is recorded continuously by the transducer while known changes in segmental fluid volume are produced with the microsyringe.
peptide with a relatively low molecular weight of about 1000 and as such should have no difficulty permeating the tissues. Previous studies have shown that hexamethonium injected into an isolated systemic vein produces dilatation of the vein, again indicating the ease with which chemical substances may penetrate the venous wall. Furthermore, angiotensin II injected into the dermis rapidly finds its way to the receptors within subdermal blood vessels to produce a blanching of the skin.

It is not likely that failure to obtain a venoconstrictive response was due to enzymatic inactivation of angiotensin II by the blood since in the presence of appropriate receptors the action of angiotensin II is immediate. In this respect the injection of angiotensin II into the isolated segment is no different than injection into any other portion of the circulation. Moreover, in the majority of the subjects studied before termination of the experiment, the venous segment was completely emptied of blood and angiotensin II mixed with saline was injected into the segment. Again in no instance was a venoconstrictor response observed.

**Group II Experiments**

*Experimental Procedure.* In an effort to learn more about the effect of angiotensin II on the venous system a second group of experiments was performed in which venous pressure in an isolated segment of vein was measured during the intravenous infusion of angiotensin II into the systemic venous system. Angiotensin II was administered intravenously in five subjects ranging in age from 29 to 60 years (mean 44 years). All subjects were males without clinical evidence of cardiovascular disease. A forearm venous segment was again isolated as in the first group.

![Diagram](image-url)
EFFECT OF DIRECT INJECTION OF SALINE, ANGIOTENSIN II AND NOREPINEPHRINE ON SEGMENTAL VENOUS PRESSURE

![Graph showing effect of direct injection of saline, angiotensin II and norepinephrine on segmental venous pressure.](image)

Effect of direct injection of equal volumes of isotonic saline, angiotensin II and norepinephrine into an isolated venous segment without first withdrawing fluid from the segment. The increase in segmental venous pressure following the injection of angiotensin II (10 μg) is of the same magnitude as occurred with saline. This rise in pressure was produced merely by an increase in segmental fluid volume. The injection of norepinephrine (10 μg) produced a marked rise in segmental venous pressure due to increase in venous tone.

In addition the brachial artery in the ipsilateral arm was cannulated with a 20-gauge Courand indwelling needle and connected to a Statham strain-gauge transducer. Intra-arterial blood pressure and the segmental venous pressure were recorded continuously and simultaneously. An indwelling needle was placed into an antecubital vein in the contralateral arm and connected by means of a three-way stopcock to a bottle containing isotonic saline and to another bottle containing angiotensin II in a concentration of 1.0 μg of angiotensin II/cc. After a suitable control period, during which normal saline was infused at a rate of 1.0 cc/min, the three-way stopcock was readjusted and angiotensin II was infused at a rate of 1.0 μg/min.

In three subjects after the response to angiotensin II was recorded, the nerves to the isolated venous segment were blocked locally with Xylocaine hydrochloride using technics previously described, and the angiotensin II was again infused into a vein of the contralateral arm.

In all experiments the infusion of angiotensin II was discontinued after a rise in arterial blood pressure of approximately 50 mm Hg.

**Results.** In three of the five subjects the infusion of angiotensin II was associated with a rise in segmental venous pressure of 25 to 58 mm water (mean 44 mm H₂O) (fig. 4). In the remaining two subjects no change in segmental venous pressure occurred during the infusion of angiotensin II. When a rise in venous pressure occurred, it always followed the rise in systemic arterial blood pressure (fig. 4). In fact, the segmental venous pres-
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Influence of Intravenous Infusion of Angiotensin II on Arterial Blood Pressure and Segmental Venous Pressure in Contralateral Arm

Fig. 4

Recording of segmental venous pressure and systemic arterial blood pressure during the intravenous infusion of angiotensin II (1.0 μg/min) in a contralateral antecubital vein. The rise in segmental venous pressure occurred after the rise in arterial blood pressure and at the time of development of reflex bradycardia.

Fig. 5

Recording of segmental venous pressure obtained a few minutes later for same preparation and subject used in figure 4. The nerve supply to the isolated venous segment had been blocked with 1% Xylocaine hydrochloride. In this instance the rise in systemic arterial blood pressure was not followed by a rise in segmental venous pressure.

Comments. The intravenous systemic infusion of angiotensin II was associated with slight venuconstriction reflected by the slight rise in segmental venous pressure in three of five subjects. Obviously since the venous segment was isolated from the circulation, except possibly for the vasa vasora, the rise in venous pressure could not have been due to the...
direct action of angiotensin on the vein. However, since angiotensin II may have been delivered to the venous wall via vasa vasora, the nerves to the venous segment were blocked with Xylocaine hydrochloride. Following regional nerve block there was no rise in segmental venous pressure.

It is of interest that the rise in segmental venous pressure occurred at the time of onset of reflex bradycardia noted in the arterial pulse tracing, indicating that the rise in segmental venous pressure may have been mediated in part through reflexes originating outside of the veins.

In previous studies in which the systemic venous pressure response to the intravenous infusion of angiotensin II was compared to that of norepinephrine in the same subjects it was noted that norepinephrine produced a significantly greater rise in systemic venous pressure (mean 111 mm H2O) than did angiotensin II (mean 64 mm H2O) and that the rise in venous pressure following norepinephrine infusion always preceded the onset of the rise in systemic arterial blood pressure, whereas the rise associated with angiotensin II always occurred simultaneously with or after the onset of the increase in arterial blood pressure.

Discussion

These studies suggest that angiotensin II has no direct effect on the forearm veins of man and that the elevation in venous pressure found in some subjects during the intravenous systemic administration of angiotensin II is reflex in nature. These observations were in agreement with previous studies of the digital vascular responses to angiotensin II in which the intra-arterial injection of intravenous infusion of angiotensin II produced relatively slight postcapillary vasoconstriction.

Despite the early studies on man of Wilkins and Duncan with natural angiotensin and the more recent studies of Wood with angiotensin II, some doubt remains concerning the venoconstrictive properties of angiotensin II. Despite the fact that these investigators have reported that angiotensin II constricts the veins in man, animal experiments have shown angiotensin II to have little or no effect on the veins. The studies described in this paper provide additional evidence that angiotensin II has no direct effect on the systemic veins of man and that the relatively small increases in venous pressure which occur in some subjects during the infusion of angiotensin II are a result of reflexes mediated through pathways originating outside the veins.

Summary

Angiotensin II was injected into an isolated venous segment in eighteen human subjects and administered intravenously into a systemic vein in five other subjects. Injections of angiotensin II into an intact isolated venous segment produced no constriction of the segment. Intravenous systemic infusion of angiotensin II produced a slight constriction of the isolated venous segment in three subjects (mean 44 mm H2O) and no constriction of the segment in two subjects. The constriction in the venous segment associated with the systemic intravenous administration of the drug could be interrupted by blocking the nerves supplying the venous segment. Thus, angiotensin II has no direct effect upon the forearm veins of man. The rise in segmental venous pressure following the intravenous infusion of angiotensin II appears to originate from reflexes located outside the venous system which influence tone of the superficial veins of the forearm of man.

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