Comparison of Direct Effects of Angiotensin and Other Vasoactive Agents on Small and Large Blood Vessels in Several Vascular Beds

By Francis J. Haddy, M.D., Ph.D., Joyce I. Molnar, M.S., Craig W. Borden, M.D., and E. Clinton Texter, Jr., M.D.

A thorough study of a vasoactive agent should include effects on resistance to blood flow (influences arterial pressure and rate of blood flow), storage of blood (influences effective circulating volume and, hence, venous return, cardiac output, and arterial pressure), capillary patency (influences diffusion distances and, therefore, rates of movement of material and heat), and filtration pressure (influences storage of water in tissues).

This paper presents a comparison of the local effects of angiotensin and other vasoactive agents on resistance to blood flow through the dog forelimb and gut beds and on "filtration pressure" in the dog forelimb and rabbit ear. Preliminary observations on blood storage in the dog forelimb are also mentioned. Inasmuch as the data contained in the paper were derived from a number of studies conducted over the last 10 years, the methods utilized are summarized as each study is presented.

Resistance to Blood Flow Through the Vascular Bed of the Dog Forelimb

A blood pump was interposed between the femoral and brachial arteries and the forelimb flow rate held constant at a rate which produced a pressure in the brachial artery approximately equal to that in the aorta (fig. 1). Pressures were measured at 4 sites along the length of the forelimb bed, namely, the brachial artery, the third superficial volar metacarpal artery, the second superficial dorsal metacarpal vein, and the cephalic vein. Various vasoactive agents were infused into the brachial artery just distal to the pump at rates which were without effect on aortic pressure. Pressures were recorded when they became steady. In some instances, the forelimb was denervated by sectioning the musculocutaneous, median, ulnar, and radial nerves high in the forelimb.

Resistance to blood flow through the foreleg increased as a function of the infusion rate of angiotensin II over the range 0 to 0.5 μg./min. (fig. 2). Further increments in infusion rate were frequently not possible without causing a rise in aortic pressure. The resistance increase resulted almost entirely from

From the Medical Service, Veterans Administration Research Hospital, and the Departments of Medicine and Physiology, Northwestern University Medical School, Chicago, Illinois.
increase in the resistance to flow through small vessels (less than 0.5 mm. diameter, which include small muscular arteries, arterioles, capillaries, venules, and small veins). Resistance to flow through large arteries (5.0 to 0.5 mm. diameter) also increased slightly in some experiments, especially with the higher rates of infusion. Resistance to flow through large veins (0.5 to 5.0 mm. diameter) was not affected. On the average, infusion of 0.3 μg./min. into a brachial arterial flow of 100 ml./min. almost immediately increased total resistance to 119 per cent (fig. 3) of the control value. The effect was gone 5 minutes after stopping the infusion.

In terms of weight of infused base, angiotensin II proved to be one of the more active vasoconstrictors studied. Figure 4 shows that its ability to increase total forelimb resistance is equal to that of levarterenol or epinephrine and is definitely greater than that of metaraminol, phenylephrine, mephentermine, and methoxamine. Because the molecular weight of angiotensin II is greater than that of the other agents, it follows that, molecule for molecule, the activity of angiotensin II is definitely greater than that of the other constrictors. Figure 4 also shows that serotonin is the only bidirectional agent, producing constriction in the denervated leg and frequently dilation in the innervated leg, and that, in terms of weight of infused base, isoproterenol is the most active dilator.

Resistance to Blood Flow Through the Vascular Bed of the Dog Gut

A blood pump was interposed between a femoral artery and the superior mesenteric artery. Flow through the gut was held constant at a rate which produced a pressure in the mesenteric artery similar to that in the
aorta. Pressures were measured in the mesenteric artery just distal to the pump, in a small artery several centimeters from the mesenteric border of the small intestine, in a small vein very close to the mesenteric border of the small intestine, in the portal vein, and in the aorta. Vasoactive agents were infused into the mesenteric artery at rates which were effective locally, but not generally, as judged by change of mesenteric arterial pressure without change of aortic pressure.

Total resistance to flow increased as a function of the infusion rate of angiotensin II, and the resistance increase resulted mainly from increase of small vessel resistance (fig. 5). Arterial resistance also increased slightly in some experiments, but venous resistance was unaffected. Small venous and portal venous pressures sometimes rose equally, suggesting a resistance increase some place on the liver side of the site of pressure measurement in the portal vein. In terms of weight.
of infused base, angiotensin II was the most active constrictor studied (fig. 6).

"Filtration Pressure" in the Vascular Bed of the Dog Forelimb

One factor which influences the rate of movement of water in and out of the capillary is capillary hydrostatic pressure. This pressure is determined by arterial pressure, the resistance to blood flow through arteries, the resistance to blood flow through veins, and venous pressure. Pappenheimer and Soto-Rivera\(^1\) have quantitated the effects of arterial and venous pressures on capillary pressure and fluid transport across the capillary membrane. However, the effects of varying precapillary and postcapillary resistances have received little attention. It may be predicted that with arterial and venous pressures constant, constriction of arteries or dilation of veins would decrease capillary hydrostatic pressure and tissue fluid, whereas arterial dilation or venous constriction would do the reverse. The effect of change of one resistance would be modified by simultaneous change of the other resistance. For example, the decrease of capillary hydrostatic pressure caused by arteriolar constriction would be minimized by

less than proportionate venous constriction, nullified by proportionate venous constriction, and reversed by greater than proportionate venous constriction. Early in our studies we obtained evidence which suggested that vasoconstrictors often cause disproportionate constriction in arteries and veins.

With the rate of blood flow in the brachial artery held constant, various vasoactive agents were injected into the brachial artery in amounts which had little effect on aortic and cephalic venous pressure. Epinephrine, levarterenol, and serotonin increased small venous pressure (fig. 7). Since brachial flow rate was constant, this increase most likely resulted from venous constriction some place between the sites of pressure measurement in the small and cephalic veins. On the other hand, angiotonin and vasopressin had little effect on small venous pressure, suggesting much less action on veins. In other experiments, the effects were quantitated by calculation of segmental resistances under steady state conditions. For example, during rapid infusion of levarterenol (2.5 \(\mu g./mL/min\)) venous resistance often increased several fold.\(^2\) The resistance rise, in terms of per cent of control, sometimes exceeded that in arteries. Angiotensin II, on the other hand, produced only a questionable increase in venous resistance, even when the infusion rate was increased to levels which produced changes in aortic pressure (figs. 2 and 3).

These findings were supported by experiments in which the blood pump was replaced by a flowmeter and the agents were injected into the brachial artery. Epinephrine and levarterenol often produced, in association with a decrease in arterial inflow, a pronounced rise of small venous pressure.\(^3\) This effect can best be explained by venous constriction out of proportion to arterial constriction. Furthermore, it suggests that capillary hydrostatic pressure rose since this pressure cannot be lower than small venous pressure. In other experiments, small venous pressure did not change, suggesting proportionate arterial and venous constriction. In still other experiments, small venous pressure decreased, an effect best
EFFECTS OF ANGIOTENSIN IN SEVERAL VASCULAR BEDS

explained by arterial constriction out of proportion to venous constriction. Kelly and Visscher observed a similar variety of changes during faradic stimulation of sympathetic nerves. The venous pressure changes were also similar in the rabbit ear. Injection of levartrenol into the carotid artery in amounts without effect on carotid arterial pressure often caused the pressure in the ipsilateral marginal vein (measured through non-occlusive needles) to fall transiently and then rise well above the control value. These small venous pressor responses were not observed during injection of angiotensin II or vasopressin into the dog forelimb or rabbit ear. Small venous pressure either did not change or decreased slightly, suggesting arterial constriction out of proportion to venous constriction.

Since these findings suggested that vasoconstrictors might vary the amount of water in tissues, through changes in capillary hydrostatic pressure due to alteration of the ratio of arterial to venous resistance and because a review of the literature revealed that prolonged intravenous administration of catechol amines can deplete blood volume, pressures and weight of the naturally perfused limb were recorded during prolonged infusion of vasoactive agents into the brachial artery at rates which barely raised the pressure in the brachial artery. Weight was used as an index of capillary filtration (the periods immediately following starting and stopping an infusion were ignored, since weight changes during these periods result mainly from changes in intravascular volume), and small venous pressure was used as an index of cap-

Figure 6
Comparison of the steady state effects of vasoactive agents on total resistance to blood flow through the dog mesenteric vascular bed. Superior mesenteric arterial flow held constant and agents infused into the superior mesenteric artery at rates indicated on abscissa. The rates of administration did not affect aortic pressure. First and second numbers following name of agent refer to rate of blood flow in ml./min. and number of experiments, respectively.
illary hydrostatic pressure (this pressure provides a minimal value for capillary hydrostatic pressure). Because the limb was slightly below heart level, it often gained weight at a slow rate during the control period. Levarterenol always produced an initial sudden fall in small venous pressure (due to arterial constriction) followed by a decrease of limb weight (due to reduction of blood volume in the limb). In some experiments, the small venous pressure fall was followed by a rise to levels well in excess of the control value, and this change was associated with an increase in the rate of weight gain. On stopping the infusion, small venous pressure, after a transient large rise, fell to the level observed during the control period, and the weight gain ceased. In other experiments, small venous pressure rose only to the control level or remained below the control level, and the rate of weight gain did not change, decreased, or become negative. In some experiments, small venous pressure was both below and above the control value for enough time to calculate the rate of weight gain at each level (table 1). This revealed a positive correlation between the 2 variables. On the other hand, angiotensin II and vasopressin never produced a measurable rise in small venous pressure or rate of weight gain. In most experiments, both variables decreased slightly (table 1). Hence, in the dog foreleg, levarterenol may increase, not change, or decrease water storage in foreleg tissues by decreasing, not changing, or increasing, respectively, the ratio of arterial to venous resistance. On the other hand, angiotensin II, if anything, decreases water storage by increasing the ratio of arterial to venous resistance.

Estensen and Gilbert observed similar changes in the gut bed during infusion of levarterenol into the superior mesenteric artery. In some experiments, small venous pressure (but not portal venous pressure) and the weight of the ileal loop increased, whereas in others, both variables decreased. When all experiments were considered, there was a rough, positive correlation between small venous pressure and weight. Angiotensin II was not studied in this preparation. However, when the gut bed is perfused at constant flow, angiotensin II does not change the pressure gradient from small vein to portal vein, suggesting little effect on mesenteric veins, but it may raise the absolute levels of the pressures in the small vein and portal vein, suggesting a constricting action on vessels in the liver (fig. 5). Hence, it is possible that angiotensin II, like levarterenol, might increase, not change, or decrease water storage in this bed. The mechanism of an increased water storage, however, would be different from that during administration of levarterenol (elevation of portal venous pressure rather than mesenteric venous resistance).

Another interesting finding is that angio-
Serotonin II potentiates the venous constrictor action of serotonin in the dog forelimb. This action, however, is by no means peculiar to angiotensin II because epinephrine, levarterenol, and vasopressin produce similar potentiation. Simultaneous infusion of a pressor agent and serotonin produced an increase in venous resistance which greatly exceeded the sum of the increases observed during separate administration of the 2 agents (table 2). This potentiation was sometimes observed when the pressor agent was infused in an amount which by itself had no effect on veins. These observations may be relevant to conditions in which blood levels of several vasoactive agents vary simultaneously (cold exposure, hemorrhage, endotoxin shock, etc.).

### Blood Storage in the Vascular Bed of the Dog Forelimb

Preliminary observations indicate that levarterenol produces a greater reduction in limb blood volume than angiotensin II. On starting an infusion of levarterenol, the weight of the limb abruptly decreased several grams. On stopping the infusion, the limb immediately regained this weight. These abrupt changes in weight were not observed on starting and stopping an infusion of angiotensin II or vasopressin. This result indicates that the latter agents squeezed less blood from the limb than levarterenol and undoubtedly reflects their lesser ability to constrict veins.

### Conclusions

Evidence is presented which indicates that angiotensin II is one of the most active vasoconstrictors. Its local ability, on a weight or molecular basis, to increase resistance to blood flow through the dog foreleg and mesenteric vascular beds probably exceeds that of epinephrine and levarterenol and certainly exceeds that of metaraminol, mephenetermine, methoxamine, and serotonin. The resistance increase occurs mainly on the arterial side of the capillary, and the resulting increase in the ratio of arterial to venous resistance probably decreases capillary hydrostatic pressure and, hence, water storage in tissues. Preliminary evidence suggests that forelimb vascular volume decreases less during intra-arterial administration of angiotensin II than during intra-arterial administration of levarterenol.
This difference undoubtedly is due to its lesser ability to constrict veins.

References


Comparison of Direct Effects of Angiotensin and Other Vasoactive Agents on Small and Large Blood Vessels in Several Vascular Beds
FRANCIS J. HADDY, JOYCE I. MOLNAR, CRAIG W. BORDEN and E. CLINTON TEXTER, JR.

Circulation. 1962;25:239-246
doi: 10.1161/01.CIR.25.1.239

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/25/1/239.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/