Regional Flow-Pressure Relationship in Response to Angiotensin in the Intact Dog and Sheep

By X. S. Assali, M.D., and Allan Westersten, E.E.

Although the pressor action of angiotensin has been investigated in animals and man, the effects of this agent on the blood flow and vascular resistance of specific organs and regions in the intact animal have not been properly assessed. Earlier observations on isolated perfused vascular preparations and exposed blood vessels in vivo in the rabbit showed constriction in the arterioles of the ear, mesentery, and intestine. In the intact rabbit and dog, however, angiotensin did not consistently change the skin temperature (considered roughly as an index of peripheral blood flow).

According to certain reports, angiotensin decreases renal blood flow as measured with the clearance techniques. The drug increases the total peripheral vascular resistance without significantly changing the cardiac output or the coronary blood flow.

The recent improvements introduced in the electromagnetic method for measuring flow rate have made possible the monitoring of the phasic and the integrated rates of blood flow in intact vessels, and in the acute, as well as in the chronic, condition. We thought it would be of interest to apply this method to the study of the circulatory response to angiotensin in different areas of the body. If the arterial pressure is measured simultaneously with the blood flow, then the vascular resistances in these areas can be calculated.

The present report deals with the results of such studies conducted in pregnant and nonpregnant dogs and sheep.

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Methods

A total of 13 female mongrel dogs (10 nonpregnant and 3 pregnant) and 6 ewes (4 pregnant and 2 nonpregnant) was studied. The dogs were anesthetized with intravenous injection of sodium pentobarbital (20 mg./Kg.) given as often as necessary to keep the animal under light anesthesia. The sheep had either local anesthesia with 2 per cent Xylocaine solution or spinal anesthesia to a level of the seventh or eighth thoracic segment. Arterial pressure was measured with a Statham strain gauge connected with a polyethylene tube to a carotid or a femoral artery.

A previously described gated sinewave electromagnetic flowmeter was used to measure the blood flow to the following regions: (a) common carotid artery exposed through a midline incision in the neck; (b) renal artery exposed through a right flank incision; (c) uterine artery exposed through a right or left inguinal incision; and (d) internal iliac or femoral artery also exposed through an inguinal incision.

A 2- to 3-cm. segment of each one of these vessels was freed from its surrounding tissues and was slipped into the sleeve of a transducer unit selected to give approximately 100 per cent fit. In order to prevent kinking of the vessel produced by movements of the animal, the transducer was provided with small wings which were anchored with two sutures to the surrounding structures. After the flow signal was observed to become stable, the structures overlying the probe were sutured with interrupted silk and the lead wires were left emerging from the edge of the incision.

Control recordings of arterial pressure and regional blood flow were then obtained for a period of 30 to 40 minutes. Thereafter, single doses of angiotensin varying between 0.1 and 2.4 µg./Kg. were injected rapidly through a polyethylene tube inserted into one of the jugular veins (in the sheep only three different doses were used). Pressure and flows were continuously recorded during and after each injection until all values had returned to control levels. An interval between subsequent injections was allowed for the effects of the first dose to subside completely.

In six dogs, angiotensin was administered by

*Synthetic angiotensin was supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.
Table 1
Effects of Single Intravenous Injections of Angiotensin on Arterial Pressure and on Renal, Femoral, Uterine, and Carotid Flows in Dogs and Sheep

<table>
<thead>
<tr>
<th>Dose µg./Kg.</th>
<th>Arterial pressure mm. Hg</th>
<th>Renal C</th>
<th>A</th>
<th>Femoral C</th>
<th>A</th>
<th>Uterine C</th>
<th>A</th>
<th>Carotid C</th>
<th>A</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10 (25)</td>
<td>110 149</td>
<td>225 79</td>
<td>36 44</td>
<td>82 93</td>
<td>108 109</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.15 (15)</td>
<td>114 157</td>
<td>208 71</td>
<td>38 53</td>
<td>80 100</td>
<td>110 120</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25 (10)</td>
<td>112 152</td>
<td>124 66</td>
<td>42 63</td>
<td>76 102</td>
<td>104 115</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.50 (12)</td>
<td>110 160</td>
<td>217 65</td>
<td>44 70</td>
<td>78 105</td>
<td>108 130</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.75 (10)</td>
<td>114 165</td>
<td>210 70</td>
<td>40 66</td>
<td>—</td>
<td>110 132</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.20 (15)</td>
<td>128 187</td>
<td>214 90</td>
<td>43 69</td>
<td>80 116</td>
<td>112 133</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.40 (12)</td>
<td>114 175</td>
<td>216 86</td>
<td>46 74</td>
<td>—</td>
<td>108 128</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.10 (6)</td>
<td>130 179</td>
<td>352 170</td>
<td>56 66</td>
<td>115 145</td>
<td>152 160</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.50 (4)</td>
<td>127 182</td>
<td>347 175</td>
<td>58 70</td>
<td>118 152</td>
<td>160 170</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.20 (4)</td>
<td>131 185</td>
<td>360 182</td>
<td>53 74</td>
<td>112 155</td>
<td>165 178</td>
<td></td>
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</tbody>
</table>

Control values (C) represent the average reading recorded before the injection. The response (A) represents the highest or lowest readings observed within the first three minutes after the injection. All flow values are in ml./minute. The figures in parentheses represent the number of tests for each dose.

Results

Table 1 lists the responses to angiotensin of the arterial pressure and of the renal, femoral, uterine, and carotid flows in the dogs and sheep. Vascular resistances in these areas can be calculated from the pressure and flows. Figures 1 and 2 illustrate typical examples of flow-pressure responses to different doses of angiotensin in the same dog.

Increasing the dose of angiotensin from 0.10 to 2.40 µg./Kg. produced an increment in the pressor response of only 20 per cent (table 1). The blood flow response to the rise in arterial pressure varied from one region to another. In the kidney, the flow decreased markedly in all instances and the fall was practically the same irrespective of the dose employed. The estimated renal vascular resistance increased consistently. Femoral, uterine, and iliac (not listed) blood flows invariably rose after the administration of angiotensin, and except after the lower doses, the rise in flow showed very little relationship with the dose injected. Vascular resistances in these areas usually diminished. Carotid flow remained practically unchanged after the injection of low doses of angiotensin, but increased by about 20 per cent after the high doses. Carotid vascular resistance rose after the low doses but fell slightly after the high doses. The pulse rate was not significantly altered.

Figure 3 compares the effects of angiotensin to those of norepinephrine and epinephrine in a pregnant dog. Although these three agents caused approximately the same degree of blood pressure rise, angiotensin increased both the uterine and the internal iliac flows, whereas norepinephrine and epinephrine evoked a marked fall in uterine flow but a rise in the iliac flow.

Figure 4 presents an example of the effects of continuous administration of angiotensin on the femoral, carotid, and renal flows and arterial pressure in a nonpregnant dog. The continuous infusion at a rate of 0.5 to 7 µg./Kg./minute. Pressure and flow were recorded before, during, and after the cessation of the infusion. In three animals, the cardiac output was determined by the conventional Fick method before, during, and after angiotensin infusion.

Mean arterial pressure and mean blood flow were obtained from the phasic record, the latter usually with an electronic integrator.
Figure 1
Comparison of the effects of intravenous injections of 0.1 μg./Kg. and 0.2 μg./Kg. of angiotensin on the arterial pressure and on the renal, femoral, and carotid flows measured with implanted electromagnetic flowmeters. Note the marked fall in renal blood flow and the rise in the femoral flow. Carotid flow was practically unchanged.

Figure 2
Effects of 1.2 and 2.4 μg./Kg. of angiotensin. The changes were closely similar to those depicted in figure 1. At the end of record (4), the speed was increased to 5 mm./sec.

Figure 3
Comparison of the effects of angiotensin and of epinephrine and norepinephrine on arterial pressure and the iliac and uterine flows in a pregnant dog. Approximately the same rise in arterial pressure was obtained with the various doses employed. Angiotensin, however, increased both the iliac and uterine flows, while the catecholamines decreased the uterine flow and increased the internal iliac flow.

Discussion
The present data show that the rise in arterial pressure caused by the intravenous injection of angiotensin in the dog and sheep is immediate, and within the range of doses employed presents little relationship to the dose.

It is evident that for any given rise in arterial pressure induced by angiotensin, the rise in arterial pressure was gradual, reached its maximum at the midperiod of infusion, and remained for three to four minutes after the infusion had been discontinued. Renal blood flow began to fall shortly after the onset of the infusion, remained low for the duration of the infusion and for a few minutes thereafter, and then began to return toward control values. The rise in the femoral flow was more delayed and did not become noticeable until the middle of the infusion. Similarly, the changes in carotid flow were gradual and remained for a few minutes after the infusion had been discontinued.

The cardiac output in the three dogs in which it was measured was 79, 90, and 110 ml./Kg./min. It did not change significantly during angiotensin administration.

blood flow behaves differently in the various areas of the body. The renal blood flow falls immediately with the rise in pressure and the fall is due to a marked increase in renal vascular resistance.

In contrast, femoral, iliac, and uterine
blood flows increase significantly after the injection of angiotensin, and the increase is due to a fall in the vascular resistances in these areas. Carotid flow is less influenced by the pressor action of angiotensin, except after large doses when a slight increase in flow may be observed. Obviously, elevation of the carotid resistance is the major factor in maintaining a nearly unchanged carotid flow in the presence of an increased perfusion pressure. This balance between pressure and carotid resistance probably represents an intrinsic homeostatic mechanism aimed at protecting the circulation of the head from excessive rise in perfusion pressure.

From these studies, it appears that the chief action of angiotensin is to constrict the renal vessels. Since this agent does not seem to alter the cardiac output, and does not require the presence of the nervous system for its vascular action, the effects on the kidney must then be directly on the renal vessels, probably on the arteriolar walls.

The increase in blood flow in the femoral, uterine, and iliac arteries is probably secondary to the increase in pressure and not to a true dilatation of these vessels.

The present studies point out the fallacy of attempting to derive information regarding regional circulation from the behavior of the so-called total peripheral resistance calculated from the arterial pressure and cardiac output. It is clear that a rise in blood pressure may elicit a regional circulatory response the direction of which depends on several factors, such as the magnitude of the pressure rise, the particular stimulus for the pressor action, and other factors related to the function of that region. This complex problem is illustrated in figure 3 which compares the response to angiotensin and to catecholamines in the same animal. When the blood pressure rise is induced by angiotensin, both the internal iliac and the uterine blood flows increase. However, if the same rise is induced by epinephrine or by norepinephrine, the flow in the internal iliac increases, but that in the uterine artery, which is a branch of the former artery, decreases. These different responses suggest a different reactivity of the various vessels even if they are branches of each other, and that such reactivity probably depends on the specific function of the area they nourish.

Summary

The effects of intravenous administration of angiotensin on the arterial pressure and on the renal, carotid, iliac, uterine, and femoral blood flows were investigated in dogs and sheep through the use of implanted electromagnetic flowmeters. The rise in arterial pressure was immediate and, within the range of doses employed, presented little relationship to the dose. The pressor effect of angiotensin was accompanied by a consistent fall in the renal blood flow and a rise in the femoral, iliac, and uterine flows. Carotid flow was less affected. These studies demonstrate the specificity of flow response to a given change in pressure in the various areas of the body.

References

REGIONAL FLOW AFTER ANGIOTENSIN


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