Effect of Angiotensin Infusion on Regional Blood Flow and Regional Vascular Resistance in the Rat

By Morris J. Mandel, M.D., and Leo A. Sapirstein, Ph.D., M.D.

The physiology and pharmacology of angiotensin have been comprehensively reviewed by Page and Bumpus. Although the literature is replete with information on its overall pressor properties and its effects on the cardiac output, the effects of angiotensin on regional blood flow and organ vascular resistance have not been adequately evaluated for most regions. Observations on the regional effects of angiotensin have been confined to a few organs or areas. As will be shown in the Discussion, the results are not always consistent in different preparations, and little information is available in the intact animal.

A method developed in the Department of Physiology at Ohio State University allows the measurement of the distribution of the cardiac output to all organs simultaneously in the intact animal. The present report is concerned with the application of this method to the determination of regional blood flow and regional vascular resistance in rats anesthetized with sodium pentobarbital and infused with varying doses of angiotensin.

Methods

Two hundred and eleven female rats of the Sprague-Dawley strain which had been fasted for 18 hours were used in these studies. Of these, 75 (51 control, 24 experimental) were used in blood pressure measurements; 38 (10 control, 28 experimental) were employed in cardiac output measurements; regional flow distribution for all organs other than the brain was measured in 71 (22 control, 49 experimental), and cerebral flow fraction was measured in 102 (37 control, 65 experimental).

Water was allowed ad libitum. The animals weighed between 190 and 250 Gm. Sodium pentobarbital (40 mg./Kg., intraperitoneally) was used as the anesthetic. Angiotensin was infused into the femoral vein by means of a Harvard infusion pump for 5 to 25 minutes at 0.05 ml./min. of solution containing concentrations of angiotensin sufficient to yield 0.05, 0.1, 0.2, 0.3, 0.4, or 0.5 mg./Kg. body weight/min.

Mean arterial pressures were measured from the femoral artery in heparinized rats with a mercury manometer connected to the artery by a 25- or 27-gauge needle. The same animals were also used for either the cardiac output or the regional flow determination. Cardiac outputs were measured by the indicator-dilution technique, using Rb80 as the indicator. The rate of sample collection was 60/min. Because of the hemorrhage produced by the cardiac output determination, different animals were used for regional blood flow studies.

Distribution of blood flow was measured by the indicator-fractionation technique employing Rb80 for all organs except the brain, and iodo 131 antipyrine for the brain. The principle of the method has been discussed elsewhere. The sacrificing times used were 30 and 60 seconds. No significant change in label uptake was noted between these times in any organ except the brain of angiotensin-infused animals. The method of handling the brain data will be discussed later. Blood flow values were obtained from the indicator fractions, when these were unchanged with time, by multiplying that fraction by the cardiac output of similarly treated animals. The resistance values were calculated as the ratio between the mean arterial pressure in dynes/cm.2 and the derived flow values in cm.3/sec. All flow values were adjusted to these for a 200 Gm. rat.

The angiotensin used in these studies was generously supplied by Dr. Robert Gaunt of Ciba Pharmaceutical Products Inc., Summit, New Jersey. The preparation used was Hypertensin Ciba, Batch E 0127.
Results

CARDIAC OUTPUT, BLOOD PRESSURE, AND TOTAL PERIPHERAL RESISTANCE

The cardiac output of control rats in this colony has averaged $231 \pm 43$ ml./Kg./min. over the last two years. In the present experiment, 10 rats receiving saline infusions had a slightly higher value for the cardiac output ($278 \pm 73$). However, the range of values was very great and the difference from the mean of untreated controls was not statistically significant.

Rats infused with angiotensin had substantially the same cardiac output as the untreated controls. Six rats, infused with five-hundredths $\mu$g./Kg./min., showed a cardiac output of $231 \pm 45$ ml./Kg./min.; at two-tenths $\mu$g./Kg./min., the value was $263 \pm 94$ in 8 rats; at 0.3 $\mu$g./Kg./min., the value was $205 \pm 42$ in 6 rats; at 0.5 $\mu$g./Kg./min., the cardiac outputs averaged $250 \pm 60$ ml./Kg./min. in 8 rats. Intermediate doses were not explored. The average of the experimental group was $240$ ml./Kg./min.

The blood pressure values at equilibrium, which always occurred within 3½ minutes, were as follows: at the infusion rate of 0.05 $\mu$g./Kg./min. (6 animals), the value was unchanged from the control value of $113 \pm 16$ mm. Hg (51 animals). Blood pressures at higher infusion rates were: 0.1, 161 mm. Hg (2 rats); 0.3, 160 min. Hg (2 rats); 0.4, 169 mm. Hg (3 rats); 0.5, 168 mm. Hg (9 rats).

The average of the experimental group, excluding the lowest concentration, where no change in blood pressure was noted, was 164 mm. Hg.

FRACTIONAL DISTRIBUTION

The fractional distribution of blood flow is tabulated in Table 1. It will be noted that the flow fraction to the heart, lungs, spleen, and brain is increased by angiotensin infusion. There is also an increase in the adrenal fraction except at the highest infusion rate. The flow fraction to the carcass is consistently elevated, but to a much smaller degree. The fractional distribution to the skin, liver, and gut also appears to be slightly but inconsistently increased. The only organ which shows a consistently diminished fraction is the kidney, which is reduced at least 40 per cent.

Because of the decrease in label content of the brain with time, the values presented are those obtained by extrapolation to 10 seconds; the rationale for this treatment of the data is presented elsewhere. Extrapolation was not necessary with the other organs since no changes were noted in the two sacrificing times used in the experiment.

Table 2 describes blood flow to the organs. The values are obtained by multiplying the values in Table 1 by the cardiac output. In the case of control animals, the value used was based on the colony average rather than

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**Table 1**

Flow Fractions of the Cardiac Output to Organs of Rats Receiving Infusions of Angiotensin by Vein

<table>
<thead>
<tr>
<th>Organ</th>
<th>Control</th>
<th>0.05</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>2.5</td>
<td>2.9</td>
<td>3.5</td>
<td>3.3</td>
<td>4.1</td>
<td>4.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Lung</td>
<td>2.6</td>
<td>2.8</td>
<td>3.9</td>
<td>3.7</td>
<td>4.4</td>
<td>4.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Kidney</td>
<td>17.8</td>
<td>17.3</td>
<td>11.5</td>
<td>10.1</td>
<td>11.0</td>
<td>9.1</td>
<td>8.8</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.00</td>
<td>1.32</td>
<td>1.40</td>
<td>1.50</td>
<td>1.30</td>
<td>1.30</td>
<td>1.15</td>
</tr>
<tr>
<td>Adrenal</td>
<td>0.20</td>
<td>0.34</td>
<td>0.28</td>
<td>0.25</td>
<td>0.29</td>
<td>0.27</td>
<td>0.19</td>
</tr>
<tr>
<td>Liver</td>
<td>6.8</td>
<td>7.6</td>
<td>8.8</td>
<td>8.6</td>
<td>10.1</td>
<td>9.2</td>
<td>6.7</td>
</tr>
<tr>
<td>Gut</td>
<td>18.6</td>
<td>20.9</td>
<td>18.5</td>
<td>19.1</td>
<td>19.7</td>
<td>17.6</td>
<td>14.4</td>
</tr>
<tr>
<td>Skin</td>
<td>6.7</td>
<td>8.6</td>
<td>7.6</td>
<td>8.1</td>
<td>6.7</td>
<td>7.2</td>
<td>6.9</td>
</tr>
<tr>
<td>Carcass</td>
<td>38.5</td>
<td>40.1</td>
<td>39.2</td>
<td>39.3</td>
<td>44.1</td>
<td>45.5</td>
<td>41.7</td>
</tr>
<tr>
<td>Brain</td>
<td>1.37</td>
<td>2.17</td>
<td>2.77</td>
<td>2.37</td>
<td>2.16</td>
<td>2.02</td>
<td>2.05</td>
</tr>
</tbody>
</table>

*All values as percentage of cardiac output.

†Numbers in parentheses refer to the number of animals used in each determination.

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TABLE 2

Regional Blood Flows to Organs of Rats Receiving Infusions of Angiotensin by Vein

<table>
<thead>
<tr>
<th>Organ</th>
<th>Control</th>
<th>0.05</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>1.15</td>
<td>1.14</td>
<td>1.62</td>
<td>1.52</td>
<td>1.80</td>
<td>1.99</td>
<td>1.76</td>
</tr>
<tr>
<td>Lung</td>
<td>1.20</td>
<td>1.29</td>
<td>1.80</td>
<td>1.71</td>
<td>2.03</td>
<td>1.94</td>
<td>1.92</td>
</tr>
<tr>
<td>Kidney</td>
<td>7.76</td>
<td>7.99</td>
<td>5.31</td>
<td>4.67</td>
<td>5.68</td>
<td>4.20</td>
<td>4.07</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.46</td>
<td>0.61</td>
<td>0.65</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
<td>0.53</td>
</tr>
<tr>
<td>Adrenal</td>
<td>0.092</td>
<td>0.157</td>
<td>0.129</td>
<td>0.116</td>
<td>0.134</td>
<td>0.148</td>
<td>0.088</td>
</tr>
<tr>
<td>Liver</td>
<td>3.14</td>
<td>3.51</td>
<td>4.07</td>
<td>3.14</td>
<td>4.67</td>
<td>4.25</td>
<td>3.10</td>
</tr>
<tr>
<td>Gut</td>
<td>8.59</td>
<td>9.33</td>
<td>9.66</td>
<td>8.55</td>
<td>8.82</td>
<td>9.10</td>
<td>8.15</td>
</tr>
<tr>
<td>Skin</td>
<td>3.10</td>
<td>3.93</td>
<td>3.51</td>
<td>3.74</td>
<td>3.10</td>
<td>3.33</td>
<td>3.19</td>
</tr>
<tr>
<td>Carcass</td>
<td>17.79</td>
<td>18.53</td>
<td>18.11</td>
<td>18.16</td>
<td>20.37</td>
<td>20.10</td>
<td>19.27</td>
</tr>
<tr>
<td>Brain</td>
<td>0.63</td>
<td>1.00</td>
<td>1.28</td>
<td>1.09</td>
<td>1.00</td>
<td>0.93</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*All values referred to 200 Gm. rat. Values as ml/min/organ: 231 ml/Kg/min. taken as cardiac output for all animals.

Discussion

Most of the pharmacological properties of angiotensin have been studied after single injections of the agent. In our experience, single injections give results which vary with the status of the blood pressure at the time of observation and are radically different from those obtained in constant infusion experiments. No attempt will be made to present these results here. It is important in comparing our experiments with those reported by previous investigators to recognize that our findings were based on constant infusions and that arterial blood pressures were at equilibrium when observations were made. It should be stressed further that the method...
employed here measures only functional blood flow, i.e., the blood which "services" the tissues; shunt flow will not be measured; however, the magnitude of shunt flow in the rat is probably inconsiderably small under the experimental conditions employed.6

CARDIAC OUTPUT, BLOOD PRESSURE, AND TOTAL PERIPHERAL RESISTANCE

The cardiac output did not change in these experiments when angiotensin was administered by a constant infusion. However, the blood pressure and total peripheral resistance were increased about 45 per cent.

In heart-lung preparations, Hill and Andrus8 noted a rise in the cardiac output in many experiments after an injection of angiotensin. In experiments on intact animals, most authors are in agreement that angiotensin does not influence the cardiac output. Maxwell et al.9 and Eckert and Rose10 noted no change in cardiac output during angiotensin infusion in intact dogs using the Fick method. Potgieter et al.11,12 noted similar results. Barer13 used synthetic angiotensin and measured blood flow with the electromagnetic flowmeter. She found no consistent change in the cardiac output. In human studies, Schales et al.,14 using the acetylene method, and Sancetta,15 using the Fick method, also found no changes in the output of the heart.

A few reports have appeared which suggest that angiotensin reduces the cardiac output. Page and Olmstead (quoted in Page and Bumpus6), using the electromagnetic flowmeter, noted a fall in the cardiac output, stroke volume, and heart rate in intact unanesthetized dogs; Middleton and Wiggers,16 using cardiometry, found a reduction in cardiac output secondary to bradycardia after small doses of angiotensin and a reduction in cardiac output secondary to a fall in stroke volume after large doses. All angiotensin was given as a single injection and the data do not indicate that the fall in cardiac output was significantly large. A number of reports have appeared which suggest that the cardiac output may be reduced in man after angiotensin. Most of these are based on the ballistocardiogram. Taylor and Page17 found angiotensin infusions in six normal subjects to reduce cardiac output 34 per cent. Wilkins and Duncan18 found a 33 per cent reduction in seven subjects receiving angiotensin infusion. Bradley and Parker,19 also using the ballistocardiograph, found an average of 25 per cent reduction in seven subjects receiving angiotensin infusions. Cournand et al.,20 using both ballistocardiographic and direct Fick measurements, found a small, but consistent fall in the cardiac output of human

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**TABLE 3**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Control</th>
<th>0.05</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.4</th>
<th>0.5</th>
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</thead>
<tbody>
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<td>Heart</td>
<td>81</td>
<td>68</td>
<td>51</td>
<td>11.7</td>
<td>19.7</td>
<td>98.5</td>
<td>29</td>
</tr>
<tr>
<td>Lung</td>
<td>76</td>
<td>70</td>
<td>73</td>
<td>76</td>
<td>64</td>
<td>67</td>
<td>81</td>
</tr>
<tr>
<td>Kidney</td>
<td>11.7</td>
<td>11.3</td>
<td>25</td>
<td>28</td>
<td>31</td>
<td>26</td>
<td>32</td>
</tr>
<tr>
<td>Spleen</td>
<td>19.7</td>
<td>149</td>
<td>201</td>
<td>218</td>
<td>218</td>
<td>218</td>
<td>247</td>
</tr>
<tr>
<td>Adrenal</td>
<td>98.5</td>
<td>577</td>
<td>1014</td>
<td>1128</td>
<td>976</td>
<td>88.4</td>
<td>149.6</td>
</tr>
<tr>
<td>Liver</td>
<td>29</td>
<td>26</td>
<td>32</td>
<td>42</td>
<td>28</td>
<td>31</td>
<td>42</td>
</tr>
<tr>
<td>Gut</td>
<td>10.5</td>
<td>9.7</td>
<td>13.5</td>
<td>14.8</td>
<td>14.4</td>
<td>16.0</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>29</td>
<td>25</td>
<td>37</td>
<td>35</td>
<td>42</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>Carcass</td>
<td>5.1</td>
<td>4.9</td>
<td>7.3</td>
<td>7.2</td>
<td>6.4</td>
<td>6.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Brain</td>
<td>144</td>
<td>91</td>
<td>102</td>
<td>120</td>
<td>131</td>
<td>141</td>
<td>138</td>
</tr>
</tbody>
</table>

*All values as dynes sec./cm.² X 10⁴ and adjusted for organs of 200 Gm. rat.
† Resistances of rats in 0.1 through 0.5 infusion series based on average blood pressure value for the group. See text.

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810

Mandel, Sapirstein

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REGIONAL EFFECT OF ANGIOTENSIN

subjects after a single injection of angiotensin. Finnerty,21 using the dye-dilution method, found a striking fall in the cardiac output in one of three subjects receiving angiotensin by infusion.

In the present experiments, the cardiac output of animals receiving angiotensin infusions was not significantly different from the colony mean. It was, however, a little smaller than that of control animals which received saline infusion. However, the differences were not significant statistically and did not appear to be biologically important. Our data certainly do not justify the conclusion that there is a fall in cardiac output after angiotensin, but neither should they be interpreted to indicate that there is not. What is clear is that any reduction in cardiac output produced by angiotensin infusion have, in the past, been found to be relatively independent of either the infusion rate or the duration of the infusion.22-23 This is not true of single injections.

The changes in blood pressure produced by angiotensin infusion have, in the past, been found to be relatively independent of either the infusion rate or the duration of the infusion.22-23 This is not true of single injections.

In our experiments, essentially the same finding was made. Infusion of 0.05 μg./Kg./min. had no effect on blood pressure. All larger infusions had approximately the same pressor effect. The effect was maximal after 3½ minutes of any infusion level. The mean blood pressure (113 mm. Hg) in these animals was elevated approximately 45 per cent.

The total peripheral resistance was increased almost precisely as much as the mean arterial pressure (44 per cent), the expected result in the face of an unchanged cardiac output. This finding is consistent with those of all others who have studied the peripheral vascular effects of angiotensin.

MYOCARDIAL BLOOD FLOW AND RESISTANCE

In perfused hearts and heart-lung preparations, angiotensin has always been found to increase the coronary vascular resistance and diminish coronary blood flow. In the Langendorff preparation, Meier et al.24 found angiotensin to have a weak vasoconstrictor activity associated with a weak positive inotropic effect. Lorber25 noted a marked fall in the coronary flow after angiotensin injection in the perfused cat heart. He concluded that the reduced flow was secondary to coronary vasoconstriction. Elek and Katz,26 using a Langendorff preparation, noted a fall in coronary flow on two occasions, an increase in flow on four occasions, and no effect in one. Lorber and Visscher27 noted a marked coronary vasoconstriction in isolated cat hearts after angiotensin.

Hill and Andrus8 noted a fall of 45 per cent in coronary flow in the cat heart-lung preparation with increased amplitude of contractions. Middleton and Wiggers16 noted myocardial depression in their heart-lung preparations after angiotensin, and suggested that this might be secondary to a fall in coronary flow, although this was not directly measured.

In intact animals, the effects of angiotensin on coronary flow and resistance are much less consistent. Maxwell et al.,9 using the nitrous oxide method in intact dogs, found a 30 per cent rise in coronary vascular resistance, a 30 per cent rise in blood pressure, and no change in coronary blood flow after angiotensin infusion. Potgeiter et al.,11-12 also using the nitrous oxide method, noted a marked increase (90 per cent) in coronary blood flow of intact dogs during angiotensin infusion. They felt that the increase in coronary flow was secondary to increased anaerobic cardiac metabolism. Barer13 noted a slight fall in coronary blood flow in cats. She used the electromagnetic flowmeter in her studies.

Some of the discrepancies in the results in intact animals may have depended on species' variability, difference in response to various dose levels, or on the limitations of the methods employed. The nitrous oxide method, for example, may have yielded misleading results because of the possibility of faulty equilibration in the experimental conditions.28

In the present experiments, after the infu-
sion of angiotensin, both the myocardial flow fraction and flow value are increased. Both are increased approximately as much as the blood pressure, and the myocardial vascular resistance remains essentially constant.

The conclusion that angiotensin exerts no specific effect on the coronary vessels is apparently indicated by our results. However, when it is recalled that angiotensin increases the work of the heart by increasing arterial pressure, the possibility must be considered that a vasoconstrictor effect due to a specific action of angiotensin is overcome by a metabolic effect due to the increased requirements made of the heart muscle. This view is supported by the findings of Potgieter et al., as previously discussed. Results in perfused preparations and heart-lung preparations, in which the work of the heart is not altered, suggest that angiotensin is, indeed, a coronary constrictor but that this effect is overridden by other mechanisms in the intact animal. This particular action requires further investigation.

**BRONCHIAL BLOOD FLOW AND RESISTANCE**

The results on bronchial flow and resistance follow the same pattern as the coronary flow values, i.e., bronchial flow is increased in proportion to the increase in pressure following angiotensin. We are not familiar with any previous investigations on the effects of angiotensin on bronchial circulation.

**RENA L BLOOD FLOW AND RESISTANCE**

Of all the regional cardiovascular effects of angiotensin, the one most widely agreed upon is the increase in renal vascular resistance and decrease in renal blood flow. In 1940, Corcoran and Page found diodrast clearance to be decreased by infusions of angiotensin. Inulin clearance rose. They concluded that angiotensin exerted its primary effect by vasoconstriction of the efferent arterioles. A year later, the same authors obtained similar results with single injections. Similar results and conclusions were reported later by Herrick et al. Hughes-Jones et al. observed a fall in diodrast clearance in the rabbit after angiotensin. Finnerty et al. found the renal blood flow to be reduced in man by angiotensin. Diodrast clearance in man was reduced by angiotensin according to Peart. In all of these experiments, the filtration fraction was consistently elevated suggesting that the efferent arteriole was predominantly affected. Results with the electromagnetic flowmeter lead to the same conclusions as the clearance determinations. Assali and Westersten found the renal blood flow to be reduced in dogs and sheep infused with angiotensin despite the rise in mean arterial blood pressure. Barer found the same in the cat. Many other authors have obtained similar results in many species and at almost every level of angiotensin infusion.

Our findings are consistent with those in the literature. Beginning with the angiotensin infusions of 0.1 µg./Kg./min., there was regularly observed a 40 per cent reduction in renal blood flow and a 100 to 200 per cent increase in renal vascular resistance. The smallest infusion, 0.05 µg./Kg./min., failed to influence renal vascular resistance, but also failed to influence the arterial pressure. This was also consistent with the findings of others who have noted that an increased renal vascular resistance and a rise in blood pressure occur together.

**SKIN FLOW AND RESISTANCE**

Abell and Page, using direct observation in the ear of the rabbit, noted vasoconstriction without a decline in the rate of perfusion after angiotonin. Landis et al., using kidney extracts presumably containing renin, noted no change in the skin temperature of the rabbit ear. Corcoran and Page, using angiotonin, found no change in the skin temperature of the dog. Using the plethysmographic method, Schales et al. noted a marked fall in hand blood flow, but no effect on forearm flow. This was also noted by Wilkins and Duncan. These results may be interpreted to indicate that cutaneous vessels constrict, muscular vessels being unaffected by angiotensin. Bock, using a thermal conductivity method, found relatively no change in skin flow during intravenous infusion of angiotensin, although skin flow was markedly re-
REGIONAL EFFECT OF ANGIOTENSIN

The flow fraction to the adrenal was increased at all infusion levels except the largest. Adrenal blood flow rose correspondingly. Adrenal resistances, although they rose, did not rise as much as the total peripheral resistance. There was, therefore, diversion of blood to the adrenal gland in animals receiving angiotensin infusion. We were unable to find any previous studies in the literature on adrenal blood flow in the presence of angiotensin.

There is recent evidence to indicate that adrenal production of aldosterone is substantially increased by angiotensin in human subjects. It is tempting to speculate that the increased blood flow is secondary to increased metabolic requirements of the gland producing excessive quantities of the steroid. The reduction in adrenal blood flow at the largest dose level may have been associated with overriding of this response of the adrenal vasculature by the nonspecific vasoconstrictor effects of angiotensin.

SPLANCHNIC BLOOD FLOW AND RESISTANCE

Information regarding the effects of angiotensin on the splanchnic bed is surprisingly sparse. Abell and Page noted a narrowing of the mesenteric vessels after angiotensin, but believed that the volume flow of blood was unaffected. Barer, using electromagnetic flowmeters, found mesenteric blood flow to be reduced between the duodenum and the terminal colon after single injections of 0.2 to 0.4 μg. in the cat.

In our experiments, intestinal blood flow was unaffected by angiotensin at any infusion rate. Increased pressure was balanced precisely by increased resistance. Although hepatic resistance appeared to fluctuate in an unpredictable fashion, flow values on the whole seemed to indicate some diversion of blood through the hepatic artery.

The spleen responded to angiotensin infusion with an increase in vascular resistance rather less in degree than the increase in blood pressure. The splenic blood flow was favored in the redistribution of flow which occurred during the infusion of angiotensin. This response is quite different from that seen after other pressor agents as epinephrine, norepinephrine, and pitressin.

CARCASS BLOOD FLOW AND RESISTANCE

In these experiments, the carcass represented all tissues remaining after removal of the internal organs and the skin. It may be assumed that its behavior is descriptive of that of skeletal muscle, which makes up most of its mass.

An increase in skeletal muscular blood flow after angiotensin infusions was found by Bock. A thermal method was used for the measurement. Meier found the blood flow of the hind limbs of animals to be decreased, as did Assali and Westersten, and Wilkins and Duncan. Schales found forearm blood flow to be unchanged in man after angiotensin. Some of these discrepancies may be due to a possible phasic nature of the response. Herrick et al. noted an initial transient fall in femoral blood flow, which was then followed by a more pronounced and prolonged increase. This phenomenon was also noted by Barer.

In our experiments, the carcass blood flow was slightly, but consistently increased, especially at the higher infusion levels. At these doses, the vascular resistance of the carcass increased about 34 per cent, while the blood pressure at the same time increased 45 per cent. Our observations, which were made only after prolonged infusions and were presumably in the hyperemic phase, tend to confirm those of Bock. The possibility that muscle blood flow behaves in a phasic fashion during angiotensin infusion would not be revealed by these experiments.

CEREBRAL BLOOD FLOW AND RESISTANCE

To our knowledge, there have been no previous reports on the effects of angiotensin on the cerebral blood flow of either man or animals.
In the present experiments, the indicator-fractionation technique was applied to the measurement of cerebral blood flow using iodo\textsuperscript{131} antipyrine as the indicator. In the control animal, a constant cerebral content of the label during the first minute shows that the extraction ratios of brain and body for the label differ from each other by an inconsiderable amount. Animals infused with angiotensin, on the other hand, show declining cerebral label content with time during the first minute.

The import of this decline is that the cerebral extraction ratio for iodoantipyrine is less than that of the body; consequently, the cerebral blood flow fraction is underestimated by the fraction of the label found in the brain after several recirculations have occurred. However, it is possible to describe the cerebral content of the label at a time when both brain and body have the same extraction ratio, i.e., 1.00, either by making observations very early (before venous removal of label has occurred), or by extrapolating later observations of cerebral label content to that time. The latter presupposes that label removal by the venous blood will proceed in an orderly and regular manner, so that the extrapolation is a legitimate one.

Actually, it has not yet been established in what fashion the observed data should be extrapolated. The simplest and most convenient type of extrapolation, i.e., a linear one, was carried out in the estimation of cerebral flow fraction. Theoretical considerations suggest that a more correct extrapolation would be an exponential one; this would make the extrapolated values higher than those obtained by the linear extrapolation. The values obtained for flow fraction by linear extrapolation probably are less therefore than the true ones.

The time to which the data should be extrapolated is also not certain. It seems probable that the best estimate can be obtained by extrapolating the data to the time when arterial delivery is complete; this is probably about 7 seconds after injection. In our extrapolation carried out here, 10 seconds was taken as the correct time; this choice of time also would serve to make the estimated flow fraction smaller than the true one.

When calculated in this manner, the cerebral flow fraction was some 70 per cent greater than the control values. This is a minimum estimate. The cerebral vascular resistance fell at infusion rates of 0.05 to 0.3 \(\mu\text{g./Kg./min.}\). At the higher infusion rates, the cerebral resistance appeared to approach normal values, but it must be recognized that a falsely low estimate of flow might have resulted in a falsely high estimate of resistance. It seems advisable to consider at the present time that cerebral vascular resistance is either decreased or unchanged by angiotensin at any dose level employed.

The most remarkable finding was made at the infusion rate of 0.05 \(\mu\text{g./Kg./min.}\). At this infusion level, there is no measurable change in blood pressure. Nevertheless, the cerebral blood flow was increased 60 per cent. Correspondingly, the cerebral vascular resistance was reduced 37 per cent.

The results suggest that angiotensin acts at vasodilator and vasoconstrictor sites in the cerebral vasculature. This may be a direct effect of the agent, or angiotensin may cause an increase in cerebral metabolism with a resultant vasodilation of the cerebral vessels. The smaller response at the higher infusion levels could represent increased vasoconstrictor activity tending to offset the metabolic effect.

Whatever the mechanism, it appears from these results that the cerebral blood flow of the pentobarbital anesthetized rat is increased by angiotensin at the infusion rates employed.

**Summary**

The effects of infusions of angiotensin of 0.05 to 0.5 \(\mu\text{g./Kg./min.}\) on the cardiac output, arterial blood pressure, and regional blood flow in the rat have been measured. Angiotensin increases the blood pressure without increasing the cardiac output; the total peripheral resistance is increased. Territorial resistances show varying degrees of increase, ranging from the cerebral vascular
resistance, which is reduced or unchanged, to the renal vascular resistance, which shows a 100 to 200 per cent increase. The smallest increases in resistance in other organs are seen in the heart and lungs, which are unchanged, and the spleen and adrenal, which show minimal elevations. Larger changes are seen in the carcass, gut, and skin. The overall appearance of the changes in the distribution of blood flow in the animal infused with angiotensin suggests that blood flow is diverted from the kidneys to those organs most concerned with the immediate response of the organism to an emergency.

References


Effect of Angiotensin Infusion on Regional Blood Flow and Regional Vascular Resistance in the Rat
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