Coronary and Myocardial Actions of Angiotensin

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Angiotensin II is a potent pressor agent in both normotensive and hypotensive states in animals and in man. Studies by Haddy et al. have placed angiotensin II among the most active vasoconstrictor substances; its principal action is upon small arteries. Finnerty et al. showed that in normotensive human subjects, angiotensin II was approximately ten times as potent as norepinephrine in raising blood pressure. Studies made in dogs by Rose et al. indicated certain qualitative differences between the actions of these two drugs. Each agent increased aortic pressure but angiotensin produced an immediate fall in aortic pressure before the rise; this preliminary depressor action was not seen with norepinephrine. A second difference observed by Rose et al. concerned left atrial pressure, which rose after angiotensin injection but, in contrast, fell after norepinephrine.

This paper reports a group of studies designed to confirm and explain certain differences in the actions of angiotensin and norepinephrine. The investigation was planned so that myocardial and vascular actions of the two drugs could be separated. Since the initial depressor action of angiotensin might be related to decreased coronary flow, the studies included observations on the action of angiotensin upon the coronary vascular bed. In part, the comparison between the two drugs utilized previously published studies of the actions of norepinephrine in the heart-lung preparation made in this laboratory.

Methods

Heart-lung preparations were made from 34 mongrel dogs anesthetized with intravenous sodium pentobarbital (22 mg/kg). The Starling resistance was set at 85 mm Hg; the blood entering the right atrium was kept at 38°C to 39°C. The volume of blood in the preparation at the beginning of each experiment was approximately 800 ml. Each animal was given 50 mg heparin intravenously. All experiments lasted less than one hour after cannulations. Direct measurements of left ventricular output (less coronary flow) were made in duplicate with a Stolnikoff stromuhr or by collecting the systemic output in a graduate cylinder while maintaining the venous reservoir level constant with donor blood. Changes in ventricular force were estimated by means of a Walton-Brodie strain gage arch which was sutured to the right ventricle in 19 animals and to the left ventricle in 15. The placement and adjustment of tension were as recommended by Cotten et al. and the force was recorded by a Sanborn multichannel direct-writing oscillograph. In all experiments heart rates were measured from the strain gage arch record. Arterial blood pressures and right and left atrial pressures were measured by means of Statham transducers.

The 34 heart-lung preparations were divided into four groups. One group of seven animals without controlled heart rates received repeated
single injections of 40 μg angiotensin* through the venous inflow cannula. A second group of eight animals were pretreated with reserpine, 0.1 mg/kg body weight intraperitoneally for each of two days prior to the experiment. These preparations also received repeated single injections of 40 μg angiotensin. In a third group of 11 animals, the heart was driven at a rate of 160 to 240 per minute through the right atrial appendage or right ventricle, using a Grass rectangular wave stimulator. These animals received single injections of angiotensin, 10 μg to 40 μg. In a fourth group of eight preparations without controlled rate, measurements of coronary sinus flow by direct cannulation and collection of the outflow into graduated cylinders were made at consecutive ten-second intervals for sixty to eighty seconds, beginning five seconds after 10 μg or 20 μg angiotensin.

Twenty-five coronary flow preparations were made from mongrel dogs of either sex,6 which were anesthetized with intravenous pentobarbital sodium (22 mg/kg). The anterior descending branch of the left coronary artery was cannulated and autogenous perfusion was established from the common carotid artery. By means of a finger pump, flow to the cannulated coronary artery was maintained constant. The output of the finger pump was adjusted so that coronary artery pressure was equal to carotid artery pressure. The animals were otherwise intact. In 17 preparations, 1.0 μg angiotensin I in 0.1 ml physiologic saline was quickly injected into the coronary arterial cannula. Drug administration was preceded by control injections of 0.1 ml physiologic saline. In eight preparations, 0.02 μg to 2 μg/min of angiotensin in a volume of 0.25 ml was infused continuously into the coronary artery cannula for two to seven minutes, employing a constant infusion pump. The effect of this infusion

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* Synthetic angiotensin II octapeptide kindly supplied as Hypertensin-CIBA by Dr. William E. Wagner of Ciba Pharmaceutical Products, Inc., Summit, New Jersey.
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upon carotid and coronary blood pressures was compared with that of an equal volume of physiologic saline. Changes in coronary perfusion pressure were interpreted as changes of coronary vascular resistance. In these studies, changes in heart rate and ventricular force were measured by a strain gage arch sutured to the surface of the right or the left ventricle. In two animals, coronary sinus pressure was measured. Pressures in the carotid and coronary arteries and in the coronary sinus were measured by means of Statham transducers and recorded by a Sanborn direct-writing oscillograph.

The myocardial action of angiotensin II was studied further in five cat papillary muscle preparations. Papillary muscles 8 mm to 10 mm long were isolated from the right ventricle of the cat and immersed in a muscle chamber containing 20 ml Krebs' solution. One end was attached to a Sanborn force transducer (no. F.T.A.-30-1), and the other was fixed by a tie around the muscle origin cut from the wall of the right ventricle. A mixture of 95% O₂ and 5% CO₂ was bubbled through the solution. Temperature was maintained at 37°C by a constant temperature circulating bath. The muscle was stimulated 60 times per minute with a Grass stimulator. Angiotensin, 2.2 μg and 4.4 μg in Krebs' solution, was added to the muscle chamber. In three cat papillary muscle preparations, the effect of 0.33 μg norepinephrine bitartrate was observed. After each administration of angiotensin, the chamber was drained and refilled with fresh Krebs' solution. A constant pH of 7.4 was maintained.

Results

1. HEART-LUNG PREPARATIONS

A. Uncontrolled Rate, Nonreserpinized

In these seven animals, following 40 μg angiotensin, cardiac function was impaired initially, followed by improved function within 10 to 20 seconds. The period of improved

![Figure 2](http://circres.ahajournals.org/)

Cardiac effects of repeated doses of 40 μg angiotensin in reserpine pretreated heart-lung preparation. For explanation of symbols, see legend of figure 1.

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cardiac function persisted for 30 to 120 seconds. Cardiac output fell initially in each animal; the range of decline was from 10% to 48% (fig. 1). In the same initial period, left atrial pressure rose 13% to 400% and ventricular force decreased 7% to 65%. Changes of right atrial pressure were always similar to left atrial pressure but smaller. During the period of improved cardiac performance, cardiac output increased 12% to 40% over control values; left atrial pressure fell in each instance, but remained above control values in some animals (fig. 1). Ventricular force returned toward the control in each instance, but tended to remain below control values (fig. 1). As a rule, changes in cardiac output, atrial pres-
sure, and ventricular force were much less after second and third injections of 40 µg angiotensin. In some animals (no. 1, 2, 6, and 7) virtually no change occurred with the second and third injections of the drug.

In these studies the heart rate showed no consistent pattern of response. Initially, the heart rate increased slightly in three animals, was unchanged in three, and fell in one. In the second period of improved cardiac performance, the heart rate increased over control in two animals, was unchanged in four, and fell in one.

B. Uncontrolled Rate, Reserpinized

In one animal of the eight in this group, progressive cardiac dilation was followed by cardiac standstill after the initial injection of 40 µg angiotensin. In the remaining seven animals in this group, the changes in cardiac output, atrial pressures, and ventricular force were similar to those observed in the non-reserpinized animals (fig. 2). Each animal demonstrated an initial decrease in cardiac function followed in 10 to 20 seconds by a return toward normal function. In many instances, cardiac performance improved above control during the following one to two minutes (fig. 3). Initially cardiac outputs fell 7% to 58%, left atrial pressures rose 39% to 192%, and ventricular force fell 35% to 60%. In one animal of the seven, left atrial pressure fell 15% initially. Ten to twenty seconds later, cardiac outputs rose 7% to 57% above control levels; left atrial pressures decreased strikingly in all, but remained above control in two animals; ventricular force increased in each animal, but remained below control in three animals. As in the nonreserpinized animals, changes following second and third injections were much less pronounced, and three animals showed little change with repeated doses (fig. 2). The initial changes in left atrial pressure, cardiac output, and in ventricular force were not significantly greater in the reserpinized animal, table 1. As in the nonreserpinized preparations, changes in heart rate were of minor degree and had no consistent pattern.

C. Controlled Rate Preparations

In this group of 11 animals, changes in cardiac output, ventricular force, and atrial pressure were measured after 10 µg or 20 µg angiotensin. The changes were similar to those described in the uncontrolled rate preparations, but were less consistent. For example, cardiac output fell initially in 8 of the 11 preparations. Ten of the 11 preparations showed a secondary rise in cardiac output. Atrial pressures rose initially in 10 of the 11 animals and then fell in each, and were below control values in seven during the period of increased cardiac output. Changes of ventricular force were variable, but were 7% to 18% above controls in 6 of 11 preparations during the period of increased cardiac output, thus giving evidence of a positive inotropic effect.

D. Coronary Sinus Flow

This was measured in eight animals with uncontrolled heart rate. In each instance coro-

| TABLE 1 |

Comparison of Hemodynamic Changes Following 40 µg Angiotensin in Reserpinized and Non-reserpinized Heart-lung Preparations

<table>
<thead>
<tr>
<th></th>
<th>Initial Change</th>
<th>Delayed Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reserp.</td>
<td>Non Reserp.</td>
</tr>
<tr>
<td>Mean cardiac output:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% change from control</td>
<td>−30.6</td>
<td>−25.7</td>
</tr>
<tr>
<td>Mean left atrial pressure:</td>
<td>+92.3</td>
<td>+81.4</td>
</tr>
<tr>
<td>% change from control</td>
<td>+45.1</td>
<td>−33.3</td>
</tr>
<tr>
<td>Mean left ventricular force:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% change from control</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reserp.</td>
<td>Non Reserp.</td>
</tr>
<tr>
<td>Mean cardiac output:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% change from control</td>
<td>+28</td>
<td>+21.1</td>
</tr>
<tr>
<td>Mean left atrial pressure:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% change from control</td>
<td>+21.1</td>
<td>+4.1</td>
</tr>
<tr>
<td>Mean left ventricular force:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% change from control</td>
<td>8.9</td>
<td>−2.7</td>
</tr>
</tbody>
</table>

nary sinus flow decreased initially, by 11% to 70%, following 10 μg or 20 μg angiotensin. In 10 to 20 seconds, cardiac output had risen 11% to 38% and coronary sinus flow had increased 4% to 55% over the control. During this period ventricular force rose and ranged from 0% to 45% (average 17%) above control.

2. CONSTANT CORONARY FLOW PREPARATIONS
   A. Single Injection of 1.0 μg Angiotensin
      In each of 17 dogs subjected to constant flow perfusion of the left anterior descending coronary artery, injection of 1.0 μg angiotensin II into the coronary artery produced an immediate increase of coronary perfusion pressure of 6% to 92% (fig. 4). Ten to 20 seconds later carotid arterial pressure changed by −17% to +23%. In all instances except one, the carotid pressure change showed less increase than the coronary pressure; in the one exception the carotid pressure rose later as it did also in the other 16 animals. Ventricular force did not increase; in fact a small decrease was usually recorded from either ventricle (fig. 5). No change was observed in coronary sinus pressure during the period of increased coronary perfusion pressure. In five dogs, intracoronary injection of 0.2 μg to 1 μg norepinephrine bitartrate had inconsistent effects upon coronary perfusion pressure, i.e., no change in three, an increase of 10% in one, and a decrease of 21% in one.

   B. Continuous Injection of Angiotensin
      In the eight studies made during continuous infusion of angiotensin into the left anterior descending coronary artery, definite increases of coronary perfusion pressure (7% to 85%) were observed with amounts of 0.02 μg to 2 μg/min (fig. 6). Initial observations were made at the 0.02 μg/min level in five of the eight animals. At this infusion rate, increases of perfusion pressure were 7% to 25% (average 14%). The coronary arteries were perfused with a constant blood flow of 29 ml to 48 ml/min. Thus evidence of increased coronary vascular resistance was found at angiotensin concentrations as low as 0.42 μg/liter of blood. The coronary perfusion pressure remained elevated for the duration of the infusion in five animals, in which the infusion was given for two and one-half minutes in one; three minutes in one; four minutes in one; and six minutes in two. In three infusions the effect persisted for 1 minute 45 seconds to 3 minutes 45 seconds but not for the entire duration of the angiotensin infusion.

3. CAT PAPILLARY MUSCLE PREPARATIONS
   In five cat papillary muscle preparations contractile force increased consistent-
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Left Ventricular Force

Coronary Blood Pressure MM Hg

Saline 0.1ml
Control

Angiotensin 1.0 ug in 0.1 ml

20 seconds

FIGURE 5
Change in coronary perfusion pressure and left ventricular force following 1.0 µg angiotensin during constant flow perfusion of left anterior descending coronary artery. Decrease in coronary blood pressure following the increase might suggest reactive hyperemia, but was not consistently observed in other animals.

Interestingly following addition of 2.2 µg of 4.4 µg angiotensin to the bath (fig. 7). The increases observed after 2.2 µg in the five preparations were 20%, 27%, 28%, 50%, and 56% with an average of 36%. Addition of 0.33 µg norepinephrine to the bath produced a lesser increase in the tension developed by the papillary muscle (3%, 15%, and 19%). The rate of contraction of the stimulated papillary muscle did not change in these studies.

Discussion

Our studies made in the dog heart-lung preparation confirm and extend the observations of Rose et al. who showed that angiotensin differed from norepinephrine in having an initial depressor action. Our observations indicate that the initial depressor effect of angiotensin may be explained by a prompt impairment of cardiac performance. In comparable studies of norepinephrine reported previously by us no initial cardiac depression was observed. The consistent decrease of cardiac response following repeated injections of the same amounts of angiotensin showed clear evidence of tachyphylaxis. Gross and Bock observed tachyphylaxis in the pressor response to high doses of angiotensin II (20 µg to 50 µg/kg), but not to medium doses (1 µg/kg). We did not, in our experiments, wait 40 to 60 minutes to determine restoration of angiotensin responsiveness. In our previous studies, no such decrement of response was observed with repeated injections of norepinephrine.

Rose et al. did not attempt to determine whether or not angiotensin had a myocardial
**FIGURE 6**
Effect of a three-minute continuous infusion of 0.04 μg angiotensin/min upon coronary perfusion pressure in a constant coronary flow preparation. Coronary perfusion rate was 44 ml/min. The initial negative transient in the record of coronary perfusion pressure was produced by the beginning of the angiotensin infusion; the others were produced by cardiac arrhythmia, and may be seen also in the carotid blood pressure record.

**FIGURE 7**
Effect of angiotensin upon tension developed by cat papillary muscle.
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The studies reported here upon the heart-lung preparation and the cat papillary muscle preparation indicate clearly that angiotensin has positive inotropic action. In the heart-lung preparation, the inotropic effect of 40 µg angiotensin was no greater than that observed after 1 µg norepinephrine in previous studies. However, the initial impairment of myocardial performance, probably caused at least in part by decreased coronary blood flow, may have limited the positive inotropic response. This is suggested by the observations that the action of angiotensin upon the cat papillary muscle was nearly as great as that of norepinephrine on the basis of the larger molecular size of angiotensin. A similar inotropic effect of angiotensin upon the isolated heart was observed by Bianchi et al. in the guinea pig and rabbit heart and by Meier et al. in the rabbit heart. The evidence of a positive inotropic effect of angiotensin in reserpinized heart-lung preparations in our study strongly suggests that myocardial catecholamines are not essential to this response.

Evidence of increased coronary vascular resistance following angiotensin was consistently found in our study. From these observations, it seems very likely that decreased coronary blood flow was at least partially responsible for the early impairment of cardiac performance observed regularly in the heart-lung preparation. Hill and Andrus and Lorber showed that angiotonin decreased coronary flow in the isolated perfused cat's heart. Bianchi et al. found decreased coronary flow following angiotensin in the isolated heart. Maxwell et al. found increase in coronary vascular resistance but no alteration of coronary blood flow after synthetic angiotonin octapeptide in dogs. Recently Mandel and Sapirstein, which was made after equilibrium was reached during a constant infusion. The same is true of the maximum increase in coronary vascular resistance. Actually, the elevated blood pressure and cardiac work in the intact animal probably tend to increase coronary flow and thus mask the effect of increased coronary vascular resistance. Similarly, in the intact animal, activation of carotid baroreceptors by the rise in blood pressure would be expected to mask the inotropic action of angiotensin by slowing the heart and depressing atrial contractility and ventricular function. Our results show more clearly the sequential effects of angiotensin upon the coronary bed of dogs, and indicate that significant increase of coronary resistance occurs at drug levels as low as 0.42 µg/liter. Although we are unable to state the biologic half life of angiotensin α, the pressor effect following a single injection is known to persist more than three minutes. Thus the usual therapeutic infusion rates in man of 2.5 µg to 5 µg/min and more could probably produce blood concentrations of this magnitude. However, if there is tachyphylaxis, the increased coronary vascular resistance may not be maintained for the duration of the infusion. In studies where 1.0 µg norepinephrine was injected into the perfused left anterior descending coronary artery, no increase of coronary vascular resistance was observed. The site of the increased coronary vascular resistance produced by angiotensin is not demonstrated in these studies. However, the magnitude of the pressure rise in some animals strongly suggests that at least some of the increased resistance occurs within the coronary arteries.

When the effects of single injections of 40 µg angiotensin were studied in the heart-lung preparation, initial impairment of cardiac performance, probably caused by decreased coronary flow, was always observed. With smaller doses of 10 µg or 20 µg, increased cardiac function without initial depression was found occasionally. Thus there was usually no dissociation between the cardiac effects of decreased coronary flow and the positive
inotropic effect, but a separation was seen at times with smaller doses. Nevertheless, these observations do not preclude the possibility that decreased coronary flow occurred initially in all such studies, since the decrease may have been too small to impair cardiac function or its effect may have been masked by the positive inotropic action of angiotensin.

It can be concluded that increased coronary vascular resistance following angiotensin has been demonstrated rather clearly in several different animals. It also seems very likely that significant, although moderate, increase of coronary resistance probably occurs at blood levels likely to be achieved in the treatment of shock. If the period of decreased coronary flow overlaps that of increased myocardial work a very unfavorable balance between heart work and coronary flow may result. Although cardiac arrhythmias were seldom seen in our studies, one reserpinized animal suffered cardiac dilation and standstill following a single large injection (40 μg) of angiotensin. Although the results of the present study cannot be applied without reservation to man, it would appear that some caution is desirable in the use of angiotensin to treat human shock, especially that caused by myocardial infarction.

Summary

In the dog heart-lung preparation, single injections of 40 μg angiotensin II produced consistently a biphasic response. Initial impairment of cardiac function was observed with decrease of cardiac output and of ventricular force, and with increase of atrial pressures. After 10 to 20 seconds, there was a positive inotropic effect, with an increase of cardiac output and of ventricular force, and a decrease in atrial pressures. Responses were comparable in reserpinized and non-reserpinized preparations. Tachyphylaxis to angiotensin was found consistently in the heart-lung preparation, with a regular decrease in response following second and third injections. A positive inotropic action of angiotensin II was demonstrated in the cat papillary muscle preparation. These studies demonstrated that angiotensin has a direct cardiac action, namely a positive inotropic effect. This action probably does not depend upon myocardial stores of catecholamines.

When the left anterior descending coronary artery of the dog was perfused with blood at a constant flow, single intracoronary injections of angiotensin (1.0 μg) consistently increased coronary resistance (6% to 92%). Continuous intracoronary infusion of angiotensin increased coronary vascular resistance when blood concentrations were as low as 0.42 μg/liter. No evidence of initial cardiac depression or of increased coronary vascular resistance was found after norepinephrine.

It is concluded that the initial impairment of cardiac performance following angiotensin is caused at least in part by decreased coronary blood flow. Caution is suggested in the use of angiotensin in the treatment of human shock because of its action upon the coronary circulation.

References

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