Hemodynamics of Angiotensin in Man

By Frank A. Finnerty, Jr., M.D.

RECENTLY, synthetic angiotensin II has become available for study. Page and Helmer\(^1\) and Braun-Menendez and coworkers\(^2\) have demonstrated that this compound represents the reaction product of renin on the a\(_2\) globulin, hypertensigen. Intensive pharmacologic studies conducted by the Cleveland group\(^3-5\) and the Swiss\(^6, 7\) have verified that synthetic angiotensin II is identical with the naturally occurring substance. The availability of this compound prompted a comparison of its pressor and hemodynamic properties with those of norepinephrine in man.

The effect of intravenous infusions of angiotensin II and norepinephrine on the arterial pressure and the heart rate was compared in 17 normotensive and 3 hypertensive patients. Angiotensin II was about 10 times as potent as norepinephrine. Thus, 0.028 ± 0.007 μg./Kg./min. of angiotensin II produced a similar increase in arterial pressure to that produced by 0.27 ± 0.007 μg./Kg./min. of norepinephrine. The pressor responses to both agents were not significantly different in the presence of uremia or hypertensive disease.

The rise in arterial pressure occurred an average of 2.6 minutes following the administration of angiotensin II and an average of 3 minutes after institution of norepinephrine. The arterial pressure returned to the baseline an average of 7 minutes after discontinuation of angiotensin II and an average of 4 minutes after discontinuation of norepinephrine. Following discontinuation of angiotensin II, postural hypotension (15 to 30 per cent below the control standing mean arterial pressure) occurred in 6 patients. A comparable degree of postural hypotension occurred in 4 patients following discontinuation of norepinephrine. The postural hypotension following discontinuation of angiotensin II lasted 18 to 24 hours as compared to 4 to 6 hours after discontinuation of norepinephrine.

The responses of the heart rate during angiotensin II and norepinephrine were similar. Both agents produced significant bradycardia in patients without cardiovascular disease, while a decreased bradycrotic response was noted in the patients with arteriosclerosis. The bradycardia following both agents could be blocked by 1 mg. of atropine.

The rise in arterial pressure with angiotensin II was not associated with a significant change in the vital capacity (6 patients) or in the caliber of the retinal arteries (30 patients). No side-effects were noted during these infusions.

A 42 ± 7 per cent increase in mean arterial pressure in 11 normotensive patients with angiotensin II was associated with a reduction in cardiac index from an average of 3.34 ± 0.55 to 2.56 ± 0.53 L./min./M.\(^2\), a 24 per cent average reduction, with no change in the plasma volume or red cell mass. If the 1 patient who demonstrated a 35 per cent decrease in cardiac index was excluded, the average percentage decrease in cardiac index would then be 14 per cent.

A 37 ± 15 per cent increase in mean arterial pressure in 7 normotensive patients with angiotensin II was associated with a 52 ± 30 per cent average increase in venous pressure. The increase in venous pressure

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following norepinephrine was almost twice that following angiotensin II.

Infusions of angiotensin II seem to have no immediate predictable or consistent effect on serum sodium or potassium.

The cardiovascular response of 5 normotensive patients to infusions of angiotensin II and l-epinephrine can be observed in table 1. The increase of arterial pressure with angiotensin II was associated with a slight decrease in cardiac output and a striking increase in total peripheral resistance. The addition of equivalent amounts of epinephrine to the infusion resulted in a slight fall in the arterial pressure, a striking increase in cardiac output, and a fall in the total peripheral resistance from the elevated levels during angiotensin II.

A 24-hour infusion of angiotensin II in 6 normotensive patients was associated with a slight decrease in urinary output. The effective renal plasma flow (I131 iodopyracet*) was reduced throughout the entire angiotensin II infusion. Figure 1 demonstrates that both the inulin and PAH clearances were significantly decreased during the angiotensin II infusion, the reduction in PAH being greater than the reduction in inulin. The filtration fraction, therefore, was increased.

Thirteen patients in shock received angiotensin II therapeutically for periods ranging from 1 hour to 14 days. Excluding those patients who were terminal—who did not respond to as much as 3 to 4 μg. of angiotensin II per minute—the average effective dose was 0.035 μg./Kg./min. In those patients who responded initially, no tachyphylaxis or drug resistance was noted. In fact, less angiotensin II was necessary on succeeding days. An increase in the urinary output was noted in every patient following the first 24 hours of infusion. No cardiac arrhythmias were noted.

The data presented demonstrate that in normotensive subjects, angiotensin II is approximately 10 times as potent as norepinephrine, which it resembles hemodynamically. The rise in systolic pressure in patients without cardiovascular disease is associated with (1) a significant increase in diastolic pressure, (2) an increase in venous pressure, (3) a decrease in heart rate, (4) a slight decrease in cardiac output, and (5) a striking increase in total peripheral resistance. It would seem then that, like norepinephrine, the primary action of angiotensin

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*Diodrast, Winthrop.
HEMODYNAMICS OF ANGIOTENSIN IN MAN

Table 1
Cardiovascular Response of Five Normotensive Patients to Infusions of Angiotensin II and l-Epinephrine

<table>
<thead>
<tr>
<th>Case</th>
<th>Time</th>
<th>State, drug</th>
<th>Dose ng/Kg/min.</th>
<th>Pulse</th>
<th>Systemic arterial blood pressure mm Hg</th>
<th>Cardiac output L/min.</th>
<th>Total peripheral resistance (dynes/cm.²/sec.)</th>
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<td></td>
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<td>76</td>
<td>137</td>
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<td>l-Epinephrine</td>
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II is to produce an intense overall vasoconstriction and that this vasoconstrictor action can be completely blocked by the simultaneous administration of an equal dose of l-epinephrine.

Similar to norepinephrine, the bradycardia accompanying angiotensin II infusion can be blocked by atropine. It is also interesting that the decreased bradycardia response during norepinephrine previously observed in patients with vascular disease was also noted in patients during angiotensin infusion. Unlike norepinephrine, however, extrasystoles and other arrhythmias did not accompany infusions of angiotensin II. Table 1 demonstrates that angiotensin II infusion is associated with a slight decrease in cardiac output. Comparable increases in mean arterial pressure with norepinephrine in this laboratory have been associated with no change of the cardiac output. Using the Fick method, Sanecetta found angiotensin II caused no significant change in cardiac output. The explanation for these discrepancies is not evident.

Studies on the renal hemodynamics during angiotensin II infusion in subjects without cardiovascular disease demonstrate the following: (1) a slight decrease in urinary flow, (2) a marked decrease in renal blood flow, (3) a moderate decrease in filtration rate, and (4) an increase in filtration fraction. It should be stressed that the infusions of angiotensin II in the patients studied here were continued over a 24-hour period. The greater decrease in renal blood flow during angiotensin II is similar to the findings of Bock and Kriech, who administered angiotensin II to patients for 54 minutes. The decrease in PAH at the end of 24 hours of angiotensin in patients presented here was no greater than at the end of 2 hours. The fact that a similar, persistent decrease was noted when the renal plasma flow was measured by the radioactive method substantiates the observation that a decrease in renal blood flow persists as long as the angiotensin is continued. Although renal blood flow measurements were not determined following discontinuance of angiotensin II.
in the patients studied here, the data of Bock and Krieeke\textsuperscript{12} demonstrate a prompt rise in these clearances to levels above control 1 hour after discontinuance of angiotensin. It would seem, then, that angiotensin II alters the renal hemodynamics only during the period of its administration.

Preliminary observations on the use of angiotensin II in patients in shock suggest that it is 2 to 3 times as potent as norepinephrine. This observation may be important from the therapeutic standpoint since less parenteral fluids would be needed to control the arterial pressure. Experience thus far with angiotensin II, both in the experiments outlined above and in shock, suggests that the desired level of arterial pressure is easier to arrive at and maintain with angiotensin II than with norepinephrine. Of particular interest also was the lack of development of drug resistance in 3 patients who received angiotensin II continuously for 10, 12, and 14 days, respectively. In these patients, there was a decrease in the dose of angiotensin II needed to maintain the arterial pressure on successive days, an increase in urinary output, and a decrease in blood urea nitrogen. During the long-term therapy of 2 of these latter patients and in 6 other instances during the experiments reported above, the intravenous infusion of angiotensin II inadvertently infiltrated the subcutaneous tissues. No sloughing occurred.

Summary

These data demonstrate that in normal subjects, angiotensin II is 10 times as potent as norepinephrine which it resembles hemodynamically. An increase in the systolic pressure is associated with a significant increase in diastolic pressure, an increase in venous pressure, a decrease in heart rate, a slight increase in cardiac output and a striking increase in total peripheral resistance, a decrease in renal blood flow, decreased glomerular filtration rate, increase in filtration fraction, and slight decrease in urinary volume.

Preliminary studies in patients in shock suggest that angiotensin II is 2 or 3 times as potent as norepinephrine. Continuous administration is not associated with the development of tachyphylaxis, and sloughing of tissues does not occur if there is leakage outside the vein.

References

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