The effect of intravenous angiotensin II on the peripheral circulation with particular reference to its bearing on general haemodynamics

M. CACHOVAN, J. BROD, J. BAHLMANN, R. SIPPEL, B. CELSEN AND H. HUNDESHAGEN
Division of Angiology and Division of Nephrology, Department of Medicine and Institute of Nuclear Medicine and Special Biophysics, Hannover Medical School, Hannover, West Germany

Summary

1. Central and peripheral haemodynamic effects of intravenous infusion of angiotensin II have been investigated in ten normotensive subjects. Angiotensin II was given at the rate of 0.12–5.0 µg/min.

2. The pressor response to angiotensin II was accompanied by a significant increase in the total peripheral resistance, central venous pressure and by a marked reduction of the intravascular forearm volume and venous distensibility. Forearm circulation time was shortened.

3. Cardiac index, heart rate, forearm vascular resistance and the forearm blood flow did not change significantly in the whole group but in the individual subjects some of the variables changed markedly in either direction.

4. Direct action of angiotensin II on the vessels and its central and peripheral sympathomimetic action as well as the role of the baroreflex as responsible causes for haemodynamic changes after angiotensin II are discussed.

Key words: angiotensin, forearm blood flow, venoconstriction, venous distensibility.

Introduction

Although many investigations have been made concerning the haemodynamic effects of angiotensin II, less attention has been paid to the relation between changes in the capacitance vascular bed and general haemodynamics after angiotensin II in man.

This point, however, seems to be of particular importance for two reasons: (1) it is believed that angiotensin may play an important role in the early stages of renal hypertension (Bianchi, Tilde Tenconi & Lucca, 1970; Laragh, 1973; Scroop, Katic, Brown, Cain & Zeegers, 1975; Ledingham, 1975), and (2) it seems to be established that the capacitance vessels share significantly in the pathogenesis of hypertension in chronic renal disease (Overbeck, 1972; Lucas & Floyer, 1974; Brod, 1974, 1975).

Therefore we studied the effects of intravenous angiotensin II on the peripheral circulation with special reference to its bearing on general haemodynamics.

Methods

In ten normotensive subjects, aged 17–43 years, the following measurements were made under resting condition and during angiotensin II infusion.

Cardiac output was measured by the dye-dilution technique with the central catheter in the superior vena cava and the sampling catheter in the external iliac artery. Indocyanine Green was used as an indicator.

Arterial blood pressure was measured through a catheter placed in the external iliac artery via a Statham P 23 Db transducer, with the mean blood pressure being integrated electrically.

From the blood pressure recordings the heart rate was estimated.

Central venous pressure in the vena cava superior and peripheral venous pressure in the basilic vein were measured with Statham P 23 Db pressure transducers.

Forearm blood flow was determined by venous
occlusion plethysmography with the mercury-in-rubber strain-gauge technique according to Whitney (1953).

Forearm blood volume was estimated by a combination of the radionuclide technique with plethysmography according to Pfeovský, Ulrych, Linhart, Vavrejn, Korsgren & Varnauskas (1968) in the modification of Pixerberg, Eckhardt & Cachovan (1972).

This approach is based on simultaneous measurement of impulse rate of the intravenously administered $^{111}$In-labelled transferrin and recording of the forearm plethysmogram at rest and during 4 min of venous occlusion with 30 mmHg. The increased activity during the occlusion is proportional to the volume change in the plethysmogram, so that from this relation and the basal activity the forearm blood volume can be estimated quantitatively.

Cardiac index, stroke index, total peripheral resistance and forearm vascular resistance were calculated according to the usual formulae.

Venous distensibility was defined as forearm blood volume per 1 mmHg intravenous pressure at a 30 mmHg collecting pressure.

Forearm circulation time as a measure of local flow velocity was calculated by dividing the forearm blood volume by forearm blood flow.

After the steady state was reached, the control period of 20 min duration was started. Then angiotensin II was infused into the femoral vein at the rate of 0.12–5.0 µg/min over the next 20 min.

### Results

There was a consistent and significant increase in the mean blood pressure in all cases after angiotensin II infusion. The cardiac index and the heart rate did not change. Both the central venous pressure and the total peripheral resistance rose significantly, the former being raised more than twofold.

Peripheral vascular response to angiotensin II was characterized by moderate but not significant increase in the forearm blood flow and the forearm vascular resistance and by a significant diminution of the venous distensibility and the forearm blood volume. Due to this, the forearm circulation time shortened significantly after angiotensin II.

The results confirm that the pressor response to a wide dose range of angiotensin II is mainly due to increase in the total peripheral resistance. Three more measurements changed constantly and regularly in every patient: the venous distensibility decreased, the volume of blood in forearm vessels rose and the central venous pressure fell. On the other hand, the cardiac index, heart rate, forearm blood flow and forearm vascular resistance changed in both directions so that a statistical level of significance was not reached.

### Discussion

In trying to explain the changes found one has to start from the known physiological effects of angiotensin II. Angiotensin II constricts the smooth vessel muscles; it stimulates the sympathetic hypothalamic centres (Bickerton & Buckley, 1961; Laverty, 1963;)

| Table 1 Effect of intravenous angiotensin infusion on central and peripheral haemodynamic parameters in ten normotensive subjects |
| Mean values±SEM are shown. For significance of difference from values in control (pair-matched Student’s t-test): n.s. = $P > 0.05$. |
| Control | Angiotensin | $P$ |
| Mean blood pressure (mmHg) | 94.07±4.16 | 123.00±5.88 | <0.001 |
| Heart index (l min$^{-1}$ m$^{-2}$) | 2.90±0.22 | 2.85±0.32 | n.s. |
| Stroke index (ml/m$^2$) | 51.54±5.44 | 46.33±3.87 | n.s. |
| Heart rate (min$^{-1}$) | 57.44±2.10 | 59.11±2.80 | n.s. |
| Total peripheral resist. (N s cm$^{-5}$) | 0.015±0.001 | 0.02±0.002 | <0.005 |
| Central venous pressure (mmHg) | 3.38±0.54 | 6.42±0.76 | <0.001 |
| Forearm blood flow (ml min$^{-1}$ 100 ml$^{-1}$) | 4.09±0.65 | 4.72±1.04 | n.s. |
| Forearm vascular resist. (N s cm$^{-5}$) | 22.52±2.58 | 27.50±4.92 | n.s. |
| Forearm blood volume (ml/100 ml) | 4.49±0.68 | 2.84±0.53 | <0.05 |
| Peripheral venous pressure (mmHg) | 6.08±0.90 | 10.29±1.05 | <0.001 |
| Venous distensibility (ml 100 ml$^{-1}$ mmHg$^{-1}$) | 0.25±0.04 | 0.14±0.03 | <0.02 |
| Forearm circulation time (min) | 1.29±0.29 | 0.75±0.17 | <0.05 |
Effects of intravenous angiotensin

Scroop & Whelan, 1966; Lowe & Scroop, 1969; Scroop et al., 1975); by its pressor effect it stimulates the baroreceptor reflex and by acting on the adrenal medulla it may release adrenaline.

The uniform response on the venous side where the simultaneous fall in intravascular blood volume and decrease in venous distensibility suggest venoconstriction is easily explained by the fact that sympathetic stimulation, adrenaline and angiotensin II all act synergistically on the vascular smooth muscle. The same is obviously true for some other areas, which were not studied in the present investigation but for which adequate evidence is available, e.g. kidneys and the splanchnic area. On the other hand, it is well established that muscle, apart from containing α-sympathetic fibres, also contains cholinergic vasodilating fibres (Uvnäs, 1960) and that adrenaline dilates muscle vessels (Barcroft & Swan, 1953). There is also ample evidence that the vessels in the skeletal muscle may reflexly dilate when tension rises in the intrathoracic low-pressure system (Roddie, Shepherd & Whelan, 1957). Venoconstriction which shifts the blood centrally may have the same effect. Thus a uniform behaviour of the blood flow and forearm resistance can hardly be expected.

On the heart, the baroreceptor reflex has a tendency to inhibit the action of angiotensin II and to lower the cardiac output, whereas central nervous stimulation and adrenaline may produce an opposite effect so that a regular change is improbable.

Thus we can conclude that angiotensin II action on the venous side will regularly be constrictor, whereas its central haemodynamic action will be irregular. The opposing forces acting on the heart may eventually frustrate the effect of the rise of the venous pressure and on the Frank–Starling forces.

References


