injury sufficient to produce unconsciousness in only 25% of his cases. Neck stiffness and positive Kernig's sign with or without further abnormal neurological signs may be found with a subdural haematoma or with primary subarachnoid haemorrhage. Blood-stained cerebrospinal fluid can be withdrawn in subarachnoid haemorrhage and is commonly seen with subdural haematoma. The fluid was blood-stained in all our cases.

A subdural haematoma may form when bleeding is primarily subarachnoid (Voris, 1946; Scott, 1949). Angiography did not show an aneurysm in our cases. While this does not exclude the presence of an aneurysm absolutely, it makes it unlikely, and the benign clinical course after operation supports the absence of a primary vascular lesion. We believe that in our cases the subdural space was the primary site of bleeding, probably caused by past trivial trauma, as discussed by Trotter (1914). In Case 3 the subdural haematoma may have arisen as a complication of anticoagulant therapy. Patients suffering from subdural haematoma while on anticoagulant medication were reported by Chawla (1968).

Because the diagnosis could be made only on carotid angiography, we recommend that all cases reminiscent of the syndrome of primary subarachnoid haemorrhage be examined by cerebral angiography lest an easily treatable lesion be overlooked.

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PRELIMINARY COMMUNICATIONS

Importance of Central Vasomotor Effects in Angiotensin-induced Hypertension

G. C. SCROOP, FRANCES KATIC, M. D. JOY, R. D. LOWE

British Medical Journal, 1971, **1**, 324–326

Summary

Ablation of the areas postrema in 10 dogs caused a highly significant reduction in the pressor response to intravenous infusions of angiotensin yet was without significant effect on the pressor response to intravenous infusions of noradrenaline. The reduction in the pressor response to angiotensin is almost certainly due to abolition of the specific central autonomic effects of the hormone which are dependent on the integrity of the areas postrema. It is suggested that this central effect also contributes to the cardiovascular response to endogenous angiotensin.

Introduction

Angiotensin has a powerful direct constrictor action on blood vessels which may make an important contribution to the hypertension seen in those patients with raised plasma levels of renin or angiotensin. The blood vessels of such patients, however, are often relatively unresponsive to the direct action of the hormone (Scroop and Whelan, 1968a), and the degree of hypertension that exists is often not well correlated with the estimated plasma levels of renin or angiotensin. For these and other reasons it has been suggested that other angiotensin-dependent mechanisms may be involved in maintaining the hypertension.

The elucidation of a variety of autonomic effects of angiotensin in recent years, both in man (Scroop and Whelan, 1966; Henning and Johnsson, 1967) and in animals (Bickerton and Buckley, 1961; Yu and Dickinson, 1965; Zimmerman, 1967), together with the demonstration of a significant neurogenic component in the chronic phase of experimental hypertension (McCubbin and Page, 1963), suggest that such actions may well make an important contribution to the hypertensive effect of the hormone. Attempts to demonstrate such a contribution in man, however, have not been successful (Laurence and Nagle, 1963; Scroop and Whelan, 1968b) largely for technical reasons.

Scroop and Lowe (1968) described a very sensitive and entirely nervously-mediated pressor effect of angiotensin in the anaesthetized greyhound in response to vertebral artery infusions at rates as low as 0·1 ng/kg/min (Lowe and Scroop, 1969). Joy and Lowe (1970) were able to abolish this response by thermocoagulation of the areas postrema in the greyhound while at the same time preserving the specific central hypertensive effects of other vasoactive substances. The response to carotid artery occlusion was unmodified by this procedure (Joy and Lowe, 1970), suggesting that both the effector autonomic pathways and the baroreceptor reflexes are intact. Since ablation of the areas postrema abolishes the central effect of angiotensin, we have used this technique to determine the contribution of this central effect in the overall response to the hormone. The results clearly show a significant reduction in the pressor response following this procedure, and the importance of this finding with regard to the cardiovascular effects of endogenously generated angiotensin is discussed.

Methods

Experiments were carried out in 10 greyhounds which were premedicated with morphine (2 mg/kg intravenous injection) and anaesthetized with alpha chloralose (125 mg/kg intravenously) and which were artificially ventilated throughout the experiments.

Arterial pressure and heart rate were recorded on a Grass Polygraph, standard techniques being used. Vertebral artery infusions of angiotensin were made through a non-obstructing

Department of Medicine, St. Thomas's Hospital, London S.E.1
G. C. SCROOP, M.D., C. J. Martin Travelling Fellow of the National Health and Medical Research Council of Australia
FRANCES KATIC, Research Assistant
M. D. JOY, M.B., M.R.C.P., Research Fellow
R. D. LOWE, M.D., M.R.C.P., Senior Lecturer

catheter inserted into one vertebral artery at the base of the neck, with the opposite vessel clamped. Intravenous infusions were given into a femoral vein. The drugs were dissolved in normal saline and each drug infusion was preceded and followed by a control infusion of saline. The areas postrema was approached dorsally through the fourth ventricle and ablated under direct vision by thermocoagulation.

Results

Fig. 1 shows the changes of blood pressure and heart rate in an anaesthetized greyhound in response to vertebral artery infusion of angiotensin and intravenous infusions of both angiotensin and noradrenaline before and after ablation of the areas postrema. The pressor response to the vertebral artery infusion of angiotensin has been abolished by this procedure and that to intravenous infusion substantially reduced. The pressor response to intravenous noradrenaline, however, is not obviously modified.

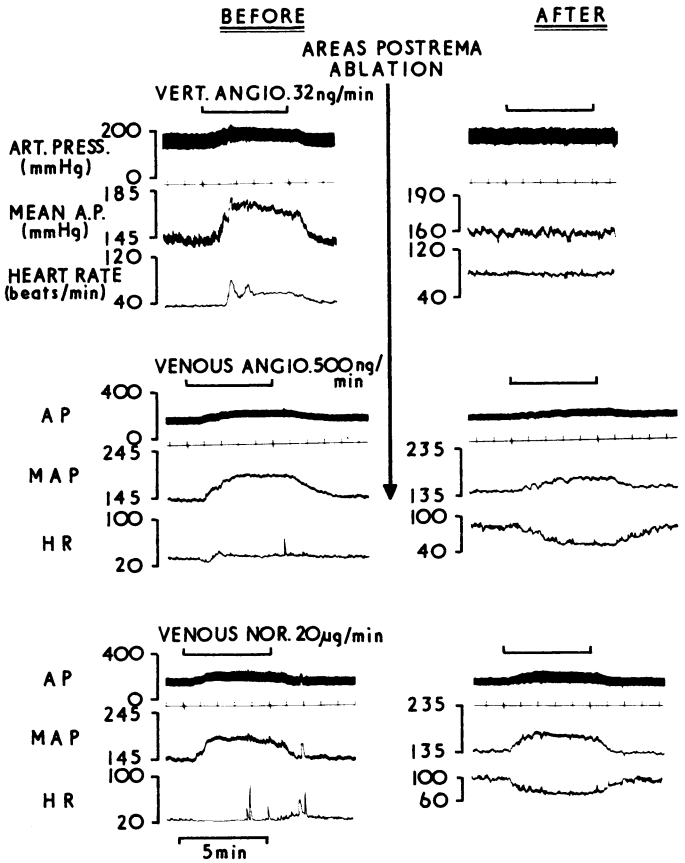

FIG. 1—Responses of pulsatile arterial pressure, mean arterial pressure, and heart rate in an anaesthetized greyhound (weight 28 kg) during vertebral artery infusions of angiotensin (32 ng/min for 5 min) and intravenous infusions of angiotensin (500 ng/min for 5 min) and noradrenaline (20 µg/min for 5 min) before (left of figure) and after (right of figure) ablation of the areas postrema. The low resting heart rate is a feature of the chloralose-anaesthetized greyhound.

Similar results were obtained at these dose levels in nine other dogs and the pooled results are shown in Fig. 2. The pressor response to intravertebral angiotensin was abolished in every case and the response to intravenous infusion of angiotensin significantly reduced ($P<0.001$) whereas that to intravenous infusions of noradrenaline was not significantly modified ($0.7<P<0.8$).

The mean pressor responses in 10 dogs at three different dose levels (125, 500, and 2,000 ng/min for 5 min) of angiotensin given intravenously before and after ablation of the

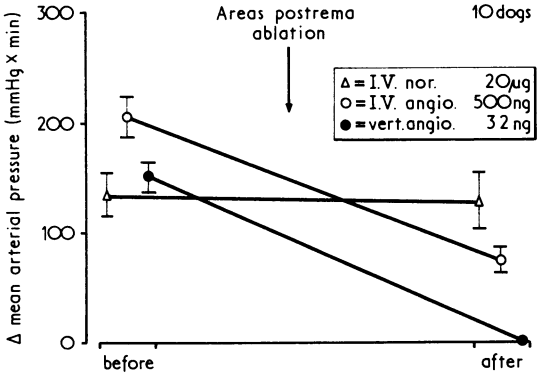

FIG. 2—Average responses of mean arterial pressure resulting from vertebral artery infusions of angiotensin (32 ng/min for 5 min) (closed circles) and intravenous infusions of angiotensin (500 ng/min for 5 min) (open circles) and noradrenaline (20 µg/min for 5 min) (open triangles) before (left of figure) and after (right of figure) ablation of the areas postrema. The changes in mean arterial pressure are expressed as the integral (mm Hg × min) by calculating the area contained in the pressor response with planimetry. Each point is the mean response from 10 dogs and the vertical lines through each point represent one standard error on either side of the mean.

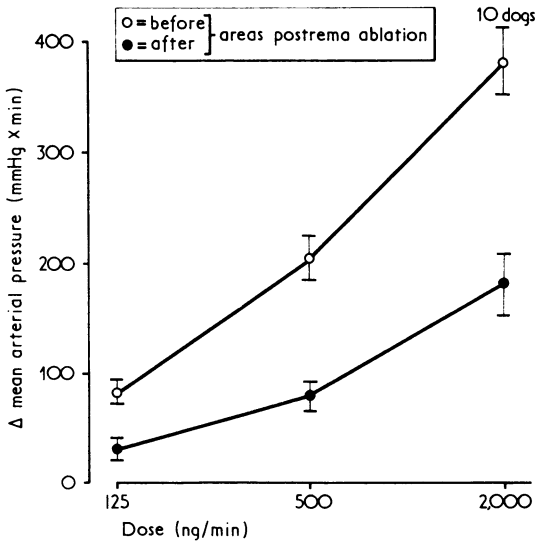

FIG. 3—Relationship between dose of angiotensin given intravenously (125, 500, and 2,000 ng/min for 5 min) and increase of mean arterial pressure (expressed as the integral) before (open circles) and after (closed circles) ablation of the areas postrema. Each point is the mean response from 10 dogs and the vertical lines through each point represent one standard error on either side of the mean.

At each dose level there is a significant reduction in the pressor response after ablation ($P<0.001$ in each case).

Discussion

The results clearly show that at all dose levels studied the pressor effect of intravenous infusions of angiotensin is significantly reduced after ablation of the areas postrema, whereas the response to an approximately equipressor dose of noradrenaline was not significantly modified. Since the pressor effect of intravenous noradrenaline is unaltered it seems unlikely that the reduction in the pressor response to intravenous angiotensin following area postrema ablation is due to any alteration in the ability of the blood vessels to respond to a drug acting directly on smooth muscle.

The blood concentration achieved in the chloralose-anaesthetized greyhound during intravenous infusions of angiotensin at 500 ng/min has been measured by Hodge, Lowe, and Vane (1966) and closely approximates the local

blood concentration during vertebral artery infusion at 32 ng/min (Lowe and Scroop, 1969). Since ablation of the areas postrema abolishes the cardiovascular response to vertebral artery infusions of angiotensin (Joy and Lowe, 1970) it seems likely that the reduction in the pressor response to intravenous infusions is due to abolition of this component and that which remains is principally the response to the direct vasoconstrictor action.

It is concluded that the specific central effect of angiotensin makes a significant contribution to the pressor response to intravenous infusions of the hormone. This finding suggests that the central effect may also be important in the response to endogenously generated angiotensin either following haemorrhage or in renovascular hypertension. Since a specific pressor response after vertebral artery injections of angiotensin has now been described in man (Ueda, Uchida, Ueda, Gondaira, and Katayama, 1969) the results of the present experiments may well have clinical implications, particularly with regard to chronic renal hypertension when a prominent neurogenic component has been described (McCubbin and Page, 1963).

We are grateful for the support provided by the Endowment Funds of St. Thomas's Hospital, by the Medical Research Council, and by the Wellcome Trust.

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MEDICAL MEMORANDA

Pregnancy and Mitral Valve Prosthesis

JOHN M. REID, R. S. BARCLAY

British Medical Journal, 1971, 1, 326–327

Several reports have been published of successful pregnancies in patients with prosthetic valves (Ueland, Tatum, and Metcalfe, 1966; Hedstrand and Cullhed, 1968; Turner and Kitchen, 1968) and more recently with a homograft aortic valve (Littler, 1970). The numbers are still comparatively small, however, and a further case is reported in which the outcome was favourable for both mother and fetus.

Case Report

The patient, who was born in 1941, had an attack of rheumatic fever when aged 11 years. Eight years later she developed symptoms due to mitral stenosis, and underwent closed mitral valvotomy in 1961. Thereafter her cardiac state remained satisfactory until 1964, when there was a return of dyspnoea associated with the recent onset of atrial fibrillation. Signs of mitral regurgitation were present, with enlargement of the left ventricle on fluoroscopy (Fig. 1), and hypertension was recorded in both left atrium and pulmonary artery at cardiac catheterization. The recommendation was to proceed with mitral valve replacement, which was accomplished without incident in 1965, using a Starr-Edwards prosthesis with a bare metal cage. Substantial improvement resulted, with decrease in cardiac size (Fig. 2). Long-term anticoagulant therapy with warfarin was started.

The patient had married in 1964, but after valve replacement she was advised initially against pregnancy. She remained very anxious to have a family and became pregnant in September 1969. During the pregnancy she remained symptom-free, warfarin being continued without any untoward effects. Three weeks from term heparin was substituted for warfarin, which in turn was discontinued at the beginning of labour. This passed without incident, and she delivered spontaneously a full-time healthy infant in May 1970. Warfarin was resumed two days later, and the patient made an excellent recovery. A minor complication was an infected perineal haematoma, which responded to local treatment and antibiotic therapy. When seen six weeks after delivery both mother and child were well.

Comment

Because of the potential hazards associated with the additional burden of pregnancy in a patient with a valve prosthesis and on long-term anticoagulant therapy, we advised strongly against this in our patient for many years. We were

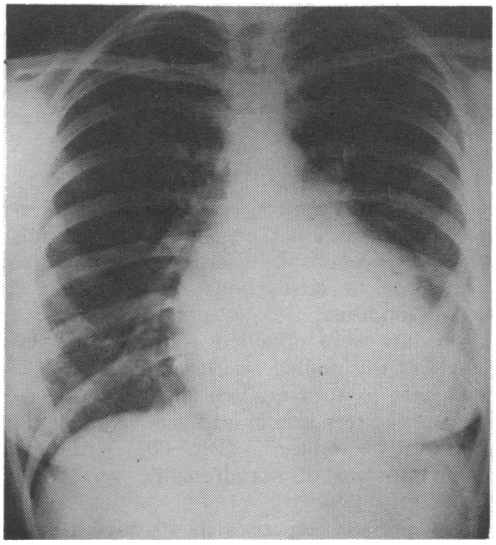

FIG. 1—Preoperative chest *x*-ray film, showing enlargement of both left atrium and left ventricle with pulmonary congestion.

Cardiothoracic Unit, Mearnskirk Hospital, Newton Mearns, Renfrewshire

JOHN M. REID, M.D., F.R.C.P.ED., Consultant Physician
R. S. BARCLAY, M.D., F.R.C.S.(ED., GLASG.), Surgeon