Brit. J. Pharmacol. (1956), **11**, 346.

THE EFFECT ON RESPIRATION OF INFUSIONS OF ADRENALINE AND NORADRENALINE INTO THE CAROTID AND VERTEBRAL ARTERIES IN MAN

BY

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(RECEIVED JUNE 27, 1956)

Intravenous injections of adrenaline and noradrenaline in man cause a striking increase in the rate and depth of respiration. This is associated with a fall in the alveolar CO_2 content and an increase in the respiratory minute volume. The hyperpnoea is abrupt in onset and does not appear to be accounted for by a general increase in metabolic rate (Whelan and Young, 1953).

The present experiments were carried out in an attempt to determine if the stimulant effect of adrenaline and noradrenaline on respiration in man is the result of a direct action on the respiratory or other centre in the brain.

METHODS

The subjects were patients on whom cerebral angiography was being carried out for diagnostic purposes. Following the first injection of contrast medium, an interval elapsed, while the films were developed and studied, before further injections were made. Advantage was taken of this interval to infuse small doses of adrenaline or noradrenaline and record their effects on respiration.

The patients lay supine with the head extended. The respiratory movements were recorded by means of two stethographs, one around the chest and the other around the abdomen (Shepherd, 1951 ; Dornhorst and Leathart, 1952). These were connected to a volume recorder which traced the movements with an ink writer on a kymograph drum.

Direct Infusion into the Common Carotid Artery.—Under local anaesthesia with 10–20 ml. of 1% (w/v) procaine, a needle, 9.5 cm. long and 2 mm. in external diameter with a short bevel, was inserted into the common carotid artery. The needle was connected to a mechanically-driven syringe by a length of polythene tubing. An infusion of 0.9% saline was maintained throughout at a rate of 4 ml./min. and was interrupted when required either for injection of contrast medium or for the infusion of adrenaline or noradrenaline solutions.

The contrast medium used was 35% (w/v) diodone given in quantities of 12 ml. for carotid angiograms and 14 ml. for vertebral angiograms. In one patient sodium acetrizoate (30% w/v) was used for the vertebral angiograms. The drug solutions were made up in sterile saline (containing 0.001% w/v ascorbic acid) from (—)-adrenaline tartrate (B.D.H. 1:1000) and (—)-noradrenaline tartrate (Levophed, Bayer) so that the minute dose was contained in 4 ml. The doses are expressed as weights of the salts. Adrenaline has been shown to remain stable in ascorbic acid saline for many hours (Gaddum, Peart, and Vogt, 1949).

Indirect Infusions into the Vertebral Artery.—In those patients on whom right-sided angiograms were being performed, once the direct common carotid infusion had been established the infusion was diverted into the vertebral artery as follows. A sphygmomanometer cuff around the right upper arm close to the axilla was inflated to 240 mm. Hg and pressure with the thumb was applied over the common carotid artery just above the position of the needle. The abolition of pulsations in the superficial temporal artery indicated successful occlusion of the common carotid. Injected fluid was thus diverted into the vertebral artery via the subclavian artery. This technique was similar to that described by Engeset (1948) and Ecker (1951), and resulted in varying amounts of contrast medium passing into the vertebral circulation.

Direct Infusion into the Vertebral Artery.—Vertebral angiograms and infusions were carried out through a needle inserted directly into the vertebral artery, the needle being passed between the transverse processes of the fourth and fifth cervical vertebrae (Fig. 1), after the manner described by Sugar, Holden, and Powell (1949) and Lindgren (1950). Five patients were under light general anaesthesia (N_2O and O_2) but were breathing naturally and did not require assisted respiration at any time. In one patient the procedure was carried out under local anaesthesia with 1% (w/v) procaine.

RESULTS

Intra-carotid Infusions.—In four patients adrenaline was infused at rates ranging from 0.01 to

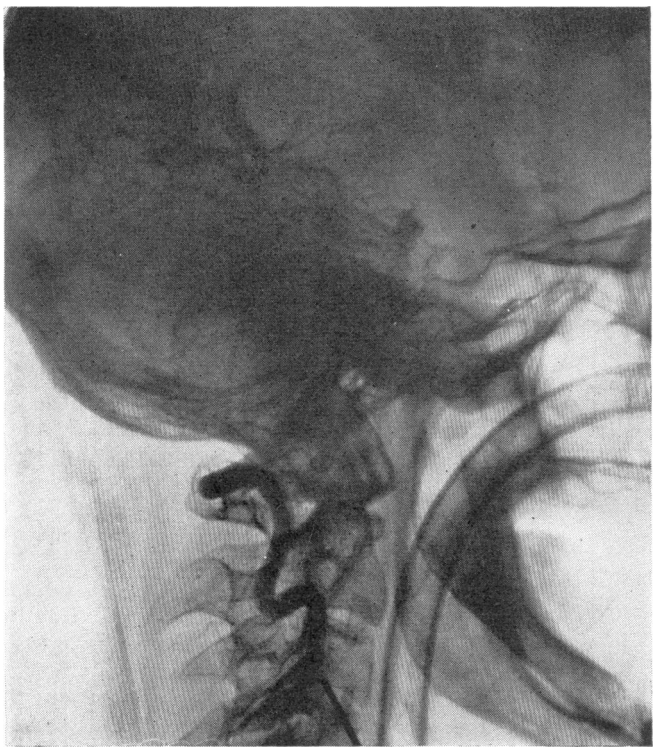

FIG. 1.—Angiogram made during infusion of adrenaline 1 μg./min. into the right vertebral artery in patient S. T. 14 ml. 35% diodone was injected.

5 μg./min. into the left common carotid artery, and in five other patients adrenaline or noradrenaline or both were given at rates of 1–2 μg./min. into the right common carotid artery. The pattern of respiration was not altered by any of these infusions. In two of the patients an infusion of 10 μg./min. was given ; this produced not only an increase in the depth and rate of respiration, but was accompanied by pallor, an increased pulse rate and palpitation, and was probably due to the drug passing into the general circulation, since this rate of infusion produces the same general effects when given intravenously (Barcroft and Swan, 1953).

Indirect Vertebral Infusions.—In preliminary experiments, which have been reported elsewhere (Duff, Shepherd, and Whelan, 1954), it was found that the diversion of adrenaline infusions from the common carotid into the vertebral artery by the technique described above resulted in stimulation of respiration. It has subsequently been found, however, that pressure alone over the common carotid artery caused, in four out of five patients, an increase in rate and depth of respiration. In the fifth patient neither the pressure alone nor pressure during adrenaline infusion had any effect on the respiratory pattern. Thus the effects of adrenaline infusions diverted into the vertebral artery by carotid occlusion could not be differentiated from the effects of carotid occlusion alone. This method of infusing the vertebral artery was, therefore, abandoned in favour of direct puncture of the vertebral artery itself.

Direct Vertebral Infusions.—Six patients requiring vertebral angiography were studied, and in no case did adrenaline or noradrenaline have any effect on the respiration when infused directly into the vertebral artery in doses of 1–2 μg./min. Fig. 2 (S.T.) shows the records obtained in the patient whose angiogram taken during the adrenaline infusion is illustrated in Fig. 1. In Fig. 2 (J. M.) the contrast medium sodium acetrizoate was used to obtain the angiogram, and injection of this had a transient inhibitory effect on the respiration. In Fig. 2 (R. G.) the respiratory record obtained during infusion of adrenaline directly into the vertebral artery at 2 μg./min. is compared with that during intravenous infusion at 10 μg./min. five minutes later. The intravenous infusion of adrenaline caused an increase in the rate and depth of respiration similar to that seen in conscious subjects, but infusion into the vertebral artery had no such effect.

In a seventh patient an attempt was made to eliminate the likelihood of streaming of the infused drug solution by giving as a single sudden injection 10 ml. of a solution of adrenaline in a concentration of 10 μg./litre into the vertebral and the internal carotid arteries. Before each injection 8 or 10 ml. of contrast material was injected in 3 seconds and shown by *x*-ray to fill the vessel and its branches. Adrenaline solution was then injected in the same way and in the same time, and presumably also filled the vessel and its branches. Ten ml. of saline alone was also injected as a control. Neither the adrenaline solution nor the saline caused any alteration in the respiration, though the major branches at least of the injected vessel were filled with the adrenaline solution, of a concentration greater than that calculated as likely to arrive in the arterial blood during an intravenous infusion at 10–20 μg./min.

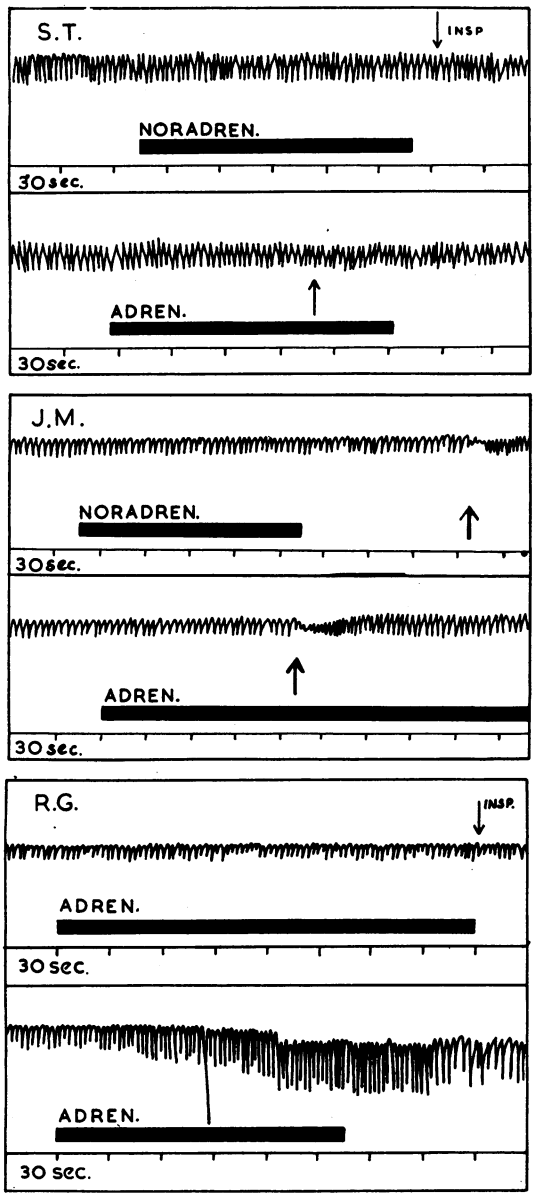

FIG. 2.—S. T.: Records of respiratory movements (inspiration downwards) during infusions of adrenaline and noradrenaline into the vertebral artery under light general anaesthesia. The black rectangles represent the duration of infusions and the arrow beneath the respiratory record indicates the time of injection of contrast (diodone). J. M.: Lightly anaesthetized patient. Contrast injected at arrows was sodium acetrizoate. R. G.: Comparison of the effect of intravertebral infusion of adrenaline (upper frame) and intravenous infusion (lower frame) 5 min. later in the same patient.

DISCUSSION

Stimulation of the respiration in man by the intravenous infusion of adrenaline has been noted by many workers (Tompkins, Sturgis, and Wearn, 1919; Lyman, Nicholls, and McCann, 1923; Cori and Buchwald, 1930; and Courtice, Douglas, and Priestley, 1939), but no explanation of this effect has been put forward.

Reale, Kappert, Skoglund, and Sutton (1950) reported an increase in the rate and depth of respiration with noradrenaline and attributed the increased amplitude to a compensatory reaction to decreased lung volume.

In a comparison of the effects of adrenaline and noradrenaline on respiration, Whelan and Young (1953) found that both amines had essentially the same stimulant effect on ventilation, but that the effect on oxygen consumption was very different, adrenaline causing an increase of about 32% whereas noradrenaline had no consistent effect. This difference in action of the two amines, associated with the abrupt onset of hyperpnoea within a minute or less of starting the infusion, made it unlikely that the increase in respiration was caused by a general increase in metabolism.

It is clear from the present results that adrenaline and noradrenaline infusions of 1–2 μg./min. into the common carotid and vertebral arteries in man have no effect on respiration. A stimulation of respiration is, however, brought about by intravenous infusion of 10–20 μg./min. of adrenaline. With a cardiac output of five litres/min. this represents an arterial blood concentration of 2–4 μg./litre. An infusion of 2 μg./min. into the vertebral artery represents a blood concentration of about 10 μg./litre if one assumes a total cerebral blood flow of 800 ml./min. (Kety and Schmidt, 1948) and the flow through one vertebral artery to be one quarter of this. The doses infused (1–2 μg./min.) were thus in excess of the amount calculated to arrive via the vertebral or internal carotid artery during intravenous infusions.

The injection of contrast medium during the infusion of the amines served to demonstrate that the needle was in fact inserted into the carotid or vertebral artery. It did not necessarily follow that the branches of the vessel outlined by the contrast were also perfused by the drug solution. This may well have had a different distribution on account of the differing dynamic effects of the two forms of introduction of the substances into the vessels.

In the present discussion the assumption is made that there is complete mixing of the drug infusion with the blood stream. It is, however, theoretically possible that laminar flow in the vessels might

have resulted in the occasional failure of adrenaline or noradrenaline to enter the branch supplying the respiratory centre or carotid body. While it is not possible to say whether such an occurrence accounts for the negative results of the present study, it is felt that it is unlikely to have taken place on every occasion on which the drugs were infused, particularly since the position of the needle in the artery varied slightly from experiment to experiment and even during the course of many of the experiments. Furthermore, the effect of single sudden injections of adrenaline solution in one patient was no different from that of the slower infusions.

It is therefore reasonable to conclude that the stimulant effects of intravenous infusions of adrenaline or noradrenaline cannot be attributed to a direct effect on a cerebral centre, and an indirect mechanism must be sought. Possibilities to be considered are stimulation of chemoreceptors in the carotid body or elsewhere, changes in blood pressure brought about by these amines, or a secondary release of a hormone or metabolite, or even a breakdown product of the amine itself. A reflex effect from the stimulation of the carotid body might have been expected during the intracarotid infusions. The rise in systolic arterial pressure during intravenous adrenaline infusions at 10 μg./min. is only 5–10 mm. Hg (Barcroft and Swan, 1953) and the mean pressure either falls or shows no change. Noradrenaline increases both the systolic and diastolic pressures by about 5–10 mm. Hg. It seems unlikely that these alterations in pressure could be responsible for the marked respiratory changes seen to a similar degree with both amines.

During the intravenous infusion of adrenaline there is an increase in the concentration of lactic acid in the peripheral venous blood (Bearn, Billing, and Sherlock, 1951 ; Barcroft and Cobbold, 1956). While the increase in lactate might account for the respiratory stimulant effect of adrenaline it cannot account for the effect of noradrenaline since there is no significant increase in the peripheral venous lactic acid concentration during infusion of the latter amine (Bearn, Billing, and Sherlock, 1951).

Bradley, Gaskell, Holland, Lee, and Young (1954) found no lowering of the arterial plasma *p*H during intravenous infusions of adrenaline in the human subject; on the contrary, an increase accompanied the hyperpnoea. They considered that the stimulant effect of adrenaline on respiration could not be the result of release of acid products of metabolism. From their studies on anaesthetized animals these workers concluded that the stimulation of respiration by adrenaline was not a direct action on the respiratory centre but due to a reflex from the thoracic region (Bradley *et al.*, 1953).

The results of the present experiments demonstrate that in the conscious or lightly anaesthetized human subject the stimulant action of adrenaline and noradrenaline on the respiration is not due to a direct action on the respiratory or other centre in the brain receiving its blood supply from the carotid or vertebral arteries.

Summary

1. Infusions of adrenaline and noradrenaline into the common carotid and the vertebral arteries during cerebral angiography in man did not cause any alteration in the respiratory pattern.

2. Angiograms taken during the drug infusions outlined the arteries and their branches.

3. It is concluded that the respiratory stimulant effect of adrenaline and noradrenaline when given intravenously cannot be a result of direct stimulation of a controlling centre receiving its blood supply from the carotid or vertebral vessels.

We wish to thank Professor H. Barcroft, F.R.S., at whose suggestion this work was initiated during the tenure by one of us (R. F. W.) of a Research Fellowship at the Sherrington School of Physiology, St. Thomas's Hospital.

We thank Dr. E. A. Carmichael and Dr. J. Bull, of the National Hospital, Queen Square, London, and the late Mr. C. Calvert, Royal Victoria Hospital, Belfast, for facilities and access to their patients, and Sister E. H. Wilson and Miss M. L. Madden for their valuable help. We are grateful to Professor A. D. M. Greenfield and Professor H. Barcroft for advice and encouragement and for reading the manuscript.

(D. R. Coles held a Medical Research Council Fellowship in Clinical Research during the course of this investigation.)

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