J. Physiol. (1954) 124, 213–218

THE ACID-BASE CHANGES IN ARTERIAL BLOOD DURING ADRENALINE HYPERPNOEA IN MAN

By R. D. BRADLEY, P. GASKELL, W. W. HOLLAND, G. de J. LEE and I. MAUREEN YOUNG

From the Departments of Physiology and Medicine, St Thomas's Hospital, London

(*Received* 17 *August* 1953)

It has been suggested previously by Reale, Kappert, Skoglund & Sutton (1950) and by Whelan & Young (1953) that the stimulating action of adrenaline on breathing in man is independent of the accompanying increase in general metabolic rate, for equivalent doses of noradrenaline giving comparable stimulation of respiration scarcely altered the overall oxygen consumption. The present investigation was undertaken to determine whether metabolic changes, too small to be detected by oxygen consumption studies, but large enough to increase the hydrogen-ion concentration of the blood, could be responsible for this stimulation of respiration by adrenaline.

METHODS

Nine male volunteers were studied. Each was rested for at least 30 min before the experiment began. An intravenous saline-ascorbic acid infusion was set up in one arm (0·9% NaCl with 0·001% ascorbic acid maintained at a rate of 4 ml./min by a mechanically driven syringe). A Cournand indwelling needle was inserted into the brachial artery of the other arm for collection of arterial samples. Respiratory tracings were obtained with a float recorder connected to two stethographs, one round the chest and the other round the abdomen; this combined movement of the chest and abdomen bears a linear relationship to the tidal volume (Dornhorst & Leathart, 1952).

When the respiratory tracing had been steady for 10 min the saline infusion was changed to an infusion of L-adrenaline tartrate B.D.H., made up in the saline ascorbic acid mixture, at the rate of 20 μg/min for 10 min. 20 ml. of arterial blood was taken anaerobically 1 min before the infusion of adrenaline began, 3, 6 and 9 min after the beginning of the infusion, and 3 min after the end of the infusion. In some experiments smaller samples were taken at more frequent intervals. The collection of each 20 ml. of arterial blood took 15 sec and was made into syringes containing 4 drops of heparin-fluoride (100 mg NH_4F in 2·5 ml. Evan's heparin 1000 i.u./ml.), glass beads for subsequent mixing and liquid paraffin; they were immediately capped and stored in ice. The following determinations were made on these samples:

(1) pH was measured on 0·005 ml. samples of whole blood using the capillary glass electrode of Claff & Swensen (1944). The measurements were made at room temperature and corrections to 37° C made by Rosenthal's factor (1948).

(2) The total carbon dioxide in whole blood was determined on 1 ml. samples by the method of Van Slyke & Neill (1924).

(3) The carbon dioxide combining capacity of the samples was compared by equilibrating 5 ml. aliquots with a gas mixture of 5·6 % CO_2 in oxygen, in tonometers in a water-bath at 37° C. The carbon dioxide contents were again determined on 1 ml. whole blood samples by Van Slyke & Neill's method.

(4) Haematocrit measurements were made in Wintrobe tubes, spun at 2000 rev/min for 30 min.

(5) The total plasma carbon dioxide and the carbon dioxide combining capacity were determined from the whole blood values and the haematocrit readings using the nomograms of Van Slyke & Sendroy (1928).

(6) CO_2 tensions were obtained from the Henderson–Hasselbalch equation using the values for pH and total CO_2 content of plasma.

(7) Plasma sodium and potassium determinations were made with a Barclay flame photometer using lithium as an internal standard.

RESULTS

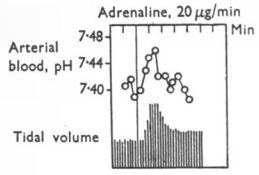
The stethograph records showed that, as previously described by Whelan & Young (1953), the adrenaline infusions caused a stimulation of respiration characterized by abrupt onset of hyperpnoea, and an increase in tidal volume, and an acceleration of respiration was observed in the more sensitive subjects. The onset of the stimulation occurred approximately 1 min after the beginning of the adrenaline infusion, and was maintained for 4 min, gradually diminishing throughout the remainder of the infusion period. Fig. 1 (subjects 1, 4, 8 and 9) shows that the changes in the acid-base chemistry of the arterial blood were related to this pattern of respiratory stimulation; these were similar in all the subjects studied.

During the first 5 min of the infusion period the pH of the arterial blood was elevated by 0·03–0·10 unit, the total carbon dioxide content of the plasma fell 1–2 m.equiv/l. and the calculated tension of carbon dioxide was smaller than the resting values by 3–8 mm Hg. During the second half of the infusion, as the respiratory stimulation diminished, the plasma pH, total carbon dioxide content and carbon dioxide tension approached the resting value again.

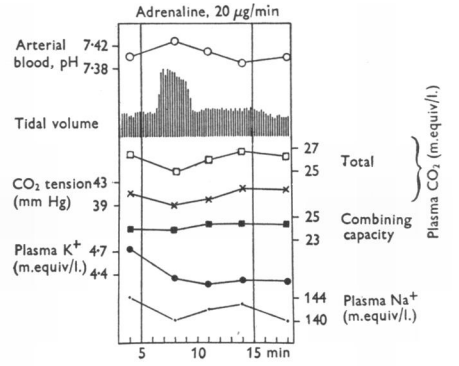
The carbon dioxide combining capacity did not show such uniformity of pattern. In two of the subjects (data for subject 8 in Fig. 1) it was unaltered throughout the experimental period. Of the remaining five subjects in which it was estimated, there was an elevation of the carbon dioxide combining capacity of 0·5–4 m.equiv/l. in four (data for subject 4 in Fig. 1) and a fall of 2 m.equiv/l. in one subject (9) during the first 5 min of the infusion. During the second half of the infusion period values for carbon dioxide combining capacity 1–5 m.equiv/l. below the resting levels were found in these five subjects. Three minutes after the end of the infusion the carbon dioxide combining capacities were returning towards, but were not equal to, the resting values.

Plasma sodium and potassium determinations were made in three subjects only (data for subjects 8 and 9 in Fig. 1). In all three the plasma potassium

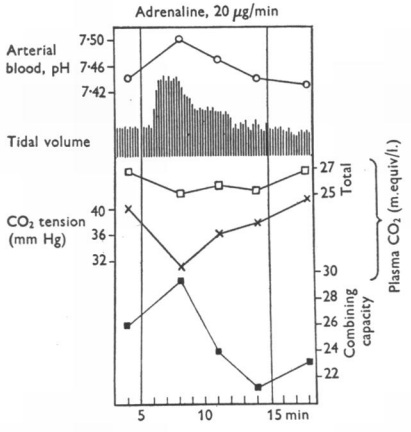
fell 0·3–0·7 m.equiv/l. during the infusion. In subjects 8 and 9 there was a fall in plasma sodium during the first half of the infusion, followed by a return towards the resting value at the end of the infusion and a further fall 3 min



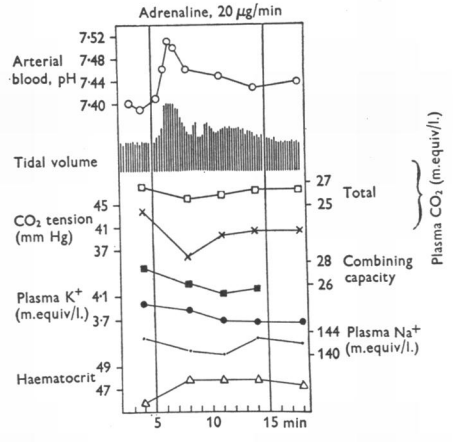
Subject 1. Resting respiratory rate 17/min and no change at height of respiratory stimulation.



Subject 8. Resting respiratory rate 18/min and decreased to 8/min at height of maximum respiratory stimulation.



Subject 4. Resting respiratory rate 13/min and increased to 21/min at height of respiratory stimulation.



Subject 9. Resting respiratory rate 17/min and increased to 20/min at height of maximum respiratory stimulation.

Fig. 1. Acid-base changes in arterial blood during the infusion of L-adrenaline, 20 μg/min for 10 min. The respiratory tracings are recorded in these diagrams every 10 sec and any alteration in rate is indicated under each subject.

after the end of the infusion. The pattern was similar in subject 6 (not shown) with the exception of the rise in plasma sodium during the first half of the infusion. These sodium changes lie on the limit of the experimental error of the technique.

DISCUSSION

It is clearly shown that the stimulating action of adrenaline on respiration is not initiated by the release of acid metabolites into the blood stream; no fall in pH of the arterial blood was observed even when samples were taken at 20 sec intervals during the initial period of the infusion (subjects 1 and 9). The hyperpnoea itself is probably responsible for the rise in pH, the fall in the total CO_2 content and the fall in CO_2 tension of the arterial blood during the first half of the infusion; moreover, these secondary changes correspond with the fall in alveolar CO_2 tension observed by Lyman, Nicholls & McCann (1923) and Whelan & Young (1953) during respiratory stimulation by adrenaline. The stimulation of respiration by adrenaline would therefore appear to be due to a direct action of the drug itself on the sensory-motor system controlling respiration. Alternatively, it is possible that the adrenaline may, in fact, be acting by producing acid metabolites and that they are acting locally, before demonstrable quantities are released into the blood stream. However, whether the sensory-motor respiratory system is stimulated directly by adrenaline, or by acid metabolites released by this drug, it adapts to the stimulating agent within 5 min.

The rise in carbon dioxide combining capacity during the first half of the infusion, in four subjects, remains unexplained. Two possible causes were suggested: the first, was that this rise formed part of a general biphasic alteration in plasma electrolytes in response to the adrenaline infusions. D'Silva (1934) and Brewer, Larsen & Schroeder (1939) have shown, in cats and dogs, that adrenaline infusions cause an immediate rise in plasma potassium, which is then followed by a fall. A fall in plasma potassium was always observed throughout our experiments. The second possibility was that the hyperventilation caused haemoconcentration by excessive loss of water from the lungs. Repeated haematocrit readings were not made in subject 4, but haemoconcentration did not account for the rise in carbon dioxide combining capacity found in another subject showing a rise in carbon dioxide combining capacity.

The fall in carbon dioxide combining capacity seen during the second half of the adrenaline infusions is more readily explained. It may be related to three mechanisms: first, the release of acid metabolites into the blood stream; Bearn, Billing & Sherlock (1951) have shown that the blood lactate is significantly increased after 10 min of a comparable adrenaline infusion. Secondly, the fall in carbon dioxide combining capacity may be secondary to the hyperventilation for Anrep & Cannon (1923), Nims, Gibbs & Lennox (1942), and Stanbury & Thompson (1952) have observed a decrease in plasma bicarbonate during over-ventilation both in man and experimental animals and have suggested that the tissues supply organic acid to offset the alkalaemia before

the renal mechanisms come into play. Lastly, the fall in carbon dioxide combining capacity may be part of an overall fall in plasma electrolytes which occurs during this period of the infusion; a fall in both the plasma sodium and potassium was observed. These changes in plasma potassium are in accord with the previous findings in man and in animals where continuous infusions or intramuscular injections of adrenaline were given (Castleden, 1937; Keys, 1938; Brewer *et al.* 1939). Stanbury & Thompson (1952) found a similar depression in the plasma potassium during voluntary hyperventilation in man.

SUMMARY

1. The stimulation of respiration by adrenaline, given intravenously at the rate of 20 μg/min in the human subject, was not initiated by a fall in plasma pH.

2. The adrenaline infusions were accompanied by a rise in plasma pH of 0·03–0·10 unit and a fall in plama CO_2 tension of 3–8 mm Hg. These changes are considered to be secondary to the hyperpnoea.

3. The plasma carbon dioxide combining power did not fall until the second 5 min of the infusion period. At this time the maximum hyperventilation was over and the plasma pH and CO_2 tension were returning to their resting values.

4. It is suggested that the stimulating action of adrenaline on respiration is not due to an altered composition of the blood accompanying any metabolic change, but is largely due to a direct action on the sensory-motor system controlling respiration.

We wish to thank Prof. H. Barcroft for suggesting the problem and for much encouragement. We are also indebted to Dr A. C. Dornhorst for advice, to the students and colleagues who acted as subjects and to Mr G. T. Hales for technical assistance. Part of the expenses were defrayed from an M.R.C. grant to Prof. Barcroft. P. Gaskell was holder of a Life Insurance Medical Research Fellowship.

REFERENCES

Anrep, G. V. & Cannon, R. K. (1923). The concentration of lactic acid in the blood in experimental alkalaemia and acidaemia. *J. Physiol.* **58**, 244–258.

Bearn, A. G., Billing, B. & Sherlock, S. (1951). The effect of adrenaline and noradrenaline on hepatic blood flow and splanchnic carbohydrate metabolism in man. *J. Physiol.* **115**, 430–441.

Brewer, G., Larsen, P. S. & Schroeder, A. R. (1939). On the effect of epinephrine on blood potassium. *Amer. J. Physiol.* **126**, 708–712.

Castleden, L. I. M. (1937). The effect of adrenaline on the serum potassium level in man. *Clin. Sci.* **3**, 241–245.

Claff, C. L. & Swensen, O. (1944). Micro glass electrode technique for determination of hydrogen ion activity of blood and other biological fluids. *J. biol. Chem.* **152**, 519–522.

Dornhorst, A. C. & Leathart, G. L. (1952). A method of assessing the mechanical properties of lungs and air-passages. *Lancet*, ii, 109.

D'Silva, J. L. (1934). The action of adrenaline on serum potassium. *J. Physiol.* **82**, 393–398.

Keys, A. (1938). The response of the plasma potassium level in man to the administration of epinephrine. *Amer. J. Physiol.* **121**, 325–330.

LYMAN, R. S., NICHOLLS, E. & MCCANN, W. S. (1923). The respiratory exchange and blood sugar curves of normal and diabetic subjects after epinephrin and insulin. *J. Pharmacol.* **21**, 343–365.

NIMS, L. F., GIBBS, E. L. & LENNOX, W. G. (1942). Arterial and cerebral venous blood changes produced by altering arterial carbon dioxide. *J. biol. Chem.* **145**, 189–195.

REALE, A., KAPPERT, A., SKOGLUND, C. & SUTTON, G. C. (1950). The effect of L-noradrenaline on the oxygen consumption of human beings. *Acta physiol. scand.* **20**, 153–159.

ROSENTHAL, T. B. (1948). The effect of temperature on the pH of blood and plasma *in vitro*. *J. biol. Chem.* **173**, 25–30.

STANBURY, S. W. & THOMPSON, A. E. (1952). The renal response to respiratory alkalosis. *Clin. Sci.* **11**, 357–374.

VAN SLYKE, D. D. & NEILL, J. M. (1924). The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. I. *J. biol. Chem.* **61**, 523–573.

VAN SLYKE, D. D. & SENDROY, J. (1928). Studies of gas and electrolyte equilibria in blood. XV. *J. biol. Chem.* **79**, 781–798.

WHELAN, R. F. & YOUNG, I. M. (1953). The effect of adrenaline and noradrenaline infusions on respiration in man. *Brit. J. Pharmacol.* **8**, 98–102.