J. Physiol. (1952) 118, 520–527

CAROTID CHEMOCEPTOR IMPULSE ACTIVITY DURING INHALATION OF CARBON MONOXIDE MIXTURES

By HELEN N. DUKE, J. H. GREEN and E. NEIL

From the Department of Physiology, Royal Free Hospital School of Medicine, London and the Department of Physiology, Middlesex Hospital Medical School, London

(*Received* 3 *June* 1952)

Spontaneous respiration of small concentrations (e.g. 1–2%) of carbon monoxide in air or oxygen causes a progressive formation of carboxyhaemoglobin, thereby reducing the blood oxygen content. Providing that the decrease in oxygen carrying power of the blood is not too great, spontaneous respiration is maintained and consequently the arterial oxygen tension can be but little affected. It is of interest, therefore, to examine the impulse activity of the chemoceptor nerve fibres in such conditions, where despite a decrease in blood oxygen content the arterial oxygen tension does not undergo a significant change.

In addition, we have investigated whether carboxyhaemoglobinaemia modifies the chemoceptor response to the lowering of arterial oxygen tension produced by the inhalation of 5% O_2 in N_2.

METHODS

Seven successful experiments were carried out using cats anaesthetized with chloralose (50 mg/kg) and urethane (250 mg/kg body weight) given intraperitoneally. The trachea was cannulated, and connected to inspiratory and expiratory water valves. Suitable gas mixtures were administered via the inspiratory valve. The carotid artery or the femoral artery which was used for the registration of arterial blood pressure was connected to a condenser manometer (devised by H. W. Ead) coupled to a cathode-ray oscillograph.

The carotid sinus nerve was dissected and cut centrally. Most of the baroceptor fibres were removed by thinning the nerve, the chemoceptor fibres being preserved. All dissections were performed with the aid of a binocular microscope, care being taken to avoid damage to the arterial blood supply and venous drainage of the carotid body. The nerve twig was laid on non-polarizable electrodes and the impulse activity recorded via a resistance-capacity coupled amplifier connected to a second cathode-ray tube. Simultaneous photographic records were taken of the systemic arterial blood pressure, the electroneurogram and a time marker.

The opposite femoral artery was cannulated; samples of blood were removed at intervals and

the CO content determined, using the Hartridge reversion spectroscope (1912). A preliminary experiment was always carried out in which the chemoceptor response to anoxic anoxia was tested by allowing the animal to breathe 5% O_2 in N_2. Unless a vigorous response was obtained under these conditions, the preparation was discarded.

Two series of experiments were performed: (1) after a preliminary period of spontaneous respiration of room air, 1 or 2% CO in air was substituted as the inspiratory gas mixture; (2) after a preliminary period of spontaneous respiration of oxygen, 1 or 2% CO in oxygen was inhaled.

After inhalation of the carbon monoxide mixtures the chemoceptor response to a reduction of the blood oxygen tension was examined by allowing the animal to breathe 5% O_2 in N_2. In some experiments a mixture of 5% O_2 plus 1–2% CO in N_2 was used. Chemoceptor impulse activity was finally recorded during inhalation of oxygen.

RESULTS

I. *Chemoceptor response of cats breathing* 1 *or* 2% CO *in air*

The experimental findings were clear-cut. No chemoceptor discharge in excess of that occurring during control inhalation of air was seen during carbon monoxide inhalation, providing that the percentage saturation of the haemoglobin with CO did not exceed 75–80. This degree of CO saturation was not exceeded during periods of 10–15 min inhalation of 2% CO or 20–25 min inhalation of 1% CO.

Fig. 1 shows the records obtained from a typical experiment. It will be observed that Fig. 1C obtained after 11 min inhalation of 2% CO (CO saturation = 73%) shows no evidence of excessive chemoceptor discharge. Fig. 1D obtained 4 min after the end of inhalation of the carbon monoxide shows that reduction of the arterial oxygen tension induced by the inhalation of 5% O_2 in N_2 is fully capable of eliciting chemoceptor impulses. Substitution of 100% O_2 as the inspired gas led to a rapid disappearance of the chemoceptor action potentials.

When the period of inhalation of the CO + air mixture was unduly prolonged so that more than 80% of the blood haemoglobin was combined with carbon monoxide, failure of the vital centres resulted from inadequate supply of oxygen. Respiration was depressed and finally ceased; the blood pressure and heart rate fell. At this stage the chemoceptor impulse activity became marked owing to the fall of arterial oxygen tension and to the reduction of blood flow through the carotid body.

II. *Chemoceptor response of animals breathing* 1 *or* 2% CO *in oxygen*

The high oxygen tension of such mixtures caused the following modifications in the response:

(*a*) It increased the competition of oxygen for haemoglobin and thereby slowed the rate of formation of carboxyhaemoglobin. Consequently, the period of inhalation required to produce a desired concentration of carboxyhaemoglobin was somewhat longer on the CO + O_2 mixtures than was the case with those made with CO + air.

(*b*) It increased the amount of dissolved oxygen in the arterial blood. Hence the animal was able to maintain spontaneous respiration even when as much as 90% of the blood haemoglobin had been converted to carboxyhaemoglobin.

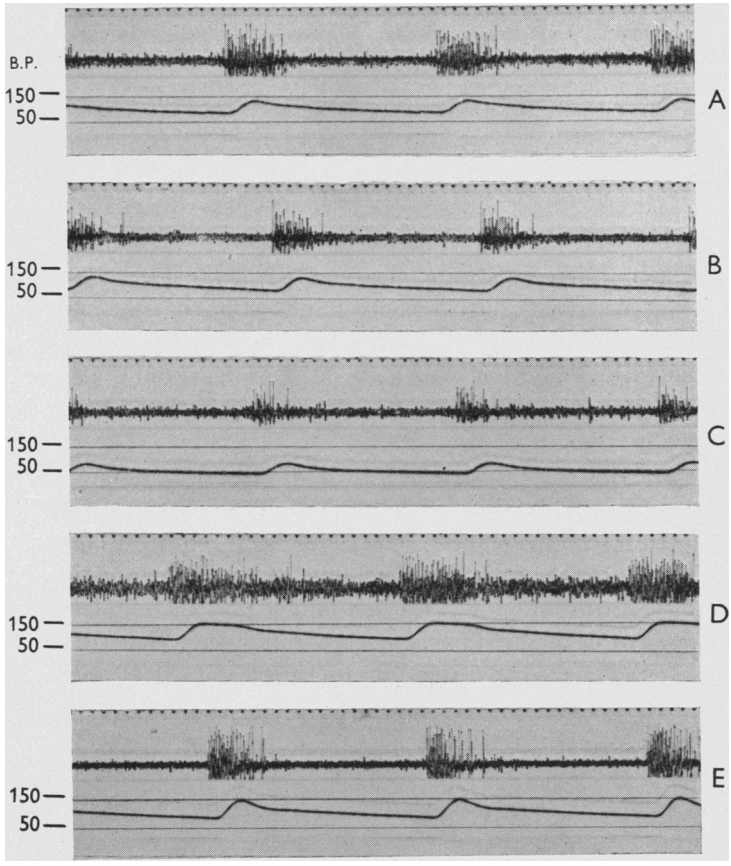

Fig. 1. Cat, 3·1 kg, chloralose–urethane anaesthesia. Spontaneous respiration. Left carotid sinus nerve cut centrally; most baroceptor fibres removed by dissection. Right femoral artery cannulated for recording blood pressure. Records on each film strip from above downwards. Time (50 c/s), electroneurogram and arterial blood pressure. Blood-pressure calibrations (mm Hg) are shown on left of each film strip. A: breathing air. B: after 3 min breathing 2% CO in air. C: after 11 min breathing 2% CO in air (CO saturation = 73%). D: after 4 min breathing 5% O_2 in N_2. E: after 1 min breathing 100% O_2. Note the very slight chemoceptor activity in C compared with the intense discharge in D.

With these reservations the results obtained in the $CO + O_2$ series were the same as those reported for animals breathing CO + air mixtures. Fig. 2 illustrates an experiment in which the cat breathed 1% CO in O_2. The carotid nerve twig consisted of chemoceptor fibres only. After 30 min inhalation of

the gas mixture 70% of the blood haemoglobin was converted to carboxy-haemoglobin but the impulse activity (Fig. 2D) did not exceed that seen in the control period (Fig. 2B). Following Fig. 2D the animal was allowed to

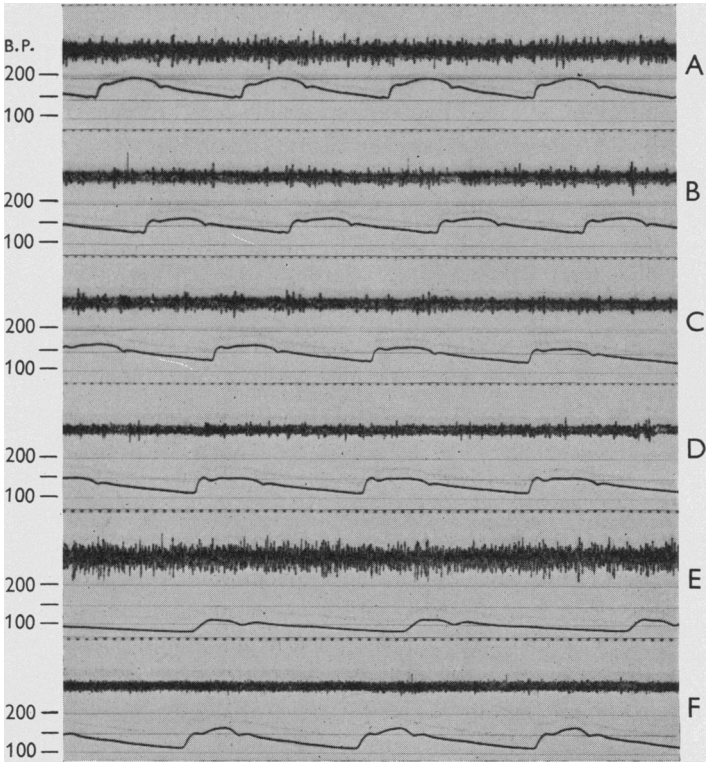

Fig. 2. Cat, 3·8 kg, chloralose–urethane anaesthesia. Spontaneous respiration. Left carotid sinus nerve cut centrally; all baroceptor fibres removed by dissection. Right carotid artery cannulated for recording blood pressure. Records on each strip from above downwards: time (50 c/s), electroneurogram and arterial blood pressure. Blood-pressure calibrations (mm Hg) are shown on left of each film strip. A: breathing 5% O_2 in N_2. B: breathing 100% O_2 (note reduction of chemoceptor activity). C: after 5 min breathing 1% CO in O_2 (CO saturation = 25%). D: after 30 min breathing 1% CO in O_2 (CO saturation = 70%). After 31 min inhalation of 1% CO in O_2, 5% O_2 in N_2 was substituted as the inspired gas. E: after 5 min breathing 5% O_2 in N_2 (CO saturation = 76%). F: after 2 min breathing 100% O_2. Note the very slight chemoceptor activity in D compared with the intense discharge in E.

breathe 5% O_2 in N_2 for 2 min, and a massive chemoceptor discharge developed in response to the reduction in oxygen tension (Fig. 2E), although no change in the carboxyhaemoglobin content of the blood had occurred. It will be noted that the chemoceptor impulse activity at this stage exceeded that shown in Fig. 2A, which was recorded during the inhalation of 5% O_2 before any

carbon monoxide had been inhaled. This discrepancy may probably be ascribed to the difference in the carotid body blood flow in the two conditions. Landgren & Neil (1951) have shown that a reduction of the blood flow through the chemoceptor tissues produced by a fall of systemic blood pressure leads to an increase in the chemoceptor discharge. The mean systemic blood pressure in Fig. 2A was 175 mm Hg and the heart rate 175/min; the mean blood pressure in Fig. 2E was 80 mm Hg and the heart rate 125/min. It is likely that the lower blood pressure in Fig. 2E was responsible for the greater chemoceptor activity. Substitution of pure oxygen as the inspiratory gas, by increasing the arterial pO_2 led to a disappearance of chemoceptor impulses; at the same time there was a rapid recovery of the systemic blood pressure (Fig. 2F).

The experiments illustrated by Figs. 1 and 2 indicate that animals in which 70–80% of the blood haemoglobin is combined with carbon monoxide can still show a chemoceptor response to a reduction of arterial oxygen tension when 5% O_2 in N_2 *replaces* the CO + air or CO + O_2 mixtures as the inspired gas. It is possible, however, that the small carbon monoxide tension of 7–14 mm Hg in the inspired gas mixtures might depress the response to a lowered arterial oxygen tension when such occurs *simultaneously* with the inhalation of carbon monoxide. This suggestion was tested by allowing animals to breathe 2% CO in O_2 for suitable periods and then substituting a mixture of 2% CO + 5% O_2 in N_2; an approximately unchanged carbon monoxide tension was thus maintained throughout the period of lowered oxygen tension. Fig. 3 shows the results of such an experiment. After 20 min inhalation of 2% CO in O_2, 82% of the blood haemoglobin had been converted to COHb, but the chemoceptor activity had undergone no significant change (Fig. 3D). The animal then breathed 2% CO + 5% O_2 in N_2 for 3 min; Fig. 3E shows the intense chemoceptor discharge which resulted. Obviously the chemoceptor response to a lowered oxygen tension had not been depressed by the maintenance of the previous level of blood carbon monoxide tension. Substitution of 100% O_2 as the inspired gas led to a great reduction in chemoceptor discharge after 2 min (Fig. 3F).

DISCUSSION

Saturation of 70–80% of the blood haemoglobin with CO produced by spontaneous respiration of 1 or 2% CO mixtures in air or oxygen causes no carotid chemoceptor excitation. Thus changes of blood oxygen content of this order are themselves incapable of exciting the carotid chemoceptors so long as the arterial oxygen tension is approximately maintained. When the arterial oxygen tension is deliberately reduced by allowing these animals to breathe 5% O_2 in N_2, chemoceptor impulse activity increases markedly, illustrating that even severe degrees of carboxyhaemoglobinaemia do not depress the ability of the chemoceptors to respond to a fall of oxygen tension. Moreover, the excitation

of the chemoceptors by a lowered O_2 tension occurs whether the blood carbon monoxide tension is maintained or not.

It is necessary to stress that the absence of chemoceptor discharge when these animals breathe 1 or 2% CO in air or oxygen depends on the maintenance

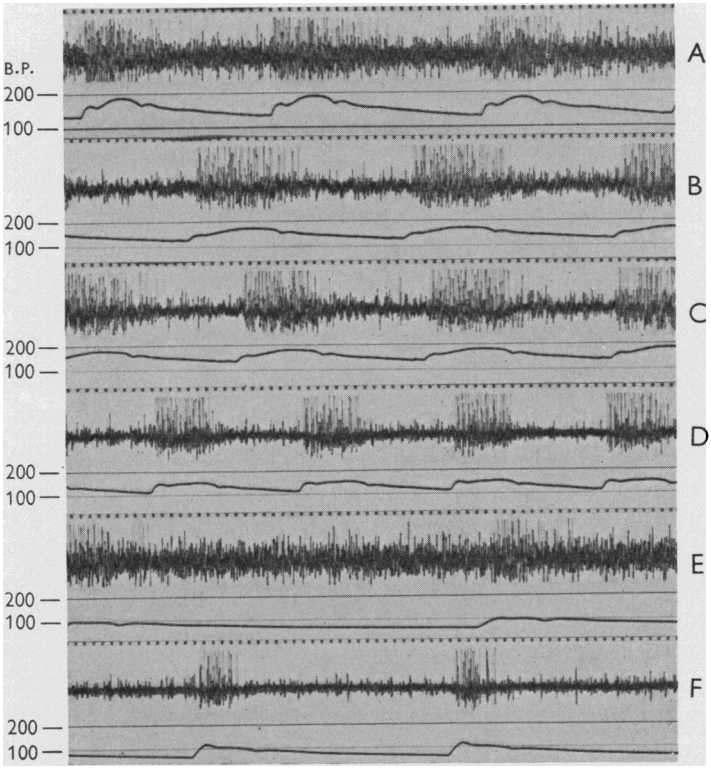

Fig. 3. Cat, 3·4 kg, chloralose–urethane anaesthesia. Spontaneous respiration. Left carotid sinus nerve cut centrally, most baroceptor fibres removed by dissection. Right carotid artery cannulated for recording blood pressure. Records on each film strip from above downwards as in Fig. 2. A: breathing 5% O_2 in N_2. B: breathing 100% O_2 (note reduction in chemoceptor activity). C: after 5 min breathing 2% CO in O_2 (CO saturation = 56%). Subsequently the amplifier became noisy, and was replaced by another calibrated to give the same gain. D: after 20 min breathing 2% CO in O_2 (CO saturation = 82%). 2% CO + 5% O_2 in N_2 was then substituted as the inspired gas mixture. E: after 5 min breathing 2% CO + 5% O_2 in N_2 (CO saturation = 90%). F: after 2 min breathing 100% O_2 (CO saturation = 90%). Note the very slight chemoceptor activity in D compared with that in E.

of adequate respiration and hence a normal level of arterial oxygen tension. When the reduction of blood oxygen content due to progressive formation of carboxyhaemoglobin becomes too severe, the oxygen supply to the respiratory centres becomes insufficient, breathing begins to fail, and chemoceptor

excitation consequently ensues. Failure of respiration, however, did not occur in our experiments so long as 20% of the blood haemoglobin was available in animals breathing air, or 10% of the haemoglobin in animals breathing oxygen. Clearly, then, chemoceptor discharge does not occur in animals breathing small concentrations of carbon monoxide until circulation and respiration fail with consequent reduction in blood-oxygen tension. The chemoceptors thus provide no *effective* stimulation of the respiration during carbon monoxide inhalation. In anoxic anoxia the chemoceptors respond early and thereby stimulate the respiratory centre. In carbon monoxide anoxia the chemoceptors are stimulated only when respiration fails.

Comroe & Schmidt (1938) tested the response of the chemoceptors to blood treated with carbon monoxide. In their experiments the carotid body was isolated and perfused, and the degree of stimulation of the chemoceptors assessed by measurement of the reflex response of the pulmonary ventilation volume. The exact composition of the perfusing blood cannot be deduced from their protocols; but it appears that when blood partially saturated with CO and at a low O_2 tension was perfused through the carotid bodies breathing was stimulated. When the O_2 tension of the perfusing blood was raised, without significant change in the degree of CO saturation, breathing returned to its control level.

Various authors, e.g. Chiodi, Dill, Consolazio & Horvath (1941) have found that inhalation of carbon monoxide mixtures in man and animals does not increase the pulmonary ventilation and inferred that chemoceptor stimulation did not occur. Our results show that their inference was correct, but it is perhaps worth stressing that conclusive information about the behaviour of the chemoceptors can only be obtained by recording impulse activity in chemoceptor fibres. There is every reason to believe that the aortic chemoceptors similarly respond to changes in blood oxygen tension and not to oxygen content.

SUMMARY

1. The effect of spontaneous respiration of 1 or 2% CO in air or oxygen on carotid chemoceptor impulse activity has been studied in cats under anaesthesia.

2. Reduction of blood oxygen content owing to combination of haemoglobin with CO did not cause chemoceptor stimulation as long as spontaneous respiration was maintained.

3. Following inhalation of CO mixtures, reduction of blood oxygen tension by inhalation of 5% O_2 in N_2 caused marked chemoceptor activity. Severe degrees of carboxyhaemoglobinaemia did not therefore depress the response of the chemoceptors to a fall of arterial oxygen tension.

REFERENCES

CHIODI, H., DILL, D. B., CONSOLAZIO, F. & HORVATH, S. M. (1941). Respiratory and circulatory responses to acute carbon monoxide poisoning. *Amer. J. Physiol.* **134**, 683–693.

COMROE, J. H., Jr. & SCHMIDT, C. F. (1938). The part played by reflexes from the carotid body in the chemical regulation of respiration in the dog. *Amer. J. Physiol.* **121**, 75–97.

HARTRIDGE, H. (1912). A spectroscopic method of estimating carbon monoxide. *J. Physiol.* **44**, 1–21.

LANDGREN, S. & NEIL, E. (1951). Chemoreceptor impulse activity following haemorrhage. *Acta physiol. scand.* **23**, 158–167.