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THE EFFECT OF HYPOXIA ON THE HEART RATE OF THE DOG WITH SPECIAL REFERENCE TO THE CONTRIBUTION OF THE CAROTID BODY CHEMORECEPTORS

By M. de BURGH DALY* and MARY J. SCOTT*

From the Department of Physiology, University College London

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Daly & Scott (1958) found that in the dog stimulation of the carotid body chemoreceptors by hypoxic blood had variable effects on heart rate. They presented evidence that chemoreceptor stimulation elicited two antagonistic reflexes on the heart, a primary reflex bradycardia from the chemoreceptors themselves and a secondary reflex tachycardia arising from receptors in the lungs as a result of the concomitant increase in respiratory minute volume. It was concluded that the directional change in heart rate depended, among other factors, on which reflex was prepotent. These experiments were made on dogs spontaneously breathing room air, and the blood supplying the medullary centres was therefore fully oxygenated. The aim of the present experiments was to find out what effects, if any, the carotid body chemoreceptors exert on heart rate in systemic hypoxia. Neil (1956) was the first to carry out an experiment of this type. Using cats, he found that the tachycardia of systemic hypoxia was not affected by changing the carotid body perfusate from hypoxic blood to oxygenated Ringer–Locke's solution. Since some of our results obtained on dogs differ from those of Neil (1956) our experiments will be described in detail.

METHODS

Dogs varying in weight from 10·5 to 17·2 kg were premedicated with morphine hydrochloride (1–2 mg/kg subcutaneously). About half an hour later they were anaesthetized with a mixture of chloralose (0·05 g/kg) and urethane (0·5 g/kg) intravenously. Systemic blood pressure was measured in a femoral artery by means of a Hürthle manometer. Heart rate was counted from the blood pressure record taken on a fast moving paper or was recorded on the kymograph by a Gaddum drop timer (Gaddum & Kwiatkowski, 1938) using the method of Daly & Schweitzer (1950).

The animals breathed room air through valves of low resistance. Respiratory minute volume was measured either by collection of expired air in a balanced spirometer for a given period of time or by passing the expired air through a gas meter, every 0·5 l. expired air being signalled on the

* Present address: Department of Physiology, St Bartholomew's Hospital Medical College, Charterhouse Square, London, E.C. 1.

kymograph. Intratracheal pressure was also recorded by means of a damped Marey tambour as a qualitative measure of the changes in respiration. Tidal air volume was calculated from values for the respiratory minute volume and the respiratory rate, the latter being obtained from the intratracheal pressure trace.

The animals were made hypoxic by substituting 7% O_2 in N_2 for room air. In some experiments, artificial respiration was applied by means of a Starling 'Ideal' pump. Under these conditions the low oxygen mixture was given via the inlet side of the pump.

Perfusion of the carotid bodies. The method was similar to that described previously by Daly & Scott (1958) and enabled the isolated carotid bodies of the recipient animal to be perfused with blood either from the same animal or from a donor dog.

Denervation of the lungs. In two animals both thoracic vagosympathetic nerves were divided between the origin of the bronchial and cardiac branches without opening the thorax. The method used was the same as that described by Daly & Scott (1958).

Experimental procedure. Both the donor and recipient animals breathed room air and the recipient's carotid bodies were perfused with its own blood. After taking the control heart rate, hypoxia was induced in the recipient animal by substituting 7% O_2 in N_2 for room air. When a steady state had been reached, the carotid body perfusate was changed from hypoxic blood to oxygenated blood from the donor animal. After 1–2 min, hypoxic blood perfusion of the carotid bodies was re-established. Finally, ventilation of the recipient animal with room air was restored.

RESULTS

In experiments made on spontaneously breathing dogs whose carotid bodies were perfused with their own blood, hypoxia induced by inhalation of 7% O_2 in N_2 invariably caused an increase in respiratory minute volume and usually an increase in systemic blood pressure. The effects on heart rate are summarized in Table 1. It may be seen that in seven out of nine tests, the heart rate increased by 15–44 beats/min (mean 27·9 beats/min). In two tests made on different animals, the heart slowed.

While the recipient animal continued to breathe the low-oxygen mixture, the carotid body perfusate was changed from hypoxic blood to oxygenated blood from the donor dog. This invariably caused a reduction in respiratory minute volume and usually a small fall of blood pressure. In eight out of nine tests an increase of heart rate of 3–138 beats/min (mean 40·1 beats/min) occurred; in the remaining test the heart slowed from 180 to 160 beats/min. These results are summarized in Table 1, from which it may be seen that the tachycardia evoked by changing the carotid body perfusate from hypoxic to oxygenated blood occurred whether the response of the heart to systemic hypoxia was an increase or a decrease in rate.

When hypoxic blood perfusion of the carotid bodies was re-established, the respiratory minute volume increased and a profound bradycardia occurred. For the next 15–60 sec the heart rate gradually increased but the final rate was always lower than that during perfusion of the carotid bodies with oxygenated blood. The typical response is shown in Fig. 1.

These effects on heart rate occurred independently of the changes in systemic blood pressure and whether the carotid sinus pressure was

TABLE 1. The effects of systemic hypoxia on heart rate in spontaneously breathing dogs. The first column shows the control heart rates; the second, the heart rates after substituting 7% O_2 in N_2 for room air, the carotid bodies being perfused with hypoxic blood from the same animal; the third, the rates after changing the carotid body perfusate from hypoxic to oxygenated blood from a donor dog breathing room air, while the recipient continued to breathe 7% O_2 in N_2

	Heart rate (beats/min)		
		During systemic hypoxia: carotid body perfusion	
Expt. no.	Control	Hypoxic blood	Oxygenated blood
11*a*	155	170	210
11*b*	180	102	240
12	130	180	160
13	144	132	174
20	80	124	141
22*a*	105	129	144
22*b*	104	123	138
22*c*	111	135	138
23	126	165	216

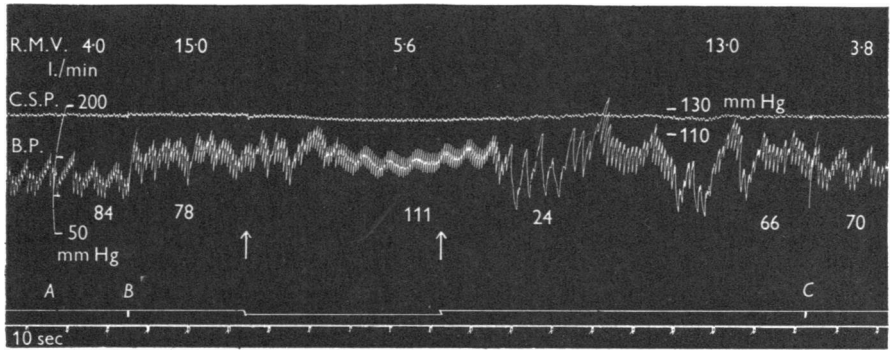

Fig. 1. Dog, ♂, 16·7 kg. Morphine–chloralose–urethane. Spontaneous respiration. Carotid sinus and body on both sides isolated and perfused. Lungs denervated by method of Daly & Scott (1958). *A*, control; ventilation of recipient animal with room air. At *B*, ventilation with 7% O_2 in N_2 instead of room air. Carotid bodies perfused with blood from recipient animal. Kymograph restarted after a steady state had been reached. Between arrows ↑↑, the carotid bodies were temporarily perfused with oxygenated blood from donor dog breathing room air. At *C*, ventilation of recipient animal with room air re-established. Note acceleration of the heart when oxygenated blood was substituted for hypoxic blood perfusing the carotid bodies and the marked bradycardia which occurred on restoring hypoxic blood perfusion. The delay in onset of the responses to changing the carotid body perfusate is due in part to the dead space in the pump and its connexions (see Daly & Scott, 1958). In both figures, R.M.V. = respiratory minute volume; C.S.P. = carotid sinus pressure; B.P. = systemic blood pressure; H.R. = heart rate; the figures below the blood pressure records are those for heart rate, (beats/min).

maintained constant or was allowed to vary with the systemic blood pressure. Furthermore, they were not dependent upon secondary reflex effects arising from the lungs as a result of the concomitant changes in respiration; they occurred in preparations after denervation of the lungs (Fig. 1).

In several experiments control tests were carried out while both dogs were ventilated with room air. It was found that changing the carotid body perfusate from oxygenated recipient blood to oxygenated donor blood had no effect on the recipient's blood pressure or heart rate.

TABLE 2. The effects of systemic hypoxia on heart rate in dogs ventilated artificially. The first column shows the control heart rates; the second, the heart rates after substituting 7% O_2 in N_2 for room air, the carotid bodies being perfused with hypoxic blood from the same animal; the third, the rates after changing the carotid body perfusate from hypoxic to oxygenated blood from a donor dog breathing room air, while the recipient continued to breathe 7% O_2 in N_2

	Heart rate (beats/min)		
		During systemic hypoxia: carotid body perfusion	
Expt. no.	Control	Hypoxic blood	Oxygenated blood
4*a*	140	90	140
4*b*	115	120	135
8*a*	216	150	216
8*b*	210	132	234
10	160	96	145
11	180	84	230
12	120	120	204
13	200	200	230
14	90	125	165
17	87	45	66

Neil (1956) found in the cat breathing 5% O_2 in N_2 that substitution of oxygenated Ringer–Locke's solution for hypoxic blood perfusion of the carotid bodies had no effect on heart rate although a bradycardia occurred on re-establishing perfusion with hypoxic blood. This latter response did not occur if the cats were artificially ventilated. It was therefore of interest to find out whether the bradycardia observed in the dog was similarly affected.

The results are summarized in Table 2 and the response obtained in one experiment is shown in Fig. 2. Eight experiments were carried out on open chest preparations under artificial respiration. Inhalation of 7% O_2 in N_2 instead of room air caused a bradycardia in six tests, a tachycardia in two, and no change in heart rate in another two tests. Despite these variable responses, substituting oxygenated blood for hypoxic blood perfusing the carotid bodies invariably caused an increase in heart rate of 15–146 beats/min (mean 60·3 beats/min). Furthermore, it was found that re-establishing perfusion of the chemoreceptors with hypoxic blood evoked a temporary marked bradycardia as in spontaneously breathing dogs. This bradycardia occurred

independently of changes in carotid sinus and systemic blood pressures. It was mediated through the vagus nerves, for it was reduced or abolished by atropine or by division of the cervical vagosympathetic nerves.

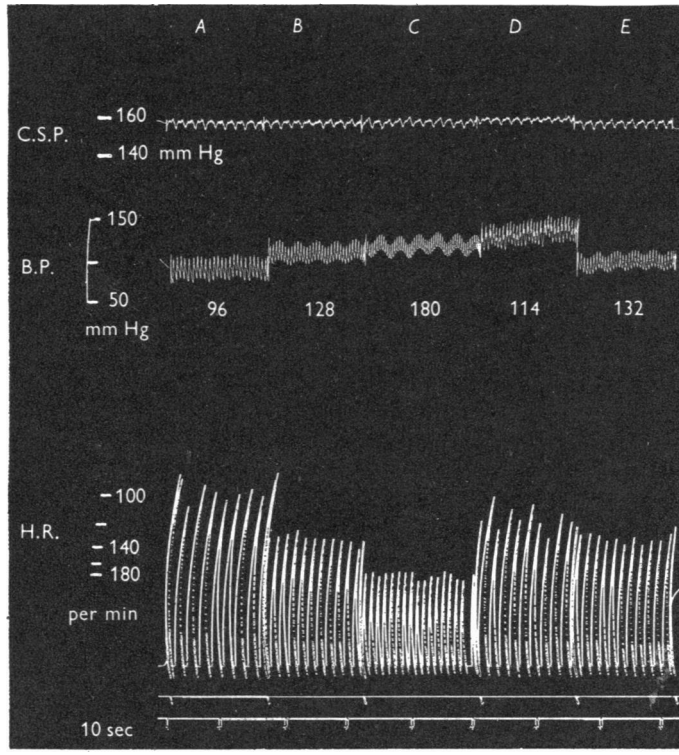

Fig. 2. Dog, ♂, 16·2 kg. Morphine–chloralose–urethane. Positive pressure ventilation. Carotid sinus and body on both sides isolated and perfused. Carotid sinus pressure maintained constant. Decamethonium 2 mg I.V. before recording began. *A*, control, ventilation of recipient animal with room air; carotid bodies perfused with blood from the same animal. *B*, ventilation with 7% O_2 in N_2 instead of room air. *C*, perfusion of carotid bodies with oxygenated blood from donor dog breathing room air. *D*, hypoxic blood perfusion of the carotid bodies re-established. *E*, control, ventilation with room air. In each case the short record was taken after a steady state had been reached.

DISCUSSION

Neil (1956) showed that, in the cat, cessation of the hypoxic stimulus to the carotid bodies during systemic hypoxia did not affect the heart rate. On the other hand, our results have shown that this procedure in the dog almost invariably causes an increase in rate. The cause of this difference is not at present clear. It may be due to species variation but, on the other hand, there are several differences in experimental technique which should be pointed out.

First, although the anaesthetic, a mixture of chloralose and urethane, was the same in both groups of experiments, our dogs were premedicated with morphine and would therefore be expected to have a higher degree of cardiac vagal tone. Secondly, whereas in our experiments the carotid bodies were continuously perfused with blood from one or other dog, Neil substituted Ringer–Locke's solution for blood when changing the composition of the perfusate. Thirdly, the aortic nerves in Neil's cats were cut; in our experiments, they were left intact. Division of the aortic nerves would result in some loss of cardiac vagal tone through cutting off of tonic baroreceptor impulses arising from the aortic arch. It also denervates the aortic bodies and this probably accounts for the fact that, during systemic hypoxia, Neil observed a considerable fall in systemic blood pressure on substituting oxygenated Ringer–Locke's solution for hypoxic blood perfusing the carotid bodies. In our experiments cessation of the hypoxic stimulus to the carotid bodies caused only a small reduction of systemic blood pressure, and on no occasion did the pressure fall below the control level taken during room-air breathing. Further information is required before these differences in technique can be fully assessed.

Previous work indicates that in the dog ventilated with room air, stimulation of the carotid bodies with hypoxic blood causes a primary reflex bradycardia (Bernthal, Greene & Revzin, 1951; Daly & Daly, 1957; Daly & Scott, 1958). In the present study we have shown that, in dogs spontaneously breathing 7 % O_2 in N_2, withdrawal of the hypoxic stimulus to the carotid body chemoreceptors by changing the perfusate from hypoxic to oxygenated blood causes an increase in heart rate. Furthermore, stimulation of the chemoreceptors by re-establishing hypoxic blood perfusion of the carotid bodies evokes a bradycardia. These effects on heart rate were not dependent on a reflex arising from pulmonary stretch receptors through concomitant changes in the rate and depth of respiration, because when respiration was maintained constant similar effects on heart rate were observed. It is concluded, therefore, that in systemic hypoxia, as in conditions in which the medullary centres receive oxygenated blood (see Daly & Scott, 1958), the primary reflex effect of hypoxic stimulation of the carotid bodies is a bradycardia.

Our results have a bearing on the role of the chemoreceptors in the initiation of the tachycardia which occurs in systemic hypoxia. The evidence at present available indicates that the tachycardia of hypoxia cannot be directly attributable to stimulation of peripheral chemoreceptors (Bernthal *et al.* 1951; Neil, 1956; Daly & Scott, 1958). The results of the present experiments indicate that not only is the response not of chemoreceptor origin, but that the chemoreceptors actually antagonize it. The evidence for this is, that if during systemic hypoxia, stimulation of the carotid bodies is stopped by changing their perfusate from hypoxic to oxygenated blood, cardio-acceleration

results which is reversed when perfusion with hypoxic blood is re-established. This antagonistic effect is probably the result of a primary reflex from the carotid bodies, because it occurred in preparations ventilated artificially. The mechanism of the tachycardia of systemic hypoxia remains obscure. In this connexion Daly & Scott (1958) presented evidence which suggested that cardio-acceleration evoked by stimulation of the carotid bodies by hypoxic blood in dogs spontaneously breathing room air was due, at least in part, to a secondary reflex from the lungs resulting from the concomitant increase in rate and depth of respiration. The present experiments, while not excluding the participation of such a mechanism in the production of the tachycardia of systemic hypoxia, indicate that it is not the sole cause, because a similar response occurred on administration of a low-oxygen gas mixture to dogs artificially ventilated.

SUMMARY

1. A method has been used in the anaesthetized dog whereby perfusion of the carotid bodies may be made with blood from the same animal or from a donor animal.

2. In spontaneously breathing animals inhalation of 7% O_2 in N_2 almost invariably caused an increase in respiratory minute volume and acceleration of the heart. If during systemic hypoxia the carotid body perfusate was changed from hypoxic blood to oxygenated blood obtained from a donor dog, a further tachycardia occurred together with a reduction in respiratory minute volume. A similar response occurred in recipient dogs which were artificially ventilated with 7% O_2 in N_2.

3. Restoration of hypoxic blood perfusion of the carotid bodies caused slowing of the heart.

4. It is concluded that the carotid bodies do not contribute to the production of the tachycardia of systemic hypoxia; on the contrary, they antagonize it.

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