Role of Carotid Chemoreceptors in Hypoxic Cardiac Acceleration (18408)

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Though the increased heart rate which accompanies acute hypoxia is well known, the mechanism of its genesis is incompletely understood. Sands and DeGraff(1) and Wiggers(2) have shown that it depends chiefly upon reduced tonic activity of the vagal cardio-inhibitory center and in lesser degree upon increased activity of the sympathetic cardio-accelerator center. However, the channels through which hypoxia operates when it alters the action of these centers have not been demonstrated.

The suggestion has been made repeatedly (3-8) that the changes in heart rate which accompany alterations of arterial oxygen tension are initiated at the chemoreceptors of the carotid and aortic bodies. Thus, it has been assumed either that hypoxic stimulation of these chemoreceptors would reflexly accelerate the heart or, conversely, that hyperoxic diminution of their tonic activity would do the reverse. Since the literature seemed devoid of experimental evidence bearing directly upon these assumptions, we have performed experiments to determine the chemoreflex response of heart rate to hypoxia. The results do not support the suggestion that hypoxic cardiac acceleration is initiated at the carotid or aortic bodies.

Method. Our procedure consisted simply of recording heart rate during the application of hypoxic stimuli carefully restricted to the carotid chemoreceptor region. Dogs were anesthetized with morphine sulphate (4 mg/kilo) and urethane (1 g/kilo) and their heart rates recorded from a carotid artery with a membrane manometer. Breathing was recorded to indicate the intensity of chemoreceptor stimulation. While preserving Hering's nerves, all vessels efferent to each carotid bifurcation were ligated a few millimeters beyond their origin. The vascularly isolated carotid regions were then supplied with blood from a perfusion source, the blood entering through cannulae placed in the common carotid arteries and leaving through cannulae in the external carotid arteries from which it returned to the perfusion source through an adjustable resistance. During controlled periods, normally aerated heparinized blood flowing in this circuit was rendered hypoxic in known degree. In some instances, the perfusion source was a donor animal inhaling a gas mixture low in partial pressure of oxygen for short periods. In other experiments, autoperfusion apparatus was used(9). Cyanide was administered by injecting directly into the carotid perfusion circuit. In most experiments, arterial blood pressure compensators(9) minimized variations of pressoreceptor stimulation. In some experiments, natural breathing was allowed. In others, constant artificial pulmonary ventilation with open pneumothorax was imposed.

Results and discussion. Representative responses of eight animals are summarized in Table I which gives only the maximum deviation of heart rate from control values during each hypoxic episode. In Fig. 1, plotted summaries of the heart rate during 3 complete hypoxic episodes and one cyanide administration are given in order to show the pattern and time relationships of the responses. Here

1. Sands, J., and DeGraff, A. C., *Am. J. Physiol.*, 1925, v74, 416.
2. Wiggers, C. J., *Ann. Int. Med.*, 1941, v14, 1237.
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4. v. Euler, U. S., and Liljestrand, G., *Acta Physiol. Scandinav.*, 1942, v4, 34.
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7. Dripps, R. D., and Comroe, J. H., Jr., *Am. J. Physiol.*, 1947, v149, 277.
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TABLE I. Effects of Hypoxic Stimulation of Isolated Carotid Chemoreceptors Upon Heart Rates of Dogs.

Exp. No.	Stimulus*	Heart rate—beats/min. Natural pulmonary ventilation Before	During†	After	% change	Controlled (constant) pulmonary ventilation Before	During†	After	% change
1	1% O_2	186	180	186	— 3.2				
2	7% O_2	201	204	201	+ 1.5				
3	1% O_2	204	204	204	0.0	189	174	183	— 7.9
4	4% O_2	191	155	191	—18.3	216	141	217	—34.7
5	4% O_2	95	103	90	+ 8.4	(Donor: +17% during same procedure)			
	8% O_2	89	93	93	+ 4.5	(Donor: +8.4% during same procedure)			
6	4% O_2	198	211	194	+ 6.5	248	240	251	— 3.2
	2% O_2					181	172	186	— 4.9
	NaCN, 1 cc	260	284	264	+ 9.0	252	246	269	— 2.3
	NaCN, 2 cc					244	215	248	—11.0
7	4% O_2	150 ± 3	150 ± 4		0.0	209 ± 3	184	202	—12.0
	4% O_2					201	182	193	— 9.4
	Whole animal—constant ventilation: 8% O_2: 175/min. to 224/min. = +28%.								
	NaCN, 0.5 cc	112	124	116	+11.0				
8	4% O_2	135	136.5	135	+ 1.0				
	2% O_2	135	142	136	+ 5.0	201	202	200	— 0.5
	NaCN, 1 cc	148	112	148	—24.0	191	113	189	—40.8
	Whole animal—natural breathing: 8% O_2: 150/min. to 220/min. = +46%								
	4% O_2: 130/min. to 213/min. = +63%								

* O_2 values = pO_2 in % of one atmosphere in inspired air of donor supplying blood to carotid perfusion circuit.
NaCN values = amount of 0.01 N solution injected into carotid perfusion circuit.
† Values in columns 4 and 8 pertain to the 30 sec. interval showing maximum deviation from control.

it can be seen that, although the changes were small, they coincided definitely with the period of carotid hypoxia, were well maintained during that time, and were reversed when the hypoxia was ended.

As Table I shows, the reactions were qualitatively consistent only when pneumothorax and constant artificial ventilation of the lungs were maintained. Under these conditions the heart rate was diminished in all instances of hypoxemia and cyanidemia at the chemoreceptors except 2 in which there were no significant changes and *in no instance was there cardiac acceleration.* On the other hand, when natural breathing was allowed so that pulmonary ventilation and stretching of the lungs were increased during chemoreceptor stimulation, the heart rate diminished in some instances, was unchanged in others and increased moderately in the remainder. Of the two sets of reactions, the first is taken to be the more nearly representative of direct uncomplicated chemoreflex responses since variable factors secondary to the reflex hyperpnea which results from chemoreceptor stimulation had been eliminated or lessened by controlling the breathing. The finding that the direct reflex effect of hypoxemia at the carotid bodies is slowing rather than acceleration of the heart harmonizes with the similar finding for cyanide stimulation (Exp. 6 and 8, Table I, and Fig. 1). Reflex bradycardia due to cyanide is well known(10) and the response to lowered oxygen tension might have been anticipated upon this basis since the effects of chemoreceptor stimulation could be expected to remain qualitatively the same whatever the identity of the stimulating agent.

In the experiments with natural ventilation, there were factors presumably secondary to the increased breathing which tended to cause cardiac acceleration and when sufficiently forceful they counterbalanced or overbalanced the direct reflex effect. Thus, in Experiment 6, a relatively moderate chemoreflex slowing was overbalanced by the secondary accelerating influence of the increased breathing, with a net effect of cardiac acceleration. In Experiment 3, a stronger reflex slowing apparently

10. Heymans, C., Bouckaert, J. J., aand Dautrebande, L., *Arch. internat. de pharmacodyn., et. de therap.*, 1931, v41, 216.

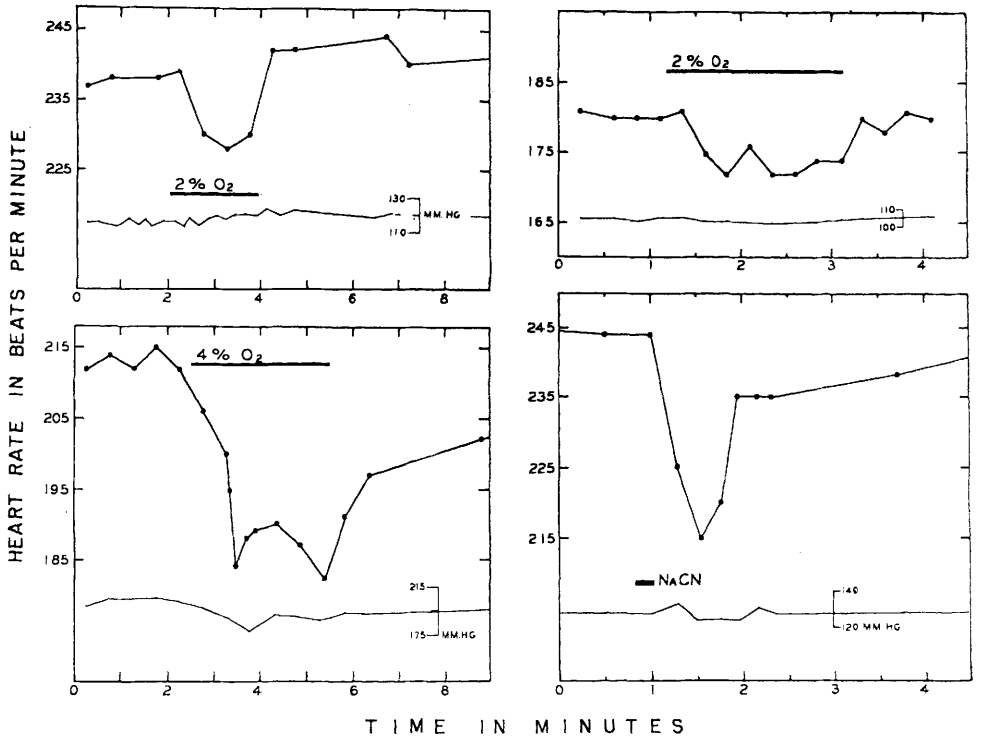

FIG. 1.

Changes in heart rate of dog during hypoxemia and cyanidemia restricted to the carotid bodies.

Percentage values: partial pressure of oxygen, in percent of one atmosphere, in inspired air of donor supplying arterial blood to isolated carotid bifurcations of experimental animal. Black bar: period during which low oxygen mixture was inhaled.

NaCN dosage: 2 cc of 0.01 N solution injected into carotid perfusion circuit.

Lower thin line: mean arterial blood pressure of experimental animal.

just counterbalanced the secondary effect so that no change of heart rate occurred. In Experiment 4, very marked chemoreflex slowing completely overbalanced the secondary acceleratory influence so that slowing occurred during both natural and artificial breathing, although less markedly in the former.

The nature of the cardiac acceleratory factor which is secondary to increased breathing and which disappears during constant ventilation with open chest is not evident although reflex inhibition of the cardio-inhibitory center resulting from increased inspiratory stretching of the lungs as analyzed by Anrep, Pascual and Rössler(11) would seem to be a leading possibility. Whatever its nature, it appears unlikely that this factor is an essential part of the mechanism producing cardiac acceleration when the whole animal is subjected to hypoxia. The cardiac acceleration of generalized hypoxia usually is not reversed by the use of constant pulmonary ventilation (see Exp. 7, Table I). Further, in none of these experiments was the acceleration secondary to chemoreflex hyperpnea as much as 10% of control values, whereas generalized hypoxia produced increases of 30 to 60% or more (Exp. 7 and 8, Table I).

We conclude, therefore, that the cardiac acceleration of generalized hypoxia does not depend upon the carotid chemoreceptors, although effects secondary to chemoreflex hyperpnea may contribute in minor degree. It might be added that the same probably holds true for the aortic chemoreceptors, since all known aspects of their function are quali-

11. Anrep, G. V., Pascual, W., and Rossler, R., *Proc. Roy. Soc. London*, 1935-36, v119B, 191, 218.

tatively like those of the carotid bodies. Moreover, Comroe(12) has demonstrated that their stimulation by cyanide or lobeline produces a reflex bradycardia just as does that of the carotid chemoreceptors.

Summary and conclusions. 1. Changes in heart rate were recorded during the application of hypoxic stimuli limited to the carotid chemoreceptors. 2. The direct reflex change in heart rate initiated by hypoxia at the carotid chemoreceptors was a slowing of moderate degree. 3. It is concluded that the cardiac acceleration of generalized hypoxia does not arise chemoreflexly at the carotid bodies.

12. Comroe, J. H., Jr., *Am. J. Physiol.*, 1939, v127, 176.

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Further Observations on Yeast in Production of Experimental Hepatic Necrosis in Rats.* (18409)

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It has been shown that in rats fed a diet deficient in tocopherol, with yeast as the sole source of protein, the occurrence of massive hepatic necrosis may vary considerably in direct relation to the brand of yeast used(1). Incorporation of a British brand of baker's yeast in the diet led to massive necrosis with great regularity (90-100%). In contrast, substitution of our American brand of brewer's yeast in the same ration deprived it of its "necrogenic" quality. By increasing the fat-content (lard) in the mixture up to 50%, necrosis occurred, even with the American brand of yeast, but the incidence remained relatively low around 50%(2). The necrogenic activity of the British yeast could not be explained by a difference in the content of the sulfur-containing amino acids (cystine, methionine) or of vit. E in these particular British and American brands of yeast. The fact that the British yeast used was a live baker's yeast and the American yeast a heat-killed brewer's yeast made it desirable to test (1) an American live baker's yeast for its necrogenic activity, and (2) to determine whether the British yeast retained its necrogenic character after inactivation through autoclaving.

Experimental. As in our previous experiments(1,3) the following "necrogenic" experimental diet was used: yeast, 18; corn starch, 79; salt mixture (U.S.P. II), 3%. Peanut oil, 0.5 ml and cod liver oil, 2 drops were added to 8 g of the dry mixture just before feeding. Further, all animals received daily supplements of 20 γ of thiamine, 25 γ of riboflavin, 20 γ of pyridoxine, and 100 γ of calcium pantothenate dissolved together in 1 ml of water, as well as 20 γ of vit. K. We used the British† (in diet Y5H) and an American‡ (in diet Y5F) type of baker's yeast.

In Exp. II, the necrogenic activity of the live British yeast was compared with that of the same brand of yeast after being autoclaved (for 5 minutes with free flowing steam, followed by 25 minutes steam sterilization at 17 lb per square inch, then a 14-inch vacuum

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1. György, P., Rose, C. S., Tomarelli, R. M., and Goldblatt, H., *J. Nutrition*, 1950, v41, 265.

2. György, P., and Goldblatt, H., *J. Exp. Med.*, 1949, v89, 245.

3. György, P., Stokes, J., Jr., Smith, W. H., and Goldblatt, H., *Am. J. Med. Sci.*, 1950, v220, 6.

† Obtained under the designation "D.C.L. Vit. B_1 Yeast" from Distiller's Co., Glasgow.

‡ Type 753-powdered Fleischman's baker's yeast. Furnished by Standard Brands, New York.