VAGAL TONE AND EFFECT OF VAGOTOMY ON THE CIRCULATORY RESPONSE TO ARTERIAL HYPOXIA

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Summary: The influence of vagotomy on resting vagal tone arterial Po2, the heart rate and blood pressure responses to different grades of hypoxia was studied in three species of anesthetized animals. Vagotomy without hypoxia produced a sustained increase in heart rate of dogs but not in rabbits or sheep. In the dogs, where this was studied more fully, heart rate showed sustained increase over several hours with no significant change in blood pressure or arterial Po2. It is concluded that there is species difference in the resting vagal tone during anesthesia.

The relationships between graded arterial hypox'a with heart rate and blood pressure have been determined with and without intact vagus nerves. Before vagotomy hypoxia significantly increased the heart rate of dogs and sheep and reduced that of rabbits. Vagotomy decreased the bradycardia observed in rabbits, but did not change the response to hypoxia in dogs and sheep. The greater increase in heart rate of dogs calculated statistically and were due to the pre-existing resting vagal tone. After vagotomy, heart rate response to graded arterial hypoxia was increased rather than decreased in all animals.

Key words: vagal tone vagotomy arterial hypoxia circulatory response

INTRODUCTION

The factors which influence the heart rate during reduced arterial oxygen tension are many and complex. Direct electroneurographic studies on the dog and cat shows that pronounced increase in cardiac sympathetic discharge to the heart occurs consequent to direct hypoxic stimulation of the central nervous system (6,7,8 and 10).

The intrinsic reflex effect of stimulation of arterial chemoreceptors with hypoxic blood is a slowing of the heart rate. This effect results from reflex reduction in cardiac sympathetic activity and increase in vagal efferent activity. Whenever there is hyperpnea the bradycardia is usually masked by the secondary effect of hyperventilation, which is mediated through vagal afferent inputs from the lungs (2,3,5,7,15 and 17).

In the present study an evaluation of vagal afferent inputs on the heart rate in response to reduced arterial p02 was assessed in three different species of spontaneously breathing anesthetized animals.

MATERIAL AND METHODS

Experiments were carried out in 12 rabbits (mean weight 2.81 *kg*., range 1.9-3.7 *kg*), 18 dogs (mean weight 11.2 *kg*, range 7.4-19.2 *kg*), and 11 sheep (mean weight 31.6 *kg*. range 22.0-43 *kg*). The effects of graded hypoxia (17, 13 and 10% in inspired air) and vagal tone were studied in the three species of animals in three stages. (Stage 1): effect of hypoxia before vagotomy. (Stage 2): animals were allowed to breathe room air and to obtain stable conditions of paCO2 and Pao_2 and pH before vagotomy and again after vagotomy before proceeding to the next step. Time to obtain equilibrium conditions was approximately 30 min before vagotomy and between 20 and 60 min after vagotomy. (Stage 3): the effects of the same level of hypoxia were studied after vagotomy. Finally stability of heart rate changes, blood pressure and arterial Po2 to vagotomy without hyperventilation were investigated for more than four hours.

Anaesthesia was induced with fluothane and maintained until surgery was completed. It was then gradually replaced by iv choralose (70-100 *mg/kg* of 1% in 0.6% saline), in dogs and sheep. To reduce the bulk of injection a mixture of 1 g chloralose in 20 *ml* of 25% urethane was used in the rabbits.

The trachea was cannulated through a midline incision. The vagus nerves (rabbit) or vago-sympathetic trunk (dog and sheep) were dissected free and loose ties placed around them. Femoral arteries and veins were cannulated. Heart rate and blood pressure were recorded with transducer and displayed on a recorder. Arterial blood samples were collected from the indwelling catheters into 1 *ml* heparinized syringes and analyzed immediately for pH, pc02 and p02 using I.L. 213 pH blood gas analyser (Instrumentation Laboratories Ltd.).

Gas mixtures were freshly prepared from cylinders and analysed using a Taylor Servomex 272 paramagnetic analyser for oxygen and a Beckman LB-1 infrared analyser for carbon dioxide. The gas mixtures were kept in plastic Douglas bags and administered for 5 min periods through an inspiratory expiratory valve. Recovery period of at least 30 min were allowed between gas mixture administrations. Student's 't' test was used to determine significance of the differences between means of the variables.

RESULTS

Effect of vagotomy on animals breathing air

Comparison of pre-and post-vagotomy values on the tone of vagal efferent fibers to the heart in three different groups of animals reveals no statistically significant increase in heart rate of rabbits and sheep, but a statistically significant increase in heart rate of dogs (Table I). There was no statistically significant change in blood pressure and arterial po2 in the three species of animals.

TABLE I: Mean ± S.E. of heart rate arterial blood pressure and arterial Po2 of rabbits, dogs and sheep before and after vagotomy.

	Rabbits (n=12)		*Dogs (n=13)*		*Sheep (n=11)*	
	I	*V*	*I*	*V*	*I*	*V*
H.R. (min^{-1})	320.0±37.2	328.6±34.4	135.2±24.3	191.2±31.7**	124.54±15.3	125.8±16.0
B.P. mmHg	80.5±10.05	85.0±15.2	123.1± 8.2	123.6±12.0	95.18±15.2	90.3±21.2
Pa02	81.0± 3.3	82.75± 2.9	77.5± 2.5	78.52± 1.5	65.0 ±3.2	67.19± 1.1

**P < 0.01 for post-vagotomy mean values compared with pre-vagotomy values.
I = vagi intact
V = vagotomized

The stability of heart rate changes, blood pressure and arterial Po2 were investigated during a period of several hours, breathing room air, in vagotomized dog. The heart rate showed sustained increase with no significant change in blood pressure or arterial Po2 (Fig.1).

Cardiovascular response to hypoxia before vagotomy

Before vagotomy the blood pressure of rabbits did not change significantly throughout the period of graded hypoxia. A small reduction in arterial Po2 caused little bradycardia, but greater reduction of arterial Po2 (down to about 60 mmHg) decreased the heart rate significantly (Fig.2a,b). These are in agreement with previous observation, that in the anesthetized rabbits, as the respiratory response to hypoxia is limited, vagal afferent input reaches to its limit, but arterial chemoreceptor stimulation will continue to increase and this will decrease the heart rate through reflex reduction of cardiac sympathetic nerve activity (1,13, 14 and 15).

In the dogs with intact vagi graded reduction of arterial po2 from 80 to about 30 mmHg was accompanied by a rise in blood pressure. This rise would inhibit cardiac sympathetic nerve activity through stimulation of baroreceptors (10). Inspite of this potential inhibition of cardiac sympathetic nerve activity the decrease in arterial po2 was accompanied by tachycardia (Fig. 3c, d). This is ascribed to the secondary effects of hyperventilation mediated through vagal afferent (2,3 and 7).

In the sheep, the blood pressure did not change significantly throughout the range of graded decrease in arterial Po2. However, this was accompanied by significant increase in heart rate at a time when Po2 was brought down to 40 mmHg or less (Fig. 4 e, f).

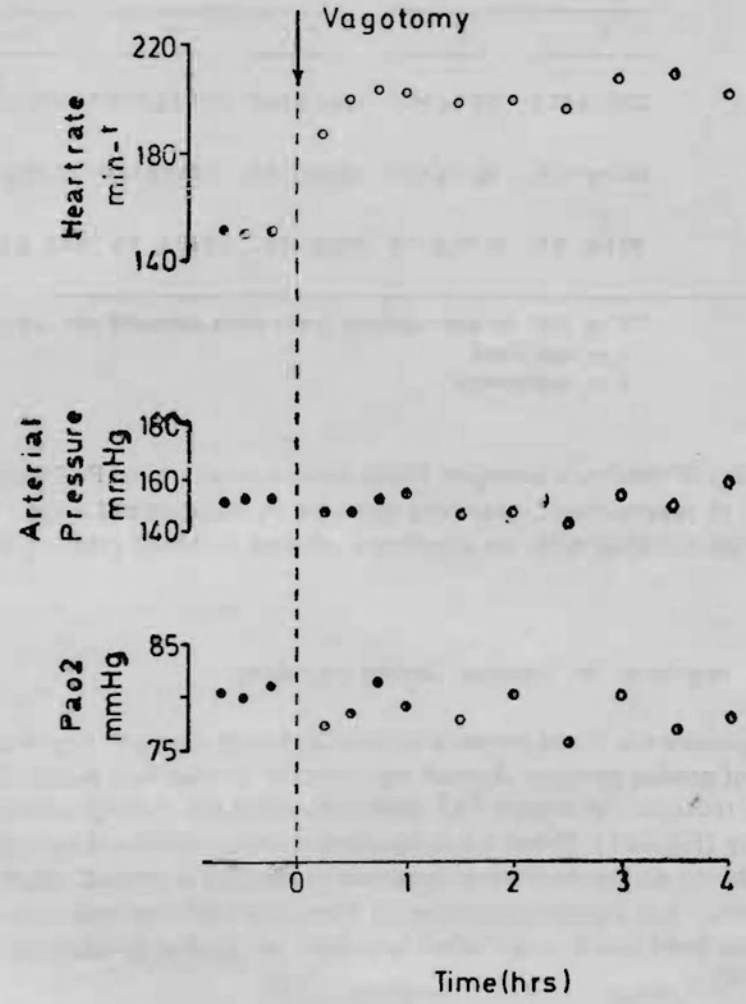

Fig.1: Effect of vagotomy on the heart rate, blood pressure and arterial Po2 of five dogs breathing room air.

Cardiovascular response to hypoxia after vagotomy

After vagotomy the blood pressure of rabbits rose slightly during gradual decrease in arterial Po2. This was accompanied by a gradual decline in heart rate. The changes in heart rate were not different from the results observed before vagotomy in the range of Po2

above 60 mmHg. However, the marked bradycardia observed before vagotomy with a Po2 of 40 mm Hg or less was reduced after vagotomy.

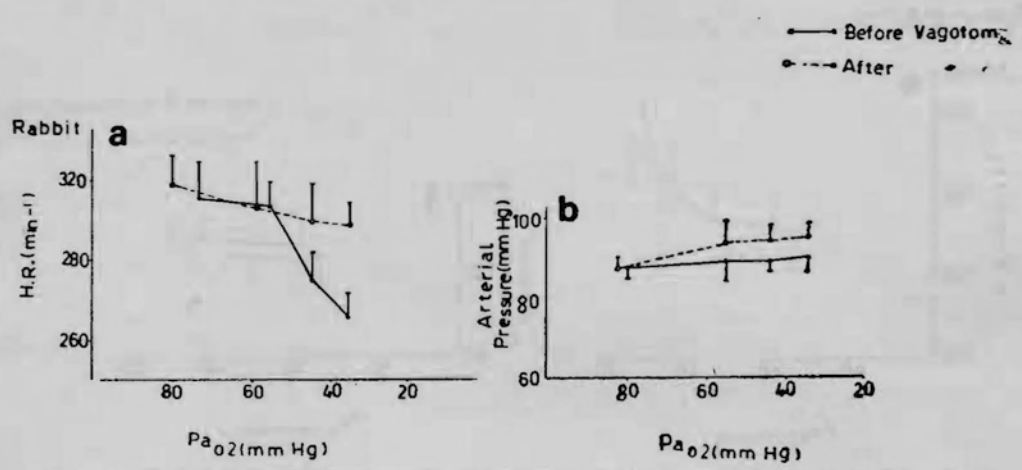

Fig.2: Effect of graded degree of hypoxia on heart rate and blood pressure of rabbits before and after vagotomy. Each point represents the mean + SE of 5-7 experiments.

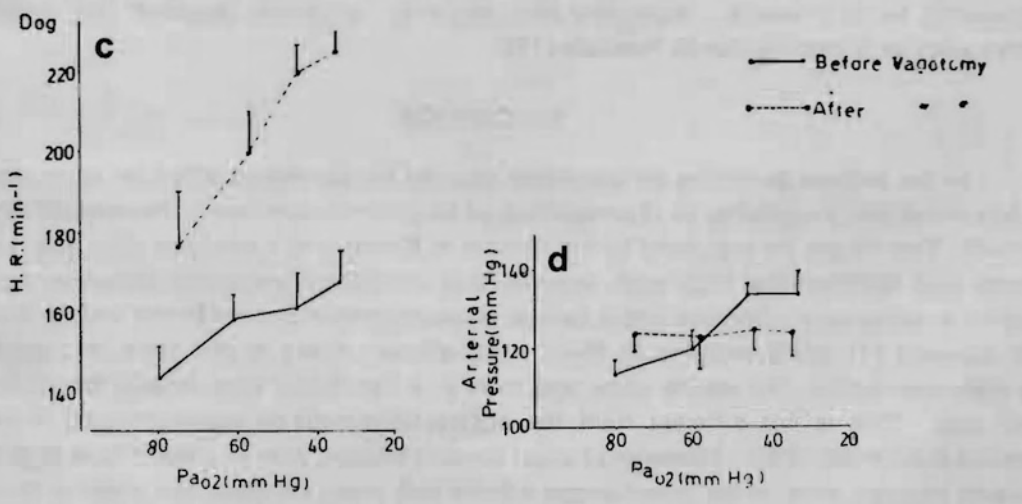

Fig.3: Effect of graded degree of hypoxia on heart rate and blood pressure of dogs before and after vagotomy. Each point represents the mean + SE of 6-8 experiments.

After vagotomy in dogs reductioin of arterial Po2 did not result in any signifcant change in blood pressure. The percent increase in heart rate during different grades of hypoxia was not statistically different from the data obtained before vagotomy. The greater increase in heart rate of dogs was due to the pre-existing resting vagal tone.

In sheep the mean blood pressure was slightly lower than the level maintained before vagotomy. With reduction of arterial Po2 it did not change significantly. The graded change in heart rate related to gradual decrease of arterial Po2 was similar to that observed before vagotomy.

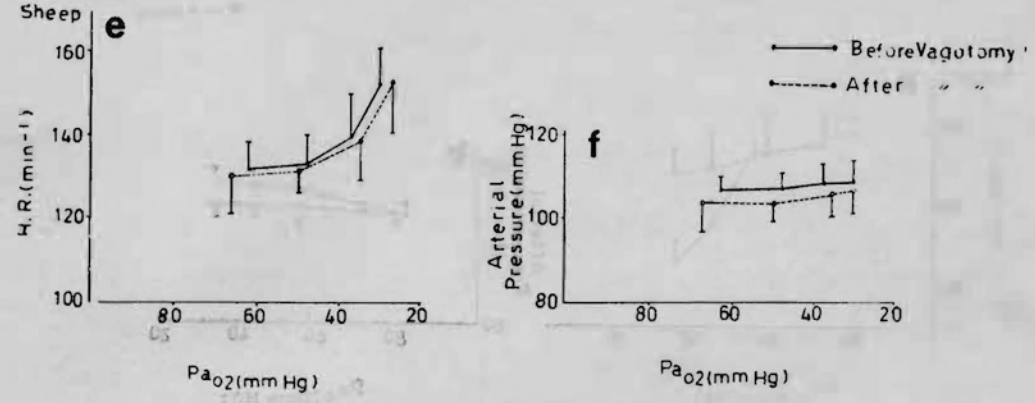

Fig. 4: Effect of graded of hypoxia on heart rate and blood pressure of sheep before and after vagotomy. Each point represents the mean + SE of 5-6 experiments.

In three species of anima's, the changes in heart rate occured independent of changes in systemic blood pressure. Vagotomy also abolished, or greatly lessened, the increase in frequency of breathing due to hypoxia (11).

DISCUSSION

In the animals breathing air vagotomy showed no significant effect on heart rate in rabbits and sheep, suggesting an absence of vagal cardioinhibitory tone in these anesthetized animals. This might be explained by the finding of Korner and associates (15) and Karezewski and Widdicombe (12) who showed that chloralose-urethane and sodium pentobarbitone anesthesia eliminate reflex cardiac parasympathetic activity in the rabbit. Croker and Johnson (1) using atropine to block vagal afferent fibers to the heart, also reached the same conclusion. Our results show that there is a significant vagal tone in the anesthetized dog. This is not different from the observations made on unanesthetized dogs of Shepard and Whitty (16). Presence of vagal cardioinhibitory tone in anesthetized dogs and absence of vagal tone in the anesthetized rabbits and sheep suggests that there is species difference in resting vagal tone during anesthesia.

Section of the vagi in dog and sheep abolishes the inhibitory effect of aortic baroreceptors on cardiac rate. The results show that in sheep this afferent pathway does not influence the cardiac rate. However, it might contribute to tachycardia observed in dogs.

The results of the present experiments in rabbits and dogs with intact vagi during hypoxia, agrees with previous publications (1,3,4,7,14 and 17). The results with sheep are similar to that of dogs (Fig. 4e). Therefore, reflex vagal afferent inputs initiated by hyperventilation might have caused the observed tachycardia.

In vagotomized hypoxic animals the heart rate is under opposing influence of chemoreceptor stimulation which decreases the sympathetic discharge and direct hypoxic stimulation of CNS which increases cardiac sympathetic tone. In the present experiments, the tachycardia observed in dogs and sheep in the absence of vagal afferent inputs, confirms direct electroneurographic studies on the dog and cat (6,7,8,9) that during total hypoxia primary mechanism of control of the heart rate is central in origin. Our results in the rabbit show that after vagotomy the bradycardia is reduced but is still present which means that chemoreceptor stimulation still dominates the effect of CNS stimulation.

REFERENCES

1. Crocker, E.F., R. O. Johnson, P. I. Korner, J. B. Uther and S.W. White. Effects of hyperventilation on the circulatory response to arterial hypoxia of the rabbit. *J. Physiol.*, **199:** 267-282, 1968.
2. Daly, M. De Burgh and M. J. Scott. The effects of stimulation of the carotid body chemoreceptors on the heart rate in the dog. *J. Physiol.*, **144:** 148-166, 1958.
3. Daly, M. De Burgh and M. J Scott. The cardiovascular responses to stimulation of the carotid body chemoreceptors in the dog. *J. Physiol.*, **165 :** 179-197, 1963.
4. Daly, M. De Burgh and J.L Hazzledine. The effects of artificially induced hyperventilation on the primary cardiac reflex response to stimulation of carotid bodies in the dog. *J. Physiol.* **168:** 872-889, 1963
5. Daly, M. De Burgh and A. Unger. Comparison of the reflex responses elicited by reflex stimulation of the separately perfused carotid and aortic body chemoreceptors in the dog. *J. Physiol.*, **182 :** 379-403, 1966.
6. De Gees, H., M. N. Levy and H. Zieske. Reflex effects of chephalic hypoxia hypercapnia and ischemia upon ventricular contractility. *Circ. Res.*, **17 :** 349-358, 1965.
7. Downing, S. E., J.P. Remensnyder and J. H. Mitchell. Cardiovascular response to hypoxic stimulation of the carotid bodies. *Circ. Res.*, **10 :** 676-685, 1962.
8. Downing, S.E., J. H. Mitchel and A. G. Wallace. Cardiovascular responses to ischemia, hypoxia and hypercapnia of the central nervous system. *Am. J. Physiol.*, **204:** 881-887, 1963.
9. Downing, D.E. and J. H. Siegel. Baroreceptor and chemoreceptor influences on sympathetic discharge to the heart. *Am. J. Physiol.*, **204 :** 471-479, 1963.
10. Downing, S.E. Autonomic influences on cardiac function in systemic hypoxia. Proceeding of the International Symposium on Cardiovascular and Respiratory Effects of Hypoxia. Ed. Hatcher J. D. and Jennings D.B., Basel: Karger. PP. 208-231, 1966.
11. Kashani, M. and A. L. Haigh. The effect of vagotomy on ventilation and blood gas composion in dog, sheep and rabbit. *Quart. J. Expet. Physiol.*, **60 :** 285-298, 1975.
12. Karczewshi, W. and J. G. Widdicombe. The effect of vagotomy vagal cooling and efferent vagal stimulation on breathing and lung mechanics of rabbits. *J. Physiol.*, **201:** 259-270, 1969.
13. Korner, P.I. Circulatory adaptation to hypoxia. *Physiol. Rev.*, **39 :** 687-730, 1959.
14. Korner, P.I. The effect of section of the carotid sinus and aortic nerves on the cardiac output of the rabbit. *J. Physiol.*, **180 :** 266-278, 1965.
15. Korner, P.I., G. Langsford, D. Starr, J. B. Uther, W. Ward and S.W. White. The effects of chloralose-urethane and sodium pentobarbitone anesthesia on the local and autonomic components of the circulatory response to arterial hypoxia. *J. Physiol.*, **199 :** 283-202, 1968.
16. Shepard, R. S. and A. J. Whitty. Bilateral cervical vagotomy: a longterm study on the unanesthetized dog. *Am. J. Physiol.*, **206 :** 265-269, 1964.
17. Scott, M. J. Effects of hyperventilation on the reflex cardiac response from the carotid bodies in the cat. *J. Physiol.*, **186 :** 307-320 1966.