J. Physiol. (1939) 95, 454–463 612.819.911:612.89.089.87

THE ROLE OF THE VAGUS IN THE CARDIO-ACCELERATOR ACTION OF MUSCULAR EXERCISE AND EMOTION IN SYMPATHECTOMIZED DOGS

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(*Received* 4 *July* 1938)

Chronically, totally sympathectomized dogs[2] manifest a cardio-accelerator mechanism which can be elicited by atropine and which is mediated by vagal cardio-accelerator fibres arising from or relayed through the vagal nucleus [Brouha & Nowak, 1939]. Supplementary to this pharmacological study, we have extended the previous investigations of Brouha, Cannon & Dill [1936] on the response of this mechanism to physiological stimuli such as muscular exercise and emotional excitation.

Methods

Muscular exercise. The technique was similar to that we reported in 1936. Dogs were trained to run on a motor-driven treadmill, the gradient and speed of which could be regulated. The tests were made 18–24 hr. after the last meal. The gradient of the treadmill was varied from 0 to 17 % and the linear speed from 88 to 176 m./min. The mechanical work varied from 70 to 200 kg.m./min./kg. body weight.

Emotional excitation. This stimulus was produced by the sudden entrance of one of us into the treadmill room, by ringing a bell that ordinarily served as a signal for starting the treadmill, or by handling the starting switch. While by no means quantitative, these stimuli produced emotional excitement with cardiac acceleration in the trained dog.

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[2] The term "totally sympathectomized" is used in the manner employed by W. B. Cannon. Strictly speaking, it refers to an animal with both thoraco-lumbar ganglionic chains and upper sacral ganglia removed.

Heart rate. The heart frequency was recorded by a modified Boas cardio-tachometer. The maximal heart rates as reported in our tables are calculated on the basis of the maximal value observed in any 6 sec. period.

Results

The results of this investigation are based upon nine completely sympathectomized dogs. Two of these were subsequently vagotomized. The dogs were observed over a period of from 14 days to 3½ years after total sympathectomy.

Effect of emotion on the heart rate of the totally sympathectomized dog

From 25 to 60 days after sympathectomy this response reaches a maximal value of 160 beats/min. From two months to three years after, the same stimulus gives maximal heart rates reaching 196 beats/min.

Effect of muscular exercise on the totally sympathectomized dog

The heart rates of these dogs during exercise varied from 173 to 268 beats/min. The minimal rate was observed in dog Foxie 14 days after total sympathectomy and represents 60 % of the normal reaction for the same exercise. This dog's maximum reached 226 beats/min. 44 days after sympathectomy, representing about 90 % of the normal response. Table I gives the details of typical reactions of two of the nine dogs.

Table I. Effect of exercise on the heart rate at various intervals after sympathectomy

Dogs	State	Time interval days	Amount of work* kg.m./min.	Duration of work min.	Heart rate, beats/min. At rest	After 1 min.	Maximum
Foxie	Sympathectomized	14	125	10	95	144	173
		16	125	10	97	152	174
		25	125	10	100	190	205
		44	135	25	88	189	226
Abel	Sympathectomized	330	100	25	90	180	186
		330	150	25	72	200	220
		330	175	25	89	197	212
	+ Unilateral adrenalectomy, contralateral demedullation; sympathectomy 11 months before	8	150	15	85	220	218
		14	150	25	88	210	215
		16	175	25	90	212	212
	+ Inferior cervical ganglia out; sympathectomy 13 months before	8	150	5	83	245	252
		10	100	25	70	218	205
		29	150	25	100	245	245
		120	175	15	105	260	268
		800	175	25	88	—	265

* The unit of work employed in this paper is kg.m./min./kg. body weight. It has been discussed in more detail by Brouha *et al.* [1936].

The nature of the cardio-acceleration is illustrated in Fig. 1. The curve has characteristics that depend also upon the time elapsed since the completion of sympathectomy. In dog Foxie, 14 days after the last operation, the heart rate rises gradually from 115 to a plateau of about 170 in 6 min. This plateau value is maintained as long as exercise continues. During recovery the heart rate decelerates gradually; the initial rate is reached in 3 min. Twenty-five days after sympathectomy the curve is steeper, reaching 178 after 30 sec. as compared with 144 in the earlier experiment. The contrast in deceleration in recovery is even more striking.

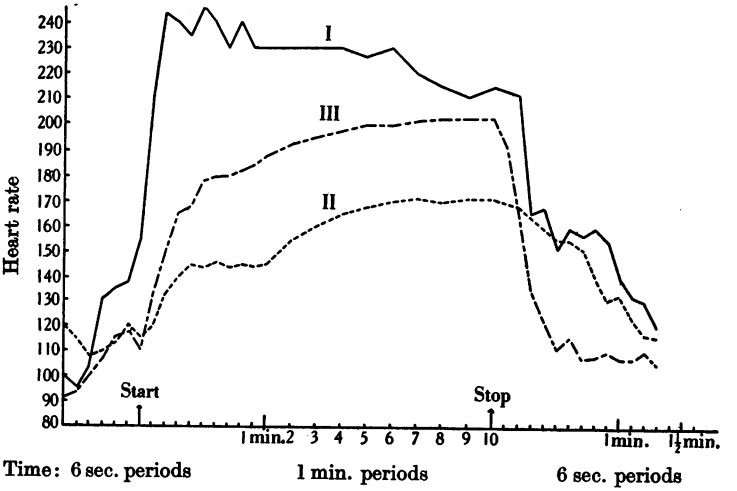

Fig. 1. Dog Foxie. Heart-rate response to exercise: 125 kg.m./min. for 10 min. I. Normal. II. 14 days after total sympathectomy. III. 25 days after total sympathectomy.

Whereas, during the early post-sympathectomy period atropine and emotion rarely raised the rate above the average value for the "denervated, adrenal-inactivated heart",[1] muscular exercise elicited a rate of 173, 14 days after sympathectomy. Eleven days later the maximum after emotional stimulation was 160, during exercise, 205, and after atropine injection, 222.

The results on dog Abel may be used to illustrate the typical curve of a chronically sympathectomized dog which resembles in every respect the normal pattern. Three and a half years after sympathectomy the heart rate at an energy expenditure of 175 kg.m./min. rises sharply from 100 to 240 in 18 sec. The corresponding values in the same work before the

[1] For definition of this term see Brouha & Nowak [1939].

operation were 120 and 253 respectively. In each case, the deceleration is immediate with return to the resting value in 1 min. The features of sharp ascent and descent seen in this curve become apparent about one year after completion of sympathectomy and remain unchanged after supplementary sympathetic procedures. The maximal rate of dog Abel increased progressively up to 268, 17 months after sympathectomy, a rate about nine-tenths the maximum observed in normal dogs. The length of time necessary for the development of this accelerator mechanism varies from dog to dog.

Effect of muscular exercise and emotion in dogs with supplementary sympathectomies following thoraco-lumbar ganglionectomy

In three dogs supplementary sympathetic procedures were carried out for the reasons and in the same manner stated in our studies on atropine. As shown in Table I (dog Abel) these procedures did not alter the typical cardio-accelerator response. The same results were obtained with respect to emotion.

Effect of muscular exercise and emotion on the totally sympathectomized and chronically vagotomized dog

Inasmuch as our results with muscular exercise and emotion were comparable to, and in fact more striking than those with atropine, we proceeded to the question of the role of the vagal cardio-accelerator fibres in these reactions.

Chronic bilateral vagotomy was performed in two dogs (Blacky and Foxie) which were previously sympathectomized. The left vagus was divided in the chest and subsequently the right vagus in the neck in dog Blacky and intracranially in dog Foxie [Brouha & Nowak, 1939].

After unilateral thoracic cardio-vagotomy these sympathectomized dogs showed an increase in the heart rate similar to that observed in the sympathectomized dog in response to muscular exercise (Table II).

On the day after bilateral vagal section the following unusual findings are of interest. Before exercise the heart rate of dog Blacky standing on the treadmill was 175–185 beats/min. This unusually high control rate was attributed to excitement. Eighteen seconds after start of the run the heart rate rose to 210, where it remained with slight variation during the exercise. The rate after the run declined slowly, requiring 50 min. to diminish to 165 beats/min.

Later on the same day this dog showed a heart rate at rest of 125–140. Atropine slowed the rate to 118. When subjected to the same muscular

work for 1 min. the heart rate rose abruptly to a maximum of 150 (under atropine). During a second run of 2 min. the heart rate increased from 140 to 168 beats/min. This rate returned to 140 in 1½ min.

TABLE II. Effect of exercise on the heart rate after sympathectomy and vagotomy

State	Time interval days	Amount of work kg.m./min.	Duration of work min.	Heart rate, beats/min. At rest	After 1 min.	Maximum
(*a*) Sympathectomized + left cardio-vagotomy	180	175	15	108	215	233
	180	125	10	110	210	215
(*b*) Sympathectomized + left cardio-vagotomy + right cervical vagotomy	½	175	2	175	210	210
	1	175	2	130	160	168
	6	175	2	128	154	162
	11	175	1½	110	149	158
	11	150	4	112	142	150
	19	175	1½	115	152	159
	19	150	4	118	148	158
	27	85	10	123	145	158
	36	175	2	110	150	150
	75	175	1½	113	142	145

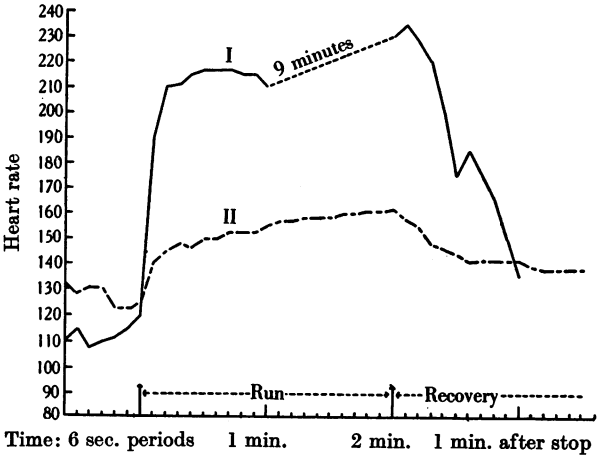

Fig. 2. Dog Blacky. Heart-rate response to exercise: 175 kg.m./min. I. Total sympathectomy and unilateral cardio-vagotomy (10 min. run). II. 19 days after cervical section of the other vagus (2 min. run).

On subsequent tests the heart rate showed a progressively decreasing response to the same intensity of work, from 162 on the 6th day to 145 on the 75th day, a value well within the limits of the automatic rate. After exercise the resting rate was attained within 2–3 min. (see Fig. 2 and Table II).

Along with this diminished accelerator response to exercise after bilateral vagotomy, dog Blacky showed a striking reduction in ability to

carry out severe work. For example, after sympathectomy and before vagotomy, this dog ran at an energy expenditure of 175 kg.m./min. for 100 min. without the slightest evidence of exhaustion. When vagotomized, running at the same rate exhausted him in about 2 min. This decreased ability for work could not be attributed to such factors as impaired health, lack of appetite, under-nourishment or pyrexia. In fact, this dog was just as eager to run after vagotomy as before.

After vagotomy light muscular exercise could be carried out with ease; only in severe work was the reduced capacity evident. For example, at 85 kg.m./min. this dog ran for 45 min. without apparent fatigue, the heart rate reaching 159. At 150 kg.m./min. he could run only for 4 min., again with a heart rate of about 160. Apparently this upper limit could not be passed regardless of the intensity of work.

During light and severe exercise at 14–19° C. this dog showed no panting and exhibited a diaphragmatic type of breathing resembling that seen in the dyspnoeic human being with respect to depth, labour and frequency.

Except for these peculiarities and occasional vomiting the general behaviour of a sympathectomized and bilaterally vagotomized dog about the laboratory does not distinguish it from a normal animal. The life span of such dogs may be short, however, because of inanition and susceptibility to pneumonia. Dog Blacky survived bilateral vagotomy 78 days and died after several days of vomiting. Post-mortem examination revealed bilateral lower-lobe pneumonia and a retrograde gastro-oesophageal intussusception involving two-thirds of the stomach. Foxie was still alive 10 months after double vagotomy.

Effect of emotion on the totally sympathectomized and vagotomized dog

After *unilateral vagotomy* emotional stimulus increased the heart rate. Dog Blacky, for example, responded by an increase from 120 to 165 about 6 months after unilateral intrathoracic vagotomy. After *bilateral vagotomy*, when atropine causes a slight decrease in heart rate [Brouha & Nowak, 1939], excitement produced an increase of 120–150 and 105–130, 1 day and 11 days, respectively, after this section. Thus, emotional excitement in the chronically vagotomized-sympathectomized dog may elevate the heart rate.

Possible factors responsible for cardiac acceleration in the sympathectomized-vagotomized dog

1. *Body temperature.* In the totally sympathectomized dog we observed that the rectal temperature after exercise showed changes which were completely within the range of normal variation, corroborating the findings of Brouha *et al.* [1936].

The results on dog Blacky may be used as an illustration. When normal, this dog running at 175 kg.m./min. for four successive periods of 25 min. with intervals of 5 min. for rest increased his rectal temperature as follows: from 38·8 to 39·6 in the first period, to 39·4, 39·5 and 39·3° C., respectively, for the subsequent periods. Two months after complete sympathectomy under the same conditions of exercise, the temperatures at corresponding times were 38·9, 39·7, 39·8, 39·7 and 39·6° C., respectively. Temperature regulation was thus unimpaired.

The effect of exercise after unilateral cardio-vagotomy was studied on dog Foxie; this procedure did not affect temperature regulation.

Bilateral vagotomy, on the other hand, caused an increase in the response of the body temperature to muscular exercise. One month after bilateral vagotomy dog Blacky showed a rise of rectal temperature from 39·8 to 40·4° C. after a run of 2 min. at 175 kg.m./min.

This dog, 20 days after bilateral vagotomy, was submitted to a four-period test as described above, except the work intensity was 85 kg.m./min. The initial rectal temperature of 39·4 increased to 40 after the first run of 25 min., to 40·7 after the second, to 41 after the third, and to 41·3° C. after the fourth. With these data in mind it is interesting to note that the highest recorded rectal temperature after exercise in this dog when normal was 41° C. after a run of 68 min. at 250 kg.m./min. and with a room temperature of 14° C. A significant impairment of capacity for temperature regulation is evident.

Is this impairment of temperature regulation responsible for the acceleration which still occurs in the sympathectomized-vagotomized dog? Knowlton & Starling [1912] have shown that the rate of the isolated heart may increase 6–15 beats/min. with a rise in temperature of 1° C. That this factor was not completely responsible for the acceleration in this type of dog during exercise was shown by the results on Blacky running in a hot room. Under constant environmental temperature of 45° C. and constant working conditions, this dog showed, for the same maximal body temperature (42·2° C.), maximal heart rates which varied as follows: 183 on the 26th, 170 on the 46th, and 160 on the 69th day after

vagotomy. It appears, therefore, that the maximal heart-rate response to muscular work in the sympathectomized-vagotomized dog is not necessarily dependent upon conditions of body temperature alone.

2. *Blood lactate.* Brouha *et al.* [1936] stated that the blood lactate concentration in the exercising dog was within normal limits after chronic sympathectomy.

Unilateral vagotomy, furthermore, in the sympathectomized dog was observed by us to cause no significant changes in lactate response. Dog Foxie, 35 days after sympathectomy, running at the rate of 135 kg.m./min., showed an increase of 10·4 mg./100 c.c. (8·9 to 19·3) in blood lactate. Eight days after unilateral vagotomy under the same conditions the blood lactate showed an increase of 10·5 mg./100 c.c. (12·3–22·8).

Bilateral vagotomy in the totally sympathectomized dog, however, produced changes which led to a striking blood-lactate response after much less muscular work, as shown in dog Blacky (see Table III).

TABLE III. Effect of exercise on the blood lactate in the sympathectomized-vagotomized dog

State	Time interval days	Amount of work kg.m./min.	Duration of work min.	Blood lactate mg./100 c.c. Control	Blood lactate mg./100 c.c. After work	Maximal heart rate beats/min.
Normal	—	175	217	10·5	19·5	266
Sympathectomized	30	175	100	9·7	17·3	220
Sympathectomized and bilaterally vagotomized	1	175	2½	11·1	89·7	210
	6	175	2	10·0	79·0	162
	11	175	2½	11·3	74·4	158
	27	175	2	11·8	65·4	161
	27	85	100	12·6	32·2	158

Although the sympathectomized-vagotomized dog shows a remarkable accumulation of blood lactate after exercise this factor could not be correlated with heart-rate changes. For example, on the 27th day after vagotomy, this dog, subjected to a severe and a mild work test, reached practically the same heart rate (161, 158, respectively) with a striking difference in lactate concentration (65·4, 32·2, respectively).

Without going into detail in regard to *p*H changes which will be reported subsequently, it suffices to say that changes in this factor could not be correlated with changes in heart rate.

DISCUSSION

It is clear that muscular exercise and emotion in the sympathectomized dog evoke a cardiac acceleration which increases progressively up to a maximum approximating that found in the normal dog exposed to

the same conditions. Exercise may elicit heart rates above the "denervated, adrenal-inactivated" level as soon as 14 days after sympathectomy. Up to a certain point the capacity for work is proportional to the amount of cardiac acceleration [Dill & Brouha, 1937; Robinson, 1938]. The limited performance during the early post-sympathectomy period is, therefore, not strictly attributable to lack of training but to inadequate cardiac acceleration.

The marked acceleration after thoracic-abdominal ganglionectomy is not due to incomplete sympathectomy or regeneration for reasons discussed in the paper by Brouha & Nowak [1939]. Neither could it be ascribed to activity of the remaining part of the sympathico-adrenal system, as shown by the results after removal of the supplementary components.

It is interesting to reflect that total suppression of the sympathetic system, with its apparently innocuous effect upon the behaviour of the dog under stress and strain, implies that various afferent mechanisms which operate via this system are deprived of their effector agent and are, therefore, functionless; chief of these are the carotid sinus reflexes. Thus it appears that the sympathectomized dog is able to regulate its metabolic needs for severe work without the mediation of these reflex agencies.

On the other hand, chronic bilateral vagotomy in the sympathectomized dog seems to be the only neurological procedure which reduces the acceleration response to within the limits of the value for the "denervated, adrenal-inactivated heart". This finding proves that vagal section interrupts accelerator fibres to the heart which previously caused acceleration well above this level in response to emotion or exercise. This accelerator mechanism, with regard to its latency of appearance, its progressive character and its comparability to the normal cardiac acceleration, is similar to that observed in response to atropine.

How is one to explain the increase in heart rate from the minimal resting level of 110 to the maximal work value of 162 after chronic vagotomy? From our data we cannot ascribe this increment to increase in body temperature or to blood lactate alone, because of the lack of quantitative relationship between these variables. Other possible factors are the unusual nature of the respiratory movements of the running dog or the liberation of some accelerator substance from the liver or other organs. The nature of this mechanism requires further study. It seems that the reduction of the running ability of the sympathectomized and vagotomized dog might be due to impairment of respiration as well as reduced cardiac acceleration.

Conclusions

1. The chronically, totally sympathectomized dog develops a cardio-accelerator response to emotion and to muscular exercise and the heart rate may attain values of 195 and 268 beats/min. respectively.

2. This accelerator mechanism comes into play in response to muscular work as early as 14 days after sympathectomy. Its effectiveness progresses with time and reaches about one year after sympathectomy a maximal value representing 80–90 % of the normal reaction.

3. Some time after bilateral section of the vagi, emotional excitement does not increase the heart rate above 140.

4. Bilateral vagotomy produces a striking reduction in the cardiac acceleration in response to muscular work. Thus, acceleration in the sympathectomized dog in response to emotion and work is explained on the basis of a vagal cardio-accelerator mechanism.

5. Emotion and exercise are still capable of eliciting a slight acceleration, the nature of which is discussed with respect to body temperature, chemical, metabolic, neurogenic and respiratory factors.

6. Bilateral vagotomy (cervico-thoracic) produces an alteration in the type of breathing during muscular exercise characterized by deep diaphragmatic respiratory movements and absence of panting.

7. Capacity for muscular exercise is markedly reduced by bilateral vagotomy.

8. Temperature regulation during exercise after vago-sympathectomy is strikingly altered.

9. Vago-sympathectomy also causes a marked increase in the blood lactate response to exercise.

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