Cardiovascular response to graded exercise in the sympathectomized-vagotomized dog

ASHKAR, EDMUNDO, AND WILLIAM F. HAMILTON. Cardiovascular response to graded exercise in the sympathectomized-vagotomized dog. Am. J. Physiol. 204(2): 291-296. 1963. Seven dogs who ran well on a motor-driven treadmill were completely sympathectomized (including adrenal denervation) and subjected to unilateral vagotomy below the recurrent laryngeal branch. After recovery and retraining, a terminal experiment was performed in which, after completing the vagotomy, direct Fick determinations of cardiac output and continuous recordings of mean arterial pressure, heart rate, and oxygen consumption were made at rest and during increasing exercise. The results were compared with those described by Barger et al. (Am. J. Physiol. 184: 613, 1956) for normal dogs running at smaller speeds and grades. The heart rate of the operated dogs increased from 117 to 134. Barger's normal dogs doubled their heart rate. The A-V oxygen difference increased with work slightly less than Barger's normal dogs but the scatter in both groups was wide, as was the case with the stroke volume. The resting cardiac output was nearly normal in the operated dogs but increased only 34% with exercise, as against 200-300% in Barger's normals. Oxygen consumption increased about twofold as against the expected normal of three- to sevenfold. Peripheral resistance in both groups went down about 40%. The blood pressure in the normal increased substantially while that in the operated dogs fell about 20% to an average of 60 mm Hg.

METHODS

Seven mongrel dogs of either sex, weighing 10-16.5 kg, were selected for their ability to run on a motor-driven treadmill. During 3 days they were trained to run easily and automatically at several rates between 3 mph-5% and 7 mph-15% grade. When the animals learned to do this, the left and right thoracicolumbar sympathetic chains were removed completely (6). The right vagus nerve was cut below the right recurrent laryngeal branch and the left vagus was left intact. The surgical procedure was carried out, step by step, over a period of 2 weeks. Ten days after the last operation, short bouts of graded exercise regained the previous training. After this retraining, minor surgery in the neck under light pentobarbital anesthesia prepared the animal for tracheal intubation and blood vessel cannulation. The trachea, right and left vagus nerve, left carotid artery and right jugular vein were dissected free and loose ligatures were placed. The right vagus nerve was cut below the right recurrent laryngeal branch and the left vagus was left intact. The surgical procedure was carried out, step by step, over a period of 2 weeks. Ten days after the last operation, short bouts of graded exercise regained the previous training. After this retraining, minor surgery in the neck under light pentobarbital anesthesia prepared the animal for tracheal intubation and blood vessel cannulation. The trachea, right and left vagus nerve, left carotid artery and right jugular vein were dissected free and loose ligatures were placed. The right vagus nerve was electrically stimulated and absence of heart rate changes confirmed with a stethoscope. A day later, a radio opaque catheter was introduced through the jugular vein and the catheter tip placed, under fluoroscopy, in the main pulmonary artery. A double...
lumen, rigid polyethylene catheter with metallic head was introduced into the left carotid artery down to the aortic arch for blood sampling and mean or pulse pressure recordings. The trachea was incised and a no. 40 Foregger endotracheal tube with an inflatable cuff introduced. Finally, the left vagus was severed in the neck and the wounds sutured. Afterwards, the dogs were exercised on the treadmill at 3 mph—5%, 5 mph—10%, and 7 mph—15% grade. The dogs seemed as willing and alert after denervation as before. They ran with good coordination and elan. Dogs 1 and 4 ran well at 3 mph but rebelled at the higher speeds. Dog 2 rebelled at 7 mph. The other dogs ran well over the whole course. They were not apathetic nor did they give any outward sign that their hearts were not responding properly and their arterial pressure was falling to ca. 50-60 mm Hg (see below).

Each bout of exercise lasted 10 min, and 60 min elapsed between bouts. All recordings and determinations were made simultaneously. Data entered in the table and figures were obtained during the terminal steady state of each bout of exercise. Continuous recording of mean aortic blood pressure was made with a Statham P 23 Gb transducer connected to a DR-8 Electronics for Medicine photorecorder. The manometers were sutured (under local anesthesia) to the skin behind the shoulder to insure an accurate zero for the record measurement. Reference recordings were made at each treadmill setting with the animal standing in position and the gauge open to the atmosphere just before the treadmill was started. Heart rate was counted from pressure recordings.

Oxygen consumption was continuously recorded during the last 8 min of exercise with a Sanborn E-I-S spirometer. The bell of this apparatus is balanced by a spring so that at the top of the excursion there is a slight positive pressure in the bell. This pressure becomes less until the middle of the excursion, when the pressure is atmospheric. Below this, the pressure in the bell is negative. Thus, if there is any leak, it would be outward at the top and inward at the bottom of the excursion, giving a curved record, convex to the base line, even with very small leaks. There was no evidence of leaks, or of CO₂ accumulation in any of the experiments reported.

The respiratory rate was counted directly and volume of ventilation measured from the spirometer record. Blood sampling was done during the last 2 min of exercise with a dual withdrawal Harvard pump, and specimens were stored in an ice bath and analyzed in duplicate between bouts of exercise by the method of Van Slyke and Neil (11). Resting values were obtained with the dog at recumbent position after a rest period of 30 min before the start of exercise. Food was withheld 24 hr before experiments and water was given ad libitum.

RESULTS AND IMPLICATIONS

Heart rate. Figure 1 and Table 1 show that the average heart rate changes from 117 to 134 as the animals increase the intensity of the work. As can be seen from Table 1, the changes are usually parallel in each dog to the changes in work level and are, therefore, regarded as significant in spite of the rather large scatter of resting and working heart rates.

The contrast between the very small shift in heart rate seen here and the response of the normally innervated heart is striking. Barger et al. (5) have followed the changes in heart rate and other physiological parameters in normal dogs during treadmill work similar to, but of somewhat less intensity than that described here. The average standing heart rate was 160, which increased to ca. 200. This was seen when the oxygen consumption might be anywhere between 800 and 1,400.

In other words, the heart rate of the normal dog may be expected to double during the transition between
standing and working. The dog without autonomic cardiovascular control has an average increase of 14% when changing from recumbency to work of an even greater intensity. This restricts the cardiac output unless the stroke volume may compensate.

A-V oxygen difference. Figure 2 and Table 1 show that this function was very similar to that listed by Barger et al. for the normal dog (5). The highest (exercising) determinations were 140, and the lowest (resting) was 50. Barger's normal dogs had a slightly larger range, 155-47, but the findings in general were of the same order in the two groups. The large scatter obscures the trend of increase with work, which is indicated by the averages and by a close inspection of Table 1 which shows this trend in the data from individual dogs. In the normal and in the denervated animals the A-V difference increases less at high levels of work than at low levels of work.

The similarity of the A-V difference in the two groups is surprising since it might be expected that the normal animal with undisturbed vasomotor control would distribute blood flow to the more active organs and keep it away from the less active ones and, hence, have a larger A-V difference than the operated animal. The tests were made some time after the denervations and the inherent myogenic tone of the blood vessels had time to become re-established. The findings are compatible with the idea that vascular relaxation serving metabolic activity is not necessarily reflex.

The regulation of heat loss during exercise is usually thought of as bringing large amounts of blood to the surface of the body, which returns to the right heart without loss of appreciable oxygen. This mechanism in the normal animal may cancel any increased A-V difference accruing from directing blood flow toward active organs and would be less effective in the denervated animal.

Stroke volume. (Stroke index). Figure 3 and Table 1 point out that in both the normal and the denervated dog, the stroke volume is characterized by a wide scatter. This obscures any significant evidence in the data from the denervated dogs that the stroke volume
is correlated with the rate of work. An increase in stroke volume is perhaps to be seen in Barger's normal dogs. This increase is apparent in case of two determinations at an O₂ consumption of 1,400 ml/min, but is hardly convincing at lower work rates (5).

Cardiac output. (Cardiac index). Figure 4 and Table 1 show that the cardiac output of the vagoto-sympathectomized dogs averaged 3.8 liters/m² body surface per minute. This is only slightly above that predicted for the basal index (3.1 liters). The fact that no important increase above basal was shown by the denervated animals may well be due to the absence of cardiovascular neurohormonal reflexes.

The effect of these reflexes is displayed in the difference between the resting and working dogs, depending on whether they were normal or vagoto-sympathectomized. The operated dogs showed an increase of 34% at intermediate work and fell to a lower figure at heaviest work. Barger's normal dogs (5), on the other hand increased their output two- or even threefold. This is parallel with the much greater heart rate changes in the normal dog mentioned above. In addition, the normal dogs may well have profited by the inotropic effects of reflex hormone and nerve stimulation, which did not act on the operated dogs but gave the normals a slightly greater stroke volume in spite of a shorter diastolic time for recovery and filling.

Oxygen consumption. As a result of restricted changes in heart rate, A-V difference, stroke volume, and total blood flow, the ability of the denervated animals to transport oxygen to the tissues was severely restricted (Table 1 and Fig. 5). The oxygen consumption (transport) in Barger's normal dogs varied under exercise from a resting average of 207 ml to as much as 1,420 (sevenfold) (5). The average O₂ consumption of our dogs at rest was 155 ml/min (240 ml/min m² body surface). This last is about 70% above the predicted basal of 140 ml. During exercise the average oxygen consumption rose to 340 ml/min (2-fold).

The variability of the two series was similar at rest. The normal dog had oxygen consumption varying between 138 and 238 ml/min and the operated dogs from 100 to 228 (these dogs were smaller and were recumbent rather than standing).

It seems impossible that at a heart rate of 134 (the average at the highest rate of work) the operated dogs could have transported the large amounts of oxygen which the normal dogs managed at their much faster heart rates. To do so, even with the larger A-V differences mentioned in Table 1, would have presupposed a stroke volume of /υ120 ml, figures that are usual for a 70-kg man.

Arterial pressure and peripheral resistance. Figures 6 and 7 and Table 1 show that the arterial pressure of the normal dogs increased about 38% when the resting figures were compared with figures during exercise at any level. In contrast to this, the vagoto-sympathectomized dogs decreased their blood pressure on the average about 20% as a result of exercise. The arterial pressures became very low after heavy work.

It is generally accepted that local anoxia or the local accumulation of resulting metabolites gives rise to a local vasodilation which occurs even in the denervated vascular bed of an active organ. The local dilation in the active muscles, unless compensated for by vasoconstriction elsewhere, would be expected to lower the ratio between the mean arterial pressure and the cardiac output, which has been called the total peripheral resistance. This so-called total peripheral resistance decreases in Barger's normal dogs by about 43% and in the denervated animals by 38% as the result of the exercise in the two groups. No conclusions are justified as to vasomotor activity from the comparison of these figures with each other since arterial pressure was higher in the normal working animals and an increase in arterial pressure is known to produce a distortion of resistance vessels (12) and an increase in flow is known to decrease the viscosity (anomalous viscosity) of the blood. These physical factors would reduce the pressure flow ratio independently of any physiological regulation.

There does not seem to be a significant physiological difference between the changes in "total peripheral resistance" produced by exercise in the two groups of animals. It is, therefore, concluded that the large increase in the cardiac output of the normal animals, and a much smaller increase in the cardiac output of the denervated animals against a similar pattern of peripheral vasomotor response is, in the main, responsible for the fact that arterial pressure rose in the normal animals and fell in the vagoto-sympathectomized animals.

Ventilation. This was measured from the spirometer record. Barger reports resting values at about 7.5 liters/min (standing) and our results were from 3.0 to 6.3 liters/min (smaller dogs recumbent). During work the Barger dogs breathed as much as 63 liters/min. Every dog went up to 39 liters or more. The denervated dogs did not ventilate more than 33 liters even at the heaviest work. The averages were: rest, 4.6 l/min; 3 mph—5%,
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FIG. 4. Relation between rate of work and cardiac index in vagoto-sympathectomized dogs.

15.1 l/min; 5 mph—10%, 17.6 l/min; 7 mph—15%, 23.7 l/min (all with a large scatter). It was noticed that none of our dogs showed the usual thermoregulatory (panting) respiration. This and the minimal dead space (motor driven gas column at the tracheal cannula) may have reduced the comparative rate of ventilation of our dogs. Unfortunately the body temperature was not recorded.

Whether the respiratory mechanisms were handicapped by the operation, or whether the failure to pant and the low dead space sufficed to explain the differences between the normal and operated dogs, we do not know. We do feel, however, that respiratory inadequacy did not hinder their running. They were breathing a high oxygen mixture, their arterial blood was fully saturated and much more oxygen was displayed to their alveolae than to those of normal dogs breathing room air in similar tasks.

DISCUSSION

The animals without autonomic cardiovascular regulation were able to do a surprising amount of running over a 10-min period with very little change in heart rate, cardiac output, or oxygen consumption.

To say that muscular work is parallel to the apparent difficulty of running on a treadmill as calculated from speed and grade is perhaps unwarranted. An animal on a treadmill does not lift his body against gravity even when the grade is steep. It seems to remain stationary in relation to the horizon and only the feet are lifted higher with a steep grade than with a horizontal setting. Before the dog is well trained he tends to pull back against his leash. It has been suggested that this gesture would lessen the dog's effort. We know of no factual evidence to this effect and are inclined to discount it. Pulling back on the leash and using muscular effort to hold the feet, as badly designed brakes, against the pull of the treadmill would seem to be harder work than letting them move back passively with the belt. Of course, when the animal actually slides his feet the experiment is terminated. The force against which a treadmill runner works is in small part gravity, air resistance, and inertia, and is mostly viscous friction of the muscles and other tissues.

At any rate, the above discussion does not set our

FIG. 5. Relation between rate of work and oxygen consumption in vagoto-sympathectomized dogs.

FIG. 6. Relation between rate of work and mean arterial pressure in vagoto-sympathectomized dogs.

FIG. 7. Relation between rate of work and total peripheral resistance in vagoto-sympathectomized dogs.
dogs apart. At the time of the final test they either ran well or were discarded. They seemed to enjoy the run and had learned to avoid the discomfort of pulling hard against the leash. Whatever the amount of muscular effort expended, we feel that it would compare closely with other treadmill dogs whose speed and grade is similarly described.

From a technical standpoint, the measurement of oxygen consumption is the key finding because upon it and the A-V differences depends the conclusion that the cardiovascular response differs in the denervated animals so markedly from the normal response to exercise. Technical reasons are given in the discussion of methods for our confidence in the method. This confidence was confirmed by the fact that the resting figures for both flow and oxygen consumption were very close to that expected of normal dogs and by the fact that a normal working oxygen consumption could hardly be transported to the tissues at the observed heart rates.

The low oxygen consumption and the vigorous work performed lead to the conclusion that a large oxygen debt must have been incurred during the 10-min working periods. Unfortunately, early planning did not include blood lactate determinations and when realization of their importance came about, it was impossible to do this test. However, Campos et al. (9) found that blood levels of lactate and sugar were not correlated with the degree of exhaustion, though they did not seem to have made these determinations in dogs whose working power was reduced by adrenal inactivation and cardiac denervation. It seems probable that the denervated animals could not have prolonged the exercise much longer. As indicated above, several of the dogs rebelled at the more strenuous tasks. This was accomplished by sitting down and letting the smooth belt of the treadmill slide under their braced feet and haunches while they were pulled against the leash. A number of normal dogs showed this behavior and were thus spared the experiment. The best reason for thinking that several of the dogs worked themselves to exhaustion is the fact that the arterial pressure declined to very low figures with strenuous work.

Similar behavior was observed by Campos et al. (9), who showed that denervation of the heart and inactivation of the adrenals would prevent cardioacceleration and restrict working ability. Denervation of the liver (but not the adrenals) restricted working capacity without preventing cardioacceleration. These workers did not measure arterial pressure or blood flow. The source of limitation in work capacity may well lie in these functions.

The low cardiac output, necessitated by the low heart rate, is responsible for the low arterial pressure since the change in peripheral resistance was similar in the two groups.

The factors which may have played a role in the failure of the cardiac output to increase normally are a) the failure of the usual cardioaccelerator responses of an anticipatory nature; b) the associated failure of inotropic effects of these same reflexes to augment the strength of the heart beat; c) presumed failure of these reflexes to constrict the great systemic and pulmonary veins insuring a more rapid flow to the left ventricle and the prevention of venous pooling; d) the abrogation of reflexes from the arterial stretch receptors which, as a result of a decline in arterial pressure, normally act to accelerate and augment the heart and to constrict the arterioles and great veins.

A clue as to what role a disturbance in venous return may have played could possibly have been gained by following changes in venous, or preferably left atrial pressure during work. Unfortunately, these measurements were not thought of in time.

REFERENCES