Response to exercise in dogs with cardiac denervation

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DONALD, DAVID E., AND JOHN T. SHEPHERD. Response to exercise in dogs with cardiac denervation. Am. J. Physiol. 205(2): 393-400. 1963.—Dogs with chronic cardiac denervation by the technic of regional neural ablation showed an unchanged capacity for work as measured by oxygen consumption. The relation of cardiac output to oxygen consumption during exercise remained unchanged from preoperational values. When the dogs started to run, the heart rate rose slowly over 1.5 min to reach a steady value proportional to the work performed. When exercise was stopped, the heart rate declined slowly. With mild exercise, the increase in cardiac output was mainly through stroke volume; with more severe exercise, increase in stroke volume and heart rate contributed equally, in contrast to the normal dog where the increase in rate predominates. Neither the pattern of the change in heart rate nor the plateau values were altered by adrenalectomy. The change in rate was not attributable to change in intravascular temperature. In an equivalent dose of base, norepinephrine caused tachycardia but little or no change in cardiac output, whereas epinephrine resulted in an increase in cardiac output with but a modest increase in heart rate.

In 1914 Patterson, Piper, and Starling (1) demonstrated that the isolated heart possessed an intrinsic mechanism whereby it met the demands of an increased volume or pressure load. However, the studies of Gasser and Meek (2) and of Samaan (3) indicated that the animal deprived of its cardiac autonomic nerves suffered severe limitation in its ability to exercise. One might infer from their work that the Starling mechanism was inadequate to furnish the increased cardiac output seen in the intact exercising dog. Indeed, the importance of vagal and sympathetic nerves in controlling the action of the heart has been emphasized repeatedly in recent years.

Sarnoff and his colleagues (4, 5) have shown how increased sympathetic activity modifies the ventricular function curve and the force of atrial contraction. Thus, as the heart accelerates, the greater vigor of atrial and ventricular systole and the shortening of systole permitting adequate filling time allow the heart to cope efficiently with any flow likely to be presented to it. Rushmer and his colleagues (6), by stimulating the sympathetic nerves to the heart and localized hypothalamic areas, have induced changes which closely simulate left ventricular responses to exertion. From simultaneous measurements of right and left ventricular outputs at the onset of exercise, Franklin and associates (7) concluded that changes in venous return are not dominant mechanisms inducing alterations in cardiac output. Warner (8) has postulated that the increased cardiac output that accompanies exercise is mediated, at least in part, by pressorceptors, although Leusen and associates (9) found that with the same work the cardiac output was similar in dogs with and without carotid and aortic pressorceptors.

However, the basic responses of the intact animal with cardiac denervation have not been defined clearly since the original method of cardiac denervation affected many organs other than the heart and it was difficult to keep the dogs in condition due to gastric dilatation and persistent vomiting. Recently a method of cardiac denervation has been described in which denervation was limited to the heart and, unlike sympathectomy or the heart-lung preparation, essentially deprived the heart muscle of catecholamines (10).

The purpose of the present study was to describe the response of the cardiovascular system to exercise in dogs in whom cardiac denervation was carried out by this technic.

METHOD

Mongrel dogs were trained to run on a treadmill at various speeds and with the treadmill platform inclined at varying degrees to horizontal. Measurements of cardiac output, heart rate, oxygen consumption, and arterial hematocrit were made on two occasions before, and two after cardiac denervation by the regional neural ablation technic of Cooper and his associates (10). On each occasion several work levels were studied up to the maximal work that the dog could be induced to carry out. In addition, bouts of exercise frequently were undertaken in which oxygen consumption and heart rate, or heart rate alone, were measured. In four dogs with chronic cardiac denervation, measurements of

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oxygen uptake and heart rate during graded exercise were made before and after adrenalectomy. In six dogs with chronic cardiac denervation, measurements of heart rate, cardiac output, and oxygen consumption were made under resting conditions during the infusion of epinephrine and of noradrenaline. As a check on the completeness of cardiac denervation, 4 mg of atropine and 30-60 μg Tyramine/kg body wt. were administered intravenously to the conscious animals at intervals throughout the study. On completion of the study the animals were anesthetized with pentobarbital and a further test of the completeness of denervation was obtained through electric stimulation of the cardiac ends of the divided cervical vagal trunks, the stellate ganglia, the thoracic paravertebral ganglionic chain, and, if identifiable, the initial portion of the cardiac sympathetic nerves. Unipolar and bipolar stimuli were used with a wide range of strength, frequency, and duration (5-30 V; 5-30 stimuli/sec; 0.3 to 5.0 msec duration).

The only difference from the published technic of Cooper and co-workers (16) was the use of bilateral thoracotomy instead of median sternotomy. Oxygen consumption was measured by collection and analysis of expired air, for which purpose a permanent tracheotomy was constructed. This was done as a two-stage procedure, the sternothyroid and sternothyrohyoid muscles being removed and the trachea left immediately beneath the skin as a first step. Three to four weeks later a circular opening, 1 cm in diameter, was made through the skin and underlying cartilage into the trachea some 4 cm from the larynx. A flanged tracheal plug was inserted and supported in position by a plastic strap fastened around the animal's neck. Collection of expired air was effected by removal of the tracheal plug and insertion into the trachea of a cuffed 4-cm Tygon tube (5' in. i.d.) attached to a glass U-tube carrying inlet and outlet valves (Collins' J type valve). The glass U-tube fitted snugly to the animal's neck and the apparatus was easily carried by the dog during exercise. Oxygen content was determined by passing gas samples through a thermostable cuvette holding two Clarke PO2 electrodes. The electrodes were calibrated with known concentrations of oxygen before and after each gas sample, and spot checks were made with the Haldane apparatus.

Cardiac output was measured by the indicator-dilution technic with injection of indocyanine green into the right atrium and sampling from the aorta. On some occasions the catheters were inserted by pereuteaneous puncture of the jugular vein, and directly into the common carotid artery exposed under local anesthesia on the evening prior to the test run. Otherwise the left kidney was removed under sterile conditions and catheters were implanted via the left renal artery and renal vein. The catheters were kept patent by daily flushing with a solution of heparin until the animals were tested a week later. Heart rate was recorded from transthoracic electrodes by means of a direct-writing Sanborn cardieter.

RESULTS

The operation for cardiac denervation was carried out in 14 dogs. The data presented were obtained on nine dogs with proven cardiac denervation. Three animals died during or immediately after operation. Cardiac denervation was incomplete in two animals. The surviving animals appeared clinically well and remained in good condition over several months of study.

Heart rate. In the dogs with cardiac denervation the resting heart rate lay between 90 and 120 beats/min. Sinus arrhythmia was absent, and if the animal was not...
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Rest Exercise Recovery

Rest Exercise Recovery

OXYGEN UPTAKE (ml/minute)

FIG. 3. Relation of heart rate to oxygen uptake at rest and during exercise in a dog: ○ before operation, ● after cardiac denervation, ○ after denervation and adrenalectomy. The dotted lines have been drawn by inspection. The points plotted represent the average heart rate during the last minute of a 3-min period of exercise.

FIG. 2. Heart rate response to severe exercise (11 km/hr, 15° tilt) in four dogs before (— — ) and after ( — — ) complete cardiac denervation. The average oxygen consumption was 60 ml/kg body wt. min.

Disturbed the R-R interval remained almost constant for 1 hr or more. When the animal was suddenly startled or excited the heart rate did not show any immediate change in contrast to the marked tachycardia seen in the normal dog. The intravenous administration of 4 mg of atropine sulphate and of Tyramine (10) in doses of 50-60 µg/kg body wt. to the conscious dog with cardiac denervation did not result in any change in heart rate. The pattern of rate response to mild exercise is seen in Fig. 1 and is characterized by a modest increase in rate and an absence of the sudden changes in rate seen in the normal control records. With severe exercise, as shown in Fig. 2, the heart rate increased slowly to reach a much reduced peak value after 1-1.5 min of running. When the dog stopped exercising, the rate returned slowly to the control level.

When compared over equal increments of oxygen consumption (Fig. 3), the increase in heart rate seen in the dog with cardiac denervation was approximately one-third of that observed in the normal control period. That this pattern of response to severe exercise was characteristic of cardiac denervation is seen in Fig. 4, which shows that in this dog the heart rate after operation rose more steeply and had a higher peak value than was seen in the other dogs. The intravenous administration of 4 mg of atropine sulphate to this dog did not cause any alteration in heart rate, but stimulation of the right stellate ganglion yielded cardiac acceleration. After removal of both stellate ganglia the rate response was changed to the pattern exhibited by the other dogs.

The stable heart rate of about 100 beats/min during rest and the peak values of 150-170 beats/min during exercise were reproducible from day to day over several weeks of observation. However, after the insertion of catheters into the aorta via the carotid artery and into the right atrium or superior vena cava by way of the jugular vein on the evening prior to a test, the resting rate the next morning was frequently 150 or even 170 beats/min. This acceleration in rate would generally disappear within 24 hr after removal of the catheters but sometimes persisted beyond this time. On exercising the dog in this condition, an acceleration of 50-60 beats/min was seen during severe work, but with the customary slow buildup on starting to run and a slow decline on stopping exercise. The peak rate, however, was now 200-230 beats/min instead of the 150-170 recorded before catheterization.
Stroke volume. In the denervated dog the increase in cardiac output during mild exercise was almost wholly by means of an increase in stroke volume, the increase in rate being about 5 or 10 beats/min. As exercise was increased in severity, the stroke volume continued to increase, but the increase in rate was more prominent until, at the severest grades of exercise, the increase in rate and the increase in stroke volume contributed almost equally to the augmentation in cardiac output. This is illustrated in Fig. 5 which, however, suggests that in the first moments of exercise the increase in stroke volume made the major contribution.

Cardiac output and oxygen consumption. Measurements of these quantities were made in six normal dogs and in five dogs with cardiac denervation, four of the dogs undergoing studies both before and after operation. The grouped data given in Fig. 6 show that two animals exceeded the preoperative maximal oxygen consumption while two dogs attained 70% of their control maximum. The maximal cardiac output and oxygen consumption of the dog without preoperative studies bear comparison with the best performance of any of the six control dogs. Figure 6 shows that there was little change in the relation of cardiac output and oxygen consumption after cardiac denervation. This is shown more clearly in Fig. 7 which illustrates the preoperative and postoperative data from a single animal. The pattern of uptake of oxygen during and immediately after exercise was similar in the normal and in the denervated dog. As shown in Fig. 8 for the denervated dog, oxygen consumption reaches a plateau value between the first and second minutes of running (left panel), and after stopping returns to pre-exercise levels in approximately the same time (right panel).

Arterial hematocrit. Arterial hematocrits were measured at rest and in the final moments of each period of exercise, the grade of exercise being selected in random fashion. When plotted against oxygen consumption, as in Fig. 9, a linear relationship was evident. Since arterial oxygen saturation was unchanged by exercise, the number in the corner of each panel indicates the amount of oxygen in milliliters per kilogram of weight per minute afforded wholly by this increased concentration of erythrocytes. Whether obtained through actual addition of erythrocytes or by withdrawal of fluid, the increased concentration of hemoglobin allowed on the average for the “free” transport of approximately 20% of the maximal oxygen requirement. These findings did not differ from those observed in normal control animals.

Adrenalectomy. Bilateral adrenalectomy was performed on four dogs with chronic cardiac denervation. Replacement therapy with cortisone acetate was begun just prior to the adrenalectomy and was continued for the remainder of the study. Neither the pattern of the response of heart rate during exercise nor the relation of heart rate to oxygen consumption, as is shown for one animal in Fig. 3, altered as a result of adrenalectomy.

Response to catecholamines. When epinephrine and norepinephrine were infused into the conscious dog with chronic cardiac denervation, tachycardia invariably resulted. Further, the denervated heart was more sensitive to norepinephrine than to epinephrine. This is illustrated in Fig. 10 which shows the increase in heart rate above the control value as plotted against dose in micrograms of base per minute in three conscious dogs. To achieve a comparable increase in heart rate the dose of epinephrine had to be raised to three or four times that of norepinephrine. A further difference in the response to these drugs in the conscious dog with chronic cardiac denervation was that the striking increase in heart rate caused by norepinephrine was accompanied by a modest increase in cardiac output and a reduction in stroke volume; by contrast, epinephrine caused only a minor
increase in heart rate but a considerable increase in cardiac output and stroke volume.

Intravascular temperature. Right atrial blood temperature and heart rate were measured during a 12-min period of exercise in which 3 min of light exercise was alternated with 3 min of severe exercise. Figure 11 shows the data from one dog. During severe exercise, the intravascular temperature rose quite steeply and was accompanied by the usual increase in heart rate. During moderate exercise and in the recovery period, the values for heart rate returned to near those obtained during resting or initial light exercise, though values for blood temperature were elevated above those obtained during resting or initial exercise.

COMMENT

In the present study, prior to the use of a method for measuring oxygen consumption, it was felt that the speed of running and the degree of inclination of the treadmill could be used as measures of the work done by the animal. The fallacy of this reasoning was exposed by the measurement of oxygen consumption during exercise. On increasing the speed of running or the degree of tilt of the treadmill platform, there frequently was no increase and often a decrease in oxygen uptake with no evidence of any oxygen debt of consequence. Further observations showed that, on these occasions, the animal was pulling to some degree on the leash attaching it to the treadmill and, by the support thus afforded, materially reducing the amount of work performed. If, however, the animal was made to run freely on the treadmill so that it had to maintain its position on the platform or be carried to the rear of the apparatus, then, for a given setting on the machine, the same dog on the same day gave closely repeatable values for oxygen consumption.

In the normal dog, on beginning exercise, there is an abrupt increase in heart rate, maximal values being reached in 6–9 sec, the rate thereafter stabilizing at a level proportional to the severity of the exercise. In severe exercise, with an oxygen consumption of 800–1,000 ml/min, the heart rate is generally in excess of 200 beats/min. When exercise is stopped, the heart rate immediately decreases, often reaching control levels in 30–60 sec. The increase in cardiac output during exercise usually is achieved principally by the increase in rate, there being but little change in stroke volume (11, 12).

By contrast, the slow rise in rate on beginning exercise and the considerable reduction in peak rate values seen in the dog with chronic cardiac denervation might suggest a limitation in cardiac output and in the capacity for exercise. Indeed such a reduction in tolerance to exercise has been described by Gasser and Meek (2) and by Samaan (3). More recently Ashkar and Hamilton (13) stated that sympathectomized dogs with denervated hearts had a modest increase in cardiac output and stroke volume with mild exercise but no further increase with heavy exercise. They also stated that the oxygen consumption and the difference in oxygen content between a systemic artery and the pulmonary artery did not increase with heavy exercise. They concluded that the animals must have incurred a severe oxygen debt, but made no measurements in this regard. An alternative explanation is that the exercise was as mild as the oxygen consumption measured during exercise would indicate. The failure of the difference in oxygen consumption...
content between systemic and pulmonary artery to widen would be consistent with this hypothesis.

The method of denervation used prior to that described by Cooper and associates (10) resulted in denervation of the lungs, viscera, and systemic vascular bed, in addition to the heart. Indeed, Gasser and Meek (2) specifically mentioned the cyanosis due to the slow respiratory rate and the inability of the animal to meet the respiratory demands of exercise. Thus, it is probable that the reduction in capacity for exercise reported by Gasser and Meek (2) resulted from pulmonary inadequacy rather than from cardiac inadequacy. The findings in the present study indicated that there was no diminution in the capacity for severe exercise after cardiac denervation. Values for cardiac output and oxygen consumption were as high in the postoperative as in the preoperative studies.

In the individual dog the relation of oxygen consumption to cardiac output was unchanged, and there was no oxygen debt. Both rate and stroke volume contributed to the increase in cardiac output, instead of the increase being due mainly to changes in rate as in the control normal dog. For example, in the data shown in Fig. 7, an oxygen consumption of 749 ml/min was associated with a cardiac output of 5.8 liters/min in the control study; after denervation an oxygen consumption of 755 ml/min was accompanied by a cardiac output of 5.2 liters/min. In the control situation, the cardiac output was obtained by heart rate of 165 beats/min and a stroke volume of 27 ml, whereas after denervation the almost similar cardiac output resulted from a heart rate of 163 beats/min and a stroke volume of 32 ml. Recently Balkisson and Hawthorne (14) reported that conscious dogs with denervated hearts appeared to obey Starling's law in that increased venous return was accompanied by an increase in end-diastolic ventricular circumference and in stroke volume.

A cardiac acceleration of 36-53 beats/min was recorded by Samaan (9) during exercise in atropinized dogs with excision of the cardiac sympathetic nerves. However, these experiments did not exclude participation in the rate response by the cardio-accelerator sympathetic nerve fibers in the vagal sympathetic trunk (15).

The increase in heart rate during exercise was not a function of the absolute level of body temperature, a finding in agreement with the statement of Brouha and associates (16) that body temperature was not an important factor in the changes in heart rate seen during exercise.

The slow increase in heart rate when exercise was started and the reduced peak value and the slow decline when running was stopped might suggest the action of a blood-borne agent, possibly secretions from the adrenal medulla. This view would be in harmony with the findings of Cannon and associates (17) who, by excision of the adrenal glands, converted the tachycardia seen during activity in cats with chronic cardiac denervation...
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FIG. 10. Effect of intravenous infusion of epinephrine and norepinephrine on heart rate in three dogs after cardiac denervation.

to a modest rise of 5 to 10 beats/min. Similarly, Gasser and Meek (2) ascribed the cardiac acceleration seen during exercise in their dogs with bilateral stellate ganglionectomy and vagotomy to release of adrenal secretion by asphyxia. They stated that when asphyxia was absent, the maximal acceleration was 16 beats/min. In the four animals reported here, bilateral adrenalectomy did not change either the pattern of response or the relation of heart rate to oxygen consumption. This was also the case when an agent (I.C.I. 38174) blocking the excitatory action of circulating catecholamine on the heart was given to the adrenalectomized dog with cardiac denervation.

In a study of the action of catecholamines on the isolated perfused dog heart, Fawaz and Tutunji (18) found epinephrine and norepinephrine to have equal chronotropic and inotropic effects, though oxygen consumption probably was increased more by epinephrine. Greenberg and Lambeth (19), who used unanesthetized dogs with chronic cardiac denervation, noted that norepinephrine was a better positive chronotropic agent than epinephrine by roughly 100%. A similar finding was observed in the present studies with, in addition, a further difference in the mode of action of these two substances. The principal action of norepinephrine was on rate, whereas epinephrine predominantly increased stroke volume. Cooper and associates (10) found the myocardial content of catecholamine to be virtually depleted shortly after complete neural ablation of the heart. Thus, in the animals reported herein, the increase in rate cannot be ascribed to the release of catecholamines from the heart or from the adrenal gland, and, as yet, no mechanism can be described for the increase in heart rate seen during exercise in the adrenalectomized dog with cardiac denervation.

The acceleration in rate, which was often noted after insertion of catheters into the vessels of the neck, is unexplained. It did not occur in the dogs subjected to unilateral nephrectomy with insertion of the catheters into the renal artery and vein.

In the normal dog, much of the cardiac acceleration during exercise may be of central origin, and Rushmer and associates (6) have shown how the response to stimulation of hypothalamic areas can mimic the normal cardiac response to exercise. When a normal dog is stood on a board placed over the platform of a treadmill so that the animal is not required to exercise, starting the treadmill results in a rapid acceleration of the heart equal to that seen during exercise. The rapidity of the onset and decline of these heart rate changes indicates that they are mediated by nerves rather than by humoral agents.

The decrease in peripheral resistance during exercise must be the major determinant of cardiac output (20). When exercise is begun there is an immediate dilatation of the vessels in the active muscles. This dilatation, aided by the pumping action of the muscles, leads to an immediate increase in inflow to the heart. In the present studies, the denervated heart depleted of catecholamines had the intrinsic ability to handle this augmented input as well as did the innervated heart. Whether the increase in output is due solely to changes in length of fiber or to the influence of humoral factors other than catecholamines remains to be determined. The finding by Hlinks (21) of a positive chronotropic effect of an increasing right atrial pressure in the isolated mammalian heart merits further consideration. The view expressed by
Franklin and associates (7), that in the normal dog the increased cardiac output during exercise is probably not initiated by increased venous return, is unlikely to be true for the dog with cardiac denervation.

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