Coronary Circulation In the Conscious Dog with Cardiac Neural Ablation

By Donald E. Gregg, Edward M. Khouri, David E. Donald, Howard S. Lowensohn, and Stanislaw Pasyk

ABSTRACT

The left coronary circulation at rest and during its response to natural stresses was studied in five conscious dogs whose hearts had been externally denervated (stripping technique). The values were compared to those obtained under similar conditions in normal dogs of comparable weight and training. A high degree of hyperemia after temporary circumflex occlusion and a coronary flow pattern with a dominant diastolic component under the different conditions were similar to that of the normal dog. At rest, circumflex flow and myocardial oxygen use were only about half the values obtained in the normal dog. In moderate exercise, the rise of circumflex flow was delayed 10-30 seconds, being always preceded by an elevation of stroke volume. In excitement, the increase in circumflex flow was delayed 7-12 seconds, and this was also generally preceded by a rise in stroke volume. The large rise of coronary flow in exercise was associated with a marked increase in myocardial blood oxygen extraction; in excitement, coronary flow also rose greatly but oxygen extraction decreased markedly. Although these trends during natural stress states were similar to those found in the normal dog, the maximum coronary flow and myocardial oxygen use were no more than half those found in the normal dog for an equivalent stress. The addition of beta-receptor blockade still further reduced the coronary responses to these natural stresses. Thus the denervated heart appears to function at a lower metabolic level than the heart with intact cardiac nerves.

KEY WORDS denervated heart normal heart circumflex blood flow coronary flow pattern exercise myocardial oxygen extraction oxygen consumption beta-receptor blockade excitement

Studies from several laboratories have demonstrated the contribution of the cardiac nerves and the catecholamines to the performance of the heart. In the presence of complete and chronic cardiac neural ablation, the papillary muscle of the cat heart has normal contractility and normal oxygen consumption (1, 2), and in the dog with a denervated heart, a normal capacity for maximal exercise is retained (3) despite the absence of catecholamines from the heart (4) and a reduced and delayed response of the heart rate (3, 5). In the dog with intact cardiac nerves, beta-receptor blockade with propranolol (1-2 mg/kg) does not affect the
work capacity of the dog (6), and in submaximal exercise it permits the same external work to be performed at a lower level of coronary blood flow, heart rate, cardiac output, and left ventricular ejection rate (7). Although cardiac performance is little reduced by the absence of cardiac nerves or absence of catecholamine action separately, the absence of both greatly reduces the level of cardiac work of the exercising dog (6).

Conflicting reports have been published concerning the effect of cardiac neural ablation on the coronary circulation of the conscious and the anesthetized dog. In the open-chest dog, acute pericoronal neurectomy increased left coronary inflow (N2O method) and decreased myocardial oxygen extraction (8). Previous chronic cardiac transplantation increased total coronary venous flow (rotameter) and decreased oxygen extraction as measured in the open-chest state with the heart on right ventricular bypass (9). Following chronic cardiac denervation by the stripping technique, both left coronary inflow (N2O method) and myocardial oxygen use decreased, as measured in the anesthetized, closed-chest state (10). In 1943, Essex et al. (11) reported that the response of the left circumflex coronary flow to treadmill exercise as measured by the thermostromuhr was less in a totally denervated heart than in a partially denervated heart. However, data were lacking from dogs with intact cardiac nerves. Except for the preceding, no detailed studies are available concerning the effects of chronic cardiac denervation on the coronary circulation in the conscious animal. Accordingly, the present investigation was undertaken in the dog to determine the effect of removal of the cardiac nerves on coronary blood flow and myocardial oxygen use at rest and during exercise and excitement.

Methods

Studies were made in healthy, conscious dogs (16–20 kg) without electrocardiographic abnormalities. They were trained to lie quietly on a table for 4–6 hours and to run freely on a treadmill. At times, a leash was around the dog's neck but this was always slack during the exercise period. When not being studied, the dogs were kept in large cages and taken for walks daily on the grounds.

Aseptic surgical technique was used. Under nembutal anesthesia, extrinsic cardiac denervation was carried out using the method of Cooper and colleagues (4), the only modification being the use of a bilateral thoracotomy rather than a median sternotomy. After completion of this procedure, the operation was continued in a manner generally similar to that previously reported from our laboratory (12, 13). Electromagnetic flowmeters were implanted on the ascending aorta and on the circumflex branch of the left coronary artery. They were calibrated on an artery in a gravity system using blood having approximately the hematocrit existing during the experiment. In one dog, the calibration of the coronary probe was made only at the end of the experiment. In four other dogs, calibrations made before and at the end of the experiment differed by 0–12% with an average difference of 8%. A pneumatic cuff was also placed on the circumflex artery distal to the flow transducer to obtain a temporary coronary flow zero. A tube was placed in the ascending aorta for sampling blood pressure.

In two of the dogs, a tube was placed in the coronary sinus for estimating metabolic changes in the heart. The catheter was made of polyvinyl chloride tubing; its internal diameter was 0.038 inch and its external diameter 0.070 inch. The end in the coronary sinus was fitted to a machined and polished stainless steel flanged piece with a right angle in the stem (Fig. 1). The flange was 0.140 inch in diameter and 0.025 inch thick; the stem had an internal diameter of 0.038
inch and an external diameter of 0.055 inch. The other end was temporarily attached to a malleable silver probe fashioned so that the probe and the tubing presented a uniform outside diameter. The end of the silver probe (not shown in the drawing) was tapered and sharp enough to penetrate the right atrium and the coronary sinus wall. The silver probe was pushed through the wall of the right atrium and directed into the coronary sinus. The coronary sinus wall was pierced from inside with the probe at a point about 1.5 cm from the ostium, and the tube was drawn through until the flange in the stainless steel end rested against the inner wall of the coronary sinus. (The flange was helped through the wall of the atrium by pushing with a pointed object placed against the opening.) A small piece of Ivalon surgical sponge about 1 mm thick was threaded over the tubing and brought to rest on the outside wall of the coronary sinus. The catheter was oriented properly and was stabilized to the surface of the heart with a ligature. The point of entry into the right atrium usually needed a stitch to stop the leakage.

Blood pressures were measured with Statham P23Db transducers. Phasic and mean blood pressures and flows were recorded on an Electronics for Medicine DR-8 recorder. Mean arterial blood pressure and mean aortic and circumflex artery blood flows were determined from the phasic curves by integrating the area under a number of representative heart beats with a planimeter and using appropriate calibration factors. Systemic peripheral resistance was computed as the mean aortic blood pressure (mm Hg) divided by the cardiac output in ml/min. Mean coronary vascular resistance was calculated as the ratio of mean aortic blood pressure (mm Hg) to mean coronary blood flow in ml/min. Cardiac work was taken as the product of mean cardiac output in liters/min and the mean arterial blood pressure in meters of water.

After recovery from surgery, control data were obtained almost daily with the dog lying on its right side. Then, measurements were made of the responses of the coronary and systemic circulations to the normal physiological stresses of exercise and excitement. Exercise was performed at a 10° incline with treadmill speed of 9 km/hour for periods of 2–30 minutes. Excitement was produced either by squirting ice water in the dog's face or by banging two metal pans together. In three of the dogs, beta-receptor blockade was confirmed after each stress state. At appropriate times during the control and stress states, arterial and coronary sinus blood samples were withdrawn and analyzed for oxygen content. In some experiments, coronary sinus blood was withdrawn as a pooled sample, the first sample starting at about the time of stimulation and extending over a period of 10–15 seconds, and its oxygen content was determined by spectrophotometry (14). In other experiments, sinus blood was continuously withdrawn through a calibrated cuvette oximeter (15). In both sets of experiments, the rate of blood withdrawal was 8–10 ml/min. The oximeter was calibrated against samples of the dog's own blood. Correction was made for the transit time from the coronary sinus to the cuvette of the oximeter.

For each dog, the completeness of extrinsic cardiac denervation was checked by weekly intravenous injections of tyramine and atropine (3). At the end of the experimental period, the cardiac fibers from the right and left stellate ganglia were exposed under anesthesia, and the effect of their stimulation on systemic and coronary dynamics observed. In three of the dogs in the open-chest state when they were killed, samples of myocardium were taken from both atria, the lateral walls of both ventricles, and the interventricular septum and analyzed for norepinephrine content (16). Despite the lack of a pericardium, at autopsy the flow transducer was found to be properly aligned with the circumflex branch and well encapsulated. Except for a slight thinning of its walls, the artery under the probe was normal with a widely patent lumen.

These findings in dogs with denervated hearts were compared to those obtained in eight dogs of comparable training (five of the same weight range) but whose extrinsic nerves had not been removed at the time of implantation of the various devices. The implantation procedures were the same in the two preparations. However, in the normal dog, the pericardium was closed, whereas in the dog with a denervated heart, the pericardium was completely removed as part of the neural ablation procedure. Accordingly, in the denervated heart, the orientation of the cables, tubing, and catheters was maintained by attaching them directly to the myocardium. Statistical evaluation of the differences between dogs with denervated and nondenervated hearts was made by Student's t-test for unpaired samples (17). Student's t-test for paired samples was used to evaluate the significance of the changes from control during exercise and excitement.
### TABLE 1

**Coronary and Systemic Dynamics in Resting Dogs with Denervated Hearts and with Innervated Hearts**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Body wt (kg)</th>
<th>Heart rate</th>
<th>Aortic blood pressure (mm Hg)</th>
<th>Cardiac output (L/min)</th>
<th>Cardiac work (kg m/min)</th>
<th>Coronary flow (ml/min)</th>
<th>Coronary flow AV blood O₂ (ml/100 ml)</th>
<th>Coronary flow Cor. blood O₂ (ml/100 ml)</th>
<th>Oxygen use (ml/min 100 g⁻¹)</th>
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<tr>
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- **Dogs with Denervated Hearts**
- **Dogs with Innervated Hearts**
- **Heavier Dogs with Innervated Hearts**

*C* Weight of circumflex area estimated from heart weight (grams) × 0.37. Factor 0.37 (range 0.35-0.40) based on more than 50 hearts from dogs with body weights similar to those used here.

†Indicates that the mean value for the five denervated dogs differs significantly (*P* < 0.05) from the corresponding value for the five dogs with innervated hearts.

Dogs 11-13 are considered in relation to Figure 7.
Results

GENERAL

Of the ten dogs whose cardiac nerves were removed, one died of aortic rupture at 21 days, three died of postsurgical complications at 2–6 days, and one died of ventricular fibrillation at 8 days. In two dogs, systemic and coronary dynamics fell progressively for about the first 10 days postoperatively, after which they were fairly stable. In three dogs, stabilization did not occur until 15 days after operation. This rate of recovery was somewhat slower than that previously found of about 10 days for many normal dogs undergoing only the implantation procedures. After recovery, meaningful data were obtained in the five dogs for periods ranging from 20 to 40 days. The dogs with denervated hearts could not be distinguished by their everyday behavior from the normal dogs with intact nerves.

The hearts of these dogs are believed to have been completely denervated at the time of operation and to have remained so during the experimental period, as evidenced by their failure to respond to intravenous tyramine and atropine, their failure at the time they were killed to respond to cardiac sympathetic nerve stimulation, and the almost total loss of

Reproduction from sections of continuous recording showing for dog 5 the effect of exercise at a 10° incline and 9 km/hour on phasic coronary and systemic dynamics before (top) and after (bottom) beta-receptor blockade with propranolol (1 mg/kg). Note that after 15 seconds blood pressure recording was changed from phasic to mean. All numbers are mean values. ABP = aortic blood pressure; LCCF = left circumflex coronary flow; CO = cardiac output; HR = heart rate; SV = stroke volume in ml. Vertical lines = 0.2 sec.
catecholamines from their myocardium. The average norepinephrine content of the myocardial samples from three of the dogs with denervated hearts was 0.06 μg/g or approximately 8% of the average value (0.71 μg/g) reported for the normal dog (4).

RESTING VALUES

Table 1 shows the average values for the systemic and coronary dynamics of dogs 1-5 with denervated hearts when they were lying quietly on a table. The data are averages from the fifteenth to the twenty-fifth day. For comparison, values are also shown for normal, conscious dogs 6-10 with innervated hearts and of comparable body weight and training. The data are averages from the tenth to the twentieth day. In this group, it was not possible to obtain data for a longer period of time since the dogs were used for different purposes and experiments were terminated before the end of the first month. In both groups, the average values are based on almost daily observations. In the dogs with denervated hearts, the heart rate was somewhat elevated, but the aortic blood pressure and cardiac output were about the same. In the denervated dogs, the hematocrits varied from 37% to 46%, in the normal dogs from 39% to 44%. The average circumflex blood flow of 19 ml/min (range 15 to 22) and the average oxygen use of 2.6 ml/min were considerably lower than the average values of 35 ml/min (range 32 to 40) and 4.3 ml/min, respectively, shown here for the normal dog and also previously reported (18). For days 15-35 the systemic values were almost the same as for days 15-25; the coronary flow averaged 10% less (data not shown).

The left coronary flow pattern at rest (Fig. 2, top) was characterized by a low systolic flow and a high diastolic flow. This is similar to that previously reported for the normal dog (18). Following release of a 10-20-second ischemia, the left coronary flow pattern at rest (Fig. 2, top) was characterized by a low systolic flow and a high diastolic flow. This is similar to that previously reported for the normal dog (18). Following release of a 10-20-second

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**FIGURE 3**

Mean changes in systemic and coronary dynamics during exercise in the same experiment as in Figure 2. Left: Before beta-receptor blockade. Right: After blockade. Broken lines represent stroke volume (SV) and stroke coronary flow (SCF). Other abbreviations as in Figure 2.
circumflex occlusion, mean coronary flow increased to 3–7 times the control value and remained above the control for 1–2 minutes. This degree of reactive hyperemic response is also comparable to that previously reported for the normal dog (12).

RESPONSE TO EXERCISE
Control hemodynamic observations were recorded in the dogs with denervated hearts while they stood quietly on the treadmill. The typical response to 3 minutes of exercise at a 10° incline and 9 km/hour, for dog 5, can be seen in the phasic curves of Figure 2 (top) and the mean curves in the graph of Figure 3 (left). The graphs in Figure 4 summarize the responses in the 5 dogs (15 experiments) at a

![Graph](http://circres.ahajournals.org/)

**FIGURE 4**
Average systemic and coronary values at standing rest and during treadmill exercise at a 10° incline and 9 km/hour, in dogs with denervated hearts (continuous lines) and in dogs with normal hearts (broken lines). A: 15 experiments in dogs 1–5 with denervated hearts, and 4 experiments in normal dogs 7 and 8 of about the same weight as the dogs with denervated hearts. B: Coronary flow and oxygen data from 6 experiments in dogs 1 and 2 with denervated hearts. The data for the normal dogs are from the same experiments as A. Each segment of graph during exercise is divided into three periods: C, control at standing rest; I, just after start of coronary flow rise; II, time of maximum coronary flow. CW = cardiac work in kg/min. TPR = mean systemic peripheral resistance. MCR = mean coronary resistance. CS O₂ = coronary sinus blood O₂ content in ml/100 ml blood. O₂ use = myocardial oxygen use in ml/min. Other abbreviations as in Figure 3. Standard errors are shown in A. Plus sign indicates that the mean value in the denervated dog during exercise differs significantly (P < 0.05) from the control value.
For emphasis, the responses during exercise (Fig. 4) are divided into three periods: C, control; I, just after circumflex flow started to rise; II, peak coronary flow response, at which time the systemic responses are also about maximal.

With the abrupt onset of exercise, the heart rate was only slightly elevated but aortic blood pressure always dropped immediately and considerably before any coronary flow increase, reaching a minimum value (average 25%) in 4-15 seconds. It did not return to the control level until 36-90 seconds. The phasic coronary flow pattern (Fig. 2, top) is similar to that of the normal dog during treadmill running (19). The rise in mean coronary blood flow and stroke coronary flow was delayed, starting in 13 experiments at 10-30 seconds after exercise, and in 2 experiments at 40 and 50 seconds. In all experiments, elevation of coronary blood flow (period I) began while the aortic blood pressure was still depressed, heart rate was only slightly increased, but cardiac output and stroke volume were considerably increased. An elevation of stroke volume (average 20%) actually occurred before any coronary flow increase and within 3-6 seconds after onset of exercise. In period II at peak elevation of systemic parameters (averages for heart rate 57%, aortic blood pressure 25%, cardiac output 132%, and stroke volume 58%), the average augmentation of coronary blood flow (108%) and stroke coronary flow (34%) were considerable, while mean and phasic coronary resistance fell markedly. The arterial hematocrit rose 3-5%. Within 7-10 minutes after the end of exercise, values for the hemodynamic parameters had returned nearly to normal. The systemic changes described are similar to those first observed by Donald and Shepherd in the denervated heart (3).

The effect of treadmill running at 10° and 9 km/hour on myocardial oxygen use was determined in nine experiments in dogs 1 and 2, in which a coronary sinus tube had been implanted (Fig. 4B). Oxygen uptake rose from an average control value of 2.2 ml/min to 6.8 ml/min, as indicated by a marked decrease in coronary sinus blood O2 content (5 ml O2/100 ml blood to 0.9 ml/100 ml), a large increase in coronary arteriovenous blood O2 (13.6 ml/100 ml to 18.3 ml/100 ml), and in coronary flow from 16 to 37 ml/min (period II). This pattern of response is similar to that reported for the exercising dog with intact cardiac nerves (19).

For comparison, Figure 4 also contains the changes in the coronary circulation in four experiments in normal dogs 7 and 8 (Table 1) of comparable training and weight that ran at the same 10° incline but at slightly lower rates (6, 8, 8, and 9 km/hour). In the normal dogs at standing rest and with about the same systemic values as the dogs with denervated hearts, mean coronary resistance was much less and coronary flow and stroke coronary flow were about twice as large. Within the first 3-6 seconds of exercise, coronary flow started to rise and the relative magnitudes of peak coronary flows were maintained (92 vs. 46 ml/min), although in the normal dogs the rise in heart rate was more rapid and larger, aortic blood pressure did not initially decrease and stroke volume was little changed. The oxygen uptake at standing rest and during exercise was more than twice that of the dogs with denervated hearts, the peak values being 15.2 vs. 6.8 ml/min (Fig. 4B). Even in normal dogs (7 and 8) that also ran on the treadmill at slower rates of 3, 4, and 6 km/hour at a 10° incline (seven experiments), the averages of peak coronary flow (74 ml/min) and oxygen use (10.7 ml/min) were much higher than in the denervated hearts at a greater level of treadmill stress (data not shown). These high levels of response of coronary flow and myocardial oxygen use in the normal dog are similar to those previously reported (19).

RESPONSE TO EXERCISE AFTER BETA-RECEPTOR BLOCKADE

After dogs 3, 4, and 5 with denervated hearts, ran on the treadmill at a 10° incline and 9 km/hour, beta-receptor blockade was produced with intravenous propranolol, and the treadmill exercise was repeated (four experiments). Figure 2 (bottom) and Figure 3 (right) show the typical phasic and mean
changes in one experiment (dog 5). In the early period, the rise in heart rate was less and the drop in aortic blood pressure in each experiment was larger after blockade (average —32%) than before blockade (average —17%). The duration of the pressure drop was greatly extended and the final peak pressure level reached (avg +11%) was less than that (avg +25%) before blockade. In one experiment, the blood pressure did not return to the control level. The early rise of cardiac output was much less although it started up as quickly. The onset of an increase in coronary blood flow (period I) was considerably delayed and the increase much less (avg +8% as compared to +26% before blockade). At peak coronary response (period II), which was also delayed, the values for coronary blood flow (+18% vs. +96%), blood pressure (+11% vs. +24%), and cardiac output (+50% vs. +130%) were much less than the values obtained during exercise before blockade. These effects after beta-receptor blockade in the denervated heart are similar to those found for normal dogs by Pitt in preliminary experiments (7).

FIGURE 5
Reproduction from sections of continuous record showing for dog 4 the effect of excitement (banging of pans) on phasic coronary and systemic dynamics before (top) and after (bottom) beta-receptor blockade with propranolol (1 mg/kg). All numbers are mean values. Abbreviations and time lines as in Figure 2.
RESPONSE TO EXCITEMENT

Control hemodynamic observations were obtained with the animal lying quietly on a table. Excitement was produced in the five dogs with denervated hearts (14 experiments). A typical response (dog 4) is in the phasic curves of Figure 5 (top) and the mean curves in the graph of Figure 6 (left). Figure 7 summarizes the responses for all dogs. The responses during excitement in Figure 7A are divided into the same periods as in Figure 4. Figure 7B has a fourth period, the time of maximum coronary sinus blood O₂ content.

In Figure 7, 7–12 seconds after excitement, a significant elevation of coronary blood flow (avg 42%) and stroke coronary flow (avg 33%) is shown in the different experiments (period I). By this time, the heart rate and aortic blood pressure had risen in all experiments (avg 5% and 19%, respectively) while the cardiac output (avg 14%) and stroke volume also had risen in all except two experiments. At 4–8 seconds after excitement and before coronary flow elevation, increase in these systemic parameters had already started. However, in five experiments, aortic blood pressure initially fell and in the same two experiments mentioned above, cardiac output and stroke volume also did not rise initially. As systemic parameters continued to increase, peak coronary flow response was reached in 15–20 seconds. At this time (period II) mean coronary blood flow increased by an average of 110% and stroke coronary flow by an average of 82%. There was an average rise in heart rate of 14%, aortic blood pressure of 22%, cardiac output of 33%, stroke volume of 18%. The calculated mean coronary and systemic resistances both fell greatly. After 1–2 minutes, hemodynamic parameters returned nearly to normal levels. The coronary flow distribution during the cardiac cycle was similar to that of

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**FIGURE 6**

Mean changes in systemic and coronary dynamics during excitement in the same experiment as in Figure 5. Left: Before beta-receptor blockade. Right: After blockade. Broken lines represent stroke volume (SV) and stroke coronary flow (SCF). Other abbreviations as in Figure 2.
the normal dog, with the dominant flow increase occurring during diastole (20).

Myocardial oxygen changes were determined in six experiments in dogs 1 and 2, in which the oxygen content of the coronary sinus blood was determined either by the cuvette oximeter (three experiments) or by pooled blood samples (three experiments). As shown in Figure 7B, circumflex flow and oxygen use, which were low in the control state, rose to only moderate levels. In all experiments, this was associated with a sustained elevation of coronary sinus blood O₂ content. The elevation observed in the three experiments in which the oximeter was used was much larger, reaching 10 ml/100 ml blood at the time of maximum coronary flow.

In previously reported (20) experiments, excitement in the dog with intact cardiac nerves greatly elevated the coronary flow and oxygen use, and only slightly and temporarily elevated the coronary sinus blood O₂ content, as determined from blood samples pooled over about 15 seconds and starting a few
seconds after beginning of excitement. Accordingly, the effects of excitement on the coronary circulation were repeated in four normal dogs in five experiments (four with the oximeter, one with a pooled coronary sinus blood sample). Figure 7 summarizes the responses of three of these dogs (dogs 7, 11, 12) whose body weight of 18.2, 25.0, and 22.7 kg (avg 22 kg) were somewhat greater (+20%) than those of the dogs with denervated hearts. As shown in Figure 7, the systemic responses of elevations in heart rate, blood pressure, and cardiac output were roughly similar to those previously reported for the normal dog, but the heart rate and cardiac output were larger than in the denervated dogs. Also, the control circumflex flow and stroke coronary flow were much greater and the mean coronary resistance was much less than the control values in the dogs with denervated hearts. These differences became larger as the circumflex flow rose quickly and to quite high levels, the average peak flow being about 3.5 times that in the denervated dog. Similarly, as shown in Figure 7A, the control and peak values for oxygen use were much larger in the normal dog, but, as in the denervated heart, the coronary sinus blood O2 content, initially averaging 4.0 ml/100 ml blood, rose markedly in the oximeter experiments, reaching 8.0 ml/100 ml blood. In the one normal dog with a pooled coronary sinus blood sample, the coronary sinus blood O2 content also rose significantly from 4.5 to 6.0 ml/100 ml blood. In the fourth normal dog (dog 13) with a weight of 29 kg, the coronary sinus blood O2 content also increased greatly (from 5.3 to 10.5 ml/100 ml blood), as measured by the oximeter (data not included in Fig. 7).

Figure 8 shows the time relationship of the response of coronary flow and of coronary sinus blood O2 content to excitement in dog 1 with a denervated heart, and in dog 12 with intact cardiac nerves, in which oximeters were used. For three such experiments in the denervated heart, circumflex flow started to rise at 9-10 seconds, peak value being reached at 18-19 seconds. Coronary sinus blood O2 saturation started to rise a little later at 13-15 seconds (3-4 seconds after rise of circumflex flow) and was maximal at 20-22 seconds (2-3 seconds after peak circumflex flow). For four such experiments in the normal heart, the time of the onset of coronary flow rise (2-6 seconds) and of peak coronary flow response (10-15 seconds) was somewhat earlier than in the dogs with denervated hearts. Coronary sinus blood oxygen saturation rose at about the same time (11-14 seconds) as that of the denervated heart but was considerably delayed relative to the rise of its coronary flow. Although in each instance the time of rise of the coronary sinus blood O2 content was corrected for instrumental lag, no correction was possible for the physiological transit time of blood from the epicardial arteries through the myocardial capillaries and into the coronary sinus. This should be longer in the control state and should be shorter and vary from moment to moment in excitement. It is therefore not possible to relate temporally the observed onset of rise of coronary sinus blood O2 saturation to the rise of coronary flow. Thus the calculated oxygen use of the myocardium on a moment-to-moment basis in such experiments is in error by an unknown amount. In both dogs, the correct oxygen uptake would be somewhat less.

Since elevation of the coronary sinus blood O2 content during excitement could be due in part to transfer of blood from the right atrium, four additional normal dogs were studied, in which, at time of surgery, catheters were implanted in the coronary sinus for sampling of blood, and in the right atrium for injection and pressure sampling. After recovery, Cardio-Green was injected at different times before and during excitement to observe its effect on the coronary sinus oximeter curve. Also, saline saturated with H2 gas was continuously injected through the right atrial tube during excitement while the coronary sinus blood was continuously withdrawn by a pump, and its H2 content detected by a platinum electrode inserted into the blood line (21). Although right atrial pressure initially rose mildly and transiently, no evidence of contamination of
Mean changes in the coronary and systemic circulations during excitement (hanging of pans) showing especially its effect on coronary sinus blood $O_2$ content and myocardial oxygen use. Coronary sinus blood was withdrawn through a cuvette oximeter. Continuous lines represent dog 1 with denervated heart (1 experiment); Broken lines, dog 12 with intact cardiac nerves (1 experiment). Abbreviations as in Figure 7.

Discussion

The evidence presented suggests that the circumflex flow and oxygen requirements of dogs with denervated hearts are less at rest and during the stress states of exercise and excitement than are those of dogs with intact cardiac nerves under similar conditions. In the denervated heart at rest, circumflex flow (five dogs) and oxygen use (two dogs) were only a little more than half the values in the hearts of normal dogs of comparable weight; there was
no overlap in the values in the two groups. With moderate treadmill exercise at a 10° incline and 9 km/hour, maximum values for these parameters were less than half those of the normal heart, and in the excited dog, peak values for coronary flow and oxygen use were only about one-third those found here for three normal excited dogs. The much higher values for the normal dogs during rest, exercise, and excitement have been previously reported (18-20).

Following beta-receptor blockade in dogs with denervated hearts, the same moderate level of external work on the treadmill was associated with a considerably lower level of coronary blood flow in the presence of a reduced response in heart rate, aortic blood pressure, and cardiac output. Excitement after blockade also caused a delayed and diminished coronary flow response as compared to that before blockade. This occurred in the presence of an increased systemic vasoconstriction and a reduced heart rate response. Donald and Shepherd (3) have shown that following beta-receptor blockade and removal of the cardiac nerves, exercise capacity is greatly reduced and the cardiac output response is induced solely by the Frank-Starling mechanism of greater ventricular diastolic fiber length. The present experiments in which beta-receptor blockade still further attenuated the already reduced coronary circulatory function of the denervated heart demonstrate further differences between normal and denervated hearts in their response to stress.

The rise in oxygen content of the coronary sinus blood after excitement in the dogs with denervated hearts was unexpected. Initially, it was thought to be peculiar to the denervated heart since, previously, excitement did not significantly elevate coronary sinus blood O₂ saturation in the normal dog. It would seem, however, that the method of pooling the coronary sinus sample for 15 seconds or so was responsible for such underestimation of the rise of coronary sinus blood O₂ saturation, since, with the use of the cuvette oximeter in the present experiments, coronary sinus blood O₂ content rose considerably in normal as well as in denervated hearts. This would appear to be a physiological response since no evidence was found for right atrial contamination of the coronary sinus blood. Since it occurred with small increases in coronary flow and oxygen use (denervated dog) as well as with large changes (normal dog), its action could result from some form of active dilatation rather than from local metabolic processes. Whether this represents flow through arteriovenous shunts or overflow through normal capillaries remains to be determined. Although elevation of coronary sinus blood O₂ content can follow the use of nitroglycerin and Persantin, excitement appears to be the only natural stress which causes such a plethora of coronary flow.

In the present experiments in the dog with a denervated heart, it was not possible to determine the mechanisms which regulate its coronary flow and myocardial oxygen consumption at rest and during stress states, and which apparently cause these measurements to be less than in the normal dog. However, brief mention of possibilities is of interest since, traditionally, the changing oxygen use by the left myocardium has been attributed to a number of determinants (22). These include myocardial contractility or the velocity of contraction, development of tension by the myocardium, and the manner of ventricular loading (the oxygen cost being far greater from aortic pressure loading than from flow or volume loading of the ventricle). Presumably, these determinants would also apply to the changes in coronary flow since, normally, the left myocardium extracts 70-80% of oxygen from its coronary blood. The reduced oxygen use at rest could be the result of an imbalance between the effect of a decreased contractile state (velocity of contraction) caused by a lack of myocardial catecholamines, and the effect of an increased tension from the higher heart rate. In exercise and excitement, the smaller maximum values for oxygen use could result from an imbalance between the effect of an increase in tension arising from the larger elevation of stroke...
volume (and therefore presumably greater diastolic size) and the effect of decreases in both tension and contractility arising from smaller increments in heart rate and aortic blood pressure and a lesser catecholamine stimulation of the myocardium. To what extent the absence of a pericardium (surgically removed) in the denervated dog influences coronary flow and oxygen consumption cannot be predicted. However, from the work of Evans and Matsuoka (23), its absence might be expected to lead to both a greater tension as the result of a larger ventricular volume both at rest and in the stress states and a lowering of tension (and ventricular pressure loading) as the result of smaller elevations in heart rate and aortic blood pressure during the stress states. A possible effect on oxygen consumption would depend on the balance between these two factors.

References


Coronary Circulation in the Conscious Dog with Cardiac Neural Ablation
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Circ Res. 1972;31:129-144
doi: 10.1161/01.RES.31.2.129

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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