Effects of Experimentally Produced Heart Failure on the Peripheral Vascular Response to Severe Exercise in Conscious Dogs

By Charles B. Higgins, Stephen F. Vatner, Dean Franklin, and Eugene Braunwald

ABSTRACT

The peripheral vascular response to severe exercise in eight dogs with heart failure produced by tricuspid avulsion and progressive pulmonary stenosis was compared to the response determined in eight control dogs. After full recovery from implantation of Doppler flow probes and miniature pressure gauges, measurements of arterial blood pressure and blood flow were telemetered from untethered dogs running behind a mobile recording vehicle at speeds of 10–25 mph over distances averaging 1 mile. Severe exercise in control dogs increased heart rate from 78 to 281 beats/min and mean arterial blood pressure from 93 to 134 mm Hg. Iliac blood flow rose from 151 to 897 ml/min, but mesenteric and renal blood flows did not change significantly. Iliac vascular resistance decreased from 0.64 to 0.15 mm Hg/ml min⁻¹, but mesenteric vascular resistance increased from 0.31 to 0.47 mm Hg/ml min⁻¹ and renal vascular resistance increased from 0.49 to 0.75 mm Hg/ml min⁻¹. Severe exercise in dogs with heart failure increased heart rate from 102 to 274 beats/min, but mean arterial blood pressure only increased from 100 to 107 mm Hg. Iliac blood flow rose from 96 to 360 ml/min, whereas mesenteric blood flow decreased from 237 to 89 ml/min and renal blood flow decreased from 226 to 79 ml/min. Iliac vascular resistance decreased from 1.09 to 0.34 mm Hg/ml min⁻¹, but mesenteric vascular resistance increased from 0.49 to 1.31 mm Hg/ml min⁻¹ and renal vascular resistance increased from 0.47 to 1.81 mm Hg/ml min⁻¹. Thus, in heart failure a distinctly abnormal peripheral vascular response to severe exercise occurs, characterized by a very small elevation in mean arterial blood pressure and intense visceral vasoconstriction resulting in diversion of visceral blood flows.

KEY WORDS arterial pressure mesenteric blood flow heart rate renal blood flow iliac blood flow telemetry

The peripheral vascular response to severe exercise in normal, intact, conscious dogs is characterized by elevations in arterial blood pressure and visceral vascular resistances (1) but does not appear to involve diversion of visceral blood flow away from the renal and mesenteric beds to active skeletal muscles (1–3). It is likely that the increase in cardiac output associated with exercise (4–7) is sufficient to supply the augmented flow requirements of active skeletal muscles and at the same time maintain visceral perfusion. In heart failure, in which the capacity to increase cardiac output and stroke volume is limited...
(8), blood flow might be diverted from the viscera to increase the perfusion of active skeletal muscles. Accordingly, in the present study, we compared the peripheral vascular response to severe, unrestrained exercise in conscious dogs with experimentally produced heart failure to the response in normal and sham-operated dogs.

Methods

In eight adult mongrel dogs weighing 25-32 kg, congestive heart failure was produced by a two-stage surgical procedure which was a modification of the technique of Barger et al. (9). Under general anesthesia (pentobarbital sodium, 30 mg/kg, iv) and with sterile surgical techniques, the tricuspid valve was avulsed and a hydraulic cuff placed around the main pulmonary artery. Progressive distention of the cuff with saline at various intervals over 2-3 weeks produced progressive pulmonary stenosis and eventually led to congestive heart failure in each of these eight dogs (Table 1). Sham operations consisting of a right atriotomy and dissection around the pulmonary artery, but not actual constriction of the artery, were performed in two additional dogs. Miniature pressure gauges (Konigsberg model P22) were implanted in the aorta and Doppler ultrasonic blood flow transducers were placed around the superior mesenteric, left renal, and left iliac arteries 3-4 weeks after operation in each of these ten dogs and in six additional normal dogs. The control group consisted of the six normal and the two sham-operated dogs.

The experiments were conducted 6 weeks after thoracotomy in both groups of dogs. During this time the dogs were subjected to similar environments. For the first 5 weeks, they were housed in small indoor cages which did not allow for regular physical exercise. In the last week before the experiments, they were kept in 30 x 20 ft outdoor enclosures which allowed extensive physical exercise. Thus, the groups of dogs were deconditioned to comparable degrees. At the time of the experiments, the dogs with heart failure had evidence of tissue loss and variable, but mild, degrees of ascites. For the study, the dogs were taken to an isolated road and allowed to recline and stand at rest while telemetered signals of blood flow and arterial blood pressure were recorded. When the commercial van, which served as a mobile laboratory containing the telemetry receiving and electronic recording equipment, drove off, the untethered dogs ran behind it at speeds of 15-25 mph over a distance averaging 1/4 miles for dogs in the control group and 10-25 mph over a distance averaging 1 mile for dogs with heart failure. These speeds were maintained during the steady-state period of exercise at which hemodynamic measurements for control dogs and dogs with heart failure were compared.

Each dog carried a backpack which contained the electronic components of the Doppler flow and the pressure telemetry system\(^1\) and the battery power supply. The flow and pressure signals were transmitted from the dog to a radio receiver in the van using standard FM radiotelemetry techniques which have been previously described (1). At a later time, the taped data were played back on a multichannel direct-writing oscillograph. Mean arterial blood pressure and mean blood flows were derived from the phasic signals with electronic resistance-capacitance filters having a 2-second time constant. A Beckman model 9857B cardiograph triggered by the instantaneous pressure signal was used to compute instantaneous heart rate.

\(^1\)Circuit diagrams are available from the authors.
Blood flow velocity was derived from the Doppler equation as previously described (10). Blood flow rate was calculated as the product of blood flow velocity and the cross-sectional area of the blood vessel measured at autopsy. Zero flow was repeatedly determined electrically, and the accuracy of the electrical zero was confirmed terminally by comparing electrical zero with mechanical occlusive zero. The Doppler flowmeter had an inherently stable zero flow and only a negligible discrepancy existed between electrical and occlusive zero flow (11). Other experiments in our laboratory (1, 11-13) have demonstrated that the relationship between blood flow velocity and volume flow is linear as long as the diameter of the vessel within the transducer is constant. Postmortem examination of these dogs demonstrated that the vessel wall had adhered to the transducer by a firm fibrous shell which minimized changes in the caliber of the vessel with alterations in arterial blood pressure.

Results

An average value for each parameter in each dog was calculated by averaging the measurements at 1-second intervals during 15 minutes of rest and at 1-second intervals during 1 minute of steady-state exercise. Thus, the average value in each dog was the average of approximately 1200 beats at rest and 300 beats during exercise. The mean values described in this section are the arithmetic means of the average values from eight dogs in each group.

Heart Rate.—In both groups of dogs heart rate increased rapidly at the beginning of exercise and remained at peak levels as long as the dog continued to run (Figs. 1-3). On the cessation of exercise, heart rate declined

![Figure 1](http://circres.ahajournals.org/)

**FIGURE 1**

Tracing showing the normal hemodynamic alterations during severe exercise in the renal bed of a sham-operated dog. Recordings at rest in the prone and standing positions are indicated on the left of the tracing. At the start of exercise, arterial blood pressure and renal blood flow decreased transiently and heart rate increased abruptly. During the course of the run, at a speed of 15 mph, arterial blood pressure increased substantially and renal blood flow remained constant and even increased near the end of the run.
VASCULAR RESPONSE TO EXERCISE IN HEART FAILURE

Tracing showing the hemodynamic response to severe exercise in the renal bed of a dog with heart failure. Recordings at rest in the prone and standing positions are indicated on the left of the tracing. In this instance, during the run, at a speed of 15 mph, arterial blood pressure remained constant and renal blood flow decreased drastically.

rapidly at first but required 45-60 minutes to return to the control level that existed before exercise. In the eight control dogs, heart rate increased from 78 ± 4 (S.E.) beats/min at rest to 281 ± 25 beats/min during severe exercise (Table 2). This rise in heart rate was comparable in normal dogs and sham-operated dogs during severe exercise. The eight dogs with experimental heart failure had a slightly higher average resting heart rate, 102 ± 2 beats/min, which similarly increased to 274 ± 9 beats/min during severe exercise (Table 2).

Arterial Blood Pressure.—In the control dogs, on commencement of exercise, mean arterial blood pressure decreased transiently below the resting control value of 93 ± 2 (S.E.) mm Hg; this decrease was followed by a gradual increase to 134 ± 6 mm Hg during the steady-state period of exercise (Figs. 1, 3, Table 2). The increases in arterial blood pressure were similar in normal and sham-operated dogs. In the dogs with experimental heart failure, mean arterial blood pressure decreased initially below the resting control level of 100 ± 3 mm Hg but, in contrast to the substantial increase in arterial blood pressure in the normal and sham-operated dogs, rose only slightly during the period of severe exercise, averaging 107 ± 3 mm Hg at the steady-state period of exercise. The alterations in arterial blood pressure were variable in the dogs with heart failure: blood pressure decreased slightly in one dog, remained essentially unchanged in two dogs, and increased slightly in five dogs (Fig. 3).

Mesenteric Bed.—The responses of the mesenteric bed of the normal and sham-operated dogs were nearly identical. The alterations in blood flow were similar to those observed in the renal bed, with an initial, small, transient decrease, but flow was essentially unchanged from the resting control.
value during the steady-state period of exercise (Fig. 3). Mesenteric blood flow was 308 ± 17 (se) ml/min at rest and 297 ± 18 ml/min during exercise (Table 2). Mesenteric vascular resistance increased from 0.31 ± 0.02 to 0.47 ± 0.03 (se) mm Hg/ml min⁻¹.

In contrast to the responses in the control dogs, mesenteric blood flow decreased markedly in the dogs with heart failure, declining from 237 ± 36 ml/min at rest to 89 ± 9 ml/min during the steady-state period of exercise (Fig. 3, Table 2). Mesenteric vascular resistance increased from 0.49 ± 0.07 to 1.31 ± 0.14 mm Hg/ml min⁻¹. This increase in mesenteric vascular resistance was several times greater than that observed in the group of control dogs.

Renal Bed.—The responses to severe exercise in sham-operated dogs and normal dogs were comparable. Although renal blood flow decreased initially and transiently, during the steady-state period of exercise, renal blood flow was near resting control levels, averaging 195 ± (se) ml/min at rest and 186 ± 15 during exercise (Fig. 1, Table 2). Calculated renal vascular resistance increased from 0.49 ± 0.04 (se) mm Hg/ml min⁻¹ at rest to 0.75 ± 0.05 mm Hg/ml min⁻¹ during exercise.

In the dogs with heart failure, distinctly abnormal responses were observed in the renal bed. Renal blood flow decreased abruptly on commencement of exercise, and during the steady-state period it was severely compromised, having declined from 226 ± 18 ml/min at rest to 79 ± 16 ml/min during exercise. Renal vascular resistance increased from 0.47 ± 0.05 mm Hg/ml min⁻¹ at rest to 1.81 ± 0.38 mm Hg/ml min⁻¹ during exercise. This increase in resistance was several times greater than that observed in the group of normal dogs.

Iliac Bed.—In the control dogs, iliac blood flow increased from 151 ± 11 (se) ml/min at rest to 897 ± 28 ml/min during the steady-state period of exercise (Table 2). Iliac vascular resistance decreased from 0.64 ± 0.05

**Figure 3**

Tracings comparing the effects of similar levels of severe exercise in a sham-operated dog and in a dog in heart failure. In contrast to the normal response observed in the sham-operated dog, mean arterial blood pressure rose only slightly and mesenteric blood flow decreased profoundly in the dog with heart failure.
### TABLE 2

Regional Hemodynamic Effects of Exercise

<table>
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<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Arterial blood pressure (mm Hg)</th>
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<th>Iliac bed</th>
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**Control**

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<tr>
<td>Exercise</td>
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</tbody>
</table>

**P**

*Sham-operated dogs.

†P < 0.01, change (Δ) with exercise in heart failure compared to control.
to 0.15 ± 0.01 (SE) mm Hg/ml min⁻¹. The changes were comparable in normal dogs and sham-operated dogs.

In the dogs with heart failure, iliac blood flow increased from 96 ± 10 ml/min at rest to 360 ± 74 ml/min during exercise (Table 2). Iliac vascular resistance decreased from 1.09 ± 0.11 to 0.34 ± 0.08 mm Hg/ml min⁻¹.

**Discussion**

The peripheral vascular responses to severe exercise in dogs with experimental heart failure in the present study contrast strikingly with the responses to severe exercise observed in normal dogs. The abnormal response to exercise was characterized by only a trivial increase in mean arterial blood pressure, drastic reductions in renal and mesenteric blood flows, and increases in visceral vascular resistances severalfold greater than those observed in the control dogs.

Earlier studies in normal dogs during severe exercise have established that the primary compensatory response to exercise in the absence of cardiac impairment involves large increases in cardiac output, resulting primarily from an increased heart rate and to a lesser extent from an enhanced stroke volume (5—7). Barger et al. (4) have demonstrated a linear relationship between total-body oxygen consumption and cardiac output during exercise in normal conscious dogs. Although it has been proposed that diversion of visceral blood flow provides an additional compensatory mechanism during exercise, the present and previous studies in conscious dogs, using methods for direct measurement of blood flow, have indicated that diversion of visceral blood flow during exercise does not occur in the normal dog (1—3, 14).

The finding that diversion of renal and mesenteric blood flows is not a normal compensatory mechanism in conscious dogs and is invoked only in the presence of impaired cardiac function is not consistent with previous observations in man during treadmill exercise. Indirect and intermittent measurements of visceral blood flow during exercise in apparently healthy human subjects indicated moderate reductions in mesenteric (15, 16) and renal (17—20) blood flows. These discrepancies between the normal canine and human visceral vascular responses to exercise could be due either to a species difference or to a difference in the techniques used to measure blood flows. In regard to the latter possibility, perturbations associated with intense sympathetic action, such as occur during exercise, cause visceral arteriovenous shunting and intraorgan redistribution of blood flow (21—26). Under these circumstances large discrepancies have been elicited between flow estimated by indirect techniques and direct measurements of blood flow (21, 22).

Since renal blood flow does not decrease in human subjects performing only moderate levels of exercise (27, 28), it might be argued that the normal dogs were not severely stressed. However, these dogs ran at speeds of 15—25 mph over distances of 1.5 miles, achieved heart rates of 281 beats/min, and required prolonged rest periods on cessation of exercise before cardiovascular functions returned to resting control levels. In spite of the fact that the normal dogs were exercised apparently to the limits of motivation, the stress of exercise relative to their cardiovascular competence was probably greater in the dogs with heart failure. However, this difference in response identifies the major finding of the present study, i.e., diversion of visceral blood flow occurs in the dog only when the requirements for increased blood flow during exercise exceed the cardiac capacity to supply it. Thus, the compensatory response to exercise in heart failure appears to involve a greater degree of sympathetic activation which results in sufficient increases in visceral vascular resistance to reduce visceral blood flow drastically. At similar levels of exercise, a greater sympathetic discharge (29) and more intense vasomotor responses (30) have been shown in patients with heart failure than in normal subjects.

Arterial blood pressure rose very slightly during exercise in the dogs with heart failure in spite of the fact that the increases in visceral resistance were severalfold greater than in
normal dogs. However, this diminished pressor response certainly does not relate to a defect in vasoconstriction, as had been previously observed in dogs with experimental heart failure in response to bilateral carotid artery occlusion (31). Rather, it appears to reflect limitation in cardiac output, a finding consonant with a severely limited increase in cardiac output observed in human subjects with heart disease with and without heart failure (8, 32). The increases in heart rate in the dogs with heart failure were comparable to those observed previously in normal dogs during severe exercise in spite of the marked depletion of their cardiac norepinephrine stores. This finding, indicating that sympathetic stimulation of the heart induced by a physiological activity—exercise—is associated with normal increases in heart rate, is at variance with the blunted response of heart rate to postganglionic sympathetic nerve stimulation (33) and bilateral carotid artery occlusion (31) observed in dogs with experimental heart failure. This difference may be due, at least partially, to a greater intensity of sympathetic activation of the heart during exercise in the dogs with heart failure compared to normal dogs, whereas the two former perturbations were designed to be identical in the normal dogs and the dogs with heart failure. Moreover, the finding of such an exercise-induced tachycardia during heart failure indicates that under severe stress the myocardial beta receptors can apparently respond normally to intense neural and humoral sympathetic activation. The abrupt increase in heart rate on initiation of exercise suggests that withdrawal of resting vagal tone as well as neural sympathetic activation occurs in a normal fashion, despite apparent defective parasympathetic cardiac compensatory responses to alterations in arterial blood pressure observed previously in animal and human subjects with heart failure (31, 34).

In conclusion, this study indicates a distinctly abnormal peripheral vascular response to exercise during heart failure. In contrast to the responses observed in normal healthy dogs, in heart failure a marked diversion of blood away from inactive viscera occurs, thereby aiding in the delivery of oxygen to active skeletal muscles in the presence of impaired cardiac function. Other studies from our laboratory have indicated similar diversion of visceral blood flow during exercise in dogs with limited heart rate (1) or oxygen-carrying capacity of the blood (35).

Acknowledgments
We gratefully recognize the technical assistance of R. Pavelec, D. F. McKown, D. Hendrick, and F. Werner.

References
radiotelemetry of blood flow velocity from unrestrained animals. Am J Med Electr


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Circ Res. 1972;31:186-194
doi: 10.1161/01.RES.31.2.186

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

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