occlusion of the aortic root, sufficient to raise left ventricular systolic pressure substantially, has little effect on left ventricular end-diastolic diameter in healthy conscious dogs. However, after general anesthesia, the same stimulus causes the heart to dilate, and when the pressure load is maintained for one minute, cardiac size returns toward control level — that is, the so-called Anrep effect is manifest. This effect, which is easily demonstrated in the isolated heart or in anesthetized animals, is difficult to discern and apparently not important in circulatory regulation in conscious animals with low spontaneous heart rates.

Thus, general anesthesia affects the base-line state of cardiac function, the distribution of regional blood flow and, the responses to a change in cardiac frequency, preload, afterload and, particularly, integrative circulatory control, as occurs with stimulation of baroreceptors. The responses to a variety of physiologic or pharmacologic interventions may thus be radically different in the presence and absence of anesthesia. Any intervention that alters blood-flow distribution, the extent of baroreceptor stimulation, cardiac frequency, preload or afterload necessarily induces different responses in the conscious and anesthetized states.

The profound influence of general anesthesia on circulatory function is also apparent when comparisons are made of the responses of conscious and anesthetized animals to the administration of identical doses of common cardiovascular pharmacologic agents.

Digitalis Glycosides

The clinical usefulness of digitalis glycosides is well known, and numerous studies of their positive inotropic effects have been conducted in isolated cardiac muscle, in isolated hearts and in anesthetized animal preparations. These studies indicate that even in the nonfailing heart, cardiac glycosides exert a powerful positive inotropic action. Myocardial contractility, as measured by the strain gauge arch, dP/dt or the velocity of myocardial-fiber shortening, has been shown to increase from 50 to 100 per cent in these studies. However, when ouabain was administered to normal conscious dogs, myocardial contractility rose only slightly, approximately 20 per cent.[10] Like the force-frequency relation, the relatively minor potency of cardiac glycosides in the conscious animal seems to be related to the higher base-line level of myocardial contractility in the heart of the normal conscious animal, that is not depressed by a general anesthetic and by the surgical manipulations necessary to implant the measuring devices. In the same animals, myocardial depression was induced acutely, by general anesthesia or in the conscious state by large doses of propranolol, or chronically, after right-sided heart failure was caused by progressive severe pulmonary stenosis. When identical doses of ouabain were administered the powerful positive inotropic effects of the cardiac glycoside were manifest. These observations indicate that general anesthesia can profoundly alter the inotropic action of drugs.

The different magnitudes of the inotropic responses elicited by ouabain in conscious and anesthetized animals may explain, in part, the differing effects of the drug on the coronary bed. When heart rate was maintained constant in the conscious animal, ouabain elicited substantial coronary vasoconstriction; in the same animal under the influence of pentobarbital anesthesia this effect did not occur. Apparently, the greater inotropic response to the drug in the anesthetized animal induced a more profound augmentation of myocardial oxygen demands than occurred in the conscious dog and therefore was responsible for a greater stimulus to metabolic coronary vasodilatation, which opposed and prevented the expression of the direct coronary constrictor effect.

Studies in anesthetized preparations have demonstrated that cardiac glycosides constrict systemic vascular beds other than the coronary beds in animals without heart failure; several studies have suggested that the vasoconstriction is most intense in the mesenteric bed. However, in the conscious animal, ouabain elicits substantial mesenteric vasodilatation, which can be blocked by atropine. Thus, the responses of conscious and anesthetized animals to many stimuli differ quantitatively and, in this instance, qualitatively as well — that is, ouabain induces mesenteric dilatation in conscious animals, whereas intense constriction is observed in anesthetized animals.

Sympathomimetic Amines

The response of the coronary vascular bed to norepinephrine is another example of a qualitatively different action in conscious and anesthetized animals. This catecholamine is known to possess a powerful alpha-adrenergic stimulating action that constricts vessels that supply the kidney, splanchnic viscera and skeletal muscle. However, it has been held that norepinephrine induces only dilatation in the coronary vascular bed, because of its beta-adrenergic-stimulating effect on myocardial contractility, which increases myocardial oxygen consumption and dilates the coronary bed on a metabolic basis. It has been demonstrated that the coronary-constricting effects of this substance mediated by alpha-receptors can be elicited in the arrested, but not in the contracting heart. Numerous studies in anesthetized preparations have supported this concept. However, when norepinephrine was administered intravenously in a bolus or by infusion to conscious animals, a period of intense coronary vasoconstriction occurred (Fig. 3), even when heart rate was held constant and when cardiac pressures, size and inotropic state were elevated — that is, when vasodilation was expected, because of an increase in myocardial oxygen consumption.[7] The norepinephrine-induced coronary constriction was reversed to vasodilatation after administration of phentolamine — indicating that it was caused by alpha-adrenergic stimulation. Whereas previous studies did identify alpha-adrenergic receptors in the coronary vessels, it has been held that these receptors are of trivial importance, since, only vasodilation was observed previously when norepinephrine was administered to open-chest anesthetized animals.

Other studies in conscious animals have supported the concept that alpha-adrenergic control of the coronary circulation is more important than studies in anesthetized animals suggested. Alpha-adrenergic-mediated coronary

vasoconstriction has been observed after hemorrhage and after intravenous administration of dopamine or morphine sulfate in the conscious dog. The effects of dopamine in conscious and anesthetized dogs are compared in Figure 3. In anesthetized dogs, only coronary vasodilation was observed, as in earlier studies by investigators who used anesthetized open-chest preparations. In conscious dogs, however, the same dose of dopamine evoked an intense and prolonged period of coronary vasoconstriction.

It is well recognized that morphine sulfate possesses adrenergic-stimulating properties. Recently, morphine was found to induce substantial coronary vasoconstriction in the conscious animal (Fig. 3), even when contractility was elevated and heart rate was constant. Since coronary vasoconstriction was not observed after alpha-adrenergic blockade, the vasoconstriction was probably due to morphine's alpha-adrenergic stimulating action. In contrast, when the same animals were studied in the anesthetized state, only coronary vasodilatation was observed.

We compared the hemodynamic effects of three sympathomimetic amines — norepinephrine, dopamine and dobutamine (a recently developed beta$_1$-adrenergic agonist, which increases contractility and has lesser effects on arterial pressure and cardiac rate) — in a group of animals studied in the conscious state and in the anesthetized state with an open chest. At each dose of each drug studied, a substantially greater positive inotropic response was elicited in the open-chest anesthetized preparations (Fig. 6). Even though base-line levels of contractility were depressed markedly in the anesthetized state, contractility rose to higher peak levels than observed in the conscious state; intermediate responses occurred in the animals in the anesthetized state with a closed chest. In addition, in the anesthetized animals, the direct chronotropic effects, mediated by beta-adrenergic receptors, were not attenuated by reflex effects to the same extent as in the conscious animals. Thus, norepinephrine and dobutamine elevated heart rate in the anesthetized state, but induced bradycardia in the conscious state, in which the baroreceptor reflex was not attenuated. The effects on cardiac size were different as well: a large bolus dose of each of these sympathomimetic amines reduced left ventricular end-diastolic dimensions in the open-chest anesthetized preparation, but did not alter end-diastolic size in the conscious state, presumably because of the accompanying bradycardia.

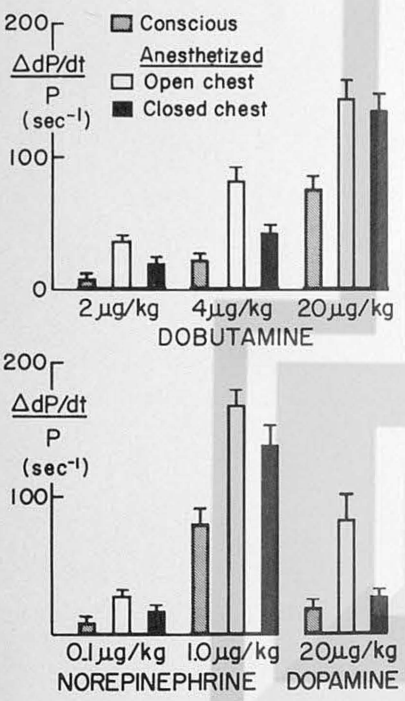

Figure 6. Inotropic Responses Elicited by Different Sympathomimetic Amines in the Same Dogs on Separate Days either Conscious, Anesthetized with Pentobarbital or Anesthetized with Pentobarbital and with an Open Chest.

Bars represent mean ± S.E.M.

Conclusions

It is now clear that although commonly employed anesthetics exert a variety of actions on every aspect of the circulatory system, the importance of general anesthesia on the circulation tends to be underestimated when only the direct effects are considered. Even more important is the modification of the organism's integrative response to any perturbation, whether it is a physiologic perturbation, such as hemorrhage, or a pharmacologic perturbation, such as a cardiac glycoside or sympathomimetic amine. Thus, although it is generally held that the overall cardiovascular responses to complex physiologic functions such as exercise or eating can be best described in the intact, conscious organism, the importance of conducting any experiment that involves integrative control of the circulation in the conscious organism should also be evident. The assumption that anesthesia and surgical trauma exert only minor effects on the response to physiologic and pharmacologic interventions is no longer tenable. Instead, general anesthesia belongs to that class of interventions imposed by the investigator, often inadvertently, on the subject under study, which has previously been referred to as "physiologic reactance."

References

1. Rushmer RF, Smith O, Franklin D: Mechanisms of cardiac control in exercise. Circ Res 7:602-627, 1959
2. Gregg DE, Khouri EM, Rayford CR: Systemic and coronary energetics in the resting unanesthetized dog. Circ Res 16:102-113, 1965
3. Van Citters RL, Franklin DL: Cardiovascular performance of Alaska sled dogs during exercise. Circ Res 24:33-42, 1969
4. Vatner SF, Smith NT: Effects of halothane on left ventricular function and distribution of regional blood flow in dogs and primates. Circ Res 34:155-167, 1974
5. Vatner SF, Higgins CB, Franklin D, et al: Extent of carotid sinus regulation of the myocardial contractile state in conscious dogs. J Clin Invest 51:995-1008, 1972
6. Vatner SF, Franklin D, Braunwald E: Effects of anesthesia and sleep on circulatory response to carotid sinus nerve stimulation. Am J Physiol 220:1249-1255, 1971
7. Vatner SF, Higgins CB, Braunwald E: Effects of norepinephrine on coronary circulation and left ventricular dynamics in the conscious dog. Circ Res 34:812-823, 1974
8. Vatner SF: Effects of hemorrhage on regional blood flow distribution in dogs and primates. J Clin Invest 54:225-235, 1974
9. Horwitz LD, Bishop VS: Effects of acute volume loading on heart rate in the conscious dog. Circ Res 30:316-321, 1972
10. Vatner SF, Higgins CB, Patrick T, et al: Effects of cardiac depression and of anesthesia on the myocardial action of a cardiac glycoside. J Clin Invest 50:2585-2595, 1971

Role of arterial baroreceptors in mediating cardiovascular response to exercise

ROBERT J. McRITCHIE, STEPHEN F. VATNER, DEDO BOETTCHER,
GUY R. HEYNDRICKX, THOMAS A. PATRICK, AND EUGENE BRAUNWALD
Departments of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, and Department of Cardiology, Children's Hospital Medical Center, Boston 02115; and New England Regional Primate Research Center, Southborough, Massachusetts 01772

AMERICAN JOURNAL OF PHYSIOLOGY
Vol. 230, No. 1, January 1976. *Printed in U.S.A.*

Role of arterial baroreceptors in mediating cardiovascular response to exercise

ROBERT J. McRITCHIE, STEPHEN F. VATNER, DEDO BOETTCHER, GUY R. HEYNDRICKX, THOMAS A. PATRICK, AND EUGENE BRAUNWALD
Departments of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, and Department of Cardiology, Children's Hospital Medical Center, Boston 02115; and New England Regional Primate Research Center, Southborough, Massachusetts 01772

McRITCHIE, ROBERT J., STEPHEN F. VATNER, DEDO BOETTCHER, GUY R. HEYNDRICKX, THOMAS A. PATRICK, AND EUGENE BRAUNWALD. *Role of arterial baroreceptors in mediating cardiovascular response to exercise*. Am. J. Physiol. 230(1): 85–89. 1976.—The role played by the major arterial baroreceptor reflexes in the cardiovascular response to exercise was examined by comparing the responses of untethered conscious dogs instrumented for the measurement of aortic pressure and cardiac output with those of dogs with total arterial baroreceptor denervation (TABD). Moderately severe levels of exercise (12 mph) in intact dogs increased cardiac output from 111 ± 5 to 366 ± 17 ml/kg per min, increased heart rate from 101 ± 5 to 265 ± 8 beats/min, and reduced total peripheral resistance from 0.039 ± 0.003 to 0.015 ± 0.002 mmHg/ml per min. Dogs with TABD responded in a very similar fashion; exercise increased cardiac output from 119 ± 8 to 356 ± 23 ml/kg per min, increased heart rate from 122 ± 7 to 256 ± 5 beats/min, and decreased total peripheral resistance from 0.042 ± 0.005 to 0.015 ± 0.001 mmHg/ml per min. The reflex heart rate responses to intravenous bolus doses of methoxamine were also examined in intact animals, both at rest and during exercise. Methoxamine caused striking bradycardia at rest, but little bradycardia during exercise. These results suggest that the arterial baroreceptor reflex is normally turned off during severe exercise and thus does not modify significantly the cardiovascular response to exercise.

autonomic nervous system; arterial pressure; cardiac output; heart rate; baroreflex; carotid sinus; telemetry; methoxamine; aortic nerve

EXERCISE IS ACCOMPANIED by a marked tachycardia, increases in cardiac output and in arterial and atrial pressures, and a reduction in total peripheral resistance (2, 11, 16). In view of these major cardiovascular alterations, it could be surmised that a cardiovascular regulating mechanism as important as the arterial baroreceptor reflex would play a significant role in mediating and modifying the exercise response. If the arterial baroreceptor reflexes were critical to the exercise response, then in the absence of these reflexes the cardiovascular adjustments would be altered (13). The increases in intravascular pressures that occur during exercise suggest that there must be altered input into both the arterial and cardiac baroreceptors, which in their absence would result in inordinate responses, e.g., extreme hypertension. However, the observed direction of the heart rate response, i.e., tachycardia in the presence of hypertension, is opposite to that expected, which suggests that the arterial baroreceptor reflexes are turned off or reset during exercise (3, 9).

This investigation was carried out to define the role of the major arterial baroreceptors during moderately severe exercise in two different ways. First, a comparison was made of the cardiovascular responses to moderately severe spontaneous exercise in dogs with and without major arterial baroreceptor afferent pathways. Second, the "baroreflex sensitivity" was compared in intact dogs at rest and during exercise by inducing a rapid increase in arterial pressure by injection of a vasoconstrictor and observing the reflex response of the pulse interval (12).

METHODS

Thirteen mongrel dogs, 25–30 kg, were anesthetized with pentobarbital sodium (30 mg/kg iv) and a thoracotomy was performed through the fourth left intercostal space under sterile surgical conditions. The pericardium was incised and then the aortic root was dissected for implantation of an electromagnetic flow transducer (Zepeda Instruments, Seattle, Wash.). In addition, miniature gauges (P22, Konigsberg Instruments, Inc., Pasadena, Calif.) were implanted in the thoracic aorta; these were calibrated in vitro and in vivo against a calibrated Statham P23Db strain-gauge manometer (Statham Instruments, Inc., Oxnard, Calif.).

Total arterial baroreceptor denervation (TABD) was performed through a midline cervical incision in six dogs, three of which had been studied prior to TABD. The carotid sinus nerves were isolated and sectioned, and the aortic nerves were divided according to the technique described by Edis and Shepherd (4). Postoperatively, adequacy of denervation procedure was confirmed by observation of the heart rate responses to bolus injections of nitroglycerin and methoxamine, 48 μg/kg. In intact dogs this dose of nitroglycerin increased heart rate by an average of 97 ± 11 (SE) beats/min; this dose of methoxamine slowed heart rate by 47 ± 2 beats/min of bradycardia. A change in heart rate of less than 6 beats/min in either direction after either an increase or decrease in arterial pressure was accepted as proof of adequate surgical denervation of all major arterial baroreceptor afferent pathways.

A modification of an electromagnetic flow system with a telemetry capability described by Fryer and Sandler (5) was used to measure aortic blood flow (16). The electronic equipment, carried by the animal in saddlebags, consisted of a battery-operated electromagnetic flow/pressure telemetry system. The signals containing pressure and flow data were telemetered by conventional frequency-modulation techniques to the mobile recording unit, containing an FM communications receiver, signal-processing electronics, and a magnetic tape recorder (16, 17).

The experiments were conducted 2–3 wk postoperatively when the dogs had recovered from the operation and were again vigorous and healthy. While the dogs were standing quietly control records of aortic pressure, cardiac output, and heart rate were obtained. The dogs were taken to an isolated area and the mobile unit carrying the electronic recording equipment then drove off. The speed of the van was 10–12 mph and the dogs followed it for a distance averaging ½ mile over a level road. Experiments were repeated on many of the dogs either on separate days or after sufficient time for full recovery on the same day, e.g., 2–4 h later. The levels of exercise attained by both the normal and denervated dogs were similar and was considered to be moderately severe.

In a separate series of experiments four intact dogs were exercised to the same moderately severe level and at the peak level of exercise were given a bolus intravenous dose of 800 μg methoxamine/kg. Bolus intravenous injections of methoxamine were administered to four of the dogs with intact baroreceptors at rest and during exercise through a catheter in the jugular vein that was connected to a syringe activated by radio control. In operation a transmitted radio signal activates a relay within the receiver carried in the saddlebags, which in turn activates an electrical current that heats a stainless steel fuse wire. The hot wire then severs a silk restraining loop attached to the syringe plunger, which is thereby closed by rubber-band action. On a separate day the same dogs were studied at rest and given 200 μg methoxamine/kg. The data were replayed at a paper speed of 50 mm/s and systolic pressure and the increasing pulse intervals were plotted by a technique described by Smyth et al. (12).

Total peripheral resistance was calculated as the quotient of mean arterial pressure in millimeters of Hg and aortic blood flow (cardiac output) in milliliters per minute. Statistical analysis of the data, assessed during preexercise control and peak steady-state exercise, was determined by the group and paired t test. Regression analysis and the analysis of variance of the regression were also performed (8).

Exercise data were recorded on a multichannel tape recorder and played back on a direct-writing oscillograph. A cardiotachometer triggered by the signal from the pressure pulse provided instantaneous and continuous records of heart rate.

RESULTS

The cardiovascular response to exercise occurring before and after total arterial baroreceptor denervation (TABD) is illustrated in Fig. 1 and the findings of all the dogs are summarized in Table 1 and Fig. 2.

Intact dogs. In the intact dogs exercise increased aortic blood flow by an average of 255 ± 16 (SE) ml/kg per min above a control of 111 ± 5 ml/kg per min. This was

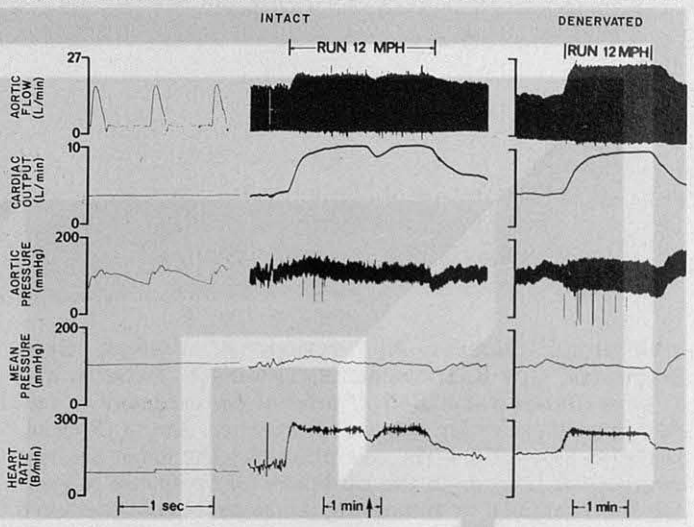

FIG. 1. Responses of aortic flow, cardiac output, phasic and mean aortic pressure, and heart rate to moderate exercise in an intact dog (*left panel*) and same dog after total arterial baroreceptor denervation (*right panel*). Note similarity of responses.

TABLE 1. *Effects of moderately severe exercise*

	Standing	Exercise	Δ
Intact (n = 10)			
Cardiac output, ml/kg per min	111 ± 5	366 ± 17*	255 ± 16
Stroke volume, ml	26.8 ± 1.5	33.3 ± 1.8†	6.5 ± 1.7
Heart rate, beats/min	101 ± 5	265 ± 8*	164 ± 8
Mean aortic pressure, mmHg	98 ± 3	125 ± 4*	27 ± 3
Total peripheral resistance, mmHg/ml per min	0.039 ± 0.003	0.015 ± 0.002*	0.024 ± 0.003
Denervated (n = 6)			
Cardiac output, ml/kg per min	119 ± 8	356 ± 23*	237 ± 23
Stroke volume, ml	23.3 ± 1.8‡	34.2 ± 3.1*	10.9 ± 2.5‡
Heart rate, beats/min	122 ± 7‡	256 ± 5*	134 ± 9§
Mean aortic pressure, mmHg	111 ± 4‡	127 ± 9†	17 ± 8
Total peripheral resistance, mmHg/ml per min	0.042 ± 0.005	0.015 ± 0.001*	0.027 ± 0.005

* Significantly different from standing, $P < 0.02$. † Significantly different from standing, $P < 0.05$. ‡ Significantly different from intact, $P < 0.05$. § Significantly different from intact, $P < 0.02$.

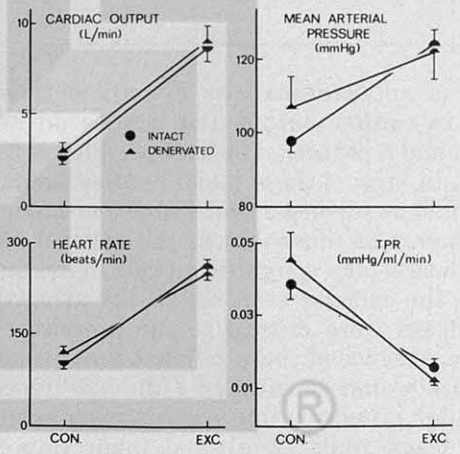

FIG. 2. Values (means ± SE) during control and steady-state exercise for cardiac output, arterial pressure, heart rate, and total peripheral resistance (TRP) for intact dogs (circles) and dogs with total arterial baroreceptor denervation (TABD) (triangles).

accompanied by a marked increase in heart rate from 101 ± 5 to 265 ± 8 beats/min and a slight increase in stroke volume from 26.8 ± 1.5 to 33.3 ± 1.8 ml. Mean aortic pressure rose from 98 ± 3 to 125 ± 4 and calculated total peripheral resistance fell from 0.039 ± 0.003 to 0.015 ± 0.002 mmHg/ml per min.

Denervated dogs. In dogs with TABD in the standing position at rest, heart rate and mean arterial pressure were slightly higher than in the intact dogs (Table 1); cardiac output and total peripheral resistance did not differ in the two groups, but stroke volume was significantly lower. Exercise increased cardiac output from 119 ± 8 to 356 ± 23 ml/kg per min and heart rate from 122 ± 7 to 256 ± 5 beats/min. The levels reached did not differ significantly from those in the intact group. Stroke volume, which was significantly lower in dogs with TABD (23.8 ± 1.8 ml) than in intact dogs, increased significantly more during exercise to 34.2 ± 3.1 ml, a level almost identical to that observed in the intact dogs (Table 1). Mean aortic pressure increased and calculated total peripheral resistance decreased, and these levels were sustained for the period of exercise. Thus, the circulatory changes during moderately severe exercise in dogs with TABD resembled very closely those seen in intact dogs during similar amounts of exertion. In addition, the dogs with TABD appeared to tolerate the moderately severe exercise as well as did the intact dogs.

Intact dogs and bolus intravenous methoxamine. Four intact dogs were administered bolus intravenous injections of methoxamine, both at rest in the laboratory and during moderately severe exercise. In order to obtain equivalent pressor responses in the two situations, the doses of methoxamine employed during exercise were approximately 4 times greater than those employed at rest. Typical records are illustrated in Fig. 3.

At rest, the expected reciprocal relation between heart rate and arterial pressure was observed (Table 2). On the other hand, when similar increases in arterial pressure were produced in the exercise state, almost no cardiac slowing occurred. This absence of cardiac slowing in the exercising dogs with intact baroreceptors was similar to that observed in the dogs with TABD at rest.

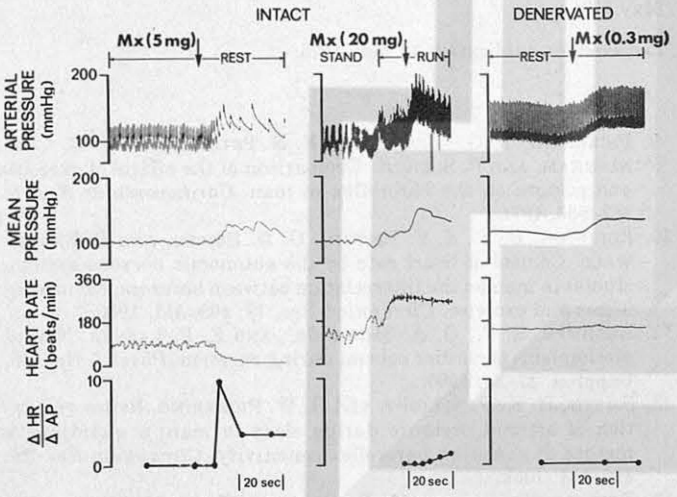

FIG. 3. Responses of arterial pressure, mean pressure, heart rate, and calculated Δ heart rate (HR)/Δ arterial pressure (AP) in an intact dog at rest to bolus of 5 mg iv methoxamine (*left panel*) and to 20 mg iv methoxamine in same dog during moderately severe exercise (*middle panel*) and in a dog with TABD at rest to 0.3 mg methoxamine (*right panel*). Note similarity of ΔHR/ΔAP responses in intact dog during exercise and that of dog with TABD at rest.

TABLE 2. *Systolic arterial pressure (SAP)/pulse interval (PI) slope in response to methoxamine*

Dog	Slope at Rest	Slope During Exercise	P*
1	34.9	0.20	<0.001
2	85.2	0.85	<0.001
3	41.6	0.30	<0.001
4	48.7	0.19	<0.001

* Significant difference between SAP/PI slope at rest and during exercise.

DISCUSSION

The findings of the present investigation on the cardiovascular response to moderately severe exercise in the conscious dog with intact arterial baroreceptors are in general agreement with previous observations (2, 11, 16), in that cardiac output and heart rate rose markedly, the former proportionately more than the latter; consequently there was an associated small increase in stroke volume. Aortic pressure rose significantly and there was a sustained reduction in calculated systemic vascular resistance. In dogs with TABD, although there were minor differences in the preexercise levels of heart rate, arterial pressure, and stroke volume, all these variables rose to levels that were essentially identical to those observed in the dogs with intact baroreceptors during exercise.

Previous investigations into the role of the arterial baroreceptor reflex in the control the cardiovascular system during exercise have yielded conflicting conclusions as to their importance. On the one hand, Heymans and Neil (6) asserted that the baroreceptor reflex is just as active during exercise as at rest. Robinson et al. (10) studied the reflex heart rate responses to pharmacologic alterations in blood pressure during exercise in man and found that the change in heart rate for any given change in pressure was similar during rest and exercise and concluded that the sensitivity of the baroreceptor reflex was not altered during exercise, thereby supporting the view of Heymans and Neil. Topham and Warner (13) also concluded that the arterial baroreceptor reflex is an essential link in the cardiovascular adjustment to exercise and in the absence of this loop normal increases in heart rate and cardiac output cannot be attained. These conclusions were supported in general by the subsequent studies of Bevegard and Shepherd (1, 2), who found that the increase in heart rate and blood pressure in man during exercise is restricted, though not prevented, by the arterial baroreceptor reflex, but that the carotid sinus mechanism is less effective in opposing the increase in heart rate than of blood pressure. These observations and conclusions suggest that, in the absence of the modifying influences of the arterial baroreceptor reflex, both arterial pressure and heart rate should increase to even higher levels than are normally seen.

On the other hand, studies conducted in dogs with and without baroreceptor isolation by Van Houtte et

al. (14) revealed little difference in the cardiovascular response to exercise in the two groups of dogs, although measurements of cardiac output were made not during but immediately after the cessation of exercise. Moreover, in that study the changes from control to the postexercise state were similar on a percent-change basis but the dogs with baroreceptor isolation showed only approximately half the normal increase in cardiac output in absolute flow. Further support for the position that the baroreceptors were of little importance during exercise came from a study by Bristow et al. (3), who observed in man that the slope of the regression line of systolic arterial pressure on heart rate after intravenous phenylephrine was depressed and who therefore concluded that the arterial baroreceptor reflex was either reset or turned off during exercise and that the higher the heart rate during exercise the greater the reductions in sensitivity of the arterial baroreceptor reflex. More recently, Krasney et al. (7) found that, although the responses of normal and baroreceptor denervated dogs to the stress of exercise were qualitatively similar, some differences occurred; the increases in cardiac output and heart rate were more sluggish, arterial pressure was less stable, and the marked decline in systemic vascular resistance was not sustained. Moreover, the peak levels attained for heart rate and cardiac output were significantly less in the dogs with TABD. These investigators concluded that arterial baroreceptor reflexes do play a role in the regulation of the circulation during exercise but that they do so in a more complex fashion than previously recognized. Our results are consistent with those of Krasney et al. (7) in that arterial pressure was more unstable during exercise in dogs with TABD, but they are inconsistent with their results in that a sustained decline in systemic vascular resistance did occur in our dogs with TABD. In the study by Krasney et al. (7), although the responses of heart rate and cardiac output were qualitatively similar in normal dogs and those with TABD, the dogs with TABD did not attain the same peak levels for cardiac output and heart rate, whereas in the present study a more severe level of exercise (12 mph) was examined, in which cardiac output rose about threefold; the exercise level in the study by Krasney et al. was only 5 mph and cardiac output less than doubled in their dogs with TABD.

The results of the present study further indicate that the normal tachycardia of exercise can occur rapidly even in the absence of an intact arterial baroreceptor reflex. These results suggest that this tachycardia is mediated either by a central mechanism (11) or, since the vagi were intact, by inputs from lung receptors in the chest wall, somatic afferents, low-pressure receptors, or some combination of these. Support for the latter hypothesis can be gathered from the findings that left ventricular filling pressure is elevated during exercise (16) and that, in the presence of an elevated atrial pressure associated with volume loading, the arterial baroreceptor reflex is also inhibited (15).

Thus, in the intact animal, the arterial baroreceptor reflex plays little role in modulating the cardiovascular response to exercise. This finding suggests that, during this stress, this reflex is inhibited or turned off. The hypothesis was tested and supported by the experiments in the intact dogs in which heart rate did not slow with sudden elevation of arterial pressure by methoxamine during exercise. In summary, although a multiplicity of afferent inputs are probably involved in the cardiovascular response to exercise, the arterial baroreceptor reflex does not modify this response in any measurable way, and it is concluded that it is inhibited during this stress.

We acknowledge the technical assistance of T. Manders, R. Peters, and P. Quinn and the help of V. Fowler in preparation of the manuscript.

This study was supported in part by Public Health Service Grants HL 15416, HL 17549, and HL 1043609, NASA-Ames Research Grant 22-036-001, and American Heart Association Grant 73-883.

R. J. McRitchie is an Overseas Research Fellow of the National Heart Foundation of Australia. S. F. Vatner is an Established Investigator of the American Heart Association. D. Boettcher and G. R. Heyndrickx are Public Health Service International Fellows.

This study was presented in part at the National Meeting of the American Society for Clinical Investigation, Atlantic City, N.J., 5 May 1974.

Received for publication 12 May 1975.

REFERENCES

1. Bevegard, B. S., and J. T. Shepherd. Circulatory effects of stimulating the carotid arterial stretch receptors in man at rest and during exercise. *J. Clin. Invest.* 45: 132–142, 1966.
2. Bevegard, B. S., and J. T. Shepherd. Regulation of the circulation during exercise in man. *Physiol. Rev.* 47: 178–213, 1967.
3. Bristow, J. D., E. B. Brown, Jr., D. J. C. Cunningham, M. G. Howson, E. J. Petersen, T. G. Pickering, and P. Sleight. Effect of bicycling on the baroreflex regulation of pulse interval. *Circulation Res.* 28: 582–591, 1971.
4. Edis, A. J., and J. T. Shepherd. Selective denervation of aortic arch baroreceptors and chemoreceptors in dogs. *J. Appl. Physiol.* 30: 294–296, 1971.
5. Fryer, T. B., and H. Sandler. Miniature battery-operated electromagnetic flowmeter. *J. Appl. Physiol.* 31: 622–628, 1971.
6. Heymans, C., and E. Neil. *Reflexogenic Areas of the Cardiovascular System.* Boston: Little, Brown, 1958, p. 41.
7. Krasney, J. A., M. G. Levitsky, and R. C. Koehler. Sinoaortic contribution to the adjustment of systemic resistance in exercising dogs. *J. Appl. Physiol.* 36: 679–685, 1974.
8. Mather, K. *Statistical Analysis in Biology* (4th ed.). New York: Interscience Publishers, 1965, p. 109–122.
9. Pickering, T. G., B. Gribbin, E. S. Petersen, D. J. C. Cunningham, and P. Sleight. Comparison of the effects of exercise and posture on the baroreflex in man. *Cardiovascular Res.* 5: 582–586, 1971.
10. Robinson, B. F., S. F. Epstein, G. D. Beiser, and E. Braunwald. Control of heart rate by the autonomic nervous system: studies in man on the interrelation between baroreceptor mechanisms and exercise. *Circulation Res.* 19: 400–411, 1966.
11. Rushmer, R. F., O. A. Smith, Jr., and E. P. Lasher. Neural mechanisms of cardiac control during exertion. *Physiol. Rev.* 40, Suppl. 4: 27–34, 1960.
12. Smyth, H. S., P. Sleight, and G. W. Pickering. Reflex regulation of arterial pressure during sleep in man: a quantitative method of assessing baroreflex sensitivity. *Circulation Res.* 24: 109–121, 1969.
13. Topham, W. S., and H. R. Warner. The control of cardiac output during exercise. In: *Physical Basis of Circulatory Transport,* edited by E. B. Reeve and A. C. Guyton. Philadelphia: Saunders, 1967, p. 77–90.
14. Van Houtte, P., E. Lacroix, and I. Leusen. The cardiovascular adaptation of the dog to the muscular exercise. Role of the

arterial pressorreceptors. *Arch. Intern. Physiol. Biochim.* 74: 201–222, 1966.

15. VATNER, S. F., D. H. BOETTCHER, G. R. HEYNDRICKX, AND R. J. MCRITCHIE. Reduced baroreflex sensitivity with volume loading in conscious dogs. *Circulation Res.* 37: 236–242, 1975.
16. VATNER, S. F., D. FRANKLIN, C. B. HIGGINS, T. PATRICK, AND E. BRAUNWALD. Left ventricular response to severe exertion in untethered dogs. *J. Clin. Invest.* 51: 3052–3060, 1972.
17. VATNER, S. F., C. B. HIGGINS, S. WHITE, T. PATRICK, AND D. FRANKLIN. The peripheral vascular response to severe exercise in untethered dogs before and after complete heart block. *J. Clin. Invest.* 50: 1950–1960, 1971.

Reprinted from Circulation Research
Volume 38, Number 4, April, 1976
Printed in U.S.A.

The Role of Arterial Baroreceptors in Mediating the Cardiovascular Response to a Cardiac Glycoside in Conscious Dogs

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ROBERT J. MCRITCHIE, M.B.,* AND STEPHEN F. VATNER, M.D.†

SUMMARY **To determine the role of the arterial baroreceptor reflex in mediating the cardiovascular response to a cardiac glycoside, we examined the effects of ouabain (G-strophanthin), 17.5 μg/kg, iv, on direct and continuous measurements of left ventricular diameters, pressures, velocity of shortening, $(dP/dt)/P$, arterial pressure, cardiac output, and total peripheral resistance. These studies were conducted on healthy conscious dogs before and after total arterial baroreceptor denervation (TABD). Maximal pressor effects were observed in the first 3–5 minutes; mean arterial pressure increased by 11 ±1 mm Hg in normal dogs compared to 33 ±4 mm Hg in denervated dogs. In intact dogs at this time heart rate decreased by 18 ± 2 beats/min and cardiac output fell by 18 ± 3%; these values gradually returned toward control over 15–30 minutes. When heart rate was kept constant, cardiac output did not fall after injection of ouabain. In contrast, heart rate and cardiac output did not change significantly after ouabain in dogs with TABD. The maximal effects on the contractile state of the heart occurred between 15–30 minutes and were similar in both groups. Arterial baroreceptor reflexes appear to be responsible for the reduction in heart rate and cardiac output caused by administration of ouabain to the intact dog. They exert an important buffering action on the vasopressor effect but a less important action on the inotropic response.**

CARDIAC glycosides increase cardiac output through a strong inotropic action on the failing heart. In contrast, cardiac glycosides, when administered to man or animals without heart failure, either reduce or do not change cardiac output.[1, 2] One of the most prevalent hypotheses offered to explain why digitalis exerts little effect on output of the nonfailing heart is that the arterial baroreceptors, stimulated either directly by the cardiac glycoside[3] or by the rise in arterial pressure that occurs, attenuate the normally powerful inotropic action of the drug and thereby prevent cardiac output from rising.[2-6] A corollary of this hypothesis, i.e., that the cardiac glycoside would cause a striking inotropic response sufficient to elevate stroke volume and cardiac output in the absence of arterial baroreceptors, was the subject of this investigation.

In order to accomplish this goal the effects of a subtoxic dose of ouabain were studied before and after recovery from denervation of arterial baroreceptors in conscious dogs which had been instrumented for direct measurements of stroke volume, cardiac output, left ventricular dimensions and pressures, dP/dt, and velocity of myocardial fiber shortening. It was considered important to conduct this study in conscious animals because general anesthesia, per se, depresses cardiac function,[7, 8] and cardiac glycosides exert a more potent action on the depressed myocardium.[8]

Methods

Ten mongrel dogs were anesthetized with pentobarbital sodium (30 mg/kg, iv). Through a thoracotomy in the 4th left intercostal space an electromagnetic flow transducer (Zepeda Instruments, Seattle) was implanted around the ascending aorta and pacemaker electrodes were sutured to the left atrium. A catheter was implanted in the ascending aorta via the femoral artery. In another group of seven dogs under pentobarbital anesthesia and through a thoractomy in the 5th left intercostal space, miniature pressure gauges (model P22, Konigsberg Instruments, Pasadena, Calif.) were implanted within the left ventricle through a stab wound in the apex. A Tygon catheter was implanted through

From the Departments of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, and the Department of Cardiology, Children's Hospital Medical Center, Boston, Massachusetts, and the New England Regional Primate Research Center, Southborough, Massachusetts.

Supported in part by U.S. Public Health Service Grants HL 15416, HL 17459, and HL 10-436009, and by NASA-Ames Grant 33 036 001.

This study was presented in part at the National Meeting of the American Federation for Clinical Research, May 5, 1975, Atlantic City, New Jersey.

* Overseas Research Fellow, National Heart Foundation of Australia.

† Established Investigator, American Heart Association.

Received August 21, 1975; accepted for publication December 19, 1975.

the left atrial appendage to measure left atrial pressure. Opposing ultrasonic diameter transducers* were implanted on the endocardial surfaces of the anterior and posterior walls of the left ventricle, and pacemaker electrodes were sutured to the left atrium. Total arterial baroreceptor denervation (TABD) was performed during a subsequent operation through an anterior cervical incision by first dividing the carotid sinus nerves and then the aortic nerves according to the technique described by Edis and Shepherd.[9] Adequacy of the denervation was confirmed postoperatively by observing the responses to intravenous bolus doses of nitroglycerin, 48 μg/kg, and methoxamine, 48 μg/kg. Any dog exhibiting a reciprocal change of heart rate of more than 6 beats/min was considered to be not denervated and was excluded from the study. Normally these drugs elicited changes of 97 ± 11 and 47 ± 2 beats/min, respectively, in heart rate.

Experiments were conducted 2–4 weeks postoperatively when the dogs had recovered fully from the surgery. While the trained, conscious, unsedated dogs of the first group were resting quietly in a darkened laboratory, control records of arterial pressure, aortic flow, cardiac output, and heart rate were obtained. In the other group of dogs control records of left ventricular pressure and diameter, the time rate of change of diameter (dD/dt), the time rate of change of pressure (dP/dt), and heart rate were obtained. Ouabain, 17.5 μg/kg, which is the largest dose that can be administered consistently to the conscious dog without producing toxic side effects, was given as an intravenous bolus and recordings were obtained continuously during the subsequent 30 minutes. In some experiments recordings were taken for periods of up to 60 minutes. Records during the control period and during peak pressor and inotropic responses also were obtained with heart rate controlled at a frequency slightly higher than the control spontaneous rate.

The electromagnetic flow probes were precalibrated in vitro. During the experiments zero flow was assumed to occur in mid-diastole and late diastole. The left ventricular pressure gauges were calibrated in vivo against a calibrated Statham P23Db strain gauge manometer. Diastolic pressure for the implanted gauge was calibrated in relation to the corresponding left atrial pressure. At autopsy the position of the miniature pressure transducer within the ventricular lumen was confirmed. Arterial pressure was measured with a Statham P23Db strain gauge manometer. An ultrasonic transit time dimension gauge was used to measure left ventricular diameter;[10] the principle of its operation is similar to that of other ultrasonic gauges which have been described previously. In brief, the instrument measured the transit time of acoustic impulses traveling at the sonic velocity of approximately 1.5 ± 10^6 mm/sec between the 3-mHz piezoelectric crystals implanted on the left ventricular endocardium at opposing sites. The transit time was calibrated by substituting signals of known duration from a pulse generator which was referenced to the frequency of a quartz crystal controlled oscillator. A voltage proportional to transit time was recorded and calibrated in terms of crystal separation. In this manner a measure of the internal diameter of the left ventricle was continuously recorded.

The signals were directly coupled to a multichannel tape recorder and played back on a direct-writing oscillograph at a paper speed of 100 mm/sec. A cardiotachometer triggered by the signal from the pressure pulse provided instantaneous and continuous records of heart rate. Continuous records of dP/dt and dD/dt were derived from the left ventricular pressure and diameter signals; Philbrick operational amplifiers (Philbrick/Nexus Research, Dedham, Mass.) were connected as differentiators. A triangular wave signal with known slope (rate-of-change) was substituted for pressure and diameter signals to directly calibrate the left ventricular dP/dt and velocity channels.

The action of ouabain on myocardial force-velocity relations was assessed by determining its effects on the velocity of shortening and intraventricular pressure at an identical ventricular diameter. When, at any given instantaneous myocardial diameter or length (isolength point), the velocity of shortening rises, a shift in myocardial force-velocity relations which reflects a positive inotropic effect is considered to have occurred. All isolength points were obtained during the first one-third of ejection. In addition, developed pressure, i.e., $(dP/dt)/P$, was examined. The latter was calculated as the quotient of dP/dt and left ventricular pressure minus end-diastolic pressure, the same level of pressure which occurred during the isovolumetric contraction period both before and after ouabain. These techniques for evaluating the myocardial contractile state have been described in detail previously.[8, 11-13] For statistical analysis of the data, both a paired t-test and group t-test[14] were used.

Results

In Table 1 are summarized the control data for both the intact and denervated dogs. Control values for arterial pressure, left ventricular pressure, heart rate, and peak dP/dt of the denervated dogs were significantly higher than in the intact group, whereas control values for end-diastolic and end-systolic diameters and stroke volume were lower.

ARTERIAL PRESSURE

Ouabain increased mean arterial pressure in the intact dogs by 1 minute; the pressure reached a maximum of 11 ± 1 mm Hg above control of 90 ± 3 mm Hg at 3–5 minutes; and declined gradually but remained above control levels at 30 minutes (Fig 1). In the dogs with TABD, arterial pressure also was significantly elevated at 1 minute, at 3–5 minutes reached a maximum of 33 ± 4 mm Hg above a control of 107 ± 4 mm Hg, and remained above control at 30 minutes. The elevation in arterial pressure in the dogs with TABD was significantly greater than in intact dogs ($P < 0.001$).

HEART RATE

In intact dogs ouabain decreased heart rate within 1 minute after injection; at 3–5 minutes reached a minimum of −18 ± 2 beats/min below a control of 82 ± 2 beats/min ($P < 0.01$); and returned slowly toward control at 30 minutes (Fig. 1). In dogs with TABD, resting heart rate was

* Construction details are available from the authors.

TABLE 1 *Control Values*

	Intact	Denervated
Mean arterial pressure (mm Hg)	90 ± 3	107 ± 4*
Heart rate (beats/min)	82 ± 2	115 ± 6*
Cardiac output (liters/min)	2.40 ± 0.11	2.44 ± 0.06
Stroke volume (ml)	32.0 ± 3	25.0 ± 2*
Total peripheral resistance (mm Hg/ml per min)	0.037 ± 0.003	0.041 ± 0.003
End-diastolic diameter (mm)	36.3 ± 1.3	30.4 ± 2.5*
End-systolic diameter (mm)	27.5 ± 1.5	23.0 ± 2.3*
Left ventricular systolic pressure (mm Hg)	115 ± 4	141 ± 7*
Peak dP/dt (mm Hg/sec)	3160 ± 240	4090 ± 380†
$(dP/dt)/P$ (sec^{-1})	54 ± 3	60 ± 3
Isolength left ventricular velocity (mm/sec)	57 ± 9	66 ± 8

Results are expressed as mean ± SEM.
* Significantly different from intact ($P < 0.01$).
† Significantly different from intact ($P < 0.05$).

significantly higher at 115 ± 6 beats/min (Table 1), there was no significant reduction in heart rate during the peak pressor response, and the rate remained at resting control levels through the entire 30-minute period of observation.

SYSTEMIC HEMODYNAMICS

In intact dogs ouabain decreased cardiac output by a maximum −0.38 ± 0.06 liters/min from a control level of 2.40 ± 0.11 liters/min ($P < 0.01$) (Fig. 1). This coincided with the peak pressor response at 3–5 minutes and had returned almost to control levels by 15 minutes. Total peripheral resistance increased by 0.012 ± 0.002 mm Hg/ml per min from a control of 0.037 ± 0.003 at the time of the peak pressor effect, i.e., 3–5 minutes ($P < 0.001$), and returned toward control levels during the 30-minute period of observation.

Maintenance of heart rate at control levels by atrial stimulation at the time of the peak pressor effect returned cardiac output to control levels, while mean arterial pressure rose by 24 ± 4 mm Hg.

In dogs with TABD, ouabain did not produce a significant change in cardiac output from the control level of 2.44 ± 0.06 liters/min throughout the entire observation period (Fig. 1), and this was associated with no significant change in stroke volume. Total peripheral resistance increased by 0.018 ± 0.002 mm Hg/ml per min ($P < 0.001$) at 3–5 minutes from a control of 0.041 ± 0.003; it did not return to control levels as rapidly as it did in intact dogs, and at 30 minutes it was still significantly elevated above control by 0.005 ± 0.002 mm Hg/ml per min ($P < 0.05$). This increase was greater than that observed in intact dogs.

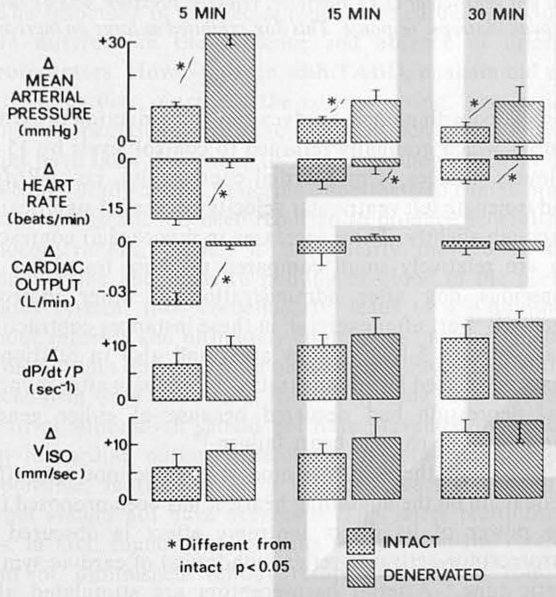

FIGURE 1 *The average* (±SEM) *changes in mean arterial pressure, heart rate, cardiac output,* $(dP/dt)/P$, *and isolength left ventricular velocity* (V_{iso}) *in intact dogs compared with denervated dogs at 5, 15, and 30 minutes after ouabain administration.*

VENTRICULAR DYNAMICS

In intact dogs, ouabain increased left ventricular systolic pressure from a control of 115 ± 4 mm Hg by 12 ± 2 mm Hg at 3–5 minutes ($P < 0.01$) (Fig. 2); subsequently, pressure gradually returned toward control levels. End-diastolic diameter increased slightly, by +0.29 ± 0.20 mm, but did not differ significantly from a control of 36.3 ± 1.3 mm (Fig. 2), while end-systolic diameter decreased by 0.51 ± 0.24 mm, but not significantly from a control of 27.5 ± 1.5 mm. By 15 minutes after injection of ouabain $dP/dt/P$ increased by 10 ± 2 sec^{-1} from a control of 54 ± 3 sec^{-1} (Figs. 1 and 2) and remained essentially at this level until the end of the 30-minute observation period. Isolength left ventricular velocity increased by a maximum of 12 ± 2 mm/sec from a control of 57 ± 9 mm/sec at 30 minutes (Figs. 1 and 2). Observations at times greater than 30 minutes indicated that myocardial contractility began to diminish.

If heart rate was restored to control levels by atrial stimulation during the peak inotropic effect there was no significant effect on the inotropic responses, although left ventricular dimensions were significantly smaller at the more rapid rate; end-diastolic size was 31.5 ± 1.5 mm and end-systolic size was 24.2 ± 1.4 mm. These values are comparable to those of dogs with TABD.

In dogs with TABD, left ventricular systolic pressure increased by 35 ± 4 mm Hg from a control of 141 ± 7 mm Hg (Fig. 2) ($P < 0.001$); this was a significantly greater increase ($P < 0.01$) than occurred in the intact dogs with

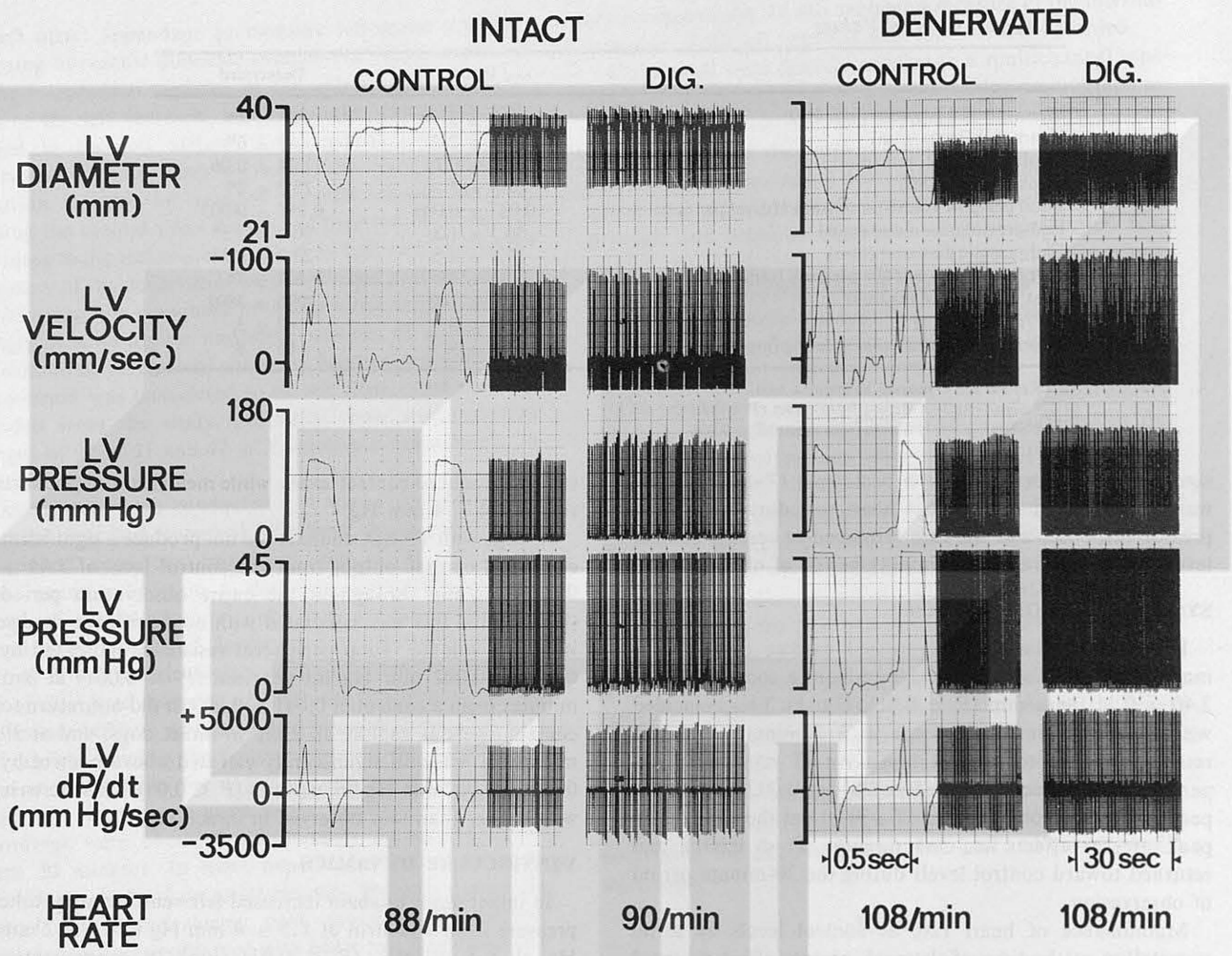

FIGURE 2 *Typical waveforms recorded from the same dog before and after ouabain when the animal was intact (left panels) and after total arterial baroreceptor denervation (right panels). The records of instantaneous left ventricular (LV) diameter, velocity, pressure, and dP/dt are shown at a fast and slow paper speed during the control period and during the peak inotropic response. This dog exhibited as large an increase in the inotropic state as was observed in this study. Dig. = digitalis.*

spontaneous rhythm or with heart rate constant. As in the intact dogs, ouabain produced little change in left ventricular diameter. $dP/dt/P$ increased by 14 ± 2 sec^{-1} above a control of 60 ± 3 sec^{-1}, while isolength left ventricular velocity increased by a maximum of 14 ± 4 mm/sec from a control of 66 ± 8 mm/sec. The peak increases in $dP/dt/P$ and isolength left ventricular velocity were slightly greater in dogs with TABD than in intact dogs. The differences, however, were not significantly greater (Fig. 1). Moreover, if percent change from control was examined, differences in inotropic responses between intact and TABD dogs would have been even smaller.

Discussion

To examine the role of the arterial baroreceptors in modifying the response to cardiac glycosides, we studied the conscious dog because general anesthesia interferes with baroreceptor control of the circulation[7, 8] and modifies the normal response to a cardiac glycoside.[8] In the conscious dog, a relatively large dose of ouabain produced a peak pressor response after about 3–5 minutes and this was associated with modest bradycardia and reduction in cardiac output which gradually returned to control levels by 15–30 minutes. Indices of myocardial contractility, i.e., $dP/dt/P$ and isolength left ventricular velocity, increased significantly although slightly. These increases in myocardial contractility are relatively small compared to those found for the conscious dog after administration of other inotropic agents[15, 16] or, after exercise; in these instances contractility may increase 5-fold.[17] They are small also in relation to changes induced by administration of ouabain after myocardial depression had occurred because of either general anesthesia[8] or chronic heart failure.[18]

To explain the relatively modest positive inotropic effect of ouabain on the nonfailing heart, it has been proposed that the power of its direct inotropic effect is obscured by baroreceptor-activated reflex withdrawal of cardiac sympathetic tone.[6] Arterial baroreceptors are stimulated after administration of cardiac glycosides in at least two ways: First, as has been shown recently, cardiac glycosides cause direct stimulation of the afferent carotid sinus and aortic nerves[3-5] and thus enhance "barosensitivity" of the animal.

Second, they elevate arterial pressure by causing systemic vasoconstriction, and this is expected to excite baroreceptor afferent pathways.[3-5] The arterial baroreceptor reflex then would be expected to buffer the rise in pressure, in part by reducing myocardial contractility and, thus, to oppose the direct effects of the cardiac glycoside.[3-6] The results of our study suggest that baroreceptor reflex activation plays a minor role in blunting the positive inotropic effect of a cardiac glycoside in the intact, conscious dog, since the maximum dose of ouabain that could be used without eliciting toxic effects induced only slight inotropic effects in the absence of arterial baroreceptors. These results are consistent with those of a previous study from this laboratory in which the carotid sinus baroreceptor reflex was found to exert only a minimal effect in the control of myocardial contractility and stroke volume but to exert important effects in the regulation of arterial pressure and cardiac rate.[13] Thus, under physiological conditions, baroreceptor control of myocardial contractility appears to be relatively ineffective.

Although inotropic responses were not markedly different between the two groups of dogs, those with TABD responded to ouabain with a 3-fold greater increase in pressure, indicating that arterial baroreceptors do play an important role in buffering the pressor response to the cardiac glycoside. The 3-fold difference in peak pressor response between intact dogs and dogs with TABD is similar to that described for responses to intravenous methoxamine;[19] this finding suggests that cardiac glycosides do not exert a major action in "sensitizing" the arterial baroreceptors.[3] If the latter phenomenon were important, a greater difference in arterial pressure response should have been observed in response to ouabain than to methoxamine, because methoxamine is not known to exert a direct effect on the arterial baroreceptors.

The responses of cardiac output to the cardiac glycoside were different in the presence and absence of arterial baroreceptors. However, even with TABD, ouabain did not increase cardiac output in the conscious dog. The initial, transient reduction in cardiac output which was observed could have been due either to venous pooling[2, 20] or to the attendant bradycardia. In normal, anesthetized canine preparations, digitalis has been reported to produce generalized venoconstriction,[2] which is particularly marked in the hepatic veins and leads to pooling of blood in the portal venous system; this, consequently, leads to a diminished venous return[20] and ultimately contributes to the decreased cardiac output observed after ouabain administration. If this mechanism were important, then controlling the heart rate by atrial stimulation should not have prevented the reduction in cardiac output, whereas if the bradycardia were responsible, in the face of a constant heart rate cardiac output should not have decreased. This latter relationship was, in fact, found. These results suggest that the mechanism of diminished venous return plays little role in reducing cardiac output after ouabain administration, as observed in the intact, conscious dog. The finding that end-diastolic size, an indication of cardiac preload, did not diminish in any group of conscious dogs studied supports this conclusion.

The precise mechanism for the cardiac slowing induced by digitalis remains controversial. In our experiments, removal of the carotid sinus and aortic nerve afferent pathways abolished the bradycardia seen in intact dogs, even though the vagus nerves were intact; this result is in agreement with those of Heymans et al.[21, 22]

In summary, arterial baroreceptor reflexes a play a minor role in attenuating the inotropic action of a cardiac glycoside. Even in the absence of arterial baroreceptor afferent pathways, ouabain did not exert an inotropic action sufficiently powerful to elevate cardiac output. The major role of the arterial baroreceptor reflex in the response to ouabain involves (1) substantial attenuation of the pressure response, and (2) mediation of the reflex bradycardia and reduction in cardiac output that normally occurs in the conscious dog without heart failure. This latter observation implies that splanchnic pooling is not an important mechanism mediating the reduction in cardiac output which results from administration of ouabain to the conscious dog.

Acknowledgments

We acknowledge the technical assistance of T. Manders, R. Peters, and P. Quinn. We are also grateful for the encouragement and support from Dr. E. Braunwald.

References

1. Smith TW, Haber E: Digitalis. N Engl J Med **289:** 945–952, 1010–1015, 1063–1072, 1125–1129, 1973
2. Mason DT, Spann JF Jr, Zelis R: New developments in the understanding of the actions of the digitalis glycosides. Prog Cardiovasc Dis **11:** 443–478, 1969
3. Quest JA, Gillis RA: Effect of digitalis on carotid sinus baroreceptor activity. Circ Res **35:** 247–235, 1974
4. McLain PL: Effects of ouabain on spontaneous afferent activity in the aortic and corotid sinus nerves of cats. Neuropharmacology **9:** 399–402, 1970
5. Reing CM, Thibodeaux H, Gillis RA, Kot PA: Influence of baroreceptor reflexex on cardiovascular responses of the dog to acetylstrophanthidin. J Pharmacol Exp Ther **184:** 641–648, 1973
6. Daggett WM, Weisfeldt ML: Influence of the sympathetic nervous system on the response of the normal heart to digitalis. Am J Cardiol **16:** 394–405, 1965
7. Vatner SF, Smith NT: Effects of halothane on left ventricular function and distribution of regional blood flow in dogs and primates. Circ Res **34:** 155–167, 1974
8. Vatner SF, Higgins CB, Patrick T, Franklin D, Braunwald, E: Effects of cardiac depression and of anesthesia on the myocardial action of a cardiac glycoside. J Clin Invest **50:** 2585–2595, 1971
9. Edis AJ, Shepherd JT: Selective denervation of aortic arch baroreceptors and chemoreceptors in dogs. J Appl Physiol **30:** 294–296, 1971
10. Patrick TA, Vatner SF, Kemper WS, Franklin D: Telemetry of left ventricular diameter and pressure measurements in unrestrained animals. J Appl Physiol **37:** 276–281, 1974
11. Glick G, Sonnenblick, EH, Braunwald E: Myocardial force-velocity relations studied in intact unanesthetized man. J Clin Invest **44:** 978–988, 1965
12. Mason DT, Braunwald E, Covell, JW, Sonnenblick EH, Ross J Jr, Marcus HS: Assessment of cardiac contractility; the relation between the rate of pressure rise and ventricular pressure during isovolumic systole. Circulation **44:** 47–58, 1971
13. Vatner SF, Higgins CB, Franklin D, Braunwald E: Extent of carotid sinus regulation of the myocardial contractile state in conscious dogs. J Clin Invest **51:** 995–1008, 1972
14. Snedecor GW, Cochran WG: Statistical Methods, ed 6. Ames, Iowa, Iowa State University Press, 1967, pp 91–98
15. Vatner SF, McRitchie RJ, Braunwald E: Effects of dobutamine on left ventricular performance, coronary dynamics, and distribution of cardiac output in conscious dogs. J Clin Invest **53:** 1265–1273, 1974
16. Vatner SF, Higgins CB, Braunwald E: Effects of norepinephrine on coronary circulation and left ventricular dynamics in the conscious dog. Circ Res **34:** 812–823, 1974
17. Vatner SF, Franklin D, Higgins CB, Patrick T, Braunwald E: Left ventricular response to severe exertion in untethered dogs. J Clin Invest **51:** 3052–3060, 1972

18. Vatner SF, Braunwald E: Effects of chronic heart failure on the inotropic response of the right ventricle of the conscious dog to a cardiac glycoside and to tachycardia. Circulation **50:** 728–734, 1974
19. McRitchie RJ, Vatner SF, Braunwald E: Effects of arterial baroreceptor denervation on the response to pharmacologically induced changes in arterial pressure in conscious dogs. Fed Proc **33:** 443, 1974
20. Ross J, Jr., Braunwald E, Waldhausen JA: Studies on digitalis. II. Extracardiac effects of venous return and on the capacity of the peripheral vascular bed. J Clin Invest **39:** 937–942, 1960
21. Heymans C, Bouchaert JJ, Regniers P: Le sinus carotidien et la zone hemologie cardio-aortique. Paris, G. Doin, 1933
22. Heymans CJ, Bouchaert J, Regniers P: Sur le mechanisme reflexe de la bradycardie provoque par les digitaliques. Arch Int. Pharmacodyn Ther **44:** 31–39, 1932

Progress in
Cardiovascular Diseases
VOL. XIX, NO. 2 SEPTEMBER/OCTOBER 1976

Cardiovascular Adjustments to Exercise: Hemodynamics and Mechanisms

Stephen F. Vatner and Massimo Pagani

THE manner in which the intact organism responds to the stress of exercise has intrigued cardiovascular physiologists for the past century. The circulatory adjustments, necessary to meet the extraordinary demands of the working musculature and which begin even before the onset of exercise, remain areas of intense investigation and speculation. These adjustments must take place in almost every organ system of the body and involve all aspects of cardiac and peripheral vascular control, including regulation by the central and autonomic nervous systems. The goal of this review is to discuss many of the compensatory mechanisms that permit the capability for severe exercise, with emphasis on directly measured experimental data radiotelemetered from intact, conscious animals spontaneously running in the field.

NEURAL MECHANISMS

The mediation of the cardiovascular response to exercise, i.e., "exercise stimulus," has been variously attributed to carotid and aortic baroreceptor and chemoreceptor activation, to effects of increased venous return on reflexes originating from the right heart, to metabolic products in muscle producing local and/or spinal reflex changes, and to central neural mechanisms.[1] Neural mechanisms appear to be of great importance in mediating the initial response to exercise, which involves very rapid changes in heart rate and blood pressure. For instance, the time to reach peak tachycardia is prolonged in dogs with cardiac denervation.[2,3] In addition, in men instructed to begin isometric effort at the onset of an auditory stimulus, tachycardia was observed within 0.5 sec.[4,5] This was not considered to be related to changes in respiration or metabolic factors but appeared to be due to a central mechanism resulting in an abrupt inhibition of vagal tone.[4,5]

Reflex adjustments initiated by the stimulation of afferent nerve fibers from the exercising muscles are also likely to play a role in the cardiovascular response to exercise. There is evidence that reflex cardiovascular adjustments originating in the contracting muscles are not mediated by muscle spindle afferents[6] but rather by small myelinated and unmyelinated afferent fibers.[7] In anesthetized animals significant pressor effects (up to 60 mm Hg) occurred in proportion to the tension developed in muscle after stimulating its efferent innervation, which were abolished by administration of curare and augmented by rendering the muscle ischemic.[8] Similar pressor responses with tachycardia were elicited in man during sustained static contraction of the forearm muscles.[9] These studies,[9,10] as well as recent work by Liang and Hood,[11] suggest that afferent neural pathways are stimulated by metabolites in the contracting muscle. Liang and Hood further demonstrated an important role for neural transmission in mediating the increase in cardiac output in the response to tissue hypermetabolism.[11]

Since exercise is accompanied by major cardiovascular alterations, including marked tachycardia, increases in cardiac output and in arterial and

From the Department of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, the Department of Cardiology Children's Hospital Medical Center, Boston, Mass., and the New England Regional Primate Research Center, Southboro, Mass.

Supported in part by USPHS Grants HL 15416, HL 17459, and American Heart Association Grants 73833, 76907, and NASA Grant NSG-2136. S. F. Vatner is an Established Investigator, American Heart Association; M. Pagani is an USPHS International Fellow.

Reprint requests should be addressed to Stephen F. Vatner, M.D., New England Regional Primate Center, 1 Pine Hill Drive, Southboro, Mass. 01772.

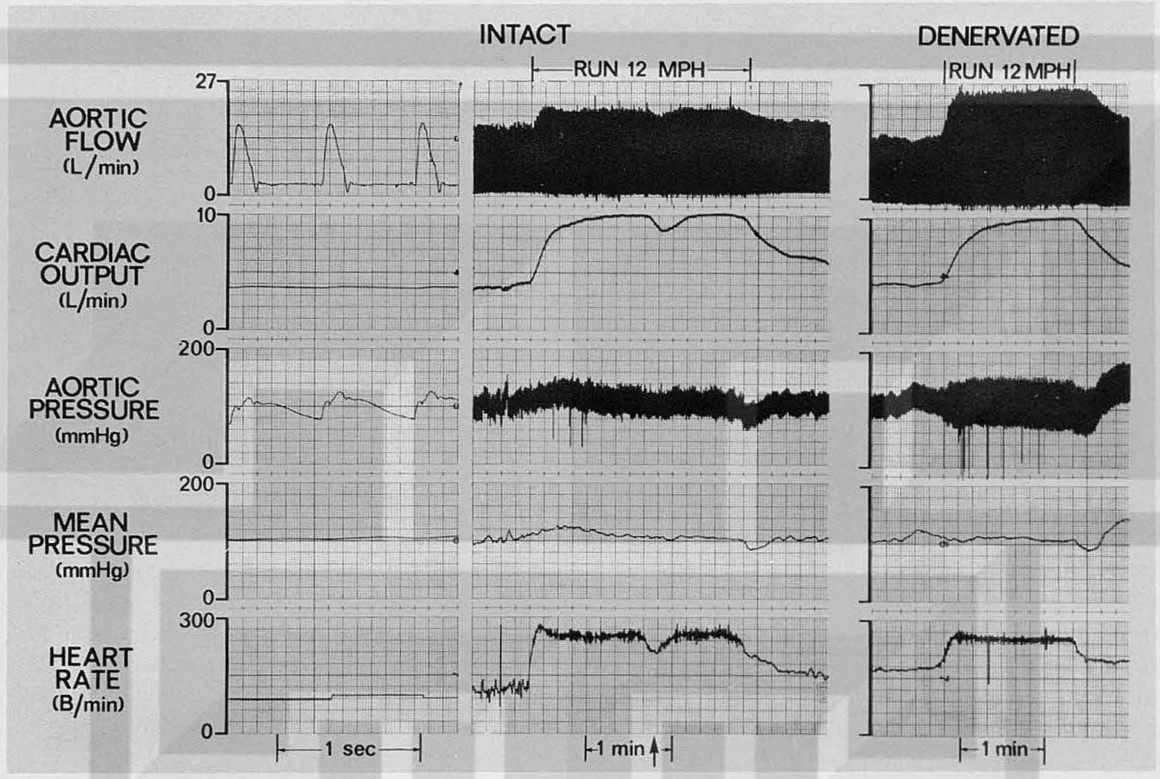

Fig. 1. Responses of aortic flow, cardiac output, phasic and mean aortic pressure, and heart rate to moderate exercise in an intact dog (left panel) and same dog after total arterial baroreceptor denervation (right panel). Note similarity of responses. (Reproduced by permission of *American Journal of Physiology.*[14])

atrial pressures, and a reduction in total peripheral resistance, it could be surmised that a cardiovascular regulating mechanism as important as the arterial baroreceptor reflex would play a significant role in mediating and modifying the exercise response. Investigations into the role of the arterial baroreceptor reflex in the control of the cardiovascular system during exercise have yielded conflicting conclusions as to their importance. At first it was suggested that the baroreceptor reflex is just as active during exercise as at rest. On the other hand, if the baroreceptor reflex was important during exercise, the occurrence of tachycardia associated with an elevated pressure is opposite to the predicted response, since the baroreceptors should act to restrain heart rate in the face of an elevated pressure. There is now a large body of evidence suggesting the lack of importance of the baroreceptors during exercise. Studies conducted in dogs with and without baroreceptor isolation by Van Houtte et al.[12] revealed little difference in the cardiovascular response to exercise in the two groups of dogs, although measurements of cardiac output were made not during but immediately after the cessation of exercise. Krasney et al.[13] also found that the responses of normal and baroreceptor denervated dogs to the stress of moderate exercise were qualitatively similar. More recently, a study was conducted in our laboratory on the effects of more severe exercise in dogs before and after recovery from denervation of both sets of carotid sinus and aortic baroreceptor nerves.[14] In dogs with baroreceptor denervation, although there were minor differences in the preexercise levels of heart rate, arterial pressure, and stroke volume, all these variables rose to levels that were essentially identical to those observed in the dogs with intact baroreceptors during moderately severe exercise (Fig. 1).[14]

Further support for the position that the baroreceptors are of little importance during exercise can be derived from studies by Bristow et al.[15] and Cunningham et al.[16] who observed in man

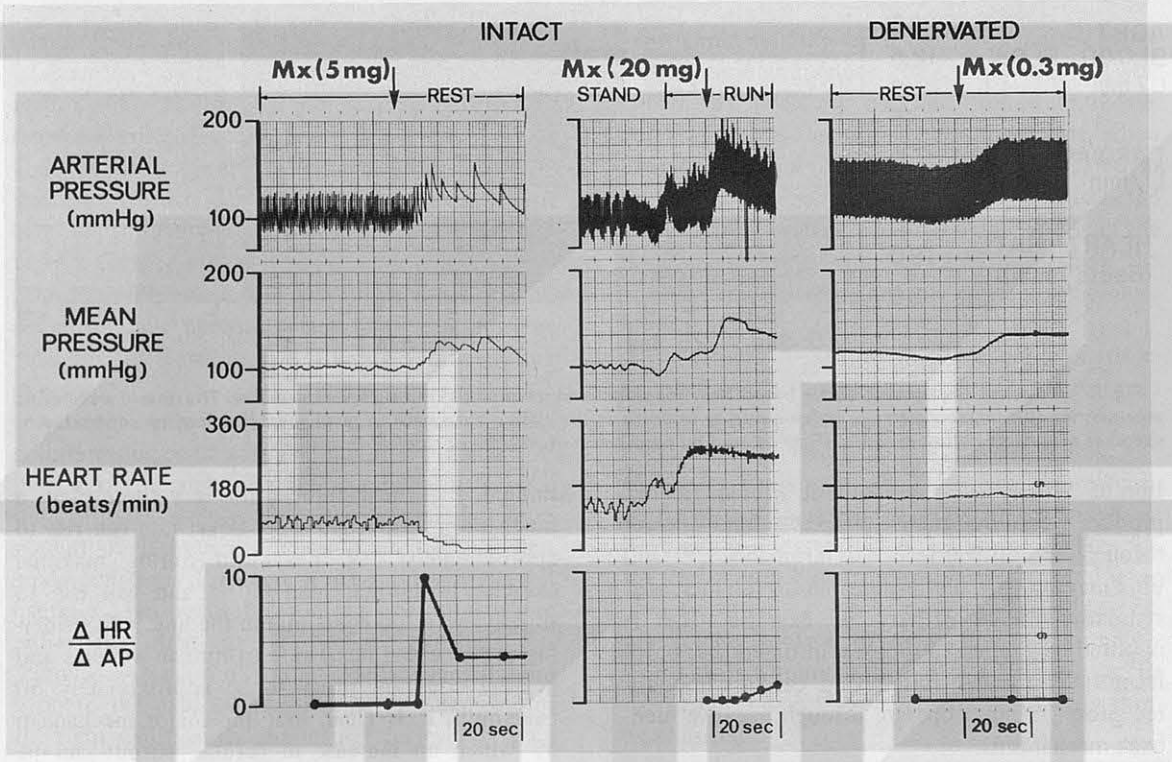

Fig. 2. Responses of arterial pressure, mean pressure, heart rate, and calculated Δ heart rate (HR)/Δ arterial pressure (AP) in an intact dog at rest in response to a bolus of 5 mg i.v. methoxamine (left panel) and to 20 mg i.v. methoxamine in same dog during moderately severe exercise (middle panel) and in a dog with total arterial baroreceptor denervation at rest to 0.3 mg methoxamine (right panel). Note similarity of ΔHR/ΔAP responses in intact dog during exercise and that of denervated dog at rest. (Reproduced by permission of *American Journal of Physiology*.[14])

that baroreflex sensitivity was reduced during exercise. They assessed baroreflex sensitivity by examining the slope of the regression line of systolic arterial pressure on heart rate. Arterial pressure was increased by intravenous injection of a pharmacologic agent, which constricts peripheral vessels and exerts little effect on the heart. Since the slope of the regression line was depressed during exercise, they concluded that the reflex was either reset or turned off during exercise and the magnitude was in proportion to the severity of exercise and resultant tachycardia.[15,16] Similar results were obtained during maximal exercise in dogs, where the vasoconstricting agent was injected remotely by activating a radio-controlled interrogator system connected to an intravenous line in the exercising dogs.[14] Heart rate did not slow appropriately with the sudden elevation of arterial pressure induced by intravenous injection of methoxamine during exercise (Fig. 2), supporting the hypothesis that the arterial baroreceptor reflex is inhibited during this stress. The mechanism by which arterial baroreflex sensitivity is depressed during exercise is not known. However, it has been shown that this reflex can be profoundly affected by stimulation of a variety of afferent pathways as well as areas within the central nervous system.[17–20]

Another physiologic situation akin to exercise, where the arterial baroreceptor sensitivity is depressed allowing heart rate to rise in the face of elevated arterial pressure, is volume loading.[21] The original observation that tachycardia is induced by volume loading dates back to the work of Bainbridge[22] and has been demonstrated in the intact conscious animal only recently.[21,23] The rapid and large increases in venous return that occur with exercise[24] point further to an important role for the Bainbridge reflex. The mechanism of the tachycardia appears to involve vagal[21,23] and spinal sympathetic reflex circuits.[25–27] The latter mechanism is important to mention, since stimula-

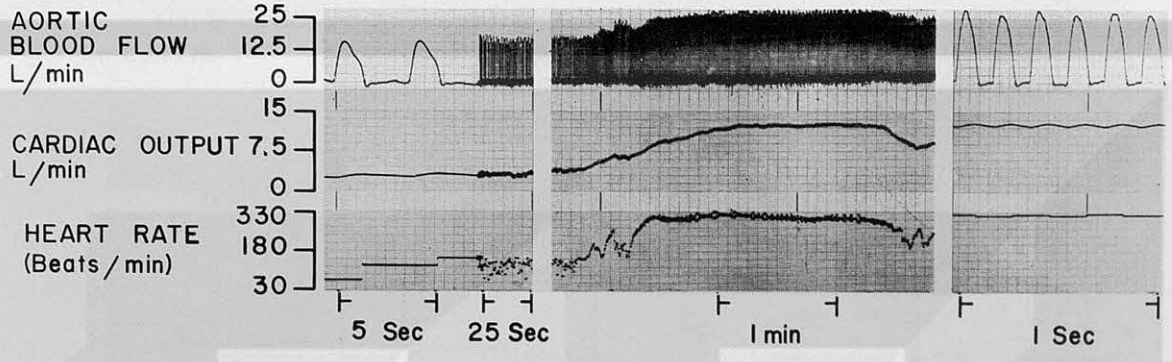

Fig. 3. A typical response of aortic blood flow measured and telemetered during severe exercise. The phasic waveforms representing instantaneous stroke volume during exercise at the right played back at fast paper speed can be contrasted to the ones at the left before exercise. (Reproduced by permission of *Journal of Clinical Investigation.*[33])

tion of cardiovascular sympathetic afferent fibers[28] produce cardiovascular reflexes that operate through a positive feedback mechanism,[25] and thus may be partially responsible for the increased sympatho-adrenal activity of exercise. This is opposed to reflex responses initiated by baroreceptors or vagally innervated cardiopulmonary receptors[29,30] that operate through negative feedback mechanisms.

CARDIAC OUTPUT

The major mechanism by which the elevated metabolic requirements of the exercising musculature are satisfied during exercise is through an increase in venous return and in cardiac output. Cardiac output can rise up to fourfold in man[31,32] and fivefold in the dog (Fig. 3).[33] Since the incremental blood flow is proportioned mainly to the exercising muscles, this additional blood flow provides the major capability for performing exercise.

That cardiac output rises during exercise has been documented extensively.[31,32] However, the manner in which the increase in cardiac output is achieved, i.e., either through an increase in heart rate or stroke volume, remains controversial. Moreover, the changes in stroke volume, whether due to enhanced inotropic stimulation or to the influence of the Frank-Starling mechanism, remains a subject under intense investigation. Recent data on these topics will be considered next.

HEART RATE

Heart rate is the predominant mechanism by which cardiac output rises during severe exercise under physiologic circumstances. Of course, in situations where the cardiac rate response is limited, e.g., heart block, stroke volume plays a much more important role. Heart rate can rise to approximately 200 beats/min during maximal exercise in normal man[32,34,35] and will rise to slightly over 300 beats/min in the dog.[33] Considering the base-line heart rate of human athletes and healthy conscious dogs to be approximately 60 beats/min, it is clear that the major mechanism by which an increase in cardiac output can be achieved is through an elevation of cardiac frequency. Naturally, if base-line heart rate is elevated prior to exercise due to excitement or anxiety, the relative importance of changes in stroke volume becomes apparently greater. This point must be kept in mind in the evaluation of any study in which the relative roles of heart rate and stroke volume are compared.

Heart rate is generally regulated predominantly by the autonomic nervous system. The two major efferent mechanisms by which tachycardia occurs are either through a decrease in parasympathetic restraint or through an increase in sympathetic stimulation. The latter can occur either by neural stimulation or by an elevation in circulating catecholamines. In order to determine the extent to which these mechanisms operate under normal circumstances, exercise has been studied in healthy dogs before and after beta adrenergic blockade with propranolol and parasympathetic blockade with atropine. As mentioned above, heart rate rises to 300 beats/min in the normal dog during maximal exercise. The administration of atropine to these animals increases base-line cardiac rate to approximately 160 beats/min. The difference between that level and the one attained during maximal exercise is on the order of approximately 140 beats/min, which can be attributed to the

sympathetic nervous system. Conversely, when propranolol is administered to these animals, resting heart rate is not altered. However, during maximal exercise in the presence of beta adrenergic blockade, heart rate rises to only 160–190 beats/min, which occurs through release of vagal tone confirming that the 110–140 beats/min difference is due to beta adrenergic stimulation. Thus both the sympathetic and parasympathetic arms of the autonomic nervous system play an important role in the regulation of cardiac rate during exercise.

A recent study by Schwartz and Stone provides an interesting concept regarding differential contribution of the right and left sympathetic cardiac innervations in mediating the adrenergic component of tachycardia during exercise.[36] In that study conscious dogs were studied during treadmill exercise after recovery from an operation where either the right or left stellate ganglion was removed. Ablation of the left stellate ganglion did little to the exercise tachycardia, but removal of the right significantly diminished the level of heart rate achieved during exercise, suggesting a more important role in mediating the response.

STROKE VOLUME

Since the classic work of Starling and coworkers[37,38] stroke volume has been assigned a preeminent role in mediating increases in cardiac output under a variety of circumstances, including exercise. It is now clear that Starling was forced to these conclusions from the experimental model that was employed, i.e., the heart-lung preparation. In that experimental model heart rate is already elevated substantially and rarely increases further. Accordingly, increases in cardiac output must occur through elevations in stroke volume.

Rushmer and colleagues challenged these classic views approximately two decades ago.[39] They developed techniques to study circulatory changes in intact conscious animals and found, in contrast to classical concepts, stroke volume was relatively constant even during exercise.[39] Studies conducted later in our laboratory[33] and also by Horwitz et al.[40] revealed that under more severe stress, during near maximal exercise, stroke volume does play a role in the increase in cardiac output, albeit not as great as the one attributed to tachycardia. In dogs running spontaneously in the field at speeds exceeding 20 mph, stroke volume rose approximately 50% from the preexercise control level in the standing position.[33] However, it is well known that heart rate rises and stroke volume falls upon assuming the upright posture. Thus, when the peak response during exercise is compared to the control response in the supine position, the maximal rise in stroke volume with exercise in the dog is only approximately 25%.[41] In man the contribution of stroke volume appears to be more important.[42–47]

The effects of posture on the response of stroke volume are also important in man.[42] Increases in stroke volume play a greater role during erect exercise as opposed to supine exercise in man.[42–47] However, studies in which a large increase in stroke volume is demonstrated with exercise must be examined carefully to determine if the preexercise control heart rate was elevated due to anxiety or stress, since that would reduce the preexercise control stroke volume. Accordingly, when stroke volume then rose with exercise, its role would be apparently greater and falsely overemphasized.

The role of stroke volume during exercise in man becomes more important with training. It has been shown that cardiac output and arteriovenous oxygen difference during maximal work increase to a slightly greater level after training.[32] While the cardiac output response was greater, the maximal heart rate remains constant and only stroke volume increases by a greater amount.[32] In subjects previously active these changes are less marked than in those that were previously sedentary.[32]

Stroke volume can increase either through a reduction in afterload, an increase in preload, or an increase in the myocardial contractile state. Since the first mechanism (decrease in afterload) does not operate during exercise, stroke volume can increase due to either an increase in preload (Frank–Starling mechanism) or an increase in myocardial contractility. The former would result in an increase in ventricular end-diastolic dimensions, whereas the latter would act to reduce end-systolic dimensions. The importance of each of these mechanisms is discussed next under the ventricular response.

LEFT VENTRICLE

The manner in which the ventricles adapt to the augmented peripheral demands imposed by the

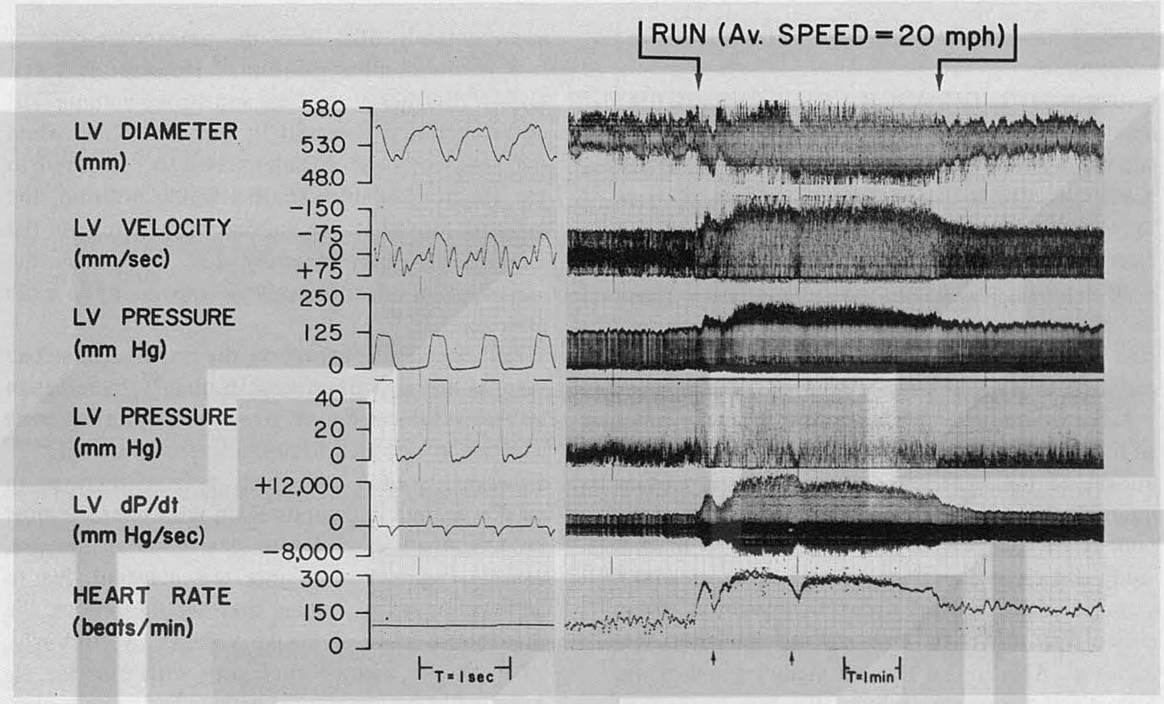

Fig. 4. A typical response to severe exercise for phasic left ventricular diameter (epicardial), velocity, pressure, diastolic pressure, dP/dt, and heart rate. Phasic waveforms at rapid paper speed in the control period (left) can be contrasted with those during severe exercise (right). The arrows denote the time when the dog paused to urinate. Note that end-diastolic diameter fell and then rapidly increased when severe exertion was resumed. (Reproduced by permission of *Journal of Clinical Investigation*.[33])

stress of severe exercise has been controversial and the subject of intense investigation for half a century. In particular, the role played by the Frank-Starling mechanism, i.e., an increase in end-diastolic myocardial fiber length, in mediating the increased contractile response of the heart has been of great interest. This mechanism was at one time considered to be of paramount importance.[37,38,48–50] Then, studies in animals during treadmill exercise[30,51,52] and in man[53–58] demonstrated that end-diastolic dimensions did not increase with moderately severe exercise. However, the level of exercise in earlier studies was not maximal, and it remained to be demonstrated whether increases in end-diastolic size could be elicited with more severe exertion. The development of the capability for telemetry of measurements of left ventricular pressure and dimensions[59] permitted an assessment of the left ventricular response to spontaneous severe exercise without the restraining or excitatory influences of the laboratory environment, leashes, tethers, or treadmills.

A recent study in our laboratory using these techniques indicated that the left ventricular response to severe exercise in healthy dogs running at speeds over 20 mph involved very profound increases in heart rate often exceeding 300 beats/min and increases in contractility, peak dP/dt increasing to fivefold.[33] With this level of exercise a reduction in end-systolic diameter and increases in end-diastolic diameter and pressure were noted (Fig. 4); relative changes were even more prominent when endocardial rather than epicardial dimensions were measured.[33,40] Thus, the Frank-Starling mechanism remains a mechanism by which the heart can augment its performance during severe exertion, although the extent of its application is limited since left ventricular end-diastolic dimensions attained during severe exercise do not exceed those at rest in the reclining position.

The major restraining influence on the increase in diastolic cardiac size during exercise is the concomitant tachycardia, which acts to shorten diastolic filling time. To dissect out the contribution of tachycardia to the exercise response, experiments were repeated after atrial rate had

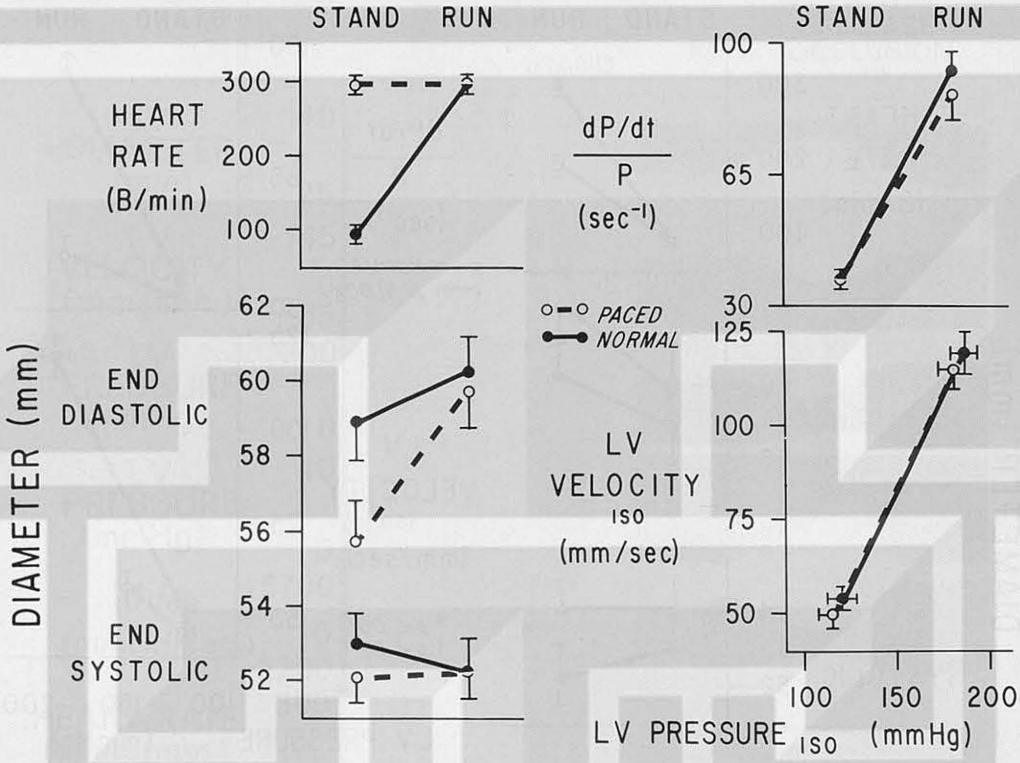

Fig. 5. The average ±SE values standing at rest and during severe exercise for seven dogs studied both in spontaneous rhythm and after heart rate had been elevated at rest to exercise levels with electrical stimulation of the atria. None of the values attained during steady-state severe exercise were significantly different in these two states. (Reproduced by permission of *Journal of Clinical Investigation*.[33])

been elevated in resting dogs and held constant at levels previously achieved during exercise.[33] Under these circumstances, similar increases in pressure and contractility occurred during exercise, as were observed in unpaced dogs, but the increases in end-diastolic dimensions were far greater (Fig. 5).[33] Thus, the major difference in the response to normal exercise, in comparison to exercise when heart rate is held constant at high levels, is the effect on left ventricular dimensions (Fig. 5); far greater increases in end-diastolic size are observed during exercise when heart rate is constant, indicating that the tachycardia which occurs during exercise counteracts the increase in dimensions which would otherwise occur and might be considered to mask the contribution of the Frank-Starling mechanism.

The role of the beta adrenergic system in mediating the ventricular response to exertion has been evaluated by examining the effects of exercise in dogs before and after beta adrenergic blockade with propranolol (Fig. 6).[33,60] As mentioned above, this maneuver resulted in a significant reduction in the tachycardia that could be achieved. A more striking effect was observed in the inotropic response, where the increases in contractility, as reflected by the force-velocity relationship and by dP/dt, were largely prevented (Fig. 6).[33] Responses of stroke shortening and of stroke volume were also attenuated.[33,60] Thus, these factors that were influenced by beta adrenergic receptor blockade with propranolol imposed significant limitation on performance during exercise, which was most evident during maximal stress.

ABNORMAL VENTRICULAR RESPONSES TO EXERCISE

Heart Failure

The earliest manifestations of heart failure generally occur upon exertion. In the presence of

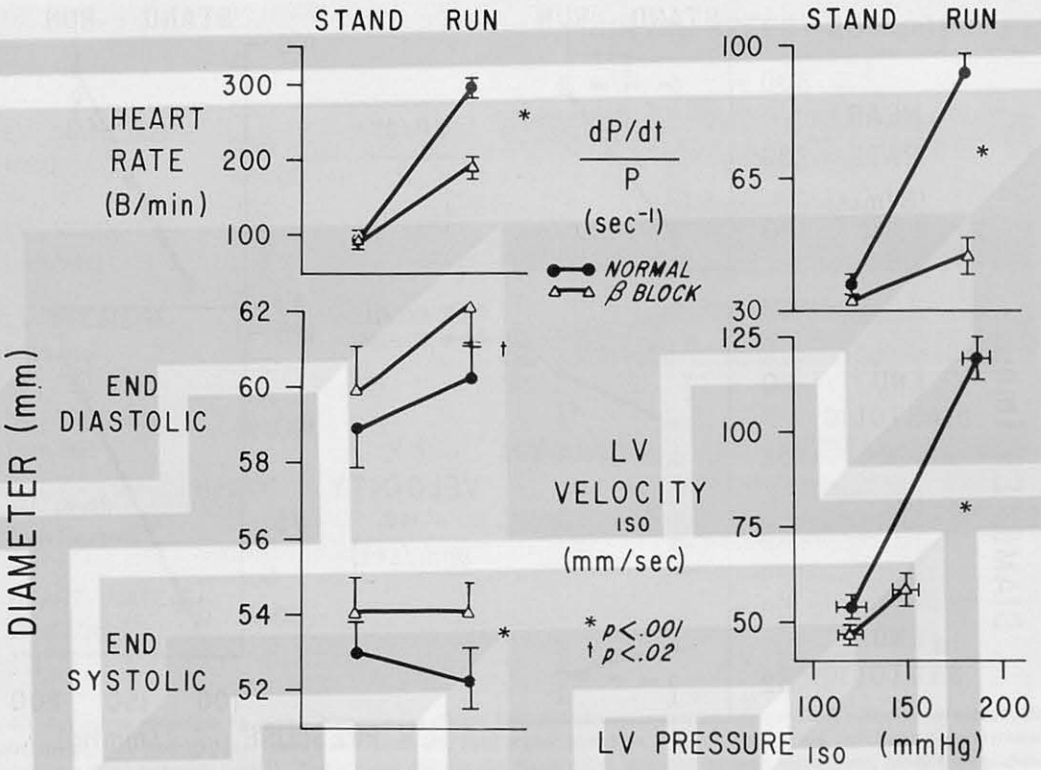

Fig. 6. Average ±SE values standing at rest and during steady-state severe exercise for seven dogs studied in both spontaneous rhythm and after 1.0 mg/kg propranolol. The values attained during severe exercise that were significantly different are noted. (Reproduced by permission of *Journal of Clinical Investigation.*[33])

heart failure the enhanced metabolic needs of the peripheral tissues during exercise can not be met by appropriate elevation of cardiac output. It is also clear that the primary limitation on the cardiac output response to exercise is the inability of stroke volume to rise, since cardiac rate can still increase.

The manner in which the failing heart responds to exercise has been studied in much less detail than the normal response. A preliminary study in our laboratory has been conducted where measurements of right ventricular pressure and dimensions have been telemetered from dogs during exercise before and after right heart failure had been induced by progressive pulmonary constriction and tricuspid regurgitation.[61] Heart failure imposed a significant limitation on the ability of the dogs to perform exercise, to the extent, in some instances, where exercise resulted in an episode of acute cardiac failure and circulatory insufficiency. The major difference in the ventricular response to exercise was the inability to increase stroke shortening, a situation similar to that described above when the beta adrenergic system was blocked with propranolol. It was surprising, however, that under these conditions end-diastolic dimensions did not increase to a greater extent. Thus, the Frank-Starling mechanism, which plays only a slight role in the normal ventricular response to exertion,[33] appears to be of no greater importance in the presence of chronic heart failure.[61] Previous studies in man with heart failure suggest a more important role for the Frank-Starling mechanism under these conditions.[62]

Coronary Insufficiency

When the ability to augment coronary flow is limited, as occurs in ischemic heart disease, the stress of exercise results in an imbalance between myocardial oxygen supply and demand, recognized clinically as angina pectoris. Coronary artery disease is usually patchy and regional in nature. However, in a situation in which coronary flow is

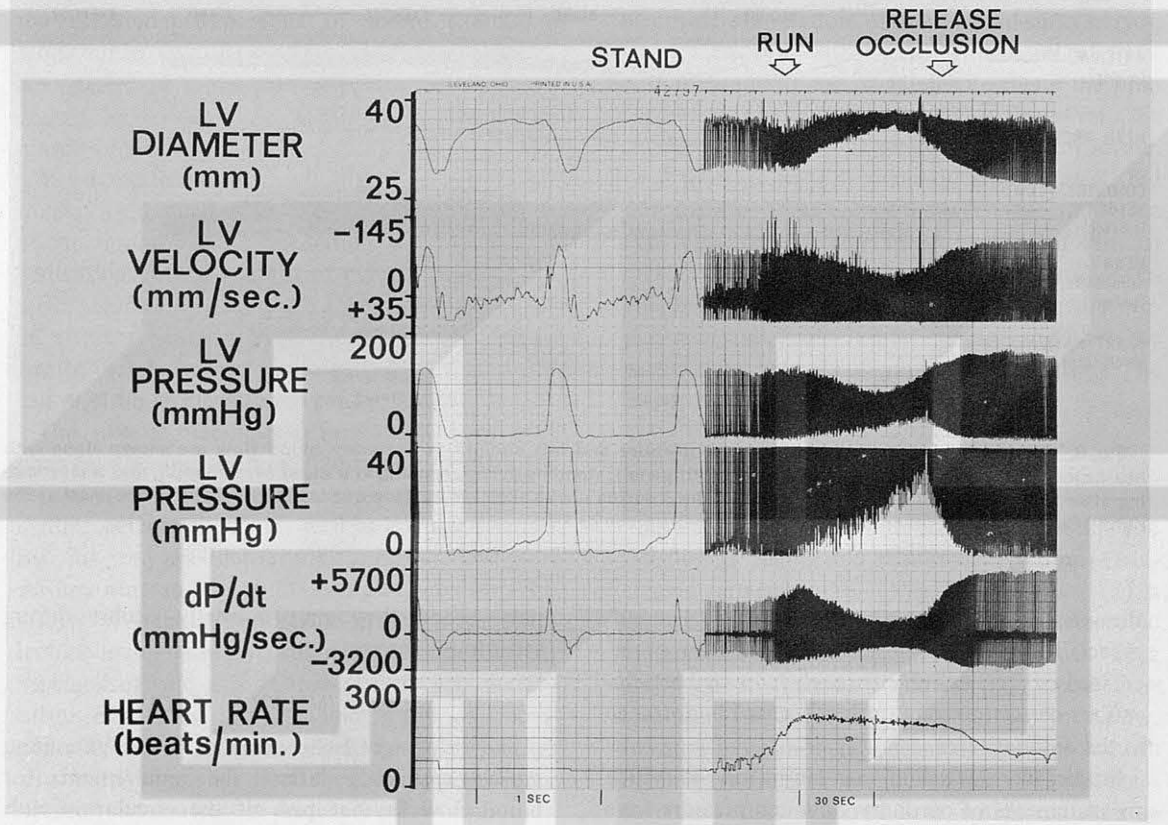

Fig. 7. A typical response to mild exercise in the presence of moderate global myocardial ischemia at rest. With exercise, after an initial transient improvement, acute cardiac decompensation occurred as reflected by increases in LV end-diastolic diameter and pressure, LV end-systolic diameter, and decreases in stroke excursion, velocity, and dP/dt. (Reproduced by permission of *Journal of Clinical Investigation.*[63])

limited to the entire ventricle and global myocardial ischemia occurs, or if a sufficient mass of myocardium is affected by local ischemia, the stress of exercise can then result in precipitation of acute cardiac failure. This was recently demonstrated in a conscious animal model of global myocardial ischemia, i.e., where a hydraulic occluder had previously been implanted around the dog's left main coronary artery, a vessel that supplies blood flow to practically the entire left ventricle in that species. This occluder was partially inflated when the animals were at rest, but not sufficiently to cause substantial impairment of cardiac function.[63] Thus, the animals had marginal global myocardial ischemia, which was tolerated well at rest. However, when the animals began to exercise, the increased myocardial metabolic demands imposed by the exercise could not be met by an appropriate elevation of coronary flow. The resultant global ventricular imbalance between myocardial oxygen supply and demand resulted in precipitation of acute cardiac failure (Fig. 7).

CORONARY VASCULAR BED

Since the primary determinant of coronary blood flow is myocardial oxygen consumption ($M\dot{V}_{O_2}$),[64,65] it follows that the major effects of exercise on the coronary circulation reflect the changes in myocardial oxygen requirements that occur. Major determinants of $M\dot{V}_{O_2}$ include heart rate, left ventricular tension, and myocardial contractility. As indicated above, severe exercise results in near maximal increases in heart rate and myocardial contractility. These changes are accompanied by substantial increases in arterial and left ventricular pressures, suggesting that wall tension must also rise substantially. Accordingly, coronary flow must also rise strikingly to meet

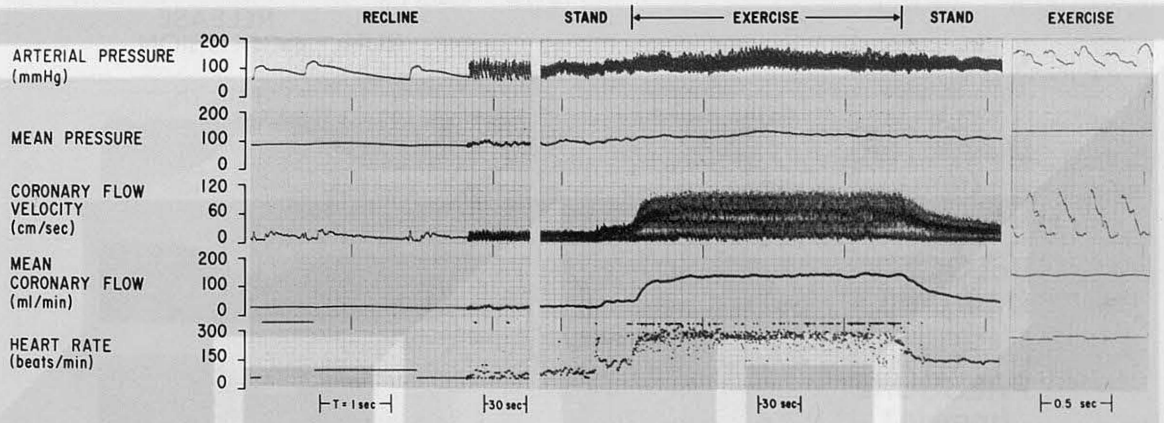

Fig. 8. Phasic and mean tracings of arterial pressure and left circumflex coronary blood flow are shown along with heart rate, while the animal is reclining at rest (left panel), standing at rest, running at a speed over 25 mph, and then standing after exercise (middle panel). Phasic waveforms during severe exercise are shown at fast paper speed in the panel at the right. (Reproduced by permission of *Bibliotheca Cardiologica.*[106])

the extraordinary increments in metabolic demand, especially since an alternative mechanism of increased oxygen delivery through increased arteriovenous oxygen extraction is of limited importance in the coronary bed.

Studies conducted in our laboratory in which measurements of coronary flow and pressure were telemetered from normal healthy dogs running spontaneously behind a mobile recording unit in the field indicated that threefold to fivefold increases in left circumflex coronary blood flow occurred (Fig. 8).[66] These findings are consistent with those reported by Van Citters and Franklin in Alaskan sled dogs[67] and by Khouri et al.[68] using electromagnetic-flowmeters for the measurement of coronary flow during treadmill exercise in dogs.

Since increasing heart rate in conscious dogs is known to increase coronary blood flow and to decrease coronary vascular resistance, it was considered important to determine the role of tachycardia in the coronary vasodilation of severe exercise. The contribution of heart rate was determined by increasing heart rate in the resting dogs to the exercise level and comparing the findings with those obtained at an identical rate during severe exercise.[66] It was found that simply raising heart rate at rest to exercise levels increased coronary flow by approximately 50% and that the increase in heart rate was responsible for approximately one-third of the increase in coronary blood flow that normally occurs during strenuous exercise.

LIMB (MUSCLE) FLOW

The rising metabolic demands in the exercising muscles primarily reflect the requirements for blood flow in that part of the circulation with exercise. While exercising muscles can partially satisfy increased metabolic demand through increases in arteriovenous oxygen extraction on the one hand and a shift to anaerobic metabolism on the other, the major compensatory mechanism involves an increase in blood flow. The marked increase in muscle blood flow provides the required oxygen and metabolic substrates, removes waste products of metabolism, and also dissipates the excess heat produced.[69] This increase in flow is partially due to the concomitant elevation in aortic pressure but is primarily due to a substantial reduction in muscle vascular resistance. Although central mechanisms may be responsible for vasodilation initiated even with anticipation of exercise, the vasodilation during exercise is thought to be mainly a local process, mediated by the influence of several metabolic factors.[70] In the exercising muscles there is an increase in heat production, a widened arteriovenous O_2 difference, with decreased pH and p_{O_2} in the venous effluent blood,[71,72] and an increase in tissue osmolality,[73] with increased interstitial K^+ concentration,[74] all of which may act additively in the production of

the functional hyperemia of severe exercise.[75] Moreover, recent evidence suggests that adenosine, considered as a possible regulator of coronary vessels, may also play a role in regulation of muscle blood flow.[76]

Metabolic factors not only play a role in regulation of local muscle blood flow, but also appear to be of importance in mediating the increase in cardiac output. In support of this concept are the recent studies by Liang and Hood, suggesting that an afferent neural pathway exists, which is sensitive to metabolic changes in peripheral tissues and can result in an elevation in cardiac output.[11]

The role of metabolic factors can change with physical training. In rats conditioned to swim for several weeks, training improved potential aerobic cardiac performance[77] as well as increased capacity for oxygen delivery and higher levels of actomyosin and myosin ATPase activity. The effects of training on skeletal muscle metabolism include increases in glycerolipids, enzymes for lipid metabolism, and a shift toward fatty acid metabolism, elevations of myoglobin, citric acid components, and cytochrome compounds.[78,79] It has also been suggested that chemical changes may occur at the contractile protein level.

The increased energy production and expenditure of the contracting muscles require in turn a greater oxygen supply, which is met secondarily through increased oxygen extraction but primarily through increased blood flow. Increases in limb blood flow, roughly fivefold to tenfold, are routinely recorded in conscious dogs during near maximal exertion.[67,80] Most of these studies have measured total limb flow including blood flow to bone and skin; accordingly, the fraction to muscle alone may well exceed the figures for total limb flow, since skin and bone requirements for blood flow do not rise with exercise.

While sympathetic vasoconstriction occurs in the muscle bed at rest, as well as visceral beds during exercise, and has also been demonstrated in the resting upper extremity during leg exercise,[81] the extent to which sympathetic vasoconstrictor tone regulates the muscle bed during exercise is not established. On the one hand, studies in dogs during treadmill exercise suggest that sympathetic vasoconstrictor tone is not completely abolished even in the presence of exercise-induced dilatation. This suggestion is based on the finding that electrical stimulation of the carotid-sinus nerves, which results in substantial withdrawal of sympathetic tone at rest, was able to dilate the limb further during exercise as well.[82] However, the exercise stimulus in these studies was not severe. On the other hand, studies by Donald et al. did not discern a difference between the dilatation occurring in limbs with intact nerves and without neural innervation in dogs during treadmill exercise,[83] suggesting that sympatholysis occurs normally in the limb during exercise and that the overriding control of muscle flow during the response is metabolic.

MESENTERIC AND RENAL BEDS

As mentioned earlier, the exercising musculature satisfies its augmented requirements from (1) increased arteriovenous oxygen extraction, (2) a shift in metabolism resulting in increased anaerobic metabolism and lactate production, and (3) a reduction in vascular resistance to blood flow resulting in an augmentation of muscle blood flow. In addition, another compensatory mechanism involving sufficient increases in vascular resistances to reduce visceral blood flow, which can then be shunted to the exercising muscle, is thought to operate. The early experimental basis for this concept was derived from studies in humans, with observations of altered renal function (i.e., proteinuria and oliguria with exercise), suggesting that renal arterial vasoconstriction occurred.[84,85] Exteriorized colons of dogs were observed to blanch during exercise,[86] and spleens of dogs were observed to decrease in size, suggesting splanchnic vasoconstriction.[87] Further support for the theory that visceral flow decreased during exercise came from studies in anesthetized animals where exercise was simulated or where stimulation of sympathetic nerves to the mesenteric and renal vessels or the infusion of catecholamines decreased mesenteric and renal blood flows.[88–90] Most important, however, are the numerous investigation utilizing indirect techniques for measuring regional blood flow in normal man, which indicate that renal and splanchnic blood flows decrease with exercise and that the reduction in flow is roughly proportional to the severity of the exercise.[31,91–95] Considering the weight of this evidence in combination with the teleologic attractiveness of an efficient mecha-

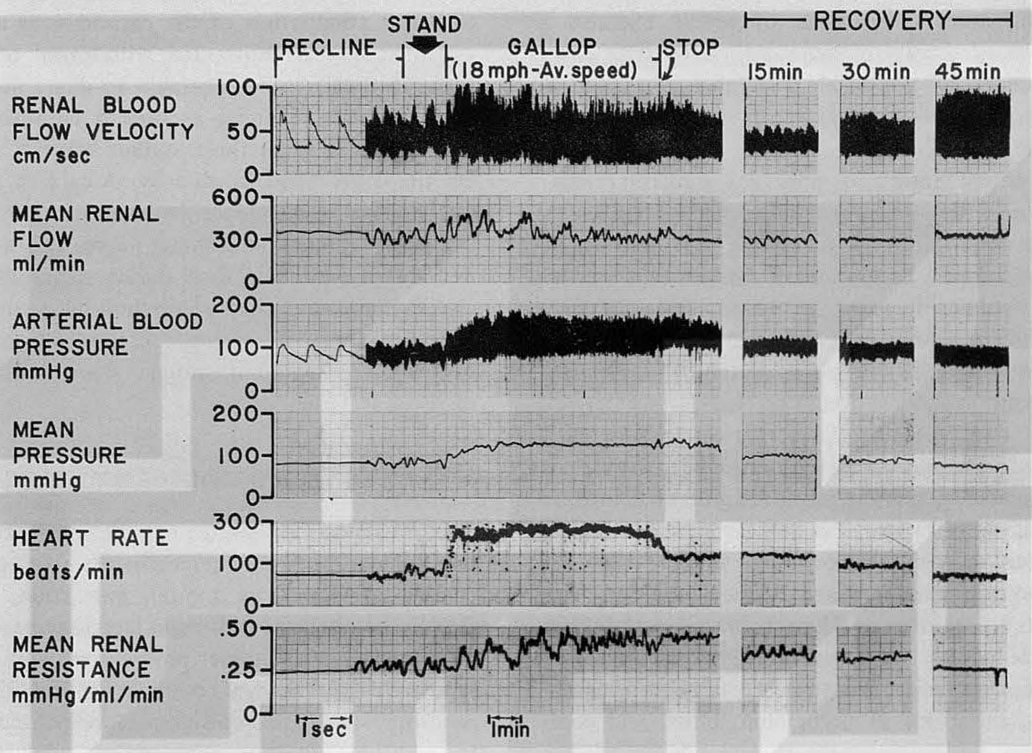

Fig. 9. Record from a normal dog reclining, then standing, then running at an average speed of 18 mph, and the subsequent recovery from exercise immediately and at 15, 30, and 45 min later. The phasic waveforms and mean values for renal blood flow and arterial pressure, heart rate, and computed mean renal resistance are shown. In this case renal blood flow actually increased slightly during severe exercise. (Reproduced by permission of *Journal of Clinical Investigation.*[80])

nism for the diversion of "nonessential" visceral flow to the exercising musculature, it is not surprising that the hypothesis of shunting of blood from the viscera to skeletal muscle during exercise has become widely accepted.

In contrast to all these studies, direct measurements of renal and mesenteric blood flows in intact conscious dogs during exercise indicate that renal and mesenteric blood flows do not decrease during exercise.[67,80,96,97] These investigations show that although flow to the hindlimb increases by as much as 12-fold, after an initial transient decline mesenteric and renal blood flows remained relatively constant during steady-state severe exercise (Fig. 9). The earlier studies utilizing treadmill exercise[96,97] were criticized on the basis that the level of exercise attained was not severe enough and that diversion of blood flow might only occur during stress. To resolve this controversy, Van Citters and Franklin studied the responses of Alaskan sled dogs running long distances in subzero temperatures while pulling a sled.[67] Even under such extreme circumstances, to the point of prostration, mesenteric and renal blood flows did not decrease. Criticism of this study was directed to the use of sled dogs, which are unusual animals specially adapted through training and breeding for exercise and thus might not show the compensatory shunting of visceral blood flow.

To obviate this criticism, measurements of mesenteric, renal, and iliac blood flows and aortic blood pressure were telemetered from normal healthy untrained mongrel dogs while they ran spontaneously behind a mobile recording unit for distances averaging 1.5 miles and ranging up to 6 miles at speeds over 20 mph, what may reasonably be considered to be near maximum workloads.[80] The dogs required 45 min of rest for cardiovascular and respiratory function to recover from this degree of exercise. In these dogs heart rate increased from 85 to 290 beats/min and iliac blood flow rose to approximately 1.2 liters/min; yet renal and mesenteric blood flows after an initial transient reduction remained essentially at preexercise control levels during steady-state severe exercise (Fig. 1).[80]

Thus in normal healthy mongrel dogs the peripheral vascular response to severe exercise does not involve a compensatory reduction of visceral blood flow, as specifically indicated by mesenteric and renal arterial blood flows. In this regard these findings are in agreement with the earlier studies utilizing treadmill exercise and the findings of Van Citters and Franklin in Alaskan sled dogs. These findings do not support the conclusions of previous investigations of visceral flow during simulated exercise in anesthetized preparations or the prior studies in conscious humans that suggested that marked reductions in visceral blood flows occurred. The differences between findings in conscious animals and those in anesthetized preparations may be explained on the basis of the inherent difficulties of studying exercise, a function intrinsically peculiar to intact conscious organisms and difficult to simulate in anesthetized animals lying on the surgical table. The differences between findings in conscious animals and those in conscious humans are more difficult to explain and may be due either to differences in species or instrumentation. Measurements of blood flow in conscious humans are necessarily indirect, whereas in animal studies blood-flow transducers are applied directly to the renal and mesenteric arteries.

Although the peripheral vascular response to severe exercise in normal dogs does not involve a reduction in visceral flow, significant increases in renal and mesenteric resistances do occur. In normal dogs during maximal exercise arterial pressure increases by approximately 50%. Since blood flow to the gut and kidney remained essentially constant, the increases in mesenteric and renal resistance parallel the increases observed in arterial blood pressure and are roughly related to the severity of exercise.

One important difference in the canine and human responses to exercise is the role of the spleen. The spleen serves as an important blood reservoir in both the cat and the dog. Splenic constriction occurs with neural adrenergic stimulation, hemorrhage, shock, anoxia, and exercise, resulting in an augmentation of hematocrit and thereby in the oxygen-carrying capacity of the blood. In man the spleen plays a lesser role, since it is much smaller in relation to total body size and is not considered to have a reservoir function. The splenic-reserve mechanism in the dog could thus be responsible for some differences between the responses of the dog and humans to exercise. Accordingly, to test this hypothesis, the responses of hematocrit and mesenteric and renal blood flows and resistances were studied in healthy normal unrestrained dogs as they ran spontaneously in the field at speeds exceeding 20 mph before and after splenectomy.[98]

Capability for severe exercise appeared to be identical before and after splenectomy, but the responses of hematocrit and visceral flows and resistances were markedly different. During severe exercise in normal healthy dogs, hematocrit increased by almost one-fifth of the resting pre-exercise value (from 40% to 49%); in contrast, no increase in hematocrit occurred with exercise following splenectomy. During near maximal steady-state exercise prior to splenectomy, renal and mesenteric blood flows remained essentially constant, although calculated resistance rose modestly, as stated earlier. In the same dogs following splenectomy the increases in mesenteric and renal resistances were significantly greater and were sufficient to reduce blood flow substantially. Although these reductions in flow and increases in renal and mesenteric resistances observed in splenectomized dogs were greater than the values prior to splenectomy, they were not as great or as sustained as those that occurred during severe exercise in dogs with experimentally induced heart failure. Furthermore, when exercise was moderate following splenectomy ($<$15 mph on the level or $<$10 mph on the incline), renal and mesenteric flows were generally maintained, and they decreased only during near maximal exertion.[98] Thus, this mechanism may explain in part the discrepancies observed between exercise responses in normal dogs and man.

EFFECTS OF CIRCULATORY IMPAIRMENT ON RENAL AND MESENTERIC RESPONSES

The responses of the mesenteric and renal beds to severe exercise were significantly different when O_2 delivery to the exercising muscles was impaired. Three types of circulatory impairment were examined: (1) surgically induced complete heart block,[80] in which normal increases in heart rate during exercise are prevented; (2) congestive right heart failure, in which normal increases in stroke volume are prevented (Fig. 10)[99,100]; and (3) severe chronic anemia in which the oxygen-

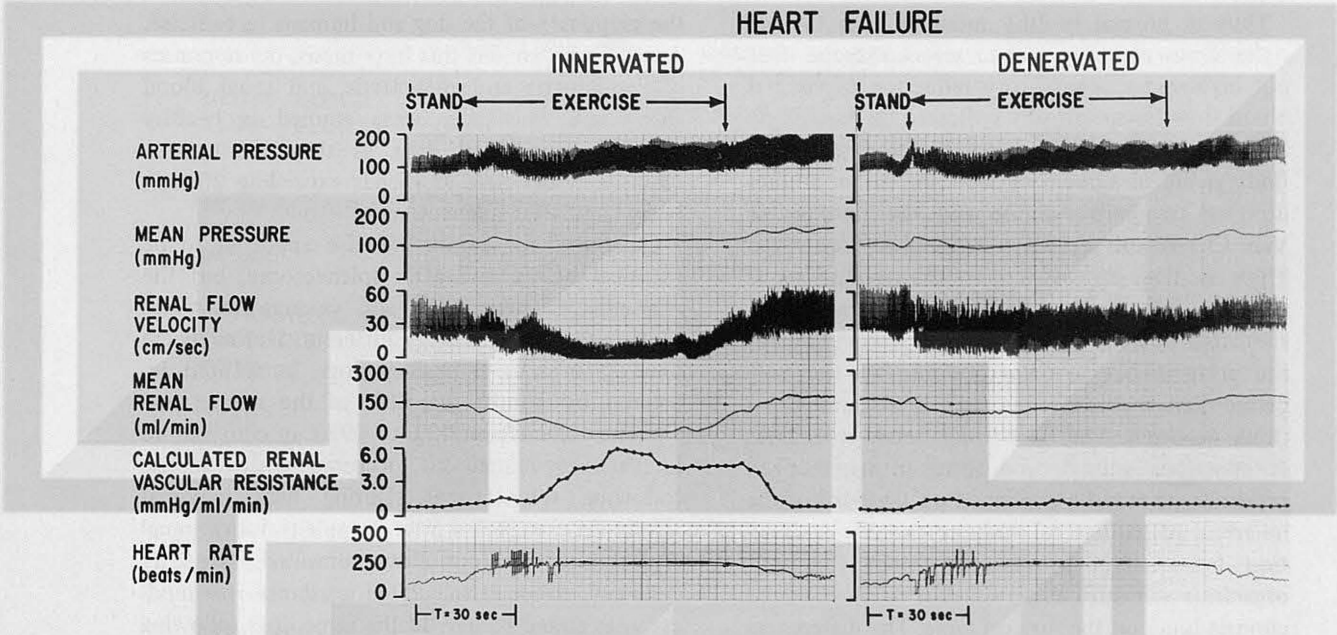

Fig. 10. Typical renal responses to severe exercise in a dog with experimental congestive heart failure. Note the severe reduction in renal blood flow and the increase in renal resistance in the innervated kidney (left) that is largely, but not completely, relieved by surgical denervation (right). (Reproduced by permission of *Circulation Research.*[100])

carrying capacity of the circulation is markedly reduced.[101] In these dogs diversion of blood flow from the inactive viscera to the exercising muscle occurred, i.e., sustained reduction in renal and mesenteric blood flows occurred during severe exercise in dogs with circulatory impairment. In some instances renal and mesenteric blood flows decreased by as much as 90% from preexercise control levels (Fig. 10).

While arterial pressure rose less during exercise in dogs with circulatory impairment, renal and mesenteric resistances rose by far greater amounts than in normal dogs; intense visceral vasoconstriction occurred, almost resulting in cessation of flow to the kidney and gut in some animals. Thus, the response to severe exercise in normal dogs does not involve sustained reductions in visceral blood flows; but when normal compensatory adjustments to exercise are limited, reductions of renal and mesenteric blood flows occur.

THE ROLE OF SYMPATHETIC CONTROL OF THE RENAL BED DURING EXERCISE

The extent of sympathetic neural control of the renal vascular bed during exercise was determined in healthy dogs by comparing responses to exercise in animals with ultrasonic-flow probes implanted on paired innervated and denervated kidneys. Although the initial transient fall in renal flow was prevented by renal denervation, the steady-state levels of renal vascular resistance during severe exercise were similar in normal kidneys, denervated kidneys, and denervated kidneys following alpha-receptor blockade, indicating that renal nerves or circulating catecholamines participated little in the normal renal vascular response to severe exercise. Thus, in the normal healthy dog the primary mechanism of regulation of renal blood flow during severe exercise does not appear to involve the sympatho-adrenal system; the evidence suggests that an autoregulatory process or another nonadrenergic mechanism prevails. Renal autoregulation has been demonstrated to be effective over the arterial pressure range encountered in these experiments and could account for the elevated renal vascular resistance observed during severe exercise.[102] Recent evidence suggests that local prostaglandin release by the kidney is responsible for autoregulation of renal blood flow in the face of reduced renal arterial pressure and hemorrhage.[103–105] The possibility exists that prostaglandins are released during exercise, counteracting the effects of alpha adrenergic vasoconstriction.

In contrast to the renal vascular response observed during exercise in healthy dogs, dogs with experimental congestive heart failure during exercise demonstrate a striking elevation in renal vascular resistance in the innervated kidney, an elevation sufficient to reduce renal blood flow drastically. Thus, although autoregulatory or other nonadrenergic mechanisms prevail during severe exercise in normal dogs, an increase in cardiovascular stress, as in the presence of heart failure, allows the adrenergic mechanism to act in reserve and to reduce and divert renal blood flow. Other studies from our laboratory have demonstrated similar powerful visceral vasoconstriction and blood flow reduction in dogs with limited heart rate or with limited oxygen-carrying capacity during exercise.[80,99–101] When renal nerves were removed, the intense vasoconstriction was markedly attenuated in dogs with heart failure (Fig. 10), indicating that the major portion of the renal vasoconstriction during exercise in dogs with heart failure is due to activation of renal sympathetic nerves.

Even in the denervated kidneys of dogs with heart failure, renal resistance increased and renal blood flow decreased during severe exercise, albeit less than in dogs without heart failure, indicating that neurally mediated renal vasoconstriction could not solely account for the vasoconstrictor response. It is possible that circulating catecholamines could produce the remaining renal vasoconstriction. This hypothesis was substantiated by studies after alpha-receptor blockade in dogs with neural denervation; the exercise-induced renal vasoconstriction tended to be further attenuated.[100]

Therefore the response of the renal vascular bed to severe exercise in normal healthy dogs is governed primarily by autoregulation or other nonadrenergic mechanisms, and little contribution is made by either renal sympathetic nerves or adrenal medullary hormones. In dogs with circulatory impairment, adrenergic renal vasoconstriction predominates, reducing renal blood flow appreciably during severe exercise. Renal blood flow reduction is primarily mediated by renal nerves in dogs under abnormal cardiovascular stress, since the renal vasoconstriction can be extensively alleviated by elimination of renal sympathetic nerves. To a lesser extent renal vasoconstriction is mediated by circulating catecholamines, which can be prevented by the addition of an alpha adrenergic antagonist.

SUMMARY

The integrated response to severe exercise involves fourfold to fivefold increases in cardiac output, which are due primarily to increases in cardiac rate and to a lesser extent to augmentation of stroke volume. The increase in stroke volume is partly due to an increase in end-diastolic cardiac size (Frank–Starling mechanism) and secondarily due to a reduction in end-systolic cardiac size. The full role of the Frank–Starling mechanism is masked by the concomitant tachycardia. The reduction in end-systolic dimensions can be related to increased contractility, mediated by beta adrenergic stimulation. Beta adrenergic blockade prevents the inotropic response, the decrease in end-systolic dimensions, and approximately 50% of the tachycardia of exercise.

The enhanced cardiac output is distributed preferentially to the exercising muscles including the heart. Blood flow to the heart increases fourfold to fivefold as well, mainly reflecting the augmented metabolic requirements of the myocardium due to near maximal increases in cardiac rate and contractility. Blood flow to the inactive viscera (e.g., kidney and gastrointestinal tract) is maintained during severe exercise in the normal dog. It is suggested that local autoregulatory mechanisms are responsible for maintained visceral flow in the face of neural and hormonal autonomic drive, which acts to constrict renal and mesenteric vessels and to reduce blood flow. However, in the presence of circulatory impairment, where oxygen delivery to the exercising muscles is impaired as occurs to complete heart block where normal heart rate increases during exercise are prevented, or in congestive right heart failure, where normal stroke volume increases during exercise are impaired, or in the presence of severe anemia, where oxygen-carrying capacity of the blood is limited, visceral blood flows are reduced drastically and blood is diverted to the exercising musculature. Thus, visceral flow is normally maintained during severe exercise as long as all other compensatory mechanisms remain intact. However, when any other compensatory mechanism is disrupted (even the elimination of splenic reserve in the dog), reduction and diversion of visceral flow occur.

REFERENCES

1. Smith OA: Reflex and central mechanisms involved in the control of the heart and circulation. Ann Rev Physiol 36:93, 1974
2. Donald DE, Shepherd JT: Response to exercise in dogs with chronic cardiac denervation. Am J Physiol 205:393, 1963
3. Donald DE, Shepherd JT: Initial cardiovascular adjustment to exercise in dogs with chronic cardiac denervation. Am J Physiol 207:1325, 1964
4. Petro JK, Hollander AP, Bouman LM: Instantaneous cardiac acceleration in man induced by a voluntary muscle contraction. J Appl Physiol 29:794, 1970
5. Borst C, Hollander AP, Bouman LN: Cardiac acceleration elicited by voluntary muscle contractions of minimal duration. J Appl Physiol 32:70, 1972
6. McCloskey DI, Matthews PBC, Mitchell JH: Absence of appreciable cardiovascular and respiratory responses to muscle vibration. J Appl Physiol 33:623, 1972
7. McCloskey DI, Mitchell JH: Reflex cardiovascular and respiratory responses originating in exercising muscles. J Physiol 224:173, 1972
8. Coote JH, Hilton SM, Perez-Gonzalez JF: The reflex nature of the pressor response to muscular exercise. J Physiol 215:789, 1971
9. Donald KW, Lind AR, McNicol GW, et al: Cardiovascular responses to sustained (static) contractions. Circ Res 20(Suppl 1):15, 1967
10. Perez-Gonzalez JF, Coote JH: Activity of muscle afferents and reflex circulatory responses to exercise. Am J Physiol 223:138, 1972
11. Liang C, Hood WB Jr: Afferent neural pathway in the regulation of cardiopulmonary responses to tissue hypermetabolism. Circ Res 38:209, 1976
12. VanHoutte P, Lacroix E, Leusen I: The cardiovascular adaptation of the dog to the muscular exercise. Role of the arterial pressoreceptors. Arch Int Physiol Biochem 74:201, 1966
13. Krasney JA, Levitzky MG, Koehler RC: Sinoaortic contribution to the adjustment of systemic resistance in exercising dogs. J Appl Physiol 36:679, 1974
14. McRitchie RJ, Vatner SF, Boettcher D, et al: Role of arterial baroreceptors in mediating cardiovascular response to exercise. Am J Physiol 230:85, 1976
15. Bristow JD, Brown EB Jr, Cunningham DJC, et al: Effect of bicycling on the baroreflex regulation of pulse interval. Circ Res 28:582, 1971
16. Cunningham DJC, Petersen ES, Peto R, et al: Comparison of the effect of different types of exercise on the baroreflex regulation of heart rate. Acta Physiol Scand 86:444, 1972
17. Kumada M, Nogami K, Sagawa K: Modulation of carotid sinus baroreceptor reflex by sciatic nerve stimulation. Am J Physiol 228:1535, 1975
18. Gebber GL, Klevans LR: Central nervous system modulation of cardiovascular reflexes. Fed Proc 31:1245, 1972
19. Hilton SM: Inhibition of baroreceptor reflexes on hypothalamic stimulation. J Physiol 165:56P, 1963
20. Korner PI: Integrative neural cardiovascular control. Physiol Rev 51:312, 1971
21. Vatner SF, Boettcher DH, Heyndrickx GR, et al: Reduced baroreflex sensitivity with volume loading in conscious dogs. Circ Res 37:236, 1975
22. Bainbridge FA: The influence of venous filling upon the rate of the heart. J Physiol 50:65, 1915
23. Horwitz LD, Bishop VS: Effect of acute volume loading on heart rate in the conscious dog. Circ Res 30: 316, 1972
24. Guyton AC, Jones CE, Coleman TG: Circulatory physiology: Cardiac output and its regulation. Philadelphia, Saunders, 1963
25. Malliani A, Lombardi F, Pagani M, et al: Spinal cardiovascular reflexes. Brain Res 87:239, 1975
26. Bishop VS, Lombardi F, Malliani A, et al: Reflex sympathetic tachycardia during intravenous infusions in chronic spinal cats. Am J Physiol 230:25, 1976
27. Gupta PD: Spinal autonomic afferents in elicitation of tachycardia in volume infusion in the dog. Am J Physiol 229:303, 1975
28. Malliani A, Recordati G, Schwartz PJ: Nervous activity of afferent cardiac sympathetic fibres with atrial and ventricular endings. J Physiol 229:457, 1973
29. Paintal AS: Vagal sensory receptors and their reflex effects. Physiol Rev 53:159, 1973
30. Mancia G, Donald DE: Demonstration that the atria, ventricles, and lungs each are responsible for a tonic inhibition of the vasomotor center in the dog. Circ Res 36:310, 1975
31. Wade OL, Bishop JM: The distribution of cardiac output in normal subjects during exercise, in: Cardiac Output and Regional Blood Flow. Oxford, Blackwell Scientific, 1962, p 95
32. Saltin B, Blomqvist G, Mitchell JH, et al: Response to exercise after bed rest and after training. A longitudinal study of adaptive changes in oxygen transport and body composition. Circulation 38 (Suppl 7):1, 1968
33. Vatner SF, Franklin D, Higgins CB, et al: Left ventricular response to severe exertion in untethered dogs. J Clin Invest 51:3052, 1972
34. Saltin B, Astrand P: Maximal oxygen uptake in athletes. J Appl Physiol 23:353, 1967
35. McArdle WD, Foglia GF, Patti AV: Telemetered cardiac response to selected running events. J Appl Physiol 23:566, 1967
36. Schwartz PJ, Stone HL: Effects of unilateral stellectomy upon cardiac performance during exercise. (in preparation)
37. Starling EH: The Linacre Lecture on the Law of the Heart. London, Longmans, Green, 1918
38. Starling EH: On the circulatory changes associated with exercise. J Roy Army Med Corps 34:258, 1920
39. Rushmer RF: Constancy of stroke volume in ventricular responses to exertion. Am J Physiol 196:745, 1959
40. Horwitz LD, Atkins JM, Leshin SJ: Role of Frank–Starling mechanism in exercise. Circ Res 31:868, 1972
41. Vatner SF, Boettcher DH: Regulation of cardiac output by stroke volume and heart rate in conscious dogs. (in preparation)
42. Chapman CB, Fisher JN, Sproule BJ: Behavior of