Role of Autonomic Hormones on Left Ventricular Performance Continuously Analyzed by Electronic Computers

By ROBERT F. RUSHMER, M.D. AND THEODORE C. WEST, PH.D.

Surgery by Allan C. Lobb, technical assistance by Dean L. Franklin and Robert W. Moss

Ventricular responses during spontaneous activity by intact dogs have been studied by using electronic computers to continuously analyze ventricular function in terms of various parameters, including effective ventricular pressure, changes in left ventricular circumference or diameter, rate of change in ventricular dimensions, myocardial "power," myocardial "stroke work," "cumulative work" per unit time and heart rate. Simultaneous recordings of these various factors permit characterization and direct comparison of the nature and sequence of left ventricular responses during infusion of autonomic hormones, spontaneous activity or exercise. Intravenous infusion of catechol amines in "physiologic doses" produces changes in ventricular performance which differ significantly from those observed during exercise, particularly with reference to heart rate. The left ventricle appears to be directly influenced by neural reflexes, some of which are probably initiated by higher centers of the nervous system.

The mechanisms for cardiac control cannot be fully elucidated by experiments on anesthetized animals in which the normal regulating mechanisms are depressed or inactivated. For this reason, changes in the performance of the left ventricle have been studied during spontaneous activity of intact dogs. Dimensional gages fastened directly to the myocardium, have been used to record continuously the diameter, the circumference and the length of the left ventricle. Effective left ventricular pressure was recorded by miniature pressure gages mounted at the apex of the heart. Continuous records of changing pressure and dimensions provide graphic indications of left ventricular responses during various types of spontaneous activity. Further, a number of functions can be derived from these variables to throw additional light on the manner in which the chamber responds. For example, information regarding the rate of ejection, the rate of performing work, the total useful work performed per unit time, and heart rate can be extracted from such records. Ordinarily, these factors are computed by laboriously measuring the records. Recent developments in electronic computers have made it possible to both measure and compute these parameters instantaneously and continuously. Thus, changes in ventricular performance can be characterized in terms of six to eight interrelated parameters, inscribed directly while the cardiovascular adjustments are occurring in the animal. Continuous data reduction has been adapted to direct-writing recorders so that the analyzed data can be inspected as it is being inscribed. The patterns of response observed during spontaneous activity by the animal can be directly compared to the changes induced by various experimental procedures. For example, the role of circulating hormones in spontaneous cardiac adjustments to exertion may be evaluated by attempting to reproduce the patterns of ventricular response by infusing various hormones at different rates.

METHODS

The techniques employed to record changes in left ventricular dimensions and effective left ventricular pressure have been previously described and are illustrated (fig. 1). Left ventricular circumference was registered from a length of delicate rubber tubing filled with mercury and effective left ventricular pressure by...

From the Department of Physiology and Biophysics and Department of Pharmacology, University of Washington School of Medicine, Seattle, Wash.

This investigation was supported in part by a research grant from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service, and the American Heart Association.

Received for publication December 10, 1956.
pressure was recorded from a differential transformer pressure transducer mounted at the cardiac apex in 31 animals. Analysis of left ventricular performance as a pump must be extended beyond independent records of changing pressures and dimensions. Engineers frequently employ pressure-volume diagrams to investigate the characteristics of pumps and engines. Similar diagrams can be inscribed continuously by applying the amplified signals from pressure and circumference gages respectively to the vertical and horizontal plates of a cathode ray oscilloscope. During each normal cardiac cycle, the beam describes a loop (fig. 1A) which is roughly quadrilateral, the sides defining the four functional divisions of each successive cardiac cycle (diastolic filling, isovolumetric contraction, ejection and isovolumetric relaxation). The area enclosed within the loop is an expression of the work accomplished during the cycle.
by those myocardial fibers which lie under the gage and contribute to the change in circumference. Pressure-circumference loops were displayed continuously on oscilloscope and photographed before and during various maneuvers. A direct comparison of the changes in the position or slope of each side of the loops was obtained by double exposures during the control period and during an experimental period without advancing the film. It was not practical to record and analyze each successive pressure-circumference loop, so methods were developed to analyze continuously the changes in left ventricular performance as reflected by changes in the recorded dimensions and pressures.

First, the rate of change of circumference (dC/dT) was derived from the output of the circumference gage by means of a differentiating circuit, which, in effect, continuously indicated the slope of the changing circumference pattern. If changes in circumference are assumed to reflect changes in ventricular volume, the product of the pressure and the rate of change of circumference is an expression of "power." A Philbrick multiplying circuit was used to record continuously the product of these two variables. The resulting "power" record is regarded as indicating the rate at which work was performed by the fibers lying under the circumference gage.

The area under the power record represents "stroke work." By means of a simple integrating circuit, the area under the positive deflection (black area) was recorded as an upward step, the height of which reflected the stroke work of the myocardial fibers under the circumference gage. By means of a timing circuit, the galvanometer was returned to the baseline at precisely timed intervals (e.g., 2, 3 or 4 sec.). The stroke work deflections added during each successive interval, so that the total height of the deflection represents the total "accumulated stroke work" per unit time. The number of upward steps per unit time was determined by the heart rate. Thus, the "accumulated stroke work" embodied three of the principal factors determining the useful work of the myocardium: change in pressure, rate of change in dimensions, and heart rate. The shape and amplitude of the various records derived by the electronic computers conformed very closely to the patterns derived by computations from direct measurements.

The same types of information were derived by the computers when a modified sonar technique was employed to record the ventricular diameter (fig. 1C). Two crystals were mounted on opposite sides of the left ventricle, near the interventricular groove (fig. 1B). One crystal was excited with a microsecond pulse and emitted a sound. The second crystal received the sound after it had traversed the distance between the two crystals. Thus, the transit time for the sound was proportional to the particular left ventricular diameter delineated by the crystals. By pulsing the transmitter crystal 2,500 times/sec., a smooth curve of changing left ventricular diameter was recorded (fig. 1C). In addition to the parameters illustrated in figure 1, heart rate was monitored by a charged condenser interval timer.

Two Sanborn Polyviso recorders were employed to simultaneously record as many as eight different variables in intact dogs during a wide variety of conditions including: reclining, sitting, standing, eating, startling and exercise. Such recordings were obtained at frequent intervals for as long as 3 months after the installation of the gages. The computers and recording equipment used to record left ventricular responses are illustrated in figure 1D. Exercise consisted of running on a treadmill at 3 m.p.h. on a 5 per cent grade. Autonomic hormones were administered to 25 dogs by constant intravenous infusion for periods of 3–5 min.

Results

Left ventricular activity was analyzed continuously in 31 dogs with circumference gages (fig. 1A) and 19 dogs with sonographic crystals installed (fig. 1C). The circumference and diameter patterns differed consistently. A sharp upward spike at the onset of systole was prominent on records from circumference gages and small or absent on diameter records from crystals mounted near the interventricular grooves. The abrupt expansion of the circumference was coincident with the initial ventricular pressure rise and apparently represented a sudden change in ventricular shape without a corresponding change in volume. This has been ascribed to early contraction of papillary muscles and trabeculae carneae. The rightward slope of the right hand border on the pressure-circumference loop also stems from the sudden increase in circumference during isovolumetric contraction. The negative spike on the power record signifies that work is being performed on the myocardium under the circumference gage at the onset of systole. In this sense it actually represents "negative work" so far as the circumferential myocardial fibers are concerned. Since the diameter delineated by the two sonocardiographic crystals (fig. 1B) was little affected during the initial systolic expansion (fig. 1C), the pressure-diameter loops are more nearly rectangular and the negative power deflections are small or absent.

A description of the voluminous records obtained from 40 dogs over periods of from 2 to 108 days under a wide variety of conditions is clearly beyond the scope of this report. Anai-
RUSHMER AND WEST

PLACED ON TREADMILL 50mm/sec. No. 1 EXERCISE 3 mph. 5% GRADE No. 3 EXERCISE 3 mph. 5% GRADE

Fig. 2. Response of the animal illustrated in figure 1D when placed on a treadmill and while running at 3 m.p.h. on a 5 per cent grade during two exercise periods on the same afternoon.

ysis and interpretation of the records are greatly complicated by the variability in reactions during repetitive exposure to the same conditions by a single animal on the same day. As a typical example, different responses by a single animal exercising at 3 m.p.h. on a treadmill at a 5 per cent grade, are presented in figure 2. The first record was taken as the dog was placed on the treadmill, producing a response closely resembling the subsequent record obtained during exercise. The first exercise period of the afternoon was characterized by a sudden elevation in heart rate, increased systolic and diastolic ventricular pressures, increased stroke deflections on the diameter record, first by the larger downward excursion during systole, then by a greater diastolic expansion and finally by a combination of both effects. The pressure-diameter loops revealed that the increase in stroke work was accomplished by greater diastolic filling, higher ventricular pressure, and more complete systolic ejection. The third exercise on this afternoon produced records which were superficially similar but revealed little initial overshoot in heart rate, systolic pressure, diameter or accumulative stroke work. In other words, the initial response was only slightly greater than the equilibrium levels during exertion. Such differences between patterns of response were frequently recorded when the animals were tested under similar experimental conditions. Although the causes of the variability were not at all obvious, it seemed likely that the higher levels of the central nervous system were involved. In dogs that were thoroughly trained on the treadmill, a ventricular response very similar to that produced by exertion could be induced by merely showing the dog the switch used to start the treadmill.

An increase in the concentration of catechol amines has been frequently postulated as an important mechanism by which the cardiovascular system may be adapted to increased loads. The ventricular response to constant infusion of various autonomic hormones was previously reported. A major objective of the present study was to compare the ventricular response to exercise with the effects of a constant intravenous infusion of various autonomic hormones while the dog rested quietly but was fully awake (fig. 3). In contrast with the pronounced tachycardia which occurred with exercise, 1-epinephrine and norepinephrine characteristically produced bradycardia with the dosage levels employed here (0.002, 0.004 and 0.008 μM/Kg./min.). The changes in diastolic and systolic left ventricular pressure,
diameter, and power were similar to those of exercise. However, the cumulative work per unit time was usually unaffected by 1-epinephrine because the increase in stroke work was compensated by the bradycardia. Marked bradycardia produced by the same dose of norepinephrine actually diminished the cumulative work. The bradycardia produced by infusion of 1-epinephrine and norepinephrine, prevented the reproduction of the exercise response by administering physiologic doses of these catechol amines.

Isuprel is a synthetic substance which produces peripheral vasodilation and a powerful stimulating effect on myocardium. Constant infusion of this substance characteristically produced a dramatic tachycardia, a reduction in diastolic pressure, systolic and diastolic diameter, but a greatly increased peak “power” and “cumulative work.” By combining the effects of Isuprel with the pressor effects of norepinephrine, a response which resembled the steady state induced by exercise was produced, but the initial response was much slower in its development (fig. 3).

The profound bradycardia which accompanied the administration of catechol amines, was clearly associated with the elevation in systolic ventricular pressure. The cardiac responses to the administration of catechol amines were generally more prominent when the nervous system was depressed by barbiturate anesthesia than when the animals were completely unanesthetized. Presumably, the pressoreceptor mechanisms induced neural reflexes which overshadowed the direct cardioaccelerator action of the hormones on the pacemaker of the heart. The extent to which the neural reflex mechanisms can override the effects of constant infusion of norepinephrine (0.4 γ/Kg./min.) is illustrated (fig. 4). Infusion of norepinephrine augmented respiratory activity but produced little net change in the various parameters of ventricular function until tetraethyl ammonium chloride (TEAC 10 mg./Kg.) was administered to block the autonomic ganglia. As the cardiovascular system was released from the neural reflexes, a marked increase in systolic pressure, stroke excursion, peak power and cumulative stroke work became manifest. Tetraethyl ammonium chloride, administered without the increased cir-
culating norepinephrine produces a pronounced depressor effect on the circulation. Thus, active neural reflexes must compensate or override the direct action of circulating catechol amines.

**DISCUSSION**

The left ventricular response at the onset of exercise is characterized by an abrupt increase in heart rate, increased systolic and diastolic ventricular pressures, and increased stroke work per unit time. The changes in ventricular dimensions are somewhat variable at the beginning of exertion, the stroke excursion being augmented by increased diastolic expansion, greater systolic reduction or a combination of the two. The heart rate and systolic ventricular pressure generally reach a maximum within a very few heart beats and then descend to a more or less steady level during the remainder of the exertion.

Increased excretion of catechol amines by the adrenal glands has been generally assigned an important role in the cardiac response to many conditions including exercise. Intravenous infusion of l-epinephrine and norepinephrine failed to reproduce the left ventricular adaptation to exercise because the onset of the response was quite gradual and a rather intense bradycardia appeared as the systolic ventricular pressure was elevated. Although the rate of discharge of catechol amines by the adrenal glands at the onset of exercise is not known, the circulation time from adrenal glands to the heart is too slow to account for an abrupt change in ventricular performance even if the reactions were similar. Increased levels of circulating catechol amines could not play a dominant role in cardiac regulation of dogs because bradycardia never occurred during exercise. Cardiac slowing under these conditions is generally attributed to an intense discharge of vagal fibers to the heart induced by increased activity of pressoreceptors monitoring systemic arterial blood pressure. Sudden and sustained tachycardia are consistently observed during increased left ventricular systolic pressure produced by both exercise and by stimulation of sympathetic nerves to the heart. Thus, the response to exercise is much more closely simulated by direct stimulation of sympathetic cardiac nerves than by elevating the levels of circulating catechol amines.

One mechanism might be invoked to explain the intense bradycardia associated with elevated arterial pressure during infusion of epinephrine and norepinephrine as opposed to the tachycardia which accompanies exercise and stimulation of cardiac sympathetic nerves.
Heymans and his associates,\textsuperscript{10, 11} have demonstrated that smooth muscle in the wall of the carotid sinus can be induced to contract by local application of epinephrine and norepinephrine. Theoretically such a mechanism could greatly increase the sensitivity of pressoreceptor mechanisms during infusion of these catechol amines. Since the administration of 1-epinephrine does not consistently produce bradycardia in humans, information regarding the role of autonomic hormones in ventricular control in dogs should be applied to man with caution.

The cardioacceleration which can be produced by Isuprel with elevation in ventricular systolic pressure (fig. 3) remains unexplained. Perhaps Isuprel has greater direct effect on pacemaker activity and less vasopressor action on the arterial walls containing pressoreceptors than either epinephrine or norepinephrine.

Complex neural regulatory mechanisms appear essential to explain many aspects of cardiac adjustments in intact unanesthetized dogs. The ventricular responses produced by placing a dog on the treadmill or by showing him the treadmill switch closely resemble the initial response to exercise. Thus, the cardiac adjustments for exercise can be initiated well in advance of increased muscular activity. The higher centers of the central nervous system can initiate cardiac adaptation without the changes in the peripheral circulation called for by traditional concepts (e.g., accumulation of metabolites from contracting muscles, dilation of peripheral arterioles, reduction in systemic arterial blood pressure, increased pressoreceptor activity, tachycardia, increased muscular pumping action, increased systemic venous return, increased right ventricular output, increased pulmonary venous return and finally increased left ventricular output).

When a particular animal is repetitively exposed to the same experimental conditions on different occasions, the ventricular response may vary a little on some occasions and strikingly on others. For example, differences in the ventricular performance during the same degree of exercise on a treadmill are frequently observed on the same afternoon. The diversity of responses observed in different animals is even greater. Variability of this sort suggests an interaction of multiple controlling factors rather than any simple form of control. A multitude of factors which may be involved in cardiac regulation have been discussed in more detail in other publications.\textsuperscript{3-5}

REFERENCES
\textsuperscript{4} ——: Pressure-circumference relations in the left ventricle. Am. J. Physiol. 186: 115, 1956.
\textsuperscript{5} ——: Anatomy and physiology of ventricular function. Physiol. Rev. 36: 400, 1956.
\textsuperscript{7} ——: The initial phase of ventricular systole; asynchronous myocardial contraction. Am. J. Physiol. 184: 188, 1956.
Role of Autonomic Hormones on Left Ventricular Performance Continuously Analyzed by Electronic Computers
ROBERT F. RUSHMER, THEODORE C. WEST, Allan C. Lobb, Dean L. Franklin and Robert W. Moss

Circ Res. 1957;5:240-246
doi: 10.1161/01.RES.5.3.240

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1957 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/5/3/240

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/