

# Left Ventricular Response to Severe Exertion in Untethered Dogs

STEPHEN F. VATNER, DEAN FRANKLIN, CHARLES B. HIGGINS,  
THOMAS PATRICK, and EUGENE BRAUNWALD

*From the Departments of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts 02115, and University of California, San Diego, and Scripps Clinic and Research Foundation, La Jolla, California 92037*

**ABSTRACT** The left ventricular response to severe exercise was studied by telemetering direct measurements of left ventricular diameter (D) and pressure (P) and aortic blood flow from healthy dogs running at speeds up to 30 mph in the field. Severe exercise increased cardiac output from 101 to 478 ml/kg per min, heart rate from 95 to 297 beats/min, stroke volume from 31 to 44 ml, left ventricular isovolumetric systolic pressure from 120 to 186 mm Hg, left ventricular end diastolic pressure from 6 to 18 mm Hg, and left ventricular end diastolic diameter from 58.9 to 60.1 mm, while end systolic diameter decreased from 53.0 to 52.2 mm. Two indices of myocardial contractility,  $(dP/dt)/P$  increased from 37 to 92  $\text{sec}^{-1}$ , while  $dD/dt$ , the velocity of myocardial fiber shortening at isovolumetric, rose from 54 to 119 mm/sec. All of these changes were statistically significant. When, in resting dogs, heart rate was first raised to exercise levels by electrical stimulation, severe exercise subsequently increased left ventricular end diastolic diameter more profoundly, from 55.7 to 59.7 mm, while end systolic diameter remained constant and the increases in left ventricular pressure,  $(dP/dt)/P$  and velocity<sub>iso</sub> were roughly comparable to those occurring during exercise in spontaneous rhythm. After propranolol, 1.0 mg/kg, severe exercise resulted in significantly smaller increases in cardiac output (from 82 to 240 ml/kg), in heart rate (from 87 to 186 beats/min), in left ventricular pressure<sub>iso</sub> (from 122 to 150 mm Hg), in  $(dP/dt)/P$  (from 32 to 44  $\text{sec}^{-1}$ ), in velocity<sub>iso</sub> (from 47 to 59 mm/sec), and in slightly greater increases in end diastolic diameter, from 59.8 to 62.0 mm

and pressure from 8 to 22 mm Hg, while end systolic diameter did not change significantly.

Thus, the left ventricle responds to severe exercise with near maximal increases in heart rate and contractility, while significant increases in end diastolic diameter (Frank-Starling mechanism) and stroke volume occur as well. When heart rate was held constant severe exercise produced similar increases in contractility but end diastolic size failed to diminish and the increases in end diastolic size were greater. Beta adrenergic receptor blockade interfered with the chronotropic and particularly the inotropic response to severe exercise and while the participation of the Frank-Starling mechanism was somewhat greater, the latter was not sufficient to increase cardiac output normally.

## INTRODUCTION

It is well established that the primary cardiovascular adjustment to exercise involves an increase in cardiac output, but the manner in which the left ventricle augments its output during severe muscular exertion remains a fundamental cardiovascular physiological question. Earlier cardiovascular physiologists, influenced by Starling's Linacre lecture on the "Law of the Heart" (1), held that increases in stroke volume mediated by an increase in end diastolic myocardial fiber length (Frank-Starling mechanism) were essential to the cardiac adjustment to muscular work (2-8). The current concepts regarding the interrelationships among heart rate, stroke volume, and ventricular end diastolic size during exercise remain controversial due to the fact that most studies in which ventricular dimensions were measured found no change or actually a decrease in end diastolic size during exercise (8-16). The possibility exists that the intensity of exercise induced by previous studies in which left ven-

This work was presented before the American Society for Clinical Investigation, 1 May 1972, Atlantic City, N. J. Dr. Higgins is a Surgical Scholar supported by U. S. Public Health Service Grant GM 01559.

Received for publication 6 June 1972 and in revised form 25 July 1972.

tricular dimensions were measured in experimental animals (9–11) or man (8, 12–16) was not maximal and that the Frank-Starling mechanism does play a role in the response to severe exertion.

The present study was designed to determine the extent to which the Frank-Starling mechanism is utilized during near maximal exercise in normal, healthy dogs. This was accomplished by recording radiotelemetered measurements of left ventricular pressure and dimensions from normal unrestrained dogs, as they ran spontaneously in the field at speeds exceeding 20 and up to 30 mph. These experiments were designed to assess the extent to which near maximal exercise: (1) invokes increases in (a) end diastolic myocardial fiber length and (b) stroke volume; (2) increases the myocardial contractile state, and (3) is dependent on (a) tachycardia and (b) beta adrenergic activation.

## METHODS

15 mongrel dogs, weighing between 25 and 33 kg were anesthetized with Na pentobarbital, 30 mg/kg, i.v. Through a thoracotomy in the fifth left intercostal space, miniature pressure gauges<sup>1</sup> were implanted within the left ventricle through a stab wound in the apex (13 dogs). In 10 of these dogs opposing ultrasonic diameter transducers<sup>2</sup> were sutured to the epicardium of the anterior and posterior walls of the left ventricle (seven dogs) or implanted through stab wounds on the endocardial surfaces (three dogs), while stimulator electrodes were sutured to the left atrium (10 dogs). Electromagnetic flow probes<sup>3</sup> were placed around the ascending aorta (five dogs); three of these dogs also had miniature pressure gauges in the left ventricle.

The miniature left ventricular gauges (17) were calibrated *in vivo* against a calibrated Statham P23 Db strain gauge manometer.<sup>4</sup> At autopsy their position within the ventricular cavity was confirmed. An improved ultrasonic transit time dimension gauge was used to measure left ventricular diameter.<sup>2</sup> Its principle of operation is similar to that of other ultrasonic gauges described previously (18, 19); it measures the transit time of acoustic impulses traveling at the sonic velocity of approximately  $1.5 \times 10^9$  mm/sec between the 5 or 3 MHz piezoelectric crystals sutured to the left ventricular epicardium or endocardium at opposing sites. It was calibrated by substituting signals of known time duration from a pulse generator which was referenced to a quartz crystal controlled oscillator frequency. A voltage proportional to transit time was recorded and calibrated in terms of crystal separation. In this manner a measure of the external or internal diameter of the left ventricle was continuously recorded. At a constant temperature the drift of the instrument is less than 0.15 mm/hr, and its frequency response is flat to 60 Hz. Since the diameter gauge was insulated by foam rubber and carried by the animal in saddle bags, drift due to temperature changes during exercise was not considered to be significant. Terminally the left ventricular diameter measure-

ments were calibrated; changes in dimensions were related to changes in stroke volume. Stroke volume, measured directly with an electromagnetic flowmeter on the aortic root, was varied over a wide range by inducing tachycardia with electrical stimulation of the atria, isoproterenol infusion, volume loading, and hemorrhage. A modification of an electromagnetic flow system with the capability for telemetry described by Fryer and Sandler was used to measure aortic blood flow (20). The probes were calibrated *in vivo* using a dye dilution technique to measure cardiac output.

The electronic equipment carried by the animal in saddle bags consisted of a battery operated transit time diameter/pressure or electromagnetic flow/pressure telemetry system. The signals containing the diameter, 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. These systems have been described in detail previously (21–23).

The experiments were conducted 3 wk to 3 months post-operatively, when the dogs had recovered from operation and were again vigorous and healthy. While the dogs were reclining and then standing quietly, control records of left ventricular pressure (P),<sup>5</sup> diameter (D), the time rate of change of diameter (dD/dt), i.e., the velocity of myocardial shortening, the rate of change of pressure (dP/dt), and heart rate were obtained. The dogs were taken to isolated roads where the mobile unit carrying the electronic recording equipment then drove off. The untethered dogs ran behind the van at speeds of 15–30 mph over level and graded roads for distances averaging 1.5 miles and ranging up to 6 miles. The normal dogs exercised also (a) while their atria were stimulated electrically<sup>6</sup> at an average frequency of 296 beats/min, the heart rate which they had previously attained spontaneously during exercise, and (b) after beta receptor blockade with propranolol, 1.0 mg/kg intravenously. Duplicate or separate experiments were conducted either on separate days or after sufficient time for full recovery on the same day, e.g., 2–4 hr later.

The level of exercise attained by the normal dogs with or without electrical stimulation of the atria was similar, but the level of exercise attained by the dogs after beta receptor blockade, was on the average lower, i.e. 14 mph. The level of exercise attained in all dogs was considered to be severe, since an average of 60 min was required to recover normal hemodynamics and respiratory rate.

Data were recorded on a multichannel tape recorder and played back on a direct writing oscillograph at a paper speed of 100 mm/sec. A cardiachometer 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 using Philbrick operational amplifiers<sup>7</sup> connected as differentiators, having frequency responses of 60 and 30 Hz, respectively. A triangular wave signal with known slope (rate-of-change) was substituted for pressure and diameter signals to calibrate directly the dP/dt and dD/dt channels.

Exercise data were assessed during peak, steady-state exercise. The effects of exercise on myocardial force-

<sup>1</sup> Konigsberg P<sub>23</sub>, Konigsberg Instruments, Inc., Pasadena, Calif.

<sup>2</sup> Circuit diagrams available from authors.

<sup>3</sup> Zepeda Instruments, Seattle, Wash.

<sup>4</sup> Statham Instruments, Inc., Oxnard, Calif.

<sup>5</sup> Abbreviations used in this paper: D, diameter; dD/dt, rate of change of diameter; dP/dt, rate of change of pressure; iso, isolength; P, pressure; V, velocity.

<sup>6</sup> Medtronic, Inc., Minneapolis, Minn.

<sup>7</sup> Teledyne-Philbrick Co., Dedham, Mass.

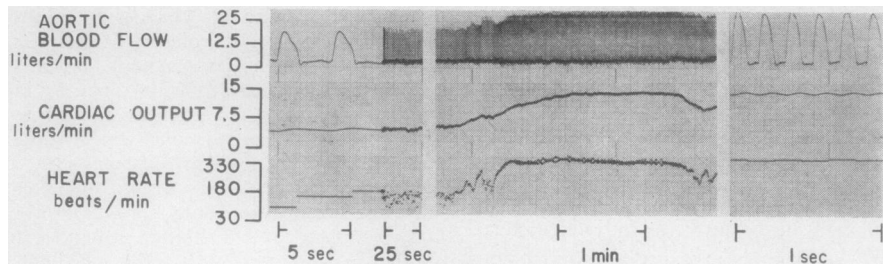


FIGURE 1 A typical response of aortic blood flow measured and telemetered during severe exercise. The phasic waveforms representing instantaneous stroke volume during exercise at the right played back at fast paper speed can be contrasted to the ones at the left before exercise. The slow rise in mean aortic blood flow (cardiac output) is due to the RC filter having an 8 sec time constant.

velocity relations were assessed by determining their effects on the velocity ( $V$ ) of shortening and intraventricular pressure ( $P$ ) at an identical ventricular diameter ( $D$ ) (isotlength point), by the technique described in detail previously (24-26). All isotlength points were obtained during the first one-third of ejection. In addition, the effects on peak  $dP/dt$  and the quotient of  $dP/dt$  and developed pressure (left ventricular minus end diastolic pressure), i.e.,  $(dP/dt)/P$ , were examined. The same level of pressure which occurred during isometric contraction, before and after each intervention and ranged from 40 to 80 mm Hg, was used for this calculation and  $dP/dt$  and pressure were determined at that level of pressure. This technique for evaluating the myocardial contractile state has also been described in detail previously (24, 25, 27, 28).

## RESULTS

### Exercise during spontaneous rhythm

*Response to standing at rest.* When dogs arose to a standing position cardiac output increased slightly, from  $90 \pm 3$  (mean  $\pm$  SEM) to  $101 \pm 3$  ml/kg per min, as did heart rate, from  $73 \pm 3$  to  $95 \pm 3$  beats/min, while stroke volume decreased slightly, from  $35 \pm 2$  to  $31 \pm 2$  ml. These changes were all significant ( $P < 0.05$ ), but no significant change occurred in systolic left ventricular pressure. End diastolic pressure fell from  $8 \pm 1$  to  $6 \pm 1$  mm Hg, as did epicardial end diastolic diameter, from  $60.5 \pm 1.3$  to  $58.9 \pm 1.1$  mm, and end systolic diameter, from  $53.3 \pm 0.9$  to  $53.0 \pm 0.8$  mm; internal diastolic and systolic diameters decreased by an average of 1.8 and 0.5 mm, respectively; peak  $dP/dt$  rose from  $3230 \pm 210$  to  $3520 \pm 190$  mm Hg/sec,  $(dP/dt)/P$  increased from  $35 \pm 3$  to  $37 \pm 3$  sec $^{-1}$ , and  $V_{1.0}$  from  $50 \pm 2$  to  $54 \pm 2$  mm/sec. These changes were all statistically significant ( $P < 0.05$ ). Since this change in posture caused significant alterations in ventricular dimensions in all dogs, the effects of exercise and the interventions were all referenced to control observations made in the standing position.

*Response to exercise.* In the five dogs in which it was measured, exercise caused cardiac output to increase to  $478 \pm 31$  ml/kg per min, and stroke volume to  $44 \pm 2$  ml (Fig. 1). In all 15 dogs heart rate increased abruptly,

to an average of  $297 \pm 5$  beats/min and remained elevated for as long as the dogs ran at full speed (Figs. 1, 2). Left ventricular pressure (systolic/end diastolic pressure) rose to  $204 \pm 9/18 \pm 3$  mm Hg, while  $P_{1.0}$  also rose, to  $186 \pm 6$  mm Hg (Table I). In the seven dogs in which it was measured, epicardial left ventricular end diastolic diameter decreased initially and transiently, but by 10-30 sec it had returned to control values and increased in all dogs above control, to  $60.1 \pm 1.1$  mm, while end systolic diameter decreased to  $52.2 \pm 0.9$  mm (Fig. 2). In the three dogs in which it was measured, endocardial left ventricular diameters showed similar responses (Fig. 3); end diastolic diameter increased from 38.7 to 40.2 mm during steady-state severe exercise. Thus, in all 10 dogs in which it was measured, end diastolic diameter increased during near maximal exercise. This increase occurred in animals with relatively low heart rates at rest (60-80 beats/min) as well as those with heart rates at rest of over 100 beats/min. Peak  $dP/dt$  increased to  $12,620 \pm 620$  mm Hg/sec while  $(dP/dt)/P$  rose to  $92 \pm 6$  sec $^{-1}$  and velocity $_{1.0}$  to  $119 \pm 6$  mm sec. Thus, in addition to profound increases in heart rate, cardiac output and contractility, severe exercise caused significant increases in end diastolic dimensions and stroke volume.

### Exercise with heart rate controlled

*Responses to pacing at rest.* In 10 standing dogs, elevating the heart rate at rest to levels previously achieved during severe exercise, i.e., to  $296 \pm 6$  beats/min, did not significantly affect left ventricular systolic pressure, but decreased left ventricular end diastolic pressure from  $6 \pm 1$  to  $1 \pm 1$  mm Hg ( $P < 0.01$ ), left ventricular end diastolic diameter from  $59.0 \pm 1.2$  to  $55.7 \pm 1.1$  mm in seven dogs ( $P < 0.01$ ), and end systolic diameter from  $53.2 \pm 0.9$  to  $52.1 \pm 0.7$  mm in seven dogs. Peak  $dP/dt$  and  $(dP/dt)/P$  increased only slightly.  $V_{1.0}$  could not be measured because of the marked reduction in left ventricular size.

TABLE I  
Effects of Severe Exercise

	Standing at rest	Exercise	$\Delta$
<b>Cardiac output (ml/kg per min)</b>			
Spontaneous rhythm ( $n = 5$ )	101 $\pm$ 3 (Mean $\pm$ SEM)	478 $\pm$ 31*	377 $\pm$ 31
Beta block ( $n = 4$ )	82 $\pm$ 2	240 $\pm$ 9*	157 $\pm$ 7‡
<b>Stroke volume (ml)</b>			
Spontaneous rhythm ( $n = 5$ )	31 $\pm$ 2	44 $\pm$ 2*	14 $\pm$ 2
Beta block ( $n = 4$ )	28 $\pm$ 2	37 $\pm$ 2*	9 $\pm$ 2‡
<b>Heart rate (beats/min)</b>			
Spontaneous rhythm ( $n = 15$ )	95 $\pm$ 3	297 $\pm$ 5*	202 $\pm$ 6
Paced ( $n = 7$ )	296 $\pm$ 6	296 $\pm$ 6	0‡
Beta block ( $n = 7$ )	87 $\pm$ 3	186 $\pm$ 3*	100 $\pm$ 3‡
<b>LV P (mm Hg)</b>			
(Peak P, P <sub>iso</sub> , EDP)			
Spontaneous rhythm ( $n = 12$ )	126 $\pm$ 4/120 $\pm$ 3/6 $\pm$ 1	204 $\pm$ 9*/186 $\pm$ 6*/18 $\pm$ 3*	78 $\pm$ 8 /66 $\pm$ 6 /12 $\pm$ 1
Paced ( $n = 7$ )	122 $\pm$ 4/ — /1 $\pm$ 1	197 $\pm$ 8*/182 $\pm$ 7*/17 $\pm$ 3*	75 $\pm$ 8 /67 $\pm$ 6 /16 $\pm$ 1‡
Beta block ( $n = 7$ )	129 $\pm$ 4/122 $\pm$ 2/8 $\pm$ 1	158 $\pm$ 7*/150 $\pm$ 5*/22 $\pm$ 3*	29 $\pm$ 7‡/27 $\pm$ 6‡/14 $\pm$ 1‡
<b>LV D (mm) end diastolic/ end systolic)</b>			
Spontaneous rhythm (ext) ( $n = 7$ )	58.9 $\pm$ 1.1/53.0 $\pm$ 0.8	60.1 $\pm$ 1.1*/52.2 $\pm$ 0.9*	1.3 $\pm$ 0.2 /0.8 $\pm$ 0.2
(int) ( $n = 3$ )	38.7/30.2	40.2/29.1	1.5/1.1
Paced (ext) ( $n = 7$ )	55.7 $\pm$ 1.1/52.1 $\pm$ 0.7	59.7 $\pm$ 1.0*/52.3 $\pm$ 0.8	3.9 $\pm$ 0.3‡/0.2 $\pm$ 0.1‡
(int) ( $n = 3$ )	35.1/29.0	40.0/29.0	4.9/0.1
Beta Block (ext) ( $n = 7$ )	59.8 $\pm$ 1.1/53.9 $\pm$ 1.1	62.0 $\pm$ 1.1*/54.2 $\pm$ 0.9	2.1 $\pm$ 0.1§/0.8 $\pm$ 0.1‡
(int) ( $n = 3$ )	39.7/30.9	42.0/31.2	2.3/0.3
<b>Peak dP/dt (mm Hg/sec<sup>-1</sup>)</b>			
Spontaneous rhythm ( $n = 12$ )	3520 $\pm$ 190	12,620 $\pm$ 620*	9,100 $\pm$ 610
Paced ( $n = 7$ )	3680 $\pm$ 190	11,650 $\pm$ 680*	8,000 $\pm$ 620
Beta block ( $n = 7$ )	3020 $\pm$ 240	4,500 $\pm$ 330*	1,480 $\pm$ 170‡
<b>(dP/dt)/P (sec<sup>-1</sup>)</b>			
Spontaneous rhythm ( $n = 12$ )	37 $\pm$ 3	92 $\pm$ 6*	54 $\pm$ 5
Paced ( $n = 7$ )	38 $\pm$ 3	87 $\pm$ 7*	50 $\pm$ 5
Beta block ( $n = 7$ )	32 $\pm$ 3	44 $\pm$ 4*	13 $\pm$ 2‡
<b>LV velocity (mm/sec) (peak/iso)</b>			
Spontaneous rhythm ( $n = 7$ )	62 $\pm$ 2/54 $\pm$ 2	137 $\pm$ 6*/119 $\pm$ 6*	75 $\pm$ 6/65 $\pm$ 5
Paced ( $n = 7$ )	56 $\pm$ 2/—	133 $\pm$ 6*/115 $\pm$ 6*	78 $\pm$ 6/65 $\pm$ 5
Beta block ( $n = 7$ )	52 $\pm$ 3/47 $\pm$ 2	67 $\pm$ 4*/59 $\pm$ 3*	15 $\pm$ 2‡/12 $\pm$ 2‡

LV, left ventricular; EDP, end diastolic pressure.

\* Significantly different from resting values  $P < 0.01$ .

‡ Significantly different from response in spontaneous rhythm  $P < 0.01$ .

§ Significantly different from response in spontaneous rhythm  $P < 0.02$ .

**Response to exercise with heart rate constant.** In seven dogs studied during exercise with heart rate constant left ventricular pressures and diameters, peak dP/dt, (dP/dt)/P, and peak velocity rose to nearly the same extent as they did during control (Table I), but the increases in end diastolic diameter and pressure were much greater (Fig. 4). Thus, the tachycardia of exercise plays only a minor role in mediating the inotropic response. Tachy-

cardia's most important effects are in modifying the changes in left ventricular dimensions which occur.

#### Exercise after beta receptor blockade

**Effects of beta receptor blockade at rest.** Propranolol, 1.0 mg/kg, in four standing dogs decreased cardiac output from 101  $\pm$  3 to 82  $\pm$  2 ml/kg per min, stroke volume from 31 to 28 ml/min, and heart rate from 95  $\pm$  3 to 87  $\pm$  3

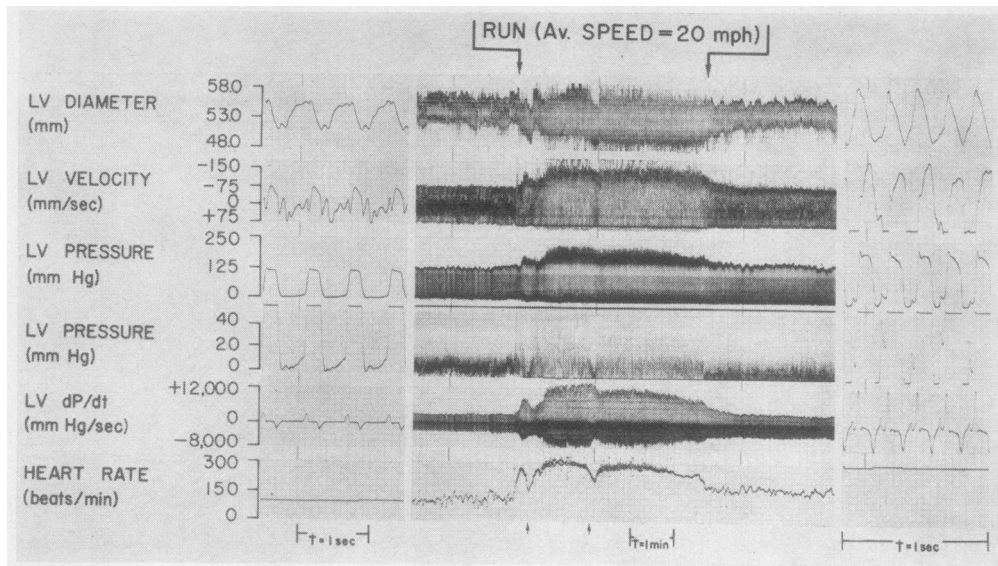


FIGURE 2 A typical response to severe exercise for phasic left ventricular diameter (epicardial), velocity, pressure, diastolic pressure, dP/dt, and heart rate. Phasic waveforms at rapid paper speed in the control period (left) can be contrasted with those during severe exercise (right). The arrows denote the time when the dog paused to urinate. Note that end diastolic diameter fell and then rapidly increased when severe exertion was resumed.

beats/min, while end diastolic pressure rose from  $6 \pm 1$  to  $8 \pm 1$  mm Hg and left ventricular diameter (end diastolic/end systolic) increased slightly; peak dP/dt decreased from  $3520 \pm 190$  to  $3020 \pm 240$  mm Hg/sec as did  $(dP/dt)/P$ ,  $37 \pm 3$  to  $32 \pm 3$   $\text{sec}^{-1}$  and  $V_{150}$  from  $54 \pm 2$  to  $47 \pm 2$  mm/sec. These changes were all statistically significant  $P < 0.05$ . However, left ventricular systolic pressure was not significantly affected by propranolol.

*Effects during exercise.* Severe exercise produced a significantly smaller ( $P < 0.01$ ) increase in cardiac output than was observed during the control exercise period, to only  $240 \pm 9$  ml/kg per min. This was due to smaller ( $P < 0.01$ ) increases in heart rate (to  $186 \pm 3$  beats/min) as well as to slightly, but significantly smaller ( $P < 0.01$ ) increases in stroke volume, to only  $37 \pm 2$  ml (Table I). The increases in isolog left ventricular

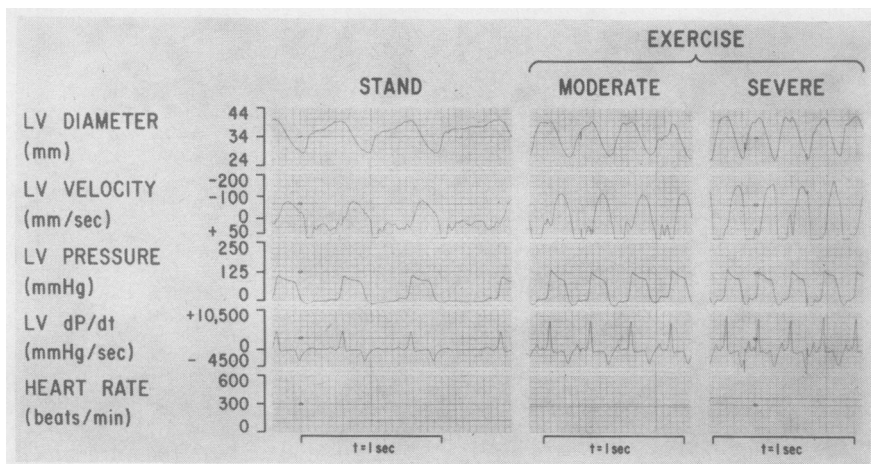


FIGURE 3 Phasic waveforms at fast paper speed of internal left ventricular diameter, velocity, left ventricular pressure, and dP/dt are shown along with instantaneous heart rate. The response at rest (left panel) is compared with the responses during moderate exercise (middle panel) and severe exercise (right panel). Note that end diastolic diameter failed to increase significantly with moderate exercise but did increase during severe exertion.

pressure and velocity, peak  $dP/dt$  and  $(dP/dt)/P$  which occurred during the control exercise period were prevented to an even greater extent (Fig. 5).

The changes in ventricular dimensions were also significantly different from normal; the decrease in end systolic diameter did not occur ( $P < 0.01$ ) and end diastolic diameter increased by a slightly greater amount ( $P < 0.02$ ) with exercise after propranolol as compared with the unblocked state.

## DISCUSSION

The manner in which the heart adapts to the augmented demands placed on it by the stress of severe exercise has been controversial and the subject of intense interest 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 subject to careful scrutiny. This mechanism which was at one time considered to be of paramount importance (1-5), has more recently been demonstrated not to play a significant role, either in experimental animals during treadmill exercise (9-11) or in man (8, 12-16, 29). However, the level of exercise in previous studies was not maximal, and it remained to be demonstrated whether increases in end diastolic size could be elicited with more severe exertion. The capability for telemetry of measurements of left ventricular pressure, dimensions, and aortic blood flow permit 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.

The present study indicates that the left ventricular response to severe exercise in healthy dogs running at speeds up to 30 mph involves very profound increases in heart rate (often exceeding 300 beats/min) and increases in contractility,  $(dP/dt)/P$  increasing to 2.5 times and isovelocity increasing to 2.2 times control levels. These values probably represent physiological maxima in conscious dogs, since maximally tolerable doses of isoproterenol or norepinephrine do not produce such marked responses (25, 30).

Although it is generally believed that end diastolic size must increase during severe exertion since large increases in stroke volume during erect exercise have been noted in man (7, 8, 31-34), this conclusion has not been substantiated by direct measurement of left ventricular dimensions during exercise. The results from studies utilizing mild or moderate exercise have been conflicting; relatively few indicated that left ventricular size increased (35, 36), while the majority found that end diastolic size either remains constant or actually decreases (8-16) (Fig. 3). In all dogs in the present study during severe exertion, reduction in end systolic diam-

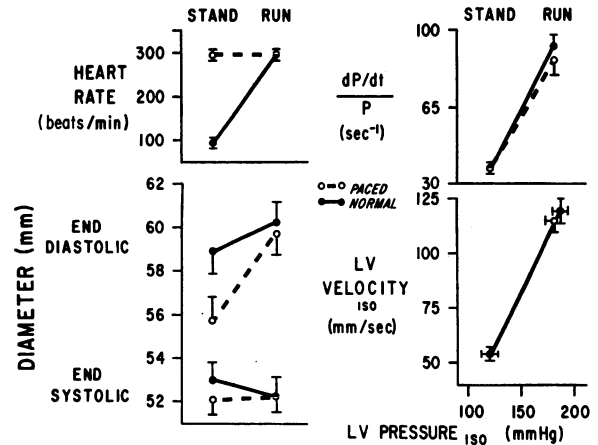


FIGURE 4 The average  $\pm$ SE values standing at rest and during severe exercise for seven dogs studied both in spontaneous rhythm and after heart rate had been elevated at rest to exercise levels with electrical stimulation of the atria. None of the values attained during steady-state severe exercise were significantly different in these two states.

eter and increases in end diastolic diameter and pressure were noted; relative changes were even more prominent when endocardial rather than epicardial dimensions were measured. Thus, the Frank-Starling mechanism remains a mechanism by which the heart can augment its performance during severe exertion. This mechanism has also been demonstrated in unanesthetized dogs while swimming (37). It should be noted that the left ventricular end diastolic dimensions attained during severe exercise did not exceed those occurring at rest in the reclining position. Thus, the importance of postural

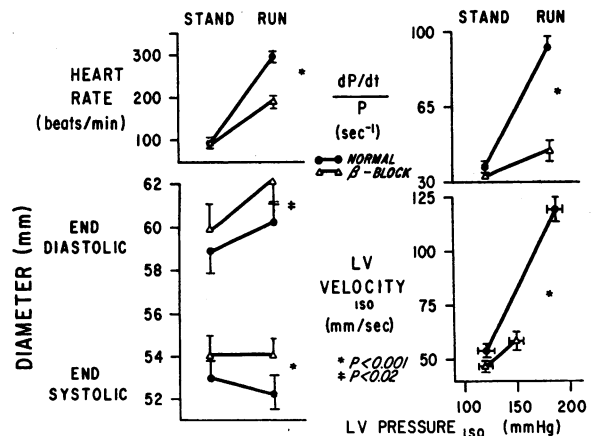


FIGURE 5 Average  $\pm$ SE values standing at rest and during steady-state severe exercise for seven dogs studied in both spontaneous rhythm and after 1.0 mg/kg propranolol. The values attained during severe exercise that were significantly different are noted.

changes on cardiac size, especially in the response to exercise, previously emphasized by Chapman, Fisher, and Sproule in man (7), is again demonstrated.

Since myocardial fiber shortening per stroke increases during exercise, in part due to greater diastolic filling (greater end diastolic dimensions) and in part due to more complete systolic ejection (lower end systolic dimensions), it can be deduced that stroke volume increased substantially as well. Estimates of stroke volume calculated from the dimensional changes indicated that roughly a 50% increase in stroke volume occurred. It is recognized that extrapolations from a transverse diameter measurement to volume calculations can be hazardous. It therefore was important to confirm these calculations by direct measurement of aortic blood flow which was accomplished in five dogs, and indicated that during severe exercise cardiac output rose 362% above control and stroke volume 48% above control. It must be pointed out that these relative increases in stroke volume were less when they were calculated on the basis of baseline, resting values in the reclining rather than the standing position; however, the increase in stroke volume was significant using either baseline value. The role played by stroke volume in the response to exercise has been controversial in that studies in man indicated that stroke volume remained relatively constant during supine exercise (12, 29, 38-40), but, as first pointed out by Mitchell, Sproule, and Chapman (31) and Chapman et al. (7, 8) was utilized during severe exertion in erect man (7, 8, 31-34). Studies in dogs utilizing indirect techniques indicated either little change (41) or increases in stroke volume (35, 36, 42, 43), but when aortic root blood flow was measured directly with ultrasonic or electromagnetic flowmeters it was not found to increase (9-11, 44). However, the present study, also employing electromagnetic flowmeters to measure stroke volume directly, indicates that it contributes significantly to the increases in cardiac output during severe exertion.

To dissect out the contribution of tachycardia to the exercise response, experiments were repeated after atrial rate had been elevated in resting dogs and held constant at levels previously achieved during exercise. In this situation increases in pressure and contractility occurred during exercise, which were similar to those occurring in unpaced dogs, indicating that simple tachycardia contributes relatively little to the inotropic response to exercise, even less than has previously been found in man (12). These findings substantiate those from another study from our laboratory which indicate that tachycardia has little inotropic effect in conscious dogs (45), although it produces considerable inotropic effects in anesthetized preparations and in isolated hearts and cardiac strips (45, 46). In resting dogs, however, tachycardia produced significant reductions in ventricular dimensions.

Hence, the major difference in the response to normal exercise, in comparison to exercise when heart rate was held constant at high levels, was the effect on left ventricular dimensions; far greater increases in end diastolic size were observed during exercise when heart rate was 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. When exercise was carried out either in the presence of beta adrenergic blockade or at a constant heart rate, end systolic size failed to decrease during exercise, even though in one instance (constant heart rate), contractility increased, and in the other instance (beta blockade), heart rate doubled while the increases in contractility were limited; both of these influences (tachycardia and increased contractility) would, by themselves, tend to reduce end systolic ventricular dimensions. Thus, the reduction in end systolic size that occurs with severe exercise appears to be dependent on a combination of the inotropic and chronotropic responses that are associated with severe exercise. When the decreases in end systolic dimensions did not occur after either pacing or beta blockade, the increases in end diastolic size during exercise were far greater.

Beta adrenergic receptor blockade with propranolol imposed significant limitations on the dogs' performance during exercise. The increases in contractility, as reflected by the force-velocity relationship and by  $(dP/dt)/P$  were largely prevented. Furthermore, heart rate increased to an average of only 187 beats/min as compared with 296 beats/min in the same dogs during exercise before blockade. Thus, a large component of the tachycardia during severe exercise can be attributed to sympathetic activation. This finding is in accord with early studies on the sympathetic control of heart rate during exercise (47, 48), but is not consistent with the findings from studies in dogs with cardiac denervation (49, 50) or those of Donald, Ferguson, and Milburn in racing greyhounds after beta receptor blockade (51). It is conceivable that the denervated hearts (49, 50) were supersensitive to circulating and intrinsic norepinephrine (52) while in the propranolol-treated normal dogs a complete blockade was not obtained (51). On the other hand, since the dogs in the present study ran at lesser speeds on the average after propranolol than during the control period, it could be argued that the level of exercise achieved was not maximal. However, this explanation appears less likely since several of these beta-blocked dogs ran to the point of complete exhaustion and collapse; one of these attained a speed of 30 mph prior to collapse while heart rate increased to only 182 beats/min.

The blunted tachycardiac response during exercise in the animals after beta blockade was associated with a sig-

nificantly reduced ( $P < 0.01$ ) increase in stroke volume, reflected in ventricular diameter measurements or measured by means of electromagnetic blood flowmeters on the aorta. Thus, propranolol interferes seriously with the increase in cardiac output which occurs during exercise; this results from reductions in augmentations both of heart rate and stroke volume. The limited increases in stroke volume that occurred after beta receptor blockade suggest that the Frank-Starling mechanism is relatively ineffective in maintaining a normal cardiac output during stress in the absence of sympathetic stimulation. Although slightly greater increases in end diastolic size occurred during exercise after propranolol, these were not sufficient to augment stroke volume normally. Thus, beta receptor activation is responsible for approximately half of the tachycardia of exercise and for a greater fraction of the cardiac output, pressure, and contractility developed by the left ventricle during severe exercise. The Frank-Starling mechanism, although utilized to a greater extent during exercise carried out in the presence of beta blockade, could not increase stroke volume sufficiently to compensate for the lack of adrenergic activation. This finding is consistent with the dogs' reduced performance during exercise and their appearance of greater exhaustion and imminent collapse after exercise. However, this finding is not consistent with the findings of Shepherd and Donald who observed that the capability for short-term exercise was not seriously impaired by cardiac denervation (49, 50). However, as mentioned above, the denervated hearts may have been supersensitive to the effects of circulating or intrinsic cardiac catecholamines (52), thereby stimulating ventricular performance on that basis.

In conclusion, the observed increase in cardiac output developed by the normal dog heart during maximal exercise was primarily due to increases in cardiac rate, but stroke volume contributes substantially as well. The increases in stroke volume are due to near maximal increases in contractility, while an increase in end diastolic myocardial fiber length, i.e., the Frank-Starling mechanism, also plays a role. When heart rate was maintained constant, the increases in end diastolic size during exercise were far greater than when it was allowed to vary, but the increases in contractility were similar. Sympathetic activation is necessary for both the normal tachycardia and stroke volume responses; although the Frank-Starling mechanism was utilized to a greater extent during exercise after propranolol, this mechanism did not stimulate ventricular performance sufficiently to augment stroke volume and cardiac output normally in the absence of sympathetic activation.

#### ACKNOWLEDGMENTS

We thank D. P. McKown, F. Werner, and D. Hendrick for technical assistance, and K. Bateman for assistance in

preparing the manuscript. We acknowledge the generous supply of propranolol hydrochloride from Ayerst Co., and the pacemaker from Medtronic, Inc. We also appreciate the advice of T. Fryer and Dr. H. Sandler on implementing the electromagnetic telemetry flow system.

This work was supported in part by U. S. Public Health Service Grants HE 12373, HE 13441, and HL 15631.

#### REFERENCES

1. Starling, E. H. 1918. The Linacre lecture on the law of the heart. Longmans, Green and Co., Ltd., London.
2. Starling, E. H. 1920. On the circulatory changes associated with exercise. *J. Roy. Army Med. Corps.* 34: 258.
3. Bainbridge, F. A. 1919. The physiology of muscular exercise. Longmans, Green and Co., Ltd. London.
4. Means, J. H., and L. H. Newburgh. 1915. The effect of caffeine upon the blood flow in normal human subjects. *J. Pharmacol. Exp. Ther.* 7: 449.
5. Lindhard, J. 1937. Ueber die Regulierung des Kreislaufes im gesunden und kranken Organismus. *Cardiologia.* 1: 366.
6. Liljestrand, G., E. Lysholm, and G. Nylin. 1938. Immediate effects of muscular work in the stroke and heart volume in man. *Skand. Arch. Physiol.* 80: 265.
7. Chapman, C. B., J. N. Fisher, and B. J. Sproule. 1960. Behavior of stroke volume at rest and during exercise in human beings. *J. Clin. Invest.* 39: 1208.
8. Chapman, C. B., O. Baker, and J. H. Mitchell. 1959. Left ventricular function at rest and during exercise. *J. Clin. Invest.* 38: 1202.
9. Rushmer, R. F. 1959. Constancy of stroke volume in ventricular responses to exertion. *Am. J. Physiol.* 196: 745.
10. Franklin, D. L., R. M. Ellis, and R. F. Rushmer. 1959. Aortic blood flow in dogs during treadmill exercise. *J. Appl. Physiol.* 14: 809.
11. Rushmer, R. F., O. Smith, and D. Franklin. 1959. Mechanisms of cardiac control in exercise. *Circ. Res.* 7: 602.
12. Sonnenblick, E. H., E. Braunwald, J. F. Williams, Jr., and G. Glick. 1965. Effects of exercise on myocardial force-velocity relations in intact unanesthetized man: relative roles of changes in heart rate, sympathetic activity, and ventricular dimensions. *J. Clin. Invest.* 44: 2051.
13. Braunwald, E., A. Goldblatt, D. C. Harrison, and D. T. Mason. 1963. Studies on cardiac dimensions in intact, unanesthetized man. III. Effects of muscular exercise. *Circ. Res.* 13: 460.
14. Gorlin, R., L. S. Cohen, W. C. Elliott, M. D. Klein, and F. J. Lane. 1965. Effect of supine exercise on left ventricular volume and oxygen consumption in man. *Circulation.* 32: 361.
15. Kjellberg, S. R., U. Rudhe, and T. Sjöstrand. 1950. The amount of hemoglobin (blood volume) in relation to the pulse rate and heart volume during work. *Acta Physiol. Scand.* 19: 152.
16. Bruce, T. A., C. B. Chapman, O. Baker, and J. N. Fisher. 1963. Role of autonomic and myocardial factors in cardiac control. *J. Clin. Invest.* 42: 721.
17. Van Citters, R. L., and D. L. Franklin. 1966. Telemetry of blood pressure in free ranging animals via an intravascular gauge. *J. Appl. Physiol.* 21: 1633.
18. Rushmer, R. F., D. Franklin, and R. M. Ellis. 1956. Left ventricular dimensions recorded by sonocardiometry. *Circ. Res.* 4: 684.



19. Stegall, H. F., M. B. Kardon, H. L. Stone, and V. S. Bishop. 1967. A portable, simple sonomicrometer. *J. Appl. Physiol.* **23**: 289.
20. Fryer, T., and H. Sandler. 1971. Miniature battery-operated electromagnetic flowmeter. *J. Appl. Physiol.* **31**: 622.
21. Patrick, T., S. Vatner, and D. Franklin. 1971. A system for radiotelemetry of left ventricular diameter and pressure in untethered animals. *Proc. 24th Conf. Eng. Med. Biol.* **13**: 315.
22. Franklin, D., S. F. Vatner, C. B. Higgins, T. Patrick, W. S. Kemper, and R. L. Van Citters. 1972. Measurement and radiotelemetry of cardiovascular variables in conscious animals: techniques. *Proceedings of the Conference on Animal Models, Washington, D. C.* In press.
23. Vatner, S. F., D. Franklin, C. B. Higgins, T. Patrick, W. S. Kemper, and R. L. Van Citters. 1972. Measurement and radiotelemetry of cardiovascular variables in conscious animals: applications. *Proceedings of the Conference on Animal Models, Washington, D. C.* In press.
24. Vatner, S. F., C. B. Higgins, T. Patrick, D. Franklin, and E. Braunwald. 1971. Effects of cardiac depression and of anesthesia on the myocardial action of a cardiac glycoside. *J. Clin. Invest.* **50**: 2585.
25. Vatner, S. F., C. B. Higgins, D. Franklin, and E. Braunwald. 1972. Extent of carotid sinus regulation of the myocardial contractile state in conscious dogs. *J. Clin. Invest.* **51**: 995.
26. Glick, G., E. H. Sonnenblick, and E. Braunwald. 1965. Myocardial force-velocity relations studied in intact unanesthetized man. *J. Clin. Invest.* **44**: 978.
27. Mason, D. T., E. Braunwald, J. W. Covell, E. H. Sonnenblick, and J. Ross, Jr. 1971. Assessment of cardiac contractility; the relation between the rate of pressure rise and ventricular pressure during isovolumic systole. *Circulation.* **44**: 47.
28. Wolk, M. J., J. F. Keefe, O. H. L. Bing, L. J. Finkelstein, and H. J. Levine. 1971. Estimation of  $V_{max}$  in auxotonic systoles from the rate of relative increase of isovolumic pressure:  $(dP/dt)$  kP. *J. Clin. Invest.* **50**: 1276.
29. Braunwald, E., E. H. Sonnenblick, J. Ross, Jr., G. Glick, and S. E. Epstein. 1967. An analysis of the cardiac response to exercise. *Circ. Res.* **20**(Suppl. I): 44.
30. Higgins, C. B., S. F. Vatner, D. Franklin, and E. Braunwald. 1972. Effects of prostaglandin  $A_1$  on left ventricular dynamics in the conscious dog. *Am. J. Physiol.* **222**: 1534.
31. Mitchell, J. H., B. J. Sproule, and C. B. Chapman. 1958. The physiological meaning of the maximal oxygen intake test. *J. Clin. Invest.* **37**: 538.
32. Bevegard, S., A. Holmgren, and B. Jonsson. 1960. Effect of body position on the circulation at rest and during exercise, with special reference to the influence on the stroke volume. *Acta Physiol. Scand.* **49**: 279.
33. Epstein, S. E., B. F. Robinson, R. L. Kahler, and E. Braunwald. 1965. Effects of beta-adrenergic blockade on the cardiac response to maximal and submaximal exercise in man. *J. Clin. Invest.* **44**: 1745.
34. Robinson, B. F., S. E. Epstein, R. L. Kahler, and E. Braunwald. 1966. Circulatory effects of acute expansion of blood volume: studies during maximal exercise and at rest. *Circ. Res.* **19**: 26.
35. Wildenthal, R., and J. H. Mitchell. 1969. Dimensional analysis of the left ventricle in unanesthetized dogs. *J. Appl. Physiol.* **27**: 115.
36. Wilson, M. F. 1962. Left ventricular diameter, posture and exercise. *Circ. Res.* **11**: 90.
37. Erickson, H. H., V. S. Bishop, M. B. Kardon, and L. D. Horwitz. 1971. Left ventricular internal diameter and cardiac function during exercise. *J. Appl. Physiol.* **30**: 473.
38. Ross, J., Jr., J. W. Linhart, and E. Braunwald. 1965. Effects of changing heart rate in man by electrical stimulation of the right atrium: studies at rest, during exercise, and with isoproterenol. *Circulation.* **32**: 549.
39. Asmussen, E., and M. Nielsen. 1953. Cardiac output in rest and work determined simultaneously by the acetylene and the dye injection methods. *Acta Physiol. Scand.* **27**: 217.
40. Holmgren, A., B. Jonsson, and T. Sjöstrand. 1960. Circulatory data in normal subjects at rest and during exercise in the recumbent position with special reference to the stroke volume at different work intensities. *Acta Physiol. Scand.* **49**: 343.
41. Wang, Y., R. J. Marshall, and J. T. Shepherd. 1960. Stroke volume in the dog during graded exercise. *Circ. Res.* **8**: 558.
42. Barger, A. C., V. Richards, J. Metcalfe, and B. Günther. 1956. Regulation of the circulation during exercise: cardiac output (direct Fick) and metabolic adjustments in the normal dog. *Am. J. Physiol.* **184**: 613.
43. Baile, M. D., S. Robinson, H. H. Rostorfer, and J. L. Newton. 1961. Effects of exercise on heart output of the dog. *J. Appl. Physiol.* **16**: 107.
44. Gregg, D. E., D. C. Sabiston, and E. O. Theilen. 1955. Performance of the heart; changes in left ventricular end-diastolic pressure and stroke work during infusion and following exercise. *Physiol. Rev.* **35**: 130.
45. Higgins, C. B., S. F. Vatner, R. W. Millard, D. Franklin, and E. Braunwald. 1972. Effect of tachycardia on left ventricular contractility in conscious dogs. *Clin. Res.* **20**: 378. (Abstr.) Manuscript in preparation.
46. Koch-Weser, J., and J. R. Blinks. 1963. The influence of the interval between beats on myocardial contractility. *Pharmacol. Rev.* **15**: 601.
47. Hodes, R. 1939. Exercise in the sympathectomized cat. *Am. J. Physiol.* **126**: 171.
48. Brouha, L., W. B. Cannon, and D. B. Dill. 1936. The heart rate of the sympathectomized dog in rest and exercise. *J. Physiol. (Lond.)* **87**: 345.
49. Donald, D. E., and J. T. Shepherd. 1963. Response to exercise in dogs with cardiac denervation. *Am. J. Physiol.* **205**: 393.
50. Donald, D. E., S. E. Milburn, and J. T. Shepherd. 1964. Effect of cardiac denervation on the maximal capacity for exercise in the racing greyhound. *J. Appl. Physiol.* **19**: 849.
51. Donald, D. E., D. A. Ferguson, and S. E. Milburn. 1968. Effect of beta-adrenergic receptor blockade on racing performance of greyhounds with normal and with denervated hearts. *Circ. Res.* **22**: 127.
52. Donald, D. E., and J. T. Shepherd. 1965. Supersensitivity to *l*-norepinephrine of the denervated sinoatrial node. *Am. J. Physiol.* **208**: 255.