Role of the Frank-Starling Mechanism in Exercise

By Lawrence D. Horwitz, James M. Atkins, and Stephen J. Leshin

ABSTRACT

The mechanisms which determine the response of stroke volume to mild, moderate, and severe exercise were compared in nine dogs running on a level treadmill. The dogs ran for 3-minute periods at 3–4 mph (mild exercise), 6–8 mph (moderate exercise), and 10–14 mph (severe exercise). Heart rate increased from a standing control value of 107 ± 6 beats/min to 191 ± 10 beats/min in mild, 221 ± 8 beats/min in moderate, and 263 ± 9 beats/min in severe exercise. Stroke volume increased 14%, 19%, and 15% for mild, moderate, and severe exercise, respectively. During mild exercise, left ventricular internal diameter decreased at end-systole but was unchanged at end-diastole. During moderate and severe exercise, end-diastolic diameter increased consistently as did left ventricular end-diastolic pressure. It was concluded that, despite extremely high heart rates, stroke volume increased during exercise. The augmentation in stroke volume was due to the combined effects of an increase in contractility, caused by increased sympathetic nervous system activity, and the operation of the Frank-Starling mechanism.

KEY WORDS sympathetic nervous system preload dog left ventricular diameter left ventricular dynamics stroke volume

In 1956, Rushmer et al. (1) reported that, in dogs performing light exercise on a treadmill, left ventricular external diameter was either unchanged or smaller at end-diastole. In a later communication, Rushmer (2) reaffirmed these diameter measurements and concluded that stroke volume did not change consistently in running dogs. On the basis of these findings it was assumed that the Frank-Starling mechanism was not evoked during exercise.

However, in 1971, Erickson et al. (3) reported that dogs performing very strenuous exercise by swimming exhibited increases in stroke volume despite extremely high heart rates. The increase in stroke volume was accompanied by an increase in end-diastolic diameter, suggesting that the Frank-Starling mechanism was a factor.

A possible explanation for the discrepancy in the conclusions of these studies is that the hemodynamic alterations during physical activity may vary according to the severity of the exercise stress. Therefore, the purpose of this investigation was to compare the mechanisms which determine the response of stroke volume to mild and strenuous running exercise. To accomplish this aim, left ventricular pressure, internal diameter, and outflow were measured in dogs undergoing graded exercise on a treadmill.

Methods

Nine mongrel dogs, weighing 17–27 kg, were trained to run on a level treadmill. Subsequently, each dog underwent a sterile thoracotomy under sodium pentobarbital anesthesia. As described previously (4), during a brief inflow occlusion of the superior and inferior vena cava, two discoid sonocardiometer transducers were implanted within the left ventricle through a stab incision in the anterior wall. The transducers were positioned across the greatest internal transverse diameter of the left ventricle, one on the anterior and the other on the posterior endocardial wall. Through
Left ventricular internal transverse diameter was obtained with a sonocardiometer which measured the transit time of 5-MHz ultrasound between piezoelectric crystals in the two transducers at a sampling rate of 5,000 times/sec (5). To ensure proper tracking, the raw signal and the unfiltered bistable output were continuously monitored with an oscilloscope. As described previously, the sonocardiometer cannot adequately track signals unless the two piezoelectric crystals are directly facing each other (4). Prior to the initiation of experiments it was apparent that tracking was inadequate in four dogs; therefore, no sonocardiometer recordings were attempted during studies of these dogs. Postmortem examinations showed that improper surgical placement (three cases) and transducer failure (one case) were responsible for the inadequate tracking. Diameter recordings were obtained in the other five dogs. All had satisfactory signals on oscillographic monitoring, and proper placement of the transducers was confirmed at autopsy.

Flow was measured with a Zepeda EDP2 square-wave electromagnetic flowmeter. Flow probes were calibrated in vitro prior to implantation, and the calibration was confirmed in vivo using a simultaneous dye-dilution determination of cardiac output obtained by injecting indocyanine green dye into the left atrium and sampling in the aorta while the dog was at rest. It was assumed that flow was zero at end-diastole.

Left atrial and aortic pressures were measured through the implanted catheters with Statham P23Db manometers. Measurements with the solid-state left ventricular pressure transducers were obtained by assuming that left ventricular end-diastolic pressure was equal to the mean left atrial pressure and that left ventricular peak systolic pressure was equal to the peak aortic pressure at rest (6). This in vivo calibration correlated closely with in vitro calibrations prior to or after implantation. All signals were inscribed on a Beckman RM or a Hewlett-Packard 7700 oscillograph and an Ampex PR 500 tape recorder.

Control measurements were obtained while the dogs stood quietly on the treadmill prior to the initial exercise period. Each dog ran, in sequence, 3-minute periods at preselected levels of mild, moderate, and severe exercise on a level treadmill (0° grade). Mild exercise ranged from 3 to 4 mph, moderate exercise from 6 to 8 mph, and severe exercise, the maximum load at which the dog could be induced to run, from 10 to 14 mph. After the mild exercise and again after the moderate exercise, 5-minute rest periods were allowed.

To reduce the effects of respiratory variation or atypical beats, data were analyzed by averaging the results of six consecutive beats. Care was taken to avoid ectopic beats or beats with poor signal quality. The exercise data were obtained during the third minute of each exercise period, at which time a reasonably steady state had been obtained. Random sampling of other groups of beats within 15 seconds of the sampling point gave identical or nearly identical results, confirming that an adequate steady state was present. Statistical analyses were performed by paired comparisons of each exercise value with the corresponding control in the same dog.

In three dogs pulmonary artery and left atrial blood samples were collected at rest and during the third minute of each exercise period, and measurements of pH and Po2 were performed with an Instrumentation Laboratories 313 pH-blood gas analyzer. With simultaneous hemoglobin determinations the oxygen content of each sample was calculated to determine the arteriovenous oxygen difference (7). Oxygen consumption at each exercise level was then estimated by multiplying the arteriovenous oxygen difference times the cardiac output measured with the aortic flow probe.

CRITIQUE OF METHODS
A major reason for the rarity of studies of left ventricular dynamics during exercise has been the imposing difficulties involved in applying standard techniques to measurement of hemodynamics during the exercise state. In this investigation an attempt was made to overcome the limitations in resolution and frequency response of older techniques, while measuring parameters which permit meaningful physiological interpretation.

The solid-state pressure gauges have a natural frequency exceeding 3,000 Hz and do not alter in sensitivity during implantation (6). Small amounts of drift from day to day were corrected.
for by assuming that the left ventricular end-diastolic pressure was equal to the mean left atrial pressure at rest (6). The end-diastolic pressure was ascertained by inspecting magnified, high-speed records. Simultaneous mean left atrial pressures were measured in three dogs during exercise, and in all cases they agreed closely with the left ventricular end-diastolic pressure measurements. Intrapleural pressure tends to become more negative during exercise (8). Therefore, since the left ventricular pressures were measured with respect to atmospheric pressure, the transmural pressure of the left ventricle during exercise could have increased slightly more than our measurements indicated.

The Zepeda electromagnetic flowmeter provides a high-quality signal which is limited in frequency response only by the response of the recorder (flat to 80 Hz for the Beckman RM). Shifts in the end-diastolic portion of the flow signal during exercise were negligible, suggesting that end-diastolic flow approached zero at all levels of activity.

The sonocardiometer (1, 5) provides a reliable, continuous dimension measurement. The resolution is approximately to the nearest 0.07 mm, and the amplitude of the signal is down 5% at 20 Hz (8). We believe that the internal diameter measurement (4) is superior to recordings made from transducers affixed to the external surface of the heart (1) for several reasons. The shorter distance between the transducers improves coupling and greatly enhances signal quality. With external transducers, the interposition of the left ventricular wall between the sensors precludes accurate determination of changes in chamber dimensions, since substantial changes in wall thickness occur during the cardiac cycle and in response to sympathetic stimulation (9, 10). In addition, lateral rotation of the heart out of the plane of measurement could influence external records but is unlikely to alter internal diameter measurements. Previous studies have demonstrated that internal left ventricular diameter is an accurate index of left ventricular volume changes (11, 12). A disadvantage of the internal diameter method is the considerably greater difficulty of performing the surgical implantation, which requires a small incision through the ventricular wall and results in a higher failure rate due to improper placement of the transducers.

The natural frequency of the system used for measurement of left atrial and aortic pressures was 22 Hz, obtained by subjecting the manometer system to a sudden step change in pressure (13). This response should be sufficient for estimation of mean pressures. No gradients appeared during exercise between peak systolic pressures in the aorta and the left ventricle, indicating that no physiological stenosis occurred at the site of flow probe implantation.

The oxygen consumption calculation is subject to slight error due to inaccuracy in extrapolation from blood gas tension and pH to oxygen content. However, direct estimation of oxygen content by the Van Slyke technique was impractical due to the time and the amount of blood which would have been required.

**Results**

Oxygen consumptions, measured in three dogs, are shown in Table 1. Mean oxygen consumption increased approximately fourfold with mild exercise (3-4 mph), fivefold with moderate exercise (6-8 mph), and sevenfold with severe exercise (10-14 mph).

Figures 1 and 2 are individual high-speed recordings of left ventricular pressure and diameter and of aortic pressure and flow, respectively, during the control and the exercise periods. The hemodynamic measurements in all nine dogs are summarized in Table 2. Exercise values were obtained during the third minute of each exercise period.

The mean heart rate rose from 107 beats/min when the dogs were standing quietly on the treadmill to 263 beats/min with severe exercise. Heart rate increased from the control value by approximately 77% with mild exercise, 107% with moderate exercise, and 146% with severe exercise.

The mean stroke volume increased from 34.5 ml during the control period to 39.2 ml with mild exercise ($P < 0.01$), 41.2 ml with moderate exercise ($P < 0.01$), and 39.8 ml with severe exercise ($P < 0.01$). These values represent increases of 14%, 19%, and 15% for mild, moderate, and severe exercise, respectively. Four dogs attained their highest stroke volumes with moderate exercise, followed by a

<table>
<thead>
<tr>
<th>Dog</th>
<th>Control</th>
<th>3-4 mph</th>
<th>6-8 mph</th>
<th>10-14 mph</th>
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<tbody>
<tr>
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<td>5.5</td>
<td>16.6</td>
<td>30.9</td>
<td>44.4</td>
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<td>8</td>
<td>6.3</td>
<td>19.7</td>
<td>29.3</td>
<td>40.3</td>
</tr>
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<td>9</td>
<td>6.4</td>
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<td>37.8</td>
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<tr>
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<td>6.1</td>
<td>24.8</td>
<td>32.7</td>
<td>45.0</td>
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</table>

*Oxygen Consumption (ml/min kg⁻¹) during Graded Treadmill Exercise*
Slight decline during severe exercise. The remaining five dogs showed a progressive increase in stroke volume as the work load increased and attained their highest stroke volume at the highest speed. Cardiac output increased 102% with mild exercise, 147% with moderate exercise, and 183% with severe exercise.

Left ventricular internal transverse diameter was measured in five dogs. The end-diastolic left ventricular diameter did not change consistently during mild exercise. However, end-diastolic diameter did increase during moderate and severe exercise; the mean increases were 0.6 mm with moderate exercise \((P < 0.01)\) and 1.3 mm with severe exercise \((P < 0.001)\). At end-systole, there were decreases in left ventricular diameter in all five...
Left Ventricular Dynamics during Graded Treadmill Exercise

<table>
<thead>
<tr>
<th>HR (beats/min)</th>
<th>SV (ml)</th>
<th>EDD (mm)</th>
<th>ESDD (mm)</th>
<th>LVEDP (mm Hg)</th>
<th>LVSP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>SV (ml)</th>
<th>EDD (mm)</th>
<th>ESDD (mm)</th>
<th>LVEDP (mm Hg)</th>
<th>LVSP (mm Hg)</th>
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<td>1.8</td>
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<td>2.0</td>
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<td>28.7</td>
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<tr>
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<td>38.0</td>
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<td>1.2</td>
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<tr>
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<td>9</td>
<td>10</td>
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<td>3.1</td>
<td>1.8</td>
</tr>
</tbody>
</table>

HR = heart rate, SV = stroke volume, EDD = left ventricular end-diastolic diameter, ESDD = left ventricular systolic diameter, LVEDP = left ventricular end-diastolic pressure, and LVSP = left ventricular end-systolic pressure. P values are for paired comparisons between the control and exercise values in the same dog. ns = P > 0.05. No diameter measurements were obtained in four dogs (nos. 1, 5, 7, and 8). No stroke volume or left ventricular pressure measurements were obtained because of technical problems in two of the runs in dog 4.

Discussion

Although Rushmer and co-workers (1, 2) reported that end-diastolic external left ventricular diameter did not increase consistently during exercise, increases in end-diastolic left ventricular dimensions have been described by others (3, 14). The results of our study indicated that the work load was an important factor determining the nature of the changes in left ventricular dimensions. Probably much of the confusion in the scientific literature regarding the size of the left ventricle during exercise is due to failure to recognize that increased left ventricular end-diastolic dimensions occur only with very strenuous effort and not with mild stress.

Most of the increment in cardiac output during exercise was due to substantial increases in heart rate. These increases exceeded...
levels attributable to vagal withdrawal alone or to distention of the sinoatrial node by the volume load (15). It is likely, therefore, that the tachycardia resulted, at least partially, from sympathetic stimulation, as has been concluded by others (16). Despite the tachycardia, stroke volume was significantly increased at all levels of exercise stress.

During mild exercise the increase in stroke volume was due to greater cardiac muscle fiber shortening to a smaller end-systolic diameter without alteration in end-diastolic diameter. Such an improvement in cardiac performance, without a decrease in afterload, is characteristic of increased contractility. In view of the likelihood that the high heart rates reflected increased sympathoadrenal activity, it is probable that much, if not all, of this increase in contractility was caused by sympathetic nervous system stimulation.

During severe exercise, the high heart rates and the high oxygen consumption estimates confirmed the strenuous nature of the exercise (17-19). During both moderate and severe exercise, increases in stroke volume were accompanied by significant increases in left ventricular end-diastolic diameter. The substantial elevation in afterload with severe exercise may have attenuated the response of stroke volume in some dogs.

Since end-diastolic diameter increased during moderate and severe exercise despite extreme tachycardia, it appears that the old concept of a limitation in ventricular filling at high heart rates (20) does not apply to the exercise state. Presumably, the muscle pumping mechanism by which skeletal muscle contraction forces large quantities of blood through the systemic veins is a major factor which enhances ventricular filling (21). In addition, sympathetic nervous system stimulation reduces ventricular pressure in early diastole (6) and, thereby, may increase inflow immediately after the atrioventricular valves open.

When the heart rate of a conscious, resting or an anesthetized dog is increased by electrical pacing or vagal block, stroke volume decreases linearly and left ventricular end-diastolic dimensions are reduced (22, 23). However, the effect of the enhanced venous return is analogous to that of a rapid intravenous infusion in a resting animal: cardioacceleration is accompanied by an increase in left ventricular end-diastolic dimensions, and stroke volume is increased via the Frank-Starling mechanism (22). If the alterations in left ventricular dynamics during exercise were due exclusively to sympathetic stimulation, then end-diastolic diameter would
fall and stroke volume would remain constant as postulated by Rushmer (2, 6). Inasmuch as the left ventricular end-diastolic diameter exceeded the levels to be expected with sympathetic stimulation alone at all levels of exercise, it is probable that this increment in preload was partially responsible for the increases in stroke volume.

During mild exercise, the augmented sympathetic tone is manifested by the decrease in end-systolic diameter. A contribution of the Frank-Starling mechanism can also be postulated, since end-diastolic diameter is unchanged from the preexercise level when it would otherwise be slightly decreased at this heart rate in the absence of an increased venous return. With moderate and severe effort, however, left ventricular diameter actually increases above its preexercise size. At these levels the contribution of the Frank-Starling mechanism appears to be substantial and results in further increases in stroke volume, despite higher heart rate and afterload, both of which oppose such a change. Therefore, the Frank-Starling mechanism plays a role in the stroke volume response to all levels of exercise effort, although its influence is most obvious with very strenuous activity. Thus, the combined effects of an increase in contractility, due to sympathetic stimulation, and the operation of the Frank-Starling mechanism determine the response of stroke volume to exercise.

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