Influence of the Force–Frequency Relation on Left Ventricular Function During Exercise in Conscious Dogs

Toshiro Miura, MD; Shunichi Miyazaki, MD; Brian D. Guth, PhD; Masashi Kambayashi, MD; and John Ross Jr., MD

Background. The magnitude of the force–frequency effect on myocardial contractility in the conscious animal has been studied at rest, but it has not been assessed during exercise.

Methods and Results. The influence of heart rate (HR) changes were evaluated during treadmill exercise in eight preinstrumented, conscious dogs in which high-fidelity left ventricular (LV) pressure, LV volume (by sonomicrometry), and aortic pressure were measured. Under resting conditions, end-systolic pressure–volume relations were obtained using inferior vena caval occlusion. Dogs were run on a treadmill, and the intrinsic exercise HR was reduced by infusion of a specific bradycardic drug (UL-FS 49 0.5 mg/kg) during continuing exercise while HR was maintained at 240 beats per minute by atrial pacing. At 6 minutes of running at a fixed, paced HR when a stable drug effect had been achieved, no effects of UL-FS 49 on measures of LV contractility were detected compared with exercise before drug administration. HR was then reduced stepwise from 240 to 210, 180, or 150 beats per minute in a random manner, returning to 240 beats per minute between steps. Progressive reductions in measures of myocardial contractility occurred as the HR was slowed, and reduction of rate from 240 to 150 beats per minute reduced the LV maximum positive dP/dt by 31% and (dP/dt)dp/dt by 21% despite increases in LV end-diastolic pressure. The entire end-systolic pressure–volume could not be determined during exercise, but beat-averaged end-systolic pressure–volume points during exercise were progressively shifted to the right and downward by slowing the exercise HR. Thus, a pronounced negative inotropic influence of slowing the heart was observed during exercise, and the rate of ventricular relaxation (τ) was also significantly prolonged.

Conclusions. These findings indicate that force–frequency effects on the inotropic state of the intact LV are markedly enhanced by exercise. (Circulation 1992;86:563–571)

KEY WORDS • heart rate • exercise • UL-FS 49 • myocardial contractility

The effect of changes in cardiac frequency on the contraction of the heart was first described by Bowditch in 1871.1 Subsequent studies have further elucidated the effects and mechanism of force–frequency responses in isolated cardiac muscle,2 in the hearts of anesthetized3–5 and conscious animals,6–8 and in human subjects.9,10 In isometrically contracting cardiac muscle, augmented frequency of contraction causes increased peak tension and velocity of tension development (positive-force treppe, or staircase; increased contractility), and decreased peak tension and velocity accompany diminished frequency of contraction (negative-force treppe, or staircase; decreased contractility).2 Although the underlying mechanisms of the force–frequency effect on inotropic state are only partially understood, there is evidence that this phenomenon is related to changes in Ca2+ availability within the myocardial cell. Thus, using aequorin to detect intracellular free Ca2+ during changes in contraction frequency, Morgan and Blanks11 showed positive correlations between contraction frequency, force development, and the magnitude of the intracellular calcium transient.

The presence of a substantial force–frequency effect on the left ventricle (LV) of anesthetized animals has been well documented,4,2 and in the isolated canine LV, a change in the slope of the end-systolic pressure–volume relation5,12 as well as a significant abbreviation of the time to end systole have been described upon increasing the heart rate (HR).12 However, the importance of this phenomenon in the regulation of cardiac performance in conscious animals has been controversial. Higgins et al13 showed only a slight increase in maximum LV dP/dt in conscious dogs compared with...
anesthetized animals after increasing the HR when preload was maintained by volume infusion. Studies by Noble et al. in conscious dogs showed small changes in cardiac contractility with changes in HR under resting conditions, but the potential effects of alterations in preload on indexes of contractility were not assessed. Mahler et al. matched preload by studying myocardial contractility immediately after rapid pacing, but the sizable increase in myocardial contractility observed represents poststimulation potentiation and may be somewhat different from the force–frequency effect. On the other hand, Freeman et al. reported a significant increase in contractility after increasing HR when assessed by the slope of the end-systolic pressure–volume relation in conscious dogs in which LV end-diastolic volumes were matched. Thus, variable expression of the force–frequency relation on myocardial contractility has been observed under conscious, resting conditions. The reasons for an apparently larger force–frequency effect in anesthetized animal preparations are uncertain, although increased adrenergic stimulation under anesthesia (or relative depression of cardiac performance) in open-chest animals has been considered.

The potential importance of increasing HR on myocardial performance during exercise was suggested from studies in patients with complete heart block. In normal human subjects, changes in force–velocity relations were substantially less with pacing alone than during exercise at the same HR. However, the possibility that effects of the force–frequency relation on myocardial inotropic state could become more pronounced under conditions of exercise, when adrenergic stimulation of the myocardium is markedly enhanced, has not been explored. Accordingly, this study was designed to investigate the effect of changing HR on LV function during exercise in normal, conscious dogs by using the specific bradycardic agent or sinus node inhibitor UL-FS 49, an agent without known significant direct inotropic effects, to reduce the sinus node rate while varying HR by electrical pacing of the atrium.

Methods

Eight mongrel dogs (weight, 20–28 kg) were handled according to the animal welfare regulations of the University of California San Diego, and the protocol was approved by the Animal Use Committee of this institution. Before instrumentation, the dogs were trained to run on a motor-driven treadmill.

Instrumentation

Dogs were premedicated with atropine sulfate (0.06 mg/kg i.v.) and morphine sulfate (1 mg/kg i.m.), anesthetized with sodium thiamylal (25 mg/kg i.v.), and intubated. Respiration was maintained by a respirator supplied with a mixture of oxygen and isoflurane (1.5%). A lateral thoracotomy was performed in the left fifth intercostal space, and the heart was suspended in a pericardial cradle. A high-fidelity micromanometer (Konigsberg P7, Pasadena, Calif.) was inserted into the LV together with a polyethylene catheter (internal diameter, 1.5 mm) via an apical incision. A polyethylene catheter was inserted through an aortic incision into the descending aorta to measure aortic pressure. A pair of miniature ultrasonic crystals was implanted in the LV anterior free wall to measure wall thickness. LV dimensions were measured as the external short-axis diameter using a pair of ultrasonic crystals (5-mm diameter) sutured on the anterior and posterior surfaces of the ventricle, and the external long-axis diameter was determined using a pair of crystals sutured to the apex and to a point on the LV between the root of the ascending aorta and the left atrium. A pacing electrode was sutured to the left atrial appendage, and a pneumatic constrictor was positioned around the inferior vena cava. All catheters and wires were exteriorized to the back, and the dogs were allowed to recover from the operation.

Measurements

LV pressure recorded with a high-fidelity manometer was matched to the LV catheter pressure, which was measured with a Statham P23(Db) transducer. Mean aortic pressure was measured through the fluid-filled catheter. The first derivative (dP/dt) of LV pressure was obtained from the micromanometer by using an RC circuit to obtain the maximum positive value (LV dP/dtmax). ECGs were recorded from one of the implanted crystals. All measurements were recorded on a forced-air ink recorder (Gould Brush 200) and on magnetic tape for subsequent data analysis (Hewlett-Packard, model HP 3955 D). Taped data were played back and digitized at 3-msec intervals with a DEC PDP11/103 digitizing system. Twenty beats were digitized and averaged to exclude respiratory changes; beats 25 msec longer or shorter than the average RR interval were excluded.

LV volume was calculated according to the method of Rankin et al. using the equation

\[ V = \frac{\pi}{6}(a - 2c)^3 \times (b - 1.1c) \]

where a equals the external short axis, c equals ventricular wall thickness, and b equals the external long axis.

Normalized values for end-diastolic volume were calculated by dividing the observed end-diastolic volume by the resting end-diastolic volume (%EDV), and normalized end-systolic volume was also obtained by dividing the observed end-systolic volume by the resting end-diastolic volume (% ESV).

An index of early diastolic relaxation of the left ventricle, \( \tau \), was determined from the LV pressure decay during the isovolumic period calculated using a monoexponential model without asymptote. This method has been shown to be valid for comparing changes in the same animal.

End diastole was defined as the onset of the rapid upstroke of LV dP/dt, and end systole (end ejection) was defined as the point within 20 msec before minimum dP/dt; end-systolic LV pressure was also determined at the latter point. Time to end systole (Tmax) was calculated as the time from end diastole to end systole. The LV dP/dt divided by the developed LV pressure at a developed pressure of 40 mm Hg [(dP/dt)Dpmax] was calculated as an index of contractility that is relatively insensitive to preload and afterload changes. The ejection fraction (EF) was calculated as

\[ EF = \frac{(EDV - ESV)}{EDV} \times 100 \]

where EDV equals end-diastolic volume, and ESV equals end-systolic volume.
Protocol

At least 8 days after surgery, when the animals had fully recovered, they were run on the treadmill at a speed of 4.5–5.5 mph and an inclination of 5.0–6.0% to obtain heart rates of ≈220 beats per minute. We confirmed that each dog was able to run steadily for 8–9 minutes at this speed and that hemodynamic variables were stable throughout the run.

At least 3 hours after the control run, when the animal had fully recovered, the following protocol was initiated. During resting, standing conditions, the inferior vena cava (IVC) was briefly obstructed using the cuff occluder to reduce LV systolic pressure by 20–30 mm Hg, whereupon the cuff was released. The IVC occlusion was repeated two or three times. For constructing the end-systolic pressure–volume relation, the first six to seven beats after the onset of vena caval occlusion were analyzed in order to avoid baroreceptor reflex effects.

The dogs were then run on the treadmill at the predetermined work load. After 1.5 minutes of running, atrial pacing was commenced at a rate of 240 beats per minute, which exceeded the intrinsic rate of approximately 220 beats per minute. After an additional 3 minutes of running with pacing during steady state, UL-FS 49.0 mg/kg i.v. was administered. This agent is 1,3,4,5-tetrahydro-7,8-dimethoxy-3-[3-[2-(3,4-dimethoxyphenyl)ethyl][methylimino]propyl]-2H-3-benzazepin-2-on hydrochloride. The drug has been shown to have little or no direct effect on myocardial contractility. The dogs continued running for another 3 minutes while atrial pacing was continued to allow sufficient time for the drug to depress the sinus rate (in pilot studies, this period was sufficient to reach steady state). At 6 minutes, the pacing rate was abruptly decreased for about 20 seconds, which was sufficient to obtain a stable condition (Figure 1), and the rate was then returned to 240 beats per minute; after pacing back to 240 beats per minute, hemodynamic variables quickly recovered to previous levels. The pacing rate was randomly changed in this manner to either 210, 180, or 150 beats per minute.

In most experiments, we were unsuccessful in obtaining satisfactory reproducible responses to IVC occlusions because of respiratory artifact during exercise. Moreover, attempts at this intervention excessively prolonged the exercise periods and the procedure was discontinued, although a few IVC occlusions were performed during exercise for illustrative purposes.

Data Analysis

Data were analyzed at rest, at 3 minutes of running while paced at 240 beats per minute, at 6 minutes of running paced at 240 beats per minute (after UL-FS 49 administration), and at the pacing rates of 210, 180, and 150 beats per minute.

Hemodynamic variables and calculated volume data were analyzed using a repeated-measures ANOVA, and
Each mean value was compared using the Newman-Keuls multiple comparison test. A value of \( p < 0.05 \) was considered significant. Data are expressed as mean \( \pm \) SD.

**Results**

Figure 1 shows representative original tracings illustrating part of the protocol.

**Hemodynamic Changes**

Hemodynamic variables at rest, at 3 minutes of running with atrial pacing at 240 beats per minute, and 3 minutes after UL-FS 49 injection with HR maintained at 240 beats per minute by pacing are summarized in Table 1. The mean resting HR while standing on the treadmill was 123 beats per minute, somewhat higher than the basal condition, representing anticipation of exercise. Injection of the bradycardic drug during exercise while HR was maintained at 240 beats per minute caused no significant effect on any variables except that peak LV pressure was slightly but significantly lower at 6 minutes than at 3 minutes of exercise (Table 1). These findings indicate that UL-FS 49 acted on the sinus node but had no direct effect on myocardial contractility or early relaxation.

When HR was reduced by pacing to slower rates (Table 2), peak LV pressure was slightly but significantly decreased at each lower HR compared with that after UL-FS 49 at a rate of 240 beats per minute. Also, mean aortic pressure decreased significantly at HRs of 180 and 150 beats per minute compared with 240 beats per minute with UL-FS 49 (Table 2). LV end-diastolic pressure, end-diastolic volume, and end-systolic volume progressively and significantly increased after slowing the exercise HR (Table 2). Stroke volume significantly increased after slowing the HR compared with that at 240 beats per minute, but the EF was only slightly changed with alterations in the HR. \( T_{es} \) was significantly prolonged when the HR was slowed (Table 2).

**LV \( \frac{dp}{dt} \)**

During slowing of the HR, \( \frac{dp}{dt}_{max} \) progressively decreased significantly from 5,930 mm Hg/sec (HR, 240 beats per minute) to 4,087 mm Hg/sec (150 beats per minute) (Figure 2A). The percent change in LV \( \frac{dp}{dt}_{max} \) from a heart rate of 240 to 150 beats per minute was 31\%. These decreases in LV \( \frac{dp}{dt}_{max} \) were associated with increased preload, indicated by increased LV end-diastolic volume and end-diastolic pressure (Table 2).

Another isovolumic phase index of contractility, \( \frac{dp}{dt}_{max} \), showed similar changes (Figure 2B), although the percent changes were less compared with those of LV \( \frac{dp}{dt}_{max} \) (21\% versus 31\%).

Although LV \( \frac{dp}{dt}_{max} \) is not a preload-independent index of contractility, the decreases in \( \frac{dp}{dt}_{max} \) despite increases in LV end-diastolic volume strongly indicate that a decrease in contractility had occurred. Figure 3 shows an example of the relations between LV \( \frac{dp}{dt}_{max} \) and LV end-diastolic volume in one dog in which several IVC occlusions were successful. At 240 beats per minute, \( \frac{dp}{dt}_{max} \) is higher than at 150 beats per minute at any level of end-diastolic volume.

Figure 4 shows averaged data from all eight dogs of the relation between LV \( \frac{dp}{dt}_{max} \) and the normalized LV end-diastolic volumes (%EDV). Compared with the resting value, when the HR was maintained at 240 beats per minute, \( \frac{dp}{dt}_{max} \) was markedly increased at approximately the same %EDV; the relations with and without UL-FS 49 were identical. However, when the HR was progressively slowed, the points were shifted to the right, with \( \frac{dp}{dt}_{max} \) decreasing despite increasing.
TABLE 2. Effect of Heart Rate Change During Exercise on Hemodynamic Variables

<table>
<thead>
<tr>
<th></th>
<th>Pace 240</th>
<th>Pace 210</th>
<th>Pace 180</th>
<th>Pace 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>242±1.6</td>
<td>212±10.1</td>
<td>182±0.5</td>
<td>152±3.8</td>
</tr>
<tr>
<td>PLVP (mm Hg)</td>
<td>149.9±14.7</td>
<td>145.7±13.9*</td>
<td>142.6±13.8³</td>
<td>135.6±13.0²</td>
</tr>
<tr>
<td>ESP (mm Hg)</td>
<td>125.3±10.1</td>
<td>122.5±12.1</td>
<td>119.5±12.9</td>
<td>108.5±16.1²</td>
</tr>
<tr>
<td>EDP (mm Hg)</td>
<td>8.4±2.6</td>
<td>11.6±3.7</td>
<td>16.9±3.9⁴</td>
<td>21.4±5.5⁴</td>
</tr>
<tr>
<td>dp/dt max (mm Hg/sec)</td>
<td>5,930±1,279</td>
<td>5,304±1,175⁴</td>
<td>4,687±795⁹</td>
<td>4,087±634⁹</td>
</tr>
<tr>
<td>dp/dt min (mm Hg/sec)</td>
<td>4,266±773</td>
<td>4,064±733</td>
<td>3,800±769</td>
<td>3,229±628⁴</td>
</tr>
<tr>
<td>(dp/dt)dp/ΔP₀  (1/sec)</td>
<td>117.9±21.0</td>
<td>110.2±20.2*</td>
<td>101.6±15.1²</td>
<td>93.9±13.6³</td>
</tr>
<tr>
<td>Tₑ (msec)</td>
<td>129.4±8.4</td>
<td>139.1±8.5⁷</td>
<td>146.6±8.8³</td>
<td>157.1±8.1⁴</td>
</tr>
<tr>
<td>τ (msec)</td>
<td>14.3±1.6</td>
<td>14.9±4.7</td>
<td>16.7±4.0⁹</td>
<td>18.7±5.5⁴</td>
</tr>
<tr>
<td>EDV (ml)</td>
<td>68.5±41.5</td>
<td>73.8±43.3*</td>
<td>77.4±44.9³</td>
<td>80.6±46.9⁹</td>
</tr>
<tr>
<td>ESV (ml)</td>
<td>36.4±31.1</td>
<td>38.5±32.1*</td>
<td>40.2±32.3¹</td>
<td>40.2±31.5¹</td>
</tr>
<tr>
<td>Stroke volume</td>
<td>32.1±13.3</td>
<td>35.3±14.1*</td>
<td>37.2±15.1¹</td>
<td>40.4±17.5³</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>51.4±16.4</td>
<td>52.2±15.8</td>
<td>52.0±14.6</td>
<td>53.6±14.0⁰</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>124.4±14.3</td>
<td>120.0±5.3</td>
<td>115.3±4.5*</td>
<td>102.4±16.2²</td>
</tr>
</tbody>
</table>

n=8 dogs.

Pace 240, paced at 240 beats per minute during exercise with UL-FS 49; Pace 210, paced at 210 beats per minute; Pace 180, paced at 180 beats per minute; Pace 150, paced at 150 beats per minute.

PLVP, peak left ventricular (LV) pressure; ESP, end-systolic LV pressure; EDP, end-diastolic LV pressure; dp/dt max, maximum positive first derivative of LV pressure; dp/dt min, minimum negative first derivative of LV pressure; (dp/dt)dp/ΔP₀, dp/dt divided by developed pressure 40 mm Hg; Tₑ, time from end diastole to end systole; τ, time constant of monoexponential LV pressure decay; EDV, end-diastolic LV volume; ESV, end-systolic LV volume.

*p<0.05.

p<0.01 vs. Pace 240.

p<0.05.

p<0.01 vs. Pace 210.

p<0.05.

p<0.01 vs. Pace 180.

%EDV, indicating a decrease in myocardial contractility as the HR was reduced.

End-Systolic Pressure–Volume Relations

To examine a load-independent index of contractility, end-systolic pressure–volume data were analyzed. The averaged end-systolic pressure–volume points at the operating end-systolic pressures of all eight dogs are summarized in Figure 5. Compared with the value at 240 beats per minute, %ESV was significantly larger at 210 beats per minute (p<0.05) as well as at 180 and 150 beats per minute (both p<0.01). In addition, the end-systolic pressure was somewhat lower after decreasing the HR, although it was significantly reduced only at 150 beats per minute (p<0.01). Although slopes could not be calculated, these data suggest a shift of the end-systolic pressure–volume relation rightward and downward, indicating a decrease in myocardial inotropic state. Figure 6 shows an example of pressure–volume loops and calculated end-systolic pressure–volume relations in a single dog obtained during exercise at HRs of 240 and 150 beats per minute using transient IVC occlusions. The end-systolic pressure–volume points are shifted to the right and downward, with a decrease in the slope of the relation after slowing the HR.

Early Diastolic Relaxation

The early diastolic relaxation index, τ, increased significantly after decreasing the HR from 14.3 msec (at 240 beats per minute) to 16.7 msec (at 180 beats per minute) to 18.7 (at 150 beats per minute) (Table 2).

Discussion

Under resting conditions, changes in the HR play a relatively small role in the regulation of cardiac output, but during exercise, the HR increase is essential for producing a markedly enhanced cardiac output, because stroke volume can rise only modestly. However, markedly increased myocardial contractility, related to reflex norepinephrine release and circulating catecholamines, is considered to be highly important in lowering the end-systolic volume, improving the velocity of ventricular ejection as well as ventricular relaxation and filling.

The relative contribution of the HR increase per se in these responses is unknown, and to what extent the force–frequency effect during exercise might influence myocardial contractility has remained an important unanswered question. In physiological settings, augmented sympathetic tone always induces both positive inotropic and chronotropic effects, so that HR changes are always coupled with contractility changes. Therefore, we sought to separate the HR effect by using a bradycardic drug that has no known β-adrenergic–blocking properties. As HR was slowed during exercise, we demonstrated a progressive decrease in isovolumetric phase contractility indexes (LV dp/dt max and (dp/dt)dp/ΔP₀). The directional change in these indexes should be a reliable indicator of a negative contractility effect because they were accompanied by increased preload, which alone would increase them. Decreased aortic pressure may reduce these indexes, but mean aortic pressure fell only slightly.

The slope of the relation between LV dp/dt max and LV end-diastolic volume also has been shown to provide a highly sensitive, load-independent measure of myocardial contractility. Although we were not able to consistently alter the preload during exercise to produce linear relations of this type (Figure 3), the shift downward and to the right of the points relating LV
entirely clear. Using aequorin in isolated cardiac muscle, Morgan and Blinks demonstrated that increased HR caused increased Ca$^{2+}$ release and also abbreviated the duration of the calcium transient. Thus, the enhancement of contractility by cardiac frequency may be mediated in part by enhanced Ca$^{2+}$ reuptake and release by the sarcoplasmic reticulum as well as by increased transsarcolemmal Ca$^{2+}$ influx caused by the increased number of action potentials and a lag in Na$^+-$Ca$^{2+}$ exchange. It seems likely that the observed increased responsiveness of contractility to HR during exercise is related to enhanced β-adrenergic stimulation. Increased Ca$^{2+}$ influx is known to result from phosphorylation of the calcium channel by adrenergic stimulation, and the inotropic force–frequency effect would therefore be more pronounced during exercise than at rest. The marked changes observed during exercise contrast with those in some studies at rest, and it is possible that exercise-induced increases in adrenergic tone and catecholamine levels modify not only the calcium transient but also the calcium sensitivity of the contractile system when HR is altered. That adrenergic stimulation alone with dobutamine in the absence of exercise also can cause a marked dose-dependent enhancement of the force–frequency effect on myocardial contractility has been demonstrated in the accompanying study from this laboratory.

**Mechanism of UL-FS 49 Action**

The drug UL-FS 49 is a benzazepine derivative produced by specific modifications of the calcium channel blocker verapamil. The compound is within a class of drugs considered to be relatively specific sinus node inhibitors, the so-called specific bradycardic agents that have different properties from standard calcium channel blockers.

The mechanism of action of UL-FS 49 in slowing the sinoatrial (SA) node is not yet completely understood.
Several currents, including two types of calcium currents ($I_{Ca}$), the decaying (deactivation) $K^+$ current ($I_K$) and the pacemaker current ($I_P$), may play a role in normal diastolic depolarization. The T-type calcium current has a low threshold ($=-50$ mV), is blocked by nickel, is insensitive to catecholamines, and appears to participate in the latter half of slow diastolic depolarization of SA nodal cells. The L-type calcium current is carried by a different channel; it is sensitive to calcium channel blockers (e.g., nifedipine and D600), increases its rate of diastolic depolarization with catecholamines, and appears to provide a larger contribution to phase 4 than the T-type channel as well as being involved in the upstroke of the action potential. Controversy exists concerning the physiological role in SA nodal cells of the pacemaker current described in Purkinje cells ($I_P$). In SA nodal cells, such a current can be recorded during hyperpolarization ($V_h$) (generally to $=-70$ to $-90$ mV), and its decay may contribute to phase 4, particularly in multicell SA node preparations, including cells adjacent to the central primary pacemaker cells. However, the sensitivity of phase 4 depolarization to catecholamines has been reported to be preserved when this current is blocked by Cs$^+$.

UL-FS 49 has been shown to reduce the pacemaker current in Purkinje cells in a use-dependent and frequency-dependent manner, and there is indirect evidence (e.g., the finding that sinus slowing caused by UL-FS 49 is diminished by high $K^+$ concentration, whereas the opposite effect of high $K^+$ occurs with verapamil) that the pacemaker rather than calcium currents may be affected by UL-FS 49. However, in recent studies in isolated SA nodal cells, UL-FS 49 continued to have a marked slowing effect when $V_h$ was blocked by Cs$^+$ and UL-FS 49 was considered to exert its bradycardic effect primarily by use-dependent and frequency-dependent block of the L-type calcium channel.

The question of whether UL-FS 49 might have a negative inotropic action under some circumstances and thereby directly contribute to the negative frequency effect observed in the LV during exercise in the present study should be considered. $I_{Ca}$ has not been described in ventricular cells, but UL-FS 49 might affect $I_{Ca}$ in the ventricles. However, Doerr and Trautwein found that a dose of UL-FS 49 that almost eliminated $I_{Ca}$ in SA nodal cells caused only a minor (11%) reduction of $I_{Ca}$ in guinea pig ventricles; this difference was due to voltage dependence of the block produced by UL-FS 49, such that it was not apparent at high resting (holding) potentials in ventricular cells and became evident only at holding potentials between $-40$ and $-60$ mV; this voltage-dependent effect appears to explain the observed lack of a negative inotropic effect of

**Figure 4.** Plot shows relations between left ventricular maximum dP/dt and percent diastolic volumes (%EDV) in all eight dogs (%EDV normalized by end-diastolic volume under resting conditions). Rest, resting conditions; ULFS(−), without UL-FS 49 and paced at 240 beats per minute; ULFS(+), with UL-FS 49 paced at 240, 210, 180, and 150 beats per minute during exercise. HR, heart rate. *p<0.01 vs. ULFS paced at 240 beats per minute for maximum dP/dt.

**Figure 5.** Plot shows changes in end-systolic pressure (ESP) and end-systolic volume caused by heart rate (HR) reductions during exercise, averaged for all eight dogs. End-systolic pressure–volume (ESP–V) points are shifted to the right and downward by reducing the HR. Dashed line represents the averaged ESP–V relation under resting conditions. %ESV, end-systolic volume normalized by end-diastolic volume at rest.

**Figure 6.** End-systolic pressure–volume loops in a single dog during inferior vena caval occlusions obtained during exercise at paced heart rate (HR) of 240 beats per minute (dashed line) and 150 beats per minute (solid line). Corresponding linear end-systolic pressure–volume relations are also shown. At the lower HR, the end-systolic points are shifted downward and rightward, and a change in the slope of end-systolic pressure–volume relation is evident. LV, left ventricular; LVP, left ventricular pressure.
UL-FS 49 on the ventricles and its relative specificity for the SA node. The frequency-dependent block by UL-FS 49 of the L-type calcium channel indicated that the bradycardic effect of the drug is more marked at higher frequencies; therefore, it seems likely that any direct negative inotropic effect of the drug on the ventricles would not be enhanced but rather reduced by slowing the frequency, as occurred in the present experiments. Moreover, no direct inotropic effect was observed when UL-FS 49 was given at a constant rapid paced rate during exercise. However, although unlikely, some effect of UL-FS 49 on \( L_c \) in the ventricles to cause an enhanced negative inotropic effect during slowing of the HR in the presence of the catecholamine stimulation cannot be completely excluded.

**Limitations**

Several potential limitations of this investigation deserve mention. First, the calculation of LV volume by using dimensions measured by the ultrasonic crystals may have introduced an error, particularly in absolute volumes. Nevertheless, the relative changes should be reliable, provided that important shape changes do not occur, as seems likely in this study in normal ventricles. We used a specific bradycardic drug, UL-FS 49, to reduce the intrinsic HR, and, as discussed above, the possibility of a rate-related drug effect on the calcium transient cannot be entirely excluded. Also, the role of potential reflex effects cannot be assessed in this study; a drop in the cardiac output probably occurred with slowing of the HR during exercise and probably contributed to the reductions in arterial pressure noted (because of potential errors in absolute volumes, cardiac outputs are not presented but, for example, calculated average cardiac output at HRs of 240 and 150 beats per minute during exercise are 7,744 and 6,080 ml/min, respectively). This pressure decrease would tend to enhance reflex positive inotropic effects caused by arterial baroreceptor activation, although because diastolic ventricular pressures increased, opposite effects caused by activation of low-pressure baroreceptors might have occurred. Finally, this study was performed in the normal heart, but it should be noted that different responses of the force–frequency effect can be observed when applied in failing myocardium.

We conclude that heart rate per se appears to have an important effect on myocardial contractility and early relaxation during exercise, with reductions in contractility and early relaxation rate when heart rate is slowed. Thus, during exercise, the force–frequency effect appears to have an important role in regulating myocardial inotropic state in the normal heart.

**Acknowledgments**

We thank Margaret R. Hill, Denice Jio, and Abdel Wahhab for their technical assistance in performing these studies. In addition, we express our gratitude to Mark Miller for his computer and electronics support and Elizabeth Gilpin for assistance in statistical analyses. We are also grateful to Penny Ganong, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn., for supplying the UL-FS 49.

**References**


38. Endo M: Calcium release from the sarcoplasmic reticulum. Physiol Rev 1977;57:71–108


44. Tytgat J, Nilius B, Vereecke J, Carmeliet E: The T-type Ca channel in guinea pig ventricular myocytes is insensitive to isoproterenol. Pfugers Arch 1988;414:704–706

45. Doerr T, Denger R, Trautwein W: Calcium currents in single SA nodal cells of the rabbit heart studied with action potential clamp. Pfugers Arch 1989;413:599–603


Influence of the force-frequency relation on left ventricular function during exercise in conscious dogs.
T Miura, S Miyazaki, B D Guth, M Kambayashi and J Ross, Jr

_Circulation_. 1992;86:563-571
doi: 10.1161/01.CIR.86.2.563

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/86/2/563

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ 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_ is online at:
http://circ.ahajournals.org//subscriptions/