Extent of Regulation of the Heart's Contractile State in the Conscious Dog by Alteration in the Frequency of Contraction

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

From the Departments of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, Massachusetts 02115, and the University of California, San Diego, California 92037; and the Department of Cardiology, Children's Hospital, Boston, Massachusetts 02115

ABSTRACT The effects of alterations in the frequency of contraction over the range from 94 to 220/min on left ventricular pressure, diameter, and dP/dt were studied in 10 dogs instrumented with ultrasonic diameter gauges and miniature pressure gauges. The same dogs were studied on separate days in the conscious state, after general anesthesia with pentobarbital Na, 30 mg/kg, and in the conscious state after pre-treatment with propranolol, 3 mg/kg. End diastolic diameter was maintained constant during alterations in frequency by infusing saline intravenously. The maximum increases in peak dP/dt and dP/dt/P in the conscious state were 14 and 10%, respectively. After anesthesia, raising the frequency of contraction from 122 to 220/min caused maximum increases in peak dP/dt and dP/dt/P of 36 and 30%, respectively. In the conscious state after cardiac depression by propranolol, the maximum increases in peak dP/dt and dP/dt/P were 23 and 23%, respectively. Thus, increasing the frequency of contraction of the normal heart of the conscious dog causes only a slight inotropic effect, but this effect is significantly greater in the presence of myocardial depression produced by anesthesia with pentobarbital Na or in the conscious animal after a myocardial-depressing dose of propranolol.

INTRODUCTION

Since the classical studies of Bowditch (1) and Woodworth (2), numerous investigators have documented the positive inotropic effect of increasing the frequency of contraction in excised myocardial strips (3-5), isolated hearts (6), and the in situ hearts of anesthetized preparations (7-11). Although it has been assumed that the positive inotropic effect of increasing frequency is applicable to the intact, conscious state, there are relatively few observations relative to this point. Studies in conscious patients after surgical correction of various cardiac lesions (12, 13) and conscious patients with angiographically normal coronary arteries (14) have indicated a substantial inotropic effect associated with tachycardia, whereas other studies have reported negligible (14) to large (15) increases in contractility in patients with coronary artery disease. On the other hand, no inotropic effect was associated with increasing the frequency of cardiac contraction in the normal conscious dog (16). Thus, the applicability of this important mechanism of adjustment of myocardial performance to the normal heart of the conscious organism is not clear.

Accordingly, the present investigation was conducted in order to determine the extent to which alterations in the frequency of contraction may regulate contractility in the normal conscious dog. A key aspect of this investigation was to compare the inotropic effect of tachycardia in dogs studied in the conscious state with that observed in the same dogs after the myocardium had been depressed with either an anesthetizing dose...
LV DIAMETER

mm

LV PRESSURE

mmHg

PEAK

dP/dt

mmHg/s

HEART RATE - beats/min

FIGURE 1 Mean values (±SEM) for measurements of left ventricular (LV) dynamics during the steady-state period over the range of frequencies of contractions studied. End diastolic diameter was not maintained constant as frequency was increased.

of pentobarbital or a myocardial-depressing dose of propranolol. Thus, we attempted to ascertain whether the prominent inotropic effects of increasing frequency of contraction in isolated and anesthetized preparations might be due in part to the presence of myocardial depression.

METHODS

10 mongrel dogs, weighing between 24 and 31 kg, were anesthetized with pentobarbital Na, 30 mg/kg, and underwent a left thoracotomy. Ultrasonic diameter crystals with lenses were sutured to the epicardium of the anterior and posterior walls of the left ventricle (LV) in eight dogs and placed in opposition on the endocardium of the LV through small stab wounds on the anterior and posterior walls in two dogs. In all dogs, miniature pressure gauges were inserted into the left ventricular cavity through an apical stab wound and stimulating electrodes were sutured to the left atrium.

The experiments were conducted 2–6 wk after operation, when the dogs were vigorous, healthy, and apparently fully recovered from the operation. While the conscious, unanesthetized animals reclined quietly, continuous recordings of LV pressure (P) and diameter (D), the time rate of change of pressure (dP/dt), the time rate of change of diameter (dD/dt) and heart rate were obtained during the control period and as heart rate was raised incrementally by atrial stimulation. The initial frequency of atrial stimulation was the lowest rate which permitted override of the sinus node; the initial rate was 8–12 pulses/min greater than the normal sinus rate. The pacemaker frequency was raised in increments of 30 stimuli/min up to 180 stimuli/min and then raised by increments of 20 stimuli/min until the onset of mechanical alternans was observed. Because of the tachycardia associated with anesthesia, the initial heart rate was higher in this state. The various parameters were compared during the steady-state period, attained 30–45 s after each change in heart rate. In some experiments, in order to permit a comparison of the parameters reflecting the contractile state under the condition of a constant end diastolic diameter at each heart rate, end diastolic diameter was maintained constant by rapidly infusing saline through a catheter placed percutaneously into a peripheral vein. The volume of saline infused during these experiments ranged from 250 to 1250 ml; this infusion caused the peripheral venous hematocrit to decline by an average of 7%.

The eight dogs in which epicardial diameter crystals had been implanted, were also studied on a separate day after general anesthesia had been induced with pentobarbital Na, 30 mg/kg. In these experiments respiration was controlled with a Harvard Apparatus pump which prevented hypoxia or acidosis during anesthesia. Seven of the eight dogs were studied also in the conscious state after administration of a large dose of propranolol, 3.0 mg/kg. This dose of propranolol is considerably in excess of that required to produce blockade of beta adrenergic receptors and exerts a direct depressant effect on the myocardium (17, 18). In both of these latter circumstances, end diastolic diameter was maintained constant by saline infusion as heart rate was increased.

The LV pressure gauges, described in detail previously (19), were calibrated repeatedly in vivo against a calibrated Statham P-23Db strain gauge manometer. Atrial pacing was produced by a commercial fixed rate electronic pacemaker. A sonic transit time diameter gauge was used to measure left ventricular diameter, the principle of which has been described previously (20, 21). The device measures the transit time of sound waves emitted from one piezoelectric crystal to another sutured to the opposing surface of the left ventricle. Since the sonic signal is known to travel through the left ventricle at approximately the speed of sound in water, 1.5 X 10^8 mm/s, the transit time of the signal at any instant indicates the instantaneous distance between the crystals on the anterior and posterior surfaces of the left ventricle and thus the diameter of the left ventricle. A voltage proportional to transit time is recorded and calibrated in terms of crystal separation. The transit time was calibrated by substituting signals of known time duration from a pulse generator which was referenced to a quartz crystal controlled oscillator frequency. During experiments the received ultrasonic signal was continuously monitored on an oscilloscope. By this method inaccuracies in instrument triggering, which are readily apparent, can be detected. If the instrument failed to track the separation of the transducer crystals reliably, due to inadequate signal to noise ratio or inadequate opposition of transducers, the animal was sacrificed and not used for experimentation.

A cardiotachometer triggered by the electrical signal from the pressure pulse recorded a precise measurement of instantaneous heart rate. Continuous records of dP/dt and dD/dt were derived from the LVP and LVD signals using Philbrick-Nexus® operational amplifiers constructed as differentiators, possessing frequency responses of 60 and 30 Hz, respectively. A triangular wave signal with known slope was substituted for LVP and LVD to calibrate the dP/dt and dD/dt tracings. Data were recorded on a direct writing oscillograph at paper speeds of 100 mm/s and recorded on a multichannel tape recorder. Data were averaged and compared statistically using the paired "t" test (22).

1 Abbreviations used in this paper: dP/dt, the time rate of the change of pressure; dD/dt, the time rate of change of diameter; EDD, end diastolic diameter; EDP, end diastolic pressure; ESD, end systolic diameter; LV left ventricle.
The contractile state was assessed by determining \( \frac{dP}{dt} \) and the quotient of \( \frac{dP}{dt} \) and developed LVP, \( \frac{dP}{dt} \frac{P}{P} \) at similar levels of isovolumic LVP during the steady-state period at each heart rate. This technique for evaluation of the myocardial contractile state has been demonstrated to reflect accurately alterations in the contractile state and to be relatively insensitive to variations in preload and after-load (23-28).

RESULTS

Normal conscious dogs. As frequency of contraction was increased from 94±2 to 220 beats/min, peak systolic pressure remained nearly constant at the control value of 128±9 mm Hg, whereas end diastolic pressure decreased slightly from 8±1 mm Hg, reaching a minimum 5±1 mm Hg at a frequency of 180 beats/min; it then showed little change as frequency was increased to 220 beats/min (Figs. 1, 2). End systolic diameter and end diastolic diameter also decreased (\( P < 0.01 \)) progressively below the control values of 57.7±2.0 and 62.5±2.1 mm, respectively, reaching minima of 56.9±1.9 and 60.1±2.0 mm, respectively, at 220 beats/min. With increasing frequency, peak \( \frac{dP}{dt} \) decreased slightly; at 220/min it had decreased by 6±4% below the control value of 3620±64 mm Hg/s (NS). 7

When external end diastolic diameter (EDD) was maintained constant at 62.6±1.5 mm by saline infusion, as frequency was increased from 94±4 to 220 beats/min in eight conscious dogs, external end systolic diameter (ESD) increased progressively above the control value of 56.5±2.4 mm (Figs. 2) to a maximum of 58.7±2.3 mm (\( P < 0.01 \)) at 220 beats/min, reflecting a slight decrease in systolic excursion per cardiac cycle. Systolic pressure (peak) rose slightly above the control value of 122±7 mm Hg to a maximum of 129±9 mm Hg (NS) at 220 beats/min, while end diastolic pressure (EDP) remained nearly constant at 8±1 mm Hg.

Over the above range of frequencies peak \( \frac{dP}{dt} \) and \( \frac{dP}{dt} \frac{P}{P} \) increased progressively; peak \( \frac{dP}{dt} \) increased by a maximum of 14±3% above the control value of 3620±137 mm Hg/s (\( P < 0.01 \)) and \( \left( \frac{dP}{dt} \frac{P}{P} \right) \) increased by a maximum of 10±2% above the control value of 43±2 s\(^{-1} \) (\( P < 0.01 \)).

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7 Not statistically significant (\( P > 0.05 \)).
In the two dogs in which internal dimensions were measured, increasing heart rate in the conscious state produced alterations in LV dynamics and internal diameters similar to those observed in the animals in which external diameters were evaluated. When internal end diastolic diameter was maintained constant, as heart rate increased, end systolic diameter increased whereas peak dP/dt and dP/dt/P changed only slightly (Table I).

![Experimental records depicting the alterations in the measurements of LV dynamics at progressively higher frequencies in the same dog as in Fig. 2 but in this instance studied in the conscious state after treatment with a myocardial-depressing dose of propranolol, 3 mg/kg.](image)

**Figure 4**

**Table I**

Effects of Increasing Cardiac Frequency on Left Ventricular Dynamics and Internal Dimensions*

| HR | LVP (internal) | LVD (internal) | Peak dP/dt | dP/dt/P | dP/dt/P
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Beats/min</td>
<td>mm Hg</td>
<td>mm Hg</td>
<td>mm</td>
<td>mm</td>
<td>mm Hg/s</td>
</tr>
<tr>
<td>Dog 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>110</td>
<td>4</td>
<td>37.1</td>
<td>29.1</td>
<td>3000</td>
</tr>
<tr>
<td>120</td>
<td>110</td>
<td>3</td>
<td>37.1</td>
<td>28.5</td>
<td>3000</td>
</tr>
<tr>
<td>150</td>
<td>105</td>
<td>2</td>
<td>36.7</td>
<td>29.1</td>
<td>2850</td>
</tr>
<tr>
<td>180</td>
<td>110</td>
<td>3</td>
<td>36.3</td>
<td>29.7</td>
<td>2850</td>
</tr>
<tr>
<td>200</td>
<td>100</td>
<td>3</td>
<td>36.7</td>
<td>30.9</td>
<td>2850</td>
</tr>
<tr>
<td>220</td>
<td>100</td>
<td>4</td>
<td>36.7</td>
<td>31.4</td>
<td>2850</td>
</tr>
</tbody>
</table>

| Dog 2 | | | | | |
| 100 | 114 | 6 | 31.0 | 23.8 | 3750 | 40.0 |
| 120 | 112 | 4 | 30.6 | 24.8 | 4200 | 43.8 |
| 150 | 116 | 4 | 30.6 | 25.2 | 3750 | 39.2 |
| 180 | 120 | 5 | 31.4 | 26.0 | 3900 | 41.0 |
| 220 | 120 | 6 | 31.2 | 25.6 | 4050 | 43.1 |

* End diastolic diameter constant.

In the two dogs in which internal dimensions were measured, increasing heart rate in the conscious state produced alterations in LV dynamics and internal diameters similar to those observed in the animals in which external diameters were evaluated. When internal end diastolic diameter was maintained constant, as heart rate increased, end systolic diameter increased whereas peak dP/dt and dP/dt/P changed only slightly (Table I).

**Anesthetized dogs.** After pentobarbital Na, 30 mg/kg, control heart rate rose to 122±7 beats/min but peak dP/dt and dP/dt/P were substantially reduced to 2730±140 mm Hg/s and 34±2 s⁻¹, respectively, values significantly lower (P < 0.01) than those observed in the conscious state. When EDD was maintained constant as heart rate was increased, ESD increased progressively, resulting in a progressive decrease in systolic excursion per cardiac cycle (Figs. 3), although pressures in the LV remained nearly constant. Increasing cardiac frequency to 220 beats/min caused substantially greater increases in those variables reflecting myocardial contractility than those observed in the conscious state; at a frequency of 220/min dP/dt/P and peak dP/dt had increased by 36±7% (P < 0.01) and 30±7% (P < 0.01), respectively. Both the relative and absolute increases in peak dP/dt and dP/dt/P, per unit increase in heart rate, were significantly greater than those observed in the conscious state (P < 0.01), but even at the highest cardiac frequency, the peak value each of these variables attained was lower than observed in the conscious state at the initial heart rate (Table II).

**Propranolol-treated dogs.** After propranolol, 3.0 mg/kg, the initial heart rate was 90±6 beats/min and peak dP/dt and dP/dt/P were again substantially reduced to 2620±210 mm Hg/s and 35±3 s⁻¹, values significantly lower (P < 0.01) than those observed in conscious dogs before propranolol. When heart rate was increased and EDD was maintained constant, ESD
increased progressively, resulting in a progressive reduction in the systolic excursion per cardiac cycle (Figs. 4). Peak systolic pressure increased slightly, from 129±9 to 138±10 mm Hg (NS), as the frequency of contraction was increased to 150/min and then remained unaltered at higher rates; end diastolic pressure did not change significantly over the entire range of frequencies. As frequency was increased to 220 beats/min, substantial increments occurred in each of the parameters used to characterize the LV contractile state; peak dP/dt and dP/dt/P reached maximum levels of 23±3% (P < 0.01) and 23±4% (P < 0.01) above control at 220 beats/min. Both the relative and absolute increases in peak dP/dt and dP/dt/P per unit increase in heart rate were significantly greater than those observed in the conscious state (P < 0.01), but the maximum level attained by each of these variables at the highest cardiac frequency was less than that observed in the conscious state at the initial heart rate (Table II).

**DISCUSSION**

In the present study, progressively increasing the frequency of atrial stimulation in the normal conscious dog caused progressive decreases in LV end diastolic and end systolic diameters and systolic excursion per cardiac cycle. Under these circumstances LV dP/dt decreased slightly at higher heart rates, but this finding is difficult to interpret since ventricular dimensions also declined. When end diastolic diameter was maintained constant during the rise in heart rate, only a slight inotropic effect was observed with increasing the frequency of contraction. However, in the same dogs studied in the anesthetized state, the maximum

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**Table II**

**Inotropic Effects of Increasing Heart Rate**

<table>
<thead>
<tr>
<th>Peak systolic pressure, mm Hg</th>
<th>90–100 beats/min</th>
<th>120 beats/min</th>
<th>150 beats/min</th>
<th>180 beats/min</th>
<th>200 beats/min</th>
<th>220 beats/min</th>
<th>Δ/100 beats</th>
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</thead>
<tbody>
<tr>
<td>Conscious</td>
<td>123±7(SEM)</td>
<td>120±6</td>
<td>123±8</td>
<td>126±9</td>
<td>128±9</td>
<td>129±9</td>
<td>5±2</td>
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<td>Anesthetized</td>
<td>125±9</td>
<td>129±9</td>
<td>128±9</td>
<td>128±9</td>
<td>127±9</td>
<td>2±1</td>
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</tr>
<tr>
<td>Propranolol</td>
<td>129±9</td>
<td>133±10</td>
<td>136±10</td>
<td>138±10</td>
<td>139±10</td>
<td>9±3</td>
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</table>

<table>
<thead>
<tr>
<th>End diastolic pressure, mm Hg</th>
<th>8±1</th>
<th>7±1</th>
<th>7±1</th>
<th>7±1</th>
<th>7±1</th>
<th>1±1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conscious</td>
<td>56±2</td>
<td>56±2</td>
<td>57±2</td>
<td>57±1</td>
<td>57±1</td>
<td>58±2</td>
</tr>
<tr>
<td>Anesthetized</td>
<td>56±1</td>
<td>57±1</td>
<td>57±1</td>
<td>57±1</td>
<td>57±1</td>
<td>57±1</td>
</tr>
<tr>
<td>Propranolol</td>
<td>62±1</td>
<td>62±1</td>
<td>62±1</td>
<td>62±1</td>
<td>63±1</td>
<td>1±1</td>
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<table>
<thead>
<tr>
<th>End systolic diameter, mm</th>
<th>62±2</th>
<th>62±1</th>
<th>62±2</th>
<th>62±2</th>
<th>62±2</th>
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</tr>
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<tbody>
<tr>
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<td>60±1</td>
<td>60±1</td>
<td>60±1</td>
<td>60±1</td>
<td>60±1</td>
<td>60±1</td>
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<td>66±1</td>
<td>66±1</td>
<td>66±1</td>
<td>60±1</td>
</tr>
<tr>
<td>Propranolol</td>
<td>66±1</td>
<td>66±1</td>
<td>66±1</td>
<td>66±1</td>
<td>66±1</td>
<td>60±1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Peak dP/dt, mm Hg/s</th>
<th>3600±±130</th>
<th>3660±160</th>
<th>3760±200</th>
<th>3860±240</th>
<th>3980±250</th>
<th>407±280</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conscious</td>
<td>2730±140</td>
<td>2930±180</td>
<td>3250±200</td>
<td>3540±280</td>
<td>3570±290</td>
<td>840±40§</td>
</tr>
<tr>
<td>Anesthetized</td>
<td>2610±200</td>
<td>2740±220</td>
<td>2910±210</td>
<td>3030±230</td>
<td>3140±240</td>
<td>3210±270</td>
</tr>
<tr>
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<td>2910±210</td>
<td>3030±230</td>
<td>3140±240</td>
<td>3210±270</td>
<td>530±30§</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>dP/dt per P, s⁻¹</th>
<th>43±2</th>
<th>43±2</th>
<th>44±2</th>
<th>45±2</th>
<th>47±2</th>
<th>47±3</th>
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<tbody>
<tr>
<td>Conscious</td>
<td>34±2</td>
<td>37±3</td>
<td>42±3</td>
<td>46±4</td>
<td>47±4</td>
<td>13±1*§</td>
</tr>
<tr>
<td>Anesthetized</td>
<td>35±3</td>
<td>38±3</td>
<td>40±3</td>
<td>45±4</td>
<td>46±3</td>
<td>10±1*§</td>
</tr>
</tbody>
</table>

* Mean change per 100 beat increase in heart rate in either anesthetized or propranolol-treated state significantly greater than in the conscious state, P < 0.01.
† Mean change per 100 beat increase in heart rate in either anesthetized or propranolol-treated state significantly greater than in the conscious state, P < 0.05.
§ Mean change from control per 100 beat increase in heart rate in any state significant, P < 0.01.
|| Mean change from control per 100 beat increase in heart rate in any state not significant.

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The interval-force relationship is influenced by a number of factors, including temperature, duration of isolation of the preparation, various drugs, ionic environment, and most important to the present study, the existing intensity of the contractile state (29). The latter modifying condition is exemplified by the attenuation of the interval-force relationship in isolated preparations of ventricular myocardium in which contractility has been increased by cardiac glycosides (34) or the provision of a bathing solution of high ionic calcium content (30, 35); and the amplification of this relationship in preparations of heart muscle depressed by prolonged isolation in physiological salt solution (5, 29, 34, 36, 37). In this regard, in the present study general anesthesia produced by pentobarbital was associated with a substantial depression of the contractile state and under these circumstances increasing the frequency of contraction exerted an effect of the magnitude observed in isolated preparations. The maximum increases in peak $dP/dt$ and $dP/dt/P$ were nearly threefold greater than those produced in the conscious state. When these increases were compared statistically over similar ranges of tachycardia (100 beats/min increments), the augmentation of peak $dP/dt$, and $dP/dt/P$ were greater ($P < 0.01$) in the anesthetized state than in the conscious state. Positive inotropic effects of this magnitude have also been observed by other investigators (8–11) when the frequency of contraction of the intact hearts of anesthetized preparations was increased over the same range of frequencies as in the present study. In these previous studies, the control levels of peak $dP/dt$ in anesthetized dogs were considerably less than those measured in the conscious animals in the present study, suggesting that the ventricular myocardium in the animals in these earlier studies was considerably depressed by the anesthetic agent. Myocardial depression by barbiturates and other anesthetics (38–41) has been well documented. Moreover, evidence suggests that barbiturates inhibit calcium uptake by the sarcoplasmic reticulum (42), thus causing a depression in intracellular calcium ion stores. Thus, the interval-force relationship in the ventricular myocardium of anesthetized preparations appears to be exaggerated by a depression in the base-line intensity of the contractile state by the anesthetizing agent. This depression may be associated with decreases in intracellular calcium ion, an effect which would amplify the effects of frequency of contraction on the intensity of the contractile state (29, 30, 35).

In order to examine this hypothesis further, the intensity of the contractile state was also depressed by a large dose of propranolol. Propranolol at the dose employed (3 mg/kg) decreases ventricular contractility both by eliminating sympathetic stimulation of the heart and also by a direct depressing action on the myocardium (17, 18). Propranolol has also been shown to interfere directly with a mechanism facilitating transfer of calcium ion into the myocardial cell (43) and this agent may by this mechanism also lower intracellular calcium stores. In these experiments, the level of the contractile state was depressed and the inotropic effects of increasing the frequency of contraction were again considerably greater than observed in
the same dogs in the conscious state before the administration of propranolol. Pacing-induced increases in peak $dP/dt$ and $dP/dt/P$ were greater ($P < 0.01$) after propranolol than in the conscious state without propranolol. This observation supports the major conclusion of the present study, namely that the prominent inotropic effects of increasing frequency of contraction in isolated cardiac muscle and the myocardium of anesthetized animals is characteristic of the depressed myocardium; however, increasing the frequency of contraction is a relatively weak inotropic mechanism and apparently of little importance in the regulation of contractility of the normal heart of conscious animals.

Since atrial pacing was employed to alter heart rate, abnormal ventricular activation and its consequent effect on ventricular contractility (44) during pacing is unlikely. In addition, increasing cardiac frequency did not significantly decrease diastolic distensibility over the range of heart rates employed under these experimental conditions, since heart rate increases in the presence of constant end diastolic diameter did not alter end diastolic pressure; hence alterations in distensibility did not prevent the elicitation of an inotropic effect.

In conclusion, this study indicates that increasing cardiac frequency exerts only a small inotropic effect on the normal hearts of conscious animals. This inotropic effect per unit increase in heart rate is severalfold greater in the same heart after myocardial depression induced by pentobarbital anaesthesia or a large dose of propranolol. Therefore, this study indicates that although the classical Bowditch Staircase is observed with increasing heart rate in the depressed myocardium, it plays only a minor role in the control of contractility in the normal heart.

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