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

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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 pretreatment 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.

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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

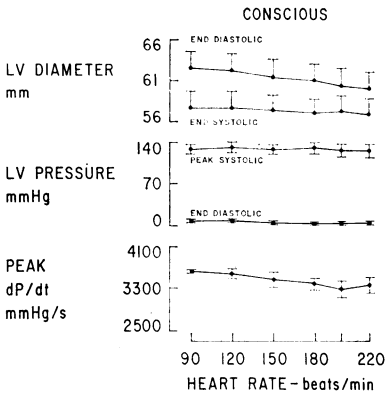

FIGURE 1 Mean values (±SEM) for measurements of left ventricular (LV) dynamics during the steady-state period over the range of frequencies of contractions studied. End diastolic diameter was not maintained constant as frequency was increased.

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)[1] 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, unsedated 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 overdrive 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[2] 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,[3] described in detail previously (19), were calibrated repeatedly in vivo against a calibrated Statham P-23Db strain gauge manometer.[4] Atrial pacing was produced by a commercial fixed rate electronic pacemaker.[5] 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, 1.5×10^6 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 provided 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[6] 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.

[2] Harvard Apparatus Co., Inc., Millis, Mass.

[3] Konigsberg P_{22}, Konigsberg Instruments, Inc., Pasadena, Calif.

[4] Statham Instruments, Inc., Oxnard, Calif.

[5] Medtronic, Inc., Minneapolis, Minn.

[6] Philbrick-Nexus Research, Boston, Mass.

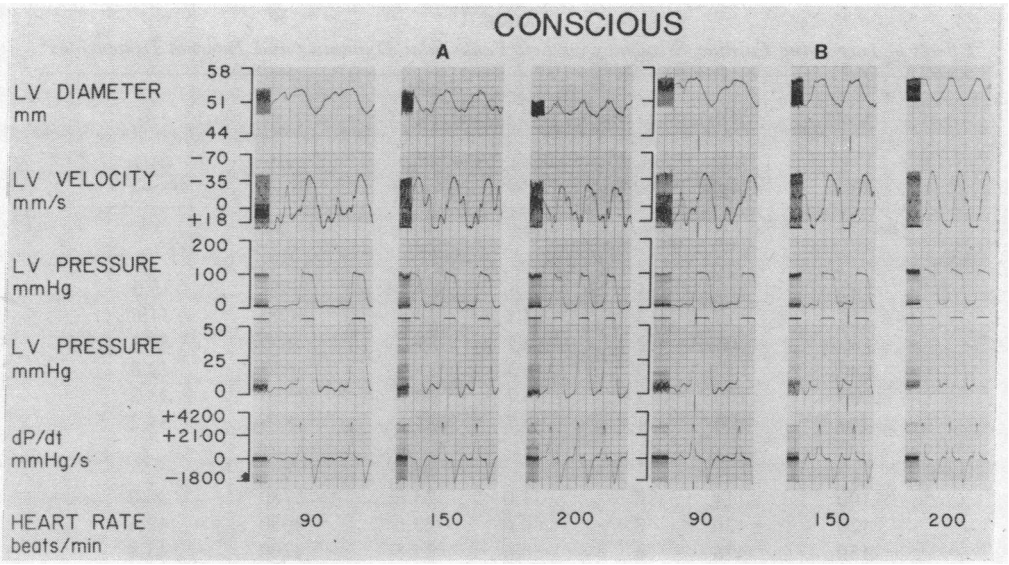

FIGURE 2 Experimental records depicting the alterations in the measurements of LV dynamics at progressively higher frequencies of contraction in the same dog when end diastolic diameter was permitted to decrease at higher frequencies (A) and when it was maintained constant (B).

The contractile state was assessed by determining dP/dt and the quotient of dP/dt and developed LVP, (dP/dt per 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 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 dP/dt and $dP/dt/P$ increased progressively; peak dP/dt increased by a maximum of 14±3% above the control value of 3620±137 mm Hg/s ($P < 0.01$) and ($dP/dt/P$) increased by a maximum of 10±2% above the control value of 43±2 s^{-1} ($P < 0.01$).

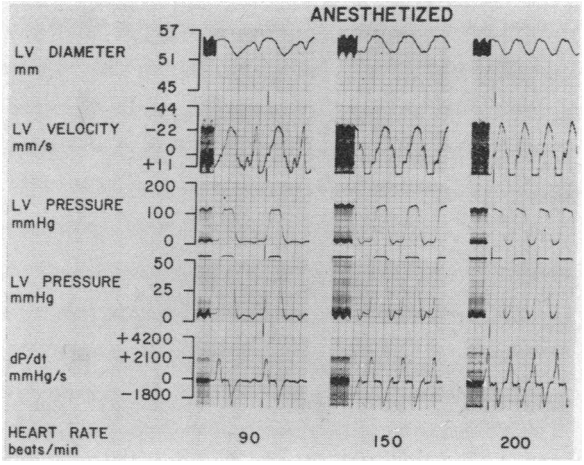

FIGURE 3 Experimental records depicting the alterations in the measurements of LV dynamics at progressively higher frequencies in the same dog as in Fig. 2 but in this instance studied in the anesthetized state.

[7] Not statistically significant ($P > 0.05$).

TABLE I

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

		LVP		LVD (internal)			
	HR	Peak systolic	End diastolic	End diastolic	End systolic	Peak dP/dt	$\frac{dP/dt}{\text{dev LVP}}$
	Beats/min	*mm Hg*	*mm Hg*	*mm*	*mm*	*mm Hg/s*	s^{-1}
Dog 1							
	100	110	4	37.1	29.1	3000	35.0
	120	110	3	37.1	28.5	3000	34.6
	150	105	2	36.7	29.1	2850	32.4
	180	110	3	36.3	29.7	2850	32.8
	200	100	3	36.7	30.9	2850	32.8
	220	100	4	36.7	31.4	2850	33.2
Dog 2							
	100	114	6	31.0	23.8	3750	40.0
	120	120	5	30.6	23.8	4050	42.6
	150	116	4	30.6	24.8	4200	43.8
	180	112	4	30.6	25.2	3750	39.2
	200	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).

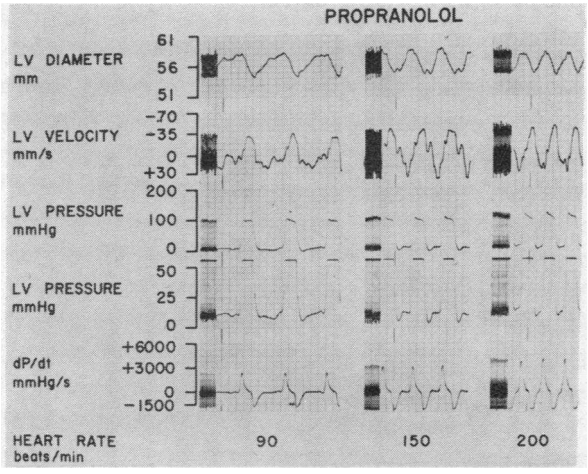

FIGURE 4 Experimental records depicting the alterations in the measurements of LV dynamics at progressively higher frequencies in the same dog as in Fig. 2 but in this instance studied in the conscious state after treatment with a myocardial-depressing dose of propranolol, 3 mg/kg.

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 were 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

TABLE II

Inotropic Effects of Increasing Heart Rate

	90–100 beats/min	120 beats/min	150 beats/min	180 beats/min	200 beats/min	220 beats/min	Δ/100 beats
Peak systolic pressure, *mm Hg*							
Conscious	123±7(±SEM)	120±6	123±8	126±9	128±9	129±9	5±2‖
Anesthetized	—	125±9	129±9	128±9	128±9	127±9	2±1‖
Propranolol	129±9	133±10	136±10	138±10	138±10	139±10	9±3‖
End diastolic pressure, *mm Hg*							
Conscious	8±1	7±1	7±1	7±1	7±1	7±1	−1±1‖
Anesthetized	—	7±1	8±1	9±2	10±2	10±2	3±1‖
Propranolol	13±1	13±1	12±1	12±1	13±1	13±1	0±1‖
End systolic diameter, *mm*							
Conscious	56±2	56±2	57±2	57±1	57±2	58±2	1±1‖
Anesthetized	—	56±1	57±1	57±1	57±1	57±1	1±1‖
Propranolol	62±1	62±1	62±1	62±1	63±1	63±1	1±1‖
End diastolic diameter, *mm*							
Conscious	62±2	62±2	62±2	62±2	62±6	62±6	0±1‖
Anesthetized	—	60±1	60±1	60±1	60±1	60±1	0±1‖
Propranolol	66±1	66±1	66±1	66±1	66±1	66±1	0±1‖
Peak *dP/dt, mm Hg/s*							
Conscious	3600±130	3660±160	3760±200	3860±240	3980±250	4070±280	380±30§
Anesthetized	—	2730±140	2930±180	3250±200	3540±280	3570±290	840±40*§
Propranolol	2610±200	2740±220	2910±210	3030±230	3140±240	3210±270	530±30‡§
dP/dt per P, s^{-1}							
Conscious	43±2	43±2	44±2	45±2	47±2	47±3	4±1§
Anesthetized	—	34±2	37±3	42±3	46±4	47±4	13±1*§
Propranolol	35±3	37±3	38±3	40±3	45±4	46±3	10±1*§

* 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.

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

inotropic effect of increasing the frequency of contraction was three times as great. Likewise, this inotropic response was also greater in the same dogs studied in the conscious state after a myocardial-depressing dose of propranolol. Thus, in the normal, healthy heart, in which the level of the contractile state is high, little inotropic effect is elicited with increasing heart rate, but in the presence of myocardial depression, increasing heart rate does exert a distinct positive, inotropic action.

The relatively constant levels of the contractile state of the left ventricle over a wide range of cardiac frequencies in dogs studied in the conscious state is at variance with the prominent increases in contractility demonstrated repeatedly in isolated preparations of ventricular myocardium (3–6). Koch-Weser and Blinks (29) have demonstrated that the frequency or interval-force relationship of cardiac muscle in the steady state may be considered to result from the net effect of three factors: (*a*) the rested state contraction, (*b*) a positive inotropic effect of activation, and (*c*) a negative inotropic effect of activation. They indicated that the accumulation of the positive inotropic effect of activation is the most important factor determining the interval-force relationship of the ventricle of most mammalian species and hence a positive inotropic effect should occur with increasing frequencies up to the maximum rate that the ventricle can follow without developing mechanical alternans. Several investigations have provided evidence that calcium influx or accumulation is probably related to the positive inotropic effect of activation and hence to the positive inotropic associated with increasing the frequency of contraction (30–32). Niedergerke (30) concluded that since the alterations in intracellular calcium ion concentration and contractile tension occurred nearly simultaneously with increasing frequency of contraction, the positive inotropic effect of activation reflected changes in ionic calcium concentration at the cell surface or in some structure extending into the cell from the surface. Winegrad (32) has shown that increasing the frequency of contraction of guinea pig atria produced parallel increases in the strength of contraction and uptake of ^{45}Ca per beat. Langer (33) maintains that the augmented influx of calcium ion associated with increased frequency is preceded and initiated by an increase in the rate of influx of ionic sodium.

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 per 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 anesthesia 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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