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Research Article

We studied the effects of acute pharmacologic and hemodynamic interventions on isovolumic left ventricular relaxation in 19 conscious dogs using micromanometer tip catheters. Isoproterenol (11 studies) augmented peak rate of rise of left ventricular pressure [(+) d*P*/d*t*] by 1,275±227 (SE) mm Hg/s ($P < 0.001$) and d*P*/d*t* at an isopressure point of 35 mm Hg during isovolumic relaxation [(–) d*P*/dt_{35}] by 435±80 mm Hg/s ($P < 0.001$). Peak (–) d*P*/d*t* decreased by 467±89 mm Hg/s ($P < 0.002$). The time constant, *T*, derived from the logarithmic fall of pressure during isovolumic relaxation, shortened from 20±2.8 to 14.9±1.8 ms ($P < 0.003$). Calcium (11 studies) increased peak (+) d*P*/d*t* and (–) d*P*/dt_{35} (both $P < 0.0001$); peak (–) d*P*/d*t* was unchanged. *T* shortened from 20.4±1.8 to 17.3±1.5 ms ($P < 0.002$). Volume (13 studies) did not affect either d*P*/d*t* or *T*. Phenylephrine (13 studies) augmented peak (–) d*P*/d*t*, but reduced (–) d*P*/dt_{35} (both $P < 0.01$); *T* lengthened from 22.1±1.5 to 32.5±1.5 ms ($P < 0.01$). In 15 studies, rapid atrial pacing increased peak (+) d*P*/d*t* and (–) d*P*/dt_{35} (both $P < 0.01$). In the first post-pacing beat, peak (–) d*P*/d*t* and (–) d*P*/dt_{35} decreased (both $P < 0.01$), although peak (+) d*P*/d*t* increased further. *T* paralleled values of (–) d*P*/dt_{35}. In five dogs, beta adrenergic blockade had no significant effect […]

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ABSTRACT We studied the effects of acute pharmacologic and hemodynamic interventions on isovolumic left ventricular relaxation in 19 conscious dogs using micromanometer tip catheters. Isoproterenol (11 studies) augmented peak rate of rise of left ventricular pressure [(+) dP/dt] by 1,275±227 (SE) mm Hg/s ($P < 0.001$) and dP/dt at an isopressure point of 35 mm Hg during isovolumic relaxation [(−) dP/dt_{35}] by 435±80 mm Hg/s ($P < 0.001$). Peak (−) dP/dt decreased by 467±89 mm Hg/s ($P < 0.002$). The time constant, T, derived from the logarithmic fall of pressure during isovolumic relaxation, shortened from 20±2.8 to 14.9±1.8 ms ($P < 0.003$). Calcium (11 studies) increased peak (+) dP/dt and (−) dP/dt_{35} (both $P < 0.0001$); peak (−) dP/dt was unchanged. T shortened from 20.4±1.8 to 17.3±1.5 ms ($P < 0.002$). Volume (13 studies) did not affect either dP/dt or T. Phenylephrine (13 studies) augmented peak (−) dP/dt, but reduced (−) dP/dt_{35} (both $P < 0.01$); T lengthened from 22.1±1.5 to 32.5±1.5 ms ($P < 0.01$). In 15 studies, rapid atrial pacing increased peak (+) dP/dt and (−) dP/dt_{35} (both $P < 0.01$). In the first post-pacing beat, peak (−) dP/dt and (−) dP/dt_{35} decreased (both $P < 0.01$), although peak (+) dP/dt increased further. T paralleled values of (−) dP/dt_{35}. In five dogs, beta adrenergic blockade had no significant effect on any variable after calcium, volume, or phenylephrine infusion or during or after atrial pacing when the pre- and post-propranolol states were compared.

We conclude that positive inotropic interventions augment both left ventricular contraction and relaxation. The changes in isovolumic relaxation are independent of alterations in sympathetic tone produced by beta-adrenergic blockade. Peak (−) dP/dt may not be a valid measure of left ventricular relaxation rate during acute alterations in inotropic state or afterload.

INTRODUCTION

Although there is considerable information on the factors that influence the rate of rise of left ventricular pressure (dP/dt)[1] during isovolumic contraction (1–3), there are few studies concerning the hemodynamic and pharmacologic factors that influence isovolumic relaxation, and most of these have been performed in papillary muscle preparations (4) or anesthetized animals (5, 6). It has been assumed that the maximum rate of left ventricular pressure decline [peak (−) dP/dt] can be employed in the analysis of isovolumic relaxation (7), but more recent information does not support this contention (6). Moreover, some interventions appear to exert an apparently paradoxical influence on the peak rate of isovolumic relaxation. Thus, isoproterenol, which augments the maximum rate of left ventricular pressure rise [peak (+) dP/dt], has little effect or actually decreases peak (−) dP/dt

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[1] *Abbreviations used in this paper*: dP/dt, rate of change of left ventricular pressure; (−) dP/dt_{35}, (−) dP/dt at an isopressure point of 35 mm Hg; EDD, end-diastolic dimension; ESD, end-systolic dimension; V_{cf}, mean rate of diameter shortening.

(1, 8–10), while acutely induced increases in left ventricular or aortic systolic pressure, which either reduce or exert little effect on peak (+) dP/dt, tend to augment peak (−) dP/dt (1, 6). Therefore, in the present study we examined the influence of several acute pharmacologic and mechanical interventions on isovolumic relaxation in the normal conscious dog by employing infusions of isoproterenol, phenylephrine, or calcium, and by atrial pacing and its abrupt cessation. In a subset of animals, studies were carried out before and after beta-adrenergic blockade. The indices compared as measures of isovolumic relaxation were peak (−) dP/dt, the value of (−) dP/dt at a common isovolumic pressure, and the time constant, T, recently described by Weiss et al. (11).

METHODS

19 mongrel dogs, ranging in weight from 22 to 28 kg (average 25 kg) underwent a left-side thoracotomy in the fifth intercostal space under sterile conditions during sodium thiamylal anesthesia. A high-fidelity micromanometer (Konigsberg P-20, Konigsberg Instruments, Inc., Pasadena, Calif.) and a Silastic rubber catheter (inner diameter 1.1 mm) for pressure calibrations were inserted at the left ventricular apex through separate stab wounds. Pacing electrodes were sutured to the left atrial appendage. In 11 dogs, two 4.5-mm ultrasonic piezoelectric crystals (12) were positioned at opposing sites on the anterior and posterior left ventricular endocardial surfaces in order to measure continuously the internal diameter of a transverse left ventricular chord (13). The pacing wires, ultrasound crystal, and micromanometer leads, and the left ventricular catheter were implanted subcutaneously in the neck, where they could be easily exposed for subsequent study. The dogs were permitted to recover from the operation for a minimum of 2 wk and were trained to lie quietly on the right side on a table. At the time of each study they were healthy and had normal temperatures and hematocrits.

Measurements were recorded on an eight-channel forced-ink pen oscillograph (model 7868A, Hewlett-Packard Co., Palo Alto, Calif.). The output from the micromanometer was adjusted to the pressure measured through the fluid-filled catheter by means of a Statham P23db transducer (Statham Instruments Div., Gould Inc., Oxnard, Calif.), calibrated with a mercury manometer; the zero reference point was at the level of the vertebral column. The tracings from the high-fidelity transducer were recorded at full scale and at high gain for accurate reading of diastolic pressure. The first derivative of the left ventricular pressure pulse (dP/dt) was obtained by electronic differentiation from the high-fidelity pressure signal. The R-C differentiator (Hewlett-Packard, model 350-16), which has a linear frequency response to 150 Hz that decreases 3 dB beyond 150 Hz, was calibrated by using a triangular waveform of known slope. The signals from the ultrasonic diameter gauges were calibrated for diameter equivalents of 15–50 mm in steps of 5 mm (12). This system permitted continuous recording of left ventricular internal diameter (13). The error in left ventricular diameter measurement induced by angular distortion up to 30° was less than 4% of the total measured distance (14). The basic oscillation rate was 5,000/s, and overall frequency response and phase shift were determined entirely by the characteristics of the output filter (12). In our current instrumentation, the output signal of the sonomicrometer was passed through a two-pole filter with a fall of 3 dB at 60 Hz.

The experiments were performed 2 wk to 4 mo after operation, while the unsedated dogs were lying quietly on the experimental table. At least 10 different dogs were employed for each protocol. For control studies, atrial pacing was performed at various rates so that heart rates could be matched with the experimental studies. A constant current stimulator (model 7150 Nuclear-Chicago, Des Plaines, Ill.) was used for atrial pacing. Volume infusion was performed to study the effects of an acute volume load on left ventricular relaxation. Because of previous observations of wide variations in the values for left ventricular end-diastolic pressure in individual dogs during phenylephrine infusion, volume (300–600 ml of 5% dextrose and water or 0.9% NaCl over 5–10 min) was administered to raise the left ventricular end-diastolic pressure to a range of 12–15 mm Hg (average 13±0.8 mm Hg). By this method, it was then possible to consistently achieve left ventricular end-diastolic pressures during phenylephrine infusions ranging from 23 to 30 mm Hg (average 26±1.0 mm Hg). Volume infusion was always carried out before phenylephrine administration (0.1–0.2 mg/min, 0.0036–0.009 mg/kg per min). During these interventions, pretreatment with atropine and subsequent atrial pacing prevented reflex alterations in heart rate. Isoproterenol was infused at a rate of 2.0–4.0 μg/min (0.09–0.18 μg/kg per min) to achieve an unequivocal positive inotropic effect (increase in peak (+) dP/dt by at least 20% of control values). Calcium chloride (100 mg/ml) in a dose sufficient to augment peak (+) dP/dt by at least 20% of control values also was infused over 60–90 s to assess the effect of this agent on isovolumic relaxation; the effective dose differed among dogs and ranged from 0.5 to 2.0 ml (2.3 to 9.1 mg/kg). In studies carried out after beta adrenergic blockade (see below), the calcium chloride dose was matched to the pre-blockade level. All interventions were carried out on different days, or if performed on the same day, were accomplished after the animal had returned to the basal state.

In a subgroup of five dogs, the interventions described above were carried out before and after beta adrenergic blockade, produced by 50 mg (1.79–2.27 mg/kg) of propranolol given intravenously over 5 min. In each dog the efficacy of beta blockade was confirmed by the lack of a change in heart rate or peak (+) dP/dt after a 3 μg intravenous bolus of isoproterenol, which had previously produced marked alterations in these parameters.

For each intervention, peak (+) dP/dt was measured. For assessment of left ventricular relaxation rate, three methods were employed: (*a* The maximum rate of isovolumic pressure fall (peak (−) dP/dt, mmHg). (*b* The rate of pressure change at a common isovolumic pressure. With recordings obtained at rapid paper spped (100–200 mm/s), the instantaneous rate of left ventricular relaxation was plotted against the simultaneously recorded high-fidelity left ventricular pressure recorded at high gain (Fig. 1). These plots were obtained at 5 or 10 ms intervals throughout isovolumic relaxation and the value of (−) dP/dt at an isopressure point of 35 mm Hg [(−) dP/dt_{35}] was determined (Fig. 2). The choice of 35 mm Hg as the isopressure point was an arbitrary one, but as can be seen in Fig. 2, virtually any other point or set of points would have served equally as well. Except for post-pacing beats, the results of two to four cycles were averaged for each determination of pressure-velocity relations during isovolumic relaxation. (*c* In addition, an adaptation of the method of Weiss et al. was also employed to assess isovolumic relaxation (11). The left ventricular pressure

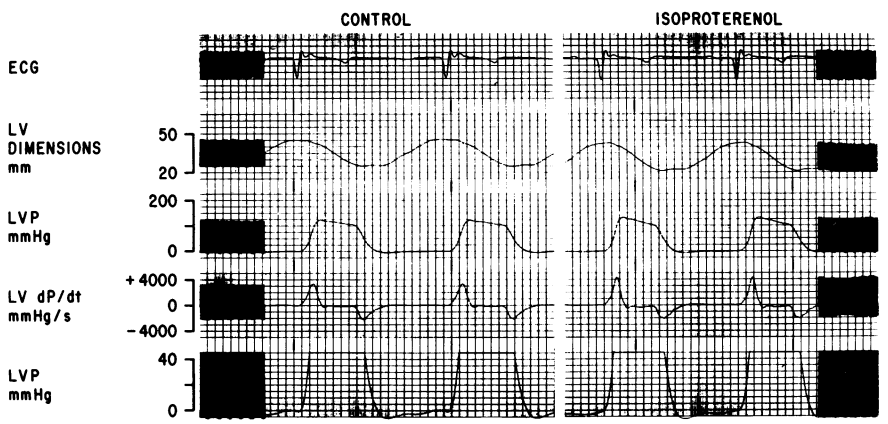

FIGURE 1 Control state and administration of isoproterenol. Peak (+) dP/dt is augmented during isoproterenol infusion, while peak (−) dP/dt is decreased. Left ventricular dimensions are decreased during isoproterenol infusion and mean V_{cf} (15, 26) is augmented.

was plotted beginning at the time of peak (−) dP/dt at 5–10-ms intervals to the level of the left ventricular end-diastolic pressure of the subsequent beat. The natural logarithm of the pressure value (average of three beats) (In P) was plotted against time and the slope derived by the method of least squares. The inverse negative of this slope is T, the time constant, which characterizes the phase of isovolumic pressure fall (11). Like Weiss et al. (11), we found that the time-course of fall in left ventricular pressure from the time of peak (−) dP/dt to the level of the left ventricular end-diastolic pressure was exponential ($r = 0.97$, $n = 170$).

It should be recognized that since the equation for a single exponential function is $dy/dt = ky$, where y equals pressure and k equals a proportionality constant, and the proportionality constant can be shown to be equal to 1/time constant, it follows that dy/dt for any pressure = 1/time constant·y. Thus, at any pressure during isovolumic relaxation, dP/dt is a function of and derivable from the time constant. The use of dP/dt at an isopressure point during relaxation as an additional index of relaxation rate offers the advantage of being more easily obtained than the time constant, which must be calculated by logarithmic transformation and the least squares method. Secondly, since both indices should provide identical information about the rate of relaxation, their combined use is helpful to insure methodologic accuracy. By contrast, since peak negative dP/dt is a function of both the time-course of relaxation and the absolute level of pressure at the onset of isovolumic relaxation, this index might not be expected to reflect the average rate of pressure fall during isovolumic relaxation reliably under all circumstances.

In the animals with diameter gauges, the association between alterations in dimensions and isovolumic relaxation rate was assessed. By using the diameter gauges, the mean rate of diameter shortening (mean V_{cf} [15–16]) was also derived and the results expressed in diameters [diam] per second.

For statistical comparisons of variables before and after a single intervention, a paired t-test was employed (17). Where two or three sequential interventions were employed (volume-afterload; pacing, post-pacing) and where control and propranolol data were compared, a repeated measures analysis of variance was used (18, 19), and for comparing individual means, Tukey's method for computing critical differences was employed (20). Data are expressed from all studies for each intervention.

RESULTS

Effects of isoproterenol infusion

Changes in heart rate and left ventricular pressures. In 11 studies isoproterenol increased the heart rate by 22±5 (SE) beats/min ($P < 0.004$). Peak left ventricular systolic pressure decreased from 139±4.6 to 134±2.7 mm Hg (NS), and the left ventricular pressure at peak (−) dP/dt decreased from 60±3.3 to 47±1.9 mm Hg ($P < 0.005$).

Contraction phase alterations. Peak (+) dP/dt increased from 3,437±333 to 4,712±453 mm Hg/s ($P < 0.001$, Table I). The end-diastolic dimension (EDD) and the end-systolic dimension (ESD) decreased significantly ($P < 0.008$ and <0.05, respectively). As indicated in Table II, mean V_{cf} increased from 1.75 ±0.17 to 2.50±0.30 diam/s ($P < 0.002$).

Measures of isovolumic relaxation. Accompanying the marked increase in peak (+) dP/dt was a significant reduction in peak (−) dP/dt from 2,936±317 to 2,469 ±333 mm Hg/s ($P < 0.002$, Table I). By contrast, (−) dP/dt_{35} changed in a manner directly opposite to peak (−) dP/dt, increasing from 1,689±161 to 2,124 ±202 mm Hg/s ($P < 0.001$, Table I). The T value decreased from 20.0±2.8 to 14.9±1.8 ms ($P < 0.003$), indicating a marked increase in the rate of isovolumic left ventricular pressure fall after isoproterenol administration.

Effects of calcium infusion

Heart rate and left ventricular pressure. Calcium chloride infusions (11 studies) were performed at fixed paced heart rates that were unchanged from control values (Table III). Left ventricular pressure also did not change during the infusion.

Contraction phase alterations. Peak (+) dP/dt in-

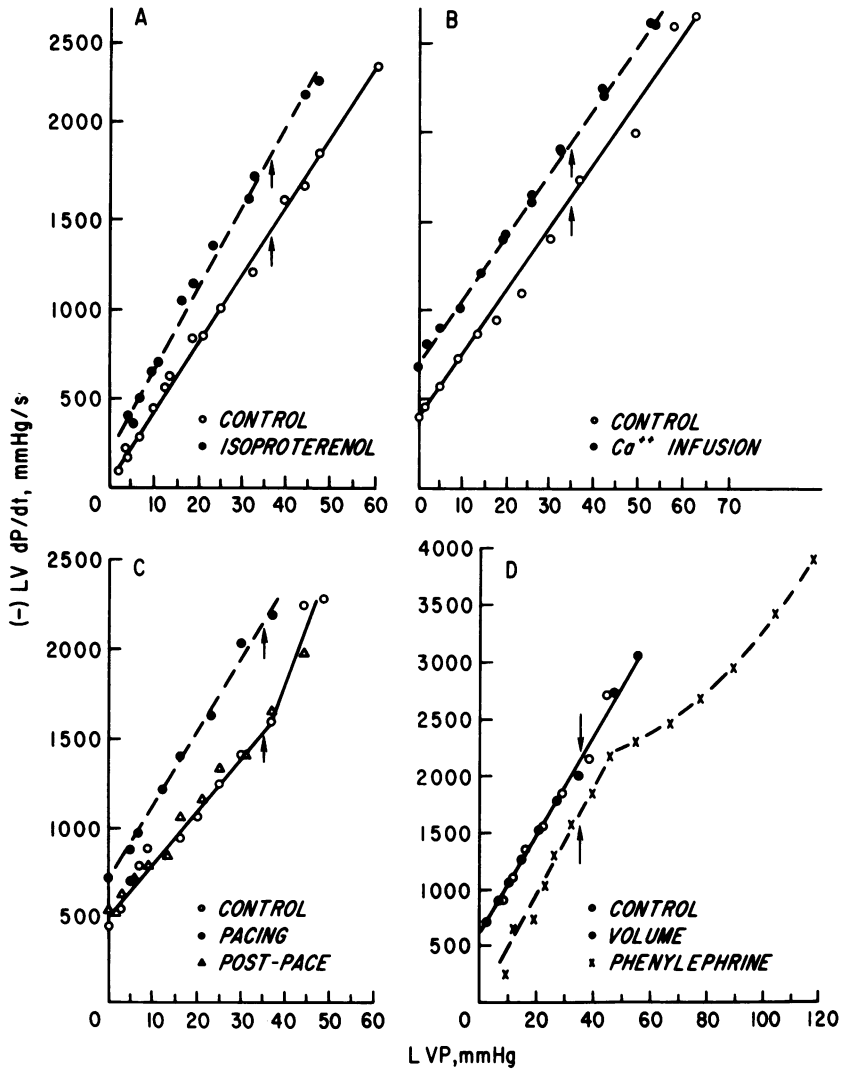

FIGURE 2 A. Representative beats in one animal during the control state and during isoproterenol infusion. The isovolumic pressure-velocity curve is shifted upward and to the left. The arrows indicate the values for (−) dP/dt_{35}. As indicated in the text, the choice of 35 mm Hg as the isopressure point was an arbitrary one, since virtually any other point or set of points along the curve would have served equally as well. B. Representative beats in one dog during the control state and during calcium infusion. The isovolumic pressure-velocity curve is shifted upward and to the left. The arrows indicate the values for (−) dP/dt_{35}. C. Control, pacing, and the first post-pacing beat are shown. During pacing, the isovolumic pressure-velocity curve is shifted upward and to the left, while the post-pacing curve is identical to that of the control beat. Arrows indicate the values for (−) dP/dt_{35}. D. Representative beats in one animal during the control state, volume expansion, and phenylephrine infusion. The isovolumic pressure-velocity curve during the afterload increase is shifted downward and to the right, while the curve obtained during volume expansion is identical to the control state. Arrows indicate values for (−) dP/dt_{35}.

creased from 3,195±156 to 3,998±206 mm Hg/s ($P < 0.0001$, Table III). ESD decreased signficantly ($P < 0.04$) and mean V_{cf} was augmented from 1.60 ±0.28 to 1.93±0.39 diam/s ($P < 0.04$, Table II).

Measures of isovolumic relaxation. There were no significant alterations in peak (−) dP/dt in the absence of changes in either heart rate or left ventricular pressure (Table III). However, (−) dP/dt_{35} increased from 1,654±140 to 1,927±140 mm Hg/s ($P < 0.0001$, Table III). The T value declined from 20.4±1.8 to 17.3±1.5 ms ($P < 0.002$), indicating an enhanced rate of left ventricular relaxation.

TABLE I
Alterations in Left Ventricular Contraction and Relaxation Produced by Isoproterenol Infusion

	Control	Isoproterenol	*P* value
Heart rate, *beats/min*	141±6.6	163±6.1	<0.004
Peak LVP, *mm Hg*	139±4.6	134±2.7	NS
LVEDP, *mm Hg*	7±1.2	1.6±0.7	<0.001
Peak (+) d*P*/d*t*, *mm Hg/s*	3,437±333	4,712±453	<0.001
Peak (−) d*P*/d*t*, *mm Hg/s*	2,936±317	2,469±333	<0.002
LVP at peak (−) d*P*/d*t*, *mm Hg*	60±3.3	47±1.9	<0.005
(−) d*P*/dt_{35}, *mm Hg/s*	1,689±161	2,124±202	<0.001
T, *ms*	20.0±2.8	14.9±1.8	<0.003

LVEDP, left ventricular end-diastolic pressure; LVP, left ventricular pressure.

TABLE III
Alterations in Left Ventricular Contraction and Relaxation Produced by Calcium Infusion

	Control	Calcium	*P* value
Heart rate, *beats/min*	125±7	120±6	NS
Peak LVP, *mm Hg*	138±2.9	138±3.3	NS
LVEDP, *mm Hg*	11±2.2	9.5±2.6	NS
Peak (+) d*P*/d*t*, *mm Hg/s*	3,195±156	3,998±206	<0.0001
Peak (−) d*P*/d*t*, *mm Hg/s*	2,733±161	2,859±163	NS
LVP at peak (−)d*P*/d*t*, *mm Hg*	61±2.8	60±3.3	NS
(−) d*P*/dt_{35}, *mm Hg/s*	1,654±140	1,927±140	<0.0001
T, *ms*	20.4±1.8	17.3±1.5	<0.002

Abbreviations as in Table I.

Effects of volume and phenylephrine infusion

Changes in heart rate and left ventricular pressure. During volume infusion (13 studies) the small changes in heart rate and left ventricular peak systolic pressure were not significant (Table IV). During subsequent phenylephrine infusion the heart rate tended to slow and atrial pacing was used to maintain the heart rate at control levels. Phenylephrine rasied peak left ventricular systolic pressure to 198±8.0 mm Hg and left ventricular end-diastolic pressure to 26±1.0 mm Hg (both $P < 0.01$ compared with control and volume values).

Contraction phase alterations. Neither volume nor phenylephrine infusion had any significant effect on peak (+) d*P*/d*t* (Table IV). Volume increased EDD significantly ($P < 0.05$), while ESD was unchanged (Table II). Phenylephrine further augmented EDD ($P < 0.005$ and <0.03 compared with control and volume values, respectively), while ESD increased ($P < 0.004$ compared with control and volume values). Mean V_{cf} was unchanged by volume, but decreased from 2.15 ±0.31 to 1.55±0.16 diam/s in response to phenylephrine ($P < 0.002$).

Measures of isovolumic relaxation. During volume peak (−) d*P*/d*t* did not change significantly, but during phenylephrine after volume this measure increased from 3,163±126 to 3,717±168 mm Hg/s ($P < 0.01$, Table IV). Volume also did not affect (−) d*P*/dt_{35}. However, in contrast to the increase in peak (−) d*P*/d*t*, phenylephrine decreased (−) d*P*/dt_{35} from 1,813±93 to 1,456±94 mmHg/s ($P < 0.01$, Table IV). The time constant tended to increase during volume but the change was not significant. During phenylephrine the

TABLE II
Alterations in Left Ventricular Dimensions and Mean V_{cf} Produced by Pharmacologic Interventions

	Control	Intervention	*P* value
Isoproterenol infusion			
EDD, *mm*	46.9±2.0	44.5±2.0	<0.008
ESD, *mm*	35.5±1.3	32.0±2.0	<0.05
Mean V_{cf}, *diam/s*	1.75±0.17	2.50±0.30	<0.002
Calcium infusion			
EDD, *mm*	42.7±3.9	41.7±4.0	NS
ESD, *mm*	34.7±4.0	33.3±4.0	<0.04
Mean V_{cf}, *diam/s*	1.60±0.28	1.93±0.39	<0.04
Volume expansion			
EDD, *mm*	47.6±1.3	50.3±0.4	<0.05
ESD, *mm*	31.8±2.3	32.5±1.9	NS
Mean V_{cf}, *diam/s*	2.15±0.31	2.04±0.25	NS
Phenylephrine infusion			
EDD, *mm*	47.6±1.3	52.2±0.4	<0.005
ESD, *mm*	31.8±2.3	38.4±2.5	<0.004
Mean V_{cf}, *diam/s*	2.15±0.31	1.55±0.16	<0.002

TABLE IV
Alterations in Left Ventricular Contraction and Relaxation Produced by Volume and Phenylephrine Infusion

	Control	Volume infusion	Phenylephrine infusion
Heart rate, *beats/min*	108±2.6	117±5.3	109±1.9
Peak LVP, *mm Hg*	128±2.5	136±5.6	198±8.0*‡
LVEDP, *mm Hg*	5±0.8	13±0.8*	26±1.0*‡
Peak (+) d*P*/d*t*, *mm Hg/s*	3,409±159	3,612±159	3,414±166
Peak (−) d*P*/d*t*, *mm Hg/s*	2,985±167	3,163±126	3,717±168*‡
LVP at peak (−) d*P*/d*t*, *mm Hg*	61±3.3	67±3.5	128±5.8*
(−) d*P*/dt_{35}, *mm Hg/s*	1,868±96	1,813±93	1,456±94*‡
T, *ms*	18.8±0.9	22.1±1.5	32.5±1.5*‡

* $P < 0.01$ vs. control.
‡ $P < 0.01$ vs. infusion.

TABLE V
Alterations in Left Ventricular Contraction and Relaxation Produced by Rapid Atrial Pacing

	Control	Pacing	First post-pacing beat	Second post-pacing beat
Heart rate, *beats/min*	99±4.7	162±4.5**	—	—
Peak LVP, *mm Hg*	128±3.1	129±3.3	125±3.3	122±3.0*‡
LVEDP, *mg Hg*	8.0±1.5	2.8±0.8§	7.8±1.0‖	7.3±1.1‖
Peak (+) d*P*/d*t*, *mm Hg/s*	2,935±158	3,226±183§	3,505±160§‖	3,212±152§¶
Peak (−) d*P*/d*t*, *mm Hg/s*	2,488±195	2,682±218§	2,311±200*‖	2,321±195*‖
LVP at peak (−) d*P*/d*t*, *mm Hg*	62±2.3	56±2.4§	58±2.5	55±2.6§
(−) d*P*/dt_{35}, *mm Hg/s*	1,640±113	1,979±135§	1,612±97‖	1,666±119‖
T, *ms*	20.1±1.1	16.5±1.4§	21.3±1.6‖	21.0±1.3‖

* $P < 0.05$ vs. control. ‖ $P < 0.01$ vs. pacing.
‡ $P < 0.05$ vs. pacing. ¶ $P < 0.01$ vs. 1st post-pacing beat.
§ $P < 0.01$ vs. control. ** $P < 0.001$ vs. control.

T value increased from 22.1±1.5 to 32.5±1.5 ms ($P < 0.01$ compared with both control and volume values), indicating a decrease in the rate of isovolumic left ventricular relaxation.

Pacing studies

Changes in heart rate and left ventricular pressure. In 15 studies the atria were paced for an average of 9.15±0.5 s. The average heart rate increased from 99±4.7 to 162±4.5 beats/min. Also analyzed were the first and second post-pacing beats, which occurred 814±43 and 1,515±105 ms, respectively, after the abrupt cessation of pacing. Peak left ventricular pressure was unchanged both during pacing and in the first post-pacing beat, but declined in the second post-pacing beat (Table V).

Contraction phase alterations. Peak (+) d*P*/d*t* increased from 2,935±158 to 3,226±183 mm Hg/s ($P < 0.01$). In the first post-pacing beat there was a further increase to 3,505±160 mmHg/s ($P < 0.01$ compared both to control and pacing studies) (Table V). In the second post-pacing beat peak (+) d*P*/d*t* declined compared with the first post-pacing beat ($P < 0.01$). However, this value was not significantly different from that obtained during rapid pacing but still exceeded the control value ($P < 0.01$, Table V).

During pacing, both EDD and ESD decreased significantly ($P < 0.01$ and <0.05, respectively) (Table VI). Mean V_{cf} increased from 1.83±0.08 to 2.10±0.13 diam/s ($P < 0.01$). In the first post-pacing beat, EDD increased ($P < 0.01$ vs. pacing but NS vs. control). ESD was unchanged from values during pacing. Mean V_{cf} increased further to 2.36±0.18 diam/s ($P < 0.01$ compared with both control and pacing values). The values for EDD, ESD, and mean V_{cf} were not significantly different when the first and second post-pacing beats were compared.

Measures of isovolumic relaxation. During pacing, peak (−) d*P*/d*t* increased significantly from the control value of 2,488±195 mm Hg/s ($P < 0.01$) [Table V]. In the first post-pacing beat, however, there was a decrease of 371±60 mm Hg/s compared with pacing values ($P < 0.01$), even though peak (+) d*P*/d*t* increased even further compared with pacing values. In the second post-pacing beat, the value for peak (−) d*P*/d*t* was significantly less than control and pacing levels ($P < 0.05$), but did not differ from the first post-pacing beat (Table V).

The value for (−) d*P*/dt_{35} increased during pacing from 1,640±113 to 1,979±135 mmHg/s ($P < 0.01$). The post-pacing value was not significantly different from control, but did decrease by 367±50 mm Hg compared with pacing ($P < 0.01$), despite the concommitant further increase in peak (+) d*P*/d*t* (Table V). The value in the second post-pacing beat was not significantly different from that of the first post-pacing beat. The *T* values were concordant with those of (−) d*P*/dt_{35}, decreasing with pacing and returning to control levels in the first and second post-pacing beats (Table V).

Interventions before and after beta-adrenergic blockade

To assess the effects of the possible role of alterations in sympathetic tone in these conscious dogs

TABLE VI
Alterations in Left Ventricular Dimensions and Mean V_{cf} Produced by Rapid Atrial Pacing

	Control	Pacing	First post-pacing beat	Second post-pacing beat
EDD, *mm*	45.9±1.8	41.1±1.8*	44.5±1.9§	44.8±2.1*
ESD, *mm*	34.1±1.3	31.9±1.6‡	31.5±1.3‡	32.0±1.7
Mean V_{cf}, *diam/s*	1.83±0.08	2.10±0.13*	2.36±0.18*§	2.23±0.16*§

* $P < 0.01$ vs. control.
‡ $P < 0.05$ vs. control.
§ $P < 0.01$ vs. pacing.

TABLE VII
*Calcium Studies before and after Beta Blockade**

	Before propranolol		After propranolol	
	Control	Calcium	Control	Calcium
Heart rate, *beats/min*	112±2.7	109±2.0	111±2.9	105±4.8
Peak LVP, *mm Hg*	139±3.8	141±2.8	146±10	151±9.0
LVEDP, *mm Hg*	11.8±2.5	11.4±2.2	10.0±1.6	10.2±2.0
Peak (+) d*P*/d*t*, *mm Hg/s*	3,310±194	4,233±296‡	2,925±363	3,934±414‡
Peak (−) d*P*/d*t*, *mm Hg/s*	2,914±208	3,146±172	3,140±355	3,353±367
LVP at peak (−) d*P*/d*t*, *mm Hg*	79±1.8	69±4.1	77±7.4	76±5.9
(−) d*P*/dt_{35}, *mm Hg/s*	1,554±213	1,842±207‡	1,702±174	2,025±162‡
T, *ms*	23.2±2.5	19.5±2.0§	21.1±1.0	18.7±0.5§

* Propranolol administration produced no significant difference for any variable when the pre- and post-propranolol states were compared.
‡ $P < 0.003$ vs. control.
§ $P < 0.009$ vs. control.

produced by the interventions detailed above, a subset of five animals was studied before and after the administration of 50 mg of intravenous propranolol. The results are shown in Tables VII–IX. Before beta adrenergic blockade, the effects of calcium, volume expansion, phenylephrine infusion, and rapid atrial pacing and its abrupt cessation were identical to the results in the larger group of dogs described above. Analysis of variance revealed that propranolol administration produced no significant difference for any variable when the pre- and post-propranolol states were compared.

DISCUSSION

Isoproterenol studies. With peak (−) d*P*/d*t* as an index of left ventricular relaxation, a variety of results after alterations in inotropic state and loading conditions have been reported (5, 6, 8–10). Thus, the response to isoproterenol has been a uniform augmentation of peak (+) d*P*/d*t*, whereas peak (−) d*P*/d*t* remained either unchanged (1, 5), or declined (9, 10). If peak (−) d*P*/d*t* is an accurate reflection of isovolumic relaxation rate, these data suggest that relaxation velocity is either unchanged or diminished despite considerable augmentation of contraction velocity. In our study, peak (−) d*P*/d*t* declined significantly during isoproterenol infusion despite marked augmentation of peak (+) d*P*/d*t* and mean V_{cf}. This decline in peak (−) d*P*/d*t* was associated with a significant decrease in the pressure at which peak (−) d*P*/d*t* occurred, and is consistent with earlier studies that

TABLE VIII
*Volume-Afterload Studies before and after Beta Blockade**

	Before propranolol			After propranolol		
	Control	Volume infusion	Phenylephrine infusion	Control	Volume infusion	Phenylephrine infusion
Heart rate, *beats/min*	108±1.4	109±1.1	109±1.9	108±2.4	110±1.3	109±2.4
Peak LVP, *mm Hg*	128±4.7	134±6.4	193±7.4‡§	136±9.5	145±9.6	204±6.6‡§
LVEDP, *mm Hg*	6±1.0	14±1.1‡	27±1.7‡§	8.6±1.4	16.4±0.6‡	26.4±2.0‡§
Peak (+) d*P*/d*t*, *mm Hg/s*	3,129±198	3,286±163	3,086±151	2,976±281	3,019±269	2,736±318
Peak (−) d*P*/d*t*, *mm Hg/s*	2,841±229	3,003±150	3,433±246	3,087±322	2,992±306	3,348±275
LVP at peak (−) d*P*/d*t*, *mm Hg*	57±4.2	62±3.8	121±8.7‡§	69±3.5	77±6.8	133±3.6‡§
(−) d*P*/dt_{35}, *mm Hg/s*	1,874±179	1,773±152	1,336±113‡§	1,855±146	1,801±212	1,419±141‡§
T, *ms*	19.2±2.1	24.5±2.7	32.1±1.6‡§	22.5±2.1	23.3±2.3	33.4±1.7‡§

* Propranolol administration produced no significant difference for any variable when the pre- and post-propranolol states were compared.
‡ $P < 0.01$ vs. control.
§ $P < 0.01$ vs. volume infusion.

TABLE IX

*Pacing Studies before and after Beta Blockade**

	Before propranolol				After propranolol			
	Control	Pace	First post-pacing beat	Second post-pacing beat	Control	Pace	First post-pacing beat	Second post-pacing beat
Heart rate, *beats/min*	102±2.5	150±1.4‖	—	—	102±3.1	149±2.9‖	—	—
Peak LVP, *mg Hg*	129±7.2	135±5.8	125±8.5	121±8.0	136±8.3	136±8.1	131±7.4	134±7.4
LVEDP, *mm Hg*	8.2±1.7	3.2±1.0§	8.0±1.2¶	7.0±1.3¶	8.8±1.4	4.4±0.6§	10.2±0.2¶	8.4±1.2‖
Peak (+) d*P*/d*t*, *mm Hg/s*	3,320±132	3,743±190‡	3,853±174§	3,495±166**	2,899±239	3,195±243‡	3,290±291§	3,065±254**
Peak (−) d*P*/d*t*, *mm Hg/s*	2,966±286	3,334±254§	2,817±294§¶	2,824±314‡¶	3,065±339	3,263±281§	2,675±290§¶	2,853±344‡¶
LVP at peak (−) d*P*/d*t*, *mm Hg*	61±3.1	59±3.8	61±4.2	55±3.1	69±5.2	65±5.0	63±3.4	65±2.9
(−) d*P*/dt_{35}, *mm Hg/s*	1,915±164	2,349±184§	1,772±163§¶	1,941±190¶**	1,792±166	2,142±172§	1,705±140¶	1,715±198¶
T, *ms*	19.2±1.2	15.0±0.9§	20.7±1.5¶	20.2±2.0¶	21.4±1.2	19.0±1.5§	21.9±0.9¶	23.2±1.4¶

* Propranolol administration produced no significant difference for any variable when the pre- and post-propranolol states were compared.
‡ $P < 0.05$ vs. control.
§ $P < 0.01$ vs. control.
‖ $P < 0.001$ vs. control.
¶ $P < 0.01$ vs. pacing.
** $P < 0.05$ vs. 1st post-pacing beat.

indicated that the magnitude of peak (−) d*P*/d*t* is primarily influenced by the level of aortic pressure (6). When d*P*/d*t* was plotted against left ventricular pressure during isovolumic relaxation, however, each curve was shifted upward and to the left (Fig. 2). When (−) d*P*/d*t* was measured and compared with control values at a common isovolumic pressure of 35 mm Hg, relaxation velocities were significantly augmented. *T* values also exhibited a significant decline, supporting the concept that isoproterenol augmented the rate of isovolumic left ventricular relaxation.

Although it has been proposed that (−) d*P*/d*t* depends on end-systolic volume (5, 21), in an isolated canine preparation it has been observed that *T* is unaffected by end-systolic volume but is largely dependent on the extent of systolic shortening when the latter is determined by the impedance to ejection (11). A mechanism that could explain our observations has been proposed by Morad and Rolett, who suggested on the basis of papillary muscle studies that catecholamines exert their relaxant effect independent of their positive inotropic effect by stimulating the sequestering system for calcium (22).

Studies on calcium. Although calcium chloride infusion increased cardiac contractility significantly in the absence of any alterations in heart rate or left ventricular systolic pressure, peak (−) d*P*/d*t* was unaffected. However, the significant alterations in (−) d*P*/dt_{35} and *T* suggest augmentation in the rate of isovolumic left ventricular relaxation. Thus, reliance on peak (−) d*P*/d*t* alone as an index of cardiac relaxation would lead to the erroneous conclusion that calcium infusion sufficient to enhance contractility has no effect on relaxation.

Any explanation of how calcium might enhance relaxation must be speculative. It may be hypothesized that increased availability of calcium during calcium infusion enhances the rate and strength of chemical bond formation between the contractile proteins while at the same time augmenting the uptake of calcium by the sarcoplasmic reticulum (23, 24). Our observations concerning the effect of calcium infusion on relaxation are at variance with those reported in papillary muscle preparations (4) and in an isolated canine preparation (11). The reasons for this difference are not readily apparent and await further experimental work.

Volume and phenylephrine studies. The effects of volume and phenylephrine infusion on peak (+) d*P*/d*t* and on mean V_{cf} are similar to previous results in normal conscious dogs (16, 25, 26) and in human subjects (27). Thus, peak (+) d*P*/d*t* is relatively insensitive to acute alterations either in preload or afterload, while mean V_{cf}, although insensitive to changes in preload, is reduced as afterload increases (26).

In previous studies it was observed that increased arterial pressure augmented peak (+) d*P*/d*t*, (6, 28–30) and peak (−) d*P*/d*t* (6). By contrast, in the conscious dog, Barnes et al. reported that an increase in mean aortic pressure of 48 mm Hg augmented peak (+) d*P*/d*t* by only 9% (25). Further, Bugge-Asperheim and Kiil observed that similar increases in mean aortic pressure had no significant effect on peak (+) d*P*/d*t* in the atropinized conscious dog (31, 32). Both in a previous report (26), and in the present study peak (+) d*P*/d*t* was unaffected by acute increases in afterload. However, when a positive inotropic agent such as isoproterenol was infused simultaneously with

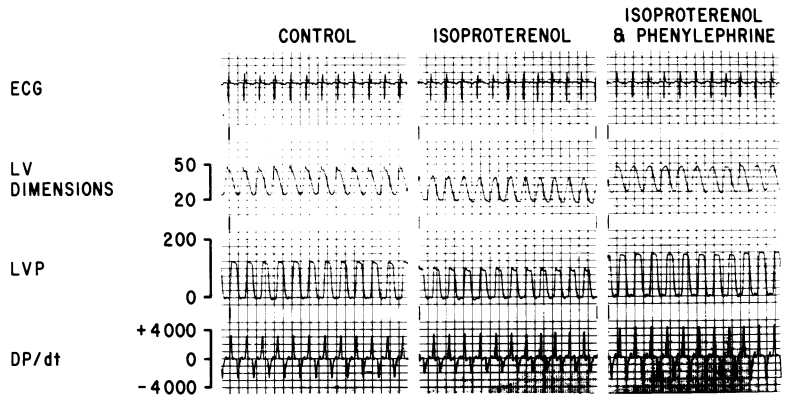

FIGURE 3 The dependence of peak (−) dP/dt on the level of left ventricular pressure is depicted. During isoproterenol infusion, peak (+) dP/dt increased, left ventricular dimensions diminished, left ventricular pressure declined, and so peak (−) dP/dt decreased. During the addition of phenylephrine, left ventricular pressure rose and consequently peak (−) dP/dt increased. Peak (+) dP/dt increased further, however, since isoproterenol infusion continued. Left ventricular dimensions increased compared with the middle panel. Thus, peak (−) dP/dt is highly sensitive to alterations in left ventricular pressure alone.

phenylephrine, both peak (+) dP/dt and mean V_{cf} were augmented (ref. 26, Fig. 3). Similarly, Bugge-Asperheim and Kiil observed that the cardiac response to increased aortic pressure can be modified by isoproterenol and stellate ganglion stimulation (31, 32).

To explain these apparently discordant results, the possibility should be considered that the type of preparation employed could modify the adrenergic responses to acute changes in loading conditions. The studies cited above in the conscious dog, in which significant changes in peak (+) dP/dt did not occur, would tend to support this hypothesis. Further, it should be noted that during acute increases in afterload, an afterload mismatch can develop at any given level of inotropic state, either if the change in afterload is inadequately compensated by an accompanying change in preload or if the limit of the Frank-Starling mechanism is reached (33). Our experiments differ from those previously reported (6, 28–30), in that volume was administered before phenylephrine in an attempt to allow maximal utilization of preload reserve during acute afterloading. During peak levels of left ventricular pressure, mean V_{cf} declined and peak (+) dP/dt did not rise, suggesting that the limit of preload reserve had been reached. Although it is possible that the peripheral effects of the pressor agent itself could have limited venous return, the very high levels of left ventricular end-diastolic pressure achieved (26±1.0 mm Hg) suggest that the Frank-Starling mechanism was maximally utilized. Thus, it is unlikely that the lack of increase in peak (+) dP/dt in response to an increase in systemic arterial pressure was the result of limitations on preload reserve imposed by the intervention itself.

The reason for the reduced rate of relaxation during acute increases in left ventricular systolic pressure is unclear. However, it has recently been shown that T depends on the extent of systolic shortening (11). This observation is consistent with our own data, in which interventions that enhance the rate and extent of systolic shortening (isoproterenol and calcium infusion, rapid pacing [Table II]), augment relaxation, while an intervention that decreases the rate and extent of shortening (phenylephrine infusion [Table II]) reduces the rate of relaxation.

Pacing studies. There is considerable evidence that augmentation of heart rate alone (Bowditch effect) exerts a positive inotropic effect on the left ventricular myocardium (34–39). In the present study, both peak (+) dP/dt and mean V_{cf} exhibited modest but significant increases during rapid atrial pacing. Changes in both T and in (−) dP/dt_{35} indicated that relaxation was also enhanced. In isolated muscle preparations the Bowditch effect depends on calcium transport (40). Previously it had been shown by Koch-Weser that epinephrine release from sympathetic nerve endings plays no role in the genesis of the fundamental interval-strength relation of heart muscle (41). Thus, the effects of rapid atrial pacing may be analogous to those of calcium infusion.

Despite further continued augmentation of peak (+) dP/dt after abrupt cessation of pacing, both peak (−) dP/dt and (−) dP/dt_{35} returned to control levels. These alterations were unrelated to changes in ESD. The explanation for this phenomenon, not previously described, is speculative, but may reside in the fundamental difference between the Bowditch effect and the Woodworth staircase (35). The latter is defined as "enhanced contractility following a long pause" (42). Hajdu has speculated that the Woodworth phe-

nomenon represents the effects of calcium originating from bound sources within the myocardial fiber itself (42). However, it has recently been demonstrated in a papillary muscle preparation that the increase in developed tension produced by paired pacing was not abolished by D600, a pharmacological inhibitor of some calcium channels (40). Since the post-extrasystolic potentiation associated with paired pacing seems to resemble the Woodworth phenomenon more closely, the role of calcium flux in these two phenomena requires further examination.

Studies before and after beta-adrenergic blockade. Because of the possibility that reflex alterations in sympathetic tone may have influenced our results, studies were performed in five dogs before and after beta adrenergic blockade with intravenous propranolol. It could be postulated that a baroreceptor response, masked by atrial pacing at a constant rate, was operative during phenylephrine infusion, leading to a withdrawal of sympathetic tone and a subsequent decrease in relaxation velocity. The data in Table VIII, however, indicate that intravenous propranolol had no effect on isovolumic relaxation rates as measured either by (−) dP/dt_{35} or by T. Similarly, the effects of calcium infusion and rapid atrial pacing and its abrupt cessation were unaltered by propranolol administration (Tables VII and IX). As indicated above, these data are most consistent with the hypothesis that the rate and extent of wall shortening is the major influence on isovolumic relation. Whether one of these two factors is more important than the other cannot be determined from our data.

Although the current study was not specifically designed to distinguish between the relative influence of hemodynamic or mechanical factors as opposed to inotropic influences on isovolumic relaxation, certain inferences may be drawn from our results. During calcium infusion, heart rate, peak left ventricular pressure, left ventricular end-diastolic pressure, left ventricular pressure at peak (−) dP/dt and peak (−) dP/dt were all unchanged. During these stable hemodynamic and loading conditions, the major change observed was an alteration in inotropic state (increase in peak (+) dP/dt and mean V_{cf}). Thus, it is likely that the alterations observed in (−) dP/dt_{35} and T were primarily the result of the inotropic influence of calcium. Further, administration of propranolol did not alter these results. We recognize, however, that the increase in systolic excursion produced by calcium could have a mechanical effect on relaxation independent of inotropic effects.

The situation with respect to isoproterenol is somewhat more complex because of the alterations in peak (−) dP/dt and the left ventricular pressure at the latter point. Moreover, both the changes in inotropic state and in dimensions were more striking during isoproterenol infusion, and the larger alterations in the measures of relaxation may have been due both to larger inotropic stimuli as well as to mechanical or hemodynamic alterations. The unexpected return to control levels of (−) dP/dt_{35} and T immediately after pacing suggests that factors other than inotropic state, possibly mechanical in nature, may influence relaxation.

Finally, it should be reocgnized that phenylephrine administration represents an entirely different type of intervention, i.e., a purely mechanical one without significant inotropic effects (no change in peak (+) dP/dt). The results of the phenylephrine studies indicate that mechanical effects alone can profoundly affect isovolumic relaxation and it is possible that these effects result at least in part from both a reduction in shortening and an increase in left ventricular systolic pressure. Removal of any inotropic stimulus due to sympathetic tone by beta adrenergic blockade did not affect these results, further supporting the concept that the effect of phenylephrine was largely if not exclusively a mechanical one.

In summary, we have demonstrated in the normal conscious dog that positive inotropic interventions such as isoproterenol and calcium infusion and rapid atrial pacing enhance the rates of cardiac contraction and relaxation. Acute increases in afterload reduce relaxation rates. Although contraction is augmented immediately after abrupt cessation of pacing, relaxation velocities are reduced. The level of peak (−) dP/dt should not be employed alone to assess cardiac relaxation when acute alterations in afterload and inotropic state occur.

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