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Research Article

The hemodynamic determinants of the time-course of fall in isovolumic left ventricular pressure were assessed in isolated canine left ventricular preparations. Pressure fall was studied in isovolumic beats or during prolonged isovolumic diastole after ejection. Pressure fall was studied in isovolumic relaxation for isovolumic and ejecting beats (r less than or equal to 0.98) and was therefore characterized by a time constant, T. Higher heart rates shortened T slightly from 52.6 +/- 4.5 ms at 110/min to 48.2 +/- 6.0 ms at 160/min (P less than 0.01, n = 8). Higher ventricular volumes under isovolumic conditions resulted in higher peak left ventricular pressure but no significant change in T. T did shorten from 67.1 +/- 5.0 ms in isovolumic beats to 45.8 +/- 2.9 ms in the ejecting beats (P less than 0.001, n = 14). In the ejecting beats, peak systolic pressure was lower, and end-systolic volume smaller. To differentiate the effects of systolic shortening during ejection from those of lower systolic pressure and smaller end-systolic volume, beats with large end-diastolic volumes were compared to beats with smaller end-diastolic volumes. The beats with smaller end-diastolic volumes exhibited less shortening but similar end-systolic volumes and peak systolic pressure. T again shortened to a greater extent in the beats with greater systolic shortening. Calcium chloride and acetylstrophanthidin resulted in no significant […]

Hemodynamic Determinants of the Time-Course of Fall in Canine Left Ventricular Pressure

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ABSTRACT The hemodynamic determinants of the time-course of fall in isovolumic left ventricular pressure were assessed in isolated canine left ventricular preparations. Pressure fall was studied in isovolumic beats or during prolonged isovolumic diastole after ejection. Pressure fall from the time of maximum negative dP/dt was found to be exponential during isovolumic relaxation for isovolumic and ejecting beats ($r \geqslant 0.98$) and was therefore characterized by a time constant, T.

Higher heart rates shortened T slightly from 52.6 ±4.5 ms at 110/min to 48.2±6.0 ms at 160/min ($P < 0.01$, $n = 8$). Higher ventricular volumes under isovolumic conditions resulted in higher peak left ventricular pressure but no significant change in T. T did shorten from 67.1±5.0 ms in isovolumic beats to 45.8± 2.9 ms in the ejecting beats ($P < 0.001$, $n = 14$). In the ejecting beats, peak systolic pressure was lower, and end-systolic volume smaller. To differentiate the effects of systolic shortening during ejection from those of lower systolic pressure and smaller end-systolic volume, beats with large end-diastolic volumes were compared to beats with smaller end-diastolic volumes. The beats with smaller end-diastolic volumes exhibited less shortening but similar end-systolic volumes and peak systolic pressure. T again shortened to a greater extent in the beats with greater systolic shortening.

Calcium chloride and acetylstrophanthidin resulted in no significant change in T, but norepinephrine, which accelerates active relaxation, resulted in a significant shortening of T (65.6±13.4 vs. 46.3±7.0 ms, $P < 0.02$). During recovery from ischemia, T increased significantly from 59.0±9.6 to 76.8±13.1 ms when compared with the preischemic control beat ($P < 0.05$).

Thus, the present studies show that the time-course of isovolumic pressure fall subsequent to maximum negative dP/dt is exponential, independent of systolic stress and end-systolic fiber length, and minimally dependent on heart rate. T may be an index of the activity of the active cardiac relaxing system and appears dependent on systolic fiber shortening

INTRODUCTION

Studies in isolated muscle preparations, intact hearts, and man suggest multiple physiological and pathophysiological determinants of the time-course of relaxation of cardiac muscle. Relaxation appears to be prolonged after hypoxia and ischemia (1, 2), in hypothyroidism (3), by aging (4), in hypertrophy (5), and in heart failure (6), and is shortened in hyperthyroidism (3) and by catecholamines (7, 8). The hemodynamic determinants of the time-course of relaxation are less clear. Studies of afterloaded isotonic contractions in isolated papillary muscle suggest that the level of total systolic load may be of importance (9). But, as pointed out by Sulman et al. (10), such afterloaded isotonic muscles undergo isotonic lengthening before the isometric phase of relaxation. This is opposite in sequence to that of the intact heart, where isovolumic relaxation occurs before ventricular filling.

Maximum negative dP/dt (max neg dP/dt) [1] has been employed in both animal and human studies (6, 11–13) as an index of the activity of the relaxing sys-

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[1] *Abbreviations used in this paper:* ACS, acetylstrophanthidin; LVEDP, left ventricular end-distolic pressure; max neg dP/dt, maximum negative dP/dt; NE, norepinephrine; P_{max}, peak pressure; Pmax neg dP/dt, pressure at maximum negative dP/dt; T, time constant; TP_{max}-max neg dP/dt, time from peak pressure to maximum negative dP/dt; TPP, time to peak pressure.

tem. In the canine heart, the determinants of max neg dP/dt have been assessed under controlled hemodynamic conditions (13). Max neg dP/dt was found to vary directly with peak aortic pressure and to be predominantly a function of peak aortic pressure. Max neg dP/dt is, moreover, a measure of the rate of fall in pressure at only one point in time. In the working heart (13), the maximum rate of pressure fall occurs shortly after the time of aortic valve closure. Thus, these studies suggest that the magnitude of max neg dP/dt depends not only upon the activity of the relaxing system of cardiac muscle but also upon peripheral factors which determine the impedance to left ventricular ejection. Changes in impedance to ejection result in changes in peak aortic pressure and/or the timing of aortic valve closure, and hence max neg dP/dt.

In the course of pilot studies, it was found that the fall in isovolumic left ventricular pressure after the time of max neg dP/dt followed an exponential time-course. This exponential time-course of pressure fall was suggested by mechanical studies of isolated cardiac (9) and skeletal muscle (14) and studies of the active muscle-relaxing system of the barnacle (15). Thus, it appeared that the entire time-course of isovolumic pressure fall after max neg dP/dt might be described in terms of the pressure at max neg dP/dt and a time constant for pressure fall. The length of this time constant is, by definition, independent of the initial value for pressure and thus does not depend upon aortic valve closure. A canine preparation that allowed determination of the entire time-course of isovolumic pressure fall, uninterrupted by mitral valve opening and subsequent ventricular filling, was employed. This preparation then permitted us to study the entire time-course of isovolumic pressure fall under conditions of varying peak ventricular pressure, heart rate, systolic fiber shortening or ejection, and end-systolic fiber length or volume. Pressure fall under these conditions was examined in terms of the extent to which the time-course appeared to be exponential and in terms of the determinants of the time constant and max neg dP/dt. Inotropic agents thought to accelerate relaxation of cardiac muscle were compared to agents thought not to accelerate relaxation, and recovery from ischemia was studied as an example of a pathophysiological state known to prolong relaxation of the cardiac muscle.

METHODS

An isolated canine left ventricular preparation was employed. The time-course of left ventricular pressure fall was studied in single isovolumic and variously loaded ejecting beats at constant coronary perfusion pressure. This preparation allowed uninterrupted isovolumic pressure fall during relaxation after ejection of blood, in contrast to the normal working heart, in which isovolumic pressure fall is interrupted by mitral valve opening and ventricular filling.

40 support and donor fasting adult mongrel dogs (20–30 kg) were anesthetized with intravenous Surital (thiamylal sodium, Parke, Davis & Company, Detroit, Mich.) (20 mg/kg) and maintained with intravenous chloralose (15 mg/kg). After institution of positive pressure ventilation, the ascending aorta was isolated through a left thoracotomy. Heparin (2.5 mg/kv i.v.) was administered. A perfusion cannula was introduced into the descending aorta *in situ* just distal to the left brachiocephalic trunk, and the pericardium removed. Retrograde aortic perfusion was instituted with blood supplied by the support dog. Then, the brachiocephalic vessels were ligated and transected, and the donor heart and proximal aorta removed from the chest. Digital rupture of the mitral chordae was performed quickly to prevent ejection of air from the left ventricle into the perfusion column.

Thus, the heart was totally isolated without interruption of coronary flow and was subsequently perfused from a

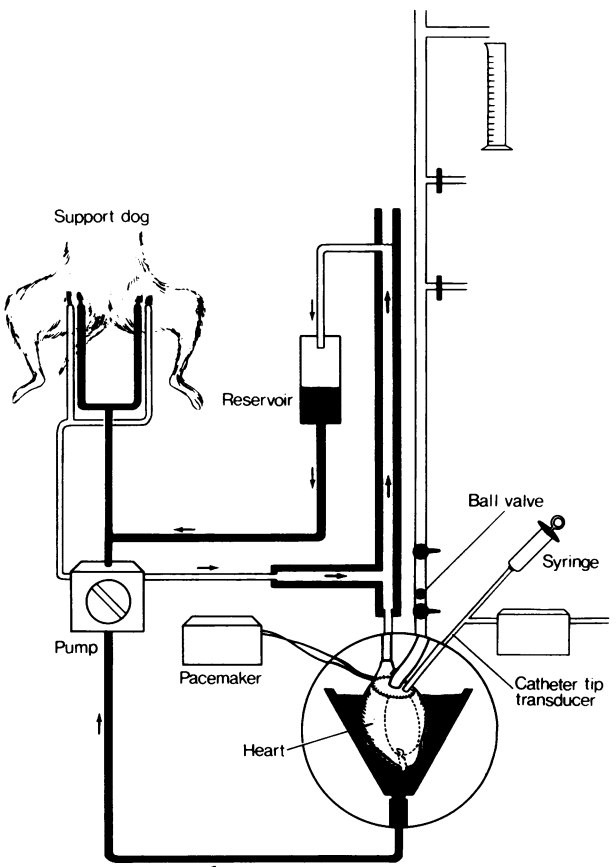

FIGURE 1 Isolated canine heart preparation. This preparation allows the study of pressure fall under isovolumic conditions or in the ejecting heart with prolonged isovolumic diastole. The aorta of the suspended donor heart is perfused at constant pressure with arterial blood supplied by a support dog. A pump maintains coronary perfusion of the donor heart and returns venous blood to the support dog. The blood perfusion column is maintained at 37°C by a water jacket. An overflow port allows return of blood from this column to the venous circulation of the support dog. Epicardial pacing electrodes are sewn into the right ventricle.

support dog at a pressure of 130 cm H_2O maintained by an overflow column (Fig. 1). Coronary venous blood from the transected pulmonary artery and left ventricular Thebesian flow from an apical left ventricular drain bathed the donor heart at constant temperature (37°C) in a funnel and was then returned to the support dog.

A stainless steel button was sewn to the aortic and mitral valve rings so as to occlude both these orifices completely. The intraventricular side of the button was affixed to a latex balloon that occupied the entire left ventricle when filled with fluid. The balloon was shown to be freely distensible over a range of volumes exceeding the ventricular volumes employed. Balloon herniation around the button could be detected at all times by direct visual inspection. The center of the button was traversed by a 1.0-cm-long metal cannula that entered the balloon. Through this cannula a No. 7-F Millar catheter tip micromanometer with a lumen (Model PC-47; Millar Instruments, Inc., Houston, Tex.) entered the balloon (16). The catheter tip was placed just beyond the end of the metal cannula to avoid catheter motion and to prevent entrapment. The catheter was balanced and calibrated at 37°C against a mercury column. Drift was detected by changes in mean pressure vs. pressures recorded from the catheter lumen with a Statham P23Db transducer (Statham Instruments Div., Gould Inc., Oxnard, Calif.). In the event of a drift, the catheter was removed and recalibrated as necessary. The volume of fluid in the left ventricle was changed by introducing known amounts of saline into the balloon via the catheter lumen. A second 8-mm cannula traversed the button entering the balloon and was occluded for isovolumic beats. For ejecting beats, the left ventricle ejected the contents of the balloon via the cannula into a fluid-filled metal ejection column that contained a Starr-Edwards ball valve prosthesis with a Silastic poppet (Edwards Laboratories, Santa Ana, Calif.), positioned to allow upward flow. The ejection column was fitted with two valves, one above and the other below the Starr-Edwards valve, and the ejection metal column was connected to a vertical length of fluid-filling tubing. Fluid could exit from the tubing at any of six ejection ports at various heights above the heart. The column was filled with fluid to the level of the ejection port chosen for a given beat. The ejectate from a single beat was collected at the port, and the volume measured. At the end of ejection in a given ejection beat, the ball valve closed when the left ventricular pressure fell below the height of the ejection port. The subsequent isovolumic pressure fall was not interrupted by mitral valve opening or ventricular filling. Thus, the entire time-course of isovolumic pressure fall could be determined. Beat-to-beat conversion from an isovolumic to an ejecting beat was achieved by opening the stop distal to the ball valve during diastole of the preceding isovolumic beat. The end-diastolic volume of ejection beats was determined by the amount of fluid placed into the balloon via the Millar catheter lumen before ejection. Left ventricular end-diastolic pressure was 5–15 mm Hg. Impedance to ejection in ejection beats was varied by changing the ejection port on the column. The intraventricular pressure measurements performed during isovolumic beats with both stops closed and with only the distal stop closed established the nondistensibility of the metal system proximal to the ball valve prosthesis. The volume of regurgitant flow through the valve prosthesis was less than 1.0 ml at the column heights employed.

Epicardial pacing electrodes were sewn to the right ventricle before the clamping of the sinus node. Hearts were paced with an impulse of 4.0 ms duration and voltage 20% above threshold. Ventricular pressure and the electrogram were recorded with a Honeywell 1856 Visicorder optical recording system (Honeywell, Inc., Test Instruments Div., Denver, Colo.) at paper speed of 500 mm/s.

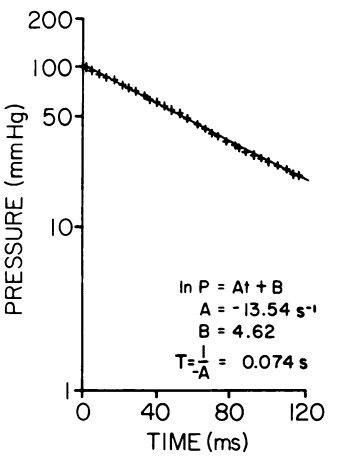

FIGURE 2 Direct computer plot of digitized data from a representative beat showing ventricular pressure on a logarithmic scale beginning at max neg dP/dt. *A*, a negative number, represents the slope of ln P vs. time in s^{-1}. *T*, the time constant, characterizes this phase of pressure fall and equals 1/-*A*. *B* is the *y*-intercept or ln P at max neg dP/dt.

The ventricular pressure tracings were digitized at 4.0-ms intervals with a Hewlett-Packard 8964A digitizing hand-held planimeter (Hewlett-Packard Co., Palo Alto, Calif.). The left ventricular pressure was digitized from a point well before max neg dP/dt to the point where pressure declined to the level of left ventricular end-diastolic pressure (LV EDP) of the same beat in isovolumic beats and to the LVEDP of the subsequent beat in ejection beats. An on-line Hewlett-Packard 9810A calculator-plotter determined the rate of pressure fall at each digitized point with a five-point numerical differentiation formula (17). Beginning at the time of max neg dP/dt, pressure was plotted and fit by the method of least squares to the function $P = e^{At+B}$. Constants for the fitted curves were reproducible to 0.1% on repeat digitization. Fig. 2 is a direct computer plot of digitized data from a representative beat, showing ventricular pressure on a logarithmic scale beginning at max neg dP/dt. *A*, a negative number, represents the slope of ln *P* vs. time in s^{-1}. *T*, the time constant, characterizes this phase of pressure fall and equals 1/-*A*. *B* is the *y*-intercept or ln *P* at max neg dP/dt. It should be recognized that the following relationship also obtains between max neg dP/dt and *A*: $P = e^{At+B}$; $dP/dt = A(e^{At+B})$, where dP/dt is negative; at $t = 0$, $dP/dt = \text{max neg } dP/dt = Ae^{B} = A \cdot (P \text{ at max neg } dP/dt)$.

The interval from the time of LVEDP to peak pressure was taken as the time to peak pressure (TPP). Peak pressure (P_{max}), pressure at max neg dP/dt (Pmax neg dP/dt), and time from P_{max} to max neg dP/dt (TP_{max}-max neg dP/dt) were also determined. Differences in group means were assessed for statistical significance with the *t* test for paired or unpaired values as appropriate (18). End-systolic volumes during an ejection beat were determined by subtracting the measured volume of ejectate from the end-diastolic volume. The extent of circumferential fiber short-

TABLE I

Effect of Heart Rate under Isovolumic Conditions

Heart rate, *beats/min*	110	120	130	140	150	160	170
T, *ms*	52.6±4.5	51.3±4.8	49.5±4.5*	49.5±5.0*	48.3±4.7‡	48.2±4.6*	50.4±6.0
Pmax, *mm Hg*	128±15	126±15	123±14	122±13	122±13	115±12*	114±11
Max neg dP/dt, *mm Hg/s*	−891±104	−983±107‡	−983±107*	−988±125	−1,023±137	−1,029±131*	−1,030±125*
TPP, *ms*	168.9±8.4	158.1±6.8§	154.0±7.2§	147.4±6.3§	140.5±6.0§	139.0±6.5§	132.8±9.7§
Pmax neg dP/dt, *mm Hg*	50±3	55±5	53±5	54±5	55±5‡	56±6	54±4
*T*Pmax-max neg dP/dt, *ms*	150.9±10.0	133.0±14.5	139.8±7.7*	135.5±8.3‡	129.3±7.0‡	126.9±5.9‡	119.5±6.4‡

Values are means±SEM for eight isovolumic left ventricular preparations; *t* test for paired values; *T*, time constant of pressure fall after max neg dP/dt; Pmax, peak LV pressure; max neg dP/dt, maximum negative dP/dt; TPP, time to peak LV pressure; Pmax neg dP/dt, pressure at max neg dP/dt; *T*Pmax-max neg dP/dt, time from Pmax to max neg dP/dt.

* $P < 0.05$ vs. rate 110/min.

‡ $P < 0.01$ vs. rate 110/min.

§ $P < 0.001$ vs. rate 110/min.

ening during ejection was approximated with a spherical model (19). Extent of circumferential fiber shortening was expressed in terms of percent change of inner wall circumference.

These hearts were studied (*a*) at heart rates between 110 and 170/min under isovolumic conditions, (*b*) with changes in end-diastolic volume in isovolumic and ejecting hearts, and (*c*) at varying levels of impedance during ejection. Also, calcium chloride (100 mg), acetylstrophanthidin (ACS) (100 μg), and norepinephrine (NE) (0.5–1.0 μg) were administered by rapid infusion directly into the coronary perfusion line to the donor heart. Global myocardial ischemia and recovery from ischemia were studied during and after cross-clamping of the coronary perfusion line for a 2-min period. Recordings were made at the end of 2 min of ischemia and between 1 and 2 min of recovery.

RESULTS

Time-course of isovolumic pressure fall. The time-course of fall in left ventricular pressure from the time of max neg dP/dt to the level of LVEDP was found to be exponential during isovolumic relaxation for both isovolumic and ejecting beats studied ($r \geqslant 0.98$, $n = 200$ [18]). Since ejection in ejecting beats was not followed by filling during diastole, the ventricle was isovolumic throughout diastole. The time-course of isovolumic pressure fall after max neg dP/dt is therefore characterized by T. As stated above, T is by definition equal to $1/-A$, where A represents the slope of the linear relationship between ln P and time in s^{-1}.

Heart rate. The effect of heart rate was studied in eight hearts under isovolumic conditions. Higher rates shortened T for isovolumic pressure fall after max neg dP/dt slightly, but statistically significantly. As shown in Table I, T shortened 8.9±3.2% from 52.6±4.5 ms at a heart rate of 110/min to minimum value of 48.2±4.6 ms at a rate of 160/min, but returned toward the control level at a rate of 170/min (50.4±6.0 ms). The effect of changes in heart rate on peak isovolumic pres-

TABLE II

Effect of Changes in Left Ventricular Volume under Isovolumic Conditions

LVEDP (mm Hg)	Range Mean (±SEM)	5–10 (7±0.5)	11–15 (13±0.5)	16–20 (18±0.5)	21–25 (22±0.5)
T, *ms*		60.8±3.8*	60.4±2.9	63.4±3.2	64.6±3.6
P_{max}, *mm Hg*		95±11	121±11‡	145±13‡	155±12§
Max neg dP/dt, *mm Hg/s*		−752±88	−919±99‡	−1,079±101‡	−1,134±89‡
TPP, *ms*		183.9±18.1	205.0±20.3‡	204.2±20.0‡	202.0±20.0
Pmax neg dP/dt, *mm Hg*		54±6	60±6	71±8	80±12‡
TPmax-max neg dP/dt, *ms*		106.3±9.0	106.1±7.0	102.0±6.0	102.0±3.0

Values are means±SEM for nine isovolumic left ventricular preparations; *t* test for paired values.

* Mean±SEM.

‡ $P < 0.01$ vs. LVEDP 5–10 mm Hg.

§ $P < 0.001$ vs. LVEDP 5–10 mm Hg.

TABLE III
*Effect of Ejection**

Beat type	T ms	P_{max} mm Hg	Max neg dP/dt mm Hg/s	TPP ms	Pmax neg dP/dt mm Hg	TPmax-max neg dP/dt ms
Isovolumic preejection	67.1±5.0	171±7	−1,166±80	157.7±9.7	82±5	165.7±14.3
Ejection	45.8±2.9	158±7	−1,266±120	150.9±11.4	66±4	162.6±11.2
P‡	<0.001	<0.001	NS	NS	<0.005	NS

Values are means±SEM for preejection and ejection beats in 14 hearts.
* One pair of beats (isovolumic and ejection) studied in each heart.
‡ t test for paired values.

sure (P_{max}), max neg dP/dt, Pmax neg dP/dt, TPP, and TPmax-max neg dP/dt are shown in Table I. There was no significant change in P_{max} at increasing heart rates, but there was a statistically significant shortening of the entire time course of contraction. TPP decreased 21.8±1.5% from 168.9±8.4 ms to 132.8±9.7 ms. The time from P_{max}-max neg dP/dt shortened 19.9±2.9% from 150.9±10.0 ms to 119.5±6.4 ms. Max neg dP/dt increased at some, but not all, increasing heart rates. Thus at higher heart rates, the shortening of T although statistically significant, was relatively less than the shortening of the time-course of contraction up to the time of max neg dP/dt.

Volume. Larger ventricular volumes under isovolumic conditions resulted in greater peak systolic wall stress by virtue of higher peak left ventricular pressure during systole and greater ventricular size. Table II shows the results of studies in nine hearts. These data are tabulated in terms of LVEDP. LVEDP was used rather than absolute volume to compare hearts of differing size at similar positions along the diastolic pressure-volume curve. P_{max} was significantly higher at higher levels of end-diastolic pressure. There were parallel changes in pressure at max neg dP/dt with significantly higher levels at the highest end-diastolic pressures. Associated with this increase in pressure at max neg dP/dt was an increase in the maximal rate of pressure fall (max neg dP/dt). In contrast, there was no significant change in the T of isovolumic pressure fall. At end-diastolic pressures of 5–10 mm Hg, T was 60.8±3.8 ms, and at end-diastolic pressures of 21–25 mm Hg, T was 64.6±3.6 ms (NS). TPP lengthened significantly between end-diastolic pressures of 5–10 mm Hg and 11–15 mm Hg, but there was no further prolongation at higher levels of end-diastolic pressure. TPmax-max neg dP/dt was not influenced significantly by increases in volume. Thus, increases in volume or fiber length and systolic stress alter neither the time from peak pressure to the time of max neg dP/dt, nor T.

Ejection. In 14 hearts the left ventricle was converted from isovolumic contraction to ejection on a beat-to-beat basis during diastole by opening the valve in the metal ejection column housing the Starr-Edwards valve. Thus, the ejection beat and the preceding isovolumic beat had the same end-diastolic pressure and volume. End-systolic wall stress was less and end-systolic fiber length or the fiber length during relaxation was shorter by virtue of ejection in the ejecting beats. In Table III, data from ejection beats and the preceding isovolumic beats are presented. T shortened with ejection from 67.1±5.0 ms to 45.8±2.9 ms ($P < 0.001$). Ejection resulted in the expected fall in peak systolic pressure and also resulted in a fall in pressure at max neg dP/dt. Max neg dP/dt did not change significantly. Other time intervals did not change significantly as a result of ejection.

To provide evidence as to whether T can be related to fiber shortening during systole, the ejection volume and thus the end-systolic volume was varied in steps by changing the impedance to ejection from the same end-diastolic volume. Fig. 3 shows a plot of the percent change in ventricular circumference vs. the de-

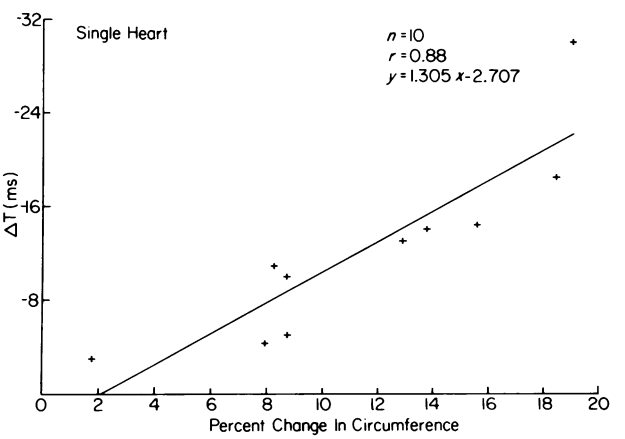

FIGURE 3 Decrease in T from the pre-ejection isovolumic beat as a function of percent change in left ventricular circumference during ejection. The line of regression was determined by the method of least squares. The mean value of T for the isovolumic beats was 60.2±2.4 ms.

TABLE IV

Effect of Changes in End-Diastolic Volume in Ejection Beats

	Change in circumference during ejection	Pmax	ESV*	EDV‡	T
	%	*mm Hg*	*ml*	*ml*	*ms*
Small EDV	7.9±1.6	117±10	28.9±4.3	36.5±4.0	55.0±3.0
Large EDV	14.6±1.9	149±9	32.3±8.7	50.8±2.6	46.0±1.0
P§	<0.001	<0.01	NS	<0.001	<0.001

Values are means±SEM in eight pairs of beats from eight hearts. The pairs of beats were chosen such that systolic pressure and end-systolic fiber length were the same or greater in the beats with greater extent of fiber shortening.

* ESV, end-systolic volume.

‡ EDV, end-diastolic volume.

§ t test for paired values.

crease in T, from 10 pairs of isovolumic and ejecting beats at various ejection volumes in a single heart. Circumference was computed from the end-diastolic and end-systolic volumes by a spherical model (19). There is an apparent correlation between circumferential fiber shortening during ejection and the decrease in T ($r = 0.88$, $P < 0.01$). Data for 51 beats from six other hearts were similar ($r = 0.62$–0.89). An increase in shortening was therefore associated with shortening of T for isovolumic pressure fall.

The isovolumic studies suggest that changes in systolic pressure or stress and end-systolic fiber length per se do not influence T for isovolumic pressure fall. The ejection studies discussed thus far demonstrate that in ejection beats in which there is (*a*) greater systolic shortening, (*b*) low systolic stress, and (*c*) shorter end-systolic fiber length, T is shorter. To differentiate more clearly the effects of systolic stress and end-systolic fiber length from the effects of systolic shortening on T, other ejection beats were studied in which the extent of fiber shortening was increased by increasing end-diastolic volume. Pairs of ejection beats from eight hearts were chosen for study. Pairs were chosen such that the systolic pressure and end-systolic fiber length were the same or greater in the beats with greater extent of fiber shortening. In Table IV the percent change in circumference during ejection for eight pairs of beats from eight hearts with small (36.5±4.0 ml) and large (50.8±2.6 ml) end-diastolic volumes are presented. It can be seen that beats with the larger end-diastolic volume have a greater percent change in circumference and thus a greater extent of circumferential shortening. Peak systolic pressure is higher in the ejecting beats with the large end-diastolic volumes. The end-systolic volume of the ejecting beats with the small end-diastolic volumes was 28.9±4.3 ml, and the end-systolic volume

TABLE V

Effect of Inotropic Agents in the Isovolumic Left Ventricle

		T	P_{max}	Max neg dP/dt	Pmax neg dP/dt	TPP	TPmax-max neg dP/dt
		ms	*mm Hg*	*mm Hg/s*	*mm Hg*	*ms*	*ms*
$CaCl_2$, 100 mg, (Five hearts)	Before	83.4±10.2	115±26	−767±197	61±13	159±19	138±18
	After	67.3±5.3	171±21*	−1,173±165*	82±21	137±9	116±12*
Acetylstrophanthidin, 100 μg (Eight hearts)	Before	58.8±10.7	118±15	−895±197	50±7	170±16	156±15
	After	54.9±10.7	141±19‡	−1,009±242§	72±14*	158±15*	141±15‖
Norepinephrine, 0.5–1 μg	Before	65.6±13.4	125±16	−934±167	62±10	175±18	145±15
	After	46.3±7.0‡	183±21§	−1,610±238‖	87±11*	129±14§	133±14

Values are means±SEM; t test for paired values.

* $P < 0.05$.

‡ $P < 0.02$.

§ $P < 0.01$.

‖ $P < 0.001$.

TABLE VI

Effect of Ischemia and Recovery from Ischemia in the Isovolumic Left Ventricle

	T	Pmax	Max neg dP/dt	Pmax neg dP/dt	TPP	*T*Pmax-max neg dP/dt
	ms	*mm Hg*	*mm Hg/s*	*mm Hg*	*ms*	*ms*
Control (Five hearts)	58.6±11.8	177±17	−1,526±321	92±6	164±17	136±19
Ischemia	92.6±31.3	43±10*	−321±75‡	26±5*	115±11*	88±9
Control (Six hearts)	59.0±9.6	164±19	−1,361±310	84±9	166±14	146±18
Recovery	76.8±13.1‡	127±18	−714±129	58±9	168±13	174±14‡

Values are means±SEM. During ischemia, the pressure of one heart was not recordable due to fibrillation; hence data from only five hearts are available; *t* test for paired values.

* $P < 0.01$.

‡ $P < 0.05$.

for the beats with the large end-diastolic volumes, 32.3 ±8.7 ml (P = NS). The beats with the larger end diastolic-volumes and the greater extent of shortening had a shorter T (46.0±1.0 ms) than the beats with the small end-diastolic volumes and smaller extent of circumferential shortening (55.0±3.0 ms), despite the higher level of peak pressure and no significant difference in end-systolic fiber length. Thus it would appear that circumferential fiber shortening rather than changes in peak systolic wall stress or end-systolic fiber length determines T for isovolumic pressure fall. Similar results were obtained in two hearts after β-blockade with 5.0 mg of *d-l* propranolol.

Inotropic agents. The effects of calcium ACS, and NE under isovolumic conditions are shown in Table V.

Calcium chloride increased Pmax from 115±26 mm Hg to 171±21 mm Hg. T did not change significantly, whereas max neg dP/dt increased from −767±197 mm Hg/s to −1,173±165 mm Hg/s after calcium chloride ($P < 0.05$). Similarly, ACS resulted in no significant change in T, an increase in P_{max}, P at max neg dP/dt and max neg dP/dt.

Nine isovolumic left ventricles were studied before and after NE. P_{max} increased significantly from 125±16 mm Hg to 183±21 mm Hg. In contrast to calcium and ACS, T shortened significantly after the administration of NE (65.6±13.4 to 46.3±7.0 ms, $P < 0.02$). Pmax neg dP/dt also increased. Max neg dP/dt increased significantly from −934±167 to −1,610±238 mm Hg/s ($P < 0.001$).

Ischemia and recovery. Ischemia was studied in six isovolumic left ventricles. T did not change significantly during ischemia, but during recovery from ischemia T increased significantly from 59.0±9.6 ms to 76.8±13.1 ms when compared with the preischemic control beat ($P < 0.05$; Table VI). P_{max} diminished markedly during ischemia from 177±17 mm Hg to 43±10 mm Hg ($P < 0.01$). The variability seen during ischemia reflects variability in the response of individual hearts to global ischemia. During the postischemic recovery period, mean P_{max} was lower than control preischemic P_{max} but the difference was not statistically significant.

DISCUSSION

The present studies demonstrate that the time-course of fall in left ventricular pressure after max neg dP/dt is exponential both in isovolumic and ejecting beats. This exponential time-course of fall in left ventricular pressure after max neg dP/dt permits characterization of this phase of isovolumic relaxation in the intact ventricle by T. The rate of pressure fall at any point in time during this phase of isovolumic relaxation can be determined from the left ventricular pressure at that point in time and T.

Other investigators have, under certain circumstances, found a deviation of this portion of pressure fall from exponential (20) and, under other circumstances, have found that the fit to the exponential fall is good (21). Two factors in the present preparation differed from those previously employed, which may explain those circumstances where deviations were found. In the present study, the mitral and aortic valves were excluded from the left ventricular cavity and the papillary muscles rendered nonfunctional by the placement of the button across both valves. Under physiological conditions there may be significant movement of the aortic valve due to a higher pressure outside of the valve during isovolumic relaxation. This would result in alterations in cavitary pressure. Secondly, in the present study the micromanometer was situated in a fixed position just beneath the button. This prevented any catheter movement or transducer movement during relaxation and minimized the chance of catheter entrapment,

since the tip was well away from the apex of the ventricle.

In the working dog heart, max neg dP/dt occurs 8–34 ms after aortic valve closure (13). Before aortic valve closure, the rate of left ventricular pressure fall is a function of the dynamic stiffness of the periphery as well as left ventricular wall stress. After the time of max neg dP/dt, the left ventricle is isovolumic until mitral valve opening in the normal heart. If one assumes the ventricle to be truly isovolumic with constant dimensions, then the rate of fall in pressure will reflect the rate of fall in left ventricular wall stress. The rate of fall in wall stress will in turn reflect the activity of the active cardiac relaxing system and any visco-elastic changes during this portion of the contraction cycle.

These results show that the T for isovolumic pressure fall after max neg dP/dt is independent of peak ventricular systolic pressure, end-systolic volume or fiber length, minimally dependent on heart rate, and principally a function of systolic fiber shortening. Since NE is thought to enhance the activity of the active cardiac relaxing system (7, 8) and shortens T, T appears to be an index of the activity of the active relaxing system. Persisting contractile activity and viscoelastic properties may also play a role in determining the time-course of relaxation. In our study, the time course of pressure fall was fit to the equation $P = e^{At+B}$ within the limits set by our data. After the return of pressure to the level of end-diastolic pressure, passive, visco-elastic properties may be of importance.

In the studies performed under isovolumic conditions where no ejection or overall shortening occurred, the value of T did not change with increases in isovolumic volume despite higher peak systolic pressure and thus stress. Thus, T appears to be independent of peak pressure or wall stress. Within the limits of heart rates studied, higher heart rates under isovolumic conditions, although resulting in significant and substantial shortening of the other time periods of the beat (TPP and TP_{max}-max neg dP/dt), resulted in small changes in T. Substantial changes in the time course of development and early decline in wall stress were not associated with changes in T. In contrast, ejection beats at varying impedance levels showed a shorter T when compared to the preceding isovolumic beat, although there was no significant change in TPP or TP_{max}-max neg dP/dt (Table III). Ejection beats differed from the preceding isovolumic beat, in that fiber shortening in the ejection beat occurred during contraction and in that the end-systolic volume or the fiber length during isovolumic relaxation was smaller in the ejection beat. To differentiate clearly the effects of systolic shortening from those of end-systolic fiber length or volume per se in ejecting beats, beats with larger ventricular end-diastolic volumes and greater extent of shortening due to the Frank-Starling effect were compared to beats with smaller end-diastolic volumes in the same hearts. The beats compared were those in which the impedance to ejection was such that end-systolic volume was similar and P_{max} as high or higher in the beats with larger end-diastolic volumes and greater shortening. T again shortened with greater systolic fiber shortening. Thus, T appears to be dependent on systolic fiber shortening and independent of peak wall stress and end-systolic volume or fiber length.

There are two general mechanisms that may explain the apparent dependence of T on systolic fiber shortening. The first is that shortening results in more rapid inactivation of the active state. In their quick release studies performed on isolated skeletal muscle, Jewell and Wilkie (14) demonstrated that inactivation of the active state, as manifest by a decline in tension after release, is a function of the extent of release. A second possible mechanism for the dependence of T on shortening is that tension falls more rapidly as a reflection of the visco-elastic properties of cardiac muscle (22). Recent studies have documented an important viscous contribution to dynamic stiffness of the intact heart under isovolumic conditions (23). Unfortunately, no data are available regarding the behavior of the viscoelastic properties with or after systolic shortening in the ejecting heart, or with or after shortening in isolated muscle preparations.

The changes in T with positive inotropic agents are similar to the changes in parameters of the isometric muscle twitch. These parameters may reflect the active cardiac-relaxing system perhaps localized to the sarcoplasmic reticulum. Studies from a number of laboratories demonstrate a marked effect of catecholamines in accelerating the rate of relaxation of isolated cardiac muscle. This effect appears functionally separable from the inotropic properties of these agents (7–9). In contrast, calcium and digitalis glycosides have little effect on these parameters of isometric relaxation in similar preparations (8, 9). In isolated cardiac muscle the period after hypoxia is characterized by a marked prolongation of these mechanical indices of the rate of relaxation (1, 2). In the present study the predicted changes in T occurred during catecholamine stimulation and after ischemia under isovolumic conditions. Calcium and ACS resulted in no significant change in T. These studies suggest that T is sensitive to the activity of the active cardiac-relaxing system.

Sulman et al. (10) studied relaxation in isolated cardiac muscle utilizing "physiological loading." This system allows isometric relaxation to occur at peak shortening before isotonic relaxation. These studies appear

to be at variance with the present investigation in that tension fall seems nearly linear with time rather than exponential. However, several points should be taken into account before attempting to draw strict parallels between this isolated muscle preparation and intact heart preparations. The relaxation phase in the studies of Sulman et al. appears extremely long relative to the phase of tension rise. The relatively low bath temperature of 28°C may in part account for this prolonged phase of relaxation (9). Hypothermia may result in a dominant viscous component or a markedly slowed calcium uptake system. Injury to the ends of muscle at the points of attachment, with possible attendant unphysiological viscoelastic behavior of these stretching injured portions of muscle, may also alter the rate of tension fall in these preparations (24).

In our studies, P_{max} did not increase as a function of increasing rate. This lack of increase in P_{max} agrees with recent observations by Kahn et al. (25) on the effect of heart rate on the *in situ* isovolumic canine left ventricle.

T appears to be a more useful index of relaxation than previously available measures. The time of P_{max} to one-half peak pressure is not applicable to the working heart. The early time-course of pressure fall likely reflects peripheral factors as well as left ventricular relaxation. Max neg dP/dt in the present study, as in a previous study (13), is principally dependent on P_{max} (Table II).

The results of the previous study (13) suggest that both fiber shortening and end-systolic fiber length or volume per se were determinants of max neg dP/dt. However, the present study points to a dependence of T on systolic fiber shortening to the exclusion of end-systolic fiber length. Despite a lower pressure at max neg dP/dt with ejection (Table III), the shorter T indicates that relaxation is more rapid and thus max neg dP/dt does not fall but tends to increase. It remains uncertain whether peripheral factors influencing the timing of aortic valve closure may affect max neg dP/dt by changing the time of onset of isovolumic relaxation and thereby the pressure at max neg dP/dt.

The extent to which T is in fact influenced by changes in the extent or velocity of systolic fiber shortening will need to be re-examined in a working preparation over a range of physiological changes in stroke volume and thus fiber shortening. In the present study only rather large beat-to-beat step function changes in fiber shortening from an isovolumic to an ejection beat were studied.

Either T or the negative reciprocal, A, could have been presented as the index of relaxation. T is an easily understood concept employed in the study of other exponential processes. In addition, T is a precise hemodynamic measure. At any time subsequent to max neg dP/dt, pressure and the rate of pressure fall can be determined from T and P at max neg dP/dt as long as the ventricle is isovolumic. Further utility of T resides in its possible value in predicting the time-course of relaxation after mitral valve opening in the intact heart.

There is a clear need for an examination of T in more intact preparations. The present study shows that T is shorted by NE under isovolumic conditions. Thus, T may be an index of the activity of the active cardiac-relaxing system. The effect of shortening on T may be due to deactivation of active state by rapid shortening or reflect viscoelastic changes as a result of shortening.

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