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Circ. Res. 1977;40;584-589
Circulation Research is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7330. Online ISSN: 1524-4571

Maximum Rate of Tension Fall during Isometric Relaxation at End-Systolic Fiber Length in Canine Papillary Muscle

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SUMMARY **We measured the characteristics of the decline in tension during isometric relaxation of canine papillary muscle. In the intact heart, relaxation begins with the isovolumic phase, but in experiments on papillary muscle previously reported the isotonic phase preceded the isometric phase during the course of relaxation. In our experiments, however, the isotonic bar was locked at the instant the muscle reached the end-systolic fiber length in order to hold the fiber at that length during the succeeding relaxation process. Therefore, we obtained a relaxation process similar to that occurring in an intact heart. The major results of these experiments are: (1) Maximum rate of the decline in tension ($-dT/dt_{max}$) is linearly related to the magnitude of total load. (2) $-dT/dt_{max}$ is augmented by positive inotropic interventions and diminished by negative inotropic interventions. (3) An increase in preload results in only a slight increase in $-dT/dt_{max}$. (4) End-systolic fiber length itself is not a principal determinant of $-dT/dt_{max}$. (5) $-dT/dt_{max}$ divided by total load is independent of the amount of muscle shortening. We, therefore, suggest that $-dT/dt_{max}$ divided by total load can be a useful index of the relaxation characteristics of cardiac muscle.**

SEVERAL investigations have correlated myocardial relaxation characteristics with hemodynamic parameters.[1] Jewell and Wilkie[2] studied the mechanics of muscle relaxation using the skeletal muscle of a frog, and observed that tension declined exponentially when the muscle was allowed to change its length, but in the case of true isometric relaxation the tension did not decline exponentially. Parmley and Sonnenblick[3] studied an isolated cat papillary muscle, and observed that tension decayed exponentially in the isometric relaxation phase following an afterloaded contraction. They mentioned that the time constant of exponential isometric tension decay ($t_{\frac{1}{2}}$) increased linearly with total load. In a true isometric relaxation following true isometric contraction, they concluded that the time required for tension to fall to one-half its peak value ($T - P_0/2$) was altered by different inotropic agents. Under conditions in which the interventions used produced similar peak contractile force (P_0) and maximum dP/dt, there were, however, significant differences in the decline in tension, depending on the intervention. On the other hand, Cohn et al.,[4] using both intact hearts in situ and isolated hearts, concluded that the primary determinants of maximum rate of pressure fall ($-dP/dt_{max}$) were the end-systolic fiber length and the contractile state of the cardiac muscle. Weisfeldt et al.[5] conducted experiments similar to those of Cohn et al.[4] and observed that $-dP/dt_{max}$ increased with mean aortic pressure. The seemingly contradictory results of these investigations make it difficult to predict exactly how myocardial relaxation is affected by various factors.

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Received February 24, 1976; accepted for publication November 4, 1976.

To explain the contradictions between these results, we must consider differences between the process of relaxation in the papillary muscle preparation and the intact heart. In the intact heart, the decline in isovolumic pressure occurs at the end-systolic ventricular volume, whereas in the conventional afterloaded contraction of the papillary muscle, tension declines isometrically after the muscle is stretched to its initial length. The differences between the experimental results of isometric relaxation in the conventional afterloaded contraction of the papillary muscle and isovolumic relaxation in the intact heart probably are caused by the different processes described above.

In a papillary muscle experiment, if one expects to simulate the mechanical process of isovolumic relaxation in the intact heart, isometric tension fall should be measured at an end-systolic fiber length corresponding to the minimum length during isotonic shortening of the muscle during an afterloaded contraction.

Methods

The number and basic characteristics of the papillary muscles studied in the present experiments are shown in Table 1. The apparatus for measuring tension and shortening of the papillary muscle consists of a light isotonic bar joined to the shaft of a photoelectric displacement transducer (Fig. 1). This shaft can rotate freely and its angular movements are measured by the photoelectric transducer. A light strain gauge tension transducer (compliance less than 5.5×10^{-7} cm/dyne) is attached to one end of the isotonic bar, and a light paramagnetic plate to the other end. An electromagnet is set near the paramagnetic plate with small clearance, and is used for locking the isotonic bar at any desired instant. An isotonic load is attached near the pivot of the lever. A fine turning screw is used for adjusting the initial position of the isotonic bar. The base of the papillary muscle is fixed on an acrylic resin board by piercing the endocardium with two needles. The

TABLE 1 *Physical Characteristics of Papillary Muscles*

Muscle	Length (mm)	Volume of the muscle (mm³)	Average cross-sectional area (mm²)	Maximum total load (g)	Maximum stress (g/mm²)
1	9.5	67.3	7.1	7.0	0.98
2	8.3	63.4	7.6	6.5	0.87
3	8.9	51.5	5.8	10.0	1.73
4	12.5	179.6	14.4	11.3	0.79
5	14.5	178.3	12.2	14.3	1.17
6	10.0	82.5	8.3	7.0	0.84
7	9.5	49.2	5.2	6.9	1.33
8	9.5	87.3	9.1	11.6	1.27
9	12.3	135.6	11.0	6.0	0.54
Mean ± SEM	10.6 ± 1.94	99.4 ± 48.9	8.97 ± 2.87	8.96 ± 2.76	1.06 ± 0.34

acrylic resin board is fixed firmly by heavy weights. The tendinous end of the papillary muscle is connected directly to the end of the strain gauge tension transducer by a short segment of fine copper wire in order to measure its tension. The initial length of the papillary muscle (preload) is controlled by adjusting the initial position of the isotonic bar. The papillary muscle is surrounded by a water jacket that maintains a constant temperature environment. The surface of the papillary muscle remains moist because the water jacket protects it from the room air.

To measure the moving equivalent mass of the lever system, a light spring is attached instead of a papillary muscle. An isotonic load corresponding to a total load of 10 g is attached near the pivot of the lever. Then the lever system is set in free oscillation. The measured frequency of oscillation (f) (Hz), amplitude of displacement (S) (cm), and force (F) (dynes) acting on the tip of the lever are 7.5 Hz, 0.022 cm, and 392 dynes, respectively. Then the moving equivalent mass $F/4\pi^2f^2S$ is 8.02 g (mass). In the present study the magnitude of acceleration of the tip of the lever is not greater than 25 cm/sec² at the isotonic contraction phase. Therefore, the estimated error in the measurement of tension due to the inertial force is given by the product of the moving equivalent mass of the lever system and the magnitude of the acceleration of the tip of the lever. It was 200.5 dynes or 0.2 g for the present experiments and was not greater than 2% of total load in the isotonic contraction phase during a total load of 10 g. During the relaxation phase, however, nearly no error is caused by the inertial force, since the lever is locked at the end-systolic position.

The preparation of the papillary muscle was basically the same as that of Endoh et al.[6,7] Mongrel dogs weighing 10–15 kg were anesthetized with an intravenous administration of sodium pentobarbital, 25 mg/kg. After intravenous injection of sodium heparin, 1 mg/kg, the dog was bled by an incision on the femoral artery. About 5 minutes after the initiation of bleeding, the heart was excised and immediately plunged into normal saline at 4°C. Spontaneous contraction stopped immediately after immersion. The anterior septal artery was exposed and cannulated with a fine polyethylene cannula, and was flushed with cold normal saline. The right ventricular wall was removed to expose the right side of the intraventricular septum. All branches except the anterior septal artery to the anterior papillary muscle were ligated with silk thread. A schematic diagram of the experimental system is shown in Figure 2. The arteries to the papillary muscle were perfused through the anterior septal artery with blood pumped from the carotid artery of a donor dog (see the next paragraph) by means of a roller pump. A pneumatic resistor was placed in parallel with the papillary muscle in order to maintain the perfusion pressure at 100 mm Hg. The blood from the papillary muscle through the Thebesian vein was returned to the donor dog via the external jugular vein. It took about 15 minutes from the time of excision of the heart to the time perfusion of the anterior septal artery was begun.

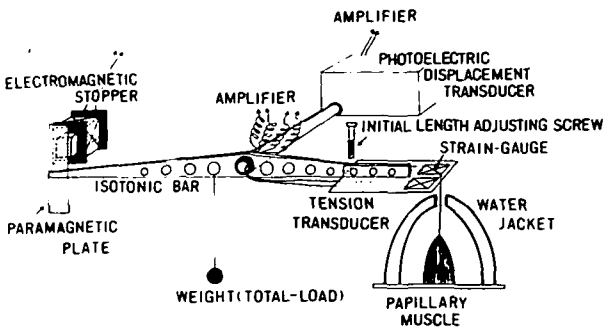

FIGURE 1 *Diagram of apparatus for the measurement of afterloaded contraction and isometric relaxation at the end-systolic fiber length.*

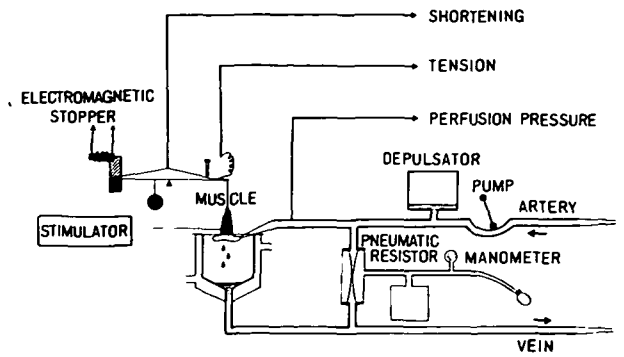

FIGURE 2 *Experimental setup for the perfusion of papillary muscle by cross-circulation.*

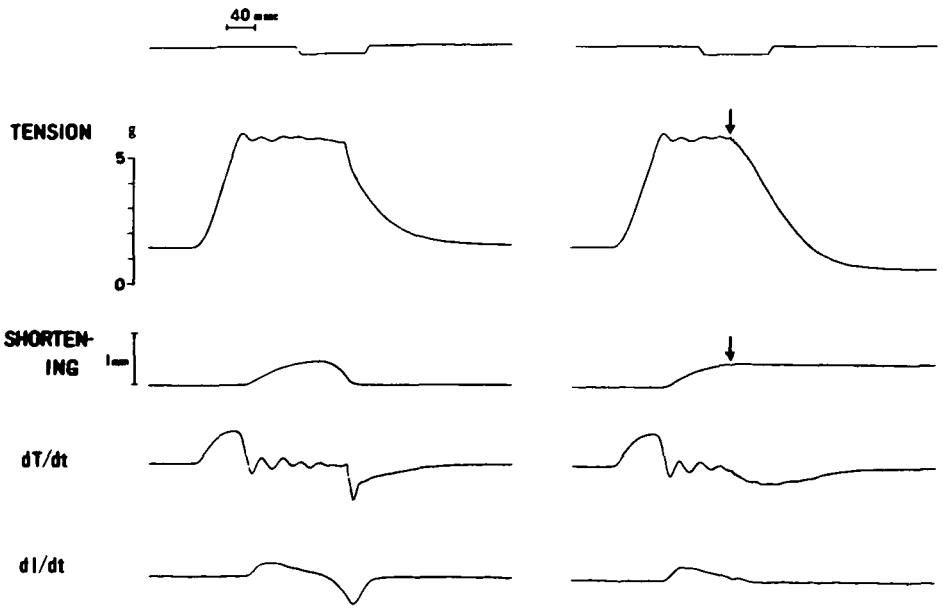

FIGURE 3 *Left: representative isometric relaxation at the initial fiber length following afterloaded contraction. Right: representative isometric relaxation at the end-systolic fiber length following afterloaded contraction. The isotonic bar was locked at end-systole (arrow) by the electromagnet. dT/dt is the first derivative of tension with respect to time. dl/dt is the first derivative of shortening with respect to time.*

All manipulation of the papillary muscle was performed at 4°C.

The blood donor dog (weight, 15–20 kg) was anesthetized intravenously with sodium pentobarbital, 25–30 mg/kg. The trachea was intubated and the dog was ventilated with a constant volume respirator. At about 10 minutes after administration of sodium heparin (1 mg/kg) the carotid artery and external jugular vein were exposed and cannulated so that the dog might serve as a blood donor. Sodium heparin (0.5 mg/kg) was added whenever necessary to prevent clotting.

About 30 minutes after the beginning of perfusion with blood, electrical stimulation with square wave pulses 1 msec in duration was begun using a bipolar electrode in contact with the base of the papillary muscle. The amplitude of the pulses was 10% above the threshold voltage and the frequency of stimulation usually was 60/min. This value was selected to prevent extrasystoles and to produce uniform contractions. After the muscle contraction became uniform, a series of afterloaded contractions was recorded. The instant the papillary muscle reached its end-systolic fiber length during an isotonic contraction, the isotonic bar was locked by the electromagnet in order to obtain an isometric relaxation at the fixed end-systolic fiber length. The electromagnet was triggered by the pacemaker spike, allowing for adequate delay time to hold the lever at the end-systole. We repeated this process for each muscle at various preloads by sequentially increasing total load until the contraction became fully isometric. In this way a series of isometric relaxations at the end-systolic fiber length was obtained. By administration of inotropic drugs such as isoproterenol (10^{-6} g), calcium dichloride (5×10^{-3} g), or propranolol (10^{-4} g), the effects of changes in contractility on myocardial relaxation were examined in three muscles. The effects of changes in the frequency of stimulation on the maximum rate of tension fall ($-dT/dt_{max}$) also were evaluated for increments of 20 beats/min over a range of 60–120 beats/min in two muscles.

Unlike isometric relaxation at the initial fiber length, in which the tension fall can be characterized by an exponential time constant ($t_{\frac{1}{2}}$), the fall in tension in the present preparation was exponential for only a short period of time. Thus, the measurement of a $t_{\frac{1}{2}}$ yielded data with poor reproducibility and large scatter, and the comparison of $-dT/dt_{max}$ with $t_{\frac{1}{2}}$, which had been previously proposed,[3] could not be performed.

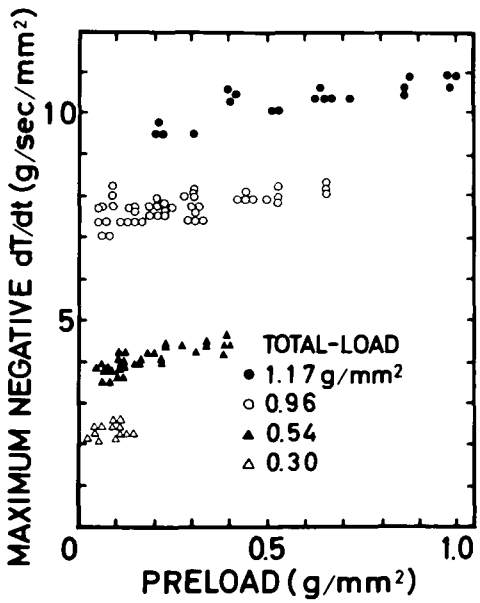

FIGURE 4 *The $-dT/dt_{max}$ values from one papillary muscle under conditions of constant contractility, different preloads and total loads. Note that $-dT/dt_{max}$ is not strongly influenced by changes in preload.*

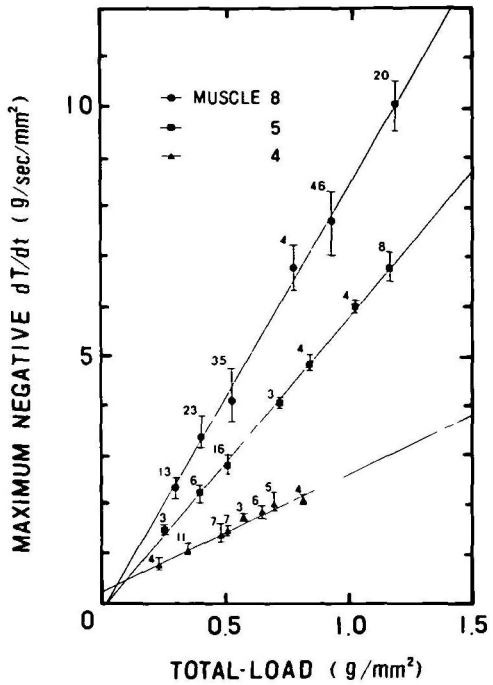

FIGURE 5 *The relation between total load and $-dT/dt_{max}$ in three different muscles. Note that $-dT/dt_{max}$ is linearly related to total load. Numbers to the left of the data points indicate the number of measurements. Bars indicate the maximum and minimum values.*

Results

During isometric relaxation at the initial fiber length following afterloaded contraction, there was an abrupt decline in tension followed by an exponential decline as shown in Figure 3 (left). However, when the muscle length was held at the end-systolic fiber length during an isometric relaxation by locking the isotonic bar with the electromagnet at the instant shown by the arrow in Figure 3 (right), no abrupt fall in tension was observed. Exponential tension decay was seen only for a short period during the last phase of isometric relaxation.

Therefore the characteristic tension decay curves were substantially different for the two preparations. The effects of increasing total load and preload on $-dT/dt_{max}$ during isometric relaxation at the end-systolic fiber length are plotted in Figure 4. As total load was increased, $-dT/dt_{max}$ became progressively greater. As preload increased, a slight increase in $-dT/dt_{max}$ was observed. However, since the increase in $-dT/dt_{max}$ due to the increment of preload was very small, $-dT/dt_{max}$ can for all practical purposes be regarded as a function of total load alone under conditions of constant contractility (Fig. 5). Slow recordings of papillary muscle tension, papillary muscle length, and their first derivatives with respect to time are shown in Figure 6. At point A in Figure 6 preload was increased, then the end-systolic fiber length was increased. Point B in Figure 6 shows the effect of increasing total load on the end-systolic fiber length. The end-systolic fiber length was increased in this case, too. Thus the end-systolic fiber length was affected by both preload and total load. $-dT/dt_{max}$ was independent of the end-systolic fiber length at various preloads under conditions of constant total load and constant contractility.

To evaluate the effect of changes in contractility on $-dT/dt_{max}$, isoproterenol (10^{-6}g), calcium dichloride (5×10^{-3}g), and propranolol (10^{-4} g) were injected into the perfusing blood under conditions of constant preload and total load. In Figure 7 the effects of administration of calcium dichloride and isoproterenol are shown in order to compare their effects on the duration of isotonic contraction. These two interventions showed nearly identical effects on the increments of shortening and $-dT/dt_{max}$. However, the duration of isotonic contraction was markedly prolonged with calcium dichloride in contrast to isoproterenol under conditions of constant preload and total

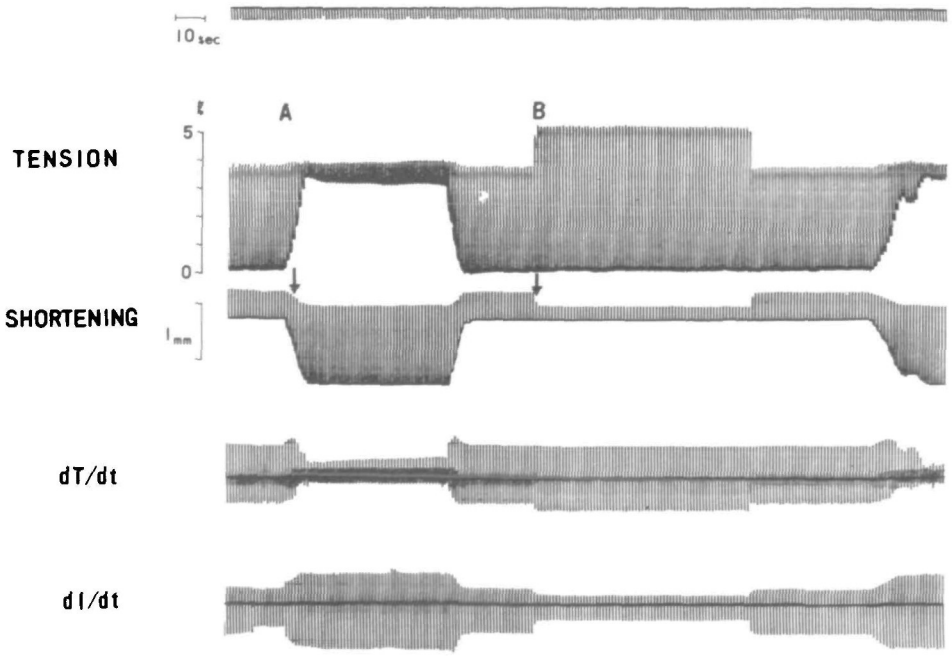

FIGURE 6 *Slow recordings of tension, shortening, and their first derivatives with respect to time. At point A, preload was increased, then the end-systolic fiber length was increased (arrow). At point B, total load was increased, then the end-systolic fiber length was increased (arrow).*

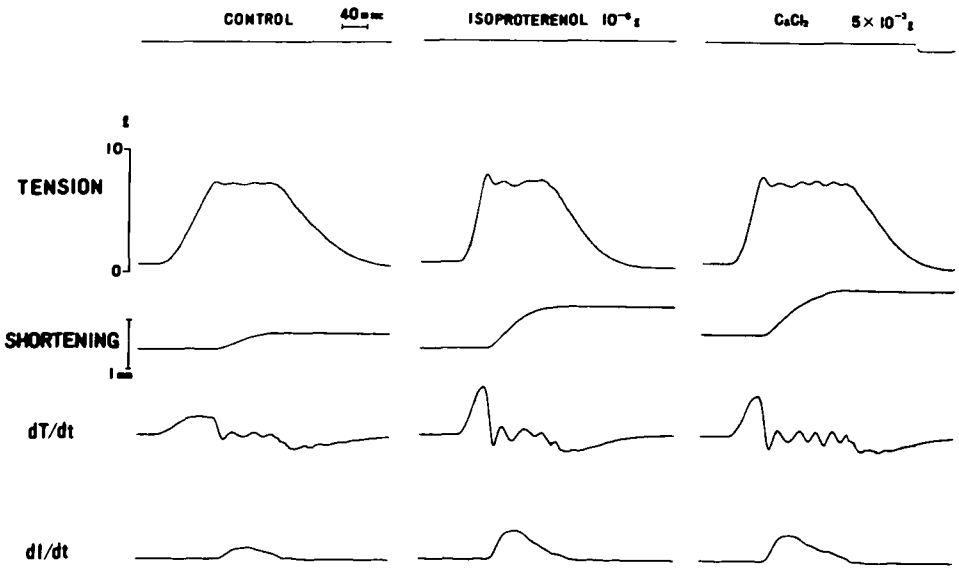

FIGURE 7 *Representative recordings of tension, shortening, and their first derivatives with respect to time in three different contractile states under conditions of constant preload and total load. Note the difference in isotonic time between two enhanced contractile states caused by different agents.*

load. The administration of propranolol markedly decreased the level of $-dT/dt_{max}$ under conditions of constant preload and total load (Table 2). Thus, the magnitude of $-dT/dt_{max}$ seemed to depend on the contractile state of the papillary muscle under conditions of constant preload and total load.

Referring again to Figures 4 and 5, $-dT/dt_{max}$ is nearly independent of preload, and in proportion to total load, as demonstrated above, $-dT/dt_{max}$ divided by total load appears to be constant at any preload and total load unless the contractile state of the muscle is changed. An increase of the frequency of contraction increases $-dT/dt_{max}$ slightly under conditions of constant total load and preload. The results of the studies are summarized in Table 2.

Discussion

Although the relationship between the mechanics of contraction and relaxation in cardiac muscle has been investigated in diverse preparations, the fundamental regulatory characteristics of cardiac muscle relaxation remain controversial. Until the present study, relaxation in the papillary muscle had not been analyzed under conditions similar to that in intact hearts, that is, an isometric relaxation process occurring at the end-systolic fiber length. In the present experiment the course of papillary muscle relaxation exhibited no abrupt decline in tension. Exponential decay of tension was observed for only a short period during the last phase of isometric relaxation (Fig. 3, right). By comparison, the course of contraction and relaxation for a conventional afterloaded contraction in the same papillary muscle is shown in Figure 3 (left).

Since our results demonstrate that $-dT/dt_{max}$ is in direct proportion to the magnitude of total load and is related to the contractile state of the muscle, the contractile state of the muscle can be represented by the slope of the $-dT/dt_{max}$ vs. total load curve. From the standpoint of the mechanics in the intact heart we interpret this as follows: Assuming that the ventricle is a thin-walled sphere, the

TABLE 2 *Summary of Results of Studies*

Muscle	Preload (g/mm²)	Total load (g/mm²)	Mean value of $(-dT/dt_{max})/T_0$ (sec^{-1})	Relation between $-dT/dt_{max}$(Y) and total load (X)	
2	0.25–0.46	0.58–0.87	4.69 ± 0.18	Y = 0.54 + 4.00X	r = 0.976 (12)
3	0.25–0.89	0.58–1.73	4.71 ± 0.85	Y = 1.22 + 3.48X	r = 0.802 (7)
4	0.07–0.23	0.23–0.79	3.07 ± 0.34	Y = 0.29 + 2.40X	r = 0.971 (47)
5	0.02–0.63	0.22–1.18	5.47 ± 0.66	Y = −0.31 + 5.97X	r = 0.971 (44)
7	0.21–1.10	1.06–1.33	3.66 ± 0.28	Y = 1.33 + 2.46X	r = 0.792 (29)
8	0.04–0.98	0.31–1.27	8.24 ± 0.48	Y = −0.26 + 8.52X	r = 0.987 (141)

			Mean value of $(-dT/dt_{max})/T_0$ (sec^{-1})			
			Control	*ISP (10^{-6} g)*	*$CaCl_2$ (5 × 10^{-3} g)*	*PROP (10^{-4} g)*
1	0.14	0.98	5.01 ± 0.18 (11)	5.95 ± 0.36* (7)	6.18 ± 0.30* (3)	
6	0.25	0.61	5.90 ± 1.35 (5)	8.50 ± 0.56* (2)		2.05 ± 0 (2)
8	0.08	0.79	8.24 ± 0.48 (114)	11.10 ± 1.46* (12)	9.90 ± 0.35* (6)	
			60/min	*80/min*	*100/min*	*120/min*
8	0.15	0.82	8.34 ± 0.34 (2)	9.51 ± 0.61 (3)	10.15 ± 0.83 (5)	11.72 ± 0.56* (6)
9	0.12	0.45	8.48 ± 0.39 (12)	9.15 ± 0.44* (24)	9.54 ± 0.38* (18)	9.89 ± 0.33* (9)

Results are expressed as mean ± SEM. Numbers in parentheses denote number of measurements. ISP = isoproterenol; PROP = propranolol.
* Statistically significant ($P < 0.05$) (response compared to its appropriate control).

relationship between ventricular wall tension, T, and intraventricular pressure, P, is written (Laplace's law) as

$$T = (r/2)\cdot P, \quad (1)$$

where r is the radius of the ventricle. Assuming that the radius of the ventricle is constant during isovolumic relaxation, the following equation is obtained from Equation 1:

$$-dT/dt_{max} = (r/2)\cdot(-dP/dt_{max}). \quad (2)$$

$-dT/dt_{max}$ is linearly related to total load from our experimental data. Therefore, $-dT/dt_{max}$ can be written as

$$-dT/dt_{max} = F_c \cdot T_0, \quad (3)$$

where T_0 is total load (end-systolic fiber tension) and F_c is a constant depending only on the contractile state of the muscle. From Equation 1, the total load T_0 is written as

$$T_0 = (r/2)\cdot P_0, \quad (4)$$

where P_0 is the end-systolic intraventricular pressure. By substituting Equation 4 into Equation 3 and equating this with Equation 2, the following equation is obtained:

$$-dP/dt_{max} = F_c \cdot P_0, \quad (5)$$

Thus, assuming that Laplace's law is applicable to the mammalian ventricle, $(-dP/dt_{max})/P_0$ is a load-independent index which is altered only by changes in contractility, and the relationship between $-dP/dt_{max}$ and P_0 is similar to that between $-dT/dt_{max}$ and T_0.

However, from their experimental results Cohn and his co-workers[4] predicted major influences of the end-systolic volume on $-dP/dt_{max}$. The data from the present study tend to indicate that changes in the end-systolic fiber length due to changes in preload have no effect on $-dT/dt_{max}$. In connection with this problem, Weisfeldt et al.,[5] referring to the work of Mitchell et al.,[8] mentioned that end-systolic volume was not a major determinant of $-dP/dt_{max}$. Weisfeldt et al.[5] observed that the level of peak aortic pressure or left ventricular systolic pressure determined the magnitude of $-dP/dt_{max}$. They concluded from indirect observation that the peak systolic wall stress was a major determinant of $-dP/dt_{max}$.

The present study demonstrates quantitatively for the first time the effects of preload on myocardial relaxation characteristics and shows that preload has nearly no effect on $-dT/dt_{max}$. Admittedly, papillary muscle preparations do not exactly simulate conditions in the intact functioning heart, but currently they provide the only means of carefully controlling all relevant parameters. The present work demonstrates that $-dT/dt_{max}$ is linearly related to total load, independent of preload, that it is related to the contractile state of the cardiac muscle, and that it increases with the frequency of muscle contraction. From these experimental results, $-dP/dt_{max}$ divided by dicrotic notch pressure might be a useful index of contractility, independent of preload and afterload.

Acknowledgments

We are grateful to Dr. Motoaki Sugawara at the Department of Surgical Science, Heart Institute of Japan, Tokyo Women's Medical College, for discussions and for help and encouragement in the completion of this work; to Dr. Norio Ohshima from the Division of Biomedical Engineering, Institute for Basic Medicine, University of Tsukuba, for many fruitful discussions; and to Dr. Michael B. Histand, visiting staff of Kyoto University from the Department of Mechanical Engineering and Physiology and Biophysics, Colorado State University, for help in the refinement of the manuscript.

References

1. Gleason WL, Braunwald E: Studies on the first derivative of the ventricular pressure pulse in man. J Clin Invest **41:** 80-91, 1962
2. Jewell BR, Wilkie DR: The mechanical properties of relaxing muscle. J Physiol (Lond) **152:** 30-47, 1960
3. Parmley WW, Sonnenblick EH: Relation between mechanics of contraction and relaxation in mammalian cardiac muscle. Am J Physiol **216:** 1084-1091, 1969
4. Cohn PF, Liedtke AJ, Serur J, Sonnenblick EH, Urschel CW: Maximal rate of pressure fall (peak negative dP/dt) during ventricular relaxation. Cardiovasc Res **6:** 263-267, 1972
5. Weisfeldt ML, Scully HE, Frederiksen J, Rubenstein JJ, Pohost GM, Beierholm E, Bello AG, Daggett WM: Hemodynamic determinants of maximum negative dP/dt and periods of diastole. Am J Physiol **227:** 613-621, 1974
6. Endoh M, Hashimoto K: Pharmacological evidence of autonomic nerve activities in canine papillary muscle. Am J Physiol **218:** 1459-1463, 1970
7. Endoh M, Tamura K, Hashimoto K: Negative and positive inotropic responses of the blood-perfused canine papillary muscle to acetylcholine. J Pharmacol Exp Ther **175:** 377-387, 1970
8. Mitchell JH, Wildenthal K, Mullins CB: Geometrical studies of the left ventricle utilizing biplane cinefluorography. Fed Proc **28:** 1334-1343, 1969