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Research Article

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ABSTRACT Recovery from hypoxia has been shown to prolong cardiac muscle contraction, particularly the relaxation phase. The present studies were designed to examine whether incomplete relaxation between beats can result from this prolongation of contraction and relaxation in isolated muscle after hypoxia and in the canine heart after both hypoxia and acute ischemia. The relationship between heart rate and the extent of incomplete relaxation is emphasized in view of the known enhancement of the velocity of contraction caused by increasing heart rate.

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These data indicate that incomplete relaxation is an important determinant of diastolic hemodynamics during recovery from ischemia or hypoxia. The extent of incomplete relaxation appears to be a function of the rate of normalization of the velocity of relaxation and tension development after ischemia or hypoxia, the heart rate, and the magnitude of developed tension or pressure.

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INTRODUCTION

More than a decade ago Mitchell, Linden, and Sarnoff suggested that incomplete relaxation of the ventricle between beats may occur at rapid heart rates (1). Markedly delayed relaxation of cardiac muscle has recently been demonstrated during the period after hypoxia by Tyberg, Yeatman, Parmley, Urschel, and Sonnenblick (2) and after regional ischemia by Bing, Keefe, Wolk, Finkelstein, and Levine (3). The present studies were undertaken to examine whether this prolongation of relaxation after hypoxia or ischemia is large enough to result in incomplete relaxation between beats both in isolated cardiac muscle and in the intact left ventricle. Since initial studies suggested that incomplete relaxation did occur under certain conditions, an attempt was made to relate the extent of incomplete relaxation to the interbeat interval, the magnitude of tension or ventricular pressure at the onset of relaxation, and the time-course of normalization of the velocity of relaxation and tension development after ischemia or hypoxia. A preliminary report of this work has been presented (4).

METHODS

Isolated cat papillary muscle. Right ventricular cat papillary muscles contracting isometrically at 29°C were utilized for the studies of isolated muscle. Adult cats were anesthetized with i.p. sodium pentobarbital, 60 mg/kg. Papillary muscles of less than 1.3-mm^2 cross-sectional area (mean±SD 0.91±0.31 mm^2) were rapidly removed and suspended in a myograph containing 16 ml of Krebs-Ringers bicarbonate solution (5) at 29°C with 16 mM glucose

added. The bathing fluid was equilibrated with 95% O_2—5% CO_2 except during hypoxic periods. Fresh solution entered the bath continuously at a rate of 7 ml/min. Both ends of the muscle were attached to spring-loaded clips. The upper clip was attached via a steel rod to a Hewlett-Packard FTA-100 force transducer (Hewlett-Packard Co., Palo Alto, Calif.). The displacement of the transducer and connections was less than 0.05 mm/10 g force over the range of tensions employed. The rate of change of force (dP/dt) was obtained by electronic differentiation of the output of the channel recording force. The dP/dt differentiator was calibrated by supplying a wave form of known slope. The lower clip was attached via a steel rod to a rigid stand that allowed muscle length to be varied. Except during rapid pacing, the muscles were paced at a rate of 12 beats/min with field platinum electrodes adjacent to the muscle. Stimulus variables were square wave impulses at a voltage of 20% above threshold and 4 ms in duration.

After a 1-h period of stabilization of the muscle at 1.0 g of resting force, the muscle was adjusted to a length 20% greater than the length of the muscle at zero resting force as previously described (5). After 30 min of stable performance, the pacing rate was progressively increased at 10-s intervals from 12 to 48, 72, 96, and 120 beats/min. At the end of each 10-s interval, pacing was interrupted briefly to identify true resting tension (see below). (True resting tension did not differ significantly from the resting tension at 12 beats/min under any conditions employed.) After this control rapid pacing period and a subsequent 10-min period of stable pacing at 12 beats/min, hypoxia (95% N_2—5% CO_2) was induced for 15 min. The Po_2 of the bath fell from 595±5 mm Hg (SD) to 18±3 mm Hg (SD) 1 min after hypoxia was initiated. During recovery from hypoxia (95% O_2—5% CO_2), a rapid pacing sequence was performed at 2, 5, and 10 min. Within 30 min after reoxygenation, all muscles reported regained at least 90% of their developed tension before hypoxia. Variations from this protocol are described in the results section.

The time to peak tension (TPT) [1] was taken as the time from the stimulus artifact to the time of peak developed tension. The half relaxation time ($RT_{\frac{1}{2}}$) (6) was taken as the time for tension to fall from peak developed tension to half of the peak developed tension. Total relaxation time (TRT) was taken as the time for tension to fall from the peak developed tension to the stable resting tension level. Values for TRT were read by two observers independently and varied by less than 5%. The presence or absence of incomplete relaxation was judged by interruption of pacing during rapid pacing. A fall in tension after interruption of pacing to a level below the lowest tension recorded during stable performance before interruption of pacing was taken as evidence of incomplete relaxation (Fig. 1). The amount of incomplete relaxation was determined by the difference between the stable resting tension during interruption of pacing (after any aftercontraction) and the lowest tension recorded before interruption. Aftercontractions were seen with interruption of pacing in some, but not all, muscles and were not more frequent after hypoxia, but were more frequent at rapid rates. In the muscle shown in Fig. 1, the tension declined to a stable resting level before the aftercontraction and therefore the incomplete relaxation observed is not due to the aftercontraction. In one muscle only, the first aftercontraction occurred early enough to account for at least a portion of the incomplete relaxation observed.

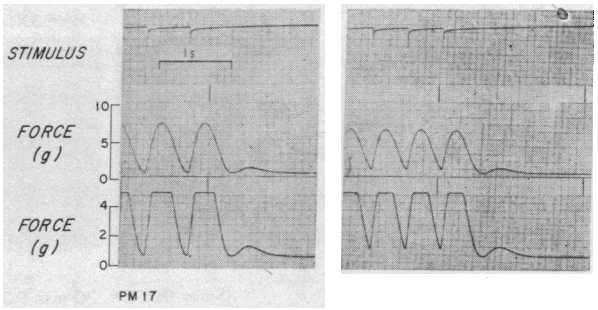

FIGURE 1 Tracings before and after interruption of pacing in a cat papillary muscle. The pacing rate is 96 beats/min (left panel) and 120 beats/min (right panel). Interruption of pacing is followed by a spontaneous aftercontraction. The diastolic force before and after the aftercontraction is the same as the diastolic force between beats in the left panel. In the right panel, 0.5 g of incomplete relaxation is present, as indicated by the diastolic force (higher between beats than before or after the aftercontraction).

Isovolumic left ventricle. Fasting adult mongrel dogs weighing 20–30 kg were anesthetized intravenously with a warmed mixture of urethane (600 mg/kg) and chloralose (60 mg/kg) and respiration was controlled with a volume-regulated Emerson ventilator (J. H. Emerson Co., Cambridge, Mass.) through a cuffed endotracheal tube. The heart was exposed through a median sternotomy and heparin (3 mg/kg) administered i.v. This preparation has been described in detail previously (7). Briefly, venous return from the cannulated superior and inferior venae cavae was directed to a reservoir from which the blood was warmed, oxygenated, and returned to the arch of the aorta for retrograde coronary artery perfusion via a calibrated occlusive roller pump. The heart was isolated *in situ* by securing occlusive tourniquets placed about the thoracic aorta immediately distal to the left subclavian artery, the brachiocephalic artery in the superior mediastinum, and the pulmonary artery and veins. Thebesian drainage from the individually cannulated left atrium and left ventricle was led directly to the venous reservoir.

An air-free distensible latex balloon affixed to the tip of a rigid Y-shaped metal cannula was inserted into the cavity of the left ventricle through the apex. The balloon could then be filled with known amounts of saline. The unstretched capacity of the balloon was larger than the volume injected. The pressure-volume curve of the balloon was determined before each experiment and the pressure effects due to distension of the balloon were negligible. The mitral valve orifice was occluded by means of a multiholed plastic button sutured to the atrial side of the valve to prevent herniation of the ventricular balloon.

The mean aortic perfusion pressure was kept constant at 120 mm Hg in the studies of recovery from hypoxia and at 140 mm Hg in the studies of recovery from ischemia by adjustment of the roller pump output. Throughout most of the experiments, this pressure was greater than peak systolic intraventricular pressure. In five experiments, peak systolic pressure exceeded perfusion pressure during the early post-ischemic period; the position of the balloon was checked at the end of each experiment and it was found to be within the left ventricular cavity.

[1] *Abbreviations used in this paper:* A-V, atrioventricular; LVP, left ventricular pressure; $RT_{\frac{1}{2}}$, half relaxation time; TPT, time to peak tension; TRT, total relaxation time.

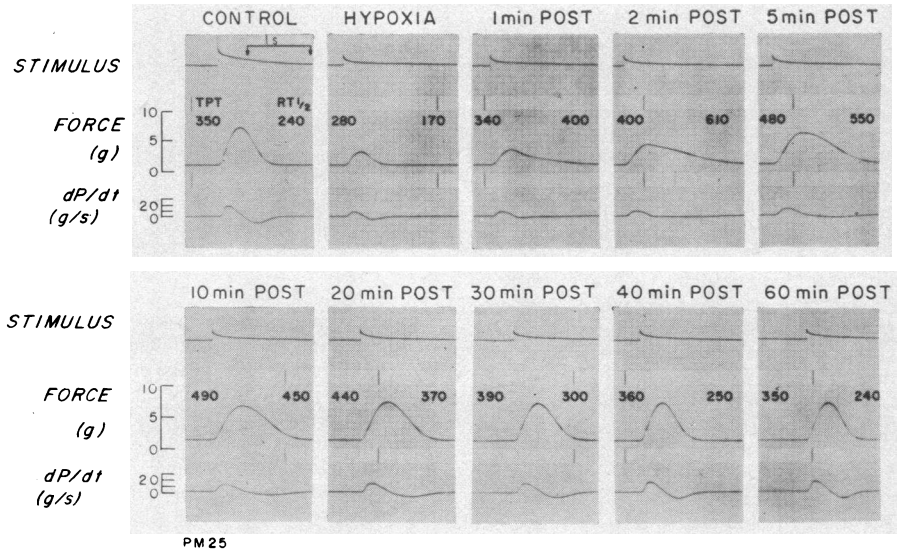

FIGURE 2 Effect of 15 min of hypoxia (95% N_2—5% CO_2) and recovery from hypoxia in a cat papillary muscle at 29°C. Pacing rate was constant throughout at 24 beats/min. The TPT and the $RT_{\frac{1}{2}}$ are shown on each tracing.

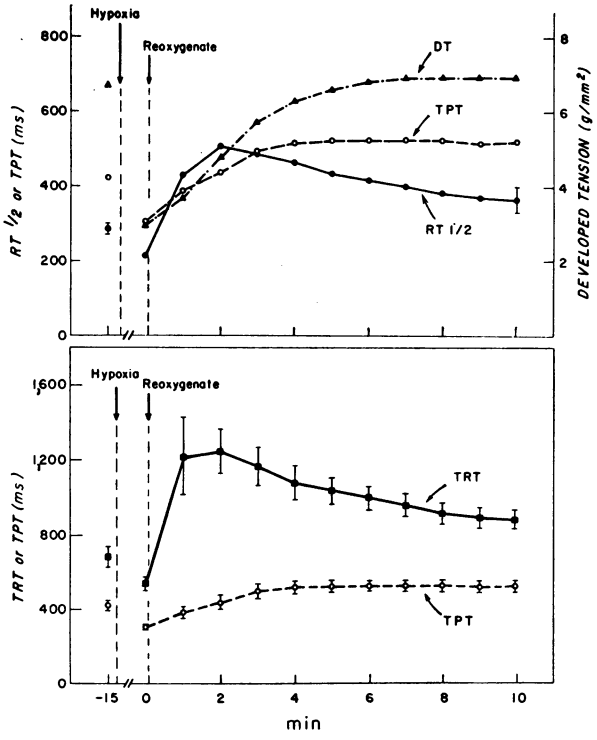

FIGURE 3 Time-course of changes in developed tension (DT), TPT, $RT_{\frac{1}{2}}$, and TRT after 15 min of hypoxia in eight cat papillary muscles paced at a rate of 12 beats/min. Bars indicate the SEM. Note relatively greater changes in TRT than TPT during recovery. At 10 min into recovery, there is little return of TPT toward control, whereas TRT and $RT_{\frac{1}{2}}$ have significantly decreased. At 1 min of recovery, TRT is more prolonged than $RT_{\frac{1}{2}}$.

Left ventricular pressures (LVP) were recorded by means of the Y-shaped cannula through the apex of the ventricle, and aortic pressure via a catheter in the aortic root with Statham P23Db pressure transducers (Statham Instruments, Inc., Oxnard, Calif.). At the end of each experiment the exposed tip of the intraventricular cannula was used as the true zero reference point for all intracardiac pressures. The frequency response of the recording system was linear from 0 to 30 Hz. The rate of rise of LVP (dP/dt) was recorded electronically and calibrated as previously described (7). After sinoatrial node crush, heart rate was controlled by sequential atrioventricular (A-V) pacing (Medtronic R wave coupled pulse generator, model 5837, Medtronics, Inc., Minneapolis, Minn.) of the right atrium and the right ventricle at an initial rate of 140 beats/min with an A-V delay of 75 ms. The ventricular electrogram was recorded continuously in each experiment. All variables were recorded on an eight-channel Beckman type S-II direct-writing oscillograph (Beckman Instruments, Inc., Fullerton, Calif.).

Recovery from hypoxia. Mean aortic perfusion pressure was held constant at 120 mm Hg. The rate of sequential A-V pacing was increased by increments of 10 from 120 to 180 beats/min at 10-s intervals with brief interruption of pacing at each rate. Subsequently, the rate was resumed at 140 beats/min, and hypoxia was initiated by conversion of the gas equilibrating in the oxygenator from 97% O_2 and 3% CO_2 to 97% N_2 and 3% CO_2 at 15 liter/min. The rate of perfusion from the pump was adjusted as necessary to maintain mean aortic pressure constant. When the peak systolic pressure had decreased to 60% of the control level (hypoxia period range: 10–30 min), reoxygenation was effected by reconversion from 97% N_2 and 3% CO_2 to 97% O_2 and 3% CO_2, flowing at 15 liter/min. At 2-min intervals after initiation of reoxygenation, hemodynamic variables were recorded at a heart rate of 140 beats/min. Rapid pacing periods similar to those of the control period were recorded 5 and 30 min after initiation of reoxygenation. The amount of incomplete relaxation

TABLE I

Effect of Rapid Pacing in Cat Papillary Muscle

Time after hypoxia	Pacing rate, (*beats/min*)				
	12	48	72	96	120
$RT_{\frac{1}{2}}$, *ms*					
Control	276±19	246±12	206±10	176±13	167±9
2 min	454±54*	345±29*	253±21	200±20	184±20
5 min	500±51*	329±36*	255±19*	203±16*	200±17*
10 min	428±36*	315±25*	244±10*	184±15	178±12
TPT, *ms*					
Control	362±12	286±11	230±9	195±11	183±9
2 min	412±44	327±22	257±16*	219±13*	202±9*
5 min	480±43*	329±21	262±23*	233±15*	218±9*
10 min	503±25*	360±26*	282±15*	237±14*	216±11*
Developed tension, g/mm^2					
Control	4.7±0.5	6.4±1.0	6.9±1.1	6.3±0.8	5.5±0.6
2 min	2.8±0.4*	4.5±0.7*	4.8±0.7*	4.6±0.6*	3.9±0.5*
5 min	3.6±0.6	5.1±0.7	5.2±0.6	5.1±0.6	4.4±0.5*
10 min	3.7±0.6*	5.2±0.8	5.5±0.8*	5.3±0.8*	4.9±0.5*
Incomplete relaxation, g/mm^2					
Control	0	0	0.04±0.03	0.12±0.09	0.51±0.15
2 min	0	0.15±0.08	0.32±0.12	0.58±0.20	0.87±0.25
5 min	0	0.08±0.05	0.29±0.11	0.80±0.21*	1.45±0.40*
10 min	0	0.04±0.03	0.29±0.11	0.56±0.19	0.91±0.33*

* $P < 0.05$ vs. control.

is the difference between the lowest diastolic pressure during pacing at a given rate and the pressure during interruption of pacing in centimeters H_2O. Time to peak pressure was taken as the time from the R wave of the electrogram to the time of peak pressure during systole. The $RT_{\frac{1}{2}}$ and TRT were determined as for the papillary muscle studies.

Recovery from ischemia. Ventricular balloon volume was selected such that the peak LVP was between 70 and 105 mm Hg. A period of 30 min was allowed at constant balloon volume for stabilization at a heart rate of 140 beats/min and a perfusion pressure of 140 mm Hg. Acute ischemia was then induced by turning off the occlusive perfusion pump. Simultaneously, ventricular fibrillation was induced with a 5-s pulse from a Medtronic A-C fibrillator. Ischemia and fibrillation were continued for 1.5–3 min. In some preparations, ventricular tachycardia was initially induced. This degenerated to ventricular fibrillation as ischemia continued, usually within 30 s. At the conclusion of the arrest period, perfusion was resumed at the control level of perfusion pressure and defibrillation was performed with a 75- W s DC countershock. During the 10-min period of recovery from ischemia, the heart rate was maintained at 140 beats/min. Pacing was interrupted at 30 and 45 s and at 1, 2, 3, 4, 5, 7, and 10 min after reperfusion to determine the extent of incomplete relaxation. There were no significant further changes in ventricular performance in three hearts followed for 30 min.

The significance of differences in group means was determined with the *t*-test for paired or unpaired values (8). All values expressed as ± indicate SEM except where indicated.

RESULTS

Isolated cat papillary muscle. The typical response of the cat papillary muscle to 15 min of exposure to 95% N_2—5% CO_2 followed by reequilibration with 95% O_2—5% CO_2 is shown in Fig. 2 and is similar to that reported by Tyberg et al. (2) and Bing et al. (3). This tracing demonstrates significant variation in the pattern of prolonged relaxation during early recovery from hypoxia. At 1 min after hypoxia, there is an initial rapid decline in tension during relaxation followed by a prolonged slow decline of tension. The decline of tension from 2 to 20 min after hypoxia is slower initially and is followed by a more rapid subsequent decline. This difference in the pattern of relaxation is reflected in the negative portion of the first derivative of tension where maximum negative dP/dt occurs earlier in the course of relaxation, at 1 min vs. 5 min after hypoxia. This variation in the pattern of relaxation raises a question as to the adequacy of $RT_{\frac{1}{2}}$ (6) as an index of relaxation in this setting. To examine this question, $RT_{\frac{1}{2}}$ and TRT were determined in eight muscles during the control period and at 1-min intervals after hypoxia (Fig. 3).

The mean ratio of $RT_{\frac{1}{2}}$: TRT at these times varied between 1/2.36 and 1/2.43 except at 1 min after hypoxia, when the ratio was 1/2.77 ($P < 0.01$). Thus, $RT_{\frac{1}{2}}$ appears to be an adequate index of the duration of relaxation except in the very early posthypoxic period. $RT_{\frac{1}{2}}$ has been utilized for analysis of these data since it can be determined with greater precision than TRT, and data are reported only after 2 min of recovery from hypoxia. The time-course observations (Fig. 2 and 3) emphasize that the prolongation of contraction and relaxation during recovery from hypoxia is due predominantly to prolonged relaxation during early recovery. The TPT becomes prolonged at a later point in recovery, is less prolonged, and is slower to return toward control levels.

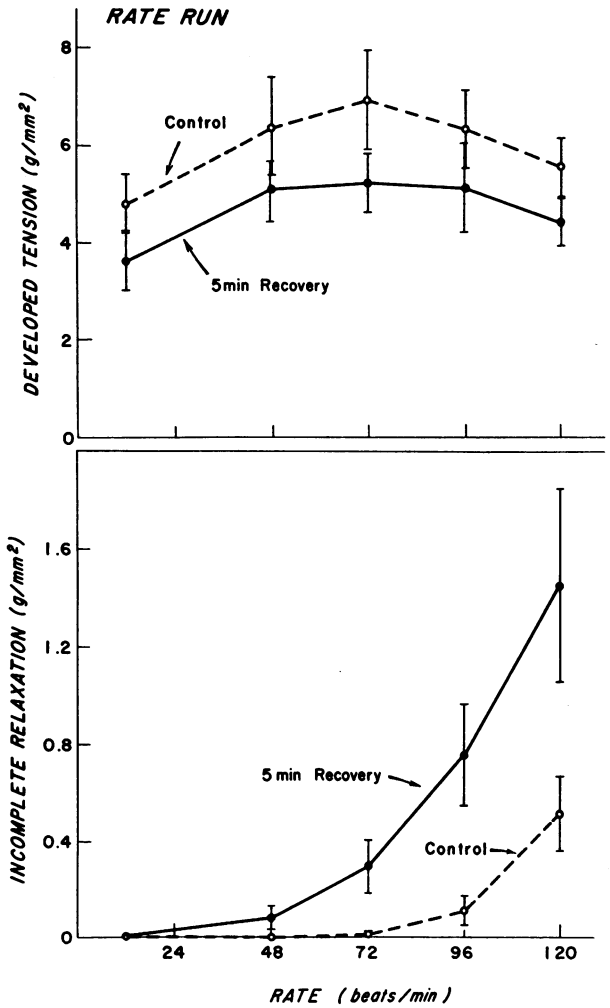

FIGURE 4 Effect of increasing pacing rate during the control period and 5 min after a 15-min period of hypoxia (95% N_2—5% CO_2) in eight muscles. Less developed tension and greater incomplete relaxation were noted 5 min into recovery. Incomplete relaxation was significantly greater at 96 and 120 beats/min ($P < 0.01$).

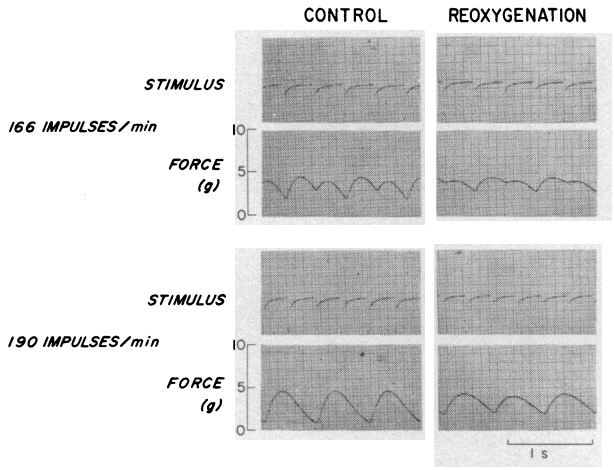

FIGURE 5 Mechanical response to pacing at 166 and 190 stimuli/min during the control period and 5 min into the recovery period. The interrupt diastolic force was 0.6 g both during the control period and recovery.

Rapid pacing was conducted during the control period and 2, 5, and 10 min after reoxygenation in eight muscles. The greatest incomplete relaxation between beats during rapid pacing was observed at 5 min of recovery (Table I). At this point, developed tension was still below the control level. At more rapid heart rates, a greater amount of incomplete relaxation was observed. Significantly greater incomplete relaxation was present at 96 and 120 beats/min ($P < 0.01$) after 5 min of reoxygenation (Fig. 4). At 120 beats/min after 2 min of reoxygenation, there was 0.87±0.25 g/mm² of incomplete relaxation (NS vs. control) and at 10 min there was 0.91±0.33 g/mm² ($P < 0.05$ vs control). There was no significant change in true resting tension during hypoxia or recovery. During the control period, true resting tension was 2.1±0.27 g/mm² and during rapid pacing at 5 min of recovery 2.15±0.33 g/mm².

Increases in heart rate between 12 and 48 beats/min resulted in a proportionately greater shortening of $RT_{\frac{1}{2}}$ and TPT after hypoxia than before hypoxia (Table I). Increases in rate above 72 beats/min for $RT_{\frac{1}{2}}$ and above 48 beats/min for TPT resulted in decreases of these time intervals essentially parallel to control values. However, both indexes remained above control levels at all rates during recovery.

In the absence of hypoxia, rapid pacing periods at identical intervals in four muscles did not show greater incomplete relaxation than the initial control run. Similar results were obtained in four muscles in which the sequence of pacing rates was reversed (120–12 beats/min). At 5 min of recovery there was 1.30±0.25 g/mm² of incomplete relaxation. There was no incomplete re-

laxation in four muscles when rapid pacing periods were performed *during* the hypoxic period.

In seven muscles, no marked difference was observed between the control and recovery period in terms of the heart rate at which an apparent one-to-one electromechanical response was no longer seen. In the experiment shown in Fig. 5, there is an apparent mechanical response to each stimulus at a rate of 166 impulses/min and one apparent mechanical response for every other stimulus at a rate of 190 impulses/min during both the control and recovery periods. Slight alternans is present at 166 impulses/min. Incomplete relaxation is again greater after hypoxia and appears to account for the lack of return of tension to the resting level when paced at 190 impulses/min (95 mechanical responses/min).

Recovery from hypoxia: isovolumic canine heart. Similar results were obtained in seven canine isovolumic left ventricle preparations after hypoxia. During the hypoxic period, the P_{O_2} of the blood entering the aorta was 14.6±6.2 mm Hg (SD). The coronary venous P_{O_2} was 47.8±3.7 mm Hg before hypoxia, 9.9±5.0 mm Hg at the end of hypoxia, and 64.5±30.2 mm Hg 5 min after hypoxia.

5 min after hypoxia, greater incomplete relaxation was observed at higher heart rates than during the rapid pacing period before hypoxia (Fig. 6, Table II). During the control period, there was no incomplete relaxation at any heart rate below 160 beats/min. At 180 beats/min, incomplete relaxation was present in only two hearts. During recovery from hypoxia, significant incomplete relaxation was present at 130 beats/min and higher. All hearts relaxed incompletely at rates greater than 150 beats/min.

Effects of increasing heart rate on time to peak pressure, $RT_{\frac{1}{2}}$, and TRT during the control period and after 5 min of recovery are presented in Table III. There was prolongation of the time to peak pressure, $RT_{\frac{1}{2}}$, and TRT after hypoxia at all rates, similar to the papillary muscle. The mean prolongation of time to peak pressure at the rates studied was from 21 to 31 ms and the mean prolongation of TRT from 56 to 76 ms.

Hypoxia was continued in all hearts until peak LVP fell to 60% of the control level (see Methods). In five of the seven hearts, there was an increase in interrupt diastolic pressure during hypoxia, reflecting an increase in resting diastolic stiffness (Table II). The interrupt diastolic pressure returned to control levels during the recovery period in two of these hearts. In three hearts, the interrupt pressure remained markedly elevated above control values after 30 min of reoxygenation. Incomplete relaxation appeared during recovery in hearts with no change in resting stiffness, as well as in those hearts with markedly increased resting diastolic stiffness.

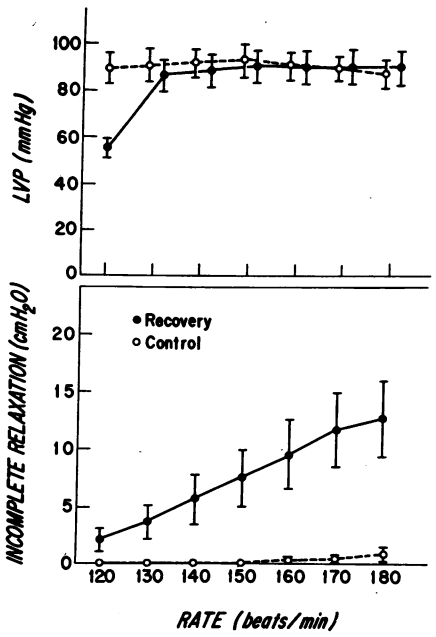

FIGURE 6 Effect of increasing pacing rate during the control period and 5 min into the recovery period after hypoxia in seven isovolumic dog hearts. Shown above is the peak LVP and below incomplete relaxation. Greater incomplete relaxation was seen during recovery from hypoxia ($P < 0.05$) at all rates above 130 beats/min.

At 30 min after hypoxia, peak LVP was 72–93% (range) of the control value. All hearts demonstrated less incomplete relaxation at 30 min than at 5 min into recovery from hypoxia. After 30 min of reoxygenation, there was 6.4±2.0 cm H_2O of incomplete relaxation at 180 beats/min.

Recovery from ischemia: isovolumic canine heart. 12 canine hearts were studied during the recovery period after a 1.5–3.0 min period of ischemia induced by interruption of coronary perfusion and induction of ventricular fibrillation. The heart rate was 140 beats/min during the control period and during the period after fibrillation.

Incomplete relaxation of less than 2.5 cm H_2O was noted before ischemia in 5 of the 12 hearts. In the remaining seven hearts, no incomplete relaxation was present. After ischemia, all hearts demonstrated significant incomplete relaxation. A representative experiment is shown in Fig. 7. No incomplete relaxation was seen in the control period or 5 min after fibrillation and ischemia. At 45 and 60 s incomplete relaxation was present. The interrupt diastolic pressure was 2.0 cm H_2O greater than control at 45 s. By 60 s after ischemia, the diastolic pressure had returned to the control level.

The time-course of the changes in peak LVP, incomplete relaxation, and the diastolic pressures during interruption of pacing in 12 hearts is shown in Fig. 8. In

TABLE II

Effect of Hypoxia and Recovery at 140 beats/min in the Canine Ventricle

Experiment	LVP	Int. press	IR	TPP	$RT_{1/2}$	TRT
	mm Hg	*cm H_2O*	*cm H_2O*	*ms*	*ms*	*ms*
Control						
1	110	5.0	0.0	160	100	215
2	100	0.0	0.0	140	85	160
3	80	6.0	0.0	250	100	190
4	106	8.0	0.0	210	90	180
5	97	8.0	0.0	220	90	180
6	61	16.0	0.0	210	95	200
7	84	7.0	0.0	130	85	180
Mean±SE	91.1±6.5	7.1±1.8	0.0	189±17	92±2	186±7
End hypoxia						
1	54	5.0	0.0	140	90	180
2	60	0.0	0.0	140	70	120
3	50	25.0	0.0	250	95	170
4	65	28.0	0.0	200	90	180
5	70	30.0	0.0	200	100	210
6	45	50.0	0.0	180	80	190
7	45	15.0	0.0	120	90	170
Mean±SE	55.6±3.7‡	21.9±6.4*	0.0	176±17*	92±4	174±10
5 min recovery						
1	100	6.0	2.0	180	110	225
2	80	0.0	0.5	160	100	200
3	93	14.0	10.0	290	110	270
4	102	12.0	12.0	280	140	280
5	105	27.0	14.0	250	130	290
6	57	44.0	1.5	230	110	250
7	95	9.0	0.0	145	100	240
Mean±SE	90.3±6.4	16.0±5.6	5.7±2.3	219±22‡	114±6*	251±12‡
30 min recovery						
1	88	5.0	0.0	180	100	210
2	72	0.0	0.0	160	90	190
3	72	6.0	0.0	270	100	230
4	88	12.0	0.0	220	100	210
5	90	23.0	2.0	240	110	200
6	53	37.0	0.0	230	100	220
7	63	7.0	0.0	140	95	195
Mean±SE	75.1±5.4‡	12.9±4.9	0.3±0.3	205±18‡	99±2*	208±5‡

Int. Press, LVP during interruption of pacing; IR, incomplete relaxation; TPP, time to peak pressure.

* $P < 0.05$ vs. control.

‡ $P < 0.01$ vs. control.

the early post-ischemic period, left ventricular performance, as indicated by peak LVP, exceeded the control level. This has been ascribed to catecholamine release (9). Performance levels subsequently declined to below control level. By 10 min after ischemia, the new stable performance level was established. There was a small, statistically insignificant change in left ventricular stiffness as indicated by the interrupt diastolic pressure in the early post-ischemic period (Fig. 8). Statistically significant incomplete relaxation was present between 3 and 5 min after ischemia when compared to control ($P < 0.025$).

DISCUSSION

Incomplete relaxation of ventricular muscle between beats has been viewed previously as physiologically important, only under conditions of marked hemodynamic stress. Extremely rapid heart rates may

TABLE III

Effect of Rapid Pacing in Post-Hypoxic Canine Ventricle

Heart rate (beats/min)	120	130	140	150	160	170	180
Time to peak pressure, *ms*							
Control	199±17	196±17	189±17	187±16	181±16	180±16	175±16
5 min recovery	230±23*	227±22*	219±22*	213±21*	205±20*	201±21*	201±22*
$RT_{\frac{1}{2}}$, *ms*							
Control	92±3	94±3	92±2	88±2	86±2	84±2	81±2
5 min recovery	116±9	116±6*	114±6*	113±8*	106±6*	102±6*	102±5*
TRT *ms*							
Control	191±7	187±8	186±7	183±8	175±7	168±6	162±7
5 min recovery	261±16*	263±16*	251±12*	239±15*	230±14*	225±15*	219±15*

* $P < 0.05$.

result in abbreviation of diastole to the extent that incomplete relaxation appears (1, 10). The present studies were performed using isometric conditions in the papillary muscle and isovolumic conditions in the intact ventricle. A fall in isometric tension or isovolumic pressure with interruption of pacing provided a sensitive and quantitative indicator of the presence of incomplete relaxation during the preceding period, assuming steady-state conditions. With this technique, it appears that in isolated muscle after hypoxia and in the intact ventricle after hypoxia or ischemia, there is sufficient prolongation of the duration of relaxation and development of contractile tension to result in incomplete relaxation between beats.

In the papillary muscle preparation, there is concern that the oxygen available to the inner core of the muscle is inadequate, especially at the more rapid rates employed (up to 120 beats/min). Hoffman and Kelly (11) paced cat papillary muscles of 0.5–1.0 mm^2 cross-sectional area at 37°C for 10-min periods at increasing rates. A significant fall in developed tension appeared only at rates greater than 120 beats/min. Whalen (12)

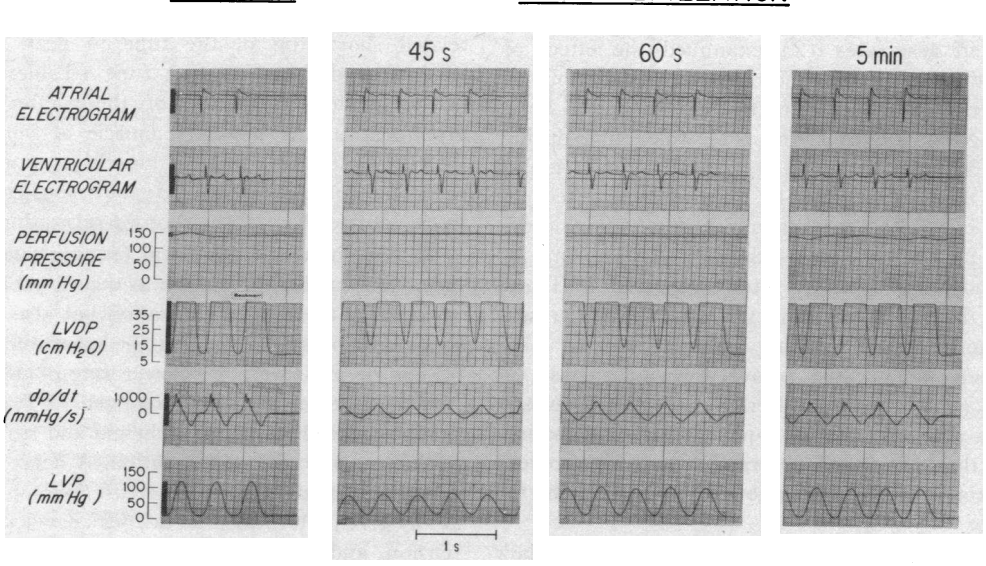

FIGURE 7 Recovery from 3 min of ischemia and ventricular fibrillation in an isovolumic canine preparation. Perfusion was stopped and fibrillation induced for 3 min after the control tracing. After 3 min of ischemia, perfusion was resumed and the heart defibrillated with a 75 W s countershock. Interrupt tracings are present on the right end of each panel. Incomplete relaxation is present 45 and 60 s after fibrillation. LVDP, left ventricular diastolic pressure.

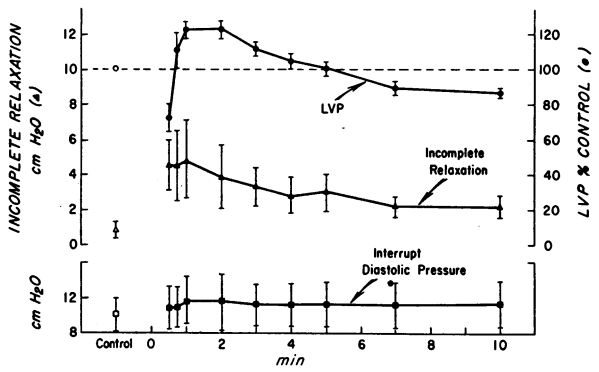

FIGURE 8 Time-course of changes in LVP, interrupt diastolic pressure, and incomplete relaxation in 12 isovolumic canine left ventricular preparations after ischemic arrest. Control values are before a 1.5–3.0-min period of interruption of perfusion and ventricular filbrillation. Zero time is the time of defibrillation and resumption of perfusion.

noted that the oxygen consumption of 4 cat papillary muscles at 37°C and 120 beats/min was nearly twice that of 12 muscles paced at 60 beats/min. In the present study, reversal of the pacing sequence did not significantly alter the amount of incomplete relaxation at a rate of 120 beats/min. With this reversal of sequence, only 4–5 s of rapid pacing (8–10 beats) and higher oxygen demand was needed before stability of performance was present and incomplete relaxation could be quantified. If hypoxia of the inner core did occur during rapid pacing, it would tend to decrease rather than increase TPT and $RT_{\frac{1}{2}}$ (2, 3).

Tyberg and associates (2) examined the effect of pacing rate during hypoxia and recovery in cat papillary muscle under similar conditions to those employed here. Less prolongation of TPT and $RT_{\frac{1}{2}}$ was found during recovery at 34 beats/min than at 12 beats/min. It is unclear from their studies as to whether this effect of higher rate is due to the greater extent of hypoxic depression of performance at 34 than at 12 beats/min or due to a tendency for higher rates to shorten TPT and $RT_{\frac{1}{2}}$ even during the recovery period. The present studies demonstrate that higher rates do shorten TPT and $RT_{\frac{1}{2}}$ even during the recovery period. These investigators (2) found no alteration in series elastic stress-strain relations during hypoxia or reoxygenation, suggesting that prolonged contraction during recovery from hypoxia is related to prolonged dissipation of the active state.

Isometric conditions were utilized in the papillary muscle studies. Under these conditions, isometric relaxation occurs at the same external fiber length as is present at the end of the contraction phase. This is similar to the intact heart before mitral valve opening. Afterloaded conditions were not employed here, since an increase in fiber length occurs before the decline in tension. Relaxation is reflected in the rate of lengthening and the subsequent rate of fall in tension in the afterloaded model. This is opposite to the sequence in the intact animal. The isometric model, though, does lack overall fiber shortening during contraction (though internal shortening may occur). The effect of systolic fiber shortening on the rate of relaxation of isolated cardiac muscle is not known.

In the intact heart, isovolumic conditions were utilized so that incomplete relaxation, when present, could be detected and quantified. Again fiber shortening during systole does not occur in this model. Frederiksen, et al. (13) recently examined the relaxation phase of canine left ventricular contraction in a working preparation using maximum negative dP/dt as the index of relaxation rate. Large changes in stroke volume (<4 ml to 15–20 ml) and thus large changes in the amount of fiber shortening at constant heart rate and peak aortic pressure were associated with a statistically significant but a remarkably small change (5–13%) in the magnitude of maximal negative dP/dt. These data suggest that fiber shortening has little effect on ventricular relaxation rate.

The extent of incomplete relaxation is related in part to the frequency of contraction. Incomplete relaxation of the isovolumic canine ventricle was present at heart rates well within the physiological range for the dog under stress (14). In both preparations, more rapid heart rates were associated with a greater extent of incomplete relaxation during reoxygenation, despite some rate-related shortening of the time to peak pressure (or tension) and the relaxation time (Tables I–III). The rate-associated shortening of these intervals is more prominent in the papillary muscle at very slow rates than in either the papillary muscle at more rapid rates or in the intact ventricle. Hypothermic conditions tend to accentuate the prolongation of relaxation (6).

At a given interbeat interval (pacing rate), the magnitude of incomplete relaxation as quantified here is related not only to the rate of relaxation but also to the rate of tension or pressure rise and the magnitude of the peak tension or pressure. The slower rate of pressure or tension rise is reflected in the prolonged TPT or time to peak pressure after hypoxia or ischemia and results in a delay in the time of onset of relaxation. A delay in the time of onset of relaxation would increase incomplete relaxation at any given interbeat interval, peak developed pressure or tension, and $RT_{\frac{1}{2}}$. During the early recovery period in the papillary muscle (Figs. 2 and 3), relaxation is prolonged to the greatest extent when developed tension has shown little or partial recovery. At a given interbeat interval, TPT and TRT, a lower developed tension would result in less incomplete relaxation. Interrelation-

ships among these determinants of incomplete relaxation are seen in the results of pacing at three time periods during recovery in the papillary muscle (Table I). For example, the magnitude of incomplete relaxation at a rate of 96 beats/min is greater at 5 min than at 2 min of recovery. This greater magnitude of incomplete relaxation reflects the higher mean developed tension (0.5 g) and longer mean TPT (14 ms) at 5 min than at 2 min since mean $RT_{\frac{1}{2}}$ is only 3 ms longer at 5 min. The magnitude of incomplete relaxation at a rate of 96 beats/min is less at 10 min than 5 min as a result of more rapid relaxation (mean $RT_{\frac{1}{2}}$ is 19 ms shorter) despite a slightly higher developed tension and slightly longer mean TPT.

The importance of incomplete relaxation of the ventricle on overall hemodynamics is probably related to diastolic ventricular filling. The studies of Templeton, Mitchell, and Wildenthal (15) demonstrate that dynamic and static left ventricular stiffness are functions of the level of LVP. The relation between both dynamic and static stiffness and pressure is the same during all phases of isovolumic contraction. Thus incomplete relaxation at the end of diastole may affect filling, as would an acute increase in resting stiffness (or decrease in compliance). Since there is no information available on the effects of filling on the rate of ventricular relaxation, conclusions in this area are speculative. Prolonged contraction or relaxation may also result in shortening of the duration of the diastolic filling period. Abbreviation of the diastolic filling period in the normal heart results in divergence of the mean left atrial and left ventricular end-diastolic pressures (10, 16).

Incomplete relaxation may be present under conditions of no change or under conditions of a change in resting diastolic stiffness. No change in resting tension during interruption was noted in the post-hypoxic papillary muscles. No change in diastolic pressure at constant volume occurred during interruption in the post-ischemic canine ventricle. Some of the canine ventricles subjected to hypoxia developed an increase in resting stiffness during hypoxia, as evidenced by an increase in the interrupt diastolic pressure at constant volume. Stiffness decreased during the post-hypoxic period, but to a variable extent. Incomplete relaxation appeared in both preparations, i.e., in those in which there was no change in static resting diastolic stiffness and in those in which stiffness increased.

The experiments at very rapid heart rate (Fig. 5) do not demonstrate any highly significant difference in refractory period for mechanical response to electrical stimulation between the pre-hypoxic and post-hypoxic muscle. Bing and his colleagues (3) have suggested that alterations in refractory period are importantly related to prolonged maintenance of contractile tension with very rapid repetitive stimulation during recovery from hypoxia. With pacing at 166 beats/min during reoxygenation, there is only slight relaxation between beats, particularly between the high and low beat of the alternans pairs. Thus, prolonged contraction alone may result in near absence of relaxation with a properly timed stimulus.

Incomplete relaxation between beats, as demonstrated here in the post-ischemic and post-hypoxic heart, may influence overall cardiac performance by retarding ventricular filling, shortening the diastolic filling period, and perhaps by altering coronary blood flow. Incomplete relaxation might be eliminated by decreasing peak systolic ventricular pressure, slowing the heart rate, or administering agents that accelerate myocardial relaxation.

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