

# Comparison of Acute Alterations in Left Ventricular Relaxation and Diastolic Chamber Stiffness Induced by Hypoxia and Ischemia

## ROLE OF MYOCARDIAL OXYGEN SUPPLY-DEMAND IMBALANCE

TAKASHI SERIZAWA, W. MARK VOGEL, CARL S. APSTEIN, and WILLIAM GROSSMAN,  
*Cardiac Muscle Research Laboratory, Housman Medical Research Center,  
Boston University School of Medicine, The Thorndike Memorial Laboratory  
and Department of Medicine, Boston City Hospital, Department of Medicine,  
Harvard Medical School, and Peter Bent Brigham Hospital, Boston  
Massachusetts 02115*

**ABSTRACT** To clarify conflicting reports concerning the effects of ischemia on left ventricular chamber stiffness, we compared the effects of hypoxia at constant coronary perfusion with those of global ischemia on left ventricular diastolic chamber stiffness using isolated, perfused rabbit hearts in which the left ventricle was contracting isovolumically. Since chamber volume was held constant, increases in left ventricular end diastolic pressure (LVEDP) reflected increases in chamber stiffness. At a control coronary flow rate (30 ml/min), 2 min of hypoxia and pacing tachycardia (4.0 Hz) produced major increases in postpacing LVEDP ( $10 \pm 1$  to  $24 \pm 3$  mm Hg,  $P < 0.01$ ) and the relaxation time constant,  $T$ , ( $40 \pm 4$  to  $224 \pm 37$  ms,  $P < 0.001$ ), while percent lactate extraction ratio became negative ( $+18 \pm 2$  to  $-48 \pm 15\%$ ,  $P < 0.001$ ). Coronary perfusion pressure decreased ( $72 \pm 5$  to  $52 \pm 3$  mm Hg,  $P < 0.01$ ), and since coronary flow was held constant, the fall in coronary perfusion pressure reflected coronary dilation and a decrease in coronary vascular resistance. Following an average of  $71 \pm 6$  s reoxygenation and initial heart rate (2.0 Hz), LVEDP and relaxation time constant  $T$  returned to control. Hypoxia alone (without pacing tachycardia) produced similar although less marked changes (LVEDP,  $10 \pm 1$  to  $20 \pm 3$  mm Hg; and  $T$ ,  $32 \pm 3$  to  $119 \pm 22$  ms;  $P < 0.01$  for both) and there was a strong correlation between LVEDP and  $T$  ( $r = 0.82$ ,  $P < 0.001$ ).

When a similar degree of coronary vasodilatation was induced with adenosine, no change in LVEDP

occurred, indicating that the increase in end diastolic pressure observed during hypoxia was not secondary to vascular engorgement, but due to an acute effect of hypoxia on the diastolic behavior of the ventricular myocardium.

In contrast, global ischemia produced by low coronary flow (12–15 ml/min) resulted in a decrease in LVEDP, as well as a marked fall in left ventricular systolic pressure. In 14 global ischemia experiments, pacing tachycardia led to a further decline in left ventricular systolic pressure, and no increase was noted in postpacing LVEDP. Changes in lactate extraction ratio were much smaller in magnitude than with hypoxia and constant coronary perfusion. In two experiments (one at normal coronary flow and one at 15 ml/min), left ventricular systolic pressure did not change markedly from control when tachycardia was superimposed, and postpacing LVEDP showed a marked rise (to  $>25$  mm Hg), which gradually recovered over 1–2 min at the control heart rate.

From these results, we conclude that left ventricular chamber stiffness increases when myocardial  $O_2$  demand exceeds supply. This change is usually masked in ischemic (reduced coronary flow) preparations, perhaps because of reduced turgor of the coronary vascular bed, marked reductions in systolic work (and therefore myocardial  $O_2$  requirements), and local accumulation of hydrogen ion and metabolites following acute severe reduction of coronary flow. The increased chamber stiffness during hypoxia is accompanied by marked slowing of relaxation, with increased diastolic pressure relative to volume persisting throughout diastole.

*Received for publication 7 July 1980 and in revised form 6 October 1980.*

## INTRODUCTION

The effects of myocardial ischemia on left ventricular diastolic chamber stiffness are controversial (1–3). In the clinical situation, dramatic increases in left ventricular diastolic pressure relative to volume have been repeatedly observed to occur within 1–2 min of the onset of angina pectoris (4–10). This prompt and reversible upward shift in the left ventricular diastolic pressure-volume relation has also been reported in dogs with coronary stenoses subjected to pacing tachycardia (11). On the basis of these studies, it has been proposed that factors directly affecting the left ventricular myocardium during ischemia alter diastolic left ventricular chamber stiffness (3, 11). In contrast to these studies, several groups have reported that reduction of myocardial blood flow either to the entire left ventricle (global ischemia) or to a region of the heart (coronary branch ligation) does not cause an increase in left ventricular chamber stiffness (which may even decrease initially) until at least 30–120 min after the onset of ischemia (12–16). The late increase in chamber stiffness is generally irreversible, and is thought to represent myocardial rigor.

We wondered whether these conflicting reports concerning the effects of myocardial ischemia on left ventricular chamber stiffness might reflect important differences between two types of myocardial ischemia: that seen with angina pectoris, and that seen with coronary ligation. With the usual form of exertion-induced angina pectoris (and in dogs with coronary stenoses subjected to pacing tachycardia), myocardial  $O_2$  demand increases to exceed the capacity for  $O_2$  delivery. This “demand-side” type of myocardial ischemia is generally associated with normal or increased myocardial blood flow, which minimizes local accumulation of metabolites and hydrogen ion. In contrast, with coronary ligation (or global reduction in left coronary blood flow), myocardial  $O_2$  demand usually decreases, tending to reduce the adverse metabolic consequences of reduced  $O_2$  delivery. In addition, in this “supply-side” type of myocardial ischemia, local accumulation of hydrogen ion may occur and protect against abnormalities of diastolic tension (17). Finally, the role of coronary vascular turgor in maintaining left ventricular chamber stiffness (“erectile effect”) could be important, since it would be expected to have opposite effects on left ventricular chamber stiffness in the two types of myocardial ischemia (18–20). To test these concepts, and to clarify the conflicting data concerning the effects of ischemia on left ventricular chamber stiffness, we used an isolated, retrograde, perfused rabbit heart preparation in which the left ventricle was contracting isovolumically (21). This preparation avoided the heterogeneity of the coronary

stenosis situation, in which ischemic and nonischemic muscle may interact in a complex fashion (22–23). It also avoided the potential complex interaction of pericardial and right ventricular forces on left ventricular compliance (24–26), since pericardium is absent and the right ventricle is detached from its venous return and is vented. We used coronary flow reduction (oxygenated perfusate) to study the type of myocardial ischemia analogous to coronary branch ligation or global low perfusion ischemia in intact animal studies. Our purpose was to assess the influence of this type of ischemia on left ventricular compliance and relaxation, and to attempt to dissect out possible confounding effects of decreased coronary vascular turgor (erectile effect) and local accumulation of metabolites by comparing the results to those with hypoxia at constant coronary flow in the same heart. Since both interventions (coronary flow reduction vs. hypoxia at constant coronary flow) decrease  $O_2$  delivery to the myocardium, important differences in their effects on ventricular compliance and relaxation might be best attributed to the modifying influences of other factors (such as the erectile effect, decreased washout of hydrogen ion, etc.). The results of this study provide strong evidence for an early reversible increase in left ventricular chamber stiffness with marked impairment of ventricular relaxation when myocardial  $O_2$  demand exceeds supply.

## METHODS

Experimental methods are fundamentally the same as our previously reported studies (16, 21, 27, 28). Briefly, albino rabbits weighing between 2.0 and 2.5 kg were decapitated. Hearts were quickly removed from the thorax and placed in a water-jacketed constant temperature chamber (37.0°C). The coronary arteries were perfused retrograde by a constant flow pump through a cannula inserted into the aortic root.

The perfusate consisted of modified Krebs-Henseleit buffer: 118 mM NaCl, 4.7 mM KCl, 2.0 mM  $CaCl_2$ , 1.2 mM  $KH_2PO_4$ , 1.2 mM  $MgSO_4$ , 25 mM  $NaHCO_3$ , 0.4 mM NaEDTA, 5.5 mM glucose, and 1.0 mM lactate. Lactic acid was neutralized with NaOH before being added to the buffer. The lactate was added to the perfusate so that aerobic myocardial lactate extraction could be measured. The perfusate was equilibrated with a 5%  $CO_2$ –95%  $O_2$  gas mixture and  $PO_2$  was >550 mm Hg.

A collapsed latex balloon, which was slightly larger than the rabbit's left ventricular chamber, was inserted into the left ventricle via a left atrial incision. The balloon was then filled with bubble-free saline and attached to a Statham P23 Db pressure transducer (Statham Instruments, Inc., Oxnard, Calif.) via a 15-cm length of polyethylene tubing. The damping ratio of this pressure measurement system was 0.54, and calculated natural resonant frequency was 75 Hz. Thus, the system was critically damped and the amplitude and wave form of the recorded pressure should accurately reflect the true pressure at frequencies up to 90% of the natural resonant frequency of 75 Hz. This result satisfied the range shown by Falsetti (29) to be required for accurate measurement of ventricular pressure and its first derivative.

Aortic pressure, which in this model is coronary perfusion pressure, was measured via a Y-shaped connector attached to the infusion cannula.

A bipolar pacemaker electrode was inserted in the right ventricle and stimulated by a Grass model S4 stimulator (Grass Instrument Co., Quincy, Mass.).

Signals were amplified and recorded on a photographic recorder (Electronics for Medicine, Inc., Pleasantville, N. Y., model DR8). The first derivative of left ventricular pressure was obtained by electronic differentiation of the left ventricular pressure signal and the time constant of left ventricular pressure decline (T) was obtained by the method of Weiss and co-workers (30) as in previous studies (11, 23).

Because the volume of the latex balloon in the left ventricular chamber was kept constant during the experiment, the left ventricular pressure-time product (the area bounded by the ventricular pressure curve in systole and end diastolic pressure) was measured and multiplied by the heart rate; this product was used as an index of left ventricular oxygen demand.

Coronary sinus flow was drained through a cannula inserted into the right ventricle, which was thereby decompressed. Percent lactate extraction ratio and lactate extraction were calculated by the following formulas: Percent lactate extraction ratio =  $100 \times [A - CS]/A$  (%); Lactate extraction =  $[A - CS] \times CF$  ( $\mu\text{M}/\text{min}$ ); A = lactate concentration in Krebs-Henseleit (mM); CS = lactate concentration in coronary sinus effluent (mM); and CF = coronary flow (ml/min). Coronary vascular resistance (CVR) was calculated as mean coronary perfusion pressure (CPP)<sup>1</sup>/coronary flow (CF) and expressed as mm Hg  $\times$  min/ml.

Before beginning each experiment, the heart was perfused for 30 min at 30 ml/min coronary flow rate, and paced at a heart rate of 2.0 Hz to allow for performance to stabilize. Hearts were perfused for at least 15 min at 30 ml/min flow rate and 2.0 Hz heart rate after any ischemic or hypoxic intervention during the experiments, to allow for recovery prior to the next experimental run.

## Experimental Protocol

### EFFECT OF CORONARY FLOW REDUCTION

The heart rate was fixed at 2.0 Hz and the left ventricular balloon volume slowly increased until the left ventricular end diastolic pressure was  $\sim 10$  mm Hg. Coronary flow was adjusted to 30 ml/min. After control measurements, coronary flow was reduced abruptly to (a) 15 ml/min ( $n = 7$ ), or (b) 12 ml/min ( $n = 7$ ), and held at this level for 1 min, at which time measurements were again recorded. Flow was then restored to control and the hearts allowed to recover.

### EFFECTS OF TACHYCARDIA AT VARIOUS LEVELS OF CORONARY FLOW

Tachycardia was used in an attempt to increase myocardial metabolic demand, analogous to pacing tachycardia in previous studies (11). Coronary flow was fixed at 40 ml/min ( $n = 7$ ), 15 ml/min ( $n = 7$ ) or 12 ml/min ( $n = 7$ ) and left ventricular end diastolic pressure was adjusted to 10 mm Hg. After control values were measured at a heart rate of 2.0 Hz, the heart was paced at 5.0 Hz for 3 min and the pacemaker then turned back to the control rate (2.0 Hz). At the

end of 3 min of tachycardia (while heart rate was still increased) pressure-time product (PTP), percent lactate extraction ratio (PLER), left ventricular pressure, and CPP were measured. Hemodynamic measurements were also made during the first 5–10 beats of the immediate post-tachycardia period. In addition, in seven experiments the heart rate was increased from 2.0 to 6.0 Hz at 30 ml/min coronary flow, and data were analyzed in the same way.

### EFFECTS OF HYPOXIA AT CONSTANT CORONARY FLOW

*Effects of hypoxia alone* ( $n = 7$ ). Coronary flow and heart rate were fixed at 30 ml/min and 2.0 Hz, respectively. Balloon volume was adjusted so that left ventricular end diastolic pressure was 10 mm Hg. After control measurements, the heart perfusion was switched to Krebs-Henseleit buffer that had the same composition as the control perfusate but was equilibrated with a 5% CO<sub>2</sub>–95% gas mixture. Measurements were made continuously during 2 min of hypoxia, following which the heart was again perfused by well-oxygenated perfusate to observe the process of recovery.

*Effects of hypoxia plus tachycardia* ( $n = 7$ ). In seven additional experiments, during the hypoxia described above, the heart rate was increased from 2.0 to 4.0 Hz for 2 min and then abruptly reduced again to 2.0 Hz. PTP, PLER, left ventricular pressure, and CPP were measured just before the cessation of tachycardia. We also measured hemodynamic parameters in the immediate post-tachycardia period during the first 5–10 beats, when left ventricular pressure changes were maximal. The hearts were then switched back to oxygenated perfusate and the process of recovery during reoxygenation was observed.

*Effects of hypoxia compared with adenosine* ( $n = 6$ ). The pressure and volume in the coronary vasculature may be one determinant of ventricular diastolic compliance (18–20). To further isolate the potential effects of coronary vasodilatation and engorgement of the ventricular wall (erectile effect), the change in ventricular diastolic pressure during hypoxia was compared with the effect of an adenosine infusion that produced an equal degree of vasodilatation under aerobic conditions. Hearts were paced at 3.0 Hz and coronary flow was 30 ml/min throughout these experiments. Balloon volume was adjusted so that left ventricular end-diastolic pressure was 10 mm Hg under aerobic (95% O<sub>2</sub>–5% CO<sub>2</sub>) conditions. Hearts were switched to hypoxic perfusion for 2 min and changes in CPP and left ventricular end diastolic pressure (LVEDP) were measured; the hearts were then reoxygenated and allowed to recover for 20 min. Adenosine was then infused via a sidearm of the aortic perfusion cannula to maintain a final concentration of 0.1 mM adenosine in the standard perfusate for 2 min. Changes in CPP and LVEDP were measured and compared with the changes observed with hypoxia.

*Definitions of stiffness and relaxation, and theoretical considerations.* Ideally, diastolic LV chamber stiffness should be evaluated from a plot of the relationship between diastolic pressure and volume over a wide range. For the isovolumic heart, this can be accomplished by increasing volume by known increments and measuring the corresponding end diastolic pressure. In the present study, however, the rapid changes in diastolic and systolic function under study precluded serial examination of such multiple diastolic pressure-volume points. Instead, we kept balloon volume constant for each hypoxia or ischemia experiment and regarded changes in end diastolic pressure as indicative of changes in diastolic stiffness. Thus, an increase in end diastolic pressure at constant chamber volume signified an increase in diastolic

<sup>1</sup> Abbreviations used in this paper: CPP, coronary perfusion pressure; LVEDP, left ventricular end diastolic pressure; PLER, percent lactate extraction ratio; T, time constant of left ventricular pressure fall.

chamber stiffness. Changes in LVEDP at constant left ventricle volume have correlated closely with changes in chamber stiffness when both measurements were made in the same hearts (16). A similar definition has been used previously by Henry and co-workers (31).

All studies before and after coronary flow reduction, pacing, and hypoxia were compared using Student's *t* test for paired data and analysis of variance when three or more experimental conditions were compared in the same heart. Values were expressed as mean  $\pm$  SEM.

## RESULTS

*Effect of coronary flow reduction alone (Table I and Fig. 1).* 1 min after coronary flow reduction from 30 to 15 ml/min, decreases occurred in left ventricular systolic pressure ( $99 \pm 8$  to  $73 \pm 5$  mm Hg,  $P < 0.001$ ); LVEDP ( $10 \pm 1$  to  $6 \pm 1$  mm Hg,  $P < 0.001$ ); CPP (mean,  $75 \pm 5$  to  $37 \pm 2$  mm Hg,  $P < 0.01$ ); left ventricular maximum (+)  $dp/dt$  ( $1,915 \pm 176$  to  $1,375 \pm 149$  mm Hg/s,  $P < 0.01$ ); left ventricular maximum (–)  $dp/dt$  ( $1,726 \pm 128$  to  $1,301 \pm 79$  mm Hg/s,  $P < 0.001$ ); PTP ( $2,076 \pm 194$  to  $1,572 \pm 138$  mm Hg s/min,  $P < 0.01$ ) and PLER ( $10 \pm 2$  to  $1 \pm 4$  %,  $P < 0.05$ ). A slight increase occurred in T ( $32 \pm 2$  to  $35 \pm 2$  ms,  $P < 0.05$ , whereas CVR was not changed.

After coronary flow reduction from 30 to 12 ml/min, decreases occurred in left ventricular systolic pressure ( $91 \pm 7$  to  $53 \pm 2$  mm Hg,  $P < 0.001$ ); LVEDP ( $11 \pm 1$  to  $5 \pm 1$  mm Hg,  $P < 0.001$ ); CPP ( $74 \pm 5$  to  $23 \pm 2$  mm Hg,  $P < 0.001$ ), CVR ( $2.48 \pm 0.16$  to  $1.95 \pm 0.14$  mm Hg  $\times$  min/ml,  $P < 0.01$ ); left ventricular maximum (+)

$dp/dt$  ( $1,714 \pm 152$  to  $1,013 \pm 47$  mm Hg/s,  $P < 0.001$ ); left ventricular maximum (–)  $dp/dt$  ( $1,688 \pm 111$  to  $926 \pm 33$  mm Hg/s,  $P < 0.001$ ); PTP ( $1,805 \pm 172$  to  $919 \pm 153$  mmHg s/min,  $P < 0.01$ ) and PLER ( $8 \pm 2$  to  $2 \pm 5$  %, NS). An increase occurred in T ( $36 \pm 1$  to  $41 \pm 3$  ms,  $P < 0.05$ ).

There were significant differences between 15 ml/min coronary flow and 12 ml/min coronary flow in left ventricular systolic pressure ( $P < 0.01$ ), CPP ( $P < 0.01$ ), left ventricular maximum (–)  $dp/dt$  ( $P \leq 0.01$ ), and PTP ( $P \leq 0.05$ ), but no differences in PLER, CVR, left ventricular maximum (+)  $dp/dt$ , T, and LVEDP.

*Effect of tachycardia at varying levels of coronary flow (Table II).* Pacing was performed at high control coronary flow (40 ml/min), control coronary flow (30 ml/min), and two levels of low coronary flow (15 and 12 ml/min).

At high coronary flow (40 ml/min), LVEDP decreased immediately after pacing tachycardia. Left ventricular systolic pressure and CPP also decreased. Although PTP increased slightly during tachycardia at flow rate 40 ml/min, it decreased at the control flow rate (30 ml/min). In neither case was any change in lactate extraction observed during pacing.

At control (30 ml/min) and low coronary flow rates (15 and 12 ml/min), LVEDP increased transiently during tachycardia but was not increased in the immediate postpacing period compared with control. Left ventricular systolic pressure decreased markedly during tachycardia and remained depressed for the first 30–60 s of the postpacing period. Despite the reduction of

TABLE I  
Left Ventricular and Coronary Hemodynamic Parameters during Reduction of Coronary Flow

Parameter	Series (a) (n = 7)		Series (b) (n = 7)		P (a) vs. (b)
	30 ml/min	15 ml/min	30 ml/min	12 ml/min	
LVP, mm Hg	99 $\pm$ 8	73 $\pm$ 5†	91 $\pm$ 7	53 $\pm$ 2†	<0.01
LVEDP, mm Hg	10 $\pm$ 1	6 $\pm$ 1†	11 $\pm$ 1	5 $\pm$ 1†	NS
CPP, mm Hg	75 $\pm$ 5	37 $\pm$ 2†	74 $\pm$ 5	23 $\pm$ 2†	<0.01
CVR, mm Hg $\times$ min/ml	2.49 $\pm$ 0.17	2.48 $\pm$ 0.16 NS	2.48 $\pm$ 0.16	1.95 $\pm$ 0.14†	NS
LV (+) $dp/dt$ , mm Hg/s	1,915 $\pm$ 176	1,375 $\pm$ 149†	1,714 $\pm$ 152	1,013 $\pm$ 47†	NS
LV (–) $dp/dt$ , mm Hg/s	1,726 $\pm$ 128	1,301 $\pm$ 79†	1,688 $\pm$ 111	926 $\pm$ 33†	<0.01
T, ms	32 $\pm$ 2	35 $\pm$ 2*	36 $\pm$ 1	41 $\pm$ 3*	NS
PTP, mm Hg $\times$ s/min	2,076 $\pm$ 194	1,572 $\pm$ 138†	1,805 $\pm$ 172	919 $\pm$ 153†	<0.05
PLER, %	10 $\pm$ 2	1 $\pm$ 4*	8 $\pm$ 2	2 $\pm$ 5 NS	NS
LAE, $\mu$ M/min	2.7 $\pm$ 0.5	0.1 $\pm$ 0.6†	3.0 $\pm$ 0.4	0.2 $\pm$ 0.6†	NS
HR, Hz	2.0	2.0	2.0	2.0	

*Abbreviations used in this table:* Coronary flow reduction series (a) 30 to 15 ml/min, (b) 30 to 12 ml/min. LVP, left ventricular systolic pressure; LVEDP, left ventricular end diastolic pressure; CPP, coronary perfusion pressure; CVR, coronary vascular resistance; LV (+)  $dp/dt$  and LV (–)  $dp/dt$ , left ventricular maximum positive  $dp/dt$  and maximum negative  $dp/dt$ ; T, time constant of left ventricular pressure fall; PTP, left ventricular systolic pressure time product; PLER, percent lactate extraction ratio; LAE, lactic acid extraction; HR, heart rate.

\*  $P < 0.05$ .

†  $P < 0.01$ .

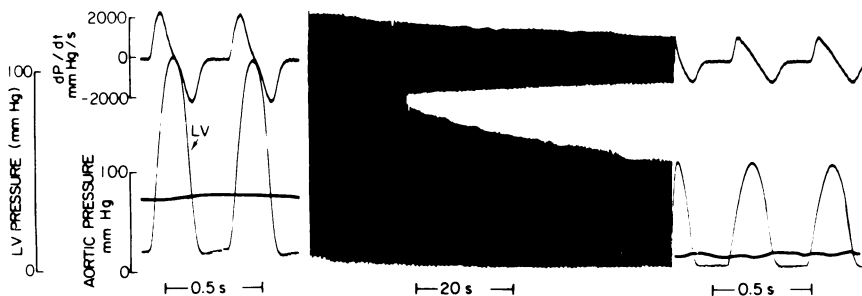


FIGURE 1 Effect of coronary flow reduction (ischemia) on isovolumic left ventricular (LV) pressure,  $dp/dt$ , and aortic mean pressure (coronary perfusion pressure) in the isolated rabbit heart at 37°C. At the onset of the slow speed recording, coronary flow was reduced from 30 to 12 ml/min. LV systolic and diastolic pressures decreased, as did  $dp/dt$  and aortic pressure.

PTP at low coronary flow, PLER became negative and left ventricular maximum ( $-$ )  $dp/dt$  and T, considered as indices of left ventricular relaxation rate, changed significantly (Table II).

At all coronary flow rates studied, although left ventricular systolic pressure sometimes increased initially during pacing, it then decreased gradually and (as shown in Table II) at the late phase of pacing tachycardia, left ventricular systolic pressure was significantly lower than before pacing (Fig. 2). Furthermore, in the first 5–10 beats after cessation of pacing, left ventricular systolic pressure remained depressed and then recovered rapidly. On the other hand, LVEDP decreased slightly or was unchanged after pacing.

In two experiments, left ventricular systolic pressure did not fall as much from control, or even increased during pacing (Fig. 3a and b). Left ventricular diastolic pressure increased progressively, and was 47 mm Hg by 1 min of tachycardia (Fig. 3a). Postpacing left ventricular diastolic pressure remained elevated for ~30 s and then gradually returned to control. CPP increased in this experiment, indicating a rise in CVR possibly secondary to high diastolic left ventricular pressure (11). Left ventricular relaxation was markedly impaired in the posttachycardia period (T increased from 37 to 142 ms).

Fig. 3b shows another example. In this experiment, coronary perfusion rate was 15 ml/min and the heart was paced at 5.0 Hz for 3 min from a control heart rate of 2.4 Hz.

**Effects of hypoxia (Table III and Fig. 4).** During 2 min of hypoxia at constant coronary flow rate (30 ml/min) and heart rate (2.0 Hz), major increases occurred in LVEDP ( $10 \pm 1$  to  $20 \pm 3$  mm Hg,  $P < 0.01$ ) and T ( $32 \pm 3$  to  $119 \pm 22$  ms,  $P < 0.01$ ). Decreases occurred in left ventricular systolic pressure ( $95 \pm 5$  to  $56 \pm 5$  mm Hg,  $P < 0.001$ ); CPP ( $70 \pm 6$  to  $53 \pm 4$  mm Hg,  $P < 0.01$ ); CVR ( $2.33 \pm 0.21$  to  $1.78 \pm 0.14$  mm Hg  $\times$  min/ml,  $P < 0.01$ ); left ventricular maximum (+)  $dp/dt$  ( $1,712 \pm 95$  to  $838 \pm 78$  mm Hg/s,  $P < 0.001$ ); left ventricular

maximum ( $-$ )  $dp/dt$  ( $1,650 \pm 86$  to  $670 \pm 60$  mm Hg/s,  $P < 0.001$ ); PTP ( $1,966 \pm 175$  to  $747 \pm 87$  mm Hg s/min,  $P < 0.001$ ) and PLER ( $11 \pm 3$  to  $-43 \pm 6\%$ ,  $P < 0.001$ ). Recovery time (time from beginning of reoxygenation to time the LVEDP returned to control level) was  $63 \pm 7$  s.

When the hearts were subjected to 2 min of hypoxia plus tachycardia (4.0 Hz), even greater increases occurred in LVEDP ( $10 \pm 1$  to  $24 \pm 3$  mm Hg,  $P < 0.01$ ) and T ( $40 \pm 4$  to  $224 \pm 37$  ms,  $P < 0.001$ ), both measured in the immediate posttachycardia period prior to reoxygenation. Decreases occurred in left ventricle systolic pressure ( $94 \pm 4$  to  $43 \pm 4$  mm Hg,  $P < 0.001$ ); CPP ( $72 \pm 5$  to  $52 \pm 3$  mm Hg,  $P < 0.01$ ); CVR ( $2.42 \pm 0.16$  to  $1.73 \pm 0.12$  mm Hg  $\times$  min/ml,  $P < 0.01$ ); left ventricular maximum (+)  $dp/dt$  ( $1,638 \pm 92$  to  $626 \pm 40$  mm Hg/s,  $P < 0.001$ ); left ventricular maximum ( $-$ )  $dp/dt$  ( $1,626 \pm 74$  to  $401 \pm 26$  mm Hg/s,  $P < 0.001$ ); PTP ( $1,955 \pm 174$  to  $634 \pm 68$  mm Hg s/min,  $P < 0.001$ ) and PLER ( $18 \pm 2$  to  $-48 \pm 15\%$ ,  $P < 0.001$ ). Recovery time was  $71 \pm 6$  s.

Correlations between LVEDP, left ventricular maximum ( $-$ )  $dp/dt$ , and T were examined. There was a good correlation between LVEDP and T ( $r = 0.82$ ,  $P < 0.001$ , Fig. 5). A modest correlation occurred between LVEDP, and maximum ( $-$ )  $dp/dt$  with  $r = 0.54$  ( $P < 0.01$ ).

**Effects of hypoxia compared with adenosine infusion.** The marked increase in ventricular diastolic pressure during hypoxic perfusion was not observed during an equal degree of vasodilatation induced by adenosine. Coronary perfusion pressure under control aerobic conditions in these six hearts averaged  $84 \pm 4$  mm Hg. Perfusion pressure decreased to  $58 \pm 3$  mm Hg during 2 min of hypoxia ( $P < 0.01$ , hypoxia vs. control) and  $60 \pm 3$  mm Hg during 2 min of 0.1 mM adenosine infusion ( $P < 0.01$ , adenosine vs. control). After 2 min of hypoxia, LVEDP increased from 10 to  $27 \pm 3$  mm Hg ( $P < 0.01$ ). In contrast, the LVEDP measured after 2 min of adenosine infusion was  $9 \pm 1$  mm Hg, not significantly different from the control

TABLE II  
Effects of Tachycardia on Left Ventricular and Coronary Hemodynamics at Various Levels of Coronary Flow

	40 ml/min (n = 7)			30 ml/min (n = 7)		
	Control	Tachycardia	Posttachycardia	Control	Tachycardia	Posttachycardia
HR, Hz	2.0	5.0	2.0	2.0	6.0	2.0
LVP, mm Hg	96±6	78±4†	69±4†	103±7	66±3†	58±4†
LVEDP, mm Hg	10±1	—	7±1†	10±1	—	8±1*
CPP, mm Hg	99±6	95±6*	89±6†	77±4	64±6†	60±5†
CVR, mm Hg × min/ml	2.47±0.15	2.37±0.15*	2.24±0.14†	2.58±0.13	2.13±0.21†	1.99±0.17†
LV(+)dp/dt, mm Hg/s	1,939±156	—	1,313±83†	1,951±157	—	1,113±95†
LV(-)dp/dt, mm Hg/s	1,700±104	—	1,239±64†	1,801±123	—	988±73†
T, ms	34±2	—	37±2	35±2	—	42±2*
PTP, mm Hg × s/min	2,043±210	2,179±212	—	2,210±184	1,648±97†	—
PLER, %	9±2	10±2	—	14±1	8±1*	—
LAE, μM/min	3.7±0.6	3.8±0.7	—	4.1±0.4	2.5±0.4*	—

Abbreviations are the same as for Table I.

\*  $P < 0.05$ .

†  $P < 0.01$ .

value. This result indicates that the increase in diastolic pressure with hypoxia was not due to a vascular engorgement or an erectile effect secondary to hypoxic vasodilation, and implicates an acute effect of hypoxia on the diastolic behavior of ventricular myocardium.

## DISCUSSION

Previous investigators have reported that global left ventricular ischemia causes no change (13) or an actual decrease (12) in left ventricular diastolic pressure relative to volume in the early ischemic phase, with an upward shift in the diastolic pressure-volume relation occurring in some studies 30–120 min after the onset of ischemia (14–16). These studies have been cited as supporting the concept that extracardiac factors are essential to explain the upward shift of the left ventricular

diastolic pressure-volume curve observed in patients during angina pectoris (1).

However, major differences exist between the pathophysiology of angina pectoris and that of myocardial ischemia produced by reduction of coronary vessel flow or coronary artery ligation. As mentioned earlier, with the usual form of exertion-induced angina pectoris (and in dogs with coronary stenoses subjected to pacing tachycardia) myocardial  $O_2$  demand increases to exceed the capacity for  $O_2$  delivery. The resultant relative or “demand-side” type of myocardial ischemia is associated with normal or increased myocardial blood flow, which minimizes local accumulation of metabolites and hydrogen ion. In contrast, with global reduction of coronary blood flow or acute coronary branch ligation a primary or “supply-side” type of myocardial ischemia ensues in which myo-

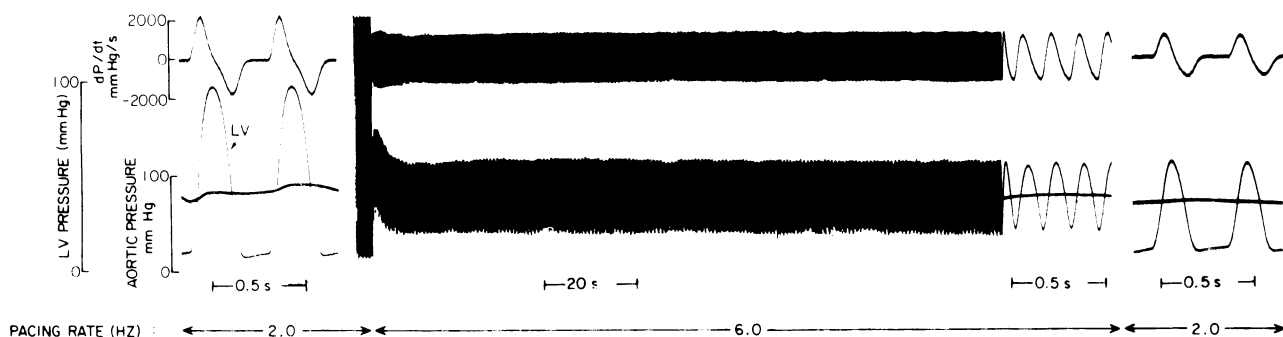


FIGURE 2 Effect of tachycardia at a coronary rate of 30 ml/min. Control heart rate (2.0 Hz) is followed by tachycardia (pacing rate 6.0 Hz) for 3 min. Tachycardia depressed LV systolic pressure, and just after cessation of tachycardia no changes in LVEDP were observed.

TABLE II (Continued)

15 ml/min (n = 7)			12 ml/min (n = 7)		
Control	Tachycardia	Post-tachycardia	Control	Tachycardia	Post-tachycardia
2.0	5.0	2.0	2.0	5.0	2.0
82±5	46±4†	43±3†	60±3	34±2†	28±2†
10±1	—	9±1	10±1	—	10±1
38±3	34±2*	31±2†	24±2	23±2	20±2†
2.51±0.18	2.34±0.15†	2.08±0.15†	1.98±0.14	1.93±0.15	1.69±0.15†
1,351±98	—	814±102†	988±45	—	451±29†
1,415±76	—	657±133†	963±50	—	337±35†
43±4	—	64±5†	47±4	—	128±10†
1,664±128	1,111±57†	—	1,182±79	625±69†	—
1±4	-5±3*	—	2±5	-27±10*	—
0.1±0.6	-0.8±0.5*	—	0.2±0.6	-3.2±1.1*	—

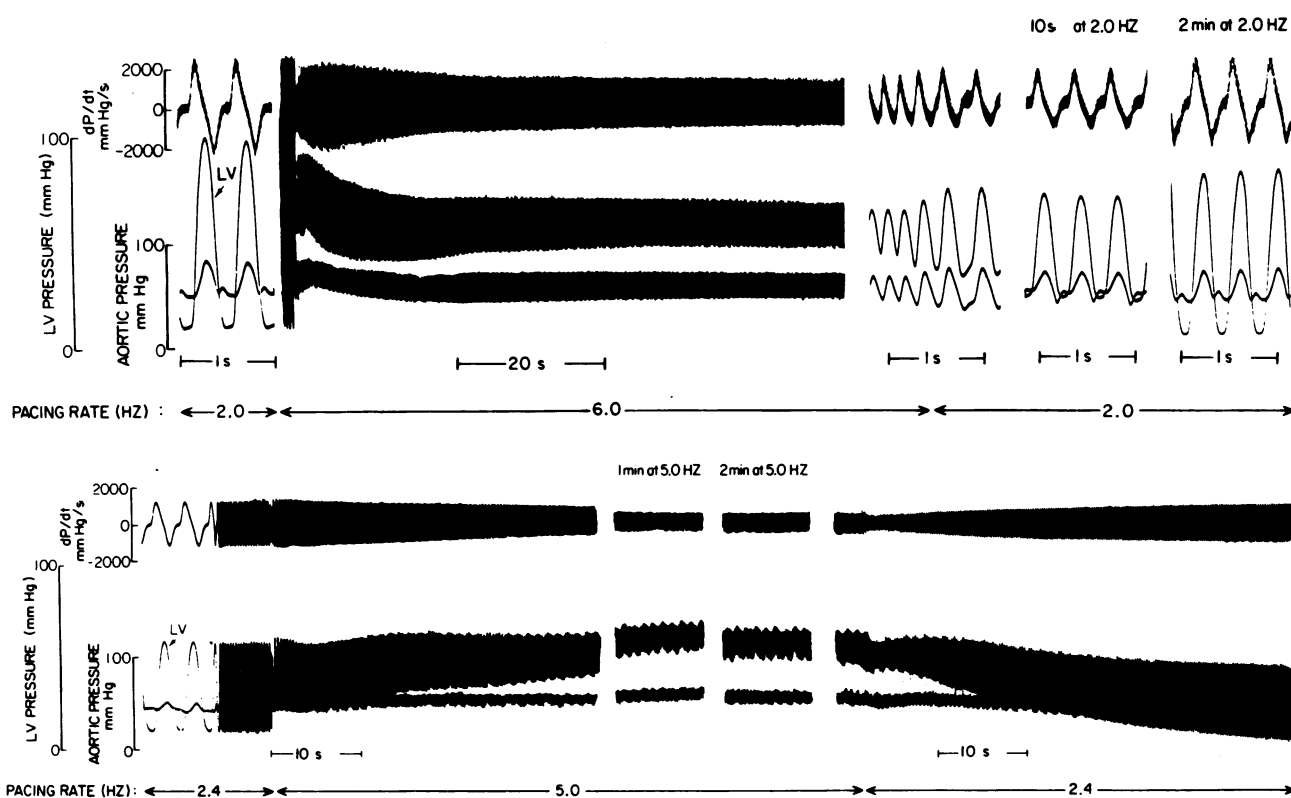


FIGURE 3 Effect of tachycardia in two experiments (panels A and B) where LV systolic pressure did not decline markedly during pacing. Panel A: coronary flow, 30 ml/min; pacing rate, 6.0 Hz for 1 min. During pacing, systolic pressure did not fall under 75 mm Hg, and a marked increase in LV diastolic pressure occurred. After cessation of tachycardia, an increase in LV diastolic pressure persisted and then gradually recovered. LV relaxation was markedly prolonged ( $T$ , 37 → 142 ms). Percent lactate extraction ratio changed from +13 to -8%. Panel B: coronary flow, 15 ml/min; pacing rate, 5.0 Hz for 1 min. Systolic pressure increased to >110 mm Hg during pacing. Percent lactate extraction ratio changed from +6 to -15%. A similar marked increase in LV diastolic pressure occurred, persisting into the post-tachycardia period and then gradually resolving.

TABLE III  
Effects of Hypoxia and Tachycardia on Left Ventricular and Coronary Flow  
Hemodynamics during Normal Coronary Flow

	Hypoxia (n = 7)		Hypoxia plus tachycardia at 4.0 Hz (n = 7)	
	Control	Hypoxia	Control	Posttachycardia
HR, Hz	2.0	2.0	2.0	2.0
LVP, mm Hg	95±5	56±5*	94±4	43±4*
LVEDP, mm Hg	10±1	20±3*	10±1	24±3*
CPP, mm Hg	70±6	53±4*	72±5	52±3*
CVR, mm Hg × min/ml	2.33±0.21	1.78±0.14*	2.42±0.16	1.73±0.12*
LV (+) dp/dt, mm Hg/s	1,712±95	838±78*	1,638±92	626±40*
LV (-) dp/dt, mm Hg/s	1,650±86	670±60*	1,626±74	401±26*
T, ms	32±3	119±22*	40±4	224±37*
PTP, mm Hg × s/min	1,966±175	747±87*	1,955±174	634±68*
PLER, %	11±3	-43±6*	18±2	-48±15*
LAE, μM/min	3.2±0.6	-12.9±1.6*	5.5±0.5	-14.4±4.5*
RT, s	—	63±7	—	71±6

RT, recovery time, time from the beginning of reoxygenation to the time LVEDP returned to control value. Coronary flow rate was held constant at 30 ml/min. Abbreviations are as in Table I.

\*  $P < 0.01$ .

cardial O<sub>2</sub> demand decreases, tending to reduce the adverse consequences of reduced O<sub>2</sub> delivery. In addition, with coronary ligation or severe reduction in coronary flow, local accumulation of hydrogen ion may occur and protect against increases of diastolic myocardial tension (17). Finally, the role of coronary vascular turgor (erectile effect) in maintaining left

ventricular chamber stiffness would be expected to have opposite effects on left ventricle diastolic pressure relative to volume in the two types of ischemia.

Our study involved a direct comparison of the acute ( $\leq 3$  min) effects of hypoxia vs. low coronary flow global ischemia on left ventricular stiffness and relaxation, a comparison that has not previously been reported.

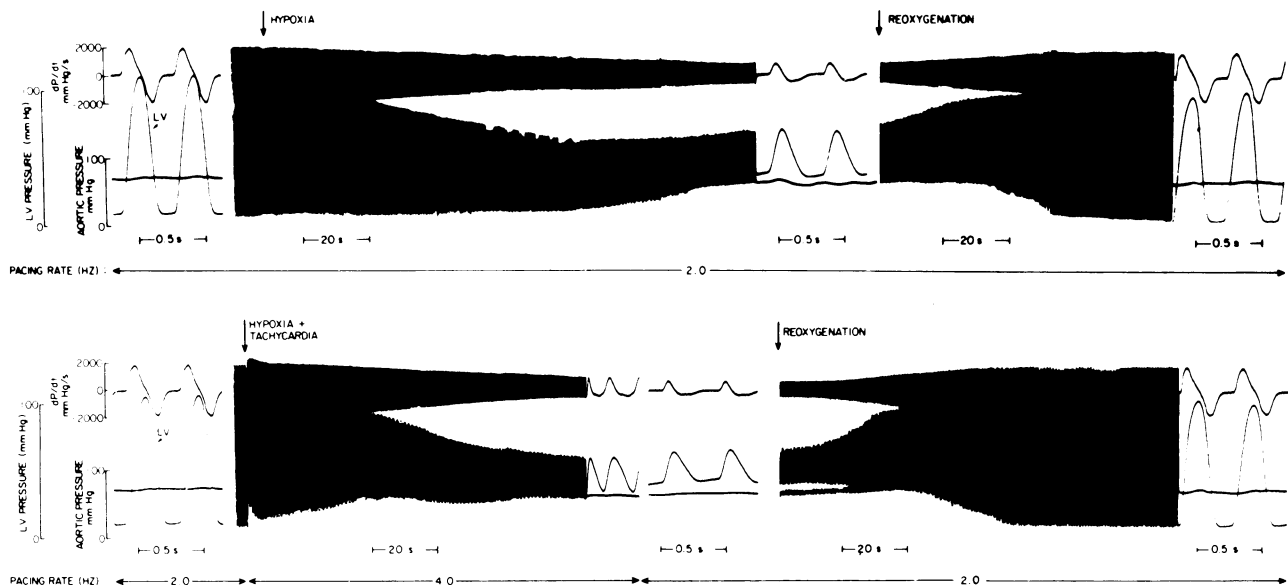


FIGURE 4 Effect of hypoxia on LV and aortic pressure and  $dp/dt$  in the isovolumic rabbit heart. Panel A: hypoxia alone. Panel B: hypoxia plus tachycardia (4.0 Hz). Coronary, flow 30 ml/min. LVEDP increased during 2 min of hypoxia or hypoxia plus tachycardia and recovered quickly after relief of tachycardia and/or reoxygenation.



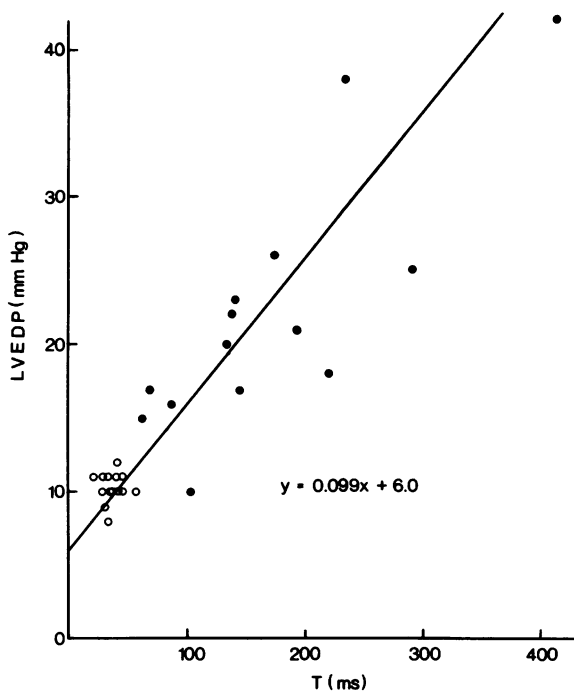


FIGURE 5 Relationship between LVEDP and the relaxation time constant  $T$ . ○, Control. ●, After 2 min of hypoxia or hypoxia plus pacing.

In the present experiments, a significant fall in left ventricular diastolic pressure relative to volume consistently and immediately followed coronary flow reduction, which is compatible with the concept that coronary artery pressure and flow (the erectile effect) are determinants of left ventricular diastolic stiffness (18–20). In contrast to the observations with low coronary flow global ischemia, hypoxia (anaerobic perfusate at control coronary flow) in this experimental model consistently caused a rise in LVEDP. This was associated with a substantial prolongation of the time constant of left ventricular relaxation,  $T$ . It is important to point out that the rise in LVEDP relative to volume, as well as the substantial prolongation of  $T$  (+300 to +500% increase) occurred during hypoxia, and within 2 min of its onset; this is distinct from the phenomenon of tension prolongation during reoxygenation following hypoxia or ischemia, as described by others (32–34).

When pacing tachycardia was superimposed on hypoxia, increases in  $T$  of 500% occurred in the post-tachycardia period prior to reoxygenation, and were associated with more than a doubling of LVEDP. Similar findings have been observed in Langendorff rat or rabbit heart preparations (35–37), although neither ventricular volume nor the relaxation time constant  $T$  was measured in those studies, and a comparison with low flow ischemia was not possible. We

used an isovolumic, contracting rabbit heart with constant balloon volume in the left ventricular chamber during each experiment so that changes in LVEDP would directly reflect changes in chamber stiffness. Our observation that LVEDP and the relaxation time constant  $T$  increased significantly during 2 min of hypoxia or during hypoxia posttachycardia, and that this was completely reversible following reoxygenation, is consistent with the observations of other investigators in isolated cardiac muscle and the Langendorff heart (35–38) and indicates a change both in diastolic ventricular stiffness and myocardial relaxation, rather than irreversible contracture. These results are strong evidence of impaired left ventricular myocardial relaxation, and indicate that without any regional inhomogeneity of the contraction-relaxation process in the left ventricular wall,  $T$  can be prolonged and LVEDP can be acutely and substantially elevated when myocardial oxygen demand exceeds supply.

To avoid confusion, we feel that it is important to clarify our use of the term “relaxation,” and what we mean by “impaired relaxation.” Most authors agree that myocardial “relaxation” refers to the decay of active tension following systolic effort, presumably related to  $\text{Ca}^{++}$  sequestration by sarcoplasmic reticulum (35, 37). Since both rate of  $\text{Ca}^{++}$  uptake and capacity for  $\text{Ca}^{++}$  binding are important characteristics of the “cardiac relaxing system” (39, 40), we prefer to consider rate and extent of relaxation as two separate and potentially independent aspects of the process. Rate of relaxation was measured by the constant  $T$  (30, 41). Weisfeldt et al. (41) have pointed out that by 3.5  $T$  after maximal negative  $dp/dt$ , 97% of relaxation would be complete, and their studies in the normal dog heart support this prediction. However, this finding depends on a large sarcoplasmic reticulum  $\text{Ca}^{++}$  binding capacity relative to cytosolic  $\text{Ca}^{++}$  concentration, so that  $\text{Ca}^{++}$  uptake and relaxation continue until cytosolic  $\text{Ca}^{++}$  concentration has fallen to a very low level. In contrast, if the myocardial cell were suddenly confronted with a very high cytosolic  $\text{Ca}^{++}$  concentration and/or a decreased sarcoplasmic reticulum capacity for  $\text{Ca}^{++}$  binding, the sarcoplasmic reticulum might become saturated while cytosolic  $\text{Ca}^{++}$  was still high enough to permit some activation of the contractile proteins. In such a situation, relaxation would be incomplete no matter what its initial rate or how long diastole lasted. One might also call such incomplete relaxation “tone” or “partial contracture;” each term has its advantages and disadvantages. Thus, we prefer to use the term slow relaxation when referring to a decrease in time constant  $T$  of relaxation, and incomplete relaxation to refer to failure of systolic tension to be completely dissipated by end diastole.

In our experiments, diastolic myocardial stiffness (LVEDP at constant volume) increased in rough pro-

portion to the disparity between myocardial oxygen demand and oxygen supply. In our hypoxia experiments, oxygen delivery was zero, but myocardial oxygen demand persisted during hypoxia at 30–40% of control PTP (Table III); this marked disparity between myocardial oxygen demand and supply was reflected in the relatively high rate of lactate production during hypoxia (Table III). In contrast, during low coronary flow ischemia oxygen delivery did not fall to zero, since coronary flow remained at 40–50% of control coronary flow. Myocardial oxygen demand, as assessed by the PTP during low-flow ischemia, was decreased in rough proportion to the decrease in coronary flow. The PTP could not be increased by increasing heart rate, as the tachycardia was accompanied by a further decrease in left ventricular systolic pressure development.

The lesser degree of lactate production in the ischemia experiments, relative to the hypoxia experiments, reflected the smaller disparity between oxygen demand and supply during ischemia relative to hypoxia. Lactate production is not always directly related to the oxygen demand-supply imbalance (21). For example, lactate production is reduced during severe ischemia, relative to hypoxia, because tissue lactate levels increase and directly inhibit the glycolytic pathway (42); the increased tissue lactate levels during more severe ischemia are reflected in a higher venous effluent lactate concentration (21, 27). Thus, when lactate production is decreased secondary to low-flow ischemia per se, there is a concomitant increase in venous lactate concentration. However, in our studies, the venous lactate concentration was lower during the ischemic periods than it was during the hypoxia periods.<sup>2</sup> This pattern of lactate metabolism indicates a lesser degree of oxygen demand-supply imbalance during the ischemia runs.

The relationship between the increase in diastolic stiffness and the degree of the oxygen demand-supply imbalance is supported by our two experiments (Fig. 3) where PTP persisted to an unusual extent during pacing tachycardia. In these two experiments, left ventricular systolic pressure was relatively well maintained during pacing tachycardia, PTP increased substantially, and postpacing LVEDP increased remarkably to >25 mm Hg. The marked disparity between oxygen demand and supply in these two experiments was also reflected by a higher than average amount of lactate production, compared with the usual low-flow ischemia experiments where PTP decreased and LVEDP did not increase. In a broader sense, diastolic stiffness may also reflect a myocardial ATP

demand-supply imbalance. During anaerobic coronary perfusion, when glycolytic blockade with iodoacetate was added to the blockade of oxidative phosphorylation induced by the anaerobic perfusion, isovolumic LVEDP increased by 70 mm Hg within 60 s (28).

Until now, few studies have examined the correlation between slow left ventricular relaxation (expressed by T or left ventricle peak negative  $dp/dt$ ) and elevation of LVEDP (41). Whether impaired left ventricular relaxation itself can contribute to elevation of LVEDP or not has been unclear. In this regard, the basic mechanisms of the impairment in relaxation and the associated elevation of LVEDP relative to volume remain uncertain. Several studies support an important role for altered  $Ca^{++}$  metabolism, possibly due to impaired sarcoplasmic reticular function secondary to ATP depletion, leading to slow and incomplete relaxation (3, 35–38). It is important to consider potential differences between slow relaxation (decreased rate) and incomplete relaxation (decreased extent). As pointed out by Weisfeldt and co-workers (41), slowed relaxation will be “incomplete” at end diastole if there is inadequate time during diastole for relaxation to run its course. In their studies, this occurred when the diastolic period per beat was <3.5 T in duration. However, as discussed above, the extent of myocardial relaxation must also depend on the  $Ca^{++}$  binding capacity of sarcoplasmic reticulum; if this becomes saturated (e.g., due to increased cytosolic  $Ca^{++}$  concentration resulting from  $Na^{+}$ - $Ca^{++}$  exchange, increased  $H^{+}$  ion, etc.), relaxation could be “incomplete” at end diastole, no matter what its initial rate (T). In our studies, diastolic pressure generally exhibited a flat or plateau phase (see Figs. 3 and 4), suggesting that relaxation had proceeded as far as it could, and that further diastolic time would not result in a return of diastolic pressure to normal. This suggests that in addition to slowed rate of relaxation, other factors (such as increased diastolic  $Ca^{++}$  concentration or decreased available sarcoplasmic reticulum binding sites) might be playing a role in the hypoxia-related rise in diastolic pressure relative to volume. Further studies concerning this mechanism are needed. Whatever the mechanisms involved, in the present study we observed a strong correlation between T and LVEDP (Fig. 5), consistent with the concept that impaired left ventricular relaxation is associated with the elevation of LVEDP with hypoxia. Left ventricular peak negative  $dp/dt$  also showed a good correlation with LVEDP but not as strong as T, presumably because peak negative  $dp/dt$  was affected by the fall in left ventricular systolic pressure and thus did not reflect the relaxation process alone (30).

As mentioned earlier, LVEDP consistently fell in response to reduced coronary flow global ischemia, and we have interpreted this finding as compatible with the

<sup>2</sup> Since the arterial lactate concentration was set at 1.0 mM in our studies, PLER values in Tables I–III directly reflect the venous lactate concentration; the values during hypoxia were much greater than those during ischemia.

importance of the "erectile effect" on left ventricular wall and chamber stiffness. According to this concept, the coronary vascular bed in the left ventricular wall was partially collapsed with low coronary flow ischemia, and this masked early wall stiffness changes, unless profound increases in diastolic myocardial tension occurred, as in the two experiments in Fig. 3. With regard to the role of the erectile effect, it might be speculated that hypoxia in the present experiments induced coronary vasodilatation and engorgement of the myocardial wall as the mechanism for the increased chamber stiffness and LVEDP (positive erectile effect). That this was not the case is shown by the experiments examining the effects of adenosine. When coronary vasodilatation was induced by adenosine in the well-oxygenated heart, left ventricular chamber stiffness did not increase. Thus, normal or increased coronary vascular volume is apparently a necessary (but not sufficient) condition for the hypoxia-related rise in LVEDP.

It should also be mentioned that edema of the ventricular wall and swelling of myocardial cells is known to occur with ischemic injury (43), but it seems unlikely that this could have occurred during the brief periods of ischemia in our experiments. In summary, 2 min of hypoxia or hypoxia plus pacing tachycardia caused significant elevation of LVEDP and impairment of myocardial relaxation prior to reoxygenation in isolated, perfused, isovolumically contracting rabbit hearts. The LVEDP elevation promptly recovered following return to control conditions. In contrast, low coronary flow global ischemia depressed both systolic function and left ventricular diastolic pressure, except in two experiments where systolic function and myocardial oxygen demand were only minimally depressed by ischemia and, in association, left ventricular diastolic pressure increased substantially. These results suggest that the changes in left ventricular chamber stiffness seen with hypoxia may be masked in low coronary flow globally ischemic preparations because of collapse of the coronary vascular bed and marked reductions in systolic work of the ischemic myocardium following acute reduction of coronary flow.

#### ACKNOWLEDGMENTS

This work was supported in part by grants HL 19089 and HL 23406 from the United States Public Health Service. Dr. Apstein holds a Research Career Development Award from the National Heart, Lung and Blood Institute (HL 00425). Dr. Grossman was supported by an Established Investigator Award of the American Heart Association during the time of this study.

#### REFERENCES

1. Glantz, S. A., and W. W. Parmley. 1978. Factors which affect the diastolic pressure-volume curve. *Circ. Res.* **42**: 171-180.

2. Ross, J., Jr. 1979. Acute displacement of the diastolic pressure-volume curve of the left ventricle: role of the pericardium and the right ventricle. *Circulation.* **59**: 32-37.
3. Grossman, W., and W. H. Barry. 1980. Diastolic pressure-volume relations in the diseased heart. *Fed. Proc.* **39**: 148-155.
4. Dwyer, E. M., Jr. 1970. Left ventricular pressure-volume alterations and regional disorders of contraction during myocardial ischemia induced by atrial pacing. *Circulation.* **42**: 1111-1122.
5. McLaurin, L. P., E. L. Rolett, and W. Grossman. 1973. Impaired left ventricular relaxation during pacing-induced ischemia. *Am. J. Cardiol.* **32**: 751-757.
6. Barry, W. H., J. Z. Brooker, E. L. Alderman, and D. C. Harrison. 1974. Changes in diastolic stiffness and tone of the left ventricle during angina pectoris. *Circulation.* **49**: 255-263.
7. Mann, T., B. R. Brodie, W. Grossman, and L. P. McLaurin. 1977. Effect of angina on the left ventricular diastolic pressure-volume relationship. *Circulation.* **55**: 761-766.
8. Mann, T., S. Goldberg, G. H. Mudge, Jr., and W. Grossman. 1979. Factors contributing to altered left ventricular diastolic properties during angina pectoris. *Circulation.* **52**: 14-20.
9. Rickards, A., and R. Seabra-Gomes. 1978. Observations on the effect of angina on the left ventricle with special reference to diastolic behavior. *Eur. J. Cardiol.* **7**(Suppl.): 213-238.
10. Grossman, W., and T. Mann. 1978. Evidence for impaired left ventricular relaxation during acute ischemia in man. *Eur. J. Cardiol.* **7**(Suppl.): 239-249.
11. Serizawa, T., B. A. Carabello, and W. Grossman. 1980. Effect of pacing-induced ischemia on left ventricular diastolic pressure-volume relations in dogs with coronary stenoses. *Circ. Res.* **46**: 430-439.
12. Forrester, J. S., G. Diamond, W. W. Parmley, and H. J. C. Swan. 1972. Early increase in left ventricular compliance after myocardial infarction. *J. Clin. Invest.* **51**: 598-603.
13. Palacios, I., R. A. Johnson, J. B. Newell, and W. J. Powell, Jr. 1976. Left ventricular end-diastolic pressure-volume relationships with experimental acute global ischemia. *Circulation.* **53**: 428-436.
14. Tyberg, J. V., J. S. Forrester, H. L. Wyatt, S. J. Goldner, W. W. Parmley, and H. J. C. Swan. 1974. An analysis of segmental ischemic dysfunction utilizing the pressure-length loop. *Circulation.* **49**: 748-754.
15. Gaasch, W. H., O. H. L. Bing, M. B. Pine, A. Franklin, J. Clement, D. Rhodes, W. P. Phear, and R. M. Weintraub. 1978. Myocardial contracture during prolonged ischemia arrest and reperfusion. *Am. J. Physiol.* **235**: H619-627.
16. Apstein, C. S., M. Mueller, and W. B. Hood, Jr. 1977. Ventricular contracture and compliance changes with global ischemia and reperfusion, and their effect on coronary resistance in the rat. *Circ. Res.* **41**: 206-217.
17. Greene, H. L., and M. L. Weisfeldt. 1977. Determinants of hypoxia and post-hypoxic myocardial contracture. *Am. J. Physiol.* **232**: H526-533.
18. Salisbury, P. F., C. E. Cross, and P. A. Rieben. 1960. Influence of coronary pressure on myocardial elasticity. *Circ. Res.* **8**: 794-800.
19. Ahn, J., C. S. Apstein, and W. B. Hood, Jr. 1977. Erectile properties of the left ventricle; direct effect of coronary artery perfusion pressure on diastolic wall stiffness and thickness. *Clin. Res.* **25**: 201A. (Abstr.)

20. Gaasch, W. H., O. H. L. Bing, A. Franklin, D. Rhodes, S. A. Bernard, and R. N. Weintraub. 1978. The influence of acute alteration in coronary blood flow on left ventricular diastolic compliance and wall thickness. *Eur. J. Cardiol.* 7(Suppl.): 147-161.
21. Apstein, C. S., F. Gravino, and W. B. Hood, Jr. 1979. Limitations of lactate production as an index of myocardial ischemia. *Circulation.* 60: 877-888.
22. Wiegner, A. W., G. J. Allen, and O. H. L. Bing. 1978. Weak and strong myocardium in series: implication for segmental dysfunction. *Am. J. Physiol.* 235: H776-H783.
23. Serizawa, T. 1978. An experimental study of left ventricular isovolumic relaxation period: on the fitting of left ventricular pressure fall to exponential function. *Tokyo J. Med. Sci.* 85: 295-308.
24. Glantz, S. A., G. A. Misbach, W. Y. Moores, D. G. Mathey, J. Lekven, D. F. Stowe, W. W. Parmley, and J. V. Tyberg. 1978. The pericardium substantially affects the left ventricular diastolic pressure-volume relationship in the dog. *Circ. Res.* 42: 433-441.
25. Shirato, K., R. Shabetai, B. Bhargava, D. Franklin, and J. Ross, Jr. 1978. Alteration of the left ventricular diastolic pressure-segment length relation produced by the pericardium: effects of cardiac distension and afterload reduction in conscious dogs. *Circulation.* 57: 1191-1198.
26. Mirsky, I., and J. S. Rankin. 1979. The effects of geometry, elasticity, and external pressures on the diastolic pressure-volume and stiffness-stress relations: how important is the pericardium? *Circ. Res.* 44: 601-611.
27. Apstein, C. S., L. Deckelbaum, M. Mueller, L. Hagopian, and W. B. Hood, Jr. 1977. Graded global ischemia and reperfusion: cardiac function and lactate metabolism. *Circulation.* 55: 864-872.
28. Apstein, C. S., L. Deckelbaum, L. Hagopian, and W. B. Hood, Jr. 1978. Acute cardiac ischemia and reperfusion: contractility, relaxation, and glycolysis. *Am. J. Physiol.* 235: H637-648.
29. Falsetti, H. J., R. E. Mates, R. J. Carroll, R. L. Gupta, and A. C. Bell. 1974. Analysis and correction of fluid wave distortion in fluid filled catheter systems. *Circulation.* 49: 165-172.
30. Weiss, J. L., J. W. Frederiksen, and M. L. Weisfeldt. 1976. Hemodynamic determinants of the time course of fall in canine ventricular pressure. *J. Clin. Invest.* 58: 751-776.
31. Henry, P. D., R. Schuchleib, J. Davis, E. S. Weiss, and B. E. Sobel. 1977. Myocardial contracture and accumulation of mitochondrial calcium in ischemia rabbit heart. *Am. J. Physiol.* 233: H677-684.
32. Tyberg, J. V., L. A. Yeatman, W. W. Parmley, C. W. Urschel, and E. H. Sonnenblick. 1970. Effects of hypoxia on mechanics of cardiac contraction. *Am. J. Physiol.* 218: 1780-1788.
33. Bing, O. H. L., J. F. Keefe, M. J. Wolk, L. J. Finkelstein, and H. J. Levine. 1971. Tension prolongation during recovery from myocardial hypoxia. *J. Clin. Invest.* 50: 660-666.
34. Weisfeldt, M. L., P. Armstrong, H. W. Scully, C. A. Sanders, and W. M. Daggett. 1974. Incomplete relaxation between beats after myocardial hypoxia and ischemia. *J. Clin. Invest.* 53: 1626-1636.
35. Nayler, W. G., and A. Williams. 1978. Relaxation in heart muscle: some morphological and biochemical considerations. *Eur. J. Cardiol.* 7(Suppl.): 35-50.
36. Nayler, W. G., C. E. Yezpey, and P. A. Poole-Wilson. 1978. The effect of  $\beta$ -adrenoceptor and  $Ca^{++}$  antagonist drugs on the hypoxia-induced increase in resting tension. *Cardiovasc. Res.* 12: 666-674.
37. Nayler, W. G., P. A. Poole-Wilson, and A. Williams. 1979. Hypoxia and calcium. *J. Mol. Cell. Cardiol.* 11: 683-706.
38. Lewis, M. J., A. C. Grey, and A. H. Henderson. 1979. Determinants of hypoxic contracture in isolated heart muscle preparations. *Cardiovasc. Res.* 13: 86-94.
39. Katz, A. M., and D. I. Repke. 1967. Quantitative aspects of dog cardiac microsomal calcium binding and calcium uptake. *Circ. Res.* 21: 153-162.
40. McCollum, W. B., H. R. Besch, Jr., M. L. Entman, and A. Schwartz. 1972. Apparent initial binding rate of calcium by canine cardiac relaxing system. *Am. J. Physiol.* 223: 608-614.
41. Weisfeldt, M. L., J. W. Frederiksen, F. C. P. Yin, and J. L. Weiss. 1978. Evidence of incomplete left ventricular relaxation in the dog. *J. Clin. Invest.* 62: 1296-1302.
42. Rovetto, M. J., W. F. Lamberton, and J. R. Neely. 1975. Mechanism of glycolytic inhibition in ischemic rat hearts. *Circ. Res.* 37: 742-751.
43. Powers, E. R., D. R. Dibona, and W. J. Powell. 1978. The development of a perfusion deficit and myocardial cell swelling with low flow ischemia. *Circulation.* 58: 11-678.