Impaired Ventricular Relaxation During Myocardial Ischemia and After Reperfusion in Isolated Perfused Canine Hearts

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The goal of this study was to investigate the mechanisms of impaired relaxation in ischemic and reperfused hearts without asynergic wall motion. To test the hypothesis that muscle elongation during ischemia does not improve the slowed relaxation, the time constant (T) of the isovolumic left ventricular pressure decay was obtained during volume loading in 14 isolated perfused canine hearts. In the nonischemic condition (coronary perfusion pressure: 107 ± 3 mmHg), T progressively decreased as the peak left ventricular pressure was increased by volume loading. In contrast, in the ischemic condition (coronary perfusion pressure: 51 ± 3 mmHg), T did not decrease despite an increase in peak left ventricular pressure by volume loading. These results indicate that during ischemia the impaired relaxation is not improved by an increase in preload. Moreover, reperfusion after a brief ischemia also increased T despite an increase in the contractile force, i.e., left ventricular pressure. The maximal change in the relaxation rate occurred much earlier than the maximal overshoot of the contractile force and coincided with an increase in coronary blood flow. These results indicate that prolongation of relaxation immediately after reperfusion is partly attributable to an increase in the electile force induced by the refilling of the coronary arteries. These mechanisms of impaired relaxation during ischemia and reperfusion may deteriorate ventricular filling and hence, cardiac output.

In acute myocardial ischemia such as in acute myocardial infarction and angina pectoris, cardiac performance is depressed immediately following the onset of ischemia.1,2 Several lines of evidence suggest that in this clinical setting an abnormality of relaxation may compromise ventricular filling and subsequent cardiac output.3–6 Although an asynchronous wall motion due to regional myocardial ischemia is the main contributor to impaired ventricular relaxation7,8 the whole picture of the underlying mechanisms of impaired relaxation in acute myocardial ischemia remains unclear. Previous experimental studies using isolated hearts or papillary muscles suggest that acute ischemia per se may minimally influence the muscle relaxation rate.2,9 However, in the ischemic heart, the involved myocardium is stretched during both systole and diastole7; during systole muscle segment in the ischemic region is stretched by contraction of the nonischemic muscle, and during diastole it is elongated by an increase in the end-diastolic ventricular volume. Since the relaxation is enhanced by volume loading in intact hearts.10

Key words: Ventricular relaxation Afterload-dependency Myocardial ischemia Coronary reperfusion

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<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Volume (ml)</th>
<th>Peak LVP (mmHg)</th>
<th>LVP min (mmHg)</th>
<th>Po (mmHg)</th>
<th>dP/dt max (mmHg/s)</th>
<th>dP/dt min (mmHg/s)</th>
<th>T (ms)</th>
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</thead>
<tbody>
<tr>
<td>(a) Nonischemic</td>
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<td></td>
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<td></td>
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<tr>
<td>low</td>
<td>7</td>
<td>11.6 ± 0.5</td>
<td>76.5 ± 1.0</td>
<td>-2.9 ± 0.7</td>
<td>40.6 ± 1.2</td>
<td>1070 ± 40</td>
<td>-820 ± 60</td>
<td>76.5 ± 3.5</td>
</tr>
<tr>
<td>control</td>
<td>7</td>
<td>13.1 ± 0.2</td>
<td>108.5 ± 1.2</td>
<td>-0.9 ± 1.0</td>
<td>57.5 ± 2.3</td>
<td>1400 ± 50</td>
<td>-1140 ± 60</td>
<td>58.5 ± 3.3</td>
</tr>
<tr>
<td>high</td>
<td>7</td>
<td>15.6 ± 0.9</td>
<td>139.0 ± 1.2</td>
<td>1.0 ± 1.2</td>
<td>70.1 ± 2.4</td>
<td>1410 ± 100</td>
<td>-1490 ± 60</td>
<td>44.6 ± 1.9</td>
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<tr>
<td></td>
<td>p &lt; 0.01</td>
<td>p &lt; 0.01</td>
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<td>(b) Global ischemia</td>
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<tr>
<td>control</td>
<td>7</td>
<td>13.1 ± 0.7</td>
<td>73.2 ± 2.4</td>
<td>-0.5 ± 1.3</td>
<td>38.3 ± 1.3</td>
<td>960 ± 70</td>
<td>-790 ± 60</td>
<td>80.4 ± 2.6</td>
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<tr>
<td>high</td>
<td>7</td>
<td>15.7 ± 0.9</td>
<td>88.4 ± 1.8</td>
<td>2.6 ± 1.2</td>
<td>48.4 ± 1.8</td>
<td>1070 ± 70</td>
<td>-860 ± 60</td>
<td>80.0 ± 2.4</td>
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<tr>
<td>higher</td>
<td>7</td>
<td>18.3 ± 1.1</td>
<td>104.3 ± 1.3</td>
<td>6.3 ± 1.6</td>
<td>62.1 ± 3.0</td>
<td>1140 ± 90</td>
<td>-940 ± 60</td>
<td>80.5 ± 3.0</td>
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<tr>
<td></td>
<td>p &lt; 0.01</td>
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<td>p &lt; 0.01</td>
<td>N.S.</td>
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</table>

Values are means ± SE.
Abbreviations: peak LVP = peak left ventricular pressure; LVP min = minimal left ventricular pressure; Po = pressure at dP/dt min; dP/dt max and dP/dt min = maximal and minimal dP/dt; T = time constant of isovolumic left ventricular pressure decay by the best exponential fitting method.
does not improve ventricular relaxation in the ischemic heart, seven isovolumically contracting hearts were studied with three ranges of volume loading. Since volume loading is equivalent with imposing afterload in isovolumically contracting hearts, we studied the ventricular relaxation rate at three different LV pressure ranges: control (100–120 mmHg), high (130–150 mmHg) and low (60–80 mmHg). After the control study, LV volume was either increased until peak LV pressure reached the high pressure range or reduced to the low pressure range. The order of loading intervention was completely randomized. Coronary perfusion pressure was maintained constant throughout this study (107 ± 3 mmHg). After the study, coronary perfusion pressure was reduced to about 50 mmHg (51 ± 3 mmHg) by clamping the perfusion tube and produced global ischemia heart at the control LV volume; peak LV pressure gradually decreased and reached a steady-state within 5 min. During this ischemic condition, peak LV pressure was increased by changing the LV volume by two steps. The pressure ranges were (1) control (70–85 mmHg), (2) high (86–95 mmHg) and (3) higher (96–110 mmHg). Control LV volumes during the normoxic and ischemic conditions were unchanged (see Table I).

**Protocol II:** Reperfusion after a one min coronary occlusion

In seven other isolated hearts, the LV volume was fixed so that peak LV pressure was more than 100 mmHg. Mean coronary perfusion pressure was 105 ± 4 mmHg. After stabilization, coronary perfusion pressure was reduced to zero by completely clamping the perfusion tube for 1 min and the heart was reperfused promptly. Subsequent LV pressures were determined 30 and 60 s after the onset of global ischemia and 5, 15, 30, 60, 120 and 300 s after the onset of reperfusion.

**Data Processing**

Hemodynamic parameters were obtained from the mean value of 2 subsequent beats. Peak LV pressure, LV diastolic minimal pressure (LVP min) and maximal and minimal dP/dt (dP/dt max and dP/dt min) were obtained from the pressure data. The relaxation rate of the left ventricle was assessed by the time constant (T) of isovolumic LV pressure decay. T was calculated by the best exponential fitting method in which the asymptote is variable, because the assumption of zero asymptote is invalid in the case of LV volume loading.\(^{10,12}\) The following equation predicts the pressure fall \(p(t)\)\(^{12}\):

\[
P(t) = (P_0 - P_\infty) \exp(-t/T) + P_\infty
\]

In this equation, \(P_0\) is the pressure at \(dP/dt\) min and \(P_\infty\) is the asymptote. \(T\) was obtained by the slope of the least squared regression line between \(dP/dt\) and pressure since \(dP/dt = -1/T (P_0 - P_\infty)\). The pressure data from \(dP/dt\) min to 10 mmHg + LVP min were employed for this analysis. The pressure signals were digitized every 4.2 ms.

Statistical comparison was made by analysis of variance in Protocol I and paired \(t\) test in Protocols I and II.\(^3\) Data were expressed as mean ± SE, and \(p < 0.05\) was considered significant.

**RESULTS**

1. Effects of ventricular volume loading on relaxation rate before and during global ischemia

Table I shows the pertinent hemodynamic parameters and the time constant (T) of isovolumic LV pressure decay obtained in isolated
canine hearts before and during global ischemia. In the nonischemic condition (Table I-(a)), T decreased progressively (p < 0.01) when peak LV pressure was increased by volume loading. A reduction of coronary perfusion pressure significantly (p < 0.01) decreased peak LV pressure from 108.5 ± 1.2 to 73.2 ± 2.4 mmHg and increased T from 58.5 ± 3.3 to 80.4 ± 2.6 ms (p < 0.01). Table I-(b) depicts the effect of volume loading on ventricular relaxation (T) in ischemic hearts. In contrast to the nonischemic hearts, the ischemic hearts did not show a load-dependent acceleration of relaxation rate; T did not altered even with volume loading. These results indicate that in nonischemic isolated hearts the relaxation rate is accelerated with volume loading, whereas ventricular relaxation is independent of volume loading in globally ischemic hearts. Thus, the impaired ventricular relaxation does not improve with volume loading by which peak LV pressure becomes comparable with the control value.

2. Effects of reperfusion on LV relaxation rate

Figure 1 shows the serial changes in peak and minimal LV pressures, coronary blood flow and time constant of LV pressure decay during global ischemia and reperfusion in a representative experiment. During complete occlusion of the perfusion line, peak LV pressure decreased with an increase in T. During reperfusion, coronary blood flow and peak LV pressure increased transiently over the control (preischemic) values and T increased further. Figure 2 shows mean changes in peak and minimal LV pressures, T and coronary blood flow before and during global ischemia. Immediately after reperfusion, T increased despite a significant increase in peak LV pressure. Figure 3 shows the times from the onset of reperfusion at which the maximal values of peak and minimal LV pressures, coronary blood flow and T were obtained. The time of the maximal value of T was much earlier than that of peak LV pressure but it coincided with those of coronary blood flow and minimal LV pressure. These results indicate that the slowed LV relaxation rate during reactive hyperemia is not primarily related to the changes of peak LV pressure but may be attributable to the engorgement of the ventricular wall by rapid coronary inflow after reperfusion.

DISCUSSION

It is well known that ventricular relaxation is markedly impaired during acute ischemia. The major cause of this impaired relaxation is attributed to the asynchrony or asynergy of the ventricular wall motion rather than to the intrinsic deterioration of muscle relaxation.

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In ischemic hearts the involved regions are stretched during systole and hence, relaxation may be accelerated since in intact hearts volume loading enhances ventricular relaxation. However, the load-dependency of ventricular relaxation in ischemic hearts has not been elucidated. In the present study, we demonstrated that ventricular relaxation is impaired in acute global ischemia and is not accelerated with volume loading; the load-dependent acceleration of the relaxation rate is lost in ischemic hearts. From our results, one can easily speculate that the relaxation of the ischemic segment is primarily impaired although the effect of asynchrony on ventricular relaxation may be superimposed.

In intact nonischemic hearts, ventricular relaxation is enhanced when afterload increases. We have demonstrated previously that the time constant obtained by the best exponential fitting method decreases as peak LV pressure increases in isolated canine hearts. This finding is consonant with the previous report of Wiegner et al that the afterload-dependency of the relaxation rate is observed in the isolated papillary muscle contracting in a physiologically sequenced fashion. In the ischemic heart, however, this afterload-dependent relaxation was abolished. Consequently, the impaired relaxation of the ischemic heart was sustained even when afterload was imposed (see Table I). This may occur in the involved segment of the ischemic heart and may contribute to the impaired ventricular relaxation. Chuck et al observed the absence of load-dependent relaxation in the hypoxic muscle. Although their study was different from ours in the experimental animals and models, loading conditions during contraction and metabolic conditions, there may be a common mechanism in the loss of load dependency of relaxation during ischemia or hypoxia. LeCarpentier et al reported that load-dependent relaxation could not be observed in frog muscle in which the sarcoplasmic reticulum (SR) is poorly developed. Therefore, the impaired function of SR during acute ischemia may contribute to the loss of load-dependent relaxation since the function of SR is highly dependent on aerobic metabolism.

The impaired function of SR may also be involved in the relaxation after reperfusion since an increase in Ca influx during reperfusion induces Ca overload; reperfusion may increase the Ca concentration in cytosol due to the increased membrane permeability of Ca and the depressed reuptake of Ca by the SR. Increased Ca concentration augments the myocardial contractile force, whereas the depressed function of SR causes the slowed myocardial relaxation. Our results showed that reperfusion slows relaxation associated with an overshooting increase in peak LV pressure in isovolumic contraction. Although our finding seems to be compatible with the Ca overload theory after reperfusion, it should be noted that the time courses of the contractile state and the relaxation rate (T) were discordant; peak LV pressure reached a peak 60 s after reperfusion whereas the time constant came to a peak much earlier (16 ± 3 ms). These results suggest that the serial changes in contractile force are different from those of the relaxation property. Tyberg et
al\(^2\) and Blaustein and Gaasch\(^{24}\) showed that reoxygenation elicits overshooting prolongation of relaxation in the papillary muscle and intact heart in which the contractile force did not overshoot. These discordant results between relaxation and contractile force could be partially attributable to the engorgement of the ventricular wall due to the rapid coronary inflow immediately after reperfusion. Ahn et al\(^{25}\) recently demonstrated that increases in coronary perfusion pressure and flow result in an increase in ventricular diastolic stiffness. This may also deteriorate the relaxation and raise LVP min. Although an enhanced electile force by rapid filling of the coronary vessels may augment the developed pressure by increasing end-diastolic muscle length, this effect was minimal in our experiment; the maximal overshoot of the peak LV pressure was not associated with those of coronary blood flow and LVP min. These results indicate that the slowed relaxation observed in the early phase of reperfusion is not due to Ca\(^{2+}\) overload but to mechanical factors, e.g., engorgement of the ventricular wall by rapid refilling of blood into the coronary vascular system\(^{25}\).

In summary, the present study supports the view that myocardial ischemia markedly impairs ventricular relaxation, and muscle stretch in the ischemic segment does not improve the relaxation properties. Thus, muscle stretch could not be a compensatory mechanism of impaired relaxation in the ischemic heart. Reperfusion from a brief ischemia is also followed by a marked, albeit transient, prolongation of relaxation. This may be due to the engorgement of the ventricular wall elicited by the rapid refilling of empty coronary vessels.

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