Mechanism of Global Functional Recovery Despite Sustained Postischemic Regional Stunning

Willie E. Lawrence, MD; W. Lowell Maughan, MD; and David A. Kass, MD

Background. The mechanisms whereby reperfusion of a 20-minute coronary occlusion result in global functional recovery despite persistent regional dysfunction were studied in 11 open-chest reflex-blocked dogs.

Methods and Results. Pressure-volume and pressure–thickness relations were simultaneously determined before, during, and after reperfusion of left anterior descending artery (LAD) occlusion. Wall thickness was determined by sonomicrometry in both ischemic and remote regions. Chamber systolic function was assessed by end-systolic pressure–volume relations (ESPVR) obtained by conductance catheter and defined by a slope (Ees) and volume shift at a common end-systolic pressure (ΔVes). LAD occlusion produced regional systolic thinning (−7±6%) and global left ventricular dysfunction (ESPVR shifted rightward (ΔVes= +8.6±5.1 ml, p<0.001) with no Ees change). After nearly 1 hour of reperfusion, LAD region thickening remained markedly reduced at 4±7% (versus 23±8%, control), yet chamber systolic function fully recovered (ESPVR shifted back leftward ΔVes= −8.9±6.5 ml). Ischemia induced a leftward shift and systolic thinning of LAD region pressure–thickness relations. Reperfusion returned end-systolic pressure–thickness relations halfway to their control position and diastolic relations fully to control position. This was primarily due to increased passive stiffening in about half the hearts and a partial return of active function in the remaining ones. The net effect was to eliminate systolic thinning over a physiological loading range, thus normalizing chamber systolic performance. Reflex activation, remote hyperfunction, or altered chamber loading did not account for the postreperfusion disparity between global and regional function.

Conclusions. These data suggest a mechanism to account for greater functional benefits of reperfusion beyond that anticipated from regional wall motion analysis. (Circulation 1992;85:816-827)

Clinical evaluations of reperfusion therapy for acute coronary occlusion usually use ejection fraction as the primary measure of ventricular function and treatment efficacy.1–3 In contrast, experimental animal studies often rely on precise regional wall motion measurements. Regional and global chamber dysfunction correlate during acute severe ischemia4–5; however, the extent to which this remains the case after reperfusion is less clear. For example, despite sustained reduced regional thickening or shortening after reperfusion (stunning), systolic pressure and maximal rate of pressure rise (dP/dt max) are typically normal.6–8 In a recent experimental study, reperfusion was also found to normalize ejection fraction despite persistent severe regional dysfunction.9

Several mechanisms have been proposed to explain such disparities between regional and global function after reperfusion. These include remote region hyperfunction, reflex sympathetic stimulation, changes in chamber loading, and altered passive properties of the reperfused myocardium.10 A limitation of prior studies, however, is the lack of simultaneous load-independent measures of both chamber and regional function. Thus, the importance of each mechanism remains undefined.

Based on previous studies of pressure–volume relations during regional ischemia,11,12 we hypothe-
sized that reperfusion might restore global systolic function independent of return of regional thickening by effectively stiffening the previously ischemic region (both passively and by partial activation) and thereby minimize regional thinning. To test this, regional pressure–thickness and global pressure–volume relations were simultaneously obtained in open-chest anesthetized dogs before, during, and after reperfusion of a 20-minute coronary artery occlusion. The results are consistent with our hypothesis and highlight potential dangers of relying solely on global or regional measurements when assessing benefits of reperfusion therapy.

Methods

Preparation

Twelve mongrel dogs of either sex (weight, 21–27 kg) were anesthetized with sodium thiamylal and chloralose-urethane (13/130 mg/kg i.m., n=2), or pentobarbital (35 mg/kg i.v., n=9). A high incidence of refractory ventricular fibrillation on reperfusion in chloralose-urethane anesthetized animals led to the switch to pentobarbital anesthesia. Because the physiological responses of the two animals anesthetized with chloralose were similar to the other nine dogs, these data are included. The dogs were intubated and ventilated on a volume respirator (Harvard Apparatus) with 3 l/min supplemental oxygen. A micromanometer-tipped catheter (PC-350, Millar Inc.) was advanced through a femoral artery and positioned in the mid left ventricle for pressure recording. A similar catheter was placed in the ascending aorta via the contralateral femoral artery. An 11-electrode conductance (volume) catheter (Webster Labs) was introduced into the left carotid artery, fluoroscopically guided into the left ventricle, and positioned straight along the long axis with the distal tip at the apex. The catheter was connected to a stimulator/signal processor (Sigma V, Leycom, The Netherlands). The conductance catheter technique has been previously described in detail. A fluid catheter was placed in the right ventricle via a jugular vein for volume signal calibration, and a large balloon occlusion catheter was placed through a femoral vein to the right atrial–inferior vena cava junction. The latter was used to transiently reduce preload and thus generate end-systolic and end-diastolic pressure–volume and pressure–thickness relations. Autonomic reflexes were blocked by intravenous hexamethonium chloride (20 mg/kg) and bilateral cervical vagotomy. Intravenous fluids were provided to maintain systolic pressure in a physiological range and above 90 mm Hg.

The chest was opened via a lateral thoracotomy and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) was dissected free and a silk thread was placed loosely around the LAD distal to its first major branch. Two pairs of miniature flat piezoelectric crystals were placed at two sites: the anterior wall, centered in the angle formed by the LAD and its second diagonal branch, and the mid lateral wall, between the first and second marginal branches of the left circumflex coronary artery (LCx). The small (1 mm) crystal of each pair was advanced tangentially to the endocardial surface and the other (3 mm) crystal was placed epicardially and aligned so that the distance between the crystals was minimized. Wall thickness was measured by a pulse transit sonomicrometer (Triton, San Diego, Calif.). Pacing wires were sutured to the left atrium and the heart returned to its normal resting position with the pericardium loosely approximated.

Data were obtained during atrial pacing using a cycle length that was at least 50 msec shorter than the native sinus rate, which produced 100% atrial pacing capture (average rate, 112±15 beats per minute). Continuous recordings of electrocardiogram, left ventricular pressure, aortic blood pressure, left ventricular volume, and LAD and LCx thicknesses were monitored on an eight-channel chart recorder. Pressure–volume and pressure–thickness loops were monitored on continuous x-y display and simultaneously digitized at 200 Hz with custom software on a 16-bit microcomputer system. Data were stored on removable hard disks for subsequent analysis.

Experimental Protocol

Animals were pretreated with intravenous heparin (2,000–3,000 IU) and lidocaine (20–30 mg). After a 15-minute stabilization period, steady-state data were recorded and pressure–volume and pressure–thickness relations were obtained by transient balloon occlusion of the inferior vena cava, with respiration held at end expiration. The LAD was then occluded and additional lidocaine (1 mg/kg) was administered if ventricular tachycardia or ≥10 premature ventricular contractions per minute occurred. Pressure–volume and thickness relations were obtained after 18±2 minutes of ischemia. In one dog (No. 1), ventricular ectopy during ischemia precluded meaningful interpretation of data obtained during preload reduction. The LAD territory was then reperfused. Ventricular fibrillation occurred early (<5 minutes) after reperfusion in five dogs (No. 4 and 8–11), and was treated with DC countershock (25–50 J). Approximately 1 hour after reperfusion, pressure–volume and pressure–thickness data were again obtained for analysis. There was no discernable difference in late reperfusion data from dogs that required countershock versus those that did not.

Analysis

Data were analyzed off-line using a desktop personal computer and custom analysis software. Digitized pressure, volume, and thickness were smoothed by three-point moving average to reduce high-frequency (>60 Hz) noise.

End-systolic pressure–volume and pressure–thickness relations. Chamber end systole was defined at maximal pressure/(volume–Vo) for each loop, with vol-
ume axis intercept (Vo) determined by an iterative method.\textsuperscript{13} Premature and postextrasystolic beats as well as beats with peak systolic pressure <60 mm Hg were excluded from analysis. The end-systolic pressure–volume relation (ESPV\textsubscript{R}) was the locus of end-systolic points (mean of 17±8 per ESPV\textsubscript{R}) fit to the linear relation \(P_{es}(\text{Tes} - \text{Tes}_0)\), \(P_{es}\), Tes, and Ees are end-systolic pressure, volume, and elastance respectively.

End-systolic pressure–thickness points (Tes) were measured at the time of chamber end systole as defined above. These points were also fit by linear regression to derive the end-systolic pressure–thickness relation (ESPTR)

\[
E_{es}^T = P_{es}(\text{Tes} - \text{T}_o)
\]

with slope \(E_{es}^T\) and intercept \(T_o\). This approach differs from that used by Aversano et al\textsuperscript{14} and others in that regional end systole was defined at the time of chamber end systole rather than at points of maximal \(P_{es}/(T_o - \text{Tes}_0)\). This was required because a major goal of the present study was to relate instantaneous regional and global end-systolic function.

Both \(V_o\) and \(T_o\) can define the horizontal placement of ESPV\textsubscript{R} and ESPTR, respectively; however, they are extrapolated and thus have limited statistical use. Instead, \(V_{es}\) and \(T_{es}\) were compared at a common \(P_{es}\) chosen at the highest value common to the relations being compared (\(\Delta V_{es}\) and \(\Delta T_{es}\), respectively).

End-diastolic pressure–thickness relations. End-diastolic thickness was determined at the rapid pressure upstroke (point at which \(dP/dt\) first exceeded 10% of \(dP/dt_{max}\)). This identifies points at the lower right corner of pressure–volume loops (lower left of pressure–thickness loops). Data from multiple cardiac cycles during inferior vena cava balloon occlusion (IVCBO) were combined to generate the end-diastolic pressure–thickness relation (EDPTR). Shifts in EDPV\textsubscript{R}s (\(\Delta T_{ed}\)) were quantified by comparing \(T_{ed}\) at a pressure common to the relations from each experimental period. (control, ischemia, and reperfusion).

Regional thickening. Percent thickening (%Th\textsubscript{es} = (Tes – T\textsubscript{es})/Tes \cdot 100) with Tes and T\textsubscript{es} determined at chamber end-systolic and end-diastolic time points, was calculated at steady state. In addition, the relation between absolute change in thickness (AT\textsubscript{th}) and preload (EDP) was determined during IVCBO. This is analogous to the Frank-Starling relation for the whole heart.

Volume signal calibration. The conductance catheter volume signal was calibrated by the hypertonic saline technique described previously.\textsuperscript{15,16} Analysis of the volume signal after injection of a small volume (1–2 ml) of concentrated saline enabled calculation of a signal offset caused by conductivity of the ventricular wall and surrounding structures. At least four separate offset estimates were made, and results were averaged. Repeat estimates were obtained throughout the experiment and adjustments made when necessary. We have previously reported that this offset is insignificantly altered by acute regional ischemia.\textsuperscript{12} The gain of the volume signal was assumed to be 1.0.

Statistical Analysis

Data are presented as a mean±SD. Differences between interventions were tested by repeated measures ANOVA. Paired t tests were used to compare individual means by using the Bonferroni correction for multiple comparisons. Analysis of relations between systolic thickening (or thinning) and end-diastolic pressure used a multiple regression model\textsuperscript{17} combining all animal data from the three experimental periods into a single linear model. This model includes dummy variables to account for individual animal variation about the mean and is analogous to an analysis of covariance.

Results

Mean hemodynamic data during the three experimental periods are provided in Table 1. End-diastolic pressure and volume and end-systolic volume all increased during ischemia (by 3.9±1.8 mm Hg, 8.2±3.8 ml, and 7.3±4.1 ml, respectively; \(p<0.01\)) but returned to control after reperfusion. End-systolic pressure and \(dP/dt_{max}\) were unchanged during ischemia.

As anticipated, coronary occlusion produced marked abnormalities of regional thickening in the ischemic zone that persisted after reperfusion. The changes in regional thickening during experimental periods are provided in Table 1. Percent wall thickening in the LAD region fell from +22.6±8.1% to −7.3±6.3% (\(p<0.01\)) during occlusion, displaying systolic bulging. On average, reperfusion eliminated paradoxical wall motion but did not restore significant positive thickening (mean, +4.1±7.4%; 95% confidence interval includes 0% thickening).

Global Pressure–Volume Responses

Despite marked sustained reductions in regional thickening after reperfusion, global chamber function fully recovered. Figure 1 displays an example of pressure–volume loops and relations during the three experimental periods. Coronary occlusion shifted the ESPV rightward without changing slope, and reperfusion returned it back to its original position with a slight slope increase.

Group ESPV responses were indexed by the shift in end-systolic volume measured at a common end-systolic pressure within the data range (\(\Delta V_{es}\)) and by the slope (Ees) (Table 2). After approximately 20 minutes of ischemia, Ees was increased by +8.4±5.2 ml, (\(p<0.0001\)) from a control of 16.1±6.8 ml, whereas Ees remained unchanged. Reperfusion fully reversed the ESPV shift (\(\Delta V_{es} = −10.2±6.0\) ml), bringing the position back to control (\(p=0.54\) versus control). Ees rose slightly with reperfusion compared with ischemia (+2.0±1.7 mm Hg/ml, \(p<0.01\)), but this was not significantly different from baseline. Evidence for recovered global function was further supported by ejection fraction and \(dP/dt_{max}\) normal-
TABLE 1. Mean Hemodynamic Data at Control, After 20 Minutes of Ischemia, and After 1 Hour of Reperfusion

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ischemia</th>
<th>Reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats per minute)</td>
<td>112±15</td>
<td>112±15</td>
<td>112±15</td>
</tr>
<tr>
<td>ES pressure (mm Hg)</td>
<td>103.3±22.1</td>
<td>99.3±24.6</td>
<td>100.3±25.2</td>
</tr>
<tr>
<td>ED pressure (mm Hg)</td>
<td>9.8±2.1</td>
<td>13.7±2.68*</td>
<td>9.7±3.2†</td>
</tr>
<tr>
<td>ES volume (mm)</td>
<td>17.7±7.1</td>
<td>25.0±8.2</td>
<td>15.9±6.4†</td>
</tr>
<tr>
<td>ED volume (ml)</td>
<td>28.6±7.4</td>
<td>36.8±9.7*</td>
<td>26.9±7.4†</td>
</tr>
<tr>
<td>dP/dt max (mm Hg/second)</td>
<td>1,456.9±632</td>
<td>1,331.4±583</td>
<td>1,398.3±674</td>
</tr>
<tr>
<td>Ischemic region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDTh (mm)</td>
<td>9.2±1.7</td>
<td>7.6±2.5*</td>
<td>9.0±1.7†</td>
</tr>
<tr>
<td>ESTh (mm)</td>
<td>11.4±2.6</td>
<td>7.0±2.1*</td>
<td>9.45±2.2†</td>
</tr>
<tr>
<td>%Th</td>
<td>22.6±8.1</td>
<td>−7.3±6.3*</td>
<td>4.1±7.4†</td>
</tr>
<tr>
<td>Remote region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDTh (mm)</td>
<td>12.2±2.4</td>
<td>11.6±2.4</td>
<td>12.7±2.4</td>
</tr>
<tr>
<td>ESTh (mm)</td>
<td>14.5±2.3</td>
<td>14.0±2.0</td>
<td>14.95±2.5</td>
</tr>
<tr>
<td>%Th</td>
<td>19.6±9.0</td>
<td>22.1±16</td>
<td>19.5±11.8</td>
</tr>
</tbody>
</table>

Results are expressed as mean±SD; n=11 dogs in each group.
ESP, end-systolic; ED, end-diastolic; Th, thickness; %Th, (ESTh−EDTh)/EDTh×100.
*p<0.01 vs. control.
†p<0.01 vs. ischemia.

ized to end-diastolic volume (Table 2). Both indexes fell during ischemia and fully recovered after reperfusion. There were no significant differences between control and reperfusion values for cardiac output, stroke work, or the slope of the stroke work–end diastolic volume relation, (REP-Con)=−0.1±0.2 1/min, −106±188 mm Hg·ml, and 3.2±20 mm Hg, respectively, (p=NS). These data indicate dissociation of global from regional function after reperfusion, which was not the result of altered chamber loading.

Pressure–Thickness Relations

To further explore mechanisms of global functional recovery despite sustained abnormalities of regional thickening after reperfusion, pressure–thickness relations were simultaneously determined with the pressure–volume data. Figure 2 displays examples of pressure–thickness relations in the ischemic (LAD) region from two example hearts (upper and middle panels). Control versus ischemia data are shown on the left and ischemia versus reperfusion on the right. After 20 minutes of ischemia, both examples displayed a leftward shift of the data with pansystolic thinning. Reperfusion (right panels) resulted in a partial rightward shift, returning the ESPTR about halfway to its control position. The two examples are typical of the two types of response observed. In the top right panel, reperfusion resulted in little to no restoration of systolic thickening, but rather persistent paradoxic thinning over the measured preload range. This pattern occurred in five of 11 hearts for which the average %Th after reperfusion was −1.8±5.8%. A second pattern (middle right panel) was observed in the remaining six hearts and was characterized by limited return of active systolic thickening at resting preload (9.0±4.4% or 46% reduced from control) and abnormal contraction pattern at reduced preload. Despite the differences in regional response, chamber systolic function (indexed by ESPVR, ejection fraction, etc.) recovered similarly in both subgroups. Pressure–thickness relation changes in the remote region (lower panels) were minimal and consistent among hearts. An example (data from the same heart shown in middle panels) is also displayed in Figure 2.

Even for hearts in which reperfusion partially restored systolic thickening, the contraction pattern...
remained abnormal with wall thinning during isovolumic contraction, and substantial thickening occurring after chamber end systole. Example plots of ischemic-region wall thickness versus time for each experimental period (at both high and low preloads) are displayed in Figure 3. These data are taken from the same hearts shown in Figure 2. Each time plot starts at end diastole, and time lines denote the end of isovolumic contraction (I) and end-systole (ES). In both examples, there was persistent isovolumic phase thinning (more marked at reduced preloads) and thickening after end systole. The top example displayed virtually no thickness changes during ejection (I→ES). Thickening did occur in the lower example, but its effect was primarily to offset preceding isovolumic phase thinning. Thus, even in hearts in which systolic thickening was apparent after reperfusion, substantial thickening occurred after mechanical end systole, contributing little to chamber end-systolic performance.
Group ESPTR and EDPVR data are provided in Figures 4 and 5 and Table 3. The former was obtained using the individual linear regression ESPTR fits (mean $r^2$ of $-0.95 \pm 0.13$) to determine $T_{es}$ at given end-systolic pressures typical of the measured data range. The results are similar to the example of Figure 2. Coronary occlusion shifted the ischemic region ESPTR leftward ($\Delta T_{es} = -4.5 \pm 1.4$ mm, $p<0.001$), and reperfusion moved it rightward ($\Delta T_{es} = +2.3 \pm 0.9$ mm, $p<0.001$), although not entirely to its baseline position ($p<0.001$). Remote-region ESPTRs were not significantly altered during ischemia. Diastolic pressure–thickness data (Figure 5) demonstrated analogous leftward shifts during ischemia as well as rightward return shifts after reperfusion (see Table 3). There were no significant changes in the remote region EDPTR during ischemia or subsequent reperfusion.

**Thickening–Preload Relations**

The combined effect of the ESPTR and EDPTR shifts after reperfusion was to eliminate passive thinning of the ischemic zone over a loading range. This could be quantified by relating thickening ($\Delta T_h$) to end-diastolic pressure (EDP). Figure 6A displays an example of this relation in the LAD territory for the three experimental periods, and Figure 6B shows mean regressions for the group data. $\Delta T_h$ was directly related to EDP at baseline, a manifestation of the Frank-Starling mechanism. With coronary occlusion, the ischemic region exhibited pansystolic bulging ($-\Delta T_h$), and the $\Delta T_h$–EDP relation shifted...
downward. ΔTh remained directly related to EDP, a phenomenon previously reported and thought due to increased passive myocardial stiffness at higher preload inhibiting systolic stretch.18,19

Reperfusion could effect the ΔTh–EDP relation in several ways. Simple refilling of the coronary bed might increase wall thickness at any load due to a change in wall geometry (i.e., pure Tc shift). This would not be expected to alter the interrelation between ESPTR and EDPTR; thus, the ΔTh–EDP would be unchanged. Alternatively, a decrease in ischemic region distensibility and/or partial return of active contractile function could occur. This would reduce the −ΔTh at any EDP, shifting the relation upward and with a lower slope. The experimental results showed that following reperfusion, the ΔTh–EDP relation indeed shifted up close to the ΔTh=0 line. In addition, although the slope of the reperfusion relation remained positive, it was less than that observed during control (0.045±0.009, reperfusion versus 0.077±0.008, control; p<0.05) and much less than that during ischemia (0.116±0.019, p<0.01). This suggests only modest return of active function and/or a significant reduction in regional distensibility. Both upward and downward shifts and slope changes were significant by multiregression analysis (Table 4).

Discussion

This study demonstrates that reperfusion after 20 minutes of severe regional ischemia can restore global chamber function to normal without requiring full recovery of regional systolic thickening. Accompanying global recovery were rightward shifts of the previously ischemic region’s end-systolic and end-diastolic pressure–thickness relations, leading to resolution of paradox systolic thinning. These results are most consistent with a mechanism of reduced distensibility of the reperfused wall at high (systolic) pressures (upper panels, Figure 2), or partial active recovery with reduced distensibility (middle panel, Figure 2).

Regional–Global Dissociation of Function

The principal intriguing observation of this study was that global function could recover following reperfusion despite little to no restoration of regional systolic thickening. A similar disparity was previously reported by Verami et al9 who found that 15 minutes of reflow after coronary occlusion (27% ischemia by mass) normalized ejection fraction and peak diastolic filling rate despite only partial recovery of regional percent wall thickening. The authors hypothesized that the restored global function resulted from 1) alterations in circulating levels of catecholamines or reflex activation, 2) hyperfunction of nonischemic myocardium, and 3) preload or afterload changes influencing ejection fraction.

The present study argues against each of these mechanisms. Animals were studied after reflex blockade (hexamethonium and vagotomy), and global recovery despite persistent regional dysfunction was still observed. Although an additional role for reflexes cannot be excluded, they would not appear necessary for the observed phenomenon. Second, although prior studies have reported remote region
Another possible explanation for the disparity is an overly small ischemic (and thus, stunned) region. However, ejection fraction fell by 24%, and there was a significant shift in the ESPVR during ischemia. The severity of postreperfusion regional dysfunction was similar to that of many prior investigations. Furthermore, prior studies in our laboratory under nearly identical conditions have shown that mid-LAD occlusion typically renders 20% of LV mass ischemic. This would not be considered clinically irrelevant. Although it is likely that reperfusion of a much larger ischemic territory would likely leave global function reduced, the present data still represent important and relevant dysfunction.

One mechanism that is supported by our data is reperfusion-induced stiffening of the previously ischemic territory. Experimental distensible aneurysms are known to limit chamber pump performance more than stiff patches. The greater the extent of systolic bulging of an artificial aneurysm, the greater the decrement of chamber systolic function. Akashi et al. demonstrated that increasing preload volume during ischemia reduces systolic bulging. Lew et al. reported that remote regional shortening (which can parallel ischemic zone bulging) is reduced by increasing preload, improving chamber function. The concept is that by operating on a steeper portion of the regional wall stress–strain curve, increased preload limits regional paradoxic wall motion and improves global performance.

Reperfusion in the present study had analogous effects: There was some persistent isovolumic phase region ESPT and EDPT change, relations with less load dependence than %Th. Last, whereas ischemia and reperfusion altered end-diastolic volume by as much as 31%, the pressure–volume analysis used in the present study provided evidence of altered systolic function independent of loading.

The present data are consistent with previous studies which have shown that global function is an important determinant of regional function. In the present study, the effect of reperfusion was to increase wall stress and strain in the remote region, whereas in the ischemic region, wall stress and strain were decreased.

The present data are consistent with previous studies which have shown that global function is an important determinant of regional function. In the present study, the effect of reperfusion was to increase wall stress and strain in the remote region, whereas in the ischemic region, wall stress and strain were decreased.
thinning, but thinning during ejection ceased and/or was replaced by modest thickening. End-systolic thickness was greater at any given systolic pressure, and the dependence of thickening on preload (ΔTh–EDP relation, Figure 6) shifted upward and became shallower compared with that during ischemia. Both increased regional myocardial stiffness at systolic loads and/or partial active recovery sufficient to counteract systolic thinning can explain these responses. In some hearts, the former mechanism appears to have dominated, whereas in slightly more than half the hearts, a combination of effects likely occurred. Regional myocardial stiffening could result from interstitial edema, cell swelling, hemorrhage, contraction band necrosis,24,25 and/or increases in intracellular calcium.26

EDPTRs did not display evidence of increased stiffness at low distending pressures. However, it is the properties at end systole that are most directly relevant toward determining the chamber end-systolic pressure–volume relation. Nonlinearity of myocardial stress–strain relations can result in little discernable change in stiffness at low (i.e., diastolic) distending pressures despite considerable differences at higher (systolic) pressures. This could well explain this disparity.

Partial return of active function also played a role, particularly in a subset of hearts. However, even in these cases, systolic regional thickening after reperfusion was often offset by preceding isovolumetric thinning. Moreover, much of the thickening occurred after mechanical systole and, therefore, could not contribute to the observed restoration of chamber function. Thus, even when partial activation was restored, thickening patterns were abnormal and demonstrated some properties more characteristic of passive material.

Global Chamber Function

Few studies of regional ischemia and reperfusion have reported concomitant effects on chamber systolic function using load-independent measures. Systolic pressure or ventricular dP/dt max are usually unchanged or only minimally decreased,6,7,27 as was the case in the present study. However, pressure–volume relations revealed substantial alterations during both experimental periods. The rightward parallel shift observed in the ESPVR during ischemia is consistent with several prior studies.11,28,29 We previously reported both rightward shifts and ESPVR slope (Ees) decrease during 3 minutes of regional ischemia in the canine heart.12 A high baseline Ees was the major determinant of Ees change during

<table>
<thead>
<tr>
<th>TABLE 3. Change in Regional End-systolic and End-diastolic Thicknesses Determined at a Common Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (mm)</td>
</tr>
<tr>
<td>T rewritten</td>
</tr>
<tr>
<td>T rewritten</td>
</tr>
</tbody>
</table>

Mean results for control data, change from control during ischemia (ISC-CON), and change from ischemia after reperfusion (REP-ISC) are shown. T rewritten and T rewritten end-systolic and end-diastolic thicknesses determined at a pressure common to all three period relations, respectively. Changes in thickness are with respect to the preceding experimental period.

*p<0.05.

Figure 6. Plots show relation between the extent of wall thinning or thickening (ΔTh) and chamber end-diastolic pressure for the left anterior descending coronary artery (ischemic) region. Panel A shows an individual example and panel B shows mean regression results for the combined data. Control data displayed a positive slope (+0.077±0.008) consistent with a Frank-Starling mechanism (see Table 4). Ischemia shifted this relation to negative thickening, but still with a positive slope. Reperfusion led to a partial return (upward shift) with reduced slope (p<0.01 by regression analysis). CON, control; REP, reperfusion; ISC, ischemia. Values that the plots in panel B are based upon are shown in Table 4.
ischemia, and in the ranges obtained in the present study, there was minimal slope change.

Global Model of Ischemia–Reperfusion

A simple model that has been shown to describe the ESPVR response to acute ischemia in isolated 11 and in vivo 12 hearts can also predict effects of ischemic region stiffening on left ventricular function. The model assumes that the ischemic region behaves passively as defined by a proportionately scaled resting chamber diastolic pressure–volume relation, and the remote region maintains the control ESPVR behavior. The two are then coupled in parallel, yielding a net chamber relation. This model yields a 10–12 ml rightward ESPVR shift with little slope change for 20% ischemia (Figure 7) similar to that observed in the present study. By altering the passive compliance properties of the ischemic zone (increasing the stiffness coefficient), the model also predicts a near full recovery of the ESPVR (right panel) without necessarily inducing much change in chamber diastolic compliance. This admittedly is a marked simplification, and there is no straightforward way to relate model parameters to measured pressure–thickness data. However, the model serves to illustrate that regional stiffening alone can substantially improve global pressure–volume performance.

Experimental Limitations

Several limitations should be considered. Our analysis of regional wall property changes were necessarily indirect, as there is no current way to directly determine in vivo regional stiffness. While several mathematical models have been proposed to estimate stress, they are largely based on simplified axisymmetric geometries using midequatorial calculations. 30 Such shapes do not apply to regionally ischemic hearts, particularly at end systole when wall

<table>
<thead>
<tr>
<th>Slope</th>
<th>Offset</th>
<th>p</th>
<th>n</th>
<th>Mult r SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.077±0.008</td>
<td>&lt;0.001</td>
<td>+1.43±0.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemia</td>
<td>0.116±0.019*</td>
<td>&lt;0.001</td>
<td>−2.05±0.21*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>0.045±0.009**</td>
<td>&lt;0.001</td>
<td>−0.086±0.07**</td>
<td>0.254</td>
</tr>
</tbody>
</table>

*The values correspond to the plots in Figure 6B.
Statistical linear model was

$$\Delta T_h = a_1 + a_2 \cdot EDP + \sum_{i=1}^{10} D_i$$

where $D_i$ were individual dog dummy variables included to account for interanimal variance. Mean slope ($a_2$) and offset ($a_1$) and respective $p$ values, number of points ($n$), total regression multiple $r$ and standard error of the mean (SEM) are provided for each experimental period.

$p<0.05$ vs. control.

$\cdot p<0.05$ vs. ischemia.

---

**FIGURE 7.** Plots show computer simulation results of the effect of acute regional ischemia (20% left ventricular mass) on the end-systolic and end-diastolic pressure–volume relations (ESPVR) as predicted by a two-compartment model. Left panel shows predicted results when ischemic regional passive properties are modeled by control diastolic pressure–volume relation. This results in a rightward shift of the end-systolic pressure–volume relation, consistent with that observed experimentally. Right panel displays predicted changes when passive properties of ischemic region are altered by increasing its stiffness coefficient. Net result is near normalization of the ESPVR with little effect on the diastolic pressure–volume relation.
deformation in the normal and ischemic zones can differ widely. Rather than resort to such models, we preferred to leave the data in their directly measured form. However, a possibility remained that abnormal regional end-systolic stresses contributed to reduced thickening after reperfusion.

The full extent of reperfused but still dysfunctional myocardium (percent of LV mass) could not be determined. It is likely that there were gradations of dysfunction from the center of the postischemic area to the border zone. Whether or not the three-dimensional extent of postreperfusion dysfunction is much smaller than that during ischemia is unknown. Potentially, studies using new three-dimensional imaging techniques such as gated nuclear magnetic resonance imaging could answer this question.

The conductance catheter technique has undergone several evaluations, and some recent studies have raised concerns about absolute volume calibration.\(^{31,32}\) Boltwood et al\(^ {31}\) reported that the parallel conductance varies with LV end-systolic volume itself, thus potentially limiting the role of the conductance catheter in situations in which absolute ESPVRs are needed. Lankford,\(^ {16}\) however, showed that the volume offset varies little during a cardiac cycle despite substantial change in left ventricular (and right ventricular) volumes. Regardless, these issues have little impact on the present findings. Prior studies have clearly confirmed the validity of using the conductance catheter to assess relative changes in pressure–volume relations "over a wide range of cardiac volumes"\(^ {32}\) and "over a range of hemodynamic states."\(^ {31}\) For the present analysis, we avoided comparisons based on data extrapolation by comparing relations over similar loading ranges and determined parallel conductance, making appropriate adjustments if required during the course of each study.

Summary

Reperfusion after a period of intense ischemia can result in essentially normal chamber systolic performance despite severe persistent regional dysfunction. This disparity is not eliminated by reflex blockade, neither is it due to remote regional hyperfunction or loading alterations. Rather, increased systolic regional stiffening, likely the result of limited active recovery and intrinsic systolic myocardial stiffness, can best explain the return of chamber performance. Thus, in studies of the efficacy of myocardial reperfusion, caution must be exerted when using recovery of global function as an index of regional myocardial salvage.

References


2. The TIMI Study Group: Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: Results of the thrombolysis in myocardial infarction (TIMI) phase II trial. Circulation 1989;320:618–627


10. Braunwald E: Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival: Should the paradigm be expanded? Circulation 1989;79:441–444


26. Peng CF, Davis JL, Murphy ML, Straub KD: Effects of reperfusion on myocardial wall thickness, oxidative phosphorylation, and Ca++ metabolism following total and partial myocardial ischemia. Am Heart J 1986;112:1238–1244

KEY WORDS • regional ischemia • stunned myocardium • ventricular function • pressure–volume relation
Mechanism of global functional recovery despite sustained postischemic regional stunning.
W E Lawrence, W L Maughan and D A Kass

Circulation. 1992;85:816-827
doi: 10.1161/01.CIR.85.2.816

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/85/2/816

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/