Relations Between Myocardial Blood Flow and Postextrasystolic Potentiation in Epicardial and Endocardial Left Ventricular Regions Early After Coronary Occlusion in Dogs

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with the technical assistance of Monique Laplace

SUMMARY Postextrasystolic potentiation was studied during control and 5 minutes after coronary occlusion in epicardial and endocardial regions of 12 open-chest dogs. Segmental behavior evaluated with ultrasonic crystals was correlated with regional myocardial blood flow (MBF) measured with radioactive microspheres. A similar correlation was found between the percentage of systolic shortening in postextrasystolic beats and MBF in epicardial ($r = 0.64$) and endocardial ($r = 0.97$) regions, although the scatter was much larger in the epicardium. The correlation was similar when segmental function was expressed as the area of the pressure-segment length loop. Three types of segments were described: completely ischemic segments (transmural MBF $< 5\%$ of control), in which end-systolic length was larger than end-diastolic length after postextrasystolic potentiation; severely ischemic segments (5$\%$ $\leq$ transmural MBF $< 25\%$ of control), in which the ischemic bulge during control beats was replaced by active shortening after premature ventricular complexes; and marginal segments (25$\%$ $\leq$ transmural MBF $< 100\%$ of control), in which depressed shortening was enhanced close to control after a premature ventricular complex. These data reconcile conflicting studies, which did not consider similar degrees of ischemia and show a rapid loss of postextrasystolic potentiation in completely ischemic segments.

POSTEXTRASYSTOLIC enhancement of shortening has been used extensively in patients with chronic coronary artery disease to unmask contractile behavior of myocardial regions that could be restored by reperfusion.\(^1\)\(^-\)\(^4\) During acute experimental ischemia with reduced coronary perfusion pressure, Dyke et al.\(^5\) showed that postextrasystolic potentiation (PESP) abolished dyskinesia. Boden et al.\(^6\) found similar results early after coronary occlusion and recently showed that augmentation of the control ischemic zone function persisted for as long as 4 hours.\(^7\) In contrast, Schelbert et al.\(^8\) and Crozatier et al.\(^9\) demonstrated a loss of contractile behavior of the ischemic zone after PESP within minutes after coronary occlusion with a reduced shortening of the marginal zone; using PESP, Boden et al. showed a return of function in these zones to control levels.

Regional myocardial blood flow (MBF) is more depressed in the endocardium than in the epicardium during ischemia.\(^10\)\(^-\)\(^11\) A possible explanation of these different findings during acute ischemia is that different myocardial layers were analyzed: Boden et al.\(^6\)\(^-\)\(^7\) studied the epicardium, whereas we studied the endocardium.\(^9\) To test this hypothesis, we examined the relationships between regional MBF and postextrasystolic contraction in the epicardium and in the endocardium before and 5 minutes after coronary occlusion in dogs. We studied these relations 5 minutes after the occlusion because our study\(^9\) and the studies of Boden et al.\(^6\)\(^-\)\(^7\) showed that postextrasystolic mechanical behavior was not modified by more prolonged periods of ischemia, and that after 5 minutes of occlusion the myocardium is viable, no ultrastructural alterations have occurred,\(^12\) and mechanical function returns after reperfusion, although functional abnormalities may persist.\(^13\)

Methods

Twelve mongrel dogs that weighed 8–25 kg were anesthetized with i.v. thiopental, 25 mg/kg, and small additional doses were given if necessary. We allowed a stabilization period of at least 5 minutes before performing interventions or recordings. Ventilation was maintained by a Harvard respirator delivering room air through an endotracheal tube. Tidal volume was adjusted according to the body weight and the respiration rate was 10 breaths/min.\(^14\) Full lung expansion was maintained during the study and the stability of hemodynamic conditions was observed throughout each experiment. A thoracotomy was performed through the fifth left intercostal space. A polyethylene catheter (2.2-mm internal diameter) filled with heparinized saline solution was introduced into the left ventricular cavity through the cardiac apex and connected to a Statham P23Db transducer to record the ventricular pressure. A Tygon catheter (2.4-mm internal diameter) filled with heparinized saline solution was placed into the left atrium through the left atrial appendage and a similar catheter was placed into the descending aorta by retrograde catheterization of the left femoral...
artery. The left descending coronary artery was dissected free below its origin above or below the first diagonal branch. Pacing electrodes were placed on the left ventricle in a region distant from the ischemic zone.

Regional Mechanical Function Measurements

Four pairs of piezoelectric crystals 2 mm in diameter were implanted in the ventricular regions that appeared to be vascularized by the left descending coronary artery: two pairs of crystals were placed in the region that appeared to be the center of this zone and two others were placed in the immediate vicinity of this zone. These zones were determined by observing venous epicardial circulation, and the segments were categorized later as indicated below. In each zone, one pair of crystals was placed in the subendocardial region, parallel to the minor equator and one pair was placed in the epicardium in a more oblique direction at an angle of about 50° to the endocardial pair. Epicardial and endocardial segments were angled parallel to epicardial and endocardial fibers according to the data of Streeter et al. The crystals were about 10 mm apart. Segmental lengths were obtained by a sonomicrometer (Schussler and Associates). The crystals were constructed as previously described.

Experimental Protocol

The external ECG, left ventricular pressure and segmental length measurements were monitored on a eight-channel graphic recorder and stored on magnetic tape (Hewlett Packard 3968 A tape recorder). After recording the control state, premature ventricular complexes (PVCs) were produced by a stimulator (CEA, DAM) connected to the pacing electrodes that delivered a 10-msec, 1-V pulse. The R wave of the ECG was used as the triggering signal and the shortest coupling interval that produced a PVC was determined in each dog. To have the slowest possible heart rate, we chose not to pace the atrium. The time separating the stimulus (close to the peak of the preceding T wave) from the preceding R wave represented 53.3 ± 1.1% of the RR interval. At least four PVCs were produced during the control state in different phases of the respiratory cycle. Control MBF was then measured in each dog using 57Co, 46Sc or 113Sn microspheres (NEN Chemicals GmbH). Before injection, the microspheres were suspended in 0.01% Tween 80 in dextran solution. Microspheres were sonicated with an ultrasonic probe during 15 minutes and mixed with a Vortex agitator. One million to 2 million microspheres were injected through the left atrial catheter. A reference sample of arterial blood was withdrawn, beginning 10 seconds before injection of microspheres and continuing for 90 seconds after the injection was completed.

The left anterior descending coronary artery was then occluded. The variables were continuously recorded and PVCs were produced as during control. The time separating the stimulus from the preceding R wave corresponded to 54.9 ± 1.6% of the RR interval (not significantly different from control). Microspheres were then injected as during control for measurement of myocardial blood flow 5 minutes after the onset of ischemia. After the dogs were killed, the correct position of the crystals within the left ventricular wall was verified, and signals obtained from incorrectly positioned crystals were rejected from the analysis. Endocardial crystals had to be within the inner third and epicardial crystals in the outer third of the wall. Eleven epicardial and 11 endocardial segments were inadequately positioned (usually obliquely within the paretial wall or in the midwall region). A block of tissue (about 1 cm3) was taken from each zone in which the crystals were implanted. The block was cut immediately outside of the crystals, which were then removed. A block was also taken from the posterior wall of the left ventricle for measurement of blood flow in the control zones. The blocks were divided into epicardial and endocardial layers, put in a counting vial, and weighed. Blood samples were weighed in a similar way.

Measured Variables: Calculations

Hemodynamic and segmental length variables were analyzed after playback of the magnetic tape on an eight-channel graphic recorder (Hewlett Packard 7758 A recorder) at a paper speed of 100 mm/sec. Hemodynamic variables included heart rate, end-diastolic pressure, systolic pressure and peak dP/dt; dP/dt was obtained by an R/C differentiator with an upper cutoff of 200 Hz. Segmental measurements included end-diastolic length (EDL) and end-systolic length (ESL) at the nadir of systolic shortening, usually 0.02 second before peak negative dP/dt. This timing was used during complete ischemia when the holosystolic bulge was present. The percent systolic shortening was calculated as 100 × (EDL − ESL)/EDL. Percent systolic shortening was expressed as an absolute value or was normalized to 100 during postextrasystolic shortening during control for the correlation of postextrasystolic shortening with regional MBF. Some beat-to-beat variations of shortening were observed during the control period for the same coupling interval of the PVC, depending upon the phase of the respiratory cycle when the PVC was produced. Since only one PVC was produced 5 minutes after the onset of ischemia, we analyzed during control the response to PVCs produced during the same phase of the respiratory cycle as that of the PVC produced during ischemia. Pressure-length loops were obtained on a storage oscilloscope and photographs were taken with a Polaroid camera. The area of the loops was measured by planimetry. Results are given as the area of the loop during ischemia divided by the loop during control for both control sinus beats and postextrasystolic beats. The areas of the pressure–segment length loops during sinus beats and postextrasystolic beats during the control period were taken as the reference value for sinus beats and postextrasystolic beats during ischemia, respectively. Regional MBF was measured after the myocardial and blood samples were counted in a gamma well counter (CG 4000 Intertechniche) for 10 minutes. The raw
There was postextrasystolic and 13

samples were corrected for background activity and energy crossover and regional MBF was obtained⁶⁶ as:

\[
\left( \frac{\text{counts/g tissue}}{\text{counts in reference blood}} \right) \times \text{reference flow rate}
\]

Results were expressed as ml/min/100 g of tissue.

Segments were categorized into three groups according to MBF measurements. Completely ischemic zones were defined by an ischemic transmural blood flow < 5% of control blood flow. Severely ischemic zones were zones in which ischemic transmural blood flow was ≥ 5% but < 25% of control and minimally ischemic zones had an ischemic transmural blood flow ≥ 25% but < 100% of control blood flow. Not all segments were present in each dog. Thirteen epicardial and 13 endocardial ischemic or marginal segments were considered for the study, and four segments were analyzed in each group (five in the endocardial completely ischemic zone and five in the epicardial marginal zone).

Statistical Analysis

All results are given as mean ± SEM. Since only one intervention (5 minutes of ischemia) was compared with the control state, analysis of variance was not performed. Hemodynamic data were compared during ischemia and during control by paired t test. The postextrasystolic shortening of segments was compared with shortening during control sinus beats by paired t test during control and during ischemia and the normalized areas of ischemic sinus beats and ischemic postextrasystolic beats were compared by paired t test. The regression between log MBF (expressed in percent of control MBF of this zone) and postextrasystolic function was calculated using the least-square method.

Results

Hemodynamic data in all dogs are given in table 1. There was no significant change in heart rate immediately after ischemia. Coronary occlusion produced a statistically significant increase of end-diastolic pressure and a significant decrease of systolic pressure and peak dP/dt. MBF (table 2) was not significantly modified after ischemia in control zones, in which the endo/epi ratio was 1.14 ± 0.07 during control and 1.11 ± 0.06 5 minutes after the onset of ischemia. MBF was more reduced in the endocardial than in the epicardial minimally ischemic zones, in which transmural blood flow was reduced to 52.0 ± 10.1% of control. The endo/epi ratio decreased from 1.06 ± 0.08 during control to 0.90 ± 0.06 during ischemia (p < 0.05). In the center of the ischemic zone, two types of segments were identified by the extent of transmural MBF reduction: (1) In the severely ischemic zones, transmural MBF was 13.3 ± 4.0% of control; MBF was more reduced in the endocardium than in the epicardium (NS). The endo/epi ratio was 0.97 ± 0.08 during control and decreased to 0.83 ± 0.14 during ischemia (NS). (2) In completely ischemic zones, MBF was close to zero in both the epicardial and the endocardial layers (table 2). The mean end-diastolic length of segments was 7.7 ± 0.7 mm in the epicardial layer and 8.5 ± 0.6 mm in the endocardial layer. It increased to 8.3 ± 0.7 mm and 9.8 ± 0.8 mm, respectively, during ischemia (both p < 0.005). The percent systolic shortening during control before coronary occlusion and during ischemia is given in figure 1. PESP significantly increased percent systolic shortening during control in the endocardial layers of completely ischemic zones, severely ischemic segments and minimally ischemic segments. This increase was not statistically significant during control in any of these three zones in the epicardial layers, for there was a large scatter in the response; when all segments were considered together, percent systolic shortening increased from 9.5 ± 1.9% in control beats to 14.3 ± 2.5% with PESP (p < 0.001). During ischemia, the responses to PESP were similar in the epicardium and in the endocardium. The holosystolic bulge of completely ischemic zones was slightly reduced (NS), whereas in severely ischemic zones the holosystolic bulge was replaced by a net positive shortening in postextrasystolic beats. In minimally ischemic zones, the reduced systolic shortening significantly increased to a level close to control after the PVCs.

The relationship between MBF and postextrasystolic shortening during ischemia was similar in the epicardium and in the endocardium (fig. 2), although the scatter was much larger in the epicardium.

Figure 3 shows the pressure-length loops in a com-

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<tr>
<th>Table 1. Hemodynamic Data</th>
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<td></td>
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<tr>
<td>Control</td>
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<tr>
<td>136.4 ± 8.8</td>
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<td>5-min ischemia</td>
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P NS < 0.01 < 0.01 < 0.001

Abbreviations: HR = heart rate; EDP = end-diastolic pressure; SP = systolic pressure.

<table>
<thead>
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<th>Table 2. Myocardial Blood Flow (ml/min/100 g)</th>
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<td>± 16.6</td>
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<td>13.4</td>
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P NS < 0.005 < 0.005 < 0.001 < 0.001 < 0.005 < 0.005

Abbreviations: CIZ = completely ischemic zone; SIZ = severely ischemic zone; MZ = marginal zone.
FIGURE 1. Segmental shortening expressed as percent systolic shortening (%ΔL) during control (C) and ischemia (I) for control beats (cb) and postextrasystolic beats (pep). (top) Completely ischemic segments. (middle) Severely ischemic segments. (bottom) Marginal segments. MBF = transmural myocardial blood flow. Postextrasystolic shortening is significantly different from shortening during control beats: * p < 0.05; ** p < 0.01.

Completely ischemic epicardial segment and in a severely ischemic endocardial segment. In completely ischemic zones, the pressure-length loop area was zero in the normal sinus beat after ischemia and it was minimally increased after a PVC. In severely ischemic zones, the pressure-length loop area was markedly reduced after ischemia in the normal sinus beats. This loop was positive, although systolic shortening was negative. Segmental length increased during the isovolumic pressure rise. There was segmental shortening both during the ejection phase and during the isovolumic relaxation phase (producing the positive loop), but end-systolic length was still longer than end-diastolic length (producing a net negative systolic shortening). The ischemic pressure-length loop increased close to the control level after a PVC. The mean values of segmental function measured by the area of the pressure-length loops are given in figure 3. The results were similar to that described when they were expressed as percent systolic shortening in severely ischemic and minimally ischemic zones, and the correlation coefficients between log MBF and function were also similar. The largest PESP was observed in the severely ischemic epicardial and endocardial zones, and the area of the loops in the marginal zones was increased. However, a difference with the results expressed as percent systolic shortening was noted in completely ischemic zones. In control beats, the area of the loops was close to zero in both epicardial and endocardial layers and it was positive in both layers after the PVCs (fig. 4) with ejection phase and relaxation phase shortening, although the net systolic shortening was negative (fig. 1).

Discussion

Endocardial shortening was shown to be linearly,27 exponentially28 or sigmoidally22 related to regional coronary blood flow in studies with graded flow reduction. The relationship we found between postextrasystolic shortening and regional MBF was also exponential (fig. 2), but because of PESP, performance was greater compared with these studies. When normal sinus beats were considered (fig. 1), segments were akinetic when blood flow was reduced to 13% of control and dyskinetic when blood flow was close to zero, as in the study of Vatner.29 In preliminary studies, Gallagher et al.20 and Genain et al.21 suggested that epicardial shortening is primarily determined by endo-

Figure 2. Correlation between percent systolic shortening and myocardial blood flow (MBF) in epicardial (top) and endocardial (bottom) regions. Myocardial blood flow and percent systolic shortening measured during control (C) were both normalized to 100 in each segment (net negative shortening was plotted as equal to zero). The equation for epicardium is y = 25.1 Log x - 10.8 and for endocardium y = 20.4 Log x + 1.5. The scatter is much larger in the epicardium, but the relations appear similar.
cardial shortening. Weintraub et al. demonstrated a correlation between shortening in the epicardium and regional blood flow, although the scatter was considerable. Weintraub et al. found a parallel decrease of epicardial and endocardial shortening during progressive coronary blood flow reduction. Our results show a similar correlation between postextrasystolic shortening and MBF reduction in epicardial and endocardial layers during complete coronary occlusion, although the scatter was much larger in the epicardial zones, as in the study of Weintraub et al. during progressive coronary blood flow reductions. However, the statistically significant correlation between MBF and PESP does not rule out a major role for mechanical interaction between epicardial and endocardial fibers.

The similar correlation found between MBF and PESP shortening in the epicardium and in the endocardium does not signify that epicardial and endocardial mechanical behavior are identical. However, this similarity indicates that differences in the evaluation of PESP during ischemia obtained in different studies cannot be attributed to major differences in behavior between epicardial and endocardial layers.

The hypothesis that differences between the studies

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**Figure 3.** Examples of pressure-length loops in a completely ischemic segment (CIZ) and in a severely ischemic segment (SIZ). CIZ is an epicardial segment and SIZ is an endocardial segment. Oscilloscopic photographs are on the right and their schematic representation is on the left. The arrowheads indicate the rotation of the tracings. In both CIZ and SIZ, the area of the pressure-length loop is increased by about 70% after a premature ventricular complex (pep beat) during control before coronary occlusion. Five minutes after the onset of ischemia, the pressure-length loop area is zero during normal sinus beats (cb) in CIZ and it is minimally increased after a premature ventricular complex in the pep beat. In contrast, after ischemia, the small cb area (29.6% of cb area during control) of SIZ is increased after a premature ventricular complex close to cb area measured during control. This ischemic pep beat area represents 51% of the pep beat area measured during control.

**Figure 4.** Pressure–segment length loop area vs myocardial blood flow in epicardial and endocardial layers. Segments were divided into three groups as in figure 1. Control beats (cb) areas were normalized to 100 during control (c) for the study of control beat loop area during ischemia and postextrasystolic beats (pep) areas were normalized to 100 during control for the study of postextrasystolic beats during ischemia. Myocardial blood flow was normalized to 100 during control in each zone as in figure 2.* Normalized loop area obtained during postextrasystolic beats is significantly larger (p < 0.05) than normalized loop area obtained during control beats. When the areas were considered individually, the correlation coefficients between myocardial blood flow and the normalized area of the pressure–segment length loop were r = 0.61 in epicardium and r = 0.82 in endocardium in control beats; the correlation coefficients in postextrasystolic beats were r = 0.60 in epicardium and r = 0.86 in endocardium.
were due to a smaller reduction of MBF in the epicardium is not confirmed by our results. MBF was indeed more reduced in the endocardium than in the epicardium, but the difference was small and not statistically significant in all zones (table 2). In studies with graded coronary blood flow reduction, the endo/epi ratio decreases below 0.50 when MBF is severely reduced.20,21 In contrast, with complete coronary occlusion, the endo/epi ratio usually decreases by a lesser amount, particularly when flow is measured early after coronary occlusion. Becker et al.,10 found a ratio of 0.76 ± 0.30 in the center of the ischemic zone, and Klener et al.22 found a myocardial blood flow of 0.12 ± 0.03 ml/min/g in the endocardium and 0.18 ± 0.05 ml/min/g in the epicardium in the center of the ischemic area 5 minutes after coronary occlusion. These results are similar to those we observed in severely ischemic zones.

Although the small difference between epicardial and endocardial MBF reduction may explain in part the difference in the evaluation of PESP during ischemia, conflicting results between studies appear to be mainly due to different MBF reductions analyzed in the studies. The mean transmural blood flow reduction was 78% in the ischemic zone in the study of Boden et al.7 and 86.6% in the severely ischemic segments of our study (fig. 1). The behavior of these segments (figs. 1 and 4) is similar to that described by Boden et al.: the holosystolic bulge of ischemic segments is replaced by a positive shortening, but not to control levels. When MBF was reduced close to zero in the completely ischemic zones, the holosystolic bulge during control beats was only slightly reduced (fig. 1), as in ischemic segments of our previous study.9

Although no net positive shortening was observed in completely ischemic segments, the area of the pressure-length loops was positive during ischemic PESP, representing 20% of the postextrasystolic area during control (fig. 4). This finding could suggest that active segmental work during the ejection phase and during isovolumic relaxation was restored by PESP in these segments with delayed relaxation. However, this response resembles that observed in ischemic segments after the injection of nitroglycerin13 and has also been noted in patients with coronary heart disease.3,4 Left ventricular unloading has been advocated to explain a positive pressure-length loop associated with a net negative shortening after nitroglycerin injection in ischemia.15 Although PESP is mainly due to an increased inotropic state, a decrease of ischemic wall stress cannot be excluded after a PVC. The pressure-length loop area is not the true segmental work that would be obtained by a stress-length loop. Intraventricular pressure varies with stress only during the early phase of systole.24 During the late phase of ejection, stress decreases faster than pressure. With PESP, the stronger contraction of control zones during the ejection phase probably produces a faster decrease of stress, and the positive area of the pressure-length loop may merely represent a passive ejection shortening of these segments caused by decreased end-systolic stress and a concomitant decrease of end-systolic length, which continues to decrease during relaxation when stress and pressure decrease. Definitive answers to the question of whether this ejection shortening is active can only be obtained by constructing the stress-length loops. However, our results do show that after closely coupled PVCs, no net systolic shortening occurs in completely ischemic regions as early as 5 minutes after coronary occlusion.9

Shortening of minimally ischemic zones was increased by PESP, but not to control levels (fig. 1), in both epicardial and endocardial layers, as in our previous study,9 Boden et al.7 showed a return to control levels of marginal zone shortening with PESP. However, when function was expressed in pressure-length loop areas, function was close to 100% of control in the epicardial zone after a PVC (fig. 4), but the large scatter observed in the ischemic function–blood flow relationship in the epicardium suggests caution in interpreting these relatively small differences. Furthermore, the nature of the „marginal” zone is unclear. Does it represent a partially perfused region or is it a heterogeneous composite of normal and ischemic cells? The existence of a marginal zone has been shown by a number of studies,25,26 and the relationship we found between MBF and shortening after complete coronary occlusion that resembles shortening during graded coronary blood flow reductions22,27,28 could suggest that ischemic myocardium is a partially perfused tissue. However, the existence of a real border zone is controversial.29,30 If it exists, it is probably smaller than the distance separating the crystals of our marginal segments.

The principal result of the present study is the characterization of two ischemic zones. In one zone, blood flow is reduced to about 15% of control and active shortening after a PVC replaces the holosystolic bulge of normal beats; the other is a completely ischemic zone in which blood flow is close to zero and no net positive shortening can be restored after a PVC as early as 5 minutes after coronary occlusion. These data allow us to reconcile conflicting studies6,7,9 that considered different degrees of ischemia. Our results also have clinical implications and confirm our previous conclusion that postextrasystolic potentiation cannot detect a net positive systolic shortening in transmurally ischemic myocardium that is still reversibly injured.

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