Influence of Left Ventricular Dimensions on Endocardial and Epicardial QRS Amplitude and ST-segment Elevations During Acute Myocardial Ischemia

JON LEKVEN, M.D., KANU CHATTERJEE, M.B., JOHN V. TYBERG, PH.D., AND WILLIAM W. PARMLEY, M.D.

SUMMARY The influence of acute myocardial ischemia and changes in ventricular dimensions on endocardial and epicardial electrograms were evaluated in 17 anesthetized open-chest dogs before and after left ventricular volume expansion and before and after coronary artery ligation. In eight dogs, regional myocardial blood flow was determined by the labeled microsphere technique. Endocardial QRS (endo-QRS) amplitude in ischemic and nonischemic zones, and epicardial QRS (epi-QRS) in nonischemic zones maintained a negative linear relation with left ventricular end-diastolic dimension before and after coronary artery ligation, although acute ischemia decreased endo-QRS independently. Epi-QRS amplitude in the ischemic zone decreased after coronary artery ligation but changed inconsistently during volume expansion. Ischemia-induced epicardial ST-segment elevation decreased during volume expansion and was associated with improved epicardial blood flow. Changes in epi-QRS in ischemic zones, however, were not related to epicardial blood flow during volume expansion. These findings indicate the potential problems of using changes in QRS amplitude for determining the extent of myocardial ischemic injury.

WE RECENTLY REPORTED that QRS potentials recorded from the myocardium bear a negative and apparently linear relationship with ventricular volume and dimensions.1 This relationship has been shown for both left and right ventricular potentials, whether recorded from endocardium or epicardium.2 These findings imply that any acute change in ventricular dimensions might be associated with changes in QRS amplitude recorded from the myocardium. It has also been reported that a reduction in right ventricular endocardial potentials might occur in patients with acute myocardial infarction.3, 4 Experimental studies in dogs have verified reduction in right and left ventricular endocardial potentials after coronary artery ligation.5 However, acute myocardial ischemia in experimental models invariably causes left ventricular dilatation and increased diastolic volume.6, 7 Therefore, it is not clear whether alterations in QRS amplitudes result from myocardial ischemia or dimensional changes or both.

Newman et al.8 and Hillis et al.9 suggested that the degree of myocardial ischemia and injury can be quantitated from changes in epicardial QRS (epi-QRS) voltage and used in evaluating the effects of pharmacologic intervention on the extent of myocardial ischemia injury. Because acute changes in ventricular volume alone can cause a significant change in QRS amplitude, however, it is pertinent to evaluate not only the effects of myocardial ischemia, but also the associated changes in ventricular volume during ischemia on the QRS potentials. Therefore, we investigated the influence of acute changes in ventricular dimension on endocardial QRS (endo-QRS) and epi-QRS amplitudes after experimental myocardial infarction, as well as changes in ST-segment elevation in ischemic areas before and after volume expansion.

Methods Experimental Preparation

Seventeen mongrel dogs of either sex that weighed 15–28 kg were anesthetized with sodium thiopental (25 mg/kg i.v.). The dogs were then given morphine sulphate (45 mg i.v.) followed by a maintenance dose of 15 mg/hr. A continuous infusion of succinyl choline chloride (20 mg/kg/hr) was given for muscle relaxation. The dogs were intubated and ventilated with a positive-pressure respirator (Harvard Apparatus, Millis, Massachusetts). A stable respiratory state was maintained by proper ventilatory adjustments guided by frequent arterial pH, PO₂ and PCO₂ determinations (BMS MK 2 radiometer, Copenhagen). The heart was exposed through a thoracotomy in the left fifth intercostal space and a pericardial incision. A pacing electrode (Grass Instruments, Quincy, Massachusetts) was attached to the right atrial appendage in 10 of the dogs.
Electrical Measurements

Unipolar electrograms were recorded from the left ventricular endocardium with 13-mm diameter wire-hook electrodes (Eligloy, Eligloy Co., Elgin, Illinois), using the Wilson central terminal of extremity leads as a reference.1, 2 Endo-QRS electrograms were recorded from three to seven sites, covering the areas of distribution of both left anterior descending (LAD) and left circumflex (CFX) coronary arteries. After the electrodes were inserted, ST-segment elevation occurred initially, but regularly declined during the first hour. Electrograms showing persistent ST-segment elevation greater than 2 mV after 1 hour were discarded from analysis. Correct position of the endocardial electrodes was verified by postmortem examination, and electrodes showing improper localization, visible hemorrhage or tissue damage were discarded from further analysis.

Epi-QRS electrograms were recorded by means of a mobile cotton-wick electrode with an area of 5 mm², as described by Maroko and co-workers.10 Epicardial electrograms were recorded from six to 11 sites from the area of distribution of the LAD and CFX coronary arteries. All electrograms were recorded on an ECG using band-pass filters that excluded signals below 0.5 Hz or above 100 Hz (Honeywell, San Jose, California). The area of the QRS complex (msec/mV) was instantaneously calculated by an analog computer (Electronics Associates, Inc., West Long Branch, New Jersey). The isoelectric TP segment of the electrogram was chosen as the baseline, and the QRS area was displayed as an integrating curve for each beat at high paper speed. By appropriate delay controls, the left ventricular pressure signal was used to trigger the integrator 20 msec before the Q deflection and to clear the integrator when the S deflection returned to the baseline. The maximal amplitudes of the QRS complex and ST segments in four consecutive beats with normal conduction were averaged for analysis.

Left Ventricular Dimensions and Hemodynamic Measurements

Two piezoelectric crystals (2 × 3 × 3 mm) were implanted intramurally on the anterior and posterior walls of the left ventricle for continuous monitoring of left ventricular diameter.11 Left ventricular pressure was measured with a high-fidelity micromanometer (P-22, Konigsberg Instruments, Pasadena, California) inserted via the left atrial appendage. The maximal value of left ventricular pressure rise (dP/dt) was determined by means of a differentiating circuit connected to the output of the pressure channel. Aortic pressure was measured through a femoral catheter connected to a Statham P23Db strain-gauge transducer. Aortic blood flow was measured with a square-wave electromagnetic flowmeter (Carolina Medical Electronics, Model 501, King, North Carolina) on the ascending aorta. The electromagnetic flow probes were calibrated in vitro by passing blood through the probe at a known rate. The flowmeter gain was preset to match the individual probes during the experiment with correction for the hematocrit value. Zero flow was determined by the late diastolic aortic flow, assuming a normal aortic valvular function. Zero flow was also checked at the end of each experiment by leaving the flow probe in situ after the circulation was stopped by cardiac arrest.

In six of the 17 dogs, the descending thoracic aorta was constricted with a snare just distal to the left subclavian artery to raise left ventricular systolic pressure (LVSP). In these dogs, the ratio between diastolic pressure time index (DPTI) and systolic pressure-time index (SPTI) was calculated from high-speed pressure recordings.12, 13

Measurements of Myocardial Flow Distribution

Microspheres with a diameter of 9 ± 2 μ (3M Nuclear Products, St. Paul, Minnesota) were injected into the left atrium through a separate cannula in eight of the 17 dogs when hemodynamics appeared stable. The spheres were labeled with 125I, 14Ce, 85Sr and 45Sc and the sequence of injection was randomized in each experiment. Approximately 2 × 10⁶ microspheres containing 15 μCi were given at each injection. Immediately before sacrificing the dogs with potassium chloride, 0.5 ml of fluorescein was injected into the LAD with a pressure of approximately 90 mm Hg. Thus, the exact area of supply for this artery could later be visualized under ultraviolet illumination. Preparation of microsphere batches and tissue pieces and counting and calculation of flow were performed according to the technique of Heymann et al.14

Experimental Procedure

After control electrograms were recorded and hemodynamic measurements determined, whole blood was infused into the jugular vein through a wide-bore cannula to increase left ventricular dimensions. The blood, taken from healthy donor dogs within a few hours of its use, was heparinized and kept at body temperature. Left ventricular end-diastolic diameter (LVEDD) and pressure (LVEDP) were then increased stepwise, adjusting the infusion rate at each step to maintain stable hemodynamic conditions when repeat measurements of QRS amplitudes and LVEDD were made. Several determinations were made to delineate the relationship between LVEDD and QRS amplitude recorded by each electrode.1, 2

Infusion of blood was continued until LVEDP reached 12–25 mm Hg. The volume of blood infused was 600–2800 ml. When maximal increases in LVEDD and LVEDP were observed, electrograms were recorded and hemodynamic measurements were repeated. (The observations at maximal LVEDP are referred to as "load" in the text.)

Blood was then withdrawn from the dog in a similar stepwise manner, and more observations on the relationship between electrograms and LVEDP were made. LVEDD, LVEDP and QRS amplitudes always returned to control values after withdrawal of blood.

The proximal portion of the LAD was then occluded by a 3–0 silk ligature. Injections of 10 mg of
lidocaine chloride were given when necessary to control ectopic ventricular activity. Fifteen minutes after occlusion, electrograms were recorded and hemodynamic measurements determined. (These data are referred to as "occlusion" in the text.)

A second infusion of heparinized blood was then performed in a similar stepwise manner, as before LAD occlusion. When the preoclusion LVEDD was attained during blood transfusion, electrograms were recorded and hemodynamic measurements were made. (These values are referred to in the text as "occlusion + load".)

Finally, blood was withdrawn until occlusion values of LVEDD were regained and the measurements of electrograms and hemodynamics were repeated. There were no consistent changes in hematocrit after infusion or withdrawal of blood (range 34–46% in experimental dogs and 35–45% in donor blood). There were no consistent changes in blood gases or pH as a result of blood infusion or withdrawal. In the dogs in which myocardial blood flow distribution was determined, the first batch of microspheres was injected after the control hemodynamics were determined and electrograms recorded, and the second batch during maximum volume expansion before coronary artery ligation. The third batch of microspheres was injected 15 minutes after LAD occlusion and the last batch during maximum volume expansion after LAD occlusion.

Statistics

The data were analyzed by multiway analysis of variance and covariance for replicate measurements. After determining the degree of interaction between the variables under consideration, the $t$ test and the nonparametric Wilcoxon test for paired data were performed. The most restrictive probability value from the two paired tests is quoted in the tables. Excerpts of the multiway analysis of variance for the most important interpretations in this study are presented in an appendix section. Testing for differences between correlation coefficients in table 3 was performed according to Zar. A $p$ value less than 0.05 was considered statistically significant. There was no basic difference in electrical or hemodynamic measurements in paced or nonpaced hearts; the data are, therefore, pooled in the final analysis.

Results

Changes in endo-QRS and epi-QRS amplitudes and ST segments in LAD and CFX areas before and after LAD coronary artery occlusion and after volume load are summarized in table 1. Before LAD occlusion and during volume expansion by blood transfusion, LVEDD increased from a control value of $42.73 \pm 1.59$ mm to a maximal value of $46.43 \pm 1.89$ mm ($p < 0.001$). The increase in LVEDD was associated with reductions in both endo-QRS and epi-QRS amplitudes. On the average, endo-QRS and epi-QRS fell to 78 ± 2% and 85 ± 3% of control values, respectively. Blood was then withdrawn and the QRS amplitude increased as the LVEDD decreased and both the QRS amplitude and LVEDD returned to control levels. There was no difference in the relative changes in endo-QRS amplitude recorded from the LAD or CFX areas during either blood transfusion or withdrawal. After LAD occlusion and before volume loading, the endo-QRS amplitude in the LAD area (ischemic) decreased by an average of $-14.2 \pm 1.8$ mV (table 1). In the circumflex area (nonischemic) endo-QRS also fell (average $-4.1 \pm 1.7$ mV), but less than in the LAD area ($p < 0.001$). Although changes in epicardial QRS amplitudes in LAD and CFX areas were similar during volume expansion before LAD occlusion, they were different after occlusion. Epicardial QRS amplitude in the nonischemic circumflex area decreased significantly by an average of $-3.9 \pm 1.5$ mV. However, the epi-QRS amplitude in the ischemic LAD area remain unchanged.

Changes in hemodynamics and left ventricular

<table>
<thead>
<tr>
<th>TABLE 1. Effects of LAD Occlusion and Left Ventricular Volume Expansion on QRS Complexes and ST Segments in 17 Dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of electrodes</strong></td>
</tr>
<tr>
<td>QRS amplitude (mV)</td>
</tr>
<tr>
<td>LAD area</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>CFX area</td>
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<tr>
<td></td>
</tr>
<tr>
<td>ST-segment elevation (mV)</td>
</tr>
<tr>
<td>LAD area</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

*$p < 0.02$ vs control.
†$p < 0.001$ vs control.
‡$p < 0.001$ vs occlusion.

Abbreviations: LAD = left anterior descending coronary artery; CFX = left circumflex artery; endo = endocardial; epi = epicardial.
dimensions after LAD occlusion and volume expansions are summarized in Table 2. After LAD occlusion, concomitant with the increased LVEDD, there was also marked reduction in systolic shortening. LVEDP was moderately elevated, whereas LVSP was only slightly reduced (p < 0.08). Stroke volume remained unchanged. Heart rate changed very little after LAD occlusion.

During blood transfusion after LAD occlusion there were further increases in LVEDD and LVEDP (Table 2). Improvement in systolic shortening and marked increases in stroke volume and cardiac output were observed. LVSP increased by an average of 26 ± 3 mm Hg and was associated with slight bradycardia in the unpaced dogs that was prevented in paced dogs. Left ventricular end-systolic diameter increased from a control average of 38.36 ± 1.42 mm to 43.16 ± 1.70 mm during occlusion (p < 0.001) and increased further to 45.03 ± 1.64 mm during loading (p < 0.001). Cardiac output calculated from the product of stroke volume and heart rate fell from a control average of 3208 ± 299 ml/min to 2798 ± 314 ml/min during occlusion (p = 0.04). During subsequent loading, cardiac output increased to 4170 ± 515 ml/min (p < 0.001). Because LAD occlusion alone increased LVEDD, it was necessary to evaluate the independent effects, if any, of ischemia on the endocardial and epicardial electrograms. To examine the relationship of QRS amplitude and ventricular size more closely, changes in the QRS amplitude and LVEDD during each dimensional change, either during blood transfusion or withdrawal, were analyzed. Thus, several observations could be made at various sizes of the ventricle. In this and other studies, the observations made during transfusion and withdrawal of blood corresponded so closely that it was justified to treat the data as a common linear regression analysis between QRS amplitude and LVEDD. Because the absolute control magnitude of QRS amplitudes varied considerably between electrodes (ranges 19–50 mV at the endocardium and 16–53 mV at the epicardium), regression analysis had to be applied for each electrode separately.

Figure 1 shows regression lines for the relationship between LVEDD and QRS amplitude from one endocardial and one epicardial electrode in the LAD and CFX areas in the same dog. Table 3 summarizes regression and correlation analyses performed for each of 171 electrodes, and tests for differences between the observed and the expected decrease in QRS amplitude after LAD occlusion. In the LAD area, the relationship between endo-QRS and epic-QRS amplitudes and LVEDD after LAD occlusion deviated significantly from that obtained during blood transfusion before occlusion. With LAD occlusion the decrease in QRS amplitude was more than would be expected at the same LVEDD (Fig. 1 and Table 3). The regression lines for endo-QRS in the LAD area during postocclusion volume loading were lower (Table 3); that is, there were further decreases in endo-QRS potentials at comparable values of LVEDD. For the overall relationship between LVEDD and epic-QRS amplitude after LAD occlusion, p was greater than 0.5. The slopes of regression lines for epi-QRS in the ischemic zone were not different from zero (–0.002 ± 0.118), and the correlation was much poorer than before occlusion. Thus, the linear and negative relationship between epic-QRS amplitude and LVEDD before LAD occlusion was lost in epicardial electrograms from acutely ischemic tissue.

In the nonischemic circumflex area, slopes and correlations of the regression lines for the relationship between endo-QRS or epic-QRS potentials and LVEDD after LAD occlusion and volume expansion did not differ from those obtained before occlusion; thus, the relationship between QRS amplitude and LVEDD in the CFX nonischemic area was not influenced by LAD occlusion.

To evaluate the influence of induced ischemia on the duration and amplitude of QRS complexes, the QRS complexes were integrated over time in six dogs (Table 4). In the ischemic zone (LAD area) there were no changes in duration of the endo-QRS complex after occlusion or during volume loading, and the integrated area changed in proportion to the changes in maximal QRS amplitude (Table 1). In epicardial electrograms from the ischemic area, however, the QRS complexes broadened significantly after occlusion.
Although the maximal QRS amplitude was less, even when adjusted for accompanying changes in LVEDD (Table 3), the integrated area increased markedly, mainly due to longer duration. This increase in duration in epi-QRS in ischemic areas after occlusion partially reversed during volume expansion (Table 4). Figure 2 shows the changes in QRS complexes that occurred in the LAD area.

In the nonischemic CFX area, the duration of endo-QRS and epi-QRS remained unchanged after LAD occlusion and volume expansion (average 40.5 ± 0.4 msec), and the integrated QRS area varied in proportion to the maximal QRS amplitude.

**ST Segments**

ST-segment elevations in both endocardial and epicardial electrograms remained stable and were less than 2 mV before LAD occlusion. An increase in LVEDD with blood transfusion before LAD occlusion was not associated with any significant ST-segment elevation. There were no further ST changes in the

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**Figure 1.** Relationship between QRS amplitude and left ventricular end-diastolic diameter (LVEDD) in a representative dog. Electrodes were located on the endocardial (ENDO) and epicardial (EPI) surfaces in the left anterior descending (LAD) region, and in the left circumflex (CFX) region. Continuous lines are regression lines for preocclusion values during blood transfusion. Broken lines are regression lines for postocclusion values. "\( \bigcirc \)" indicates values after LAD occlusion but before volume expansion.

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**Table 3. Regression and Correlation Analyses of the Relationship Between Left Ventricular End-diastolic Diameter and QRS Amplitude Before and After Occlusion of the LAD**

<table>
<thead>
<tr>
<th></th>
<th>LAD area</th>
<th>CFX area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endocardial ((n = 36))</td>
<td>Epicardial ((n = 69))</td>
</tr>
<tr>
<td>Slopes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preocclusion</td>
<td>(-0.972 \pm 0.068)</td>
<td>(-0.363 \pm 0.034)</td>
</tr>
<tr>
<td>Postocclusion</td>
<td>(-0.926 \pm 0.113)</td>
<td>(-0.002 \pm 0.118)</td>
</tr>
<tr>
<td>(p)</td>
<td>NS</td>
<td>(&lt; 0.005)</td>
</tr>
<tr>
<td>Correlation coefficients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preocclusion</td>
<td>0.949</td>
<td>0.700</td>
</tr>
<tr>
<td>Postocclusion</td>
<td>0.864</td>
<td>0.512</td>
</tr>
<tr>
<td>(p)</td>
<td>(&lt; 0.05)</td>
<td>(&lt; 0.07)</td>
</tr>
<tr>
<td>Occlusion (mV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expected</td>
<td>29.4 (\pm 0.8)</td>
<td>31.5 (\pm 0.9)</td>
</tr>
<tr>
<td>Observed</td>
<td>21.6 (\pm 1.4)</td>
<td>29.0 (\pm 1.2)</td>
</tr>
<tr>
<td>(p)</td>
<td>(&lt; 0.001)</td>
<td>(&lt; 0.05)</td>
</tr>
</tbody>
</table>

\(n\) = number of regression lines, one for each electrode. See figure 1 and text for discussion.

Abbreviations: LAD = left anterior descending coronary artery; CFX = left circumflex coronary artery.
nonischemic CFX area after LAD occlusion. In the LAD area, however, marked ST elevation was seen in both the endocardial and epicardial electrograms. An increase in LVEDD during blood transfusion after LAD occlusion caused a significant reduction of epicardial ST-segment elevation, but the endocardial ST-segment did not change (table 1). There was no consistent relationship between left ventricular end-systolic diameter and epi-QRS or ST segments during ischemia.

**Influence of Arterial Blood Pressure on QRS Potentials and ST-segment Changes**

An increase in left ventricular volume by blood transfusion consistently increased LVSP. To evaluate the independent effect of increased LVSP on endo-QRS and epi-QRS potentials and ST-segment deflections in the ischemic area, LVSP was increased by aortic constriction after LAD occlusion in six of the 17 dogs. LVSP was elevated to almost the same level as during volume expansion by blood transfusion (table 5). Endo-QRS potential in the ischemic area decreased after aortic constriction by an average of 11%, compared with the 25% decrease during maximum volume expansion ($p < 0.05$). However, the increase in LVEDD during aortic constriction was also comparatively less than during volume expansion; thus, the relationship between endo-QRS and LVEDD appeared to be maintained during aortic constriction. Changes in epi-QRS potential in the LAD area were inconsistent.

As during volume expansion, the ST-segment elevation in the endocardium was not influenced by aortic constriction. Epicardial ST-segment elevations in the LAD area did not decrease, despite elevation of LVSP during aortic constriction. In contrast, during volume expansion after LAD occlusion, epicardial ST-segment elevation decreased significantly and LVSP increased significantly. Thus, reduction in epicardial ST-segment elevation during volume expansion could not be solely related to an increase in arterial blood pressure. In contrast to volume expansion with blood, stroke volume and myocardial systolic shortening decreased during aortic constriction; the DPTI/SPTI ratio, an indirect index of myocardial oxygen supply and demand, also declined.12

To evaluate the relationship between changes in regional blood flow and changes in endo-QRS and epi-QRS potentials and ST-segment changes, measurements of regional myocardial blood flow were performed in eight dogs by injecting labeled microspheres. Volume expansion by blood transfusion before LAD occlusion increased blood flow in all parts of the left ventricle without changing endocardial/epicardial ratios (table 6). Occlusion of the LAD artery caused a marked fall in flow in the ischemic area, notably in endocardial layers. Volume expansion with blood transfusion further reduced the endocardial/epicardial ratio in the ischemic area; however, the decrease in the endocardial/epicardial ratio was primarily due to an increase in flow in the epicardial layers as the endocardial flow remained unchanged.

In the nonischemic CFX area, a minor reduction in flow was seen after LAD occlusion, but the endocar-

<table>
<thead>
<tr>
<th>Table 4. Changes in Duration and Integrated Areas of QRS Complexes in the LAD Area in Six Dogs</th>
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<tbody>
<tr>
<td>No. of</td>
</tr>
<tr>
<td>electrodes</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Duration (msec)</td>
</tr>
<tr>
<td>Endo</td>
</tr>
<tr>
<td>Epi</td>
</tr>
<tr>
<td>Integrated QRS (msec · mV)</td>
</tr>
<tr>
<td>Endo</td>
</tr>
<tr>
<td>Epi</td>
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</tbody>
</table>

Values are mean ± SEM.

*p < 0.001 vs control.

†p < 0.02 vs occlusion.

‡p < 0.001 vs occlusion.

Abbreviations: LAD = left anterior descending coronary artery; CFX = left circumflex coronary artery; epi = epicardial; endo = endocardial.
dial/epicardial ratio was not altered. During volume expansion after LAD occlusion, flow increased to both the endocardium and epicardium, slightly more to the endocardium.

The relationship between changes in epicardial blood flow and changes in epicardial ST segments and QRS amplitude in the ischemic area after LAD occlusion and volume expansion is illustrated in figure 3.

Reduction in the ST-segment elevation was associated with increments in epicardial blood flow, but there was no consistent relationship between changes in epicardial QRS amplitude and epicardial blood flow.

Discussion

This study corroborates previous observations that endo-QRS and epi-QRS amplitudes are negatively

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**Table 5.** Changes in QRS Complexes and ST Segments in the Ischemic Area, Hemodynamic Alterations During Blood Transfusion and Aortic Constriction After LAD Occlusion in Six Dogs

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Occlusion</th>
<th>Occlusion + load</th>
<th>Occlusion + aortic constriction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QRS amplitude (mV)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Endo</td>
<td>36.7 ± 3.4</td>
<td>16.3 ± 2.5</td>
<td>12.1 ± 2.7†</td>
<td>14.4 ± 2.6†</td>
</tr>
<tr>
<td>Epi</td>
<td>36.7 ± 2.1</td>
<td>30.5 ± 3.3 NS</td>
<td>31.5 ± 4.1 NS</td>
<td>29.7 ± 4.4 NS</td>
</tr>
<tr>
<td><strong>ST-segment elevation (mV)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo</td>
<td>1.5 ± 0.6</td>
<td>6.7 ± 0.8†</td>
<td>6.9 ± 0.9 NS</td>
<td>7.8 ± 1.5 NS</td>
</tr>
<tr>
<td>Epi</td>
<td>0.2 ± 0.1</td>
<td>5.0 ± 0.7†</td>
<td>2.6 ± 0.7§</td>
<td>5.2 ± 0.9§</td>
</tr>
</tbody>
</table>

**Hemodynamic variables**

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<table>
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<tr>
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</thead>
<tbody>
<tr>
<td>LVEDD (mm)</td>
<td>43.4 ± 1.39</td>
<td>46.37 ± 1.89*</td>
<td>49.01 ± 1.58§</td>
<td>47.46 ± 1.90¶</td>
</tr>
<tr>
<td>Systolic shortening (mm)</td>
<td>2.88 ± 0.32</td>
<td>0.85 ± 0.39†</td>
<td>2.09 ± 0.47§</td>
<td>0.58 ± 0.42¶</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>5.7 ± 1.5</td>
<td>8.7 ± 2.1*</td>
<td>18.5 ± 3.3§</td>
<td>12.5 ± 1.9¶</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>124 ± 9</td>
<td>121 ± 8 NS</td>
<td>148 ± 9§</td>
<td>148 ± 7 NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>153 ± 11</td>
<td>153 ± 10 NS</td>
<td>150 ± 12 NS</td>
<td>149 ± 14 NS</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>24.7 ± 2.9</td>
<td>24.2 ± 3.4 NS</td>
<td>37.0 ± 2.3§</td>
<td>19.3 ± 3.7**</td>
</tr>
<tr>
<td>dP/dt)/IP (sec⁻¹)</td>
<td>40.1 ± 5.8</td>
<td>31.4 ± 5.9 NS</td>
<td>32.6 ± 7.1 NS</td>
<td>25.2 ± 2.7 NS</td>
</tr>
<tr>
<td>DPTI/SPTI</td>
<td>1.46 ± 0.27</td>
<td>1.14 ± 0.17*</td>
<td>1.09 ± 0.25 NS</td>
<td>0.76 ± 0.18§</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* p < 0.05 vs control.
† p < 0.005 vs control.
‡ p < 0.05 vs occlusion.
§ p < 0.005 vs occlusion.
¶ p < 0.05 vs occlusion + load.
** p < 0.005 vs occlusion + load.

Abbreviations: LVEDD = left ventricular end-diastolic diameter; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; (dP/dt)/IP = maximal value of left ventricular pressure rise divided by the instantaneous pressure; DPTI = diastolic pressure-time index; SPTI = systolic pressure-time index; endo = endocardial; epi = epicardial; LAD = left anterior descending coronary artery.

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**Table 6.** Regional Myocardial Blood Flow (ml/min/100 g) During Blood Transfusion Before and After LAD Occlusion

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Load</th>
<th>Occlusion</th>
<th>Occlusion + load</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD area (n = 40)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo</td>
<td>93 ± 6</td>
<td>130 ± 9†</td>
<td>33 ± 4†</td>
<td>35 ± 5 NS</td>
</tr>
<tr>
<td>Epi</td>
<td>108 ± 6</td>
<td>144 ± 9†</td>
<td>42 ± 4†</td>
<td>57 ± 6§</td>
</tr>
<tr>
<td>Ratio</td>
<td>0.86 ± 0.02</td>
<td>0.90 ± 0.03 NS</td>
<td>0.73 ± 0.05*</td>
<td>0.59 ± 0.05‡</td>
</tr>
<tr>
<td>CFX area (n = 32)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endo</td>
<td>108 ± 8</td>
<td>137 ± 9†</td>
<td>77 ± 3*</td>
<td>111 ± 5§</td>
</tr>
<tr>
<td>Epi</td>
<td>101 ± 7</td>
<td>123 ± 8†</td>
<td>77 ± 3*</td>
<td>105 ± 6§</td>
</tr>
<tr>
<td>Ratio</td>
<td>1.09 ± 0.04</td>
<td>1.15 ± 0.04 NS</td>
<td>1.02 ± 0.04 NS</td>
<td>1.10 ± 0.04‡</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* p < 0.02 vs control.
† p < 0.001 vs control.
‡ p < 0.002 vs occlusion.
§ p < 0.001 vs occlusion.

Abbreviations: LAD = left anterior descending coronary artery; CFX = left circumflex coronary artery; epi = epicardial; endo = endocardial.
Correlated with changes in LVEDV.\textsuperscript{1, 2} Thus, an increase in LVEDD in this study was associated with a decrease in endo-QRS and epi-QRS potentials and a decrease in LVEDD resulted in increased potentials. The precise mechanism of such reduction in ventricular potentials with an increase in ventricular diameter remains unclear. Alterations in ventricular geometry and wall thickness and the relative changes in the tissue mass in the immediate vicinity of the recording electrodes may account to some extent for the changes in ventricular potentials during acute changes in left ventricular volume.\textsuperscript{1, 2} Changes in intracavitary blood volume and consequent alterations in conductive mass might also have contributed.

Although the mechanism of changes in ventricular potentials induced by alterations in ventricular volume is conjectural, the present study indicates that after acute myocardial ischemia, changes in endo-QRS and epi-QRS amplitudes recorded from the ischemic and nonischemic zones may be different. Acute myocardial ischemia after LAD occlusion caused some increase in LVEDD; however, QRS amplitude in the ischemic area decreased more than could be attributed to increased ventricular dimensions (fig. 1 and table 3). Thus, some reduction in endo-QRS or epi-QRS voltages seems to be an inherent effect of acute myocardial ischemia. This conclusion is further supported by the finding that the endo-QRS and epi-QRS amplitudes recorded from the nonischemic zone did not decrease more than would be expected from an increase in LVEDD.

This study also suggests that after induction of ischemia the influence of an acute increase in left ventricular volume on endo-QRS potentials may be different from that on epicardial potentials (when recorded from the ischemic area). Endo-QRS potentials from the ischemic areas decreased linearly as the LVEDD increased. In contrast, epi-QRS amplitude, although decreased initially, did not show any consistent changes when LVEDD was increased further by blood transfusion. Moreover, epi-QRS complexes were most often widened (table 4 and fig. 2), sometimes with a bizarre appearance, whereas there was no prolongation of the endo-QRS complex when recorded from the ischemic zone. The endocardial surface becomes ischemic more readily than the epicardial layers after coronary artery ligature.\textsuperscript{12, 17, 18} Changes in regional myocardial flow observed in this study support this view. In the ischemic zone, endocardial blood flow decreased more than the epicardial blood flow after LAD occlusion; however, the depolarization disturbances were more pronounced in the epicardial layers. These findings suggest that electrical changes may not parallel changes in blood flow in different layers of the myocardium. Purkinje fibers are more abundant in endocardial than in epicardial layers, and appear to be more resistant to ischemia.\textsuperscript{19, 20} Therefore, despite a greater reduction in endocardial blood flow, depolarization activity might be better maintained in the endocardium than in the epicardium.\textsuperscript{21, 22} Profound disturbances have been shown in the propagation pattern of depolarization in ischemic tissue, particularly in the sequence of activation, so that the normal depolarizing wave front is broken into an extremely irregular and unpredictable pattern.\textsuperscript{23, 24} This might explain the bizarre appearance and the broadening of the epi-QRS complexes seen in the ischemic areas in this study. Increased epicardial blood flow during volume expansion after coronary artery occlusion was associated with a modest decrease in the duration of the epi-QRS complex.

The present study indicates that the influence of changes in ventricular dimensions on the ischemia-induced ST-segment elevations and on the QRS amplitude may be different. After coronary artery occlusion there was a marked elevation in both endocardial and epicardial ST segments. During blood transfusion with a concomitant increase in LVEDD, endocardial ST elevations did not change, while epicardial ST elevation decreased. However, the decrease in epicardial ST-segment elevations could not be related to changes in LVEDD, because a similar increase in LVEDD occurred during aortic constriction, and yet the magnitude of epicardial ST elevation actually increased. The mechanism of the differential effects of changes in ventricular volume on ST elevation and QRS amplitude is unclear.

Changes in epicardial and endocardial ST segments in ischemic zones could be better correlated to changes in regional blood flow (fig. 3). Marked ST elevations in the endocardial and epicardial electrograms in the ischemic zones were associated with expected decrease in endocardial and epicardial blood flow after coronary artery occlusion. During volume expansion, the magnitude of epicardial ST elevation decreased and was associated with a relative increase in epicardial blood flow. In contrast, neither the endocardial ST-segment elevation nor the endocardial blood flow changed during volume expansion. The mechanisms
for improved epicardial flow during volume expansion after coronary artery ligation are unclear. Profound ischemia disturbs autoregulation of the peripheral coronary vascular bed, especially in endocardial layers. In the absence of autoregulation, flow is predominantly determined by the pressure gradient across the coronary arterial bed and the diastolic perfusion time. Blood transfusion after LAD ligation consistently increased both systolic and diastolic arterial pressures, tending to enhance collateral flow to the ischemic myocardium. However, during volume expansion, left ventricular diastolic pressure also increased, tending to impede diastolic flow to the endocardium, presumably because tissue pressure was higher in the endocardium than in the epicardium. The net result might, therefore, be an increase in epicardial blood flow with no significant change in endocardial flow, as in this study. An increase in arterial systolic pressure alone, however, was unlikely to cause the increase in epicardial flow. During aortic constriction, aortic systolic pressure increased significantly, to almost the same level as during volume expansion; yet, there was no increase in epicardial blood flow and there was a further increase in ST-segment elevations. During aortic constriction, however, aortic diastolic pressure did not rise and the duration of diastole shortened, accounting for decreased DPTI and DPTI/SPTI. In contrast, during blood transfusion, the duration of diastole and diastolic pressure increased, causing a higher DPTI/SPTI ratio. These differences in hemodynamics might explain the difference in regional blood flow in ischemic zone during volume expansion and aortic constriction after coronary artery ligation.

In this study, reduction in epicardial ischemic injury indicated by decreased ST-segment elevation was observed during volume expansion, and was associated with increased epicardial blood flow. The functional significance of ST-segment changes is not yet completely understood. In studies in which local tissue flows were determined, ST-segment elevation did not occur until flow was reduced by 50% or more, and the disturbance of the contractile function was shown to precede ST-segment elevation. In this study, total coronary artery occlusion was produced to induce ischemic injury, so the precise relationship between the magnitude of reduction of coronary blood flow and the degree of ST-segment elevations could not be determined. Nevertheless, using labeled microspheres to determine the distribution of flow, we found a general linear relationship between ST-segment changes and changes in myocardial blood flow. Decreased ST-segment elevation and increased epicardial blood flow was associated with improvement in regional myocardial contractile function, as demonstrated by improved systolic shortening. Such improvement in regional mechanical function during volume expansion after coronary artery ligation has been reported.

Increased duration of the epi-QRS complex after coronary artery ligation also normalized partially during volume expansion, which might indicate improvement in profoundly disturbed electrical depolarization. Thus, it is tempting to hypothesize that the improvements in ischemic injury, electrical disturbances and mechanical function may all be related to improved epicardial blood flow, although the precise mechanism is still unclear. Hillis and co-workers recently suggested that changes in the epi-QRS potentials could be used to determine the extent of myocardial ischemic injury, and thus the effects of pharmacologic interventions on the magnitude of myocardial injury could be evaluated. We found that endo-QRS and epi-QRS potentials in ischemic and nonischemic areas may be influenced by changes in ventricular volumes and dimensions. Although acute ischemia after coronary artery ligation decreased endo-QRS potential in the ischemic zone independent of left ventricular dimension changes, volume expansion caused a further decrease in endo-QRS amplitude without causing any significant change in endocardial blood flow. Epi-QRS amplitude did not increase despite an increase in epicardial blood flow. Further, in the nonischemic areas, both endo-QRS and epi-QRS amplitudes declined with volume expansion, although both endocardial and epicardial blood flow increased. Thus, interventions that alter cardiac function and change ventricular dimensions affect QRS amplitude, regardless of changes in myocardial ischemia. Surface potentials recorded from the surface electrograms reflect the total cardiac electrical activity. It is likely, therefore, that the variable changes in endocardial and epicardial potentials in the ischemic and nonischemic areas during left ventricular volume changes cause a variable and unpredictable change on surface potentials as well. Further, alterations in electrical conductance dependent on changes in intracavitary blood volume also influence the surface potentials. These findings suggest that the evaluation of the extent of myocardial ischemia-injury from the changes in QRS amplitude recorded from the surface electrograms may not be precise when there is a concomitant acute change in left ventricular volume.

Holland and Brooks suggested that early changes in epi-QRS complexes after coronary artery ligation may be related to release of potassium from ischemic myocardial cells and can be influenced by large elevations of plasma potassium concentrations. Plasma potassium concentrations were not measured in this study and, therefore, the independent influence of changes in potassium concentrations on endo-QRS or epi-QRS potentials could not be determined. It is unlikely, however, that changes in QRS amplitude during volume expansion after LAD occlusion could result solely from changes in potassium concentration, because the changes in QRS amplitude were qualitatively similar to changes in left ventricular dimensions with or without coronary artery ligation. In summary, changes in ventricular volume and dimensions may have profound and variable influence on endo-QRS and epi-QRS amplitudes in the presence of acute myocardial ischemia. Acute ischemia causes a consistent reduction in both endo-
QRS and epi-QRS amplitudes. However, endo-QRS amplitude is also influenced independently by changes in ventricular volume. Changes in the epi-QRS complex in the ischemic area are erratic and unpredictable during volume changes, although in nonischemic areas both epi-QRS and endo-QRS amplitudes consistently decrease during volume expansion. Because changes in ventricular volumes might occur in acute infarction and appear to produce variable changes in endo-QRS and epi-QRS amplitudes in ischemic and nonischemic zones, precise quantification of the extent of myocardial ischemic injury from the changes in QRS amplitude may be difficult, if not impossible.

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Appendix

The results of multiway analysis of variance is presented below for the most important data interpretations in this study. The results are expressed by the p value for a probable relationship between variables, avoiding tabulation of a great number of sums of squares, degrees of freedom and F values.

Tables 1 and 2

The original observations in these two tables were subjected to a common multiway analysis in one operation. There are one to eight replicates for the QRS amplitude and ST-segment measurements for each dog. No significant replicate-factor effect could be detected. Endo-QRS amplitude showed a significant relationship between LAD and CFX areas (p = 0.04). For the variables control, occlusion, and occlusion + load, a significant relationship was present (p < 0.001), and the interaction effect between the two levels of variables was highly significant (p < 0.001). Similar analysis of epi-QRS amplitude from LAD and CFX areas showed no significant relationship (p = 0.29). For the variables control, occlusion and occlusion + load, a significant relationship was present (p = 0.002).
The analysis also revealed significant interaction \((p = 0.04)\) between the two levels of variables, suggesting that LAD/CFX differences were present in the three experimental settings. Thus, it can be concluded that LAD/CFX differences in QRS amplitude were much greater in epicardial than in endocardial regions.

ST-segment elevation showed a probable relationship for the variables endocardial and epicardial \((p = 0.07)\), and a clearly significant relationship for the variables control, occlusion, and occlusion + load \((p < 0.001)\). There was also a significant interaction effect \((p < 0.001)\) between the two levels of variables. Subsequent breakdown analysis located most of this interaction effect to the control and occlusion subsets, suggesting that the ST-segment elevation changed differently in endocardial and epicardial layers during occlusion + load.

**Table 5**

A significant replicate-factor effect could not be identified (one to six replicate QRS and ST measurements in each dog). For QRS amplitude, a significant relationship between endocardial and epicardial layers was obtained \((p = 0.03)\). Variance of QRS amplitude at the four experimental settings in table 5 was highly significant \((p < 0.001)\), with a significant interaction between the two levels of variables \((p < 0.001)\). Further analysis located this interaction effect to control, suggesting that endocardial/epicardial differences occurred in ischemic tissue only.

For ST-segment elevation, a clear relationship between endocardial and epicardial could not be found \((p = 0.06)\), whereas the variance with the four experimental settings was highly significant \((p < 0.001)\). Interaction between the two levels of variables was not significant \((p = 0.20)\). Further analysis suggested that epicardial ST-segment elevation was significantly reduced during occlusion + load \((5.0 \pm 0.7 \text{ mV} \text{ to } 2.6 \pm 0.7 \text{ mV})\), while endocardial ST-segments remained unchanged \((6.7 \pm 0.8 \text{ mV} \text{ to } 6.9 \pm 0.9 \text{ mV})\). For the variables LVEDD and systolic shortening, highly significant differences were found between the four experimental settings \((p < 0.001 \text{ and } p = 0.007)\).

**Table 6**

There was no significant replicate-factor effect (four to six replicate measurements of myocardial blood flow in each dog). The endocardial/epicardial ratio was treated as a dependent variable in each set of replicates. The data were analyzed at three levels of variables: A) LAD, CFX areas; B) control, load, occlusion, occlusion + load; and C) Endocardial and epicardial. Significant source of variation was found for the variables A and B \((p < 0.001)\), but not on an overall analysis for C \((p = 0.12)\). However, a significant AC interaction effect was detected \((p < 0.001)\) that could be located to the ischemic LAD area by breakdown analysis. This finding suggests that the endocardial/epicardial flow ratio in the ischemic LAD area was different from that in the CFX area and the nonischemic LAD area \((p < 0.001)\). Next, the AC interaction effect could be located to the epicardial LAD flow values, indicating that volume loading was associated with a significant elevation of epicardial LAD flow \((42 \pm 4 \text{ to } 57 \pm 6 \text{ ml min/100 g; } p = 0.002)\), while endocardial LAD flow remained unchanged. Significant AB interaction was found \((p < 0.001)\), reflecting that coronary occlusion reduced myocardial blood flow significantly more in the LAD area than in the CFX area. Significant BC or ABC interactions were not found.
Influence of left ventricular dimensions on endocardial and epicardial QRS amplitude and ST-segment elevations during acute myocardial ischemia.
J Lekven, K Chatterjee, J V Tyberg and W W Parmley

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