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EXPERIMENTAL STUDIES

The Natural History of Regional Wall Motion in the Acutely Infarcted Canine Ventricle

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Two-dimensional echocardiography was employed to define the natural history of regional wall motion abnormalities in a canine model of acute experimental myocardial infarction. Serial short-axis two-dimensional echocardiograms were recorded in 11 closed chest dogs before coronary occlusion and 10, 30, 60, 180 and 360 minutes after permanent coronary ligation. Radiolabeled microsphere-derived blood flows were obtained in each study period and the histochemical (triphenyltetrazolium chloride) extent of infarction was determined at 6 hours. Previously published methods were used to quantitate field by field (every 16.7 ms) excursion of 36 evenly spaced endocardial targets. The circumferential extent of abnormal wall motion was followed sequentially using previously published definitions of abnormality: 1) systolic fractional radial change of less than 20%; 2) dyskinesia (systolic bulging) at the point in time (echocardiographic field) in which there is maximal dyskinesia; and 3) correlation with composite normal ray motion falling outside the 95% confidence limits defined in the control period. On the basis of the triphenyltetrazolium chloride staining pattern, the ventricle was divided into five zones: central infarct zone, zone with greater than 25% transmural infarction, total infarct zone, border zones and normal zone. Mean systolic fractional radial change was calculated for each zone and used as an index of the magnitude of abnormal wall motion.

Regardless of the definition of abnormality employed, the circumferential extent of abnormal wall motion manifested at 10 minutes after occlusion did not significantly change, even up to 6 hours later. Similarly, 10 minutes after coronary occlusion the three infarct zones and border zones demonstrated significantly reduced systolic fractional radial change. This remained stable over the remainder of the 6 hour study period.

It is concluded that once established at 10 minutes after coronary occlusion, the circumferential extent and magnitude of abnormal wall motion do not significantly change in the immediate postinfarct (6 hour) period.

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The ability of two-dimensional echocardiography to detect changes in left ventricular function and structure after acute myocardial infarction is well established, and numerous studies (1–15) have successfully related echocardiographically documented abnormal wall motion to other correlates of infarction. Surprisingly little is known, however, about the natural history of these echocardiographic changes, particularly during the critical hours immediately after infarction. There has been only one experimental echocardiographic study of regional wall motion that provides information on multiple points in the early postinfarct period (4), and the method it used was based only on visual assessment of regional function. All other such studies have tended to focus on more subacute and chronic postinfarction changes, and in so doing, have examined only isolated points in the acute period.

Clinical echocardiographic studies have also focused on more long-term mechanical sequelae of infarction, reflecting, in part, the difficulty of acquiring multiple sequential studies early in the course of acute ischemic injury. Thus, most clinical natural history studies have enrolled patients days rather than hours after infarction. Because the immediate postinfarct period is the subject of both clinical and experimental studies aimed at infarct reduction, it was be-

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lieved critical to establish an echocardiographic "baseline" against which the functional results of such interventions could be compared.

The purpose of this study, therefore, was: 1) to employ two-dimensional echocardiography to document the natural history of both the *circumferential extent* and *magnitude* of abnormal wall motion observed over the initial 6 hours after acute experimental myocardial infarction; and 2) to relate this to the course of radiolabeled microsphere-derived regional blood flow over the same time period.

Methods

Serial left ventricular short-axis cross-sectional echocardiographic studies were performed on closed chest dogs at six study periods: preinfarction (control) and 10, 30, 60, 180 and 360 minutes after acute coronary ligation.

Animal Preparation

Studies were performed on 11 mongrel dogs with a mean weight of 18.6 kg (range 16 to 22). A closed chest model in which animals were specifically prepared to facilitate echocardiographic imaging was used. In this model, under general anesthesia, a left lateral thoracotomy was performed in the region of the fifth and sixth ribs. Approximately 6 to 8 cm of both ribs was resected and a pericardial cradle was created. A silk snare with a Teflon occluder was placed around either the left anterior descending coronary artery (four dogs) or left circumflex coronary artery (seven dogs) and a Silastic catheter was placed in the left atrium. Both the snare and catheter were tunneled under the skin to a pouch at the nape of the neck. To permit precise alignment of the imaging planes during subsequent echocardiographic studies, epicardial markers made from acrylic-coated metal spheres (3 mm diameter) were sutured in place at 2 cm intervals along the anterior, lateral and posterior walls of the left ventricle. The thorax was then closed and the pneumothorax evacuated.

Forty-eight to 96 hours later, dogs were reanesthetized, intubated and ventilated with oxygen-supplemented air, adjusted according to arterial blood gas measurements. The anesthetic agent used was alphachloralose (60 mg/kg body weight) in the circumflex series, and sodium pentobarbital (30 mg/kg) in the left anterior descending series. The anesthetic agents were varied in an attempt to reduce the possibility that any experimental findings might be agent-specific. A femoral artery line was placed for monitoring blood pressure and for arterial blood sampling.

Control echocardiographic images were recorded, and radiolabeled microspheres were injected for control perfusion determination. The preplaced coronary snare was then tightened to achieve permanent coronary artery occlusion.

The echocardiographic examination and radiolabeled microsphere injections were repeated 10, 30, 60, 180 and 360 minutes after occlusion. At the termination of the experiment (360 minutes after occlusion) the dogs were killed with a pentobarbital overdose.

Data Acquisition and Analysis

A. Infarct definition. At the termination of the experiment, the hearts were excised completely and the coronary ligature was removed. The left coronary artery was cannulated using a Gregg cannula and perfused with approximately 300 cc triphenyltetrazolium chloride solution (2,3,5,-triphenyltetrazolium chloride, 5 g/250 cc normal saline solution) at a pressure of approximately 85 mm Hg. The right coronary artery was subsequently perfused in similar fashion with 200 cc triphenyltetrazolium chloride. The left ventricular cavity was then packed with gauze and the heart was frozen to facilitate sectioning.

The great vessels and atria were trimmed and the heart was cut into 2 cm transverse sections using the three rows of beads to define the sectioning planes. After formalin fixation, slices were photographed and the extent of infarction was determined by planimetry of the color photographs. The area of infarction was defined as the region that did not stain with triphenyltetrazolium chloride (16). The pattern of staining was used to divide the ventricle into different zones, as illustrated in Figure 1, where the triphenyltetrazolium chloride-defined region of infarction is represented as the deeply stippled area.

First, the centroid was defined as the endocardial center of mass. Radii were then extended to intersect the outer margins of the triphenyltetrazolium chloride defined region of infarction. The segment within these delimiting radii thus incorporated the entire histochemically defined region of infarction and was termed the infarct tangent. The subsegment in which there was greater than 25% transmural involvement and the central portion of the infarct zone in which there was maximal transmural involvement were then defined. In all dogs, the central zone represented a region with greater than 50% transmural involvement, and in the majority greater than 75% transmural involvement. Once the region of infarction and subareas within it were defined, the infarct border zones were then arbitrarily defined as the 30° segments on either side of the infarct tangent. A 50° segment of the wall opposite the central infarct zone was considered to be representative of normal nonischemic myocardium. This triphenyltetrazolium chloride-derived division of the ventricle was used as a framework for analysis of wall motion and microsphere-derived perfusion.

B. Radiolabeled microsphere perfusion assessment. The technique of regional blood flow measurement using radiolabeled microspheres is well established (17). In this protocol, measurements in each study period were carried out using 8 to 10 μm microspheres labeled with either io-

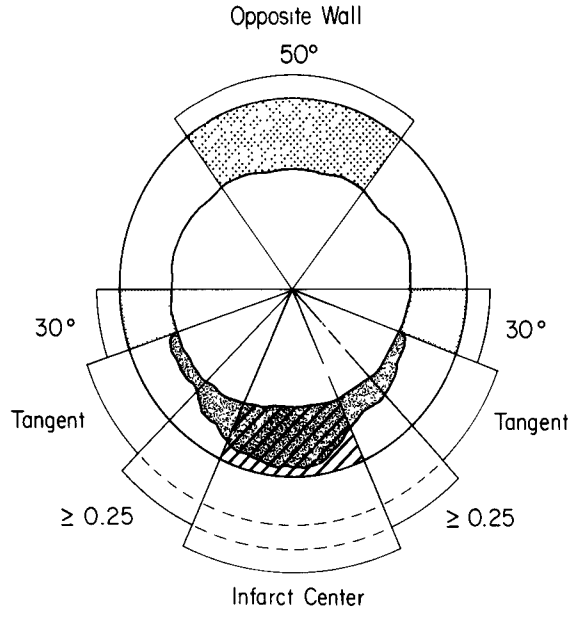

Figure 1. Schematic representation of a ventricular short-axis slice illustrating the zone definition based on the pattern of triphenyltetrazolium chloride staining. The triphenyltetrazolium chloride-defined extent of infarction is depicted with a **coarse stipple**. The reference center of the slice is defined as the endocardial center of mass. The central infarct zone (zone of maximal transmural involvement) is indicated with the **superimposed diagonal lines**. The zone with greater than 25% transmural involvement (≥0.25) incorporates the central infarct zone. Similarly, the region in which there was any evidence of infarction is labeled tangent. The 30° segments on either side of the infarct zone (**fine dotting**) were considered border zones, and a 50° segment in the wall opposite the site of infarction (**coarse dotting**) was considered representative of nonischemic myocardium. Although the endocardial circumferential extent of infarction was greater than the epicardial extent, this discrepancy has been exaggerated in the schematic for illustration purposes.

dine-125, cesium-141, chromium-51, strontium-85, niobium-95 or scandium-46. Flow assessments were made on the formalin-fixed slice that corresponded to the echo imaging plane. Its sectioning for counting was guided by the triphenyltetrazolium chloride staining, which allowed the identification of infarcted tissue, border zones (the 30° segments on either side of the infarcted region) and normal tissue. Within each zone, wedges (approximately 2 g each) were sectioned and subsequently divided into endocardial and epicardial portions for counting. Using standard techniques (17), myocardial blood flow was determined.

The radial profile of transmural flow was derived using a computer-aided method that uses the endocardial center of mass as a centroid and calculates transmural flow at 5° increments around the circumference of the ventricle through an area weighting of the raw microsphere-derived flows. To compensate for dog to dog and period to period fluctuations in global flow, absolute flows for the various zones were normalized to those in regions remote from the site of infarction.

Thus, normalized blood flow was calculated as:

$$\frac{\text{Absolute transmural flow (region of interest)}}{\text{Absolute transmural flow (region remote from infarction)}}.$$

The percent circumferential extent of reduced blood flow was then defined as:

$$\frac{\text{No. of degrees demonstrating normalized blood flow of } <0.75}{360^\circ} \times 100.$$

C. Echocardiographic wall motion analysis. Two-dimensional echocardiographic studies were obtained using an ATL Mark III mechanical sector scanner with a 3 or 5 MHz transducer and were stored for subsequent analysis on ½ inch (1.27 cm) videotape (60 fields/s). A midpapillary muscle short-axis view was used. To assure that the same imaging plane was used on serial echocardiographic studies and that the echocardiographically imaged "slice" was comparable with that subsequently used for histochemical and flow data, the echocardiographic imaging plane was aligned to include three equiplanar epicardial beads. As described previously, the same beads were used to guide postmortem sectioning of the heart. In this way, the plane in which the echographic beam transected the ventricle corresponded to one of the pathologic sections.

As the initial step in the analysis of the echocardiographic images, the raw data were reviewed to identify cycles in which endocardial visualization was optimal. For selected cycles, serial endocardial outlines recorded at 16.7 ms intervals from end-diastole to end-systole were digitized using an I^2S video digitizing system interfaced with a VAX 11-780 computer. The end-diastolic echocardiographic field was selected as the one demonstrating the largest endocardial area. This generally corresponded to within one to two fields of the peak of the R wave of the QRS complex noted on the simultaneously recorded electrocardiogram. Similarly, end-systole was defined as the smallest endocardial area. This generally corresponded to the end of the T wave. Once digitized, the endocardial center of area for each field was calculated and where necessary, the endocardial outline was rotated until the 0 reference (midpoint between the papillary muscles) occupied the 3 o'clock position. The average center of area for all digitized fields was computed and each field was reoriented to this fixed average center.

In addition to processing the raw (unsmoothed) endocardial outlines in this fashion, we also performed the same analysis on outlines in which the papillary muscles and endocardial surface aberrations were "removed" by a smoothing algorithm. This approach was included because of a concern that artifactual irregularities of regional wall motion might be produced by our analysis when a papillary muscle crossed from one radius to the next during contraction. The smoothing was done using a convex hull algorithm, which eliminates all points that are not concave to-

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ward the left ventricular centroid and therefore cannot contribute to active contraction. This process may be simply understood by drawing an analogy to stretching a rubber-band around a solid irregularly surfaced object. If the path taken by the band is used to redefine the surface, all indentations (analogous to endocardial surface projections into the left ventricular cavity) will be smoothed away. A more detailed discussion of the rationale behind this problem and the mathematical approaches to it is provided by Preparata and Shamos (18).

Both the unsmoothed (n) and the smoothed convex hull (c) data sets were used in all subsequent analyses. As the next step, field by field (every 16.7 ms) motion of endocardial targets along rays drawn at 10° increments around the circumference of the ventricle was examined using two previously described computer-assisted methods (19).

Definitions of abnormality. To address the question of the natural evolution of the *circumferential extent* of abnormal wall motion we employed three definitions of abnormality; two were based on single points in the contraction sequence and one was based on a method that integrates the entire systolic contraction sequence.

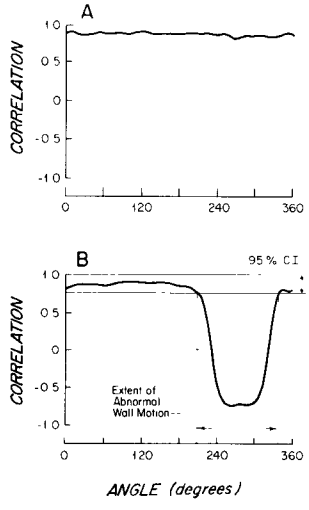
The first method considered only the two endpoints of systolic motion: end-diastole and end-systole. Motion along a given ray was considered abnormal if the end-diastolic to end-systolic radial change was less than 20% of the end-diastolic radius. A cutoff of 20% was used because preliminary comparison with fixed cutoffs of 0.0, 5, 10, 15, 20, 25 and 30% suggested that, although there was no significant correlation ($r = 0.3$ to 0.39, $p = 0.42$ to 0.29) between the extent of wall motion, defined at 6 hours, and the histochemical extent of infarction, the "best" correlation was obtained using cutoffs of either 20 or 25% ($r = 0.35$ and 0.39, respectively). Twenty percent was then selected because, unlike 25%, it did not identify any rays as being abnormal in the control period. The number of rays demonstrating abnormal motion, thus defined, was calculated and expressed as a percent of the circumference.

The second method considered the number of rays that demonstrated outward bulging or dyskinesia at that point (echocardiographic field) in systole where the extent and absolute magnitude of dyskinesia were greatest. This typically occurred one-third to one-half of the way through systole. The number of rays moving outward, again expressed as a percent of the total circumference, yielded a second quantitative estimate of the extent of abnormal wall motion.

The third definition of abnormality was based on a method of analysis that integrates the entire course of systolic radial motion. This is accomplished by correlating, for each of the 36 evenly spaced rays, the course of motion of the endocardial target along that ray to the course of normal motion, derived by averaging the systolic motion of endocardial targets taken along all 36 radii in the heart of six normal dogs (prepared as described in Methods). The details and validation of this method have been previously reported (19).

Two-step process of correlation analysis. To summarize, the correlation analysis is best thought of as a two step process. As the initial step, for each ray, the observed fractional radial change (end-diastolic radius − observed radius)/end-diastolic radius measured at sequential times in systole [every 16.7 ms]) is plotted against the pooled normal value at comparable times. A line is then fitted to the data points using the least squares linear regression technique and the correlation coefficient is calculated. As the second step, the correlation coefficients for each individual ray are plotted against ray location, progressing in a counterclockwise direction around the circumference of the ventricle (Fig. 2). The correlation coefficients are plotted along the x axis and the ray position from 0 to 360° is plotted along the y axis. The upper plot (Fig. 2A) contains data from a normal systolic contraction sequence: motion around the circumference is uniformly similar to composite normal ray motion and the correlation coefficients for all rays are near unity. The lower plot (Fig. 2B) is typical of that obtained after coronary occlusion. As previously, the correlation coefficients for the normal rays (0 to 210°) are near unity. In the infarcted region of the ventricle (210 to 340°) the correlation coefficient abruptly decreases and usually becomes negative.

Figure 2. Second step of the correlation method of wall motion analysis. Correlation coefficients derived for endocardial targets positioned along each of 36 equally spaced rays (**y axis**) are plotted against ray location (**x axis**). **A**, Plot derived from a normal control contraction sequence. Because radial motion is uniformly similar to composite normal ray motion, the correlation coefficients for all the rays are near unity. **B**, Plot obtained in the same animal after acute coronary ligation. The **horizontal lines** labeled 95% CI represent the 95% confidence intervals for the normal correlation coefficients. Rays whose correlation coefficients fall outside these limits are considered abnormal.



In general, the correlation coefficient derived for each ray simply reflects how much motion along that ray resembles composite normal ray motion. A value of 1 implies normal motion; a value of 0 indicates random or no motion and a negative value indicates dyskinesia (systolic bulging). To define the circumferential extent of abnormal wall motion using the correlation method, the statistically defined 95% confidence limits for the correlation coefficients of the baseline normal radii were used. Radii whose correlation coefficients fell outside these limits were considered abnormal.

To define the natural history of the magnitude of wall motion within ventricular zones, a method that generates field by field percent fractional radial change for each of the 36 evenly spaced endocardial targets was employed. On the basis of previously described triphenyltetrazolium chloride-based framework, radii were grouped into different regions as described earlier (central infarct zone, zone with greater than 25% transmural infarction, infarct tangent, border zones and normal zone). Mean zonal function was derived simply by averaging the end-systolic fractional radial change values for individual rays falling within each region.

In addition, in order to further our understanding of the observed changes in fractional radial change, and to determine whether the ventricular short axis had dilated at each time period, the sum of the 36 individual ray lengths (relative to the average endocardial center of area centroid) was calculated as an index of ventricular short-axis circumference and the sum of their squares was calculated as an index of cross-sectional area.

Interobserver and intraobserver error estimates. A detailed description of the assessment of the errors inherent in the methods of quantitative wall motion analysis employed in this study has been previously published (19). To summarize, the best estimate of error expected in a single percent excursion measurement is 5%. This error is due to both normal intercycle variation and interobserver variation. Intraobserver error, as estimated by the components of variance model, was found to be negligible.

Statistical analysis. Comparisons of the circumferential extent of abnormal wall motion, circumferential extent of reduced blood flow and area and circumference indexes at each time period were carried out using repeat measures multivariate analysis of variance. Where the initial phase of this analysis indicated significant ($p < 0.05$) temporal variation of the variable in question, further analysis was performed to identify the temporal points between which there were significant differences (20). In this aspect of the analysis, there is no statistical consensus as to which probability (p) value defines significance. If the liberal approach of Duncan's procedure (21) is applied, a p value of less than 0.05 is significant, whereas a more conservative approach using Bonferroni protection for the multiple comparisons would suggest that a p value of 0.005 should be used. Therefore, in our analysis, p values of greater than 0.05 are considered not significant, p values of less than 0.005 are considered significant and intermediate p values are considered to be of borderline significance. All results are reported as the mean ± 1 SD.

Comparison of the mean fractional shortening in myocardial zones and at different time periods was carried out using factorial analysis of variance with repeated measures followed by modified *t* tests with Bonferroni theorem protection for multiple comparisons (20). A p value of less than 0.01 was considered statistically significant.

Results

Hemodynamics. Heart rates in the control period and 10, 30, 60, 180 and 360 minutes after occlusion studies were 115 ± 15, 118 ± 17, 110 ± 16, 113 ± 14, 120 ± 16 and 122 ± 18 beats/min, respectively. Mean blood pressure measurements obtained at the same study periods were 96 ± 20, 88 ± 14, 88 ± 12, 92 ± 13, 94 ± 15 and 90 ± 19 mm Hg, respectively. No significant difference in either variable was noted over the course of the study.

Triphenyltetrazolium chloride-defined circumferential extent of infarction. The circumferential extent of triphenyltetrazolium chloride-defined infarction ranged from 25 to 67% (mean 42%).

Radiolabeled microsphere perfusion assessment. The circumferential extent of reduced blood flow (normalized blood flow < 0.75) for study periods one through six was 0, 44 ± 19%, 44 ± 15%, 44 ± 15%, 50 ± 15% and 49 ± 14%, respectively. There was no significant difference between the extent of reduced blood flow from 10 minutes to 6 hours after infarction.

Circumferential extent of abnormal wall motion. The temporal course of the circumferential extent of abnormal wall motion calculated according to each of the previously described methods is depicted graphically in Figure 3. When the correlation analysis was used, the extent of abnormal wall motion obtained using the unsmoothed data was 5 ± 4%, 43 ± 10%, 44 ± 10%, 46 ± 10%, 46 ± 10% and 46 ± 9% for periods one to six, respectively. Comparable values obtained with the smoothed "c" data were 1 ± 2%, 45 ± 10%, 46 ± 10%, 48 ± 7%, 47 ± 9% and 46 ± 8%, respectively.

When we used an end-diastolic to end-systolic fractional radial change of less than 20% to define abnormality, the circumferential extent of abnormal wall motion using the unsmoothed data for periods one to six was 0 ± 0%, 43 ± 12%, 47 ± 12%, 49 ± 14%, 39 ± 18% and 44 ± 14%, respectively. Comparable values derived from the smoothed data were 0 ± 0%, 45 ± 11%, 47 ± 15%, 51 ± 12%, 52 ± 18% and 39 ± 19%, respectively.

The last method, the maximal radial extent of dyskinesia, yielded the following values for the unsmoothed data: 3 ± 7%, 31 ± 11%, 42 ± 13%, 42 ± 12%, 40 ± 10% and

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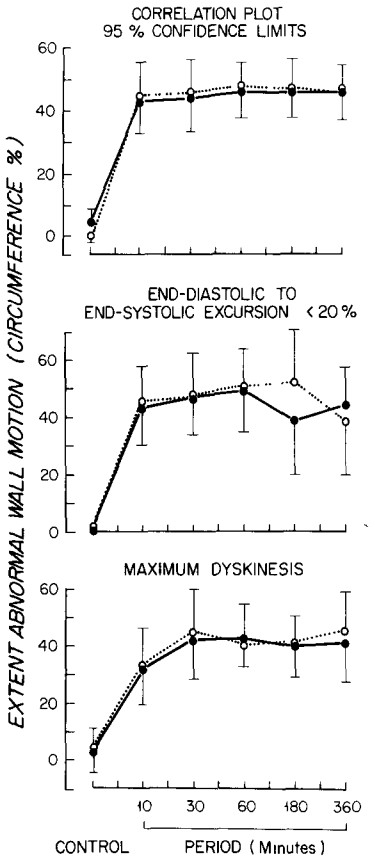

Figure 3. Circumferential extent of abnormal wall motion over time. In the **upper panel**, rays were considered abnormal if their correlation with composite normal ray motion fell outside the 95% confidence limits. In the **middle panel**, abnormality was defined as a systolic fractional radial change of less than 20%. In the **lower panel**, the maximal circumferential extent of dyskinesia was measured. Data from unsmoothed outlines (n data) are depicted with **closed circles**. Data from smoothed outlines (c data) are depicted with **open circles**. All values are given as the mean ± 1 SD.

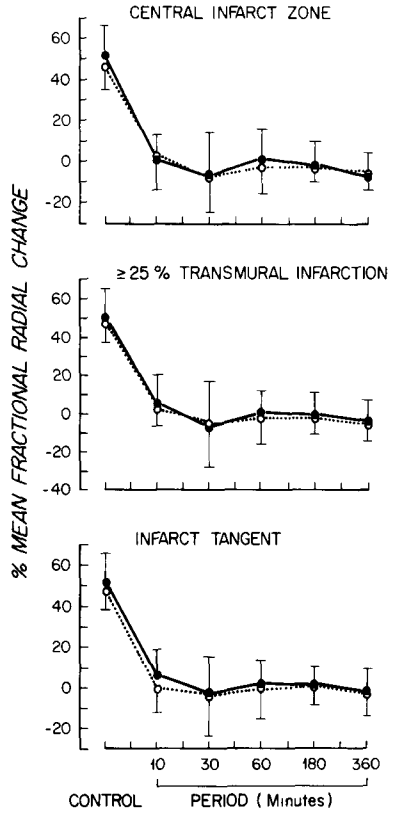

Figure 4. Mean zonal function (percent fractional radial change) in infarct zones over time. **Upper panel**, Central infarct zone; **middle panel**, zone with greater than 25% transmural involvement; **lower panel**, infarct tangent (entire infarct zone). Data indicated as in Figure 3.

41 ± 13% for periods one to six, respectively. Values obtained using the corresponding smoothed data were 4 ± 7%, 33 ± 12%, 45 ± 10%, 40 ± 7%, 41 ± 8% and 45 ± 13%, respectively. Regardless of the data set or the definition of wall motion abnormality employed, there was no statistically significant difference between the extent of abnormal wall motion in each postocclusion study period.

Magnitude of abnormal wall motion. The temporal course of the magnitude of wall motion within the five previously defined myocardial zones is depicted graphically in Figures 4 and 5. Motion within the central infarct zone, zone with greater than 25% transmural infarction, infarct tangent (total infarct) zone, border zones and normal (nonischemic) zone are each plotted as a function of time.

In the control period, there was no significant difference in mean fractional radial change between the different ventricular short-axis segments. From the control to the initial postocclusion (10 minute) study, however, a reduction in radial contraction was observed in each myocardial zone. For the central infarct zone, zone with greater than 25% transmural involvement, infarct tangent and border zones, this was significant at the $p = 0.01$ level. For the nonischemic zone, this decrease was not statistically significant.

Once established (by the 10 minute study period), the magnitude of abnormal wall motion did not vary significantly up to 6 hours after infarction. Although there was an initial trend toward improvement in the normal zone, this did not reach statistical significance. Similar patterns were obtained using either the unsmoothed "n" data or smoothed "c" data.

Circumference and area indexes. There was a statistically significant increase in the c data area and circumference indexes from the control period to 10 minutes after occlusion. There was no further change over the course of the study. Increases in the n data area and circumference indexes from the control to initial postocclusion study were of borderline significance ($p = 0.04$). No change was noted over the remainder of the study.

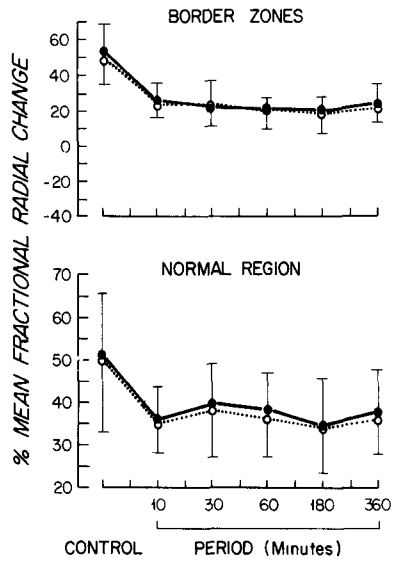

Figure 5. Mean zonal function (percent fractional radial change) in border zones (**upper panel**) and normal zones (**lower panel**) over time. Data indicated as in Figure 3.

Discussion

In this study, we employed rigorous quantitative methods to define the natural history of regional wall motion in the critical initial (6 hour) period after coronary occlusion. We have demonstrated that, once established (that is, at 10 minutes after occlusion), there is no significant change in either the circumferential extent or magnitude of abnormal wall motion over this period. This information, which has not been available from previous studies, provides a framework for assessing the functional effects of interventions, such as those aimed at infarct limitation.

Circumferential extent of abnormal wall motion. Our finding that the *circumferential extent* of abnormal wall motion is stable over 6 hours is in agreement with the study of Meltzer et al. (4) in which the endocardial extent of abnormal wall motion was assessed visually. They noted that, in the absence of interventions, there was no significant change in the extent of myocardial dysfunction at 20 and 40 minutes and 5 ½ hours after coronary occlusion. Their study was limited, however, in terms of its spatial resolution, because of the semiquantitative visual methods of analysis used and the somewhat arbitrary way in which regions with abnormal and partial abnormal motion were summed to derive a measure of "total abnormal motion." Furthermore, the study did not address the degree of dysfunction within and surrounding the infarct zone.

The method used in our study, on the other hand, is a rigorous quantitative one which examines wall motion at 10° increments around the circumference of the ventricle. This provides a description of radial wall motion with sufficiently high spatial resolution that even subtle changes in regional function should be detectable. Furthermore, it offers the advantage that the need for a highly trained observer has been eliminated by the use of previously validated computer-assisted methods of analysis.

In this study, the circumferential extent of abnormal wall motion was followed using three different definitions of abnormality. Of the three, we believe the correlation-based method to be superior. Indeed, in a previous report (19), it was demonstrated that this method correlates better with the triphenyltetrazolium chloride-defined extent of infarction than did methods based on only two points in the systolic contraction sequence. However, because such approaches continue to be widely used in both clinical and experimental echocardiography, two (end-diastolic–end-systolic fractional radial change <20% and maximal extent of dyskinesia) have been included. Because each method has different criteria for abnormality, the absolute values obtained for the circumferential extent of abnormal wall motion in each study period vary according to the method used. However, regardless of the approach, no significant change in the extent of abnormal wall motion was observed in the postocclusion study periods.

No previous echocardiographic study, other than that of Meltzer et al. (4), has attempted to follow the extent of abnormal radial wall motion after acute coronary occlusion. However, in agreement with our data, the echocardiographic study of wall *thinning* performed by Ellis et al. (22) demonstrated no significant change in circumferential extent of systolic thinning from 90 minutes to 6 hours after coronary ligation.

Magnitude of abnormal wall motion within infarct, border and normal zones. In this study, all regions of the canine ventricle demonstrated reduced radial shortening after coronary occlusion. Although significant impairment occurred in the infarct and border zones, the slight reductions noted in the regions remote from the site of coronary occlusion were not statistically significant. Once established, the degree of abnormal wall motion within individual zones did not vary significantly during acute follow-up (to 6 hours).

The abnormal function noted in infarct zones is an expected consequence of acute ischemic injury (23), and our observation that this decreased function is fully established by 10 minutes after ligation is consistent with previous studies (24,25). Furthermore, our demonstration that this appears to be stable over 6 hours is in agreement with the results of the sonomicrometer study of Theroux et al. (26) in which they found no significant change in systolic segment length percent shortening from 5 minutes to 2 hours after occlusion. It is also supported by the wall thinning data of Ellis et al. (22), who reported no significant change in the degree of central infarct thinning from 90 minutes to 6 hours after occlusion.

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The changes observed in the infarct border zones deserve further comment. Our observation that there is significantly reduced function in regions bordering on the histochemically defined zone of infarction is in keeping with previous observations that the extent of abnormal wall motion measured with two-dimensional echocardiography overestimates the extent of myocardial infarction (3,8–10). The same phenomenon, hypofunction of infarct border zones, has also been demonstrated with other experimental methods (24–28). The two major theories advanced to explain this malfunction are ischemia of the infarct border zones and mechanical tethering of such regions to adjacent infarcted myocardium. As discussed more fully in a previous communication (29), the data from this study favor the latter theory, in that although there was a postocclusion reduction in fractional radial change in border zones, there was no significant reduction in normalized blood flow in these regions (mean normalized blood flow in border zones = 91%).

Previous studies of the functional status of nonoccluded regions of the myocardium have yielded contradictory results, which may be related to differences in experimental animal preparation (open versus closed chest), vessel ligation or functional variable measured, or any combination of the three. Wyatt et al. (28), using mercury in Silastic length gauges to study the functional properties of regions remote from the site of experimental occlusion, demonstrated reduced systolic shortening within the first 30 minutes after occlusion. Similarly, Heyndrickx et al. (30) showed a tendency for a deterioration of function in the "normal" regions of conscious dogs with experimental left anterior descending coronary occlusion. In their study, animals with circumflex occlusion were, however, unaffected.

Other investigators have observed, as we did, that there is no significant early change in the function of normal zones. Using an open chest pig model, Heikkila et al. (31) found no significant change in systolic epicardial segment length shortening and transmural wall thickening in regions remote from the site of infarction. Similarly, Banka and Helfant (32) found minimal and inconsistent changes in preejection tension and epicardial segment length in the normal regions of open chest dogs undergoing left anterior descending coronary artery occlusion, and Komer et al. (27), in an M-mode echocardiographic study, found no change in wall thickening in regions remote from the site of occlusion. Using sonomicrometers in a chronic closed chest preparation, Theroux et al. (26) noted that although there was augmentation in function of control segments 1 week after left anterior descending coronary artery occlusion, at 5 minutes and 2 hours no significant change had occurred. These findings, therefore, are all consistent with the echocardiographic observations made in this study.

In contrast, Pashkow et al. (33) found significant increases in contractility in regions distant from the site of coronary occlusion in pigs. Similar observations were made by Kerber et al. (34) in an M-mode echocardiographic study of open chest dogs and by Theroux et al. (25,26) in sonomicrometer studies of open chest and conscious animals performed 2 to 5 minutes after coronary occlusion. More recently, Lew et al. (35) also demonstrated, with sonomicrometers, that there is an increased total segment shortening in nonischemic regions which appears to be due to an increase in isovolumic shortening with no change in ejection shortening. It should be noted, however, that the absolute changes noted in the sonomicrometer studies are small. Our inability to demonstrate such changes may therefore, in part, reflect the relative spatial resolution of sonomicrometers versus two-dimensional echocardiography.

Methodology: sources of false positive regional wall motion abnormality in control periods. The fact that small regions of control wall motion "abnormality" were detected when the maximal extent of dyskinesia or correlation analysis was used deserves comment. As there were no corresponding perfusion abnormalities at this time, these are considered false positive findings. With regard to the maximal extent of dyskinesia method, it should be pointed out that the majority of the false positive findings occurred in the n data set. We attribute this to a slight systolic shift in the registration of the papillary muscles that may occur despite our correction for rotation of the epicardial reference point. For example, the end-diastolic length of a ray intersecting a papillary muscle is relatively shorter than that of a ray that does not intersect. If, during contraction, there is rotation so that a ray that initially intersected a papillary muscle no longer does so, an artifactual increase in ray length (dyskinesia) will be perceived. This source of error is eliminated by the convex hull (smoothing) analysis. The remaining cases of control false positive findings identified by the maximal extent of dyskinesia method reflect small (-0.1 to -2.6%) early systolic negative fractional radial changes which we attribute to slight rearrangement of ventricular geometry during early systole.

Similarly, of the small number of rays identified as being abnormal in the correlation analysis, most were derived from the unsmoothed analysis of rays in the region of the papillary muscles. The fact that these were no longer identified as abnormal when the smoothed data were used supports our theory that they arise from a slight shift in the ray registration of the papillary muscles that may occur when there is systolic rotation. The motion of the 1% of control period rays considered to be "abnormal" regardless of whether n or c data were used fell between the 95 and 99% confidence limits. Statistically, it is not surprising that the analysis of 396 normal rays will yield this result.

Limitations. Left ventricular wall motion, as assessed by the endocardial excursion-based methods used in this study, is obviously dependent on ventricular loading conditions as well as myocardial contractility. It is thus important that no significant change in systemic blood pressure

occurred over the course of this experiment. Furthermore, no drugs such as inotropic or antiarrhythmic agents (which may have a negative inotropic effect) were employed. Had loading conditions or the pharmacologic milieu changed over the study period, it is possible that wall motion may have been less stable.

It should also be kept in mind that fraction radial change is a derived variable calculated simply as the

$$\frac{\text{End-diastolic radius} - \text{Systolic radius}}{\text{End-diastolic radius}}$$

Thus, it is a function not only of the endocardial excursion (end-diastolic radius − systolic radius) but of the absolute value of the end-diastolic radius. In these experimental animals, there was a slight increase in the midventricular cavity size (as estimated by area and circumference indexes) in all c data postocclusion studies versus the control. The n data showed the same trend but the change was of borderline significance. Although direct comparisons cannot be made, this is in keeping with the observations in previous studies that after coronary occlusion, end-diastolic endocardial (24–27), epicardial (31) and midwall (30) segment lengths acutely increase in nonishchemic as well as ischemic and border zones. In our study the reduced fractional radial change noted in the infarct regions and border zones was the result of both a decrease in absolute endocardial excursion and an increase in end-diastolic radius. On the other hand, the slight decrease in fractional radial change in the normal regions is due exclusively to an increase in end-diastolic radius, because there was no significant change in absolute endocardial excursion.

Although considerable effort was invested in duplicating our analysis with smoothed and unsmoothed data, neither the magnitude nor circumferential extent of abnormal wall motion was significantly affected by the choice of data set used. There was some justification, however, for our motivating concern that the unsmoothed data may generate artifactual wall motion abnormalities because, as previously discussed, there was more control wall motion "abnormality" (false positive) with the n than with the c data sets. We believe, therefore, that the inclusion of similar smoothing algorithms in programs for quantitative echocardiographic analysis is desirable.

Clinical implications. Unfortunately, despite the fact that the early postinfarction hours have been the focus of a number of interventions aimed at reducing infarct size, the clinical echocardiographic literature has, to date, not addressed this period. This is no doubt in large part due to the difficulty in obtaining echocardiographic studies so soon after an acute ischemic event. Thus, there are as yet no clinical studies with which to compare the data derived from our experimental canine model. Although it might be tempting to extrapolate from our study to the clinical setting, this must be done with caution. The canine model employed here is essentially one of single vessel coronary occlusion with a rich and uncompromised collateral bed. In contrast, the clinical myocardial infarction population is a heterogeneous group and includes a significant number of patients with multivessel disease or variable collateral coronary supply, or both. Thus, the functional sequelae of acute infarction in this group might vary from those observed in our model. Although a clinical study comparable with this canine study would be logistically difficult, the information derived from it would be invaluable.

Conclusions. We conducted a quantitative two-dimensional echocardiographic study of the natural history of both the circumferential extent and magnitude of abnormal wall motion in a canine model of acute myocardial infarction. In this preparation, once established at 10 minutes after occlusion, there is no significant change in the circumferential extent of abnormal wall motion over the initial 6 hours. Furthermore, after occlusion, there is a significant reduction in fractional radial change in infarcted and immediately adjacent regions of the ventricle which does not significantly change over the subsequent 6 hours. These data provide the necessary control information with which the functional effects of reperfusion and various pharmacologic interventions can be compared.

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