Serial Evaluation of Myocardial Thickening and Thinning in Acute Experimental Infarction: Identification and Quantification Using Two-dimensional Echocardiography

MARKKU NIEMINEN, M.D., ALFRED F. PARISI, M.D., JOSEPH E. O'BOYLE, B.S.,
EDWARD D. FOLLAND, M.D., SHUKRI KHURI, M.D., AND ROBERT A. KLONER, M.D., PH.D.

SUMMARY Regional left ventricular function was studied serially by quantitative two-dimensional echocardiography (2-D echo) in 20 dogs after left anterior descending coronary artery ligation. Normal values for regional myocardial thickening were established in 20 healthy dogs and used as a standard to recognize abnormally contracting segments (ACS). In normal hearts, the mean percent thickening tended to increase from base (25.8%) to apex (34.0%), but showed considerable diversity from segment to segment (range 20.0–40.0%); nevertheless, at least some degree of thickening was seen in every segment. After coronary occlusion, myocardial segments either thinned or failed to thicken. At the papillary muscle level, there was an improvement in function between 2 and 48 hours, with thinning at 2 hours and thickening at 48 hours. Tissue infarct size (IS) determined at 48 hours was related to IS derived from a weighted summation of ACS at 2, 24 and 48 hours. At 2 hours, ACS considerably overpredicted and correlated poorly with tissue IS (25.3% vs 13.4%; r = 0.60); by 48 hours, IS predicted by ACS had decreased to 15.3% (p < 0.05) and had an improved, but only fair correlation with tissue IS (r = 0.73, see = 4.9%).

We conclude that there is considerable heterogeneity to myocardial thickening by 2-D echo, but failure to thicken is not seen in the normal dog heart. In many dogs, the extent of myocardial dysfunction 2 hours after coronary occlusion exceeds that seen later. Tissue IS is difficult to predict accurately from ACS. Since the amount of muscle dysfunction is not necessarily equivalent to the amount of tissue necrosis in acute myocardial infarction, ACS may be more appropriately used to track the course of infarction rather than to predict IS.

USING M-MODE echocardiography, several investigators have shown the potential of ultrasonic examination of the heart in patients with myocardial infarction, preparing the way for advances in instrumentation.1–6 The application of two-dimensional echocardiography (2-D echo) to the problem of acute myocardial infarction (AMI) poses an important challenge to the clinical cardiologist. Reports have emerged that infarcted areas can be detected from left ventricular (LV) wall motion abnormalities present by 2-D echo.7,8 Most recently, several investigations suggest further that infarct size can be predicted, based on a comparison of the extent of wall motion abnormality to thallium-201 perfusion defects9 or to peak CK-MB serum enzyme activities.10 In a postmortem study the circumferential extent of infarct size correlated well with 2-D echo findings, even though infarct size was systematically overpredicted.11 Reports of using 2-D echo to size infarction in animal models have been more circumspect. Using an open-chest canine model, Lieberman et al.12 reported that the transmural extent of infarction has a nonlinear relationship to the extent of wall motion abnormality determined at 48 hours after coronary ligation. This was characterized by a “threshold” phenomenon, i.e., various degrees of transmural infarction in excess of 20% almost always produced 100% dysfunction.12 Pandian et al.13 made a preliminary report that 2-D echo overpredicts infarct size but underpredicts the total amount of tissue at risk.

The problem of infarct size determination is even more complicated in a clinical setting because early dysfunction (i.e., in the first 2–4 hours), rather than late dysfunction (after 24–48 hours), will be the focus of inquiry and possibly intervention. To simulate this sequence of clinical events, we produced AMI by coronary artery ligation in a series of experimental animals and performed serial closed-chest 2-D echo observations of regional myocardial function at 2, 24 and 48 hours after coronary occlusion. While tissue infarct size may be difficult to predict accurately, serial changes in regional myocardial performance assessed by thickening and thinning must be evaluated for their relevance to managing patients with AMI. All 2-D echo analyses were performed quantitatively using an extension of applications recently developed in our laboratory.14,15

Methods

Experimental Procedures

Mongrel dogs that weighed 15–20 kg were anesthetized with sodium pentobarbital (25 mg/kg) and screened by 2-D echo using a modification of the approach described by Wyatt et al. Each dog was imaged from the right side to obtain a long-axis view and three short-axis views at the levels of the mitral
valve leaflet tips, the midpapillary muscles, and cardiac apex immediately below the papillary muscles. Transducer position and rotation were adjusted to produce the most circular sections of the left ventricle in an attempt to obtain orthogonal short-axis sections. All 2-D echo studies were performed with a Varian V-3000 phased-array sector scanner and recorded on a reel-to-reel Panasonic NV3160 videotape recording system using Scotel 361 videotape. An ECG was simultaneously recorded. Of 54 dogs, nine (16.6%) lacked high resolution of their epicardial and endocardial surfaces on their 2-D echo exams. The remainder were evaluated in two groups: a control population and an infarct population.

All dogs of the infarct group were anesthetized with sodium pentobarbital (25 mg/kg) before surgery. The dogs were intubated, connected to a Harvard respirator, and ventilated with room air. A thoracotomy was performed through the fifth intercostal space, the heart was exposed, and the pericardium opened. The left anterior descending artery (LAD) was inspected and a site for ligation was dissected free from the myocardium. To produce variably sized infarcts, different ligation sites were used. Ligation sites included areas of the LAD after the first diagonal, after the second diagonal, and branches of the diagonals of the LAD. After occlusion of the artery, the chest wall was closed.

After 2 hours, 24 hours and 48 hours after ligation, the infarct population was studied once again by 2-D echo. After the 48-hour examination, the dogs were killed and histochemical studies of infarct size were performed.

Quantitative Analysis of the 2-D Echo Examination

In all quantitative analyses of echocardiograms, end-diastole was defined at the onset of the QRS complex and end-systole as the smallest image related to the last half of the T wave. Epi- and endocardial outlines of the 2-D echo examinations were traced at end-diastole and end-systole from stop-frame images on the screen of a high-resolution Conrac SNA-14/c monitor. In all instances, the outlines were confirmed by playing through preceding and succeeding beats using both real-time and slow-motion playback speeds.

The outlines were then entered into a computer system14, 17 with a light-pen video digitizer, an Electronics for Medicine VVF, and analyzed by a Digital Equipment Corporation PDP-11/05 computer using an extension of an approach to analysis of regional ventricular function.15 For each one of a diastolic-systolic pair of epicardial and endocardial outlines, the midpoint of the interventricular septum was indicated by the observer. This point was ascertained by identifying the intersection of the right ventricular anterior and posterior walls with the right side of the septum and then finding the distance halfway between them on the right ventricular endocardial surface of the septum (fig. 1). From this initial point, the point on the opposite LV lateral wall was found that divides the total left ventricle (myocardium plus wall) into halves of equal area. The midpoint of this initial bisecting line is determined and additional bisectors are constructed every 45° to divide each outline into eight octants (fig. 2). Systolic outlines were translated and rotated to be superimposed on the diastolic outline in such a manner that the centers and axes of each coincided. The area of myocardium of each octant was computed, and its mean thickness derived by dividing this area by the length of the midoictantal perimeter. This allowed the mean systolic thickness of each myocardial octant to be related to its diastolic counterpart. Percent thickening (%T), defined as thickness at end-diastole – thickness at end-systole ÷ (thickness at end-diastole) × 100, was then derived for each octant. Values less than 0% represent myocardial thinning.

The percentage of LV mass infarcted in a cross section was arbitrarily defined as (number of abnormal octants in the cross-section ÷ 8) × (estimated percentage of LV mass of the cross section). For this study, the mitral valve level image was calculated at 34.0% LV mass, the midpapillary level cross section as 47.8% LV mass, and cardiac apex as 18.2% LV mass. The latter figures of relative LV myocardial mass distribution were determined from appropriate sections of the isolated left ventricle in a series of 10 healthy dog hearts at postmortem examination. The total percentage of infarcted myocardial mass is the

Figure 1. Two-dimensional echocardiographic cross section of the left ventricle at the tips of the mitral valve. The arrows indicate the intersection of the right ventricular (RV) wall and the interventricular septum. The midseptal point (arrowhead) is half of the circumferential distance between the anteroseptal-RV junction and the posteroseptal-RV junction. Due to image degradation in still-frame image photography, the posteroseptal-RV junction is not as clear as in real-time imaging.
summed of all the cross-sectional infarct percentages in a particular study.

The reproducibility of this method of estimating infarct size was assessed by retracing the entire set of images from a series of 10 dogs with infarcts. The mean difference between paired observations in each dog was 4.9 ± 1.4% (± SEM).

Quantitative Determination of Tissue Infarct Size

After the dogs were killed, the chest was opened and the heart excised. The atria and the right ventricle were dissected away and the mitral valve was excised, leaving an isolated left ventricle. The left ventricle was cut in breadloaf fashion into 1-cm-thick slices. These slices were incubated for 15 minutes in triphenyl tetrazolium chloride (TTC) at 37°C. After TTC staining, the slices were dipped into 10% formalin to enhance the differences in color.

The epicardial and endocardial outlines of both the basal and apical sides of each slice were traced onto a transparent plastic sheet protected by a glass plate. The infarct area on each side was also traced within the myocardial borders. Then, each slice was weighed and the total LV weight was obtained by summation of the weights of each slice. Pathohistologic infarct size was determined by planimetering the area of the apical and basal side of each slice and the infarct areas contained on each side. The percentage of infarcted tissue of each slice was calculated as the average infarct areas divided by average total area of each side. Infarct weight of each slice was determined by multiplying slice weight with percentage of infarcted tissue. Summation of individual infarct weights of each slice divided by total LV weight results in infarct size as a percentage of LV weight.

Analysis of the data was performed on a Monroe 325 programmable calculator and a HP97 programmable calculator using standard statistical methods.

Results

The Normal Thickening Pattern

Figure 3 shows individual values and the mean percent thickening (± 2 SD) around the circumference of the ventricle derived from short-axis views in 20 dogs with infarcts. The mean percent thickening of infarcted tissue of individual values in 20 dogs with infarcts. The mean percent thickening of infarcted tissue of

![Diagram](http://circ.ahajournals.org/)

FIGURE 2. Diastolic-systolic myocardial short-axis outline pairs traced at the papillary muscle level. Continuous lines represent the epicardium and endocardium at end-diastole and dashed lines the same surfaces at end-systole; the arrow indicates the midseptum. (top left) Observation from a normal dog. (top right) Observation from dog 2 hours after coronary ligation. (bottom left) End-diastole from a normal dog separated into octants. (bottom right) End-systole from a normal dog separated into octants.

![Diagram](http://circ.ahajournals.org/)

FIGURE 3. Regional percent thickening (mean ± 2 SD) by octant for 20 healthy dogs; data from the mitral valve (MV) level short section, papillary muscle (PM) cross section, and the apex. The mean is depicted as a square at the center of the vertical ± 2 SD range line. Individual data points are plotted as solid circles to the right and left of the range. S = septal; PS = posteroseptal; P = posterior; PL = posterolateral; L = lateral; AL = anterolateral; A = anterior; AS = anteroseptal.
healthy dogs at the mitral valve, papillary muscle and apical levels. In no dog did the myocardium fail to thicken in any region and at any ventricular level. However, there was considerable heterogeneity in the degree of thickening from dog to dog, which accounts for a broad 2-SD range falling slightly below the zero level in a number of segments. The distribution of points in figure 3 also suggests considerable heterogeneity of thickening from region to region within the same dog. This was most apparent in the mitral valve cross section, with a 20% mean thickening in the septal region and 35% mean thickening in the anterior region.

In general, somewhat less variability was found at the apex than at the base of the heart. Concurrently, as the apex was approached, the mean percent thickening for all octants at that level increased, to 25.8% (range 20.0–34.9%) at the mitral valve level, 31.6% (range 28.8–38.4%) at the papillary muscle level and 34.0% (range 31.9–40.0%) below the level of the papillary muscles. Based on these specific observations, the lower limit of normal regional performance was taken as any value with thickening.

Effect of Coronary Ligation on Myocardial Thickening

Twenty-five dogs were subjected to coronary ligation; 20 survived for the initial 2-hour 2-D echo study, but only 16 survived for the 48 hours before sacrifice. High-quality, arrhythmia-free studies were obtained from 19 dogs at 2 hours, 13 dogs at 24 hours and 14 dogs at 48 hours.

The effects of ligation of the LAD on regional wall motion at 2, 24 and 48 hours are shown in figures 4–6, wherein the mean percent thickening/thinning of the infarct population is plotted in comparison to the control dogs. In all but one dog, one or more segments either thinned or failed to thicken in relation to the distribution of the LAD. Mitral valve level function did not significantly decrease from normal over the course of these three serial observations. In fact, compensatory hyperactivity was frequently seen in dogs with larger infarcts, accounting for some increased thickening in some mitral level octants. At the papillary muscle level, abnormal function was readily evident in anterior regions at 2, 24 and 48 hours. This was most pronounced at 2 hours, when four abnormally contracting segments (ACS) were detected in the infarct population (fig. 4), two of which demonstrated net thinning for the group as a whole. By 48 hours, only two of these four regions showed significantly depressed function (fig. 6) and the mean thinning for the group in anterolateral and lateral segments was replaced by mean thickening. The greatest amount of dysfunction was recorded at the cardiac apex, where in the infarct population as a whole, all segments deviated from the thickening pattern seen in the normal canine myocardium, with the most marked difference in anterior segments. Although these differences from normal persisted in the 24- and 48-hour observations, they became less pronounced at the papillary muscle level.

Correlation of Myocardial Thickening Patterns with Histologically Determined Infarct Size

Because of the heterogeneity of regional wall thickening in the normal ventricle, prediction of infarct size was based on summation of myocardial segments that either thinned or failed to thicken, since these contraction patterns were never observed in the normal canine heart. Figure 7 shows the relationship of total LV systolic dysfunction at 2 and 48 hours to the size of myocardial necrosis assessed by TTC after each dog was killed at 48 hours. At 2 hours, the mean 2-D echo infarct size was 25.3%, while the ultimate pathologic infarct size in these 19 dogs was 13.4%. In 16 of 19
five of 11 paired observations, infarct size was smaller between 24 and 48 hours. The mean 2-D echo infarct size was 25.3% at 2 hours, 17.6% at 24 hours, and 15.3% at 48 hours. Analysis of variance showed that this decrease over the three points in time was statistically significant (F = 3.54; p < 0.05).

**Discussion**

Our observations are consistent with a potentially salvageable dysfunctional border zone and accord with the postulates of several investigators who have made serial observations on evolving canine infarction by chemical and histologic criteria.

In assessing segmental myocardial thickening by dogs, the ultimate infarct size was overpredicted based on 2-D echo (fig. 7). One dog had no ACS identified by 2-D echo; however, on tissue examination this dog had a very small (1%) infarction. The correlation of 2-D echo to tissue findings was poor (r = 0.60, SEE = 5.9%). By 48 hours, the mean infarct size had decreased by 2-D echo (mean 15.3%) and correlation of infarct size by 2-D echo with histologic findings had improved (r = 0.73; SEE 4.9%).

Figure 8 shows the serial course of calculated infarct size by 2-D echo at 2, 24 and 48 hours after coronary ligation. In 10 of 13 instances of paired observations, infarct size became smaller between 2 and 24 hours; in
2-D echo in dogs, Pandian et al., also noted considerable heterogeneity in regional thickening in normal dogs. Consistent with their observations (as well as a limited number of observations from humans) is the finding that thinning is the hallmark of acute myocardial injury. If these abnormal areas are summed in order to estimate histologic infarct size by 2-D echo, infarct size at 2 hours is overpredicted considerably. Moreover, the overall correlation with 48-hour tissue infarct size is poor. By 48 hours, dysfunction detected by 2-D echo had a fair correlation with tissue infarct size \( r = 0.73 \). While the see for the echocardiographic observations was apparently low (4.9%), as a fraction of the tissue infarct size (15.3%), the estimating error is considerable, consistent with observations of Pandian et al. The results of other reports examining dysynergic areas by 2-D echo at 48 hours after coronary ligation have been mixed. Wyatt et al. reported that 2-D echo dysynergic areas correlated reasonably \( r = 0.87 \) with nitroblue tetrazolium infarct areas in 16 slices from five dog hearts. In contrast, Lieberman et al. found no correlation between the presence of systolic thinning and the transmural extent of infarction, and felt that this may preclude accurate estimation of infarct size by two-dimensional echocardiography. In these latter two studies, however, the total mass of infarcted myocardium was not predicted. In an earlier intervention study that involved a much wider range of tissue infarct size (up to 60%), Meltzer et al. reported a fair correlation \( r = 0.82 \) in 19 dogs between the extent of abnormal 2-D echo wall motion and infarct size 5/2 hours after coronary occlusion. In that study, infarct size was determined by technetium pyrophosphate scintigraphy and the approach to integration of 2-D echo wall motion abnormalities was different from ours. In addition to different timing of observations, some of their dogs received nitroglycerin and phenylephrine. The considerable variation in methods used in that study compared with ours precludes definitive statements about their differences.

Whether examination of humans with acute infarction will reveal comparable findings will not be known until further use of 2-D echo in emergency wards and coronary care units. The clinical findings of Weiss et al., that 2-D echo correlates well with, but overpredicts, infarct size, dealt with a large number of patients who were survivors of more remote infarction and of

**Figure 7.** Relationship of infarct size as determined by TTC staining at 48 hours and regional wall motion abnormalities by two-dimensional echocardiography (2 DE) at 2 hours (left) and at 48 hours (right). The regression equation (solid line) at 2 hours is \( y = 0.32x + 5.31\% \) \( r = 0.60, \text{SEM} = 5.86\% \). The regression equation at 48 hours is \( y = 0.60x + 6.35\% \) \( r = 0.73, \text{SEM} = 4.91\% \). The dashed line is the line of identity.

**Figure 8.** Changes in infarct size for individual dogs as determined by two-dimensional echocardiography (2 DE) as a function of time (hours after ligation). The mean infarct size at each hour is represented as an open square. The number of observations at each time is given in parentheses at the top. The dashed line indicates that the 24-hour 2 DE examination was not analyzed.
necessity had to characterize a number of hearts with myocardial scarring rather than acute necrosis, a situation not analogous to the early observations reported herein. Other 2-D echo approaches to the size of acute myocardial infarction have correlated indirect estimates using radionuclides and measurements of serum enzyme activities. Nixon et al. reported that 2-D echo scores made 2–4 days after admission correlated with thallium-201 (r = 0.87) and technetium pyrophosphate (r = 0.74) estimates of infarct size. Visser et al. reported a close linear correlation (r = 0.87) between visual 2-D echo estimates of myocardial infarct size 2–12 hours after onset of symptoms and enzymatic (CK–MB) estimates of myocardial involvement. In serial observations on 60 patients studied at <12, 48 and 72 hours after infarction they did not detect a significant change in the myocardial dyssynergic area.

Our data and those of others indicate that 2-D echo observations, particularly ones made in the first few hours after coronary occlusion, must be used with caution to extrapolate histologic or histochemically determined myocardial infarct size. This is not to say, however, that echocardiography cannot be used routinely to advantage in managing patients with acute myocardial infarction. Several groups have recently reported using regional dysfunction as a guide to detecting infarction. The value of the quantitative use of regional dysfunction awaits further clinical scrutiny. In particular, serial 2-D echo observations using initial findings made within the first few hours of symptom onset as a baseline guide to the extent of regional systolic dysfunction should be examined further. Noting the progress of segmental dyskinesia may provide an important hallmark of patient progress in the course of acute infarction.

References

17. Folland ED, Parisi AF, Moynihan PF, Jones DR, Feldman CL, Tow DE: Assessment of left ventricular ejection fraction and volumes by real-time, two-dimensional echocardiography. Circulation 60: 760, 1979
Serial evaluation of myocardial thickening and thinning in acute experimental infarction: identification and quantification using two-dimensional echocardiography.

M Nieminen, A F Parisi, J E O'Boyle, E D Folland, S Khuri and R A Kloner

Circulation. 1982;66:174-180
doi: 10.1161/01.CIR.66.1.174

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/66/1/174