CESIUM-129 MYOCARDIAL SCINTIGRAPHY TO QUANTIFY MYOCARDIAL INFARCTION IN DOGS

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The sizes of surgically induced acute myocardial infarctions were quantified in a study of 28 dogs. Four projections (right and left anterior oblique, anterior, and left lateral) were obtained with ^{129}Cs myocardial scintigraphy. Control images, taken before surgery, were compared with images taken 24–72 hr after coronary artery ligation. From postmortem examination the size of the infarct was determined and expressed as a percentage of the total left ventricle. On a standard diagram four independent observers marked the infarcted areas in each projection, expressed the severity of involvement in each area, and determined overall infarction size as a percentage of the total left ventricle. A nonlinear least-squares method was also employed to derive the size of the infarct, using the results from each observer's diagram. There were positive correlations between each observer's percentage estimate and the autopsy results. The overall accuracy of the least-squares method was similar to that of the individual observers. In this study, Observer 3 proved that acute myocardial infarcts can be quantified accurately from multiple scintigraphic projections of the myocardium, but the other three observers had difficulty in estimating infarct size. This difficulty probably resulted from the lack of well-validated criteria to aid the observer in determining the area of infarction, the severity of involvement within that area, or the total size of a myocardial infarct. Improvement in these estimates will require the development of definitive criteria, the use of optical scanners or computer processing, and combinations of radionuclides.

The need for a noninvasive means of quantifying myocardial infarctions was apparent from the report of Page et al (*1*) that the size of the acute myocardial infarction in patients who died in cardiogenic shock was greater than 40% of their myocardium. Such a diagnostic procedure would allow earlier medical and surgical intervention in patients with large myocardial infarcts. Such a procedure would also permit the evaluation of various therapeutic regimens reported to decrease infarct size in experimental animals (*2*). Previous approaches to the quantification of myocardial infarction have included the use of radionuclides (*3–6*), total CPK and the specific MB-CPK isoenzyme (*7,8*), ST-segment mapping (*9*), and echocardiography (*10*).

We have previously reported the use of ^{129}Cs myocardial scintigraphy for the detection of myocardial infarction (*11*). Cesium-129 localizes in the normal myocardium but is not taken up by the infarcted area, thereby visualizing the infarct as a "cold" area. The present study sought to evaluate the accuracy of observers and to compare their estimates with a computer technique for quantification of acute infarct size, determined at postmortem examination, in dogs. To our knowledge there has been no previously reported systematic blind study designed to evaluate subjective quantification of acutely infarcted myocardium from multiple scintigraphic projections.

MATERIALS AND METHODS

The cesium-129, produced at the Cyclotron Facility of the Naval Research Laboratory in Washington, D.C., by the bombardment of sodium iodide targets through the $^{127}I(\alpha,2n)$ reaction, was separated from the dissolved target by the method of Sodd et al (*12*). Images were obtained 30–90 min after intra-

Received July 26, 1975; revision accepted Sept. 30, 1975.

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venous administration of 3–4 mCi of ^{129}Cs in dogs weighing 20–25 kg. Images were taken with a scintillation camera and a coarse pinhole collimator with an energy setting of 360 keV and a 35% window. Each view, involving 200,000 counts, required 5–8 min. Four projections of the heart (right anterior oblique, anterior, left anterior oblique, left lateral) were obtained in each dog before and after coronary artery ligation.

One week before intervention control myocardial images were obtained for each of 28 mongrel dogs. Myocardial infarctions were produced by two-stage ligation of a coronary artery. To produce infarcts of different sizes, ligations were carried out at various levels along the anterior descending or circumflex coronary arteries. In an effort to produce large infarctions, some dogs underwent ligation of both coronary arteries on separate occasions. Myocardial images were obtained 24–72 hr after ligation.

One week after the surgically induced infarction, the dog was killed and the heart placed in formalin. After fixation for 1 week the size of the myocardial infarction was determined (postmortem estimate) as follows. The atria, right ventricle, and any epicardial fat were removed. The aorta was removed at the level of the aortic valve. The left ventricle was weighed and then cut in breadloaf fashion into sections at 5-mm intervals. The size of the infarct was estimated visually in each section and then expressed as a percentage of the total left ventricle. The infarcted area was then excised and weighed separately. This weight was expressed as a percentage of the weight of the left ventricle. The final estimate was obtained by averaging the results from the breadloaf and weighing techniques. The percentages determined by these two methods did not differ by more than 5% in any of the 28 dogs.

The scintigrams were interpreted independently by four observers. The sets of scintigrams for each of the 28 dogs were blinded (except for the designation of before or after surgery) and randomized from 1 to 28. Using standard diagrams which divide each projection into seven areas (Fig. 1), the observers identified the area of infarction and estimated the severity of involvement within each subarea (to the nearest 25%) in each of the four projections. From the estimate in each projection, the observers then estimated the overall size of the infarct as a percentage of the left ventricle.

Since no criteria have been established for observer estimates of infarct size, a least-squares technique was used in an effort to make the estimates more objective. First, each projection was assigned the arithmetical average of the severity gradings for the seven subareas of that projection. Since concentrated regions of infarction were not expected to localize in the same projections for each case, the estimates were arranged in descending order as $x_1 \geqq x_2 \geqq x_3 \geqq x_4$ for the four projections. A least-squares estimate was applied after this ordering procedure to determine coefficients a_0, a_1, a_2, a_3, a_4 such that the overall percentage infarction equalled $a_0 + a_1x_1 + a_2x_2 + a_3x_3 + a_4x_4$. These coefficients were obtained from a test set of data in which the autopsy results

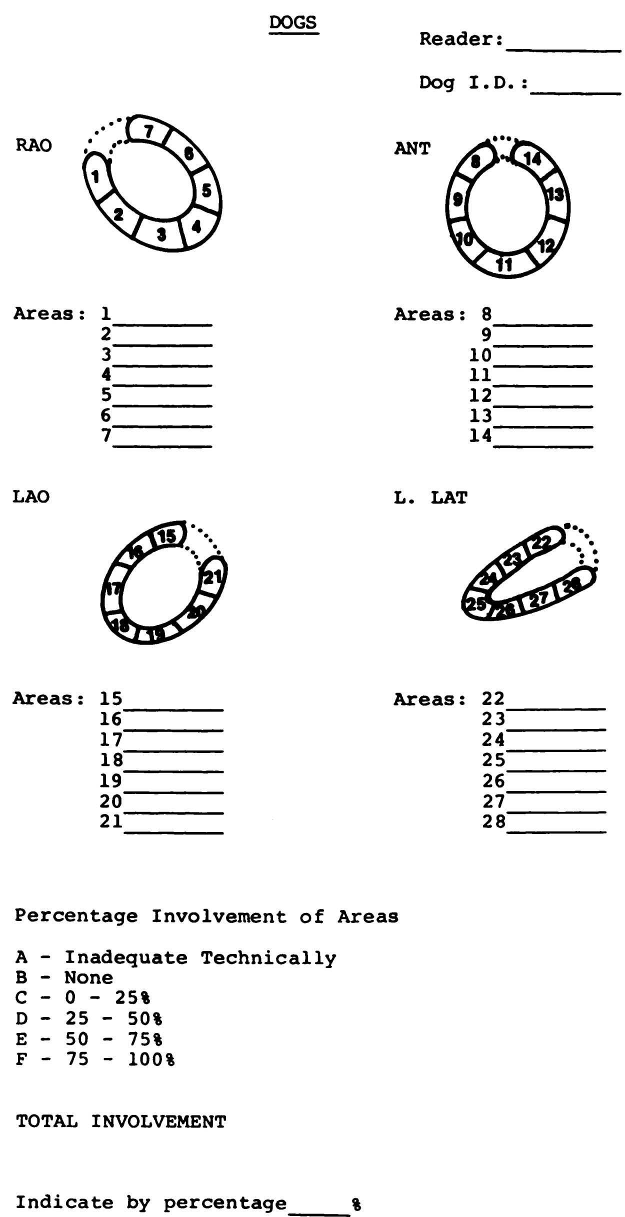

FIG. 1. Myocardium in each projection was divided into seven areas. Each observer marked areas of involvement in each view and graded severity of involvement in each of 28 areas. Each observer then estimated total percentage of left ventricular involvement.

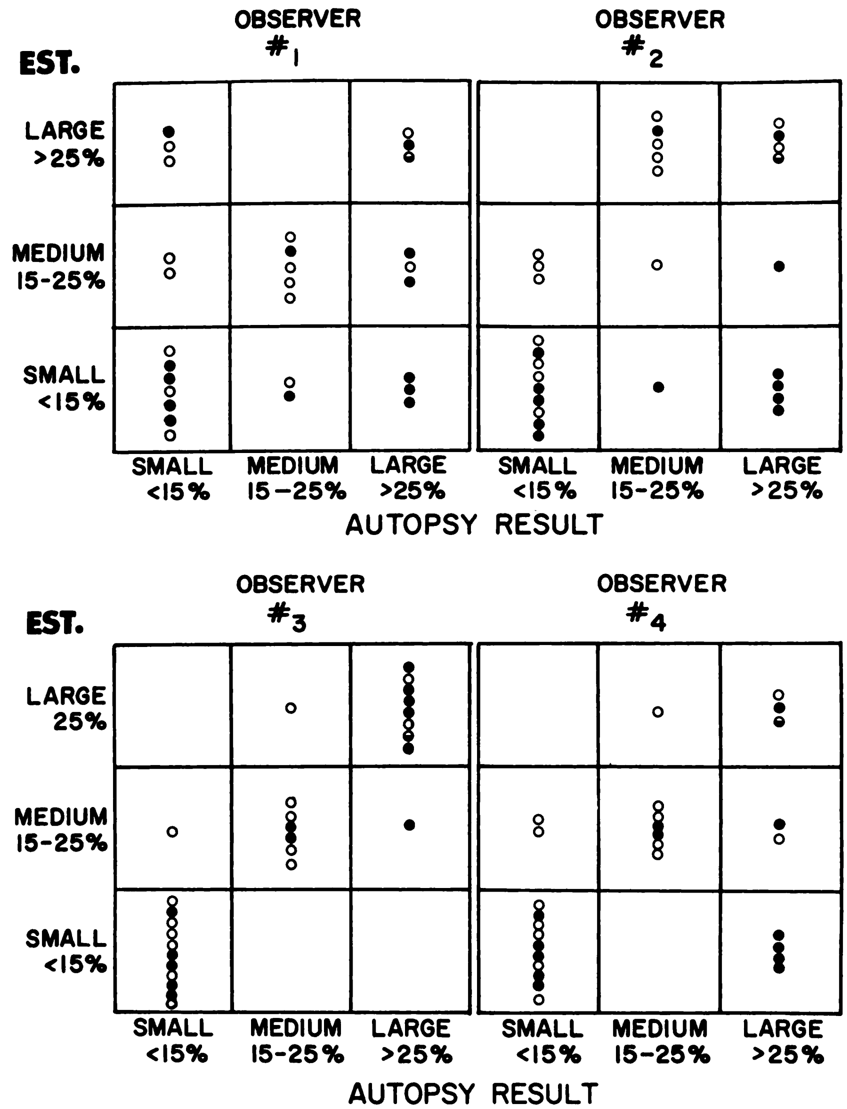

FIG. 2. Myocardial infarctions were classified as small, medium, and large. Graph correlates each observer's estimate of infarct size with postmortem measurements. Infarctions were also identified as anterior or posterior: open circle, anterior; closed circles, posterior; half-open circles, combination.

were entered as part of the data. Coefficients for a quadratic solution were also applied where the postmortem percentage equalled

$$b_0 + \sum_{i=1}^{4} (b_i x_i + c_i x_i^2),$$

where the b_i and c_i were coefficients derived from a set of test data. The purpose of this computer approach was to combine objectively the observers' evaluation of each of the four projections into a single composite percentage of infarction.

Each observer's estimate and the percentage estimate obtained from the least-squares method were correlated separately with the postmortem infarction percentage. In addition, the infarctions were classed as small (<15%), medium (15–25%), and large (>25%) and each observer's estimate was correlated with the postmortem figure as to small, medium, or large. If the observer's estimate fell exactly on the border between small and medium (15%) or medium and large (25%), it was placed in the correct autopsy category (Fig. 2).

RESULTS

A wide range of positive correlations was obtained with each observer's estimate of infarct size: Observer 1, $r = 0.22$, $p = NS$; Observer 2, $r = 0.43$, $p < 0.03$; Observer 3, $r = 0.92$, $p < 0.0001$; Observer 4, $r = 0.32$, $p < 0.1$ (Table 1). Positive correlations were also present for each observer using the result of the least-squares method to calculate the size of the infarct: Observer 1, $r = 0.32$, $p < 0.1$; Observer 2, $r = 0.44$, $p < 0.02$; Observer 3, $r = 0.57$, $p < 0.01$; Observer 4, $r = 0.20$, $p = NS$. The least-squares calculation improved the estimates of Observers 1 and 2 but decreased the corre-

TABLE 1. SIZE OF INFARCTION ESTIMATED BY EACH OBSERVER

Dog No.	Location	Pathology	Observer 1	2	3	4
1	Anterior	18.60	18.0	30.0	22.5	15.0
2	Anterior	7.40	9.0	8.0	7.5	5.0
3	Posterior	34.95	5.0	14.0	25.0	10.0
4	Posterior	11.55	28.0	14.0	10.0	10.0
5	Anterior	14.65	18.0	18.0	15.0	15.0
6	Anterior	18.00	10.0	15.0	15.0	20.0
7	Anterior	25.50	33.0	28.0	25.0	25.0
8	Anterior	12.65	23.0	12.0	10.0	15.0
9	Posterior	18.15	16.0	35.0	25.0	20.0
10	Anterior	9.95	30.0	24.0	15.0	20.0
11	Anterior	11.10	41.0	14.0	17.5	15.0
12	Posterior	11.20	12.0	10.0	15.0	10.0
13	Posterior	29.45	6.0	10.0	22.5	5.0
14	Posterior	16.45	12.0	14.0	15.0	15.0
15	Posterior	27.45	21.0	18.0	25.0	15.0
16	Posterior	4.80	7.0	8.0	7.5	5.0
17	Posterior	27.80	14.0	8.0	25.0	10.0
18	Anterior	12.15	11.0	12.0	15.0	10.0
19	Posterior	5.85	4.0	10.0	7.5	5.0
20	Posterior	27.75	42.0	35.0	30.0	30.0
21	Anterior	41.55	17.0	32.0	32.5	20.0
22	Anterior	18.30	24.0	40.0	25.0	35.0
23	Anterior	18.00	25.0	28.0	22.5	25.0
24	Posterior	3.70	4.0	8.0	5.0	15.0
25	Combined	45.40	34.0	32.0	45.0	25.0
26	Anterior	10.20	11.0	18.0	12.5	15.0
27	Posterior	31.90	16.0	12.0	27.5	10.0
28	Anterior	23.95	20.0	30.0	27.5	20.0

lation for Observers 3 and 4. Although Observer 3 had the highest correlation with either method of size estimation, the correlation coefficient decreased from 0.92, using the individual estimate of infarct size, to 0.57, using the least-squares method.

Each observer correctly identified most infarctions as either anterior or posterior. The following correct percentages were obtained: Observer 1, 89%; Observer 2, 100%; Observer 3, 100%; Observer 4, 96%.

Positive correlations were higher between the four observers' estimates of infarct size than between an individual observer's estimates and postmortem estimates. The correlation between observers' estimation of infarct size was lowest between Observers 1 and 3 ($r = 0.43$, $p < 0.03$) and highest between Observers 2 and 4 ($r = 0.86$, $p < 0.001$).

The division of the infarcts into small, medium, and large revealed that Observer 3 again had the best correlation with the postmortem estimates (Fig. 2). Observers 1, 2, and 4 had considerable scatter in the large-infarct group. These three observers all underestimated infarctions in the same five dogs (Nos. 3, 13, 15, 17, and 27), all involving ligations of the circumflex coronary artery, which resulted in an inferior posterior infarct (Fig. 3). In addition, Observer 1 had some scatter in the interpretation of small infarcts, and Observer 2 had considerable scatter and overestimation of medium-sized infarcts.

When the infarcts were classed as anterior and posterior, the correlation coefficients for Observers 2 and 4 were higher for the quantification of anterior infarcts (Observer 2, $r = 0.63$; Observer 4, $r = 0.43$) than for posterior infarcts (Observer 2, $r = 0.27$; Observer 4, $r = 0.21$). Despite his underestimation of the posterior infarcts, Observer 1 had a higher correlation coefficient for posterior infarcts ($r = 0.27$) than for anterior infarcts ($r = 0.04$). There was no difference in the estimation of anterior or posterior infarcts by Observer 3.

DISCUSSION

In this study Observer 3 showed that it is possible to quantify myocardial infarcts accurately by myocardial scintigraphy. This observer had the most experience in interpreting myocardial scintigrams. Although the other three observers were able to localize the area of infarction, they had difficulty estimating its size. At this time there are no established criteria to aid an observer in estimating the area of infarction, the severity of involvement within that area, or the total percentage of myocardial infarction. Thus, each observer was forced to make these estimates subjectively, which probably explains the wide variation in accuracy.

The least-squares method was employed to try to improve the estimates for total percentage of the myocardial infarction. This process avoided making the individual observers estimate the total percentage of infarction and relied only on their estimate of the area of infarction and the severity of involvement within that area. The disadvantage was the lack of established validity of the least-squares method for determination of infarct size, which introduced another source of potential error. The overall accuracy of the least-squares method to predict infarct size was about the same as the overall ability of the observers.

Myocardial ischemia or hypoxia or both have been shown to cause decreased or absent uptake of potassium or potassium analogues when these are used for myocardial scintigraphy (*13,14*). It is possible that an ischemic zone was present at the time of imaging but had resolved before the dog was killed 1 week later. If an ischemic zone was present, interfering with the estimate of infarct size, then the observers should consistently overestimate the size. Since this did not occur, it is unlikely that an ischemic zone contributed significantly to the difficulties of size estimation.

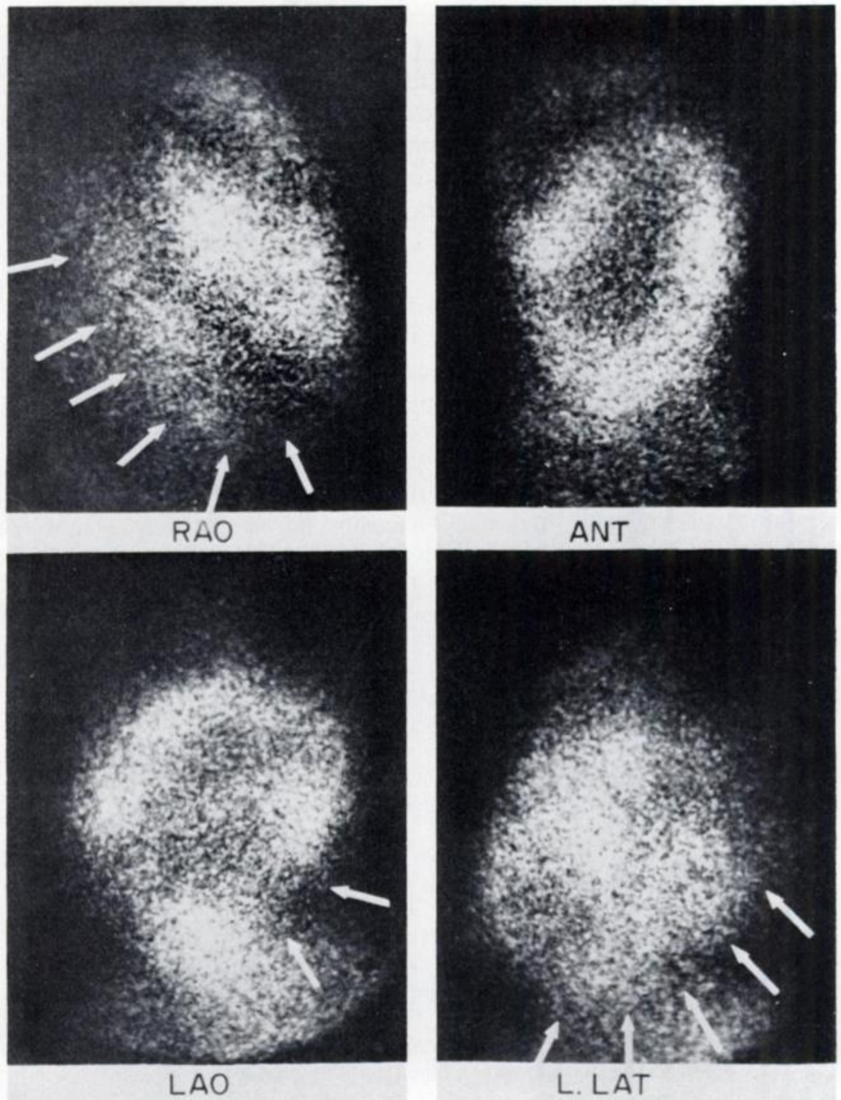

FIG. 3. Myocardial scintigrams of dog (No. 15) with large posterior myocardial infarct that Observers 1, 2, and 4 underestimated. Infarct involved entire posterior wall and measured 27.5% of left ventricle at postmortem examination.

The observer estimate of infarct size was more accurate for small and (with the exception of Observer 2) for medium infarcts than for large. Observers 2 and 4 were considerably more accurate in their estimates of anterior infarcts than posterior. Observers 1, 2, and 4 each underestimated the size of the infarcts in the same five dogs with large inferior posterior infarcts due to ligation of the circumflex coronary artery (Fig. 3). The inferior posterior wall is the most difficult myocardial area to image, and this may also have caused some difficulties.

The underestimation of large infarcts is of concern since patients with large infarcts develop shock and congestive heart failure (*1,15*). This group of patients could potentially benefit from the early recognition of a large infarct through noninvasive myocardial scintigraphy. However, development of shock and congestive heart failure with acute infarction is considerably more common in patients with anterior-wall than with inferior-wall infarction (*16,17*). The septum, anterior wall, lateral wall, and apex are easier to image and large infarcts in these areas were recognized accurately by the observers.

There are several approaches that should improve the scintigraphic estimation of infarct size. Observers will gradually acquire more experience in the interpretation of myocardial scintigrams. Also, the development of definite criteria for infarct sizing should improve observer accuracy. However, more objective methods will probably be needed. In this study the use of a nonlinear least-squares method to combine information from the four projections was an attempt in this direction. A more rigorous three-dimensional reconstruction with projections at every 10–15 degrees may improve the estimate of infarct size.

The use of optical scanners or computer processing to detect areas of involvement and degrees of severity within such areas, as has been reported for regional myocardial perfusion studies (*18,19*), should also lead to improvement in the estimate of infarct size. In addition, radionuclides that are actively taken up by the infarcted myocardium are now available for clinical use (*20,21*). Initial studies with ^{99m}Tc-pyrophosphate and computer quantification of infarct size in dogs report good correlation with postmortem determinations (*22,23*). A combination of images using an agent that is actively taken up by the infarcted myocardium with an agent that is not taken up by infarcted or ischemic myocardium should improve the delineation of infarct borders.

ACKNOWLEDGMENTS

This study was supported in part by NIH Contract NHLI 71-2489, by the Myocardial Infarction Program of the National Heart and Lung Institute, and by the Southwestern Ohio Heart Association. Dr. Levenson was supported by VA Training Grant TR-200.

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