DIGITALIS is commonly used early in the treatment of congestive heart failure complicating acute myocardial infarction despite scant evidence in support of such therapy. Although some clinicians, since 1912, have recommended the use of digitalis after myocardial infarction, its use in acute myocardial infarction is controversial. Results from animal studies, performed mostly in dogs with normal hearts before experimental myocardial infarction, have been conflicting. The net effect of digitalis on the relation between myocardial oxygen supply and demand remains unclear. By its inotropic action, digitalis increases myocardial oxygen demands; concurrently, it may limit oxygen supply by direct coronary vasoconstriction. Conversely, by decreasing ventricular chamber size, digitalis may decrease myocardial oxygen requirements and improve oxygen delivery to the subendocardium by reducing left ventricular (LV) filling pressure. While it appears possible to limit the extent of myocardial infarction with digitalis in experimental animals in congestive heart failure and in conscious animals not in failure, experimental evidence in open-chest animals suggests that digitalis may be deleterious to ischemic regions in the nonfailing heart.

With the development of acute phase independent descriptors of myocardial infarct size and ventricular performance in man, it appears possible to assess the effect of pharmacologic intervention during the acute phase of myocardial infarction.

Although there is still no standard method for quantitating infarct size in living patients, enzymatic estimates of infarct size in studies from several centers have correlated with biochemical and morphologic analyses of the myocardium in experimental animals and with morbidity, mortality, contrast angiographic assessment of infarct size and histochemical assessment of necrosis in patients. Estimates have been improved by quantifying the CK-MB isoenzyme. Although some controversy exists as to the validity of CK infarct sizing when the mathematical model is extrapolated to patients with acute myocardial infarction, extensive data by Sobel and associates in experimental animals and man indicate that serum CK systems have at least qualitative validity in assessing the magnitude of myocardial destruction.

There is evidence that radiouclide-gated blood pool wall motion and thallium-201 (TI-201) perfusion scintigrams are useful descriptors to estimate LV performance and infarct size, respectively, during acute myocardial infarction. Coromilas et al. reported a reasonable inverse correlation between CK-MB infarct size and LV radionuclide ejection fraction (EF) in patients with neither right ventricular infarction nor prior myocardial infarction. Certain animal studies have shown a linear relationship between TI-201 distribution and both regional
myocardial blood flow and CK depletion. A study by Wackers et al. demonstrated a correlation \( r = 0.72 \) between postmortem infarct size and infarct area determined scintigraphically with TI-201 before death.

In this report we describe radionuclide and enzymatic assessment of LV infarct size and LV function in patients with acute LV myocardial infarction and the effect of digitalis upon these independent descriptors of myocardial infarction.

Methods

Clinical Studies

The study population was composed of consecutive patients admitted to the coronary care unit of North Shore University Hospital from December 1978 through September 1979 who satisfied the following inclusion criteria: (1) acute myocardial infarction confirmed by rise and fall of CK-MB serum isoenzyme; (2) admission within 6 hours of the episode of most severe chest pain; and (3) the presence of at least two of the following findings indicative of congestive heart failure: early diastolic gallop (S3), moist rales, abnormal neck vein distention, and signs of pulmonary venous hypertension on an upright chest radiograph.

Excluded from the present study were patients with: (1) pulmonary edema or cardiogenic shock; (2) significant hypertension, defined as a diastolic blood pressure greater than 90 mm Hg on two or more occasions before acute myocardial infarction, or use of antihypertensive drug therapy at any time; (3) valvular heart disease; (4) electrocardiographic evidence or history of prior myocardial infarction; and (5) presumed right ventricular infarction. We previously reported a group of patients with a right ventricular component to their myocardial infarction. In this group, right ventricular EF, as determined by gated blood pool scintigraphy, was one-half or less of the LVEF, and enzymatic infarct size did not correlate with LVEF or %ACR. Hence, patients with right ventricular infarction were excluded from the present study.

Informed consent was obtained. Immediately after the first radionuclide assessment, patients in the digitalis group received 0.5 mg of digoxin followed 6 hours later by 0.25 mg. Both dosages were given intravenously; the first dose was given 18.0 \( \pm \) 23.0 hours (mean \( \pm \) sd) after the rise of CK-MB serum isoenzyme from baseline. The following morning each patient was placed on a daily oral maintenance dose of 0.25 mg of digoxin. Concurrent controls who received furosemide were nonrandomly assigned and basically formed a separate group in which the stability and reproducibility of repeat radionuclide assessments were determined.

Enzymatic Assessment of Infarct Size

After informed consent was obtained, a percutaneous polyethylene catheter was positioned in an antecubital vein for serial sampling of blood every 2-6 hours for CK determination; sampling was discontinued when serum CK-MB returned to baseline. Venous blood samples were collected in tubes containing sodium EDTA and centrifuged immediately at 10,000 rpm for 10 minutes at 4°C; the sera were frozen at −70°C. Studies showed that CK-MB isoenzyme activity remained stable for up to 1 month under these conditions.

CK-MB isoenzyme activity was separated from sera by DEAE-Sephadex column chromatography using minicolumns (Roche Diagnostics). Total serum CK activity was determined according to Rosalki, as were CK-MM and CK-MB isoenzyme activities of the column eluates. The coefficient of variation of replicate assays for CK-MB was 4.0%. Completed infarct size was calculated from all available serial CK-MB data by use of the mathematical model described by Sobel and associates. The enzyme clearance rate for each patient was estimated from a computerized mathematical inspection of CK-MB vs. time plot at those times when myocardial enzyme release was zero. Enzyme clearance rate values were then used to calculate infarct size.

Quantitative Radionuclide Angiography

Multiple gated blood pool acquisition imaging was accomplished with a mobile Anger scintillation camera (Searle Radiographics Inc.) interfaced with a PDP 11/34 computer with 48K memory (Digital Equipment Corp.). Wall motion algorithms were modifications of those described by Green et al. and Maddox et al.

Wall motion studies were performed with the patient in the 45° left anterior oblique position, with a 15° caudal tilt to the camera head and with the ventricular septum in vertical alignment on the video display of the computer. According to the procedure of Pavel et al., with minor modifications, patients received an initial antecubital i.v. injection of 7.7 mg of stannous pyrophosphate (Malinkrodt) in 1 ml of physiologic saline, followed 20 minutes later by 20 mCi of technetium-99m pertechnetate (Union Carbide). Data collection, in the gate synchronized mode, was begun 10 minutes after administration of the radionuclide.

Scintillation X-Y coordinates were sorted additively into 21 64 \times 64 \text{ matrix frames after each R wave for approximately 900 cardiac cycles. The time interval per frame was determined independently by the computer from the initially recorded RR intervals. Data collection continued until 8 million counts had been accumulated (20,000-40,000 counts per frame within the region of interest). A time-activity curve was generated from the 21 frames and the end-systolic and end-diastolic frames were identified. A LV region of interest was defined with a user-dependent, irregular region-of-interest program. An automated computer macroalgorithim was then used to find the greatest vertical and horizontal dimensions of the region of interest and to construct the associated rectangle by which it would be circumscribed. The circumscribing rectangle was divided into eight segments...
and superimposed on the region of interest. Portions of the rectangle that were outside the region of interest were erased. Three rectangular background areas were defined by computer and placed at the region of interest’s lateral, septal and apical sides. For each study, a global EF value, as well as EFs for each of the eight regions, was generated from global and regional time-activity curves. Using similar computer algorithms, gated regional wall motion analysis of the right ventricle was also performed.

The percent of abnormally contracting regions (%ACR) was calculated from the eight regions of the left ventricle. In patients with a history of angina and without prior myocardial infarction who were free of pain at the time of sequential regional wall motion assessments, one standard deviation of the mean EF for any given region of the left ventricle never fell below 0.40. Hence, in patients with acute myocardial infarction, any LV region with an EF below 0.40 was scored as abnormal.

In 12 hospitalized patients with healed prior myocardial infarction and EFs below 0.40, the reproducibility of the LVEF was assessed. The coefficient of variation for replicate EFs obtained 3 or more days apart in each patient was 3.5%.

Right Ventricular Infarction

We previously reported a group of patients with a right ventricular component to their myocardial infarction. In this group, right ventricular EF determined by gated blood pool scintigraphy was one-half or less of the LVEF, and enzymatic infarct size did not correlate with LVEF or %ACR. Hence, patients with right ventricular infarction were excluded from the present study.

Left Ventricular Perfusion

TI-201 scintigraphy was performed 30 minutes after the intravenous injection of 1.8–2.4 mCi of TI-201 (New England Nuclear), immediately before gated blood pool acquisition imaging. Analog images were obtained by the scintillation camera and digitized by the computer. Images were collected in the zoom mode and presented on a color video scope (Conrac) for data analysis. A low-energy, high-resolution, converging-hole collimator was used on the camera. Anterior and left anterior oblique projections at 15° and 45° and the left lateral projection were obtained with 500,000 counts per view in a 128 × 128 matrix. The perfusion scintigrams were enhanced with a nine-point computer smoothing technique before data analysis. With algorithms, the perimeter of the myocardial image was circumscribed in a regular region and all matrix cells outside of this region were changed to zero counts. The minimum count within the regular region circumscribing the left ventricle was considered as background and then subtracted from each cell in the matrix.

LV perfusion scintigrams were presented on a video scope in 16 levels of color gradation. Seven equal square regions were drawn to fit the left ventricle on each projection. On each projection, the region with the highest count density was used as a relative index of normal to compare with the other six regions. Counts in each region were subtracted from the region with highest count density, and the percent perfusion in each region was determined as:

\[
\frac{A \text{ (highest)} - B \text{ (another region)}}{A} \times 100
\]

Deficits greater than 20.5% perfusion were considered abnormal. A mean value of all abnormal percent regional perfusion scores from the four views was determined and this value was considered the "percent abnormal perfusion."

Scintigrams were also scored as to the number of abnormal regions (X) in all views obtained.

\[
\frac{X}{28} \times 100 = \% \text{ abnormal area}
\]

Using percent abnormal perfusion and percent abnormal area, a LV TI-201 "perfusion index" was calculated.

In 12 patients with healed prior myocardial infarction, the reproducibility of the computer-generated TI-201 perfusion index was assessed. The coefficient of variation of replicate TI-201 perfusion indexes, obtained 3 or more days apart in each patient, was 3.0%.

Ventricular Premature Complex Quantitation

All study patients were placed on a computerized (PDP 11/34) ventricular premature complex (VPC) quantitation system (Electronics for Medicine) upon admission to the unit. In this system, VPC detection is based on complex prematurity, morphology, compensatory pause and multitemplating. In each patient these criteria were manually edited. We have previously reported the accuracy rate of this system at 94.2%, with a false-negative rate of 8.8% and a false-positive rate of 4.5%.

Serum Digoxin Levels

Serum digoxin levels were obtained at the second radionuclide study. Samples were assayed in duplicate by radioimmunoassay, as previously described.

Statistics

Linear correlations were found by the method of least-squares analysis. Paired and nonpaired t tests were used to assess differences between groups of data; comparisons between multiple groups of data were carried out by analysis of covariance. Data are expressed as the mean ± sd.

Results

Clinical, Enzymatic and Radionuclide Angiographic Data

Twenty-three patients (table 1) admitted during the study interval satisfied the study criteria. Of these,
nine patients served as controls, while 14 patients received intravenous digoxin after initial radionuclide assessments. While the controls basically form a separate, nonrandomly selected group, certain similarities to the digoxin group were present. Thus, CK-MB release curves showed a mean infarct size of 59.9 ± 45.7 CK-MB-g-Eq in the controls and 69.8 ± 32.8 CK-MB-g-Eq in the digoxin-treated group (p = NS). In the controls the mean initial LVEF was 0.33 ± 0.12 vs 0.29 ± 0.09 in the digoxin group (p = NS). In the controls the mean time from the rise in serum CK-MB from baseline to the first radionuclide assessments was 21.2 ± 41.5 hours, compared with 18.0 ± 23.0 hours in the digoxin group (p = NS); corresponding mean times for the second radionuclide assessments were 92.7 ± 73.4 hours for controls and 129.3 ± 123.1 hours for the digoxin group (p = NS). The two groups were also similar with respect to mean age, myocardial infarction classification, and location of infarction.

Radionuclide Ejection Fraction and Regional Wall Motion vs Enzymatic Estimates of Infarct Size

In the 23 patients in this study, the initial LVEF and enzymatic infarct size were correlated. \( r = -0.73 \), fig. 1). In these same patients there was a correlation between % ACR and enzymatic infarct size \( r = 0.71 \), fig. 1). We previously reported similar correlations between LV wall motion and CK-MB release data in a separate group of patients with neither prior myocardial infarction nor right ventricular infarction.23

Left Ventricular TI-201 Perfusion Data

TI-201 perfusion scintigrams were obtained at the first wall motion study in eight of nine controls and in 13 of 14 patients in the digoxin group. The mean initial TI-201 perfusion index was 18.2 ± 8.8 in controls and 29.2 ± 6.2 in the digoxin group (p = NS). TI-201 perfusion scintigrams were obtained at the second wall motion study in five of nine controls and 12 of 14 patients in the digoxin group. The mean second TI-201 perfusion index in the controls was 19.8 ± 10.8 and 24.9 ± 8.7 in the digoxin group (p = NS).

Serum Digoxin Levels

The mean digoxin level was 0.9 ± 0.2 ng/ml in serum samples \( n = 14 \) drawn at the time of the second radionuclide studies. Serum samples were obtained 23 ± 2 hours (range 21–26 hours) after the last administered dose of digoxin.

Controls vs Digoxin-treated Patients

Figure 2 shows the effect of digoxin on LVEF. In nine control patients the mean LVEF on the first study was 0.33 ± 0.12 and 0.30 ± 0.08 on the second study (p = NS). However, in the digoxin group the LVEF after digoxin administration (mean 0.33 ± 0.11) was significantly different from the initial LVEF (mean 0.29 ± 0.09, n = 14, p < 0.03).

Serum CK-MB

To compare the nine control patients and the 14 digoxin-treated patients, linear regression lines were derived (second LVEF vs first LVEF) for each group and compared by covariance analysis. The regression line \( y = 0.23x + 22.63 \) (n = 9, r = 0.41) was obtained for control patients. Similarly, the linear estimate \( y = 1.03x + 2.81 \) (n = 14, r = 0.88) was derived for the digoxin-treated group. A significant alteration in the linear relation of the first and second LVEF deter-

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Correlation of initial global and regional left ventricular wall motion and enzymatic estimates of infarct size. (left) A reasonable correlation was obtained between ejection fraction and CK-MB infarct size; the linear least-squares regression line is shown with the equation \( y = -0.2x + 43.4 \). (right) An acceptable correlation in the same patients was obtained between percentage of abnormally contracting left ventricular regions and CK-MB infarct size. The linear least-squares regression line is shown with the equation \( y = 0.4x + 42.8 \). None of these patients had prior myocardial infarction or right ventricular infarction.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Ejection fraction for each patient at the first study and at the second study is shown for control and digoxin groups. The open circles represent the mean. The digoxin group had a minimal but significant increase in left ventricular ejection fraction.
Table 1. Clinical, Electrocardiographic, Enzymatic and Radionuclide Data

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**Digoxin group**

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**Abbreviations:** MI class = acute classification; t = time elapsed in minutes between rise of serum CK-MB from baseline and first radionuclide studies (Δt₁) and second radionuclide studies (Δt₂); CK-MB-g-Eq = CK-MB-gram-equivalent infarct size; EF₁ = first ejection fraction; EF₂ = ejection fraction on the second study; %ACR₁ = percentage abnormally contracting regions on the first study; %ACR₂ = percentage abnormally contracting regions on the second study; PI₁ = TI-201 perfusion index on the first study; PI₂ = TI-201 perfusion index on the second study; MI = myocardial infarction; DMI = inferior; AMI = anterior; ASMI = anteroseptal; PLMI = posterolateral; ALMI = anterolateral; DLM1 = inferolateral.

**Percentages was found in comparing the two groups (F ratio = 9.19, p < 0.01, analysis of covariance).**

Digoxin had no effect upon %ACR (fig. 3). In control patients the mean %ACR on the first study was 63.1 ± 16.7 and 66.7 ± 14.0 on the second study (n = 9, p = NS). In the digoxin group the %ACR from the second study (mean 66.1 ± 25.7, n = 14) was not significantly different from the initial %ACR (mean 72.3 ± 19.1, n = 14). Similarly, analysis of covariance indicated no significant alteration in %ACR when the two groups were compared (p = 0.62).

Sequential TI-201 perfusion data were obtained in five controls and 11 digoxin patients. As shown in figure 4, digoxin had no significant effect upon the TI-201 perfusion index. The mean initial perfusion index was 18.9 ± 9.1 vs 19.8 ± 10.8 on the second study in the controls (n = 5, p = NS) In the digoxin group, the

**Figure 3.** Percentage of abnormally contracting regions at the first regional wall motion study and at the second study is shown for control and digoxin groups. The open circles represent the mean. No significant alteration in the percentage of abnormally contracting regions of the left ventricle occurred in either group.
Table 1. (Continued)

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Mean initial Tl-201 perfusion index was 29.3 ± 6.7 vs 25.9 ± 8.2 after digoxin (n = 11, p = NS). From the first study to the second study the mean change in the Tl-201 perfusion index in the controls was 4.0 ± 18.9% and -11.5 ± 28.5% in the digoxin group (p = NS). Analysis of covariance indicated no significant alteration in the Tl-201 perfusion index between the two groups (p = 0.28).

Ventricular Premature Complex Frequency

Analysis of covariance of cumulative VPC frequency at 2-hour intervals from the time serum CK-MB rose from baseline to the second radionuclide study in the controls (n = 6) and the digoxin-treated group (n = 12) showed no significant difference between the two groups in VPC frequency (p = 0.24).

Discussion

The use of digitalis in acute myocardial infarction is controversial. The hemodynamic effects of digitalis in patients with acute myocardial infarction associated with congestive heart failure have been variable, and its effect on performance during evolving infarction appears dependent on the time of administration, the
clinical class of the patient and the degree of hemodynamic impairment.²

Mason et al.⁴⁰ reported the results of intravenous digoxin in patients with LV failure and acute myocardial infarction. These authors found that cardiac output was raised substantially in over half of the patients whose cardiac output was below normal. Kumar et al.⁴¹ compared the effects of acetylcholinesterase in unanesthetized dogs 1 hour after myocardial infarction and found that changes in heart rate, cardiac output, stroke volume, LV end-diastolic pressure and mean pulmonary artery pressure were not significant. Hudd et al.⁴² compared the effects of acetylcholinesterase to that of isoproterenol in experimentally induced infarction in dogs. There was diminished inotropic effect to both agents when the infarct size exceeded 20% of the LV mass. Reduto et al.⁴³ reported an initial mean EF of 0.35 ± 0.04 in nine patients who developed congestive heart failure requiring treatment with diuretics and digoxin, and a final EF before discharge of 0.34 ± 0.05. However, in this study no mention was made of when after infarction digoxin was administered or the serum digoxin level at the time of the final study.

In the present study, there was a small but significant increase in global mean LVEF after digoxin.

Studying stable ambulatory patients with abnormal EF, Wackers et al.⁴⁴ found that absolute change in EF should be 0.05 or more for the change to be attributed to other than random physiologic variation, and suggested this limit for assessing serial alterations in LV ejection in individual patients. However, smaller changes may be significant in patients confined to bed. Indeed, in patients at bedrest with healed myocardial infarction, we have found the coefficient of variation of replicate LVEFs to be 3.5%.

In the present study, seven of the 14 digoxin-treated patients had an absolute change in EF of 0.05 or more. In six of these patients the LVEF improved after digoxin, while in one patient the EF decreased from 0.38 to 0.32. In this subgroup the mean initial LVEF was 0.31 ± 0.09, while the mean LVEF after digoxin was 0.37 ± 0.10 (n = 7, p < 0.04).

Using serum creatine kinase computer prediction models, there is evidence that digitalis preparations, given to patients not in cardiac failure after myocardial infarction, may enhance CK efflux,⁴⁴ whereas earlier preliminary data from our laboratory indicate that there is a decreased CK efflux in some patients who have large infarcts and high pulmonary artery wedge pressures who received digoxin.⁴⁵

In the present study, CK-MB prediction models were not used. However, %ACR derived from regional LVEFs, which is dependent upon the number of LV regions with depressed function, correlated reasonably well with the total CK-MB release curves. After digoxin, there was no significant change in the %ACR, which implies that the area of the infarction, as assessed by regional LV function, was not altered. That digitalis did not alter the magnitude of infarction or ischemia is further suggested by the finding in 11 patients that the initial mean TI-201 perfusion index was not significantly different from the second TI-201 perfusion index, obtained after digoxin.

The majority of published data⁴⁶–⁴⁸ indicates that digitalis has no effect on myocardial TI-201 kinetics in the absence of myocardial infarction, although there are conflicting reports. The results of the present study show clearly that digoxin did not result in a worsening of TI-201 perfusion defects. Hence, the slight improvement noted in LVEF after digoxin appears not to be at the expense of LV perfusion.

Certain problems exist with TI-201 and radionuclide wall motion that may limit the accuracy of these systems in detecting small alterations of infarct size. TI-201 perfusion scintigrams may be falsely negative in small subendocardial myocardial infarctions,⁴⁹–⁵² and falsely positive in the well-documented problem of misidentifying apical TI-201 defects caused by apical thinning.⁵³ The TI-201 technique detects abnormalities in tangential, geometrically dependent projections. Conversely, the regional wall motion technique uses radioactive count changes in the blood pool and hence is not dependent upon geometry. With both techniques, the measurement of abnormalities is perhaps influenced, to different degrees, by adjacent normal myocardium that may “overlie” nonperfused or dyskinetic regions. The precise ability of regional wall motion and thallium-201 myocardial scintigraphy to recognize small changes in myocardial infarction size will have to be studied in patients in whom relatively small spontaneous extensions have been documented by other means. The use of TI-201 to detect small extensions probably cannot be tested reliably without three-dimensional quantitative myocardial scintigraphy.

The studies by Reimer et al.⁵⁶ have shown that after experimental myocardial infarction the average relative proportion of transmural myocardium at risk, but still potentially salvageable, is 33% at 3 hours and 16% at 6 hours after coronary artery ligation. In the present study, digoxin was administered a mean of 18.0 ± 23.0 hours after the rise in CK-MB from baseline, when most cells may have sustained irreversible damage.

Using phased-array ultrasound studies, Eaton et al.⁵⁷ have identified acute dilatation and thinning of the area of infarction, not explained by infarct extension, in 42% of patients with acute anterior myocardial infarction. These authors used the term “infract expansion” to describe this slowly developing, apparently common complication of acute myocardial infarction that can worsen cardiac function through LV dilatation. Infarct expansion appears to occur progressively over a period of days-to-weeks, and was felt by these authors to be secondary to intramural rupture of necrotic muscle fibers. Theoretically, digitalis might cause accelerated intramural rupture of necrotic muscle fibers secondary to increased stress imposed by increased afterload and by improved segmental dynamics in normal areas of myocardium.² Conversely, digitalis, which is known to alter LV chamber dimensions⁵⁸ and hence decrease LV wall tension,³ might be a useful pharmacologic intervention...
in the setting of infarct expansion. It remains to be determined whether in patients with early regional infarct expansion digitalis can interrupt or attenuate the process. The recent development of systems to assess LV volumes from gated blood pool scans,** may shed light on this important point.

The present study, which included primarily patients with low EFs and large infarcts, indicates that digitalis can be administered safely in proper dosages to such patients with acute myocardial infarction. LV performance improved slightly; however no alteration in LV infarct size, as assessed by regional wall motion and LV perfusion, was shown. Although there has been concern that cardiac glycosides may increase myocardial infarction size, such a detrimental effect was not observed in the present study.

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