METHODS

Augmentation of Mortality Risk Discriminating Power of Left Ventricular Ejection Fraction by Measures of Nonuniformity in Systolic Emptying on Radionuclide Ventriculography

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Employing equilibrium-gated radionuclide ventriculography in the left anterior oblique view, six geometric models and five mathematical coefficients of nonuniformity in regional left ventricular emptying were tested for their relative mortality risk-stratifying power and capacity to augment the risk-discriminating potency of the continuous and dichotomized global ejection fraction. Radionuclide ventriculography was performed an average of 7.6 days after acute myocardial infarction. All geometric models significantly separated 20 normal subjects from 137 patients with recent myocardial infarction (p < 0.001).

Cumulative mortality data demonstrated that significant independent univariate dichotomizing potency and augmentation of the mortality risk-discriminating power of the global ejection fraction were provided by models of regional emptying that 1) conformed to coronary artery perfusion areas, 2) encompassed total ventricular counts, 3) expressed variability in regional relative to global ejection fraction, and 4) simulated a pattern of emptying directed toward the center of geometry of the left ventricle.

The combination of a four quadrant geometric model with axes drawn 45° above the horizontal and a coefficient of variation calculated as $\sqrt{\frac{\sum(GEF - REF)^2}{4}} \times 100$ GEF (where GEF = global ejection fraction and REF = regional ejection fraction) proved to be optimal. This coefficient averaged 12.2% in normal subjects and 32.2% in patients with recent acute myocardial infarction (p < 0.001). It dichotomized the initial patient cohort into those with a synergic left ventricle (n = 64) with a 4 year cumulative survival rate of 9.1% and those with an asynergic left ventricle (n = 73) with a cumulative survival rate of 29.3% (p = 0.005). The coefficient augmented the risk-discriminating power of the continuous global ejection fraction (p = 0.020) and the ejection fraction dichotomized at 0.40 (p = 0.009).

These data demonstrate that measures of nonuniformity in ventricular emptying add significantly to the mortality risk discrimination provided by the global ejection fraction after acute myocardial infarction.

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The severity of left ventricular dysfunction, determined by the measurement of the global left ventricular ejection fraction, is among the most powerful predictors of mortality risk in coronary artery disease, particularly in patients with recent acute myocardial infarction (1-9). It is generally appreciated that myocardial infarction results in nonuniform ventricular wall contraction and emptying, a pathophysiologic change that is not reflected in the determination of the global ejection fraction (10-12). In several previous studies (1,10,11,13-26), radionuclide methods were used to assess the presence and magnitude of left ventricular regional contraction abnormalities after acute myocardial infarction. However, none of the studies tested a quantitative measure of global nonuniformity as a predictor of postinfarction death.

In the present study we tested several geometric and mathematic expressions of global nonuniformity in left ventricular emptying for their potential application in augmenting the risk-discriminating power of the left ventricular
Methods

Study patients. Patients who were admitted to Rose Medical Center between April 1982 and March 1988 with a documented acute myocardial infarction and who underwent equilibrium-gated radionuclide ventriculography 3 to 42 days thereafter were enrolled in this study when they met the following criteria: 1) age \( \leq 75 \) years, 2) discharge alive from hospital, 3) sinus rhythm at the time of gated blood pool scan, 4) New York Heart Association functional class I or II for dyspnea and angina pectoris (1973 classification), 5) absence of left bundle branch block on electrocardiogram (ECG), and 6) absence of other life-limiting systemic disease.

A total of 137 patients were enrolled. No patient was lost to follow-up study. The average time from the onset of acute myocardial infarction to evaluation of ventricular function by nuclear ventriculography was 7.6 days (standard deviation [SD] 5.3). Myocardial infarction was diagnosed by a history of \( \geq 30 \) min typical ischemic chest pain and significant elevation of serum creatinine kinase (CK) MB fraction and the occurrence of typical sequential ECG ST segment changes with \( (n = 109) \) or without \( (n = 21) \) development of pathologic Q waves. In seven patients, the presence of previous Q waves preempted classification of the infarction by the presence or absence of Q wave development. Among the 109 patients with distinct new Q waves, 50 had anterior infarction and 6 had inferior infarction in both anterior and inferior sites. Acute myocardial infarction occurred as a first event in 113 patients; 24 patients had a history of at least one previous acute myocardial infarction. There were 115 men and 22 women; the mean age was 58 \( \pm \) 10 years. During the follow-up period, there were 13 deaths (6 from sudden death, 4 from congestive heart failure and 3 from recurrent acute myocardial infarction).

Normal group. There were 20 adult healthy volunteers (10 men, 10 women) <45 years of age with no clinical or ECG evidence of heart disease who served as subjects for the determination of normal left ventricular performance by nuclear ventriculography.

Radionuclide imaging. Gated radionuclide ventriculograms were obtained after intravenous administration of 20 to 25 mCi of technetium-99m-labeled human serum albumin (Syncor Nuclear Pharmacy). Imaging was accomplished using a single crystal Picker Dynamo Camera (254 mm diameter field of view) equipped with a high sensitivity parallel hole collimator oriented in a modified left anterior oblique projection and an ADAC 2800 semiautomated computer system. The camera was positioned in the 45° left anterior oblique position with approximately 15° of caudal tilt. Recording of gamma counts was initiated after clear visualization of the interventricular system and the left ventricular region of interest on preliminary display of the radionuclide ventriculogram. High temporal resolution cardiac sequences were constructed in a 64 \( \times \) 64 pixel matrix. Counting was triggered by computer-based ECG gating. The counting interval for each cycle was divided into 16 frames. Maximal count density was preset at 220 counts/pixel. Premature depolarizations were excluded (that is, beats with <80% of the average baseline cycle duration during pretest monitoring of sinus rhythm). A semiautomated edge detection algorithm based on a Laplacian filter was used to define the frame by frame left ventricular region of interest. Three point left ventricular spatial and temporal smoothing algorithms were applied in defining the left ventricular regions of interest for each frame.

Geometric models of nonuniformity. Left ventricular global ejection fraction was calculated as \( 1 - \) (end-systolic counts/end-diastolic counts), where end-systolic and end-diastolic counts were background corrected. The end-systolic and end-diastolic areas were selected from the 16 frames as the ventricular regions with highest and lowest background-corrected counts. The uniformity of ventricular emptying was tested for six geometric models (1 through 6). The models were derived from a basic 45° octant configuration constructed about a computer-derived fixed center of geometry during diastole (Fig. 1). Studies in 10 normal subjects, comparing models with fixed and floating centers of geometry during systole and diastole, revealed that the model with a fixed center of geometry during diastole provided maximal uniformity among values for regional ejection fraction.

The selection of these geometric models (Fig. 1) was designed to allow analysis for 1) regionalization by coronary artery perfusion areas, 2) regionalization by quadrants versus octants, and 3) regionalization that includes or excludes the upper regions. Regional ejection fraction values were calculated from background-corrected end-diastolic and...
end-systolic counts summated for the appropriate octant area configurations, employing the formula $1 - (\text{end-systolic counts/end-diastolic counts})$ for the observed region.

**Mathematic models of nonuniformity.** Five mathematic coefficients of synergy (a through e) were tested. The coefficients are quantitative expressions of the magnitude of dispersion among the respective regional ejection fractions as follows:

$$\sqrt{\frac{\sum (\text{GEF} - \text{REF})^2}{n} \times 100/\text{GEF}}$$ (a)
$$\sqrt{\frac{\sum (\text{REF} - \text{REF})^2}{n} \times 100/\text{REF}}$$ (b)
$$\sqrt{\frac{\sum (\text{GEF} - \text{REF})^2}{n}}$$ (c)
$$\frac{\text{Max REF - Min REF}}{\text{Max REF}} \times 100$$ (d)
$$\frac{\text{Max REF - Min REF}}{\text{REF}} \times 100$$ (e)

where GEF is global ejection fraction, REF is regional ejection fraction, REF is mean regional ejection fraction. Min is minimal and Max is maximal.

Coefficients a and b are based on the coefficient of variation principle. For coefficients a, b and c, n = number of sectors in the geometric model tested. Coefficient c is an estimate of the standard deviation of the regional ejection fraction about the global ejection fraction. Coefficients d and e are measures of normalized maximal dispersion.

**Study design and data analysis.** The primary aim of the study was to test the hypothesis that a quantitative measure of the nonuniformity of ventricular emptying augments the global ejection fraction in risk stratification among patients with recent acute myocardial infarction. A secondary aim was to compare various geometric configurations of the nuclear ventriculogram and several mathematic expressions of nonuniformity to permit discrimination of models that may provide best risk stratification. The study protocol was divided into two sequential phases: phase I = the testing of six geometric models employing coefficient a as the prototype mathematic expression of nonuniformity, and phase II = the testing of alternative coefficients of nonuniformity of ventricular emptying employing the geometric model that demonstrated optimal risk discrimination in phase I.

**In phase I analysis, three tests of the clinical applicability were applied:** 1) determination of the significance of the difference in coefficient a between normal subjects and patients with acute myocardial infarction for each geometric model, employing the independent samples Student's t test; 2) determination of the magnitude and significance of the difference in the cumulative mortality rate between subgroups with uniform (synergic) and nonuniform (asynergic) ventricles, employing the Mantel-Haenszel and Wilcoxon tests of significance (univariate mortality analysis); and 3) determination of the relative significance of each geometric model in augmenting the risk-stratifying power of the continuous global ejection fraction and the global ejection fraction dichotomized at 0.40, employing the Cox proportional hazards analysis with continuous or dichotomized global ejection fraction entered into the equation first (bivariate survival analysis). The normal limit for uniform (synergic) ventricular emptying was set at the 99% normal confidence limit. Nonuniform (asynergic) left ventricular emptying was denoted for a ventricle that exceeded the 99% normal limit.

**In phase II analysis, the optimal geometric model selected in phase I was used for comparing coefficient a with four alternative mathematic coefficients. The tests of clinical applicability of the coefficients in phase II analysis employed the same pattern as that for phase I. On the basis of these tests of clinical applicability, the coefficient yielding the most significant univariate and bivariate mortality risk discrimination was selected as optimal for clinical use.

**Survival analysis.** Survival analysis employed the end point of total mortality. The mean follow-up period for the patient group was 644 days. Cumulative survival analysis was continued through 1,600 days. The level of significance accepted for differences in calculated coefficients of ventricular synergy between normal and patient groups was considered to be p < 0.01; for differences in cumulative mortality on univariate analysis p < 0.05; for augmentation of mortality discrimination by global ejection fraction p < 0.05.

**Methodologic reproducibility.** Reproducibility of sector regional ejection fraction determination was tested among 7 normal subjects and 18 patients with a global ejection fraction ranging from 0.20 to 0.75. The correlation of replicate determinations of sector regional ejection fraction (octants and quadrants) on repeat determination of the same image was 0.95 (mean difference between replicates 0.0 ± 0.04). The correlation of replicate determinations of the coefficient of ventricular synergy a for the four quadrant geometric model 3 on repeat determination of the same image was 0.95 (mean difference between replicates 1 ± 7.6%).

**Results**

**Global ejection fraction.** The mean global ejection fraction was 0.63 ± 0.55 in normal subjects compared with 0.44 ± 0.013 among the patients with acute myocardial infarction (p < 0.001). Among the patients with recent infarction, there was a significant relation between continuous global ejection fraction and mortality (p = 0.029). The 83 patients with an ejection fraction ≥0.40 had a 4 year (1,600 day) cumulative mortality rate of 14.6% ± 7.7% compared with a rate of 30.0 ± 12.6% in the 54 patients with a global ejection fraction
Comparison of Six Geometric Models Employing Coefficient a

<table>
<thead>
<tr>
<th>Geometric Model</th>
<th>Mean ± SD (%)</th>
<th>p Diff</th>
<th>4 Year Cumulative Mortality, Univariate (synergic versus asynergic group)</th>
<th>Augmentation of Mortality Risk by:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>p Diff</td>
<td>Cont GEF (p value)</td>
</tr>
<tr>
<td>1 N, AMI</td>
<td>9.5 ± 4.0</td>
<td>&lt;0.001</td>
<td>S (60) 10.0 (9.5)</td>
<td>0.011</td>
</tr>
<tr>
<td>2 N, AMI</td>
<td>25.9 ± 17.9</td>
<td>&lt;0.001</td>
<td>A (77) 26.4 (8.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>3 N, AMI</td>
<td>34.1 ± 24.3</td>
<td>&lt;0.001</td>
<td>S (64) 28.2 (9.3)</td>
<td>0.005</td>
</tr>
<tr>
<td>4 N, AMI</td>
<td>11.2 ± 5.0</td>
<td>&lt;0.001</td>
<td>A (73) 29.3 (9.3)</td>
<td>0.034</td>
</tr>
<tr>
<td>5 N, AMI</td>
<td>32.2 ± 21.7</td>
<td>&lt;0.001</td>
<td>S (64) 31.8 (8.3)</td>
<td>0.023</td>
</tr>
<tr>
<td>6 N, AMI</td>
<td>12.2 ± 5.0</td>
<td>&lt;0.001</td>
<td>A (73) 32.5 (8.6)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

A = asynergic; AMI = acute myocardial infarction; Cont = continuous; Dichot = dichotomized; GEF = global ejection fraction; MH = Mantel-Haenszel test; N = normal subjects; p Diff represents the p value for difference between groups for each geometric model; S = synergic; W = Wilcoxon test. See Figure 1 for illustrations of geometric models 1 to 6.

<0.46. This difference was significant (p = 0.044 by Mantel-Haenszel test, p = 0.015 by Wilcoxon test).

Phase I analysis. The results of phase I analysis for clinical application of the six geometric models of nonuniformity employing coefficient of synergy a are summarized in Table 1. In the first column, the mean coefficient for the six geometric models in normal subjects and patients with acute infarction is shown. For each geometric model, the mean synergy coefficient in patients with acute infarction was significantly greater than that in normal subjects (p < 0.001).

The second column of Table 1 shows the results of the univariate analysis for the difference in the 4 year (1,600 day) cumulative mortality rate between patients with a synergic and an asynergic left ventricle. For the six geometric models, the 4 year cumulative mortality rate was significantly higher by two tests of significance in the patients with left ventricular asynergy (p = 0.034). Geometric models 2 and 3 yielded 4 year cumulative mortality differences of highest significance (p ≤ 0.005).

The third column of Table 1 summarizes the results of the bivariate analysis for augmentation of mortality risk. Significant augmentation of mortality risk stratification of continuous global ejection fraction and global ejection fraction dichotomized at 0.40 was present for geometric models 1, 2 and 3. Models 4, 5 and 6 did not significantly augment the risk-stratifying power of continuous global ejection fraction or global ejection fraction dichotomized at 0.40. Models 2 and 3 yielded augmentation of continuous and dichotomized global ejection fraction at the highest levels of significance.

Geometric models 2 and 3 are quadrant models drawn 45° from the horizontal axis. They differ only in the inclusion of the upper quadrant in model 3 and its exclusion in model 2. Because inclusion of the upper quadrant in model 3 (that is, total ventricular counts) yielded no disadvantage in mortality-augmenting power, it was considered the optimum among the six geometric models for inclusion in phase II analysis.

Phase II analysis. The results of phase II analysis for the comparison of five coefficients of synergy employing geometric model 3 are summarized in Table 2. In the first column, the mean coefficients of synergy (±SD) in normal subjects and patients with acute myocardial infarction are shown. For each coefficient, the mean levels for the patient group were significantly greater than those in the normal group (p < 0.001).

The second column of Table 2 summarizes the results of the analysis for the difference in the 4 year (1,600 day) cumulative mortality rate between patients with acute myocardial infarction having a synergic or an asynergic left ventricle, as calculated by the respective coefficients. For four of the five coefficients (a, b, d and e), the 4 year cumulative mortality rate was significantly higher in the patients with left ventricular asynergy by two tests of significance. Coefficient c failed to dichotomize the rate significantly.

The third column of Table 2, summarizes the results of the analysis for augmentation of mortality risk stratification by continuous global ejection fraction and global ejection fraction dichotomized at 0.40. Among the five coefficients,
significant augmentation of the relation of continuous global ejection fraction to mortality was present only for coefficient a (p = 0.02). Significant augmentation of mortality stratification by global ejection fraction dichotomized at 0.40 was present for coefficients a, b, d and e. Among these, coefficient a yielded the most significant augmentation (p = 0.009).

On the basis of phase I and II analysis, the combined formulation of the coefficient of ventricular synergy a and geometric model 3 yielded the most potent risk stratification on univariate mortality analysis and most significant augmentation of the risk-discriminating power of the continuous and dichotomized global ejection fraction. The upper normal limit (99% confidence) for the coefficient of ventricular synergy defined by this formulation is 24%.

Covariate attributes. To discern covariate attributes that might influence the mortality-augmenting potency of coefficient a and geometric model 3, patient characteristics associated with left ventricular synergy and asynergy were compared. There were 64 patients with a synergic and 73 patients with an asynergic ventricle (Table 3). Among clinical descriptors of significance, patients with left ventricular asynergy were slightly older, had a lower frequency of thrombolytic therapy during the acute episode of myocardial infarction and had a lower frequency of non-Q wave infarction. A higher frequency of prior myocardial infarction among the patient with an asynergic ventricle approached significance. There were no statistically significant differences (p > 0.10) between asynergic and synergic groups with regard to gender distribution or poststudy frequency of myocardial infarction, coronary bypass surgery or coronary angioplasty.

Maximal likelihood function relating continuous global ejection fraction and mortality. The maximal likelihood function expressing the cumulative mortality rate versus time relations at varying levels of global ejection fraction for the total study group and for the patient subgroups with synergic and asynergic ventricular emptying as defined by coefficient of ventricular synergy a and geometric model 3 was derived from the Cox proportional hazards analysis (see Appendix). From the respective equations, a family of mortality curves through the range of deciles of ejection fraction from 0.30 to 0.70 were plotted for the entire patient group and for the synergic and asynergic subgroups (Fig. 2). Panel 2A illustrates the continuous relation between global ejection fraction and cumulative mortality rate for the total patient cohort. Panel 2B illustrates the upward shift of the

Table 2. Three Tests of Clinical Application of Measures of Nonuniformity in Ventricular Emptying: Comparison of Five Coefficients Employing Geometric Model 3

| Measures of Nonuniformity (normal subjects versus patients with AMI) | 4 Year Cumulative Mortality, Univariate (synergic versus asynergic group) | Augmentation of Mortality Risk by: |
|---|---|---|---|
| Coefficient | Mean ± SD | p Diff | (No.) | % (SE) | MH | W | Cost GEF | GEF Dichot | (p value) | p Diff (p value) |
| a | N | 12.2 ± 5.0% | <0.001 | S | 64 | 9.1 (8.7) | 0.005 | 0.003 | 0.020 | 0.009 |
| AMI | 32.2 ± 21.3% | | | A | 73 | 29.3 (9.3) | | | | |
| b | N | 11.8 ± 4.8% | <0.001 | S | 60 | 10.0 (9.5) | 0.042 | 0.006 | 0.055 | 0.028 |
| AMI | 30.3 ± 18.8% | | | A | 77 | 27.0 (8.6) | | | | |
| c | N | 0.078 ± 0.027 | <0.001 | S | 89 | 15.8 (6.7) | 0.960 | 0.740 | 0.780 | 0.900 |
| AMI | 0.125 ± 0.065 | | | A | 48 | 26.2 (12.3) | | | | |
| d | N | 26.0 ± 9.0% | <0.001 | S | 56 | 10.0 (9.5) | 0.018 | 0.011 | 0.080 | 0.042 |
| AMI | 32.9 ± 25.2% | | | A | 81 | 26.1 (8.6) | | | | |
| e | N | 24.8 ± 11.6% | <0.001 | S | 55 | 10.9 (5.1) | 0.019 | 0.011 | 0.085 | 0.042 |
| AMI | 78.1 ± 49.6% | | | A | 82 | 26.1 (8.6) | | | | |

p Diff represents the p value for difference between groups for each coefficient; other abbreviations as in Table 1. See text for definitions of coefficients a to e.

Table 3. Comparison of Covariate Attributes in 137 Patients

<table>
<thead>
<tr>
<th></th>
<th>LV Synergy*</th>
<th>LV Asynergy*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± SD (yr)</td>
<td>56 ± 9</td>
<td>60 ± 11</td>
<td>0.010</td>
</tr>
<tr>
<td>Gender (M/F) (no.)</td>
<td>55/10</td>
<td>60/12</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombolytic therapy (%)</td>
<td>52</td>
<td>35</td>
<td>0.003</td>
</tr>
<tr>
<td>Non-Q wave AMI (%)</td>
<td>25</td>
<td>7</td>
<td>0.005</td>
</tr>
<tr>
<td>Prior AMI (%)</td>
<td>11</td>
<td>24</td>
<td>0.880</td>
</tr>
<tr>
<td>CAB surgery at FU (%)</td>
<td>15</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>PTCA at FU (%)</td>
<td>11</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>AMI at FU (%)</td>
<td>9</td>
<td>10</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Defined by coefficient of ventricular synergy, coefficient a, geometric model 3 (upper normal confidence limit of 24%). AMI = acute myocardial infarction; CAB = coronary artery bypass; F = female; FU = follow-up; LV = left ventricular; M = male; PTCA = coronary angioplasty.
continuous relation between global ejection fraction and cumulative mortality rate in the asynergic group. Panel 2C illustrates the downward shift and compression of the cumulative mortality curves in the synergic group.

**Discussion**

**Models of nonuniform ventricular emptying.** Since the pioneering studies of Herman and Gorlin (27), in which the various forms of left ventricular segmental contraction abnormality were explicitly delineated by contrast ventriculography, much investigative attention has been directed to analysis of ventricular function in coronary artery disease in terms of regional contraction disorders. Such investigations have involved a wide array of technical approaches, including contrast ventriculography (28-39), echocardiography (22,40-42) and radionuclide ventriculography (1,10,11,13-26). These studies have focused largely on the site and extent of segmental abnormalities and their contribution to global dysfunction. Several studies (1,9,22,40-45) have tested qualitative measures of the localized disorder in wall motion as risk indicators. However, to date, no quantitative expression of the nonuniformity among all ventricular segments has been reported as a means of augmenting the risk-stratifying power of the global ejection fraction.

It was the purpose of the present study to test several models of nonuniformity of ventricular emptying for their capacity to add to the global ejection fraction in mortality risk prediction. Six geometric models and five mathematic expressions of nonuniformity were selected. The geometric models were adapted from previous studies (10,11,17,21,23-25,46,47) wherein various concentric configurations employing three, four, six or eight segments were used in identifying the presence and extent of regional ejection fraction abnormalities. Some of the models were constructed to conform with regional coronary perfusion areas (models 1, 2 and 3), whereas others followed a simple geometric order (models 4, 5 and 6). The mathematic formulations of nonuniformity were based on the coefficient of variation principle or on estimates of maximal dispersion among levels of regional ejection fraction relative to the mean or maximal regional ejection fraction. An estimate of the standard deviation of regional ejection fraction about the global ejection fraction was included.

It is of special interest to consider the relatively high level of uniformity in regional ejection fraction observed in this study in the normal ventricle when regions were drawn concentric to the diastolic center of geometry. This is in contrast to the impression that regional emptying in the normal ventricle is nonuniform. This impression derives from studies (15,29,37-39,48) employing contrast and radionuclide ventriculographic images, wherein regions are drawn about a long axis or a center line. On the basis of the present observations, it appears that normal left ventricular emptying approximates uniformity when the image is visualized in the left anterior oblique view in a pattern wherein regional systolic emptying is directed toward the geometric center of diastole.

**Selection of models on basis of mortality risk discrimination.** It is notable that the presence of nonuniformity in ventricular emptying, as assessed by each of the geometric and mathematic models in this study, significantly separated normal individuals from patients with acute myocardial infarction. When survival analysis was added as a test of clinical applicability, the geometric models varied considerably in their risk-discriminating power. These data provide evidence that a ventricular function measure that separates normal subjects from patients with cardiovascular disease, even at a high degree of significance, does not have to be a significant indicator of mortality risk. The observations highlight the usefulness of survival analysis itself as an independent test of the potential clinical applicability of a new measure of cardiac function.

In considering the various coefficients of nonuniformity in this study, it should be noted that the formulas for all but one (coefficient c) include normalization of the measured variance. Coefficient c lacked significant independent mortality-dichotomizing power, whereas all other coefficients retained significant univariate risk-discriminating potency. The normalized coefficients express the dispersion among regional
ejection fraction values as a percent of variation about a reference measure (global ejection fraction, mean or maximal regional ejection fraction). Coefficient \( c \), in contrast, is a measure of the average absolute deviation of regional ejection fraction from global ejection fraction. The clear lack of mortality risk-discriminating power for coefficient \( c \) suggests that measures of dispersion in regional ejection fraction need to be normalized to have optimal value as mortality risk indicators.

It is well appreciated that the site of left ventricular wall dysfunction in myocardial infarction bears a close relation to the area of myocardium perfused by the obstructed arterial segment (that is, the infarct-related artery). The geometric models chosen in this study permitted comparison of sector distribution by perfusion area with distribution by a simple geometric order. As expected, models that divided the left ventricular chamber into perfusion-related regions (that is, anterior, inferior and posterolateral sectors [models 1, 2 and 3]) provided the most significant mortality risk discrimination.

In previous studies (10,21,24,48) in which ventricular asynergy was studied by nuclear ventriculography, the upper ventricular segment was deleted, ostensibly to diminish the adverse influence of overlapping scintigraphic activity of the left atrium and the proximal aorta. The geometric models selected in this study permitted comparison of the mortality risk-discriminating power of models in which the upper segments were excluded (models 2 and 5), with equivalent models in which the upper segments were included (models 3 and 6). In neither model with the upper segment deleted was there evidence for more significant univariate dichotomization or mortality risk augmentation. On this basis, the practice of deleting the upper segment in models designed to study abnormalities in regional ventricular emptying by the nuclear ventriculographic technique cannot be supported.

Covariate analysis. In attempting to explain the basis for the risk-discriminating power of coefficient of ventricular synergy \( a \) and geometric model 3, those clinical events that may influence the extent of ventricular dysfunction before the nuclear ventriculographic studies or that affect the survival function thereafter were compared in synergic and asynergic groups (Table 3). Compared with the synergic group, patients with ventricular asynergy had a significantly lower frequency of thrombolytic therapy and non-Q wave myocardial infarction and a somewhat higher frequency of remote myocardial infarction. The mean age of patients with asynergy was slightly and significantly older. Thus, the presence of global ventricular asynergy was associated with clinical events and interventions that would be expected to accentuate left ventricular dysfunction (49–54). During the follow-up period, there was no statistically significant difference between the groups in terms of the occurrence of recurrent myocardial infarction or the frequency of coronary angioplasty and coronary bypass surgery. The differences in

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Cause of Death</th>
<th>GEF</th>
<th>CVS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SD</td>
<td>0.21</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>SD</td>
<td>0.59</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>SD</td>
<td>0.27</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>SD</td>
<td>0.24</td>
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</tr>
<tr>
<td>5</td>
<td>SD</td>
<td>0.33</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>SD</td>
<td>0.32</td>
<td>34</td>
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<tr>
<td>7</td>
<td>CHF</td>
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<tr>
<td>8</td>
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<td>9</td>
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<td>0.32</td>
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</tr>
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<td>12</td>
<td>RAMI</td>
<td>0.30</td>
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</tr>
<tr>
<td>13</td>
<td>RAMI</td>
<td>0.63</td>
<td>16</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; CVS = coefficient of ventricular synergy defined by coefficient \( a \); geometric model 3; GEF = global ejection fraction; Pt. = patient; RAMI = recurrent acute myocardial infarction; SD = sudden death.

In a second analysis directed to elucidating the basis for the risk-discriminating power of nonuniformity in ventricular emptying, the levels of global ejection fraction and ventricular asynergy were compared among patients who died during the follow-up period (Table 4). All 13 deaths were related to coronary artery disease. All 10 patients who died either suddenly \( \left( n = 6 \right) \) or from congestive heart failure \( \left( n = 4 \right) \) had an abnormal coefficient of ventricular synergy and 2 had an ejection fraction \( \geq 0.50 \). Three patients died immediately after recurrent acute myocardial infarction, one of whom had a normal global ejection fraction and a normal coefficient of ventricular synergy after the first infarction. These observations, although limited in number, suggest that the coefficient of ventricular synergy retains predictive potency for the risk of sudden death and death due to left ventricular power failure rather than for the risk of death from recurrent acute myocardial infarction. This impression is consonant with studies (55,56) documenting a close parallelism between regional asynergy and the extent of myocardial damage.

Conclusions. On the basis of these studies, it can be concluded that an optimal model for quantitating nonuniformity in ventricular emptying by nuclear ventriculography is one that 1) is constructed to allow distribution of the regional ejection fraction in accord with coronary perfusion areas, 2) encompasses total ventricular counts without deletion of the upper cardiac regions, 3) expresses variability in regional relative to global ejection fraction, and 4) simulates a pattern of contraction wherein regional emptying occurs toward the left ventricular diastolic center of geometry in the left anterior oblique image. A four quadrant configuration drawn
with axes rotated 45° from the horizontal and a coefficient of ventricular synergy based on the variability in regional ejection fraction about the global ejection fraction provides an optimal model.

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Appendix

The cumulative percent survival rate (S) at any time (t) and for any set of predictors \( x_1, x_2, \ldots, x_n \) can be derived from the Cox proportional hazards program (57) according to the following equation:

\[
S(t, x_1, x_2, \ldots, x_n) = S_0(t)^{-a_1 x_1 - a_2 x_2 - \cdots - a_n x_n}.
\]

where \( S_0(t) \) is the maximal likelihood function expressing the cumulative survival rate versus time relation for the total study sample, and \( a_1, a_2, \ldots, a_n \) are coefficients derived from the computerized Cox proportional hazards analysis (BMDP 2L program). For continuous data, \( x \) is the quantitative measure for the predictor. For dichotomized data, \( x \) is assigned a code (for example, a numeric value of 1 for data below and 2 for data above the dichotomizing limit.

The derived cumulative survival equation based on the continuous global ejection fraction (GEF) as the only predictor in the Cox analysis of the data in this study is

\[
S(t, x) = S_0(t)^{-a_1 x}.
\]

The derived cumulative survival equation for combined continuous global ejection fraction and ejection fraction dichotomized for synergic and asynergic groups using coefficient \( a \) and geometric model 3 is

\[
S(t, x) = S_0(t)^{-2} \cdot e^{-c x + a t},
\]

where \( C = 1 \) for the synergic ventricle and 2 for the asynergic ventricle.

To construct a family of cumulative survival curves to illustrate the relation of continuous global ejection fraction to survival, deciles of global ejection fraction are substituted for global ejection fraction in equation 2. To construct a family of cumulative survival functions that illustrates the influence of synergy and asynergy on the relation of continuous global ejection fraction to survival, deciles of global ejection fraction are substituted for global ejection fraction in equation 3 and \( C \) is assigned a value of 1 for synergy and a value of 2 for asynergy.

The cumulative survival function at any time interval is converted to a cumulative mortality function by the relation: cumulative mortality (%) = 100 - cumulative survival (%).

References

22. Van Reeth RE, Quinaoes MA, Poliner LR, et al. Comparison of two-dimensional echocardiography with gated radionuclide ventriculography


