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Reasons for the Lack of Benefit of Immediate Angioplasty During Recombinant Tissue Plasminogen Activator Therapy for Acute Myocardial Infarction: A Regional Wall Motion Analysis

ALFRED E. R. ARNOLD, MD,*† PATRICK W. SERRUYS, MD, FACC,†
WOLFGANG RUTSCH, MD,‡ MAARTEN L. SIMOONS, MD, FACC,† DAVID P. DE BONO, MD,§
JAN G. P. TIJSSEN, PHD,† JACOBUS LUBSEN, MD,*† MARC VERSTRAETE, MD,‖
FOR THE EUROPEAN COOPERATIVE STUDY GROUP

Rotterdam, The Netherlands; Berlin, West Germany; Leicester, England; and Leuven, Belgium

Regional ventricular wall motion analysis utilizing three different methods was performed on predischarge left ventriculograms from 291 of 367 patients enrolled in a randomized trial of single chain recombinant tissue-type plasminogen activator (rt-PA), aspirin and heparin with and without immediate angioplasty in patients with acute myocardial infarction.

With univariate analysis, no difference in regional wall motion variables between the two treatment groups was observed. However, with individual baseline risk assessment by multivariate linear regression analysis using baseline characteristics known to be related to left ventricular function after thrombolytic therapy or outcome of coronary angioplasty, or both, an excess of high risk patients in the invasive treatment group was detected. To adjust for this unequal distribution of baseline risk, multivariate linear regression analysis was performed. No benefit of immediate coronary angioplasty was observed after adjustment.

Reocclusion or reinfarction, or both, occurred more frequently in the invasive than in the noninvasive treatment group (18% versus 13%, respectively). Among patients with a patent infarct-related vessel on angiography between days 10 and 22 and without reinfarction before angiography, there was a trend toward benefit from the invasive strategy, indicating that reocclusion and reinfarction might be responsible for the lack of benefit of the invasive strategy. This implies that immediate coronary angioplasty may be beneficial in selected patients, provided that these complications can be prevented.

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In 1988, the European Cooperative Study Group (1) published the results of a trial comparing an invasive strategy, combining thrombolysis with recombinant tissue-type plasminogen activator (rt-PA), heparin, aspirin and immediate coronary angioplasty, with a noninvasive strategy of intravenous rt-PA, heparin and aspirin in patients with acute myocardial infarction. Contrary to expectations when the trial was initiated, the invasive treatment strategy did not result in smaller enzymatic infarct size, better global left ventricular function and lower mortality rate. In fact, complications were more frequent and the mortality rate was higher after the invasive strategy (1).

Additional analyses were performed to evaluate whether: 1) a true benefit of immediate angioplasty was not detected because of an excess of high risk patients in the invasive treatment group, despite randomization; 2) a true benefit in one subgroup was obscured by an adverse effect in another, which would have important implications if these subgroups could be identified on admission or if they would be characterized by an adverse event like reocclusion or reinfarction, which may be prevented by new treatment strategies; and 3) preservation of function in the infarct territory was missed by using global function as the variable because of compensatory hyperkinesia of the contralateral wall (2).

The results of these investigations are presented in this report. Multivariate analysis was used to adjust for unequal baseline risk and assess treatment effects in subgroups of patients. Regional left ventricular wall motion analysis in the infarct territory was performed to evaluate the role of compensatory hyperkinesia of the noninfarcted area.

Methods

Study patients. Of 367 patients <71 years of age with ≥30 min of chest pain and electrocardiographic (ECG) evidence of extensive transmural myocardial ischemia, 184

From the *Center of Clinical Decision Analysis and †Thoraxcenter, Erasmus University, Rotterdam, The Netherlands; ‡Division of Cardiology, University of Berlin, Berlin, West Germany; §Department of Cardiology, University of Leicester, Leicester, England; and ‖Center for Thrombosis and Vascular Research, University of Leuven, Leuven, Belgium. Dr. Arnold was supported by a grant from The Netherlands Health Research Promotion Programme (SGO), The Hague, The Netherlands.

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Address for reprints: Alfred E. R. Arnold, MD, Erasmus University, PO Box 1738, 3000 DR Rotterdam, The Netherlands.

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Table 1. Reasons for Missing Angiography Between Days 10 to 22 for Analysis of Regional Wall Motion

Angiography at 10 to 22 Days	Noninvasive (n = 184)	Invasive (n = 183)
Not performed because of:		
Death	5	12
Cardiac reason	1	3
Noncardiac reason	1	2
Patient refusal	3	4
Other	1	2
Performed	173	160
Not analyzable because of:		
Extrasystole	15	15
Inadequate filling	4	1
Ventricle outside screen	2	1
Other	2	1
Available and analyzable	149	142

were allocated to noninvasive treatment and 183 to immediate angiography and coronary angioplasty, provided that thrombolytic therapy could be started within 5 h after onset of symptoms. Patients with a previous myocardial infarction at the same site or with previous coronary artery bypass surgery were excluded, but patients with heart failure or shock were not. Further details of patient selection have been published elsewhere (1). Left ventricular angiography of adequate quality for analysis was available in 291 patients (Table 1). These patients form the study group of the present analysis.

Patient management. After providing informed consent, patients were treated with heparin (a 5,000 IU bolus injection, followed by 1,000 IU/h intravenously), aspirin (250 mg) and single chain rt-PA (Alteplase, 100 mg over 3 h). Coronary angiography was performed as soon as possible in all patients who had been randomized to the invasive strategy. Angioplasty was to be attempted, provided that there was a luminal diameter stenosis of ≥60% in the infarct-related coronary artery. In case of complete occlusion, mechanical perforation had to be performed.

Aspirin (75 to 125 mg) was continued on alternate days until hospital discharge. Heparin could be replaced by oral anticoagulant agents after 3 days, provided that full anticoagulation was maintained until cardiac catheterization.

Electrocardiographic analysis. Infarct localization was determined from the admission ECG by the core laboratory. It was judged anterior if ST segment elevation was present in leads V_1 to V_4 and inferior if ST segment elevation occurred in leads II, III and aVF. In case of ST segment elevation in leads I, aVL, V_5 and V_6, infarct localization was deemed anterior unless ST segment elevation was also present in leads II, III or aVF or ST depression was present in leads V_1 to V_4, in which cases the localization was inferior. The ST segment shift was measured at the J point.

Coronary arteriography and ventriculography. Coronary arteriography and left ventriculography were performed 10 to 22 days after treatment allocation. To enhance comparability between the two groups, each clinic was required to perform angiography within a preselected time window of 10 to 14, 12 to 16, 14 to 18, 16 to 20 or 18 to 22 days after allocation. Beta-adrenergic blocking agents, calcium channel antagonists and nitrates were stopped the night before angiography. All angiograms were assessed by members of the Angiography Assessment Group. Perfusion of the infarct-related vessel was assessed using the Thrombolysis in Myocardial Infarction (TIMI) perfusion score (3–5).

Left ventriculography was performed with a 0.5 to 1 ml/kg nonionic contrast injection at a flow of 6 to 20 ml/s in the 30° right anterior oblique projection. End-systolic and end-diastolic contours were digitized. Left ventricular volumes in the right anterior oblique projection were calculated according to Simpson's rule after calibration with a phantom of known volume filmed after ventriculography and were indexed for body surface area. No corrections for trabeculae and papillary muscles were applied. All analyses were performed at the core laboratory for quantitative angiography without knowledge of treatment allocation.

Regional Left Ventricular Wall Motion Analysis

Regional wall motion was analyzed according to: 1) the "regional contribution to ejection fraction method," which assesses wall motion along experimentally determined and validated vectors (2,6) and detects small differences in regional wall motion (2); 2) the "centerline method," which assesses fractional shortening in 100 chords perpendicular to a centerline between the end-diastolic and end-systolic contours (7–9); and 3) the "radial axes method," which assesses fractional shortening in 300 radii from the center of mass of the end-diastolic contour (10). In none of the methods were translational or rotational corrections made. A description of each model is given in Figures 1 to 5.

The extent of hypokinesia (wall motion in the infarct territory). This was assessed by quantitative regional wall motion with all three models. In the regional contribution to ejection fraction method, it was the number of segments with abnormal regional contribution to ejection fraction (below the 10th percentile of a group of 31 normal individuals) per patient. In the centerline method, it was the number of contiguous chords in which the shortening fraction differed by >1 standard deviation from the mean shortening fraction in a group of normal individuals (so-called circumferential extent of wall motion abnormality). In the radial axes method, it was the percent of radii in which the shortening fraction differed by >2 standard deviations from the mean normal shortening fraction in a group of normal individuals (so-called hypokinetic circumference).

The severity of hypokinesia. This was assessed with the regional contribution to ejection fraction method as the mean regional contribution to ejection fraction per abnormal segment (%) and was calculated by dividing the sum of regional contributions below the 10th percentile of normal by the number of abnormal regions (11).

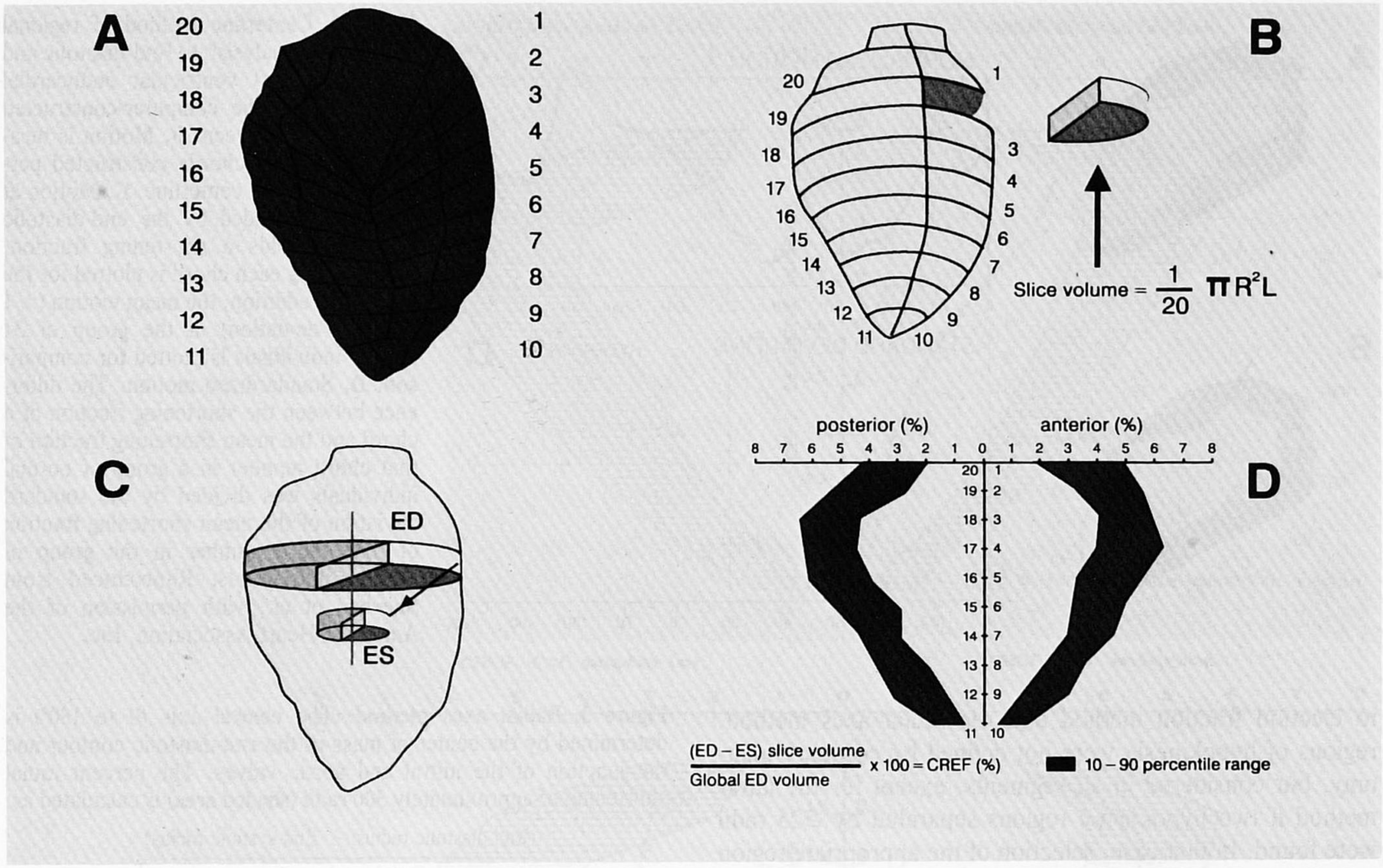

Figure 1. Regional contribution to ejection fraction (CREF) method of regional wall motion analysis. **A,** End-diastolic left ventricular endocardial contour in 30° right anterior oblique left ventriculogram. The 20 coordinates along which left ventricular wall motion occurs are superimposed. **B,** The volume of each slice in the end-diastolic volume is calculated from the radius of the slice (R) and 1/20th of the left ventricular long-axis length (L) as:

$$V_i = 1/20 \times \pi \times R_i^2 \times L.$$

The slices or segments are numbered from 1 to 10 for the anterior wall and from 11 to 20 for the inferoposterior wall. **C,** Similarly, the volume of each slice in the end-diastolic volume (ED) is calculated. The regional contribution to global ejection fraction is determined as:

$$\frac{\text{(End-diastolic} - \text{End-systolic [ES])} \text{ Slice volume}}{\text{Global end-diastolic volume}} \times 100\%.$$

D, An example of a plot of regional contribution to ejection fraction in which the values for regional contribution to ejection fraction (x axis) for all 20 segments (y axis) are given. The **shaded zones** represent the 10th and 90th percentiles of the regional contribution to ejection fraction for each segment in normal individuals. Reproduced from Serruys et al. (2), with permission.

In the centerline method, hypokinesia was defined as maximally abnormally contracting 50% (expressed in standard deviation/chord), computed as follows. The difference between shortening fraction of each chord and mean shortening fraction of the corresponding chord in a group of normal individuals was divided by 1 standard deviation of normal for each chord in the hypokinetic area. This difference divided by 1 standard deviation of normal is called "standardized motion" of a chord. The hypokinetic area was defined as a set of contiguous chords chosen in such a way that half the number of chords in the infarct territory are included and that the mean standardized motion in that set of chords is most abnormal. This mean standardized motion in the hypokinetic area is called maximally abnormally contracting 50% (7–9).

In the radial axes method, the severity of hypokinesia was given by the contribution to the global ejection fraction by the sector of radii with wall motion abnormality >2 standard deviations of normal wall motion (called regional ejection fraction in the infarct territory).

Hyperkinesia. Similarly, the extent and severity of hyperkinesia (wall motion abnormality in the contralateral area) were determined with the regional contribution to ejection fraction method as the number of segments with abnormal regional contribution to ejection fraction and the mean regional contribution to ejection fraction per abnormal segment (%). Abnormal segments were defined as those with regional contributions exceeding the 90th percentile of normal. For the centerline method, only the severity of hyperkinesia was calculated (7) as maximally abnormally contracting 50% (standard deviation/chord).

Localization of infarct and noninfarct territories. In the centerline method, these were defined by the angiographically assessed infarct-related vessel and the number of diseased coronary arteries (7–9). In the regional contribution

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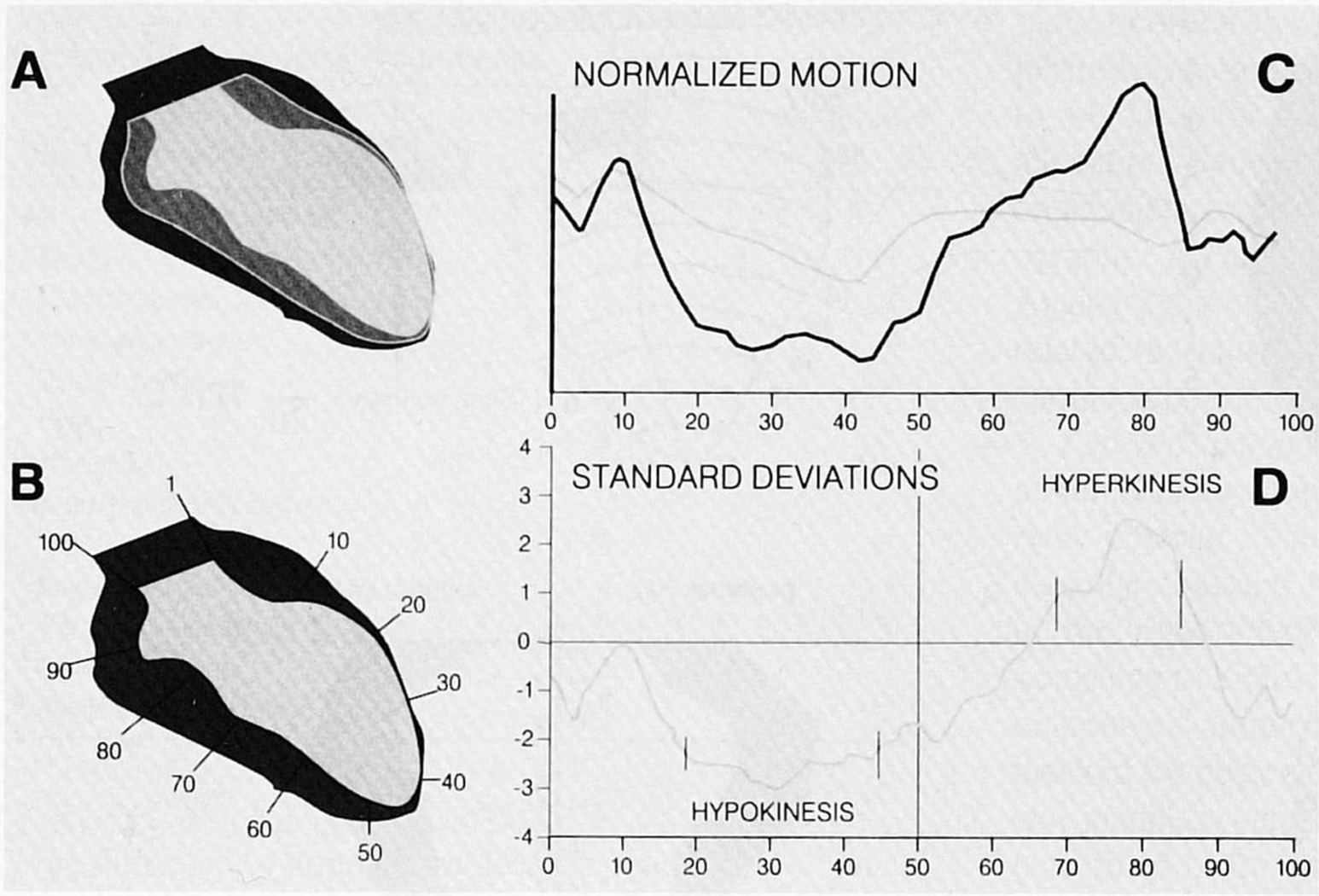


Figure 2. Centerline method of regional wall motion analysis. **A,** End-diastolic and end-systolic left ventricular endocardial contours with the computer-constructed centerline in between. **B,** Motion is measured along 100 chords constructed perpendicular to the centerline. **C,** Motion at each chord divided by the end-diastolic perimeter yields a shortening fraction. Motion along each chord is plotted for the patient. In addition, the mean motion (± 1 standard deviation) in the group of 31 normal individuals is plotted for comparison. **D,** Standardized motion. The difference between the shortening fraction of a chord and the mean shortening fraction of that chord number in a group of normal individuals was divided by the standard deviation of the mean shortening fraction of that chord number in the group of normal individuals. Reproduced from Sheehan et al., with permission of the American Heart Association, Inc.

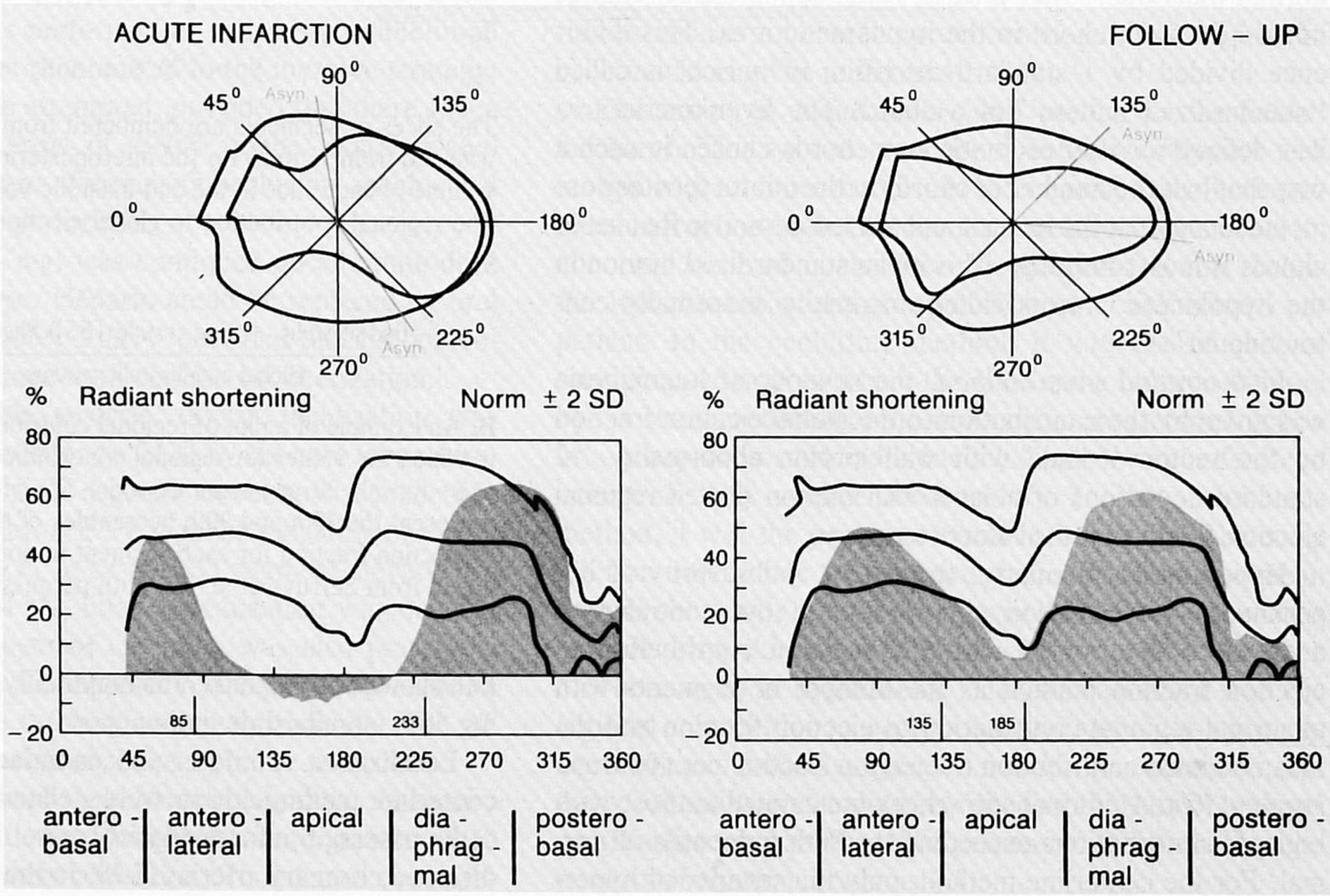
to ejection fraction method and the radial axes method, regions of hypokinesia were not defined by coronary anatomy, but considered in all segments, except for the latter method if two hypokinetic regions separated by ≥25 radii were found. In that case, selection of the appropriate region was made on the basis of infarct localization on the qualifying ECG.

Enzymatic infarct size. Cumulative release of plasma alpha-hydroxybutyrate dehydrogenase was determined centrally in the core laboratory for enzyme determinations from

Figure 3. Radial axes method. The central axis (0 to 180°) is determined by the center of mass of the end-diastolic contour and the junction of the mitral and aortic valves. The percent radial shortening of approximately 300 radii (**shaded area**) is calculated as:

$$\frac{\text{(End-diastolic radius} - \text{End-systolic radius)}}{\text{End-diastolic radius}},$$

and plotted together with the mean (± 2 standard deviations [SD]) of a group of 31 normal (Norm) subjects (**three solid lines**). The sector in which radial shortening was less than the mean normal radial shortening minus 2 standard deviations is called the hypokinetic region (in this example, from 85 to 233°).



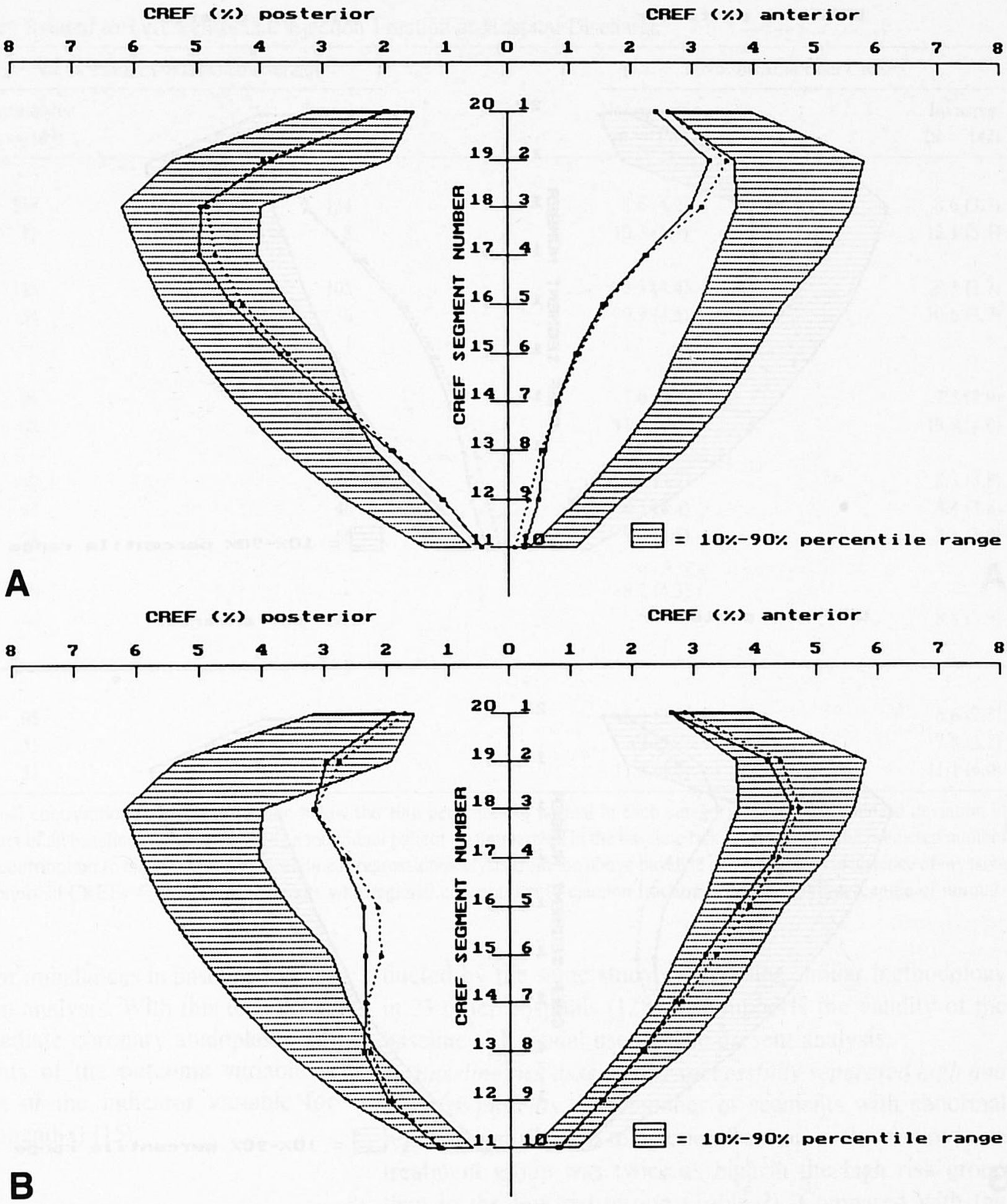


Figure 4. Mean regional contribution to global ejection fraction (CREF) in 20 segments of the left ventriculogram in patients with anterior (**A**) and diaphragmatic (**B**) infarct localization. The **hatched area** represents the normal 10% to 90% range. Patients allocated to the noninvasive strategy are represented by the **dotted line**; patients allocated to invasive treatment by the **solid line**. Analysis was done with the regional contribution to ejection fraction method.

serial plasma samples at 12, 24, 36, 48 and 72 h after treatment onset. Details have been published elsewhere (1,12).

Data Analysis

Baseline risk assessment. Because more patients in the invasive treatment group did not undergo cardiac catheterization because of death or cardiac contraindications than in the noninvasive group (Table 1), unequal distribution of high risk patients among the two treatment groups in the present analysis was likely to influence the measured treatment effect of the invasive strategy. Therefore, individual baseline risk was assessed.

Baseline risk assessment consisted of three steps. First, the relation between baseline characteristics and the number of segments with regional contribution to ejection fraction below the 10th percentile of normal was assessed with multivariate linear regression analysis. Only baseline characteristics known to be related to left ventricular function (13) or outcome of coronary angioplasty (14), or both, were considered: 1) age, 2) gender, 3) history of previous infarction, 4) history of angina >4 weeks, 5) sum of ST segment elevation on the ECG, 6) infarct localization, 7) hemodynamic status before thrombolytic treatment, and 8) delay

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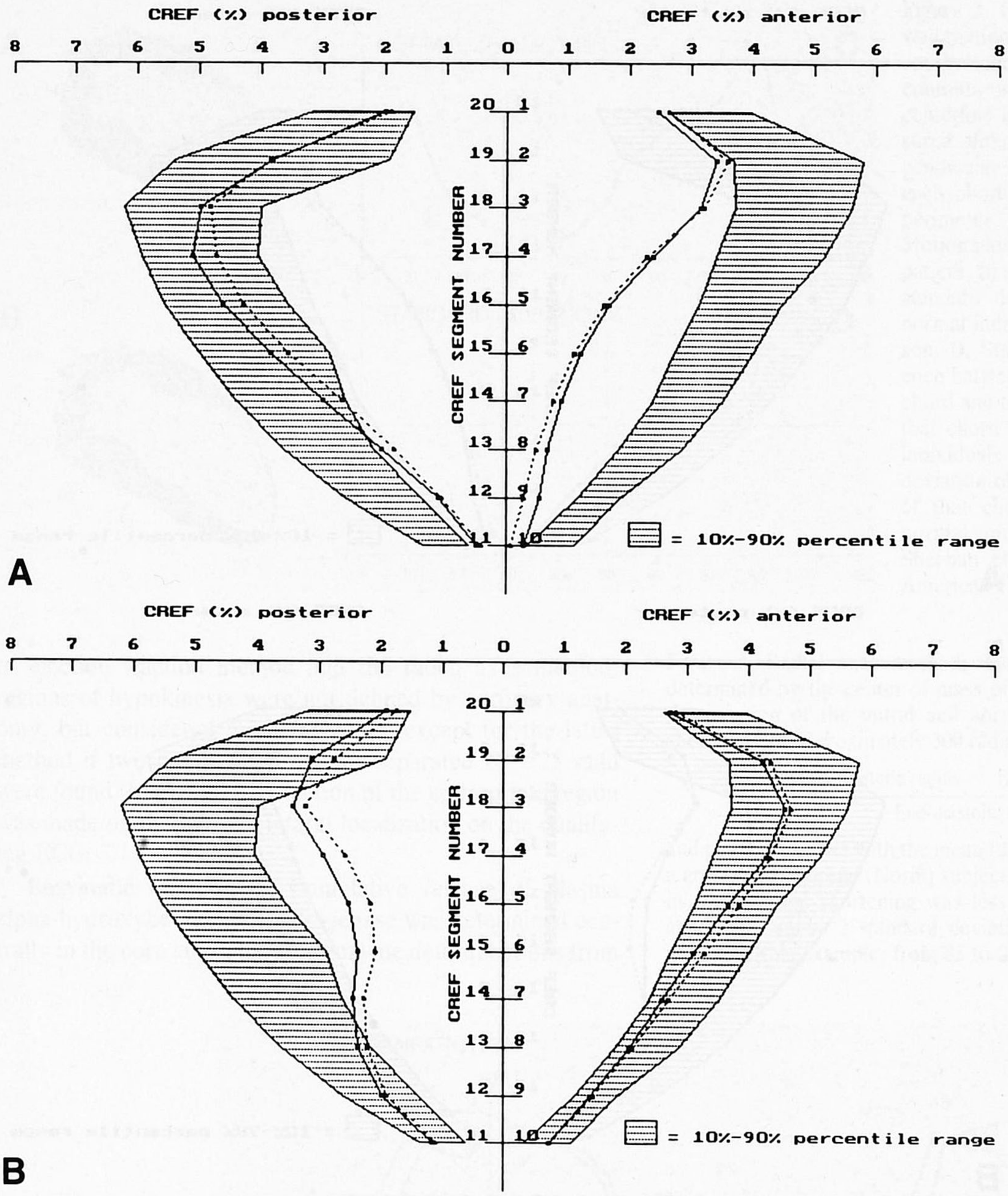

Figure 5. Mean regional contribution to global ejection fraction (CREF) in 20 segments of the left ventriculogram in patients with a patent infarct-related vessel on angiography between days 10 and 22 (Thrombolysis in Myocardial Infarction perfusion grade 2 or 3) and without reinfarction. Anterior (**A**) and diaphragmatic (**B**) infarct localization. The **hatched area** represents the normal 10% to 90% range. Patients allocated to the noninvasive strategy are represented by the **dotted line**; patients allocated to invasive treatment by the **solid line**.

from symptom onset to start of rt-PA infusion. Details of the multivariate linear regression analysis are given in the Appendix. Second, the number of segments with regional contribution to ejection fraction below the 10th percentile of normal was calculated from this multivariate model in each patient by setting the indicator variable for treatment allocation to values indicating noninvasive treatment. Finally, patients were subdivided in three equally sized groups of low, medium and high baseline risk.

Subgroup analysis. The number of segments with regional contribution to ejection fraction below the 10th percentile of normal was assessed in both treatment groups stratified according to variables available before treatment allocation. The regional contribution to ejection fraction method was chosen for the baseline risk assessment and subgroup analysis because it has the advantage that it is applicable without knowledge of the infarct-related vessel. The method is therefore available in a higher proportion of patients. Furthermore, the method is validated in both animal and patient studies (2,6). The multivariate methodology is described in the Appendix.

Adjustment for imbalances in baseline risk. Differences between both treatment groups for all variables of regional

Table 2. Baseline Characteristics Related to Left Ventricular Ejection Fraction at Hospital Discharge

	No. of Patients With Characteristic		No. of Abnormal CREFs	
	Noninvasive (n = 149)	Invasive (n = 142)	Noninvasive (n = 149)	Invasive (n = 142)
History of infarction				
No	138	134	8.6 (4.2)	8.6 (3.7)
Yes	11	8	10.3 (5.7)	12.1 (5.1)
Sum ST (mV)				
<2	115	105	8.3 (4.4)	8.3 (3.7)
≥2	34	36	9.9 (4.1)	10.6 (3.7)
Missing	—	1		
Anterior infarct localization				
No	86	78	7.0 (3.2)	7.2 (2.9)
Yes	63	64	11.0 (4.6)	10.8 (4.0)
Delay to rt-PA (h)				
<2	42	30	7.4 (3.7)	8.3 (3.8)
2–3	53	46	8.5 (4.4)	8.4 (3.8)
≥3	54	66	9.8 (4.5)	9.4 (3.9)
Allocation to invasive strategy				
No	149	—	8.7 (4.3)	—
Yes	—	142	—	8.8 (3.9)
Baseline risk score				
Low	43	35	6.2 (2.8)	6.6 (2.3)
Medium	55	49	7.7 (3.7)	7.8 (3.2)
High	51	58	11.8 (4.3)	11.1 (4.0)

Number of segments with regional contribution to ejection fraction below the 10th percentile of normal in each category (mean and standard deviation in parentheses). The simultaneous impact of all baseline characteristics in an individual patient is summarized in the baseline risk score (that is, the predicted number of segments with abnormal regional contribution to ejection fraction, with linear regression analysis from the above baseline characteristics in absence of invasive treatment) (see Methods). No. of abnormal CREFs = number of segments with regional contribution to ejection fraction below the 10th percentile of normal.

wall motion were adjusted for imbalances in baseline risk by multivariate linear regression analysis. With this technique, the treatment effect of immediate coronary angioplasty adjusted for other determinants of the outcome variable is provided by the coefficient of the indicator variable for treatment allocation (see Appendix) (15).

Results

The regional contribution to ejection fraction method could be assessed in all 291 patients with an analyzable left ventriculogram between days 10 and 22. Determination of the maximally abnormally contracting 50% (centerline method) was not possible in 28 patients in the noninvasive and 9 patients in the invasive treatment group because of uncertainty about which vessel was infarct-related.

Baseline characteristics related to regional left ventricular wall motion (Table 2). Anterior infarct localization and previous myocardial infarction were strong predictors of poor regional left ventricular function. Other contributors to reduced wall motion were the sum of ST segment elevation and delay to start of rt-PA therapy. Linear regression coefficients (Table 3) indicate the contribution of each determinant of baseline risk. Intercept and coefficients as observed in this trial were very similar to those in 577 other patients entered in the rt-PA/placebo trial, which is conducted by the same study group using similar methodology in 23 other hospitals (12). This supports the validity of the baseline risk model used in the present analysis.

Baseline risk assessment successfully separated high and low risk patients. The number of segments with abnormal regional contribution to ejection fraction in the noninvasive treatment group was twice as high in the high risk group than in the low risk group (Table 2). Compared with the noninvasive treatment group, there was an excess of high risk patients with an assessable left ventriculogram in the invasive treatment group (40.8% versus 34.2%, respectively). As a consequence, any true difference in regional wall motion between treatment groups cannot be assessed without adjustment for this unequal distribution of baseline risk.

Left ventricular function (Table 4). After such adjustment, ventricular function was similar in the two treatment groups, both for global and regional wall motion. Confidence intervals for the differences were nearly symmetrically around zero, indicating that no real difference in treatment effect between the two treatment strategies was present.

Subgroup analysis. None of the patient subsets defined by the baseline characteristics mentioned in the Methods section benefited from immediate angioplasty as determined by either univariate (Table 2) or multivariate analysis.

Table 3. Multivariate Linear Regression Analysis to Predict the Number of Segments With Abnormal Regional Contribution to Ejection Fraction

Model	All Patients (n = 291)	Patent IRV/No Reinfarction (n = 242)	rt-PA/Placebo Trial (n = 577)
Intercept	5.6	5.8	6.5
History of infarction			
No	—	—	—
Yes	2.5 (0.8)	2.6 (0.9)	2.4 (0.6)
Sum ST (mV)			
<2	—	—	—
≥2	1.8 (0.5)	1.7 (0.5)	1.6 (0.3)
Anterior infarct localization			
No	—	—	—
Yes	3.7 (0.4)	3.6 (0.4)	3.1 (0.3)
Delay to rt-PA (h)			
<2	—	—	—
2–3	1.0 (0.5)	1.1 (0.6)	0.6 (0.4)
≥3	1.5 (0.5)	1.3 (0.6)	1.1 (0.4)
Allocation to invasive strategy			
No	—	—	
Yes	−0.1 (0.4)	−0.4 (0.4)	
Allocation to rt-PA			
No			—
Yes			−0.5 (0.3)

In the first model, all 291 patients were included. A second model was developed in 242 patients with a patent infarct-related vessel at angiography between days 10 and 22 and without reinfarction. To test the reproducibility, a similar multivariate model was developed in an independent group of 577 patients with analyzable left ventriculograms from the rt-PA/placebo trial of the European Cooperative Study Group (12). Coefficients for treatment allocation represent the treatment effect of immediate angioplasty in the first two models and the effect of treatment with rt-PA in the third model. The number of abnormal segments in an individual patient is determined by adding up intercept and all relevant coefficients. For example, a patient without previous infarction, >2 mV ST elevation, inferior infarction, Killip class 1, treated with rt-PA within 2 h and allocated to invasive strategy has 5.6 + 1.8 − 0.1 = 7.3 segments with abnormal contribution to ejection fraction. The same patient after noninvasive therapy has 7.4 abnormal segments. Values are linear regression coefficients with their standard error in parentheses.

Occlusion of infarct-related vessel and reinfarction. Patency of the infarct-related vessel could not be assessed in 4 of the 149 patients in the noninvasive treatment group and in 1 of the 142 patients in the invasive treatment group with analyzable left ventriculograms. An occluded infarct-related vessel at angiography between days 10 and 22 or reinfarction, or both, occurred more often in the invasive treatment group (25 of 141 patients) than in the noninvasive treatment group (19 of 145 patients).

In patients with a patent infarct-related vessel at angiography between days 10 and 22 and without reinfarction, global left ventricular ejection fraction was 1.9 percentage points better in the invasive strategy group (Table 5). This was merely due to a smaller area of hypokinesia. The severity of hypokinesia and hyperkinesia was similar in both treatment groups. Findings for all three models of regional wall motion analysis were consistent. In this subset of patients, enzymatic infarct size was similar in both treatment groups (median alpha-hydroxybutyrate dehydrogenase plasma activity 615 U/liter [90% confidence range 46 to 1,882] in 126 patients in the noninvasive treatment group and 660 U/liter [90% range 115 to 1,576] in 116 patients in the invasive treatment group). The same was found after adjustment for unequal baseline risk (infarct localization, time to rt-PA infusion and ST segment elevation) with linear regression analysis.

Discussion

Despite thrombolytic therapy with rt-PA, the infarct-related vessel remains occluded in approximately 25% of patients (1,4,16). Furthermore, some patients have a hemodynamically significant stenosis after thrombolysis. Immediate coronary angioplasty has been proposed to recanalize the remaining occluded vessels and improve blood flow in patients with severe residual stenosis.

Recovery of left ventricular function and the incidence of reocclusion were reported to be related to the degree of residual stenosis after thrombolysis (17–19) and the results of small randomized trials (20,21) assessing immediate angioplasty with and without intracoronary streptokinase suggested that recovery of left ventricular function might be improved by angioplasty. However, the present larger randomized trial of the European Cooperative Study Group failed to confirm this. Other investigators also reported lack

Table 4. Treatment Effect of Immediate Coronary Angioplasty Before and After Adjustment for Unequal Baseline Risk in All 291 Patients

	Mean (SD)		Difference (invasive − noninvasive)		
	Noninvasive (n = 149)	Invasive (n = 142)	Crude	Adjusted	95% Confidence Interval*
Global LV function					
LVEF (%)	49.7 (11.4)	49.7 (10.8)	0.0	0.7	−1.6 to 2.9
Extent of hypokinesia					
CREF	8.7 (4.3)	8.8 (3.9)	0.2	−0.1	−0.8 to 0.7
Centerline	32.4 (21.4)	33.2 (20.9)	0.8	−0.1	−4.3 to 4.1
Radial axes	44.7 (21.0)	43.8 (20.1)	−0.9	−1.5	−6.1 to 3.0
Severity of hypokinesia					
CREF	1.4 (0.7)	1.5 (0.7)	0.1	0.1	−0.1 to 0.2
Centerline	−2.8 (1.6)	−2.7 (1.6)	0.1	0.1	−0.3 to 0.5
Radial axes	0.6 (0.8)	0.7 (0.9)	0.1	0.1	−0.0 to 0.3
Extent of hyperkinesia					
CREF	2.1 (2.3)	2.0 (2.2)	−0.1	0.0	−0.5 to 0.5
Severity of hyperkinesia					
CREF	4.3 (2.2)	4.2 (2.1)	−0.1	−0.3	−0.8 to 0.3
Centerline	0.2 (1.2)	0.1 (1.3)	−0.0	−0.1	−0.4 to 0.2

*For adjusted difference. The regional contribution to ejection fraction (CREF), centerline and radial axes methods were used to determine the extent of hypokinesia in 291, 289 and 291 patients, respectively; severity of hypokinesia was assessed in 289, 255 and 285 patients, respectively. The severity of hyperkinesia was assessed in 189 patients with the regional contribution to ejection fraction method (in 102 patients, no hyperkinesia was present with this method) and in 255 patients with the centerline method. The extent of hyperkinesia was assessed in 291 patients. Values are mean and standard deviation (in parentheses). LV = left ventricular; LVEF = left ventricular ejection fraction.

of benefit of immediate (4,16) or delayed (18 to 48 h) (5) angioplasty in patients treated with rt-PA.

Baseline comparability. There was an excess in baseline risk in the invasive treatment group in the present analysis. This could not be explained by the fact that patients without predischarge left ventriculography were excluded in the present analysis because lack of left ventriculography was related to poor left ventricular function and the fact that more patients in the invasive treatment group did not undergo left ventriculography (Table 1). The explanation is that randomization did not yield groups of identical baseline risk. Although randomization is the best way of achieving patient

Table 5. Treatment Effect of Immediate Coronary Angioplasty Before and After Adjustment for Unequal Baseline Risk in 242 Patients With a Patent Infarct-Related Vessel at Angiography Between Days 10 and 22 (TIMI perfusion grade 2 or 3) and Without Reinfarction Before Angiography

	Mean (SD)		Difference (invasive − noninvasive)		
	Noninvasive (n = 126)	Invasive (n = 116)	Crude	Adjusted	95% Confidence Interval
Global LV function					
LVEF (%)	49.0 (11.5)	50.8 (9.9)	1.9	1.9	−0.5 to 4.4
Extent of hypokinesia					
CREF	9.1 (4.3)	8.6 (3.7)	−0.5	−0.5	−1.3 to 0.4
Centerline	34.5 (22.1)	32.1 (19.5)	−2.4	−2.1	−6.7 to 2.5
Radial axes	46.3 (20.5)	42.4 (19.3)	−3.9	−3.9	−8.7 to 0.9
Severity of hypokinesia					
CREF	1.4 (0.6)	1.6 (0.7)	0.1	0.1	−0.0 to 0.3
Centerline	−2.9 (1.6)	−2.6 (1.5)	0.3	0.2	−0.2 to 0.6
Radial axes	0.6 (0.7)	0.8 (0.9)	0.2	0.2	−0.0 to 0.4
Extent of hyperkinesia					
CREF	1.9 (2.1)	1.8 (2.0)	−0.1	−0.1	−0.6 to 0.4
Severity of hyperkinesia					
CREF	4.3 (2.3)	4.2 (2.2)	−0.1	−0.3	−0.9 to 0.3
Centerline	0.1 (1.2)	0.2 (1.3)	0.1	0.1	−0.3 to 0.4

Utilizing the regional contribution to ejection fraction (CREF), centerline and radial axes methods as in Table 4, the numbers of patients respectively evaluated were: extent of hypokinesia = 242, 239 and 242; severity of hyperkinesia = 242, 215 and 237; severity of hyperkinesia = 152 with the regional contribution to ejection fraction method (90 with no hyperkinesia) and 214 with the centerline method. Abbreviations as in Table 4.

groups with identical baseline risk, it is not always successful, especially in small and medium-sized trials (22).

Multivariate linear regression analysis provides an estimation of relative efficacy of treatment strategies, adjusted for imbalances in baseline risk. After adjustment, no benefit of immediate angioplasty was found.

Occlusion of infarct-related vessel and reinfarction. In the present trial, immediate angioplasty was associated more frequently with an occluded infarct-related vessel and reinfarction during the hospital stay, which might have abolished a benefit from immediate angioplasty. In fact, a trend toward improved regional wall motion was observed in those patients with a patent infarct-related vessel and without recurrent infarction at the time of hospital discharge. The magnitude of treatment effect of immediate angioplasty in these patients was of the same order of magnitude as that found for thrombolytic therapy with rt-PA in comparison with placebo (Table 3). This suggests that immediate angioplasty may be beneficial if the complications of angioplasty (that is, reocclusion and reinfarction) can be prevented.

Better left ventricular function after immediate coronary angioplasty in patients without reocclusion or reinfarction, or both, may be explained by further limitation of infarct size and by enhancement or acceleration of left ventricular recovery. The fact that enzymatic infarct size was not reduced favors the latter explanation. In addition, this is in agreement with the observation that recovery of left ventricular function is related to residual stenosis after thrombolytic therapy (17).

One might argue that excluding patients in whom infarct-related vessel patency could not be assessed might have influenced the effect of immediate angioplasty in patients with a patent infarct-related vessel and without reinfarction. However, the same results were obtained if these patients were included in the analysis.

The lack of benefit of the invasive strategy in the present trial may also be partly due to sudden and complete reperfusion during angioplasty. There is evidence from animal experiments that recovery of left ventricular function is accelerated after gradual reperfusion (over 2 h) in comparison with recovery after sudden reperfusion. The underlying mechanism is unknown, but the no-reflow phenomenon and increased calcium influx with contraction band necrosis may contribute (23). Thus, a certain degree of residual stenosis after thrombolysis may help protect myocardium against reperfusion damage. This would favor an approach of immediate thrombolytic recanalization or mechanical recanalization with a guidewire, followed by coronary angioplasty after a few hours. This regimen requires further study.

Patient selection. In the present trial, no patient subset benefited from coronary angioplasty; angioplasty was attempted in most patients (92%), including patients with an occluded infarct-related vessel. Initial experience with immediate coronary angioplasty in patients with an occluded infarct-related vessel at 90 min after start of thrombolysis with rt-PA ("rescue angioplasty") was not favorable (16), but promising results were obtained when rt-PA was combined with urokinase (24). The concept of rescue angioplasty deserves further study in connection with a treatment regimen for the prevention of reocclusion or reinfarction. This is especially true if patients with persistent occlusion (failed thrombolysis) can be recognized noninvasively. At present, angioplasty and coronary bypass surgery should be reserved for treatment of recurrent postinfarction ischemia not responding to medical treatment. The role of thallium myocardial perfusion scintigraphy in the selection of patients for revascularization procedures remains unknown.

Conclusion. No benefit of an invasive strategy of immediate coronary angioplasty in addition to rt-PA, heparin and aspirin could be documented when compared with a noninvasive strategy with rt-PA, heparin and aspirin alone. Nevertheless, a trend toward benefit of immediate angioplasty was found in selected patients with a patent predischarge infarct-related vessel and without reinfarction. This suggests that reocclusion and reinfarction are responsible for the lack of benefit from immediate coronary angioplasty after thrombolytic therapy for acute myocardial infarction. At present, an invasive strategy with immediate angiography and angioplasty cannot be recommended, but angioplasty in selected patients (for example, those with failed thrombolysis) warrants further investigation provided that reocclusion and reinfarction can be prevented.

Appendix

Linear regression analysis. This was performed (BMDP statistical software package, program 1R and 2R) to assess the relation between the variables mentioned in the Methods section (independent variables = X_i) and each variable of left ventricular function (dependent variable = Y):

$$Y = A + \sum_i B_i X_i.$$

Independent and dependent variables. Indicator variables were defined by assigning zero to patients in whom an event or characteristic was absent and 1 in those in whom an event or characteristic was present. Continuous variables were not used directly. For these variables, patients were categorized in three equally sized subgroups according to patient values for that variable. The category with the lowest value for the variable of wall motion under study was chosen as the reference group. For the second and third subgroups, indicator variables were designed: 1 in case a patient belonged to that subgroup, zero if not. Thus, patients in the reference group were characterized by zero for the design variable for the second and third subgroup.

Design of the linear regression models. For the baseline risk model, all indicator variables representing the baseline characteristics mentioned in the Methods section were simultaneously entered in the model. Only indicator variables with coefficients of $p \leq 0.1$ were retained in subsequent models unless a product term of that term with another term had to be included in the model. In that case, the indicator variable was forced into the model. The same applied for the indicator variable of treatment allocation.

For each variable of regional wall motion, the same independent

variables as used for the baseline risk assessment were entered in a model to adjust for unbalanced baseline risk of regional wall motion.

To assess the contributions of the various determinants in both treatment groups separately, "product terms" (indicator variable for determinant under study multiplied by the indicator variable of treatment allocation) were tested in the model (25).

Interpretation of results of linear regression model. Because all independent variables are zero/1 variables, the coefficients (B_i) reflect the difference (DIF) in the number of segments with regional contribution to ejection fraction below the 10th percentile of normal between a patient with characteristic X_i and a patient without that characteristic, all other determinants of regional wall motion being equal. The 95% confidence limits for this difference may be calculated from the standard error (SE_i) of the coefficient (15):

$$DIF_i \pm 1.96 * (SE_i).$$

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