

Preservation of Global and Regional Left Ventricular Function After Early Thrombolysis in Acute Myocardial Infarction

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The effect of early myocardial reperfusion (within 4 hours after onset of symptoms) on regional left ventricular function in patients with acute myocardial infarction has been quantitated by analysis of segmental wall motion. Of 533 patients randomized either to conventional coronary care unit therapy or to a reperfusion strategy, in 332 high quality angiograms were obtained 2 to 8 weeks after the onset of myocardial infarction. In those assigned to thrombolytic therapy, angiographic data were also available after acute reperfusion. Analysis on an "intention to treat" basis revealed significant preservation of left ventricular function after thrombolytic therapy (ejection fraction 53%) compared with conven-

tional treatment (ejection fraction 47%). In addition, wall motion analysis showed significant improvement of regional function in the infarct zone in both inferior and anterior infarction. In addition, significant changes occurred in regional function of the remote "noninfarct zone" in the acute as well as the chronic stage. It is concluded that improved regional and global left ventricular function can be achieved with early reperfusion and that this is the likely explanation for the reduction of early and late mortality after thrombolysis observed in this study.

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Since the clinical investigations of Rentrop et al. (1), many studies have confirmed that acutely occluded coronary arteries in patients with acute myocardial infarction can be recanalized by intracoronary infusion of thrombolytic agents (2). It is assumed that early reestablishment of anterograde flow can prevent myocardium, rendered temporarily ischemic by coronary thrombotic occlusion, from progressing to complete necrosis. Animal experiments have shown that timely restoration of coronary blood flow can salvage myocardium (3-6) and improve survival (4). However, reported human data are still conflicting, largely because of differ-

ences in the dose and route of administration of the thrombolytic agent and because of the long intervals between the onset of symptoms and reperfusion. Furthermore, the risks of undergoing angiography in the first hours of myocardial infarction are not negligible (7) and may even outweigh the potential benefits of recanalization in some patients. Reperfusion of ischemic myocardium has been shown to cause arrhythmias (8), intramyocardial hemorrhage (9,10) and calcium overload of myocardial cells with subsequent death as a result of rapid reperfusion (the oxygen paradox) (11). All these factors may negate the beneficial effects of reperfusion.

To determine whether thrombolysis is a clinically useful approach in acute myocardial infarction, a randomized trial was started in June 1981. This report details the analysis of the influence of myocardial reperfusion on left ventricular function after attempted recanalization in comparison with similar studies in patients randomly assigned to conventional treatment. Follow-up data from this study have been published recently (12) and demonstrated improved 1 year sur-

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vival after thrombolysis (91%) compared with conventional treatment (84%, $p = 0.01$). This improved survival is associated with a limitation of infarct size, estimated from myocardial enzyme release, and with preservation of global left ventricular function measured by radionuclide angiography (12a).

In the randomized trials published thus far (13-19), the assessment of global ejection fraction has prevailed because it is relatively easily obtainable. However, improvement in global left ventricular function after successful recanalization might be attributed to several factors: salvage of jeopardized myocardium, compensatory hyperactivity of opposite wall segments (20,21) or changes in preload and afterload. In an effort to unravel these factors, the effect of myocardial reperfusion on left ventricular function was analyzed by measuring systolic regional wall motion along 20 coordinates.

Methods

Patient selection. This randomized trial of thrombolysis in acute myocardial infarction is a multicenter study supported by the Interuniversity Cardiology Institute in the Netherlands. The protocol and some initial results were published in 1982 (7,22-24). Because preliminary data (25-27) indicated that reocclusion of the coronary artery occurred predominantly in patients with severe residual stenosis, immediate percutaneous transluminal coronary angioplasty was added to the procedure in those patients in whom visual inspection of the coronary arteriograms suggested residual stenosis in excess of 60%. When it also became evident that possibly crucial time was lost by preparation for catheterization, while other studies (28-30) reported angiographic confirmation of thrombolysis after intravenous streptokinase infusion, it was decided (January 1984) to give intravenous streptokinase (500,000 U) at the time of hospital admission. This meant that thrombolytic therapy was begun approximately 1 hour before intracoronary streptokinase could be started in the treatment arm. Admission to the study was discontinued in March 1985.

During the study period all patients up to the age of 70 years with chest pain and electrocardiographic signs of typical myocardial infarction who were admitted within 4 hours after the onset of symptoms were eligible for the trial. The usual exclusion criteria for thrombolytic therapy were applied as described in detail in previous reports (12a,22-24). The protocol is summarized in Figure 1. After inclusion, the 533 patients were registered by a central telephone answering service that also provided treatment allocation (12a). Informed consent was obtained from the 269 patients allocated to thrombolytic therapy only, as proposed by Zelen (31). Patients who refused consent were treated according to the same guidelines as the control group (32).

Conventional treatment in all patients was directed

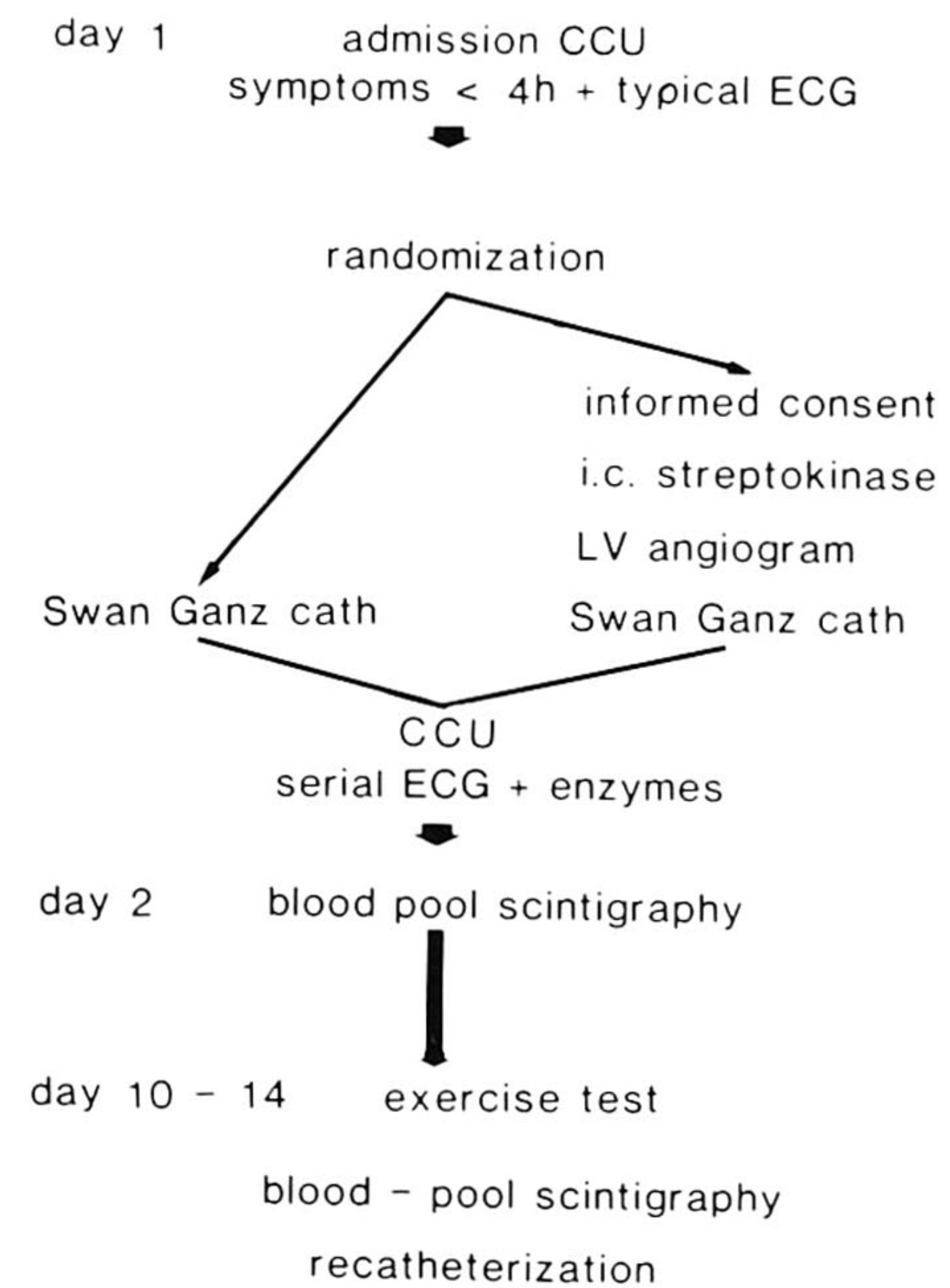


Figure 1. Flow chart of the procedures in the current randomized trial at the Thoraxcenter and other members of the Interuniversity Cardiological Institute. cath = catheterization; CCU = cardiac care unit; ECG = electrocardiogram; i.c. = intracoronary; LV = left ventricular.

toward rapid achievement of an "optimal" hemodynamic state characterized by light sedation, heart rate between 60 and 90 beats/min, systolic blood pressure between 100 and 140 mm Hg and the absence of signs of left ventricular failure or a pulmonary capillary wedge pressure below 12 mm Hg.

All patients were treated with heparin followed by acenocoumarol (Sintrom) until hospital discharge. After discharge, anticoagulant agents were continued only in patients with ventricular aneurysm, intraventricular thrombus, mitral incompetence or a large ventricle with a poor contraction pattern. Metoprolol, 100 mg two times daily, was prescribed in the majority of patients from the 7th to the 14th study day onward unless contraindications were present.

Reperfusion protocol. In the 269 patients assigned to streptokinase treatment, nitroglycerin infusion (100 $\mu\text{g}/\text{min}$) was started immediately and the patients were transferred to the catheterization laboratory as soon as possible. Lidocaine was given intravenously in a dose of 2 mg/min. After puncture of the femoral vein and artery, a pacemaker catheter was positioned in the right ventricle. Next, coronary arteriography of the artery suspected to be thrombosed was performed. No evaluation of the collateral circulation was performed before thrombolysis because such effort would have postponed the actual onset of recanalization and perhaps reduced its possible benefit. The disastrous consequence of injection of ionic contrast medium into the contralateral artery, particularly when it is the right coronary artery, has been previously reported (7). After identification

of the thrombosed coronary branch, 5,000 U heparin was administered intravenously together with 250 mg of acetylsalicylic acid and 100 mg of a corticosteroid (Diadreson F), in order to reduce possible antigenic effects of streptokinase.

Intracoronary perfusion was carried out at a rate of 4,000 U/min to a maximum of 250,000 U streptokinase, diluted in 500 ml of physiologic solution, at a flow rate of 8 ml/min. Coronary angiograms were repeated every 15 minutes until the vessel was patent or the chest pain had disappeared. The appearance or reappearance of ventricular extrasystoles or any conduction disturbance was also an indication to revisualize the artery. If there were no signs of recanalization, an attempt was made to administer streptokinase locally in a higher concentration by passing a thin catheter with a radiopaque tip through the Judkins catheter (8F).

After completion of the streptokinase infusion, the nitroglycerin and lidocaine infusions were interrupted and complete left and right coronary arteriography was performed. If the clinical condition was stable with left ventricular end-diastolic pressure below 35 mm Hg, left ventriculography was performed in the right anterior oblique projection. Coronary arteriography and left ventricular angiography were performed in both the control and thrombolysis-treated groups, either before hospital discharge or 4 to 8 weeks after the acute phase of infarction.

Analysis of global and regional left ventricular function. Global and regional left ventricular function was studied from the 30° right anterior oblique left ventricular cineangiogram with an automated hard-wired endocardial contour detector linked to a minicomputer (33). For each analyzed cineframe, left ventricular volume was computed according to Simpson's rule. After the end-diastolic and end-systolic frames were determined, stroke volume, global ejection fraction and total cardiac index were computed. Figure 2A shows an example of the end-diastolic and end-systolic contours of the left ventriculogram, as displayed by the analysis system. Systolic regional wall displacement is determined along a system of 20 coordinates based on the pattern of actual endocardial wall motion in normal individuals (34), and generalized as a mathematical expression amenable to automatic data processing (23,35).

For each segment, segmental volume is computed from the local radius (R) and the height of each segment (1/10 of left ventricular long-axis length (L) according to the formula: $1/20 \pi R^2 L$). When normalized for end-diastolic volume, the systolic segmental volume change can be considered as a variable of regional pump function (Fig. 2B and C). During systole this variable expresses quantitatively the contribution of a particular segment to global ejection fraction, termed regional contribution to global ejection fraction (24). The sum of the values for all 20 segments equals the global ejection fraction. The hatched zones in Figure 2D represent the segmental values of this variable between the 10th and 90th percentiles, as determined in 20 normal in-

dividuals. The regional contribution to ejection fraction in the anterobasal (segments 1 to 5), anterolateral (segments 5 to 9), apical (segments 9, 10, 11 and 12), inferior (segments 12 to 16) and posterobasal (segments 16 to 20) wall regions was compared in the control group and thrombolysis groups.

Statistics. Data are expressed as mean \pm SD. Paired or unpaired Student's *t* tests were applied to the hemodynamic data whenever appropriate and differences in baseline characteristics between groups were tested by Fisher's exact test.

Results

Early and late angiography. A total of 533 patients were admitted to the trial in five participating hospitals; 264 patients were allocated to conventional therapy and 269 patients to thrombolysis. In 35 patients allocated to thrombolysis, angiography could not be performed because informed consent was refused (20 patients), a contraindication occurred before angiography (1 patient), the coronary could not be reached from the femoral artery (6 patients) or pain and ST elevation resolved shortly after randomization (5 patients).

Of 234 patients who underwent early angiography (Table 1), 65 had a patent infarct-related coronary artery and in 169 this artery was occluded. In 136 patients undergoing catheterization without previous intravenous streptokinase infusion, the infarct-related vessel was occluded in 111 (82%) and recanalization was achieved in 88 (79%) of these after 30 minutes (median) of intracoronary infusion of streptokinase. An occluded artery was found in 58 (59%) of 98 patients who received intravenous streptokinase before its intracoronary administration. Subsequently, intracoronary streptokinase caused recanalization in 39 patients while in 5 the thrombus was perforated by guidewire or angioplasty catheter. Ultimately, the infarct-related artery remained occluded in 36 of 234 patients who underwent angiography and at least one attempt at recanalization (15%), and the artery was open at study time or became recanalized in 198 patients (85%). In addition, transluminal coronary angioplasty succeeded in 44 of 46 patients in whom it was attempted. The median time between onset of symptoms and angiographic documentation of a patent infarct-related vessel was 200 minutes (Table 2).

Follow-up angiograms of high quality were available in 332 of the 533 patients. These data were missing in 42 patients who died in the intervening period, 24 who underwent early bypass surgery, 23 who were transferred to another hospital and 41 who refused the second angiographic study; in 71 patients angiograms were obtained, but were inadequate for quantitative analysis. The angiograms that were available in 332 patients are described in this report. These angiograms were made before discharge in 279 patients (median 11 days after entry) and after discharge in

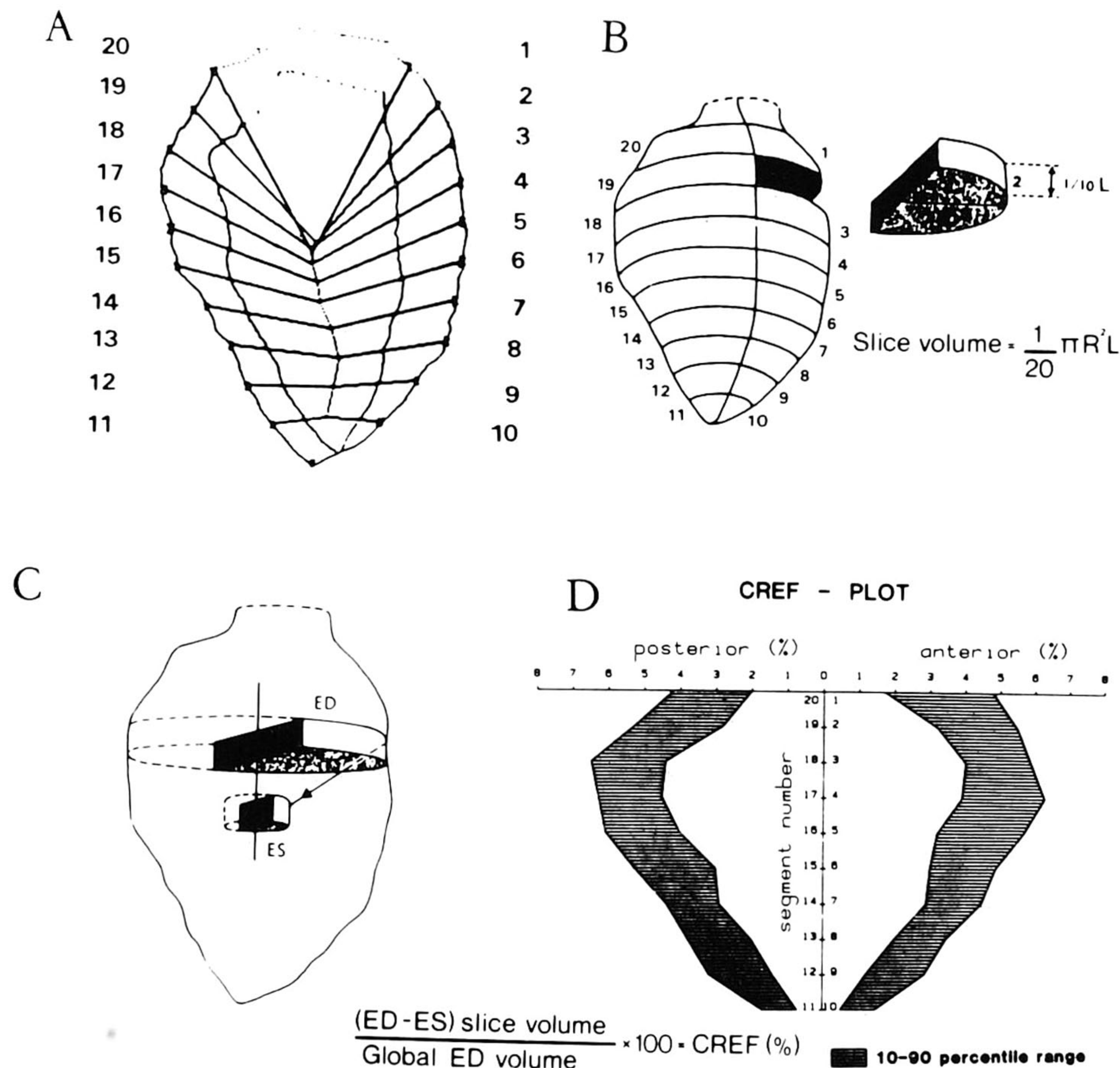


Figure 2. **A**, Example of the computer output showing the end-diastolic and end-systolic contours of the 30° right anterior oblique left ventriculogram and the system of 20 coordinates along which left ventricular segmental wall displacement is determined. **B**, The left ventricular end-diastolic cavity is divided into 20 half slices. The volume of each half slice is computed according to the formula $\frac{1}{20} \pi R^2 L$, where R is radius and L is left ventricular long-axis length. **C**, The regional contribution to global ejection fraction is determined from the systolic decrease of volume of the half slice which corresponds to a particular wall segment. The systolic volume change is mainly a consequence of the decrease of radius (R) of the half slice. ED = end-diastolic; ES = end-systolic. **D**, The shaded zones represent the 10th to 90th percentile areas of values of regional contribution to global ejection fraction in normal individuals. On the x axis the global ejection fraction values of the anterior and inferoposterior wall areas are displayed (%), while on the y axis the segment numbers of the anterior wall (1 to 10) and of the inferoposterior wall (11 to 20) are depicted.

124 patients (median 42 days after entry). During follow-up angiography, the rate of vessel patency in the control group and thrombolysis group was, respectively, 52% (90 of 174) and 77% (122 of 158) ($p = 0.0001$). The reocclusion rate in patients with arterial recanalization by intracoronary streptokinase was 21% (19 of 91 patients), while late occlusion in the patients with a patent infarct-related vessel at

first angiogram was 6% (2 of 36 patients). Baseline data in Table 3 were comparable in both groups.

Global left ventricular function: thrombolysis versus conventional treatment. When the hemodynamic data of the control group are compared with those of the thrombolysis group, almost all the variables listed in Table 4 show significant differences. The global left ventricular ejection fraction in the thrombolysis group was on average 6% higher ($p = 0.0001$) than in the control group, a difference mainly due to a smaller end-systolic volume in the thrombolysis group (41 versus 53 ml/m² in the control group, $p = 0.0004$). In addition, the end-diastolic volume was significantly higher and abnormal in the control group compared with the thrombolysis group (95 versus 84 ml/m², $p = 0.006$) whereas mean aortic pressure and heart rate were not different at the time of the hemodynamic investigation. In Table 5 the hemodynamic data of both groups are shown after exclusion of those 65 patients who had had a previous infarction (40 in the control group and 25 in the thrombolysis group). The differences observed between conventional or thrombolytic therapy in the entire group of 332 patients remain present to a significant degree, but in the thrombolysis group, the ejection fraction is now 6% higher ($p = 0.0002$) than in the control group, while the end-systolic volume is 10 ml/m² smaller ($p = 0.0015$) than in the control group.

Table 1. Results of Early and Late Angiography

Group	Early Angiography	No Late Angiography (not performed or data missing)					Late Angiography	
		Patient Refusal	Death	CABG	Inadequate Quality of LV Angiogram	Other	○	●
Control (n = 264)		19	27	4	31	9	90	84
Thrombolysis (n = 269)	35 no early angiography	5	4	2	8	2	6	8
	65 ○ → 65 ○	1	1	9	13	5	34	2
	169 ● → 133 ○	11	4	4	17	6	72	19
	36 ●	5	6	5	2	1	10	7
Total (n = 533)		41	42	24	71	23	212	120

Patent vessels are indicated by (○) and occluded vessels by (●). CABG = patients without late angiography because of coronary bypass surgery; death = patients who died before late angiography was performed; LV = left ventricular; other = other missing data, for example, because of transfer to another hospital.

Because angiography was not performed in the control group initially, it might be argued that the thrombolysis group had a more favorable outcome because of the higher incidence (28%) of subtotally occluded vessels. Although the randomized approach makes this bias unlikely, we analyzed separately the outcome of patients with subtotal occlusion and compared it with results in patients in whom reperfusion of totally occluded vessels was achieved during catheterization. The actual beneficial effects of reperfusion in these patients with total occlusion are clearly demonstrated in Table 4; the hemodynamic outcome of these patients did not differ from the outcome of the group with subtotal occlusion.

Global and segmental function in anterior or inferior infarction: thrombolysis versus conventional treatment.

Table 6 and Figure 3 present the data on patients with inferior infarction. The global ejection fraction shows an 8% difference (p = 0.0001) in favor of the thrombolysis group and this difference in ejection fraction is due to a significantly smaller (p = 0.007) end-systolic volume (37 ml/m²) when compared with the end-systolic volume of the

control group (48 ml/m²). In Figure 3A, the regional contribution to ejection fraction values of the patients with inferior infarction assigned to thrombolysis is compared with that of patients assigned to conventional treatment. Depressed regional contribution to ejection fraction values was observed in the inferoposterior wall (segments 11 to 18) as expected, while regional pump function was significantly better in patients assigned to thrombolysis, although not (yet) normal. In these patients no difference was observed in regional function of the anterior wall. Thus, when recanalization is successful and the infarct-related vessel remains patent, there is a significant improvement of function of the inferior wall associated with the subsidence of the initially compensatory augmented functioning of the anterior wall. This latter phenomenon was particularly prominent in the patients who underwent the combined procedure of recanalization and angioplasty (Fig. 3B) in the acute phase.

Global and regional left ventricular function of patients with anterior myocardial infarction is shown in Table 7 and Figure 4. A significant (p = 0.0025) 7% difference in global ejection fraction is found between both groups because of a smaller end-systolic volume of 45 ml/m² in the thrombolysis group versus 60 ml/m² in the control group (p = 0.006). As Figure 4A clearly indicates, this 7% difference in global ejection fraction in favor of the thrombolysis group is essentially due to a better regional pump function of the anterior wall (segments 1 to 20) and, to a smaller extent, better regional pump function of the inferoapical segment (segments 11-15) of the inferior wall.

The preceding analysis was based on original treatment allocation, disregarding whether treatment was actually given

Table 2. Time Between Onset of Symptoms and Thrombolysis in 127 Patients With Late Angiography

	Minutes
Range	70 to 240
First quartile	160
Median	200
Third quartile	255

Table 3. Baseline Data in Patients With and Without Follow-up Angiography

	Follow-up Angiography		No Follow-up Angiography	
	Control Group	Thrombolysis Group	Control Group	Thrombolysis Group
No. of patients	174	158	90	111
Male	152	130	72	87
Age (mean \pm SD)	55 \pm 8	55 \pm 10	55 \pm 9	57 \pm 9
Previous infarction	40 (23)	25 (16)	20 (22)	31 (28)
Previous bypass surgery	6 (3)	2 (1)	2 (2)	3 (3)
Infarction				
Anterior wall	69 (40)	79 (50)	47 (52)	51 (46)
Inferior wall	105 (60)	79 (50)	43 (48)	60 (54)

The number in each group is presented as well as the percentage (%).

and whether reperfusion was achieved. The actual effects of reperfusion can be better understood when four subgroups of patients are compared: a) patients who refused the intervention or otherwise did not undergo acute angiography, b) patients with either unsuccessful recanalization or late reocclusion, c) patients with successful recanalization and late patency of the infarct-related vessel, and d) patients who underwent successful recanalization, immediately followed by angioplasty. Segmental function of the anterior wall was poorest in patients whose artery could not be recanalized, and greatest in those patients who underwent a combined procedure of thrombolysis and angioplasty (Fig. 3D and 4D). The magnitude of change in regional function at the infarct site was also related to the time from the onset of chest pain to treatment. Patients treated with thrombolytic therapy within 3 hours of symptoms had a significantly greater improvement than did patients treated later (Fig. 3C and 4C). The regional contribution to ejection fraction of the infarct zone, either anterior or inferior, improved by at least 1.5% in the group treated early.

Serial changes in global and segmental function in patients allocated to thrombolytic therapy. Eighty-two of the patients allocated to thrombolytic therapy had left ventriculograms performed in the acute phase of myocardial infarction and at a follow-up catheterization. Table 8 presents the serial changes in global left ventricular function of the patients with anterior and inferior infarction. After successful recanalization, no significant change in ejection fraction could be demonstrated. In the patients with inferior infarction, the improvement of the inferior wall observed between the acute and chronic stage was partially masked by the disappearance of the compensatory actions of the initially enhanced function of the anterior wall (Fig. 3B). Conversely, when recanalization was unsuccessful, a significant deterioration of the global variables of function resulted: a decrease of 4% in ejection fraction ($p = 0.004$) and an increase in end-systolic volume from 37 to 48 ml/m² ($p = 0.0006$) and in end-diastolic volume from 74 to 93 ml/m² ($p = 0.0003$).

Similar trends were observed in the patients with anterior

Table 4. Left Ventricular Hemodynamics Before Discharge (n = 332)

	Controls (n = 174)	p Value	Thrombolysis (n = 158)	None (n = 14)	Artery at Angiography*		
					○---○ (n = 36)	●---○ (n = 91)	●---● (n = 17)
HR (bpm)	78 \pm 15	NS	76 \pm 13				
Mean AoP (mm Hg)	88 \pm 13	NS	90 \pm 15				
EDP (mm Hg)	20 \pm 9	NS	20 \pm 8				
EDV (ml/m ²)	95 \pm 37	0.006	84 \pm 33	94 \pm 42	80 \pm 24	NS	81 \pm 30
ESV (ml/m ²)	53 \pm 31	0.0004	41 \pm 27	48 \pm 29	36 \pm 17	NS	40 \pm 23
EF (%)	47 \pm 14	0.0001	53 \pm 13	50 \pm 12	56 \pm 11	NS	54 \pm 12
SV (ml/m ²)	42 \pm 16	NS	43 \pm 15				45 \pm 16
CI (liters/min per m ²)	3.3 \pm 1.3	NS	3.2 \pm 1.1				

Values are expressed as mean \pm SD; Student *t* test for unpaired data. Only p values below 0.1 are tabulated. AoP = aortic pressure; CI = cardiac index; EDP = end-diastolic pressure; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; HR = heart rate; None = no acute angiography performed; SV = stroke volume. *○---○ = patent artery at angiography remained patent; ●---○ = occluded artery recanalized after the intervention; ●---● = occluded artery remained occluded.

Table 5. Left Ventricular Hemodynamics Before Discharge in Patients *Without* Previous Myocardial Infarction

	Controls (n = 134)	Thrombolysis (n = 133)	p Value
HR (bpm)	77 ± 13	75 ± 13	NS
Mean AoP (mm Hg)	88 ± 13	90 ± 15	NS
EDP (mm Hg)	19 ± 9	19 ± 9	NS
EDV (ml/m ²)	91 ± 37	82 ± 31	0.03
ESV (ml/m ²)	48 ± 29	38 ± 22	0.0015
EF (%)	49 ± 13	55 ± 12	0.0002
SV (ml/m ²)	43 ± 17	44 ± 15	NS
CI (liters/min per m ²)	3.3 ± 1.2	3.3 ± 1.2	NS

Abbreviations as in Table 4.

infarction. In these 82 patients serial changes in regional contribution of the infarct zone to ejection fraction were studied according to the success of thrombolysis either with or without angioplasty (Fig. 5). In the angioplasty group, global ejection fraction increased significantly ($p = 0.03$) from 51 to 55% from the acute to the chronic stage, an improvement primarily due to a 16% increase in the value of the regional contribution to ejection fraction of the infarct zone. In the patients undergoing successful thrombolysis without angioplasty, the global ejection fraction remained unchanged at 57% and was associated with a small increase of 1.7% in the value of the regional contribution to ejection fraction of the infarct zone. Conversely, in patients with unsuccessful thrombolysis, the global ejection fraction actually decreased significantly from 53 to 49% ($p = 0.03$), a change consistent with the 11% decrease in the value of the regional contribution to ejection fraction of the infarct zone.

Discussion

Results of thrombolysis versus conventional therapy. The results of the present study show, for the first time in a large randomized multicenter trial, that early recanalization of an occluded coronary artery in the acute phase of myocardial infarction is followed by preservation of global and regional left ventricular function. Whereas in most patients randomly assigned to conventional treatment,

left ventricular function deteriorated, the heart in treated patients maintained normal end-diastolic and end-systolic volumes, thus explaining their normal ejection fraction.

These results are in agreement with the findings of our pilot study (36) in which left ventricular function was assessed sequentially, at the acute and chronic stage of infarction, in patients with "successful" or "unsuccessful" recanalization. Similar results have been reported in previous studies (37-43). From these nonrandomized studies it appeared that patients with "successful" recanalization had a higher global ejection fraction (by 5 to 12%) compared with those with "unsuccessful" recanalization or conventional treatment. Also, it appeared that left ventricular damage was less in those patients who demonstrated spontaneous recanalization of the infarct-related vessel 4 to 6 weeks after the acute event (40). Schwartz et al. (41) found improvement of left ventricular function only when recanalization was achieved within 4 hours. Rentrop et al. (42) suggested that improved left ventricular function after thrombolysis occurred only in patients with collateral vessels, those with incomplete obstruction before intervention and those in whom complete obstruction was permanently recanalized. Although all of these studies have aroused great interest, their interpretation is difficult, as selected patients with successful thrombolysis were compared with patients with persistent coronary occlusion. Such interpretation can carry considerable bias, because patients in whom thrombolysis succeeded are not necessarily similar to those in whom the

Table 6. Left Ventricular Hemodynamics in *Inferior* Infarction Before Discharge

	Controls (n = 105)	Thrombolysis (n = 79)	p Value
HR (bpm)	77 ± 16	74 ± 12	NS
Mean AoP (mm Hg)	88 ± 13	91 ± 15	NS
EDP (mm Hg)	19 ± 8	18 ± 8	NS
EDV (ml/m ²)	91 ± 35	82 ± 32	0.07
ESV (ml/m ²)	48 ± 28	37 ± 24	0.007
EF (%)	49 ± 13	57 ± 11	0.0001
SV (ml/m ²)	43 ± 16	44 ± 15	NS
CI (liters/min per m ²)	3.3 ± 1.3	3.3 ± 1.2	NS

Abbreviations as in Table 4.

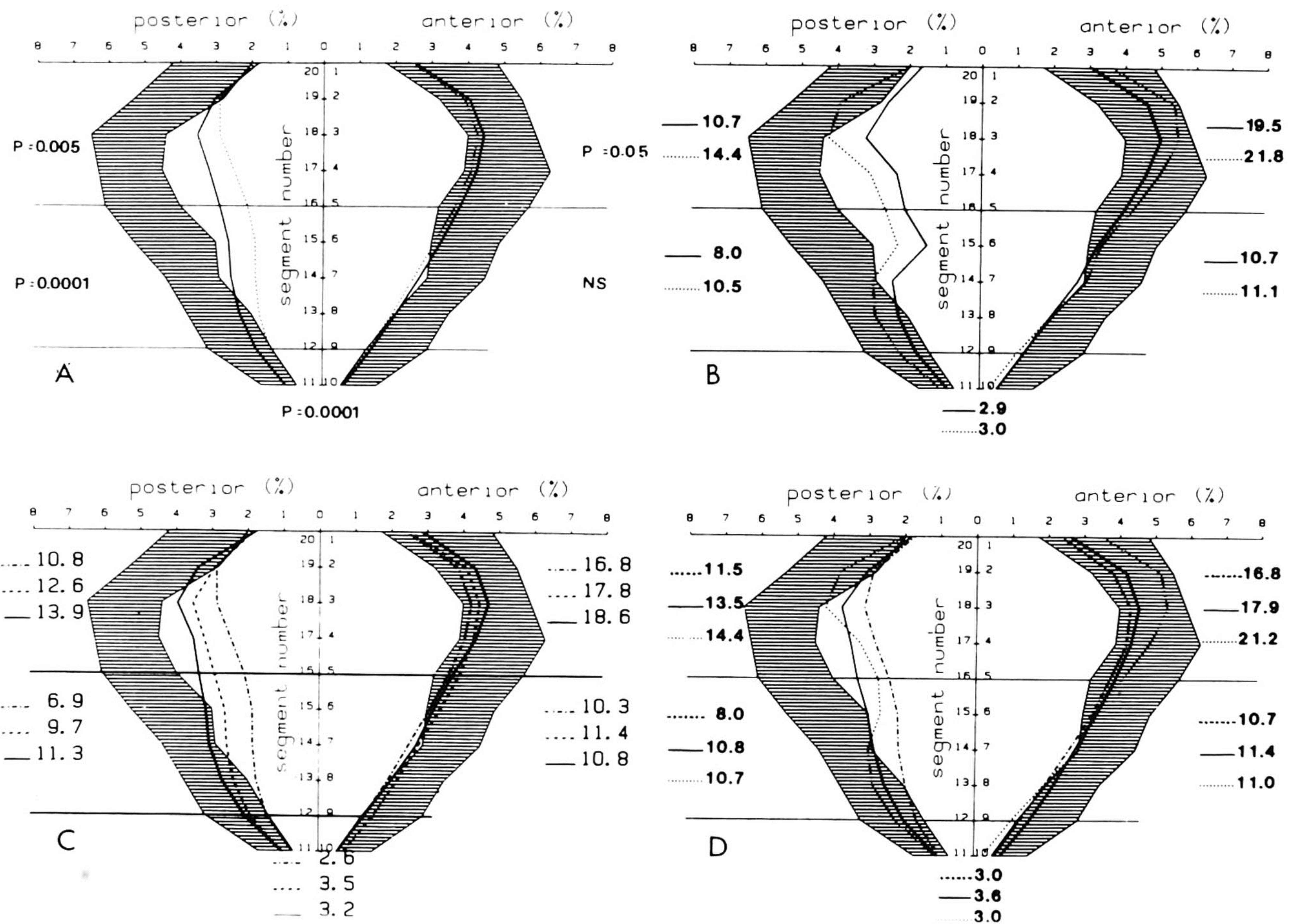


Figure 3. A, Regional contribution to global ejection fraction in 20 segments of the left ventriculogram in patients with inferior infarction. **Shaded areas** represent the normal range. The regional pump function of the inferior wall (segments 11 to 20) in the thrombolysis treated group ($n = 79$, **solid line**) is markedly less depressed than in the conventionally treated group ($n = 105$, **dotted lines**). $P = p$ value; NS = nonsignificant. B, Change in regional contribution to global ejection fraction from the acute (**solid line**) to the chronic (**dotted line**) stage in patients ($n = 6$) with an inferior infarction who underwent a combined procedure of thrombolysis and angioplasty. C, Regional contribution of the inferior wall to global ejection fraction at the chronic stage in the control group and in the thrombolysis group, according to the success of the recanalization at the acute stage and to the time elapsed from the onset of symptoms to treatment. --- = Control ($n = 105$); --- = thrombolysis > 180 minutes ($n = 41$); — = thrombolysis ≤ 180 minutes ($n = 22$). D, Regional contribution of the inferior wall to global ejection fraction at the chronic stage in the thrombolysis group ($n = 79$), according to the initial success and late patency after thrombolysis either with or without angioplasty. --- = Unsuccessful thrombolysis ($n = 31$); — = successful thrombolysis ($n = 41$); ··· = angioplasty after successful thrombolysis ($n = 7$).

intervention failed. Such bias can be overcome only by means of randomized trials and analysis of the data on an "intention to treat" basis. However, in such a trial it is

difficult to follow the sequence: determination of patient eligibility, coronary arteriography, randomization and attempted reperfusion in patients randomized to special therapy. In this sequence, patients with an evolving infarction who are randomized to conventional therapy would be obliged to undergo emergency coronary arteriography without sufficient potential benefit to outweigh the attendant risk. To overcome this difficulty we randomized all patients who were eligible on clinical grounds but obtained consent for performing coronary arteriography only from those assigned to reperfusion therapy. This procedure has been proposed by Zelen (31) for the comparison of a new method of treatment with an accepted mode of therapy.

Because angiography was not initially performed in the control group, radionuclide angiography was carried out at the bedside on the first or second day after admission and repeated before hospital discharge in the control group as well as in the thrombolysis group (Simoons et al., unpublished observations). The results indicate no change in global left ventricular ejection fraction between the second day and hospital discharge in the control group. In the thrombolysis group left ventricular ejection fraction before discharge was 3.7% higher than during the first measurement. Accordingly, left ventricular ejection fraction after 10 to 20 days

Table 7. Left Ventricular Hemodynamics in *Anterior* Infarction Before Discharge

	Controls (n = 69)	Thrombolysis (n = 79)	p Value
HR (bpm)	79 ± 13	77 ± 13	NS
Mean AoP (mm Hg)	87 ± 13	89 ± 14	NS
EDP (mm Hg)	21 ± 10	21 ± 9	NS
EDV (ml/m ²)	101 ± 39	86 ± 34	0.02
ESV (ml/m ²)	60 ± 34	45 ± 29	0.006
EF (%)	43 ± 14	50 ± 13	0.0025
SV (ml/m ²)	41 ± 16	42 ± 15	NS
CI (liters/min per m ²)	3.2 ± 1.3	3.2 ± 1.1	NS

Abbreviations as in Table 4.

was approximately 4% higher when thrombolysis was compared with conventional treatment. This difference was significant in the whole group, in patients treated with intracoronary thrombolysis only, in patients with a first infarction and in both anterior and inferior infarction. In fact, the beneficial effects of thrombolysis in the currently reported trial gain great significance as infarct size, ventricular function and survival all were found to be significantly improved when the "intention to treat" principle was applied to consecutive patients.

Comparison with previous randomized trials. The results of the five reported but smaller randomized trials with intracoronary streptokinase (13,15,17-19) conflict with the data presented here. Khaja et al. (13) found that intracoronary streptokinase was more effective than placebo (intracoronary infusion of dextrose) in achieving reperfusion, but they detected no difference in left ventricular function at 12 days and at 5 months. Three of the studies (15,17,19) also demonstrated no difference in the radionuclide ejection fraction at discharge in patients with anterior or inferior myocardial infarction treated with intracoronary streptokinase or in control patients, although they achieved reperfusion and a decreased mortality. In all these studies the intervention was instituted much later than in our current one. The median interval between the onset of symptoms and angiographic documentation of a patent infarct-related vessel in the present study was 200 minutes while the other two major trials (14,20) included patients up to 12 hours after the onset of symptoms. In the studies of Khaja et al. (13) and Raizner et al. (19) the time period between chest pain and onset of infusion of streptokinase was 5.4 and 5.6 hours, respectively. In the Western Washington trial (15,16) the mean time to randomization and the start of streptokinase infusion was 276 minutes, while Rentrop et al. (18) started intracoronary streptokinase an average of 350 minutes after the onset of symptoms. The shorter delay achieved in our study is also reflected by the higher recanalization rate (79%) compared with that in the Western Washington trial (68%). These differences from the Western Washington trial, the only other large (250 patients) randomized trial, may be crucial, because they confirm experimental data (44) that

recovery of ischemic myocardium cannot be achieved after 4 hours of coronary occlusion. As recurrent episodes of occlusion alternating with spontaneous reperfusion may occur in some patients (45), it remains possible that the salutary effect of thrombolysis in such patients extends beyond 4 hours. However, such beneficial influences are completely outweighed by the inability to achieve recovery of function and tissue injury in the majority of patients and the increased chance of reperfusion injury as ischemic time lengthens. Schwartz et al. (41) clearly demonstrated no benefit from late reperfusion (4 hours), a finding in agreement with all animal experiments (3,46,47). Previous data (14,41) and our data agree in demonstrating streptokinase to have a major beneficial effect on left ventricular function, provided it is given within 4 hours after onset of symptoms.

The magnitude of change in regional function in the infarct zone was also significantly influenced by the time elapsed between the onset of chest pain and actual recanalization. Patients with an infarct-related vessel recanalized within 3 hours had significantly greater improvement than patients treated later. The regional contribution to ejection fraction of the infarct zone improved by at least 1.5% in patients treated within 3 hours with either anterior or inferior infarction. As recently demonstrated by Mathey et al. (48), thrombolysis should be administered within 2 hours after the onset of symptoms to obtain maximal recovery of ventricular function.

The inclusion of mechanical perforation and transluminal coronary angioplasty as part of the recanalization procedure and the introduction of intravenous administration of streptokinase in the second treatment arm before cardiac catheterization provide major differences from previously reported studies. Transluminal coronary angioplasty was employed in two of the five hospitals that had extensive experience with this procedure. It was carried out to prevent reocclusion when residual vessel obstruction was considered to be 60% or more after thrombolysis (25,26). Patients so treated had a lower mortality and a lower incidence of reinfarction than did patients successfully treated with streptokinase alone. Although these results may be biased by the selection of patients who had lesions suitable for translu-

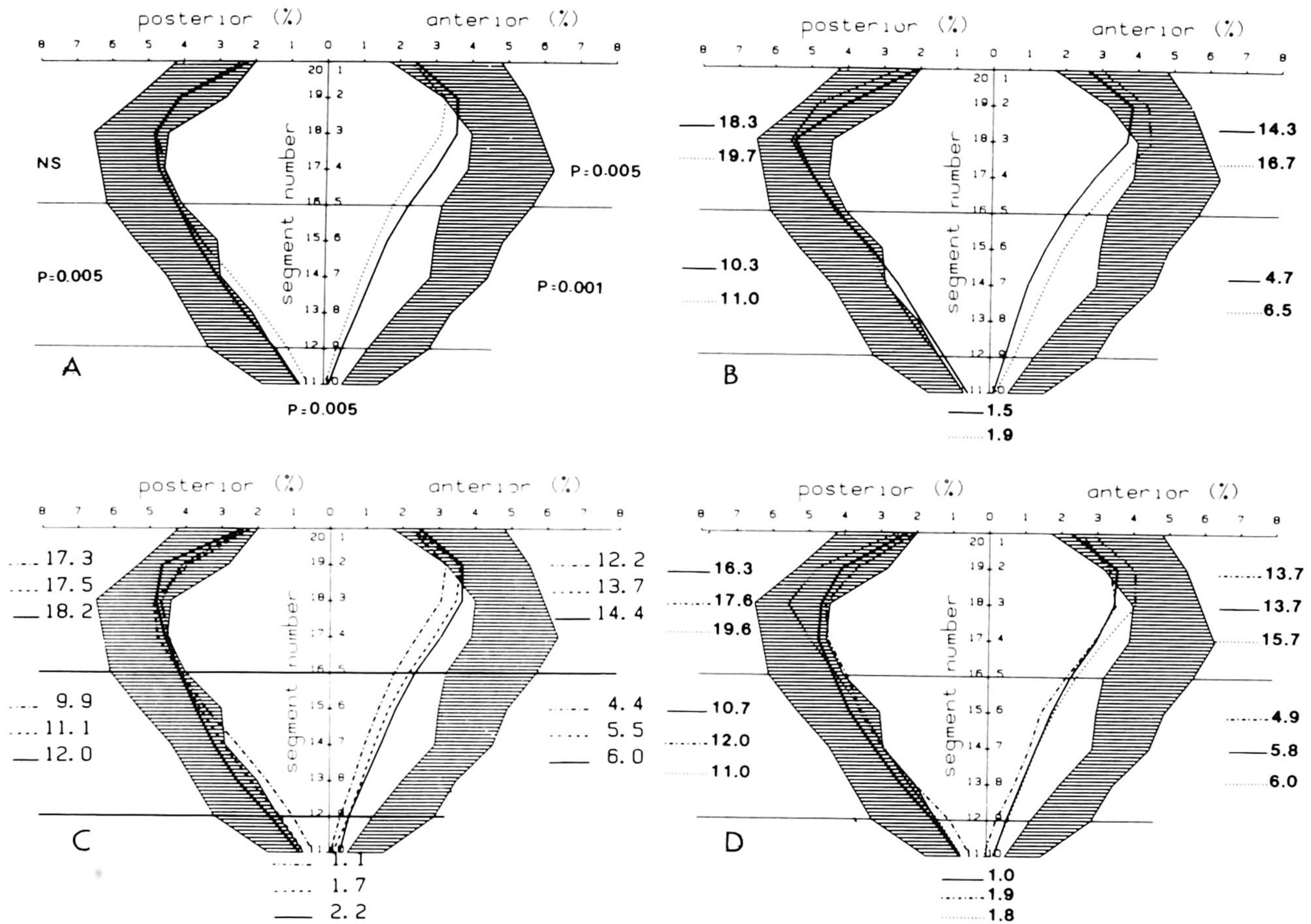


Figure 4. A, The mean values of regional contribution to ejection fraction in patients with anterior infarction are shown as in Figure 3. The regional pump function of the anterobasal, anteroapical and inferoapical segments (1 to 10, 11 to 15) is significantly better in the thrombolysis group (n = 79, **solid line**), compared with conventional treatment (n = 69, **dotted line**). B, Change in regional contribution to ejection fraction from the acute (**solid line**) to the chronic (**dotted line**) stage in patients (n = 17) with an anterior infarction who underwent a combined procedure of recanalization and angioplasty. C, Regional contribution of the anterior wall to global ejection fraction at the chronic stage in the control and the thrombolysis group, according to the success of the recanalization at the acute stage and to the time elapsed from the onset of symptoms to treatment. - - - = Control (n = 69); - · - = thrombolysis > 180 minutes (n = 40); — = thrombolysis ≤ 180 minutes (n = 24). D, Regional contribution of the anterior wall to global ejection fraction at the chronic stage in the thrombolysis group (n = 79), according to the initial and late patency after successful thrombolysis either with or without angioplasty. - · - = Unsuccessful thrombolysis (n = 15); — = successful thrombolysis (n = 44); · · · = angioplasty after successful thrombolysis (n = 20).

minimal coronary angioplasty and who were hemodynamically stable after thrombolysis, the data are in agreement with earlier observations (21,49) that the recovery of regional left ventricular function is greatest in patients with minimal

residual stenosis after the intervention. Experimental studies (50) also have shown that restriction of flow during reperfusion results in relative underperfusion of, and continued ischemia in, the subendocardium.

Analysis of global and regional wall motion. Measurement of the global ejection fraction is a rather crude method that may not detect improvement in regional left ventricular function. Therefore, analysis of left ventricular wall motion in the infarct area at risk, which potentially should benefit most from reperfusion, must be carried out to detect any real effect of reperfusion (21,51,52). In fact, increased motion of the noninfarcted regions of the heart often kept the global ejection fraction within normal limits despite severe regional hypokinesia in the infarct area. Contractile performance of the noninfarcted area may be enhanced by the Frank-Starling mechanism and by increased levels of circulating catecholamines in the first hours after infarction. After subsidence of compensatory augmented motion in the noninfarcted regions of the heart, which masked significant deterioration in regional wall motion, initially maintained global left ventricular function declined. Here, again, regional wall motion must be measured to adequately assess this effect. Significant improvement of regional function in the "infarct zone" was observed in inferior as well

Table 8. Thrombolysis Group: Serial Left Ventricular Hemodynamics

	Acute	p Value	Chronic	Acute	p Value	Chronic
A. Anterior Infarction (n = 38)						
	Successful (n = 34)			Unsuccessful (n = 4)		
HR (bpm)	84 ± 13	0.007	75 ± 14	84 ± 16	NS	80 ± 3
Ao (mm Hg)	82 ± 12	0.07	85 ± 9	87 ± 12	NS	89 ± 30
EDP (mm Hg)	23 ± 10	0.06	19 ± 8	22 ± 9	NS	26 ± 8
EDV (ml/m ²)	81 ± 32	NS	83 ± 27	58 ± 22	NS	77 ± 11
ESV (ml/m ²)	42 ± 24	NS	41 ± 22	28 ± 9	NS	39 ± 4
EF (%)	49 ± 11	0.06	53 ± 12	50 ± 9	NS	48 ± 7
SV (ml/m ²)	38 ± 14	0.04	42 ± 13	30 ± 15	NS	38 ± 10
CI (liters/min per m ²)	3.2 ± 1.1	NS	3.1 ± 1.1	2.4 ± 0.9	NS	3.0 ± 0.7
B. Inferior Infarction (n = 44)						
	Successful (n = 29)			Unsuccessful (n = 15)		
HR (bpm)	82 ± 13	0.02	75 ± 11	87 ± 21	0.03	75 ± 13
Ao (mm Hg)	86 ± 15	0.02	94 ± 10	85 ± 10	NS	87 ± 15
EDP (mm Hg)	18 ± 8	NS	19 ± 9	20 ± 10	NS	19 ± 8
EDV (ml/m ²)	71 ± 22	NS	78 ± 29	74 ± 27	0.0003	93 ± 28
ESV (ml/m ²)	27 ± 11	0.05	32 ± 15	37 ± 19	0.0006	48 ± 26
EF (%)	61 ± 9	NS	60 ± 8	55 ± 10	0.004	51 ± 11
SV (ml/m ²)	43 ± 16	NS	46 ± 16	40 ± 15	0.08	45 ± 9
CI (liters/min per m ²)	3.6 ± 1.3	NS	3.5 ± 1.2	3.4 ± 1.4	NS	3.3 ± 0.8

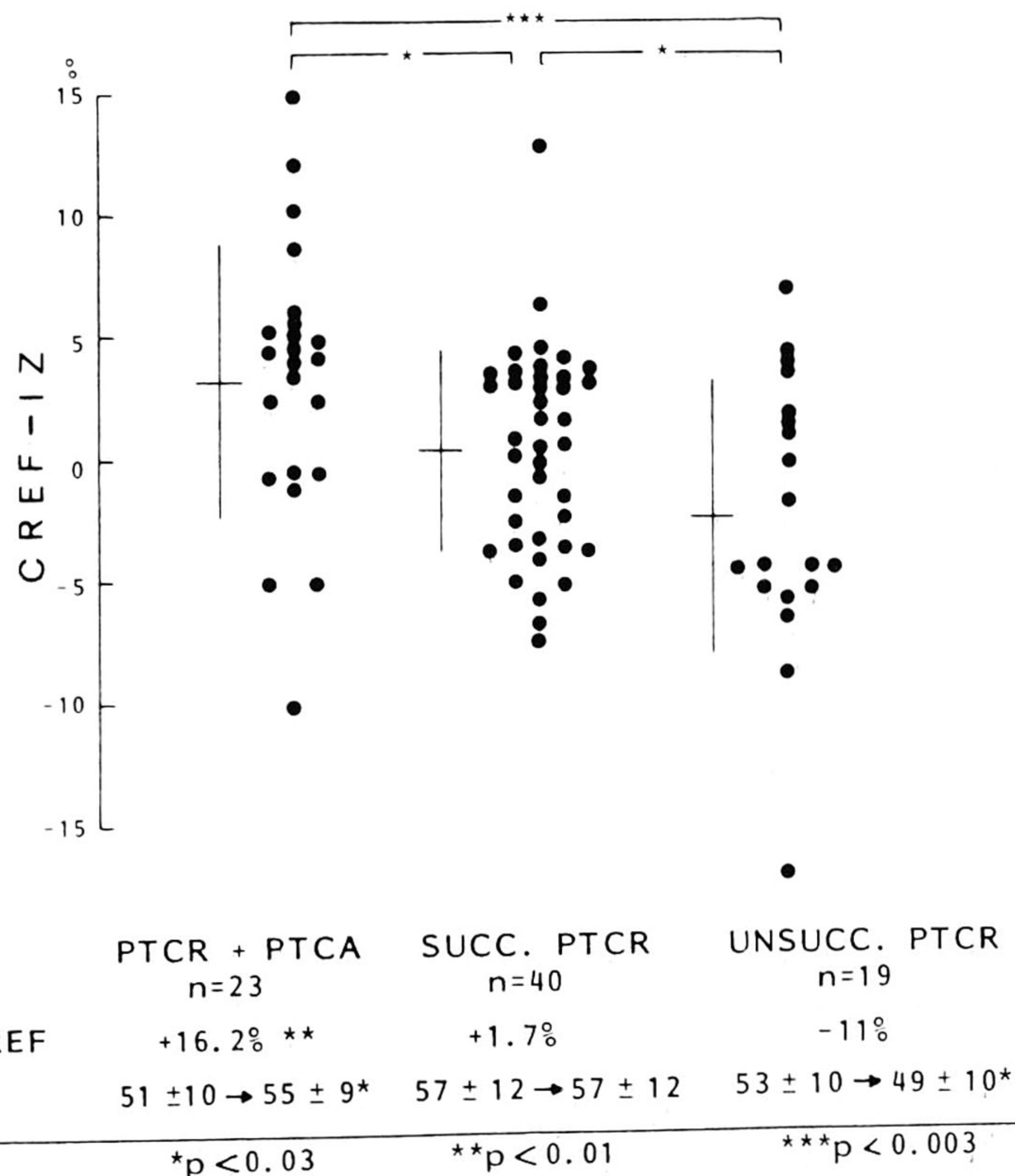
Values are expressed as mean ± SD; Student *t* test for paired data. Abbreviations as in Table 4.

as anterior locations although significant changes in regional function of the remote noninfarct zone occurred at the acute as well as the chronic stage.

The analysis of regional left ventricular function was based on automated, high resolution, frame to frame edge

detection of left ventricular contour. This system allows fast and reliable acquisition of single left ventricular contour, every 20 ms, all over a complete cardiac cycle (33,34). Many wall motion models have been proposed to approximate actual endocardial motion; this reflects the problems

Figure 5. Changes in regional contribution to global ejection fraction of the infarct zone (CREF-IZ, %) (anterior: segments 1 to 10; inferior: 11 to 20) between the acute phase and the late control. **Right**, Patients with either unsuccessful recanalization or late reocclusion (UNSUCC. PTCR). **Middle**, Patients with successful recanalization and late patency of the infarct related vessel (SUCC. PTCR). **Left**, Patients who underwent a successful recanalization, immediately followed by angioplasty (PTCR + PTCA). p values < 0.05 are reported (paired or unpaired Student's *t* test). glob. EF = global ejection fraction; Δ = relative increment or decrement.



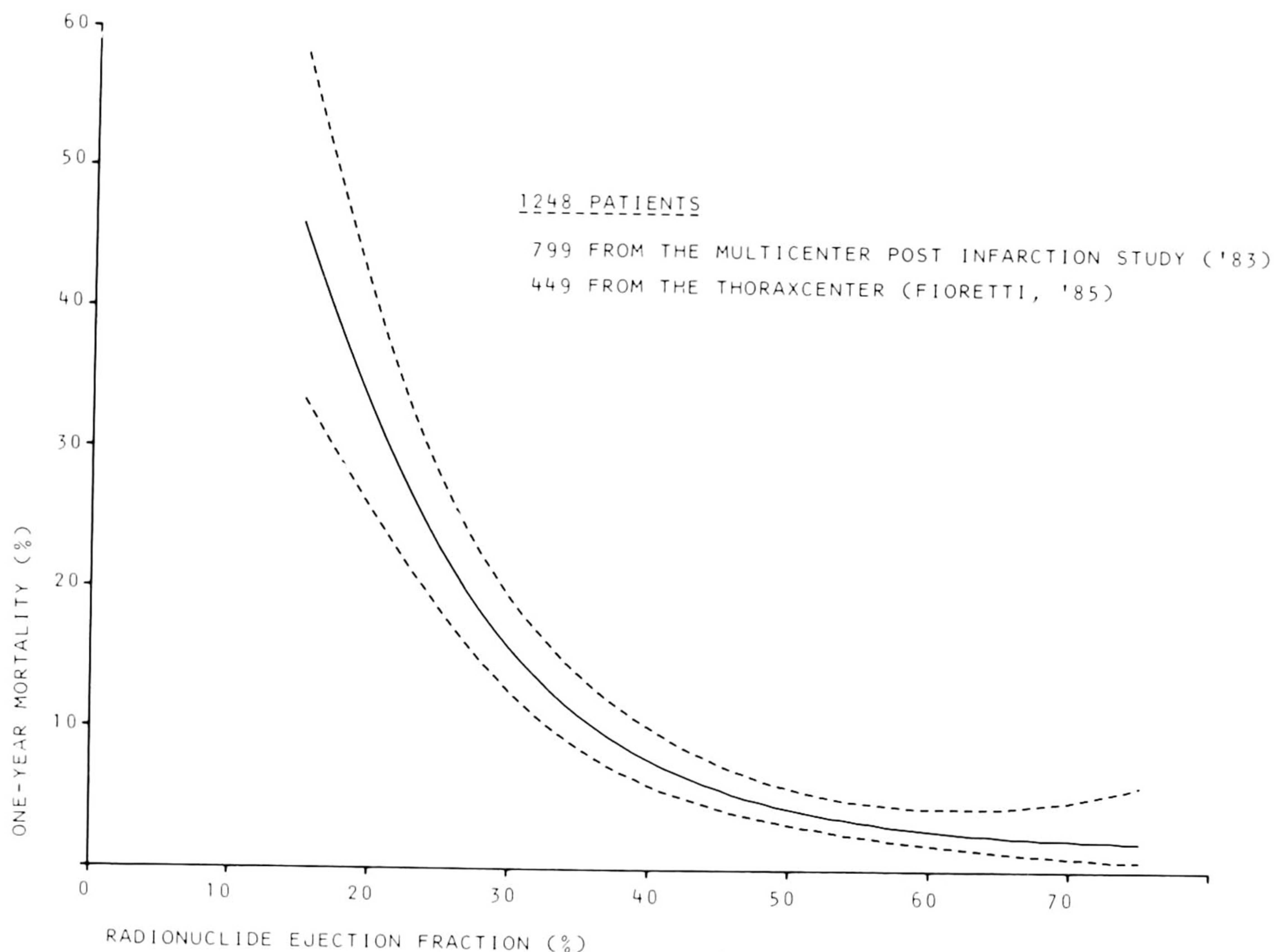


Figure 6. One year mortality as a function of radionuclide ejection fraction (%) measured at hospital discharge after acute myocardial infarction. The **solid line** between the **dashed lines** indicates the corresponding 95% confidence interval. The calculations are based on pooled data from the Multicenter Postinfarction Study (60) and the Thoraxcenter (Fioretti P, personal communication, 1985).

investigators have had in establishing a geometric framework from which to judge whether the motion of the endocardial contour is normal or abnormal (53). All these methods assess wall motion in terms of extent of shortening at specific points on an axis reference system, although it is highly unlikely that a particular endocardial site coincides with one of these axes during the entire cardiac cycle. The wall motion analysis system we used is based on the motion pattern of small irregularities at the left ventricular endocardial border (endocardial landmarks) that can be detected in the contrast cineangiogram with the automated endocardial outlining system (33,34). This endocardial landmark pathway was tested previously in 23 normal human left ventricles and validated in pigs with metal endocardial markers inserted with a percutaneous, retrograde, transvascular approach (23,54). This wall motion analysis is unaffected by the translation and rotation of the heart, thus permitting an actual study of the segmental wall motion and derived variables.

Early after myocardial infarction, the uninvolved portion of the heart is generally thought to maintain normal function and metabolism, unless coexisting stenosis of additional vessels causes ischemia of the noninfarcted segments (55). Yet, after experimental myocardial infarction, the clearly nonischemic portions of the heart muscle also show changes in energy metabolism and a decline in norepinephrine content (56,57). Other investigators have reported decreased lactate extraction and ischemic histologic changes, such as swelling of mitochondria or reduction in tissue glycogen content, in areas of myocardium remote from the site of coronary occlusion. However, when the infarcted area is reperfused early, the decline in contractility of noninfarcted heart muscle appears to be reversible, but this is limited to the early postinfarction period (10 days) (58). Other data (59), during and after open heart surgery, indicate that a longer delay of up to 4 weeks might be needed to achieve a full recovery. This overall improvement in the ischemic areas and the high patency (85%) of the infarct-related artery after the intervention, as well as other aspects of the design of our study, show the major significance of early recanalization in order to achieve the goal of preservation of left ventricular function. The results of our study also indicate that reperfusion may need to be supplemented by revascularization procedures such as angioplasty to optimize the chances of obtaining full functional recovery. The beneficial effects of early thrombolysis evident in this large series of

patients studied over an extended time period might explain the observed reduction (from 16 to 9%) in 1 year mortality (12,12a).

Prognostic implications. The multicenter postinfarction research group (60) reported that patients with higher global ejection fraction had better 1 year survival after myocardial infarction independent of the extent of coronary disease. Similar data were found in a follow-up study of 449 hospital survivors at the Thoraxcenter (Fioretti P, personal communication, 1985). Pooling the results of these studies, a curvilinear relation between the 1 year mortality rate and global ejection fraction can be constructed (Fig. 6). When the currently observed improvement of left ventricular ejection fraction from 47% in control patients (estimated probability of cardiac death = 0.050) versus 53% in patients allocated to thrombolysis (estimated probability of cardiac death = 0.037) is interpreted in this manner, the 1 year mortality should indeed be reduced by 24% after thrombolysis, a projection that corresponds to our observations. Thus, the explanation for the reduced mortality must mainly be ascribed to the restoration of left ventricular function, rather than to any other mechanism.

Appendix

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