Catheterization and Cardiovascular Diagnosis 13:223–232 (1987)

Original Studies

Value of Immediate Coronary Angioplasty Following Intracoronary Thrombolysis in Acute Myocardial Infarction

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A total of 533 patients with acute myocardial infarction of less than 4-h duration were enrolled in the multicenter randomized trial of intracoronary thrombolysis compared to conventional treatment. In two of the five participating centers, an additional coronary angioplasty immediately after thrombolysis was attempted in 46 patients. According to the treatment allocation and early and late patency of the infarct related vessel, patients were subdivided into three groups: conventionally treated (group A); successful coronary angioplasty following thrombolysis with persistent patent infarct related vessel (group B); and late patency of the infarct related vessel postthrombolytic therapy without angioplasty (group C). The highest global ejection fractions were observed in group B (54% ± 10%) and group C (55% ± 13%), while the lowest ejection fraction was found in group A (47% ± 14%). The sequential changes in global ejection fraction from the acute to the chronic stage was + 4% (p = 0.05) in group B, while no significant changes could be demonstrated in group C. Furthermore, in the group successfully treated by angioplasty, the improvement in global ejection fraction was more pronounced and persisted up to three months after the intervention. This was supported by analysis of regional myocardial function of the infarct zone (+ 16% improvement, p = 0.01). The long-term clinical follow-up (median 24 months) of the patients successfully treated by combined procedure of thrombolysis and angioplasty (group B) was most favourable with a lower incidence of re-infarction (6%), and late coronary bypass surgery (13%) and/or (re)-percutaneous transluminal coronary angioplasty (3%) was performed less frequently.

These results suggest that reperfusion may need to be supplemented by additional revascularization procedures in order to optimize the chances of obtaining full functional recovery and so to improve the prognosis.

Key words: acute PTCA, intracoronary streptokinase, myocardial function

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INTRODUCTION

Since the first study by Rentrop et al [1], we and many others have demonstrated that rapid recanalization can be achieved by intracoronary streptokinase in approximately 80% of patients [2–5]. The large multicenter trial conducted by the Interuniversity Cardiology Institute in the Netherlands has documented that early recanalization is associated with a limitation of infarct size, preservation of left ventricular function, and improved survival when compared to conventional treatment [6–8]. However, a frequent finding after recanalization is severe recurring or residual coronary stenosis which may restrict antegrade flow and limit the recovery of regional left ventricular function. Therefore, additional interventions, such as coronary angioplasty, have been advocated in this setting to improve this incomplete restoration of flow and maximize myocardial salvage [4,9–22]. The aim of this study was to investigate whether immediate angioplasty after thrombolysis indeed provided additional benefit in the preservation of regional myocardial function in the infarct zone by retrospectively reviewing the results of the Netherlands multicenter trial of thrombolytic therapy [6–8] in which selected patients underwent angioplasty.

PATIENTS AND METHODS

Between June 1981 and March 1985, 533 patients with an acute myocardial infarction were enrolled in a multi-

From the Netherlands Interuniversity Cardiology Institute.

Received November 1, 1986; revision accepted January 24, 1987.

K. Beatt was supported by a Fellowship from the British and Netherlands Heart Foundations.

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center randomized trial of intracoronary thrombolysis compared to conventional treatment; 264 patients were allocated to conventional and 269 to thrombolytic therapy. The initial protocol [23–26] was modified in two ways: the first was as a result of data which suggested that reocclusion of the coronary artery occurred predominately in patients with severe residual stenosis [4,12,15,16]. It was therefore decided to proceed to immediate coronary angioplasty in such patients at two of the five participating centers (predominately the Thoraxcenter, Rotterdam). This combined procedure was performed in 46 out of 269 patients allocated to thrombolysis (Fig. 1). The second change (January 1984) was to introduce intravenous streptokinase (500,000 U) at the time of admission to hospital [6–8,27–29]. During the study period consecutive patients up to the age of 70 years with chest pain and ECG signs of typical myocardial infarction, who arrived within 4 h of the onset of symptoms, were admitted to the trial, as described in previous reports [6–8,23–26,30–34]. As the object of this study was to assess the additional value of a successful coronary angioplasty as compared to successful thrombolysis alone, the study population was retrospectively divided into three groups:

group A: patients allocated to conventional treatment (n=264);

group B: patients recanalized by coronary angioplasty following thrombolysis with persistent patency of the infarct related vessel at follow-up angiography (n=31); and

group C: patients recanalized by thrombolysis without angioplasty with subsequent late patency of the infarct related vessel (n=102).

Patients with persistent occlusion in spite of attempted recanalization procedures (n=36) and patients with initial patency after recanalization in whom the infarct related vessel was found reoccluded at follow-up angiography (n=25) were excluded from analysis in this study. The necessary angiographic data was unobtainable in the remaining 75 patients; the recanalization procedure could not be performed in spite of allocation to thrombolysis (n=35), or the late patency of the infarct-related vessel could not be evaluated (n=40).

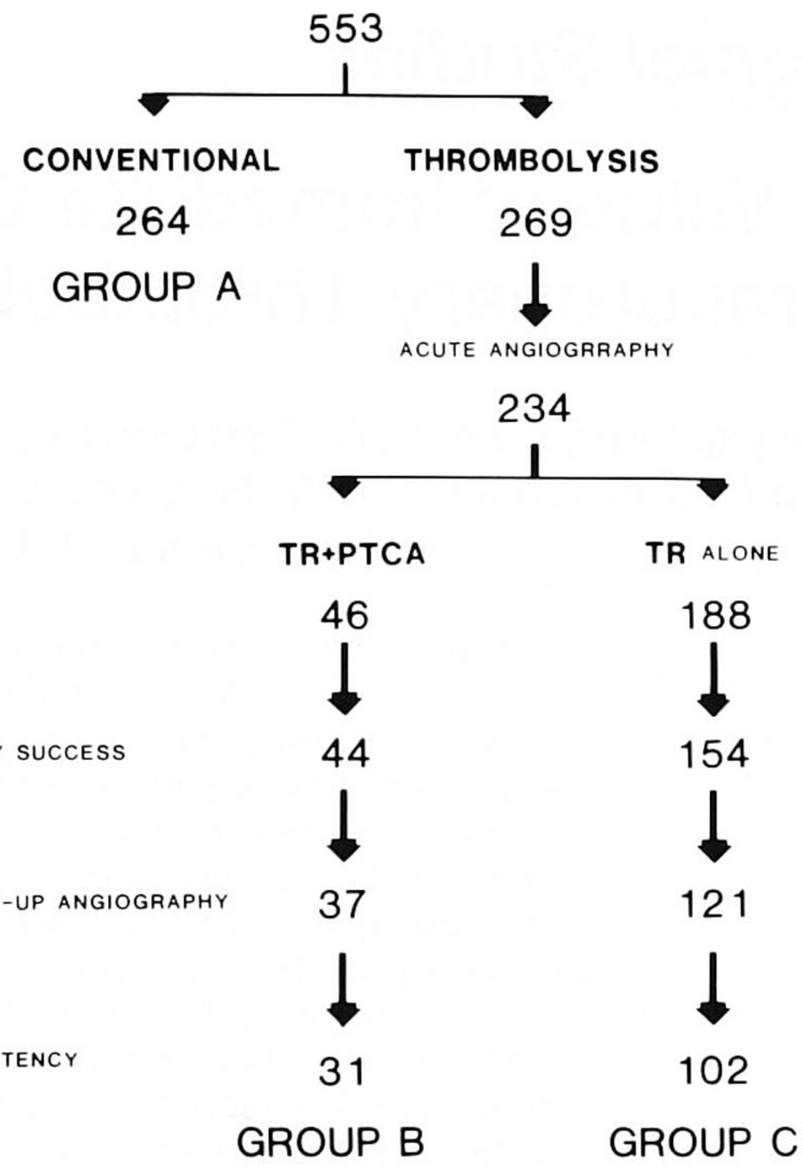

Fig. 1. Flow chart. TR, thrombolysis; PTCA, percutaneous transluminal coronary angioplasty.

Electrocardiographic Assessment [31,32]

ST-segment elevation of at least 0.1 mV in one or more extremity leads, 0.2 mV in one or more precordial leads, or at least 0.2 mV ST segment depression in one or more precordial leads are compatible with posterior infarction. The sum of ST-segment elevation on the ECG was defined for anterior infarcts as the sum of ST-segment elevation in leads I, aVL, V1–V6 and for inferior infarcts as the sum of ST-segment elevation in I, II, III, AVL, AVF, V5, V6, and ST-segment depression in V1–V4.

Measurement of Serum Alpha-Hydroxybutyrate Dehydrogenase (HBDH)

Serum alpha-hydroxybutyrate dehydrogenase levels were determined on admission, every 12 hours for the first 2 days and then every 24 hours until 5 days after admission. Cumulative release of alpha-hydroxybutyrate dehydrogenase (HBDH) in the first 72 hours was calculated from these data as described earlier [33,35]. In two of the five participating hospitals total lactate dehydrogenase was measured instead and converted to alpha-hydroxybutyrate dehydrogenase by exchange of standards.

Intracoronary Thrombolysis and Coronary Angioplasty

Initial coronary angiography and the administration of intracoronary streptokinase was performed as previously described [6–8]. Briefly, intracoronary streptokinase was carried out at a rate of 4,000 units per minute to a maximum of 250,000 units. Coronary angiograms were repeated every 15 minutes. Coronary angioplasty was attempted in 46 patients in whom it was judged to be technically and organisationally feasible. It was carried out only when the residual stenosis was 60% or more after thrombolysis. Successful dilatation was defined as an improvement in the diameter stenosis from greater

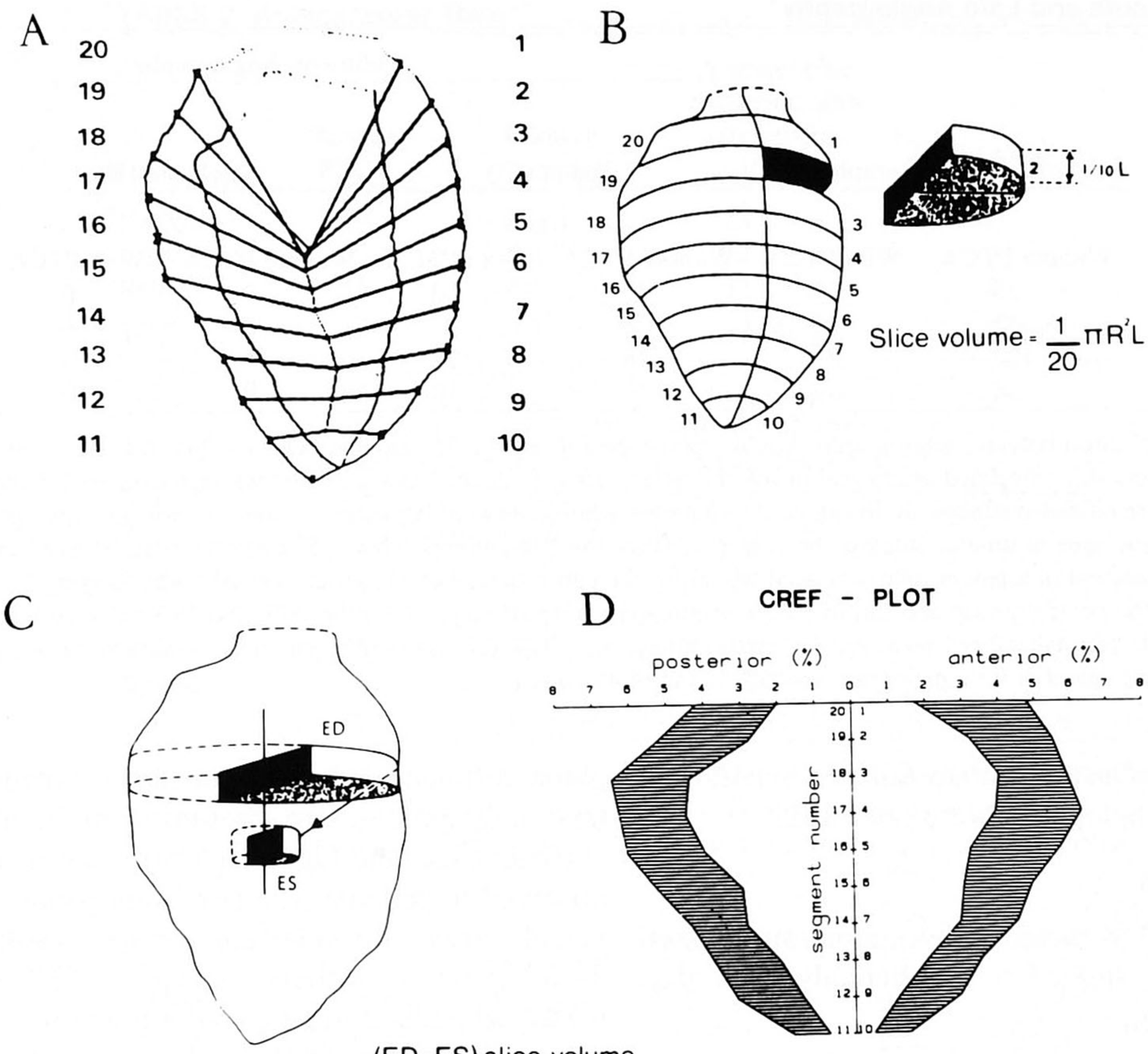

Fig. 2. A: Example of the computer output showing the end-diastolic (ED) and end-systolic (ES) contours of the 30° RAO left ventriculogram. Systolic regional wall displacement was determined along a system of 20 coordinates on the pattern of actual endocardial wall motion in normal individuals and generalized as a mathematical expression amenable to automatic data processing [38–40]. B: The left ventricular end-diastolic cavity is divided into 20 half-slices. The volume of each half-slice is computed according to the given formula; R is radius and L is left ventricular long axis length. C: The regional contribution to global ejection fraction (CREF) 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. When normalized for end-diastolic volume, the systolic segmental volume change was considered as a parameter of regional pump function. D: The shaded zones represent the 10th–90th percentiles area of CREF values in normal individuals. On the x-axis the CREF values of the anterior and inferoposterior wall areas are displayed (%), while on the y-axis the segment numbers of the anterior wall (1–10) and of the inferoposterior wall (11–20) are depicted.

than 60% to less than 50%. Left ventriculography was performed at the end of the procedure. From the patients who agreed to follow-up catheterization, coronary and left ventricular angiography were obtained both in the control and the thrombolysis-treated group, either before discharge or 4–8 weeks after the acute phase.

Radionuclide Angiography

Radionuclide angiography was carried out at the bedside on the first or second day after admission and repeated before hospital discharge and at three months. Gated images were obtained with 20 frames in each heart cycle after in vivo labelling with 15 mCi Technetium 99m. Data were analysed by a fully automated computer program on a DEC-gamma 11 or an ADAC system [36], or with a MDS or a Philips data analysis system.

Analysis of Global and Regional Left Ventricular Function

Global and regional left ventricular function was studied from the 30° right anterior oblique view using an automated hardwired endocardial contour detector linked to a minicomputer. This method of analysis has been described in detail previously [37–40]. Figure 2 shows examples of the end-diastolic (ED) and end-systolic (ES) contours of the left ventriculogram as well as the segmental contribution to the global ejection fraction, as displayed by the analysis system.

Clinical Follow-Up

All patients were followed at the outpatient clinic for at least one year after admission and survival status was assessed at six-month intervals. Recurrent myocardial

TABLE I. Results of Acute and Late Angiography*

			Follow-up angiography				
	Acute angiography		Patent (○)		Occluded (●)		Adequate LV angiography
Controls (n=264)			106		99		174
Thrombolysis (n=269)	Without PTCA	With PTCA	Without PTCA	With PTCA	Without PTCA	With PTCA	
35 no angiography	35	0	13	0	9	0	14
65 ○—○	52	13	36	10	3	0	36
133 ●—○	102	31	66	21	16	6	91
36 ●—●	34	2	11	0	8	0	17

*In spite of allocation to thrombolysis, angiography could not be performed in 35 patients. Out of 234 patients who underwent acute angiography, 65 had a patent infarct-related artery and in 169 this artery was occluded. Recanalization was achieved in 133 patients. Ultimately the infarct-related artery remained occluded in 36 out of 234 patients who underwent angiography and at least one attempt at recanalization (15%), while the artery was open at time of study or became recanalized in 198 patients (85%). The median time between onset of symptoms and angiographic documentation of a patent infarct-related vessel for the entire thrombolysis group was 200 min, ranging from 55 to 375 min. The late patency rates in the control group and thrombolysis group were, respectively, 52% (106/205) and 79% (157/199) ($p = 0.0001$). The reocclusion rate in patients recanalized by intracoronary streptokinase was 20% (22 out of 109 patients), while late occlusion in the patients with a patent infarct-related vessel at first angiogram was 6% (3 out of 49 patients).

infarction, angina pectoris, cardiac failure, bypass surgery, and coronary angioplasty were recorded.

Statistical Analysis

Data are expressed as mean ± SD. Paired or unpaired Student t-tests were applied to the hemodynamic data whenever appropriate.

RESULTS

Early and Late Angiographic Findings

Table I shows the results of early and late angiography. Coronary angioplasty was attempted in 46 patients and was successful in 44 patients, including 5 patients with occluded vessel after intracoronary streptokinase in whom subsequent mechanical perforation and angioplasty was performed. Table II details the angiographic data concerning the infarct-related vessel, primary success, and the reocclusion rate. The patients with a persistent patent infarct-related vessel with angioplasty (group B) and without (group C) and patients allocated to conventional treatment (group A) formed our study population (Fig. 1).

Baseline Data

The baseline data were distributed evenly, including the median time delay for hospital admission, infarct location, history of previous myocardial infarction and previous bypass surgery (Table III).

Global and Regional Left Ventricular Function

Acute angiography (at admission) was performed only in patients allocated to thrombolysis, while late angiography (before discharge or at 4–8 weeks) was performed in the thrombolysis as well as in the control group. The global left ventricular volume data determined from contrast angiography are presented in Table IV. At the chronic stage, the highest global ejection fractions were observed in patients with persistent patent infarct-related vessel after thrombolysis either with (group B, 54% ± 10%) or without (group C, 55% ± 13%) angioplasty, while the lowest ejection fraction was found in the control group (group A, 47% ± 14%). In Table IV, the sequential changes in global ejection fraction from the acute to chronic stage are also shown. In the angioplasty group (group B), the global ejection fraction improved significantly by 4.2% ($p = 0.05$), while no significant change in global ejection fraction could be demonstrated in the subset of patients undergoing successful thrombolysis without angioplasty (group C). Similar trends were observed in the regional myocardial function of the infarct zone (Table V). Figures 3 and 4 show the sequential changes in regional myocardial function from the acute to the chronic stage in the patients in whom the left ventriculogram was performed at the acute as well as at a follow-up catheterization. In the angioplasty group (group B), the significant improvement in global ejection fraction was primarily due to a 16% increase in regional myocardial function of the infarct zone as shown in Figures 3 and 4. In the group of patients with persistent patent infarct related vessel after thrombolysis without angioplasty (group C), the regional myocardial function of the infarct zone remained unchanged.

Radionuclide Angiography

Left ventricular ejection fraction as determined by radionuclide angiography at the acute stage (days 1–3), before discharge (days 10–20), and at three months are presented in Table VI. Paired analysis of the sequential changes in global radionuclide ejection fraction from

TABLE II. Angiographic Data*

IRV	Attempted PTCA	Primary success	Angiographic follow-up after successful PTCA	Reocclusion
LAD	29	27	23	1
LCX	2	2	2	1
RCA	15	15	12	4
Total	46	44 (96%)	37 (84%)	6 (16%)

IRV	Attempted TR alone	Primary success	Angiographic follow-up after successful TR alone	Reocclusion
LM	1	1	0	—
LAD	75	61	50	5
LCX	36	31	24	5
RCA	74	60	46	8
Bypass	2	1	1	1
Total	188	154 (82%)	121 (79%)	19 (16%)

*Abbreviations: IRV = infarct-related vessel; PTCA = percutaneous transluminal coronary angioplasty; TR = thrombolysis; LM = left main coronary artery; LAD = left anterior descending coronary artery; LCX = circumflexus; RCA = right coronary artery.

TABLE III. Baseline Characteristics*

	Controls (group A)	TR + PTCA (group B)	TR alone (group C)
N	264	31	102
Female	41 (16%)	4 (13%)	18 (18%)
Age (yr: mean ± SD)	55 ± 8	57 ± 8	55 ± 10
Anterior infarction	116	22	50
Previous infarction	60 (23%)	8 (26%)	12 (12%)
Previous CABG	8 (3%)	0	1 (1%)
Time to admission (median, min)	90	95	90
Sum of ST elevation (median, mm)	12	14	12

*Baseline characteristics of the three subdivided groups: TR + PTCA = recanalization with angioplasty following thrombolysis with late patency; TR alone = recanalization following thrombolysis alone with late patency; CABG = coronary bypass surgery.

TABLE IV. Left Ventricular Volumes†

	Controls (A)	TR + PTCA (B)	TR alone (C)
EDV 2	95 ± 37 (n=180)	80 ± 21* (n=29)	82 ± 32* (n=86)
Δ EDV	–	−0.4 ± 19 (n=24)	9 ± 23** (n=43)
ESV 2	53 ± 31 (n=177)	38 ± 14* (n=27)	39 ± 24* (n=80)
Δ ESV	–	−3.4 ± 14 (n=23)	5 ± 13** (n=40)
EF 2	47 ± 14 (n=174)	54 ± 10* (n=27)	55 ± 13* (n=79)
Δ EF	–	4.2 ± 9** (n=23)	−0.5 ± 8 (n=40)

†Abbreviations: EDV, ESV, EF = end-diastolic volume, end-systolic volume, ejection fraction at chronic (2) stage; Δ EDV, Δ ESV, Δ EF = sequential change in end-diastolic volume, end-systolic volume, and ejection fraction from acute to chronic stage where both were available; see also Table III. Values are expressed as mean ± SD; Student t-test for unpaired and paired (Δ) data.
*p = .005 versus controls.
**p = .05 acute versus chronic.

days 1–3 to days 10–20 and from days 1–3 to three months, respectively, showed a significant improvement in the patients with persistent patent infarct-related vessel after thrombolysis with or without angioplasty (groups B and C), and this was most marked when intracoronary thrombolysis was followed by angioplasty (group B). No significant changes in radionuclide ejection fraction could be detected in patients treated conventionally. These data are in agreement with the contrast angiographic findings.

Enzymatic Infarct Size

Enzymatic infarct size was estimated by cumulative HBDH release in the first 72 h after onset of symptoms. As shown in Figure 5, the median cumulative HBDH release in the control group (1,136 U/L) was significantly higher than in the two other groups.

Long-Term Follow-up

Median clinical follow-up of 24 months in all subsets of patients are presented in Table VII. The clinical follow-up of patients treated by thrombolysis and angioplasty was most favourable when the patency of the

TABLE V. Regional Myocardial Function of the Infarct Zone*

CREF-IZ	Controls (group A)	TR + PTCA (group B)	TR alone (group C)
Anterior infarction (n)	69	20	40
Anterobasal (%)	12.2	15.7	13.7
Antero-apical (%)	4.4	6.0	5.8
Apex (%)	1.1	1.8	1.9
Inferior infarction (n)	105	7	39
Apex (%)	2.6	3.0	3.6
Infero-apical (%)	6.9	10.7	10.8
Inferobasal (%)	10.8	14.4	13.5

*Regional contribution to global ejection fraction (%) of the infarct zone (CREF-IZ) at follow-up angiography. Anterobasal = segments 1–5; antero-apical = segments 5–9; apex = segments 9–12; infero-apical = segments 12–16; inferobasal = segments 16–20. See also Table 3 and Figure 3.

infarct-related vessel could be demonstrated prior to discharge (group B). These patients had a low reinfarction rate (6%); late coronary bypass surgery (13%) and/or (re)-PTCA (3%) was performed less frequently than in the other groups, while only 1 patient died. Conversely, the incidence of late reinfarction was 21% in the group treated by thrombolysis alone.

DISCUSSION

There have been many clinical trials of the efficacy of thrombolytic therapy in achieving reperfusion. However, the efficacy of thrombolysis in randomized trials has varied widely in several studies [41–48]. Our data from the multicenter randomized trial [6–8] and the data from the GISSI study [49] have shown the beneficial effects of early thrombolysis in acute myocardial infarction. However the very efficacy of this initial treatment has created a new problem: how to manage the patients with residual atheromatous lesions whose ischemic symptoms persist after thrombolysis, and who may constitute up to half of the patients treated. In order to maintain the initial benefit

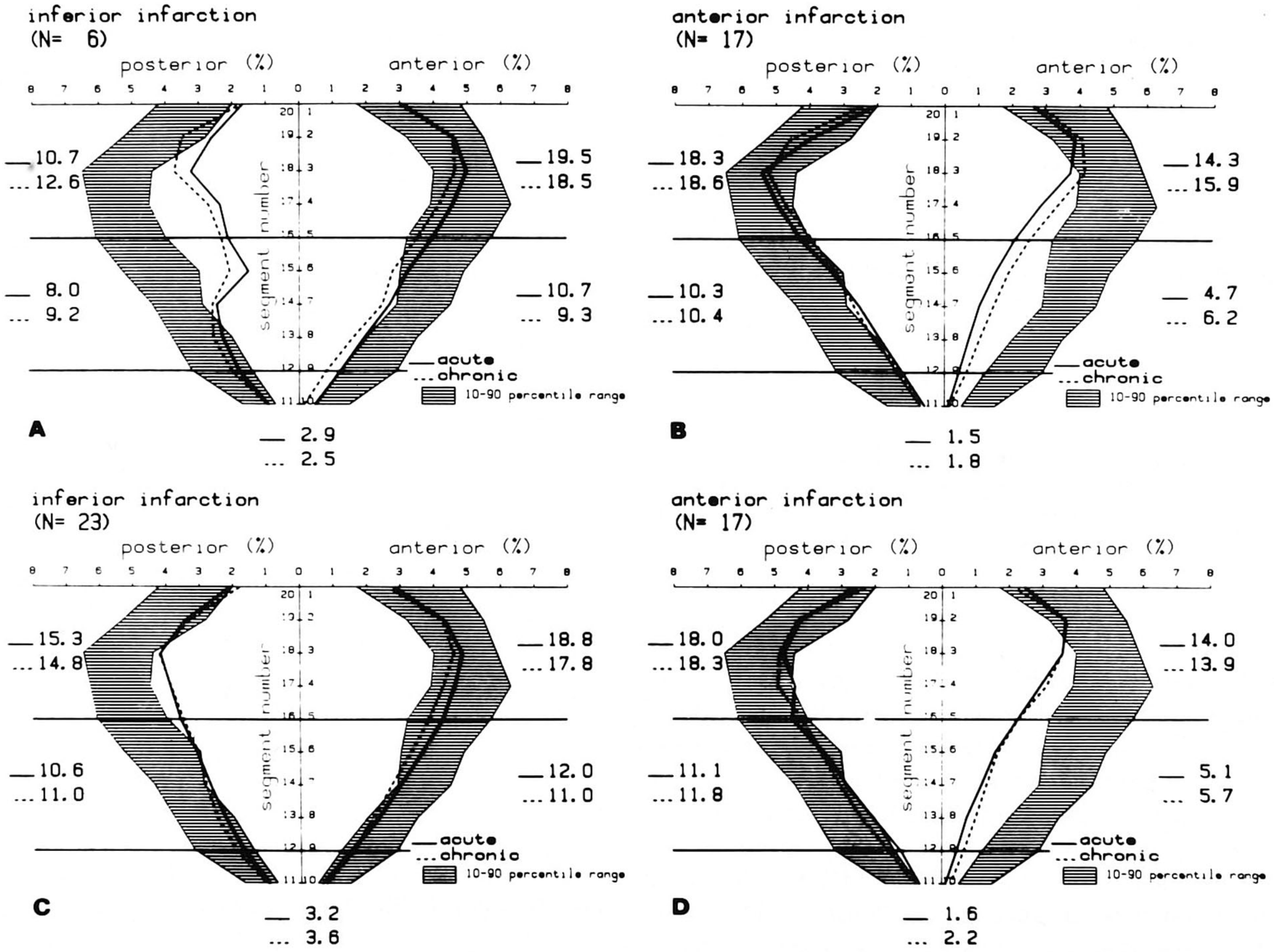

Fig. 3. Sequential changes in regional contribution to global ejection fraction from the acute (at admission, solid line) to the chronic (before discharge, dotted line) stage in patients with inferior (left sided) and anterior (right sided) infarction treated by a combined procedure of thrombolysis and angioplasty (A and B) as well as treated by thrombolysis alone (C and D). The improvement in global ejection fraction of patients treated by angioplasty following thrombolysis was due to significant improvement of the regional myocardial function of the infarct zone even after the disappearance of compensatory actions of the initially enhanced function of the noninfarct zone.

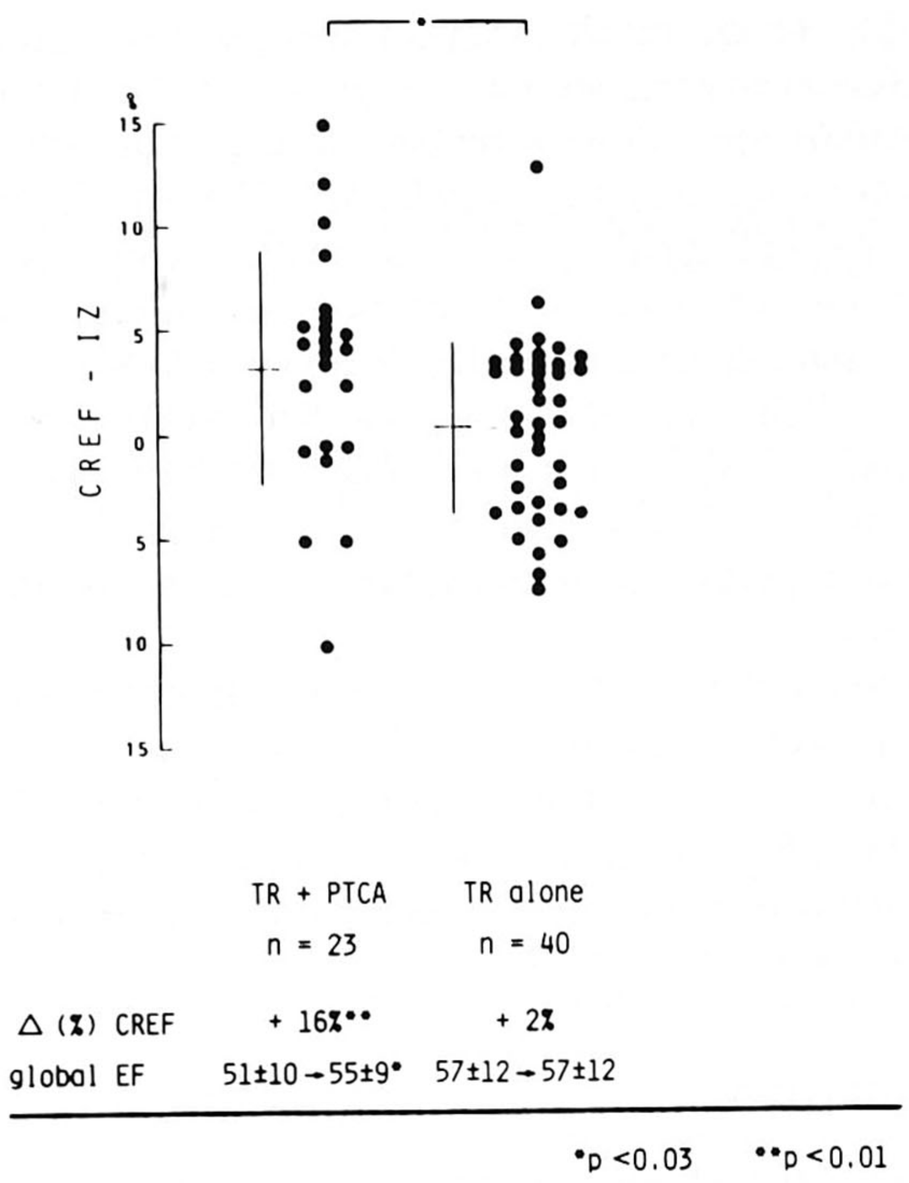

Fig. 4. Sequential changes (%) in regional contribution to global ejection fraction (CREF) of the infarct zone (anterior = segment 1 to 10; inferior = segment 11 to 20) from the acute to the chronic stage in the patients in whom both angiograms were available. In the group of patients successfully treated by thrombolysis followed by angioplasty with late patency (TR + PTCA), the significant increase in global ejection fraction (from 51% to 55%, p = 0.03) was primarily due to a 16% improvement in regional contribution to ejection fraction of the infarct zone. In the group of patients with persistent patent infarct related vessel after thrombolysis without angioplasty (TR alone), the regional contribution to ejection fraction of the infarct zone remained unchanged.

achieved by thrombolysis, it is necessary to deal with the underlying obstruction. Percutaneous transluminal coronary angioplasty or surgery may play a valuable role in attaining these goals.

Limitations of the Study

Although the data from this study support the results from recently published randomized trials [54,55], there are limitations to the study, and the results should be interpreted with this in mind. The group of patients undergoing angioplasty following thrombolysis was relatively small because of the selection criteria and the fact that recruitment for this group occurred predominantly in one of the participating centers. Although randomization would have been desirable this would have further reduced the number of patients in this group. However, retrospective matched analysis on the basis of lesions suitable for coronary angioplasty show similar results (unpublished data from the Data Processing Center, Interuniversity Cardiology Institute).

TABLE VI. Radionuclide Angiography†

	Controls (A)	TR + PTCA (B)	TR alone (C)
RNAEF 1	43 ± 14 (n=200)	40 ± 15 (n=26)	47 ± 14*·*** (n=90)
RNAEF 2	44 ± 15 (n=172)	49 ± 16 (n=49)	51 ± 15** (n=85)
RNAEF 3	45 ± 15 (n=144)	56 ± 14* (n=17)	52 ± 15** (n=78)
Δ EF 2-1	0.9 ± 11 (n=141)	10 ± 7***** (n=18)	4 ± 9***** (n=76)
Δ EF 3-1	1.7 ± 13 (n=115)	9 ± 14**** (n=14)	3 ± 12 (n=68)

†RNAEF = radionuclide ejection fraction (%) at day 1–3 (1), day 10–20 (2) and at 3 months (3); Δ EF = sequential change in radionuclide ejection fraction.
*p = .05 and **p = .005 versus controls; ***p = .05 versus TR + PTCA; ****p = .05 and *****p = .005 acute versus chronic. See also Tables III and IV.

Reocclusion

The rationale behind the decision to perform angioplasty immediately after thrombolysis was to augment perfusion, reduce infarct size, and improve left ventricular function as well as to prevent reocclusion. Although we have been able to demonstrate a favourable influence of angioplasty on left ventricular function and recurrent myocardial infarction, it is clear that the procedure does not influence the rate of reocclusion before discharge (Table II). This seems to be due to the disproportionately high incidence of reocclusion in those patients with a right coronary artery lesion. Why lesions in this artery should be susceptible to reocclusion is open to speculation.

Preservation of Left Ventricular Function and Need for Regional Assessment

Although the present study shows that rapid recanalization can be achieved by intracoronary thrombolysis alone with a reperfusion rate comparable with the combined procedure (intracoronary thrombolysis followed by additional angioplasty), analysis of serial global, and regional left ventricular function demonstrated the additional benefit of correcting the residual obstructive lesions. Global left ventricular ejection fraction was measured by contrast and radionuclide angiography (Tables IV, VI). Both methods showed higher ejection fractions at the follow-up study when recanalization had been successful either with (group B) or without (group C) additional angioplasty. This finding is supported by analysis of regional wall motion and enzymatic infarct size measurement. Furthermore, in the group successfully treated by angioplasty, the improvement in global ejection fraction was more pronounced and persisted up to

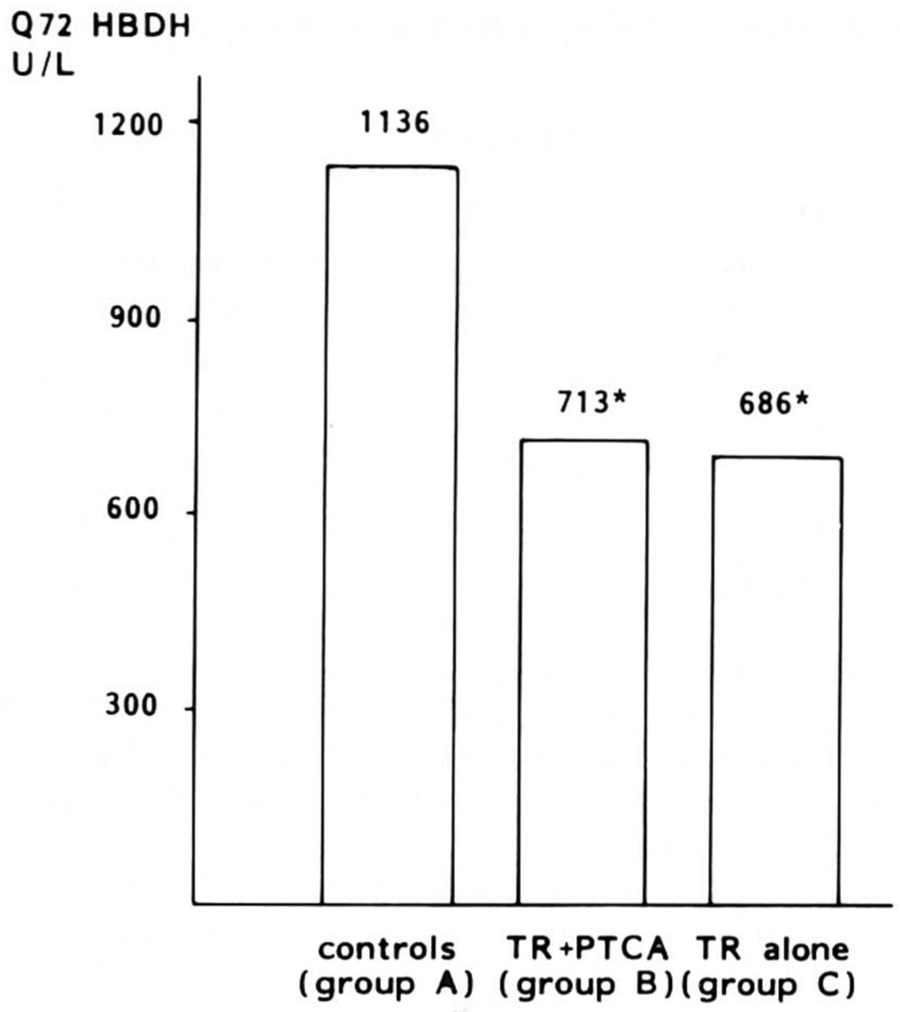

Fig. 5. Median cumulative serum alpha-hydroxybutyrate dehydrogenase release in the first 72 hours after onset of symptoms (Q72 HBDH).

three months after the intervention. In most studies published thus far, the assessment of global ejection fraction has prevailed since it is relatively easily obtainable. 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 infarction area. Therefore, analysis of left ventricular wall motion in the area at risk which potentially should benefit most from reperfusion must be carried out in order to detect any real benefit of reperfusion [8,50–53]. In this study, the regional contribution to global ejection fraction of the infarct zone was most improved in the group of patients successfully treated by thrombolysis followed by angioplasty. In this subset of patients, global ejection fraction increased significantly ($p = 0.03$) from 51% to 55% from the acute to the chronic stage, an improvement primarily resulting from a 16% increase in the regional contribution to ejection fraction of the infarct zone (Figs. 3, 4). This finding was in accordance with the results of recently published randomized trials [54,55]. These results suggest that in some patients, reperfusion may need to be supplemented by additional revascularization procedures such as angioplasty in order to optimize the chances of obtaining full functional recovery. The additional value of immediate angioplasty in preserving left ventricular function and limiting infarct size might help to explain the observed reduction in one-year mortality and other major cardiac events. The present study shows that intracoronary streptokinase combined with coronary angioplasty can be safely used to provide reperfusion in the setting of acute myocardial infarction.

The high survival rate, the lower incidence of reinfarction, as well as the preserved regional and global left ventricular function in the subgroup successfully treated with thrombolysis and coronary angioplasty suggests that this combination may be the optimal mode of therapy for selected patients.

TABLE VII: Long-Term Clinical Follow-Up (Median 24 months)*

	Controls (A) n = 264	TR + PTCA (B) n = 31	TR alone (C) n = 102
Re-infarction	17 (6%)	2 (6%)	21 (21%)
CABG	33 (13%)	4 (13%)	14 (14%)
(Re)-PTCA	13 (5%)	1 (3%)	14 (14%)
Death	46 (17%)	1 (3%)	2 (2%)

*See Table III.

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