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Effect of intracoronary thrombolytic therapy on global and regional left ventricular function. A three year experience with randomization

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Die Wirkung intrakoronarer thrombolytischer Therapie auf die globale und regionale linksventrikuläre Funktion. Eine randomisierte 3-Jahres-Studie

Zusammenfassung: Die Wirkung myokardialer Reperfusion auf die regionale linksventrikuläre Funktion wurde durch Analyse der segmentalen Wandbewegung an 185 Patienten in einer randomisierten Untersuchung quantifiziert, die die Thrombolyse mit konventioneller Therapie bei Patienten mit akutem Myokardinfarkt verglich. Wenn wir die hämodynamischen Daten auf der Basis eines „Behandlungsversuchs" analysierten, fanden wir eine signifikante Erhaltung der linksventrikulären Funktion nach thrombolytischer Therapie im Vergleich zu konventioneller Behandlung. Darüber hinaus zeigte die Analyse der Wandbewegung, daß eine signifikante Verbesserung der regionalen Funktion in der „Infarktzone" festzustellen war, und zwar sowohl beim inferioren als auch beim Vorderwandinfarkt, obwohl signifikante Änderungen in der regionalen Funktion der entfernteren „Nicht-Infarktzone" im akuten wie im chronischen Stadium zu beobachten waren.

Unsere Katamnesedaten zeigen jedoch, daß die Frage bisher nicht gelöst wurde, ob diese Therapiemethode tatsächlich die Prognose bei Patienten mit akutem Myokardinfarkt verbessert. Dementsprechend sind wir der Überzeugung, daß eine solche invasive Therapie nicht allgemein angewandt werden sollte, bevor mehr katamnestische Daten aus größeren randomisierten Untersuchungen zur Verfügung stehen.

Summary: The effect of myocardial reperfusion on regional left ventricular function has been quantitated by analysis of segmental wall motion in 185 patients enrolled in a randomized trial comparing thrombolysis with conventional treatment in patients with acute myocardial infarction. When analyzing the hemodynamic data on an "intention to treat" basis we found a significant preservation of left ventricular function after thrombolytic therapy when compared to conventional treatment. In addition, the wall motion analysis showed that a significant improvement of regional function in the "infarct zone" was observed in inferior infarction as well as in anterior infarction, although significant changes in regional function of the remote "non infarct zone" were observed at the acute as well as at the chronic stage.

However, our follow-up data indicate that as yet it has not been resolved whether this method of treatment does indeed improve prognosis in patients with acute myocardial infarction. Accordingly, we maintain the view that such invasive treatment should not be generally applied until more follow-up data become available from larger randomized trials.

Key words: intracoronary thrombolysis, acute myocardial infarction, randomized trial, global and regional left ventricular function

Introduction

Since the initial publication of Rentrop et al. it has been confirmed that acutely occluded coronary arteries can be recanalized by intra-coronary infusion of a fibrinolytic agent (29). Reestablishment of antegrade flow might prevent myocardium, made temporarily ischemic by coronary occlusion, from progressing to complete necrosis or alternatively might support marginally viable cells (28). Animal experiments have shown that restoration of coronary blood flow may save myocardium (2, 4, 21) and improve survival (2) if the reperfusion is instituted within a few hours of coronary occlusion. However, it is still uncertain whether these results are applicable in humans. The risk of angiography in the first hours of myocardial infarction is not negligible (35) and may outweigh the potential benefit of the recanalization; reperfusion of ischemic myocardium might be harmful because of the occurrence of serious arrhythmias (7), intramyocardial hemorrhage (3, 26) and calcium overload of myocardial cells with subsequent death as a result of too rapid reperfusion – the oxygen paradox (16).

To answer the question of whether this approach to the treatment of patients with acute myocardial infarction will be ultimately beneficial to most of these patients, a carefully designed randomized trial was started in June 1981 at the Thoraxcenter. This study includes detailed analysis of the influence of myocardial reperfusion on left ventricular (LV) function two weeks after attempted recanalization as well as identical studies on those patients assigned to conventional treatment (CT) in addition to a long-term follow-up with end-points such as mortality and reinfarction rate.

In the randomized trials published thus far, the assessment of global ejection fraction has mainly been employed for this purpose (1, 19, 20, 22). However, any improvement of global LV function after successful recanalization of a coronary artery might be caused by several factors: salvage of jeopardized myocardium, compensatory hyperactivity of other wall segments (30, 39) or changes in pre- and afterload.

In an effort to solve this problem, the effect of myocardial reperfusion on regional LV function has been quantitated by analysis of segmental wall motion.

Patient selection and methods

The randomized trial of thrombolysis in acute myocardial infarction is a multicenter study supported by the Interuniversity Cardiology Institute in the Netherlands. The study was initiated at the Thoraxcenter in June 1981. The Free University in Amsterdam and the Zuiderziekenhuis in Rotterdam have participated in the trial since January 1983, and the St. Annadal Hospital in Maastricht since August 1983. The present analysis is limited to the first 185 patients enrolled at the Thoraxcenter between June 1981 and June 1984.

Patient selection

Patients were eligible for the trial if they were admitted within 4 hours of the onset of chest pain with a duration of 20 minutes or more and with ECG signs compatible with myocardial infarction. ST segment elevation of 0.2 mV or greater should be present in one of the precordial leads and/or 0.1 mV in a limb lead, in spite of treatment with oral or intravenous nitroglycerine and/or nifedipine. In addition patients were included with 0.2 mV ST segment depression in precordial leads, compatible with posterior wall infarction.

The following exclusion criteria were used:
- age over 70 years
- previous treatment with streptokinase
- bypass surgery of the vessels corresponding to the infarct location
- recent trauma including traumatic resuscitation
- gastro-intestinal bleeding or ulcer within 3 months
- hematuria within 3 months
- cerebro-vascular accident within 3 months
- pregnant or menstruating women
- mental confusion precluding informed consent
- anticipation of follow-up problems.

Study protocol

A flow chart of the protocol is presented in Fig. 1. Eligible patients who did not meet the exclusion criteria were entered in the trial. These patients were registered by a central telephone answering service. The physician at the CCU called the answering service and provided administrative data including patient's initials, sex, date of birth and clinical state. The answering service then opened the randomisation envelope and provided treatment allocation. Informed consent was asked from patients allocated to thrombolytic treatment only (49). Seven patients refused the intervention while informed consent was obtained in 86 patients; 92 were assigned to conventional treatment (CT). Patients who refused consent were treated according to the CT protocol. Data analysis was based on the "intention to treat" principle. Thus patients who refused acute angiography were analysed as part of the thrombolysis group, following original treatment allocation.

Conventional treatment was guided by hemodynamic monitoring. Both in the control group and in patients allocated to thrombolysis it was attempted to achieve an "optimal" hemodynamic state characterized by light sedation, a heart rate

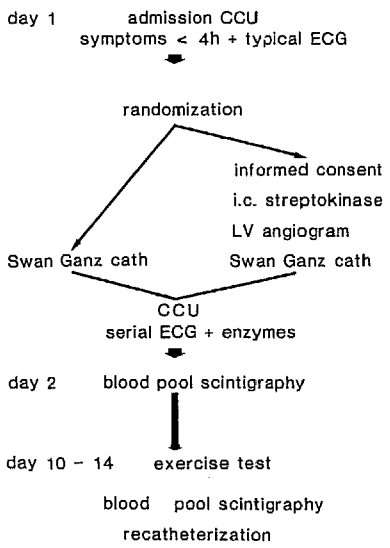

Fig. 1. Flow chart of the procedures in the current randomized trial at the Thoraxcenter.

between 60 and 90 beats per minute, systolic blood pressure between 100 and 140 mmHg and absence of LV failure with the pulmonary capillary wedge pressure below 12 mmHg. Guidelines for treatment have been described in detail (40) and include the use of beta blockers when heart rate was greater than 90 bpm with systolic blood pressure over 100 mmHg in the absence of heart failure; nitroprusside when systolic blood pressure was greater than 150 mmHg; nitroglycerine and furosemide in the presence of heart failure; atropine and/or temporary ventricular pacing in the case of bradycardia and dobutamine in patients with systolic blood pressure lower than 100 mmHg. In addition intra aortic balloon counter pulsation was used for the treatment of cardiogenic shock.

All patients were treated with heparin followed by acenocoumarol (Sintrom®) until hospital discharge. After discharge anticoagulants were continued only in patients with ventricular aneurysm, intraventricular thrombus, mitral incompetence or large ventricles with a poor contraction pattern.

Beta blockers, metoprolol 2 × 100 mg, were prescribed in the majority of patients starting between 7 and 14 days unless contra-indications were present. Other therapy was prescribed as needed.

In patients assigned to streptokinase treatment, a nitroglycerine infusion (100 ug/kg/min) was started immediately and the patients were transferred to the catheterization laboratory as soon as possible. Lidocaine was also given intravenously in a dose of 2 mg/min. After puncturing 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. A non-ionic contrast agent (Amipaque®) was employed as contrast medium. After identification of the thrombosed coronary branch, 50 mg heparin was administered intravenously together with 250 mg acetylsalicylic acid and 100 mg diadresone F®, a corticosteroid.

Before starting the intracoronary perfusion with streptokinase, 3 mg isosorbide dinitrate was injected into the thrombosed coronary artery over 1 min, with monitoring of the aortic pressure. Coronary arteriography was then repeated to evaluate any spasmolytic effect on the coronary occlusion. Intracoronary perfusion with streptokinase was carried out at a rate of 4000 units/min to a maximum of 250000 units of streptokinase, diluted in 500 ml of physiological solution, at a flow rate of 8 ml/min. Coronary angiograms were repeated every 15 minutes until the chest pain disappeared. The appearance of ventricular extrasystoles or any other conduction disturbance was also an indication to reangiogram 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 cathether (French 2) with a radiopaque tip through the Judkins catheter (French 8). After completion of the streptokinase infusion, nitroglycerine and lidocaine infusions were ceased and complete left and right coronary arteriography was performed. If the clinical condition was stable with LV end-diastolic pressure lower than 35 mmHg, left ventriculography in the RAO projection was done. In 31 patients, percutaneous transluminal coronary angioplasty was performed in the same session, 20 to 60 minutes after end of streptokinase infusion, in order to prevent early and late reocclusion (36). The day before discharge from the intermediate care area, coronary arteriography and LV angiography were obtained both in the control group (CT) and the thrombolysis-treated (TR) group.

In 125 patients, left ventriculograms of sufficient quality were obtained to permit automated analysis (42). The small number of late angiograms was due to the following factors. In the thrombolysis group, 7 patients refused the thrombolytic therapy after randomization, three of whom died within 10 days; 3 other patients died during attempted fibrinolysis; one patient sustained a fatal reinfarction shortly after successful fibrinolysis; two were transferred to another hospital; eight underwent coronary artery bypass-grafting after thrombolysis because of symptoms and 12 refused to cooperate with the follow-up study. In the conventionally treated group, six patients died in hospital before catheterization could be performed; eighteen refused the catheterization and there were three LV angiograms of insufficient quality to permit automated analysis. Thus, at the chronic stage, 65 LV angiograms were available for analysis in the control group and 60 angiograms in the thrombolysis group.

Both groups are similar with regard to the infarct localization on the electrocardiogram and the involved vessel. The CT-group includes 20 patients with previous infarction compared with 13 in the thrombolysis group (ns). Their data provide the essence of this study (Table 1).

Analysis of global and regional LV function

Global and regional LV function was studied from the 30° right anterior oblique LV cine-angiogram with an automated hardwired endocardial contour detector linked to a minicomputer (43). For each analyzed cineframe LV volume was computed according to Simspon's rule. After the end-diastolic and end-systolic frames were determined, stroke volume, global ejection fraction and total cardiac index were computed. In Fig.

Table 1. Clinical and angiographic data in 125 patients with LV angiogram at 2 weeks

	Conventional treatment (CT)		i. c. thrombolysis (TR)
Number of patients	65	ns	60
Infarct localisation			
Anterior/lateral	33 (51%)	ns	34 (57%)
Inferior/posterior	32 (49%)	ns	26 (43%)
Previous infarction	20 (31%)	ns	13 (22%)
Infarct related vessel			
LAD	26 (40%)	ns	29 (48%)
LCX	11 (17%)	ns	8 (13%)
RCA	28 (43%)	ns	23 (38%)
Infarct related vessel Patency	30 (46%)	p=0.003	48 (80%)

Abbreviations: i.c.=intracoronary; LAD=left anterior descending coronary artery; LCX=left circumflex; RCA=right coronary artery.

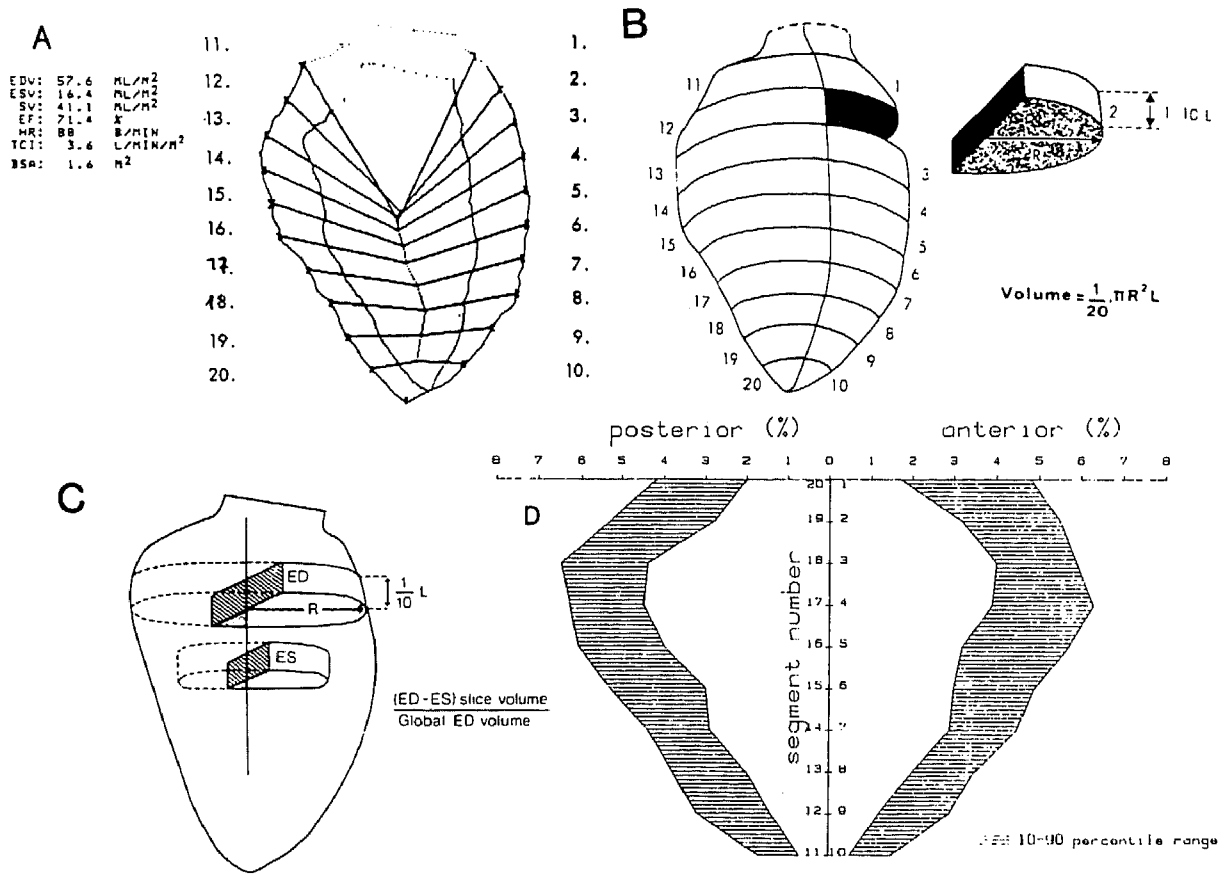

Fig. 2. A. Example of the computer output showing the end-diastolic and end-systolic contours of the 30° RAO left ventriculogram and the system of coordinates along which LV segmental wall displacement is determined. The corresponding volume data, ejection fraction and other parameters are shown in the upper left corner.
B. The LV end-diastolic cavity is divided into twenty half-slices. The volume of each half-slice is computed according to the given formula, R is radius and L is LV 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, which is expressed by the X-component of the displacement vector.
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 infero-posterior wall areas are displayed (%), while on the y-axis the segment numbers of the anterior wall (1–10) and of the infero-posterior wall (11–20) are depicted.

2A, an example of the end-diastolic (ED) and end-systolic (ES) contours of the left ventriculogram, as displayed by the analysis system, is shown. Systolic regional wall displacement is determined along a system of 20 coordinates based on the pattern of actual endocardial wall motion in normal individuals (43), and generalized as a mathematical expression amenable to automatic data processing (17, 37).

For each segment, segmental volume is computed from the local radius (R) and the height of each segment (1/10 of LV long axis length (L) according to the formula: $\frac{1}{20} \pi R^2 L$). When normalized for end-diastolic volume, the systolic segmental volume change can be considered as a parameter of regional pump function (Fig. 2). During systole this parameter expresses quantitatively the contribution of a particular segment to global ejection fraction, termed regional contribution to global ejection fraction or CREF (17). The sum of the values for all 20 segments equals the global ejection fraction. The cross-hatched zones in Fig. 2D represent the segmental CREF values between the 10th and 90th percentiles, as determined in 20 normal individuals. The segmental CREF-values in the anterobasal (segments 1–5), anterolateral (segments 5–9), apical (segments 9, 10, 19 and 20), inferior (segments 15–19) and posterobasal (segments 11–15) wall regions were compared in the CT-group and in the TR-group.

Statistical analysis

Data are expressed as mean ± SD; paired or unpaired Student's t-tests were applied to the hemodynamic data whenever appropriate, differences in baseline characteristics between groups were tested by Fisher's exact test.

Results

The effect of the thrombolytic therapy is shown by 80% patency of the infarct related vessel in the intervention group versus 46% patency in the control group ($p = 0.003$) at two weeks (Table 1).

In Table 2 the hemodynamic data of the control group are compared to those of the thrombolysis group. Almost all the parameters listed in this table are significantly different in both groups. The global LV ejection fraction in the thrombolysis group was 10% ($p < 10^{-5}$) higher than in the control group and this was mainly due to a smaller end-systolic volume in the thrombolysis group (38 ml/m^2 versus 55 ml/m^2 in the control group, $p < 0.0001$). Most prominent is the smaller percentage of abnormally contracting segments (11) in the thrombolysis group: 7.8% versus 15.5%. In addition, the end-diastolic pressure and volume were significantly higher in the control group than in the thrombolysis group whereas the mean aortic pressure and heart rate were not different at the time of the hemodynamic investigation. Table 3 shows the hemodynamic data of both groups after the exclusion of patients with a previous infarction (20 in the control group and 13 in the thrombolysis group). It appears that the differences observed in the entire group (n = 125 patients) after conventional treatment or thrombolytic therapy are still present and significant, although less marked, when corrected for the uneven incidence of patients with previous infarction. In the thrombolysis group, the ejection fraction is 6% ($p < 0.02$) higher than in the control group while the end-systolic volume is 11 ml/m^2 ($p < 0.02$) smaller than in the control group. From these results we may conclude that attempted treatment with intracoronary streptokinase leads to preservation of global LV function even when the results are presented on an "intention to treat" basis. However, the crucial question remains as to whether we can ascribe these differences in global LV function to the salvage of previously jeopardized myocardium in the area supplied by a recanalized vessel.

Table 2. Left ventricular hemodynamics prior to discharge

	CT (n = 65)	TR (n = 60)	p Value
HR bpm	79 ± 16	75 ± 13	ns
Mean AoP mmHg	92 ± 14	94 ± 14	ns
EDP mmHg	22 ± 8	18 ± 8	0.003
EDV ml/m^2	99 ± 27	81 ± 20	0.001
ESV ml/m^2	55 ± 27	38 ± 15	0.0001
EF %	45 ± 14	55 ± 11	0.001
SV ml/m^2	42 ± 13	44 ± 12	ns
CI l/min/m^2	3.2 ± 0.9	3.3 ± 0.9	ns
ACS %	15.5 ± 15	7.8 ± 10	0.002

Values are expressed as means ± SD; Student t-test for unpaired data.
Abbreviations: HR = heart rate; AoP = aortic pressure; EDP = end-diastolic pressure; EDV = end-diastolic volume; ESV = end-systolic volume; EF = ejection fraction; SV = stroke volume; CI = cardiac index; ACS = abnormally contracting segments (24).
CT: conventional treatment; TR: thrombolysis.

Table 3. Left ventricular hemodynamics prior to discharge in patients *without* previous myocardial infarction

	CT (n = 45)	TR (n = 47)	p Value
HR bpm	79 ± 17	74 ± 12	ns
Mean AoP mmHg	94 ± 15	94 ± 16	ns
EDP mmHg	21 ± 8	18 ± 8	0.05
EDV ml/m^2	94 ± 25	82 ± 20	0.02
ESV ml/m^2	48 ± 23	37 ± 15	0.02
EF %	50 ± 14	56 ± 11	0.02
SV ml/m^2	45 ± 14	46 ± 11	ns
CI l/min/m^2	3.3 ± 0.9	3.4 ± 0.8	ns
ACS %	11.7 ± 14	7.3 ± 10	ns

Abbreviations as in Table 2.

In an effort to answer this question, segmental wall motion was analyzed in patients with anterior and inferior infarction. In Table 4 and Fig. 3 the global and regional LV functions of patients with inferior infarction are presented. The global LVEF shows an 11% difference ($p<0.01$) in favour of the thrombolysis group, and this difference in EF is due to a significantly ($p<0.005$) smaller end-systolic volume (35 ml/m^2) as compared to the end-systolic volume (56 ml/m^2) of the control group. Also the end-diastolic pressure, the end-diastolic volume and the percentage of the abnormally contracting segments are smaller in the thrombolysis group. In Fig. 3A the CREF values of patients with inferior infarction assigned to thrombolysis are compared with those assigned to conventional treatment. Subnormal CREF values were observed in the infero-posterior wall (segments 11–18) as expected, but a significantly less marked depression in regional pump function was observed in patients assigned to thrombolysis. No difference in regional function of the anterior wall was observed. In Table 7 and Fig. 3C the changes in global and regional LV function from the acute stage (immediately after recanalization) to the chronic stage (two weeks later) in the patients with inferior infarction are presented. When the recanalization is successful and the infarct related vessel remains patent at two weeks, no significant change in the global hemodynamics is observed. This contrasts with a significant improvement within 2 weeks of the inferior wall associated with the subsidence of the

Table 4. LV hemodynamics in *inferior* infarction prior to discharge

	CT (n=32)	TR (n=26)	p Value
HR bpm	80 ±17	72 ±12	ns
Mean AoP mmHg	92 ±15	98 ±17	ns
DEP mmHg	21 ± 8	18 ± 7	ns
EDV ml/m^2	100 ±26	75 ±23	0.001
ESV ml/m^2	56 ±26	35 ±16	0.005
EF %	45 ±13	56 ±11	0.01
SV ml/m^2	43 ±12	42 ±11	ns
CI l/min/m^2	3.3± 0.9	3.0± 0.8	ns
ACS %	13.9±15	2.5± 4	0.001

Abbreviations as in Table 2; CT=conventional treatment; TR=thrombolysis.

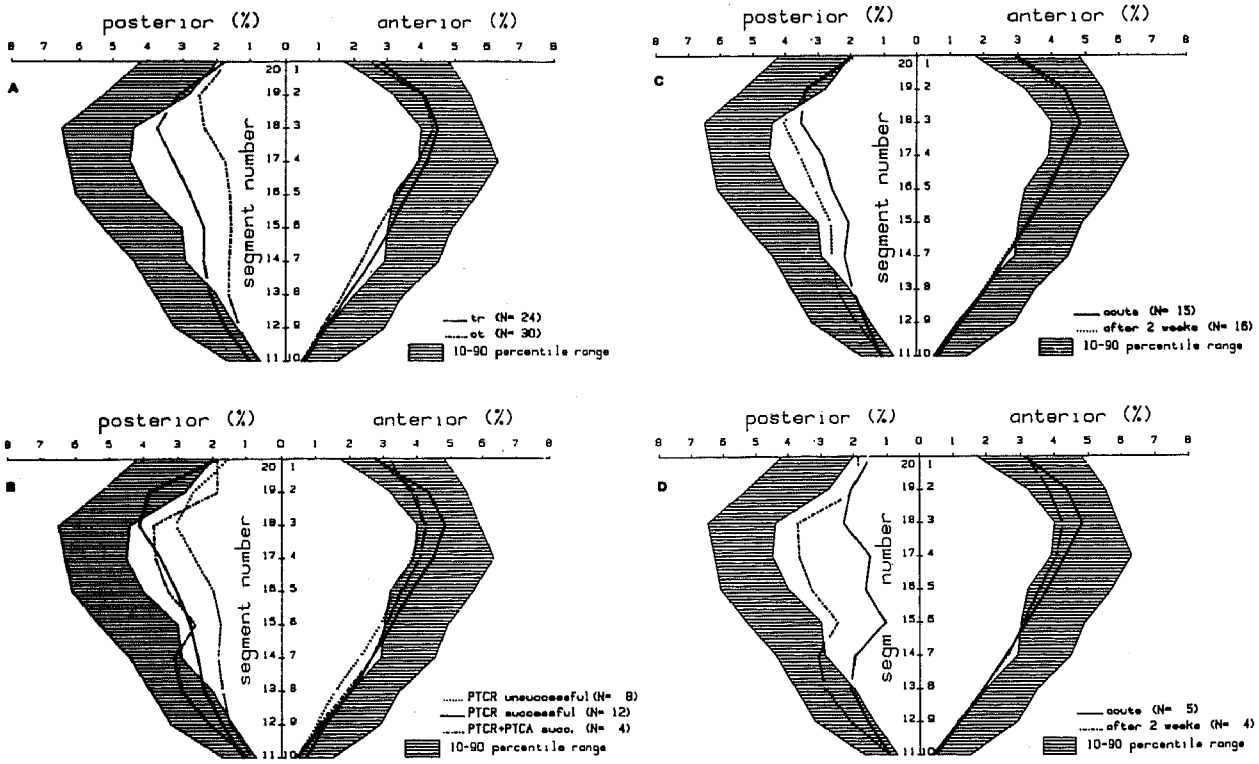

Fig. 3. A. Regional contribution to global ejection fraction (CREF) in 20 segments of the left ventriculogram in patients with inferior infarction. Shaded areas represent the normal range. The regional pump function of the inferior wall (segments 11 to 20) in the thrombolysis treated group (solid line) is markedly less depressed than in the conventionally treated group (dotted lines).
B. Regional contribution of the inferior wall to global ejection fraction at the chronic stage, in the thrombolysis group, according to the success of the recanalization at the acute stage.
C. Change in CREF from the acute (solid line) to the chronic stage (dotted line) in patients (n=16) with an inferior infarction who underwent a successful recanalization.
D. Change in CREF from the acute (solid line) to the chronic stage (dotted line) in patients (n=5) with an inferior infarction who underwent a combined procedure of recanalization and angioplasty.

Table 5. LV hemodynamics in *anterior* infarction prior to discharge

	CT (n=33)	TR (n=34)	p Value
HR bpm	77 ±14	78 ±13	ns
Mean AoP mmHg	92 ±14	91 ±14	ns
EDP mmHg	23 ± 7	18 ± 8	0.02
EDV ml/m^2	97 ±27	86 ±17	=0.05
ESV ml/m^2	55 ±29	40 ±14	0.02
EF %	46 ±14	54 ±11	0.01
SV ml/m^2	42 ±14	46 ±11	ns
CI l/min/m^2	3.1± 0.9	3.5± 0.9	ns
ACS %	16.9±16	11.2±12	ns

Abbreviations as in Table 2.

compensatory functioning of the anterior wall (3C). This latter phenomenon is particularly prominent in the patients who underwent a combined procedure of recanalization and angioplasty at the acute phase (3D).

In Table 5 and Fig. 4, the global and regional LV functions of patients with anterior myocardial infarction are shown. A significant ($p<0.02$) 8% difference in ejection fraction is shown between both groups due to a smaller end-systolic volume in the thrombolysis group, 40 ml/m^2 versus 55 ml/m^2 in the control group ($p<0.02$). Figure 4 clearly indicates that this 8% difference in LVEF in favour of the thrombolysis group is essentially due to a better regional pump function of the inferior wall and, to a smaller extent, better regional pump function of the basal segment of the anterior wall (Fig. 4A).

Moreover, it must be pointed out that these results have been analyzed on an "intention to treat" basis and that the thrombolysis group can be subdivided into three subsets of patients: a) patients with either unsuccessful recanalization or late occlusion, b) patients with successful recanalization and late patenty of the IRV, c) patients who underwent a successful recanalization, immediately followed by angioplasty.

The worst segmental function of the anterior wall was found in the patient who could not be successfully recanalized while the greatest preservation of regional function of the anterior wall was observed in the patients who underwent a combined procedure of recanalization and angioplasty (Fig. 4B).

In Table 6 and Fig. 4C, the serial (acute, and after 2 weeks) changes in global and regional LV function of the patients with anterior infarction are shown. Following successful recanalization, no significant change in global hemodynamics could be demonstrated. In these patients the small

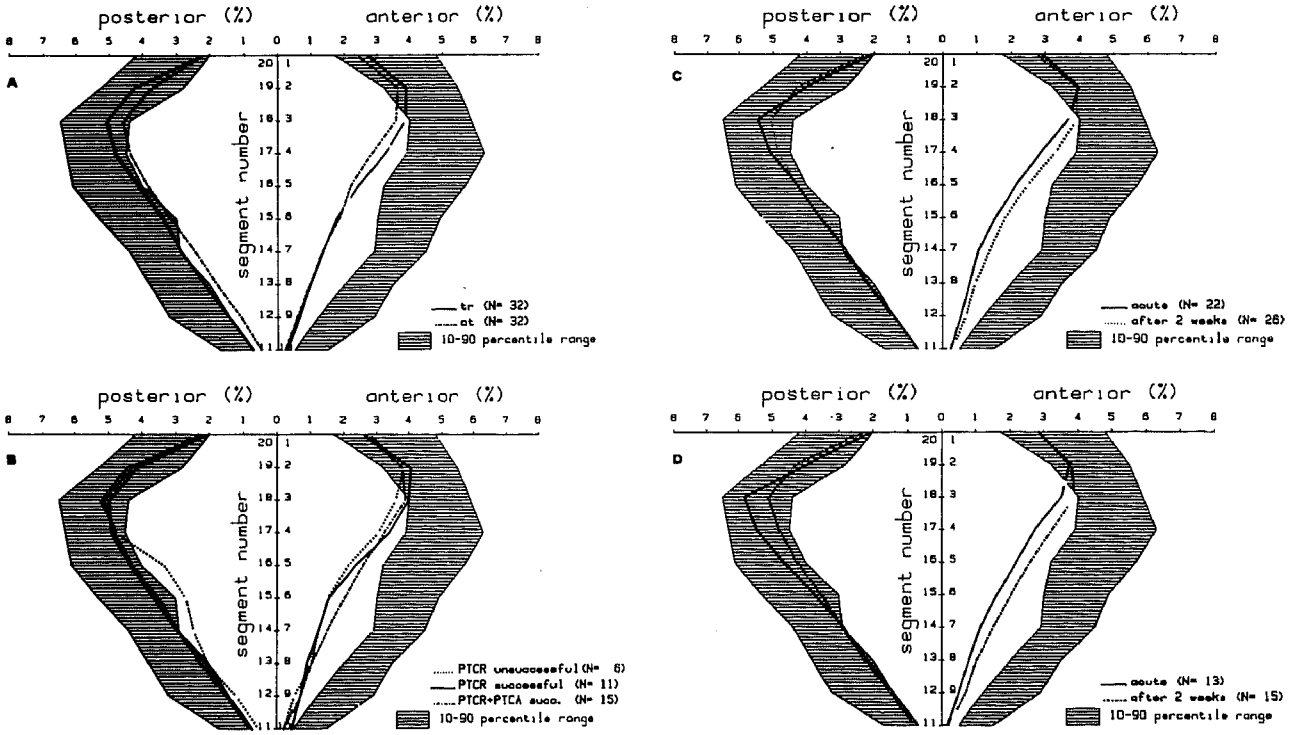

Fig. 4. A. The mean CREF values in patients with anterior infarction are shown as in Fig. 3. The regional pump function of the antero basal segment (segments 1 to 5) is slightly better in the thrombolysis group, while the function of the whole opposite inferior wall is better after thrombolysis as compared to conventional treatment.
B. Regional contribution of the anterior wall to global ejection fraction at the chronic stage in the thrombolysis group, according to the success of the recanalization at the acute stage.
C. Change in CREF from the acute (solid line) to the chronic stage (dotted line) in patients (n=26) with an anterior infarction who underwent a successful recanalization.
D. Change in CREF from the acute (solid line) to the chronic stage (dotted line) in patients (n=15) with an anterior infarction who underwent a combined procedure of recanalization and angioplasty.

but significant improvement of the anterior wall observed between the acute and chronic stages was partially masked by the disappearance of the compensatory functioning of the inferior wall (Fig. 4C). Conversely, when recanalization was unsuccessful this resulted in a significant deterioration of the global parameters: decrease of 5% in ejection fraction ($p<0.05$), increase in ESV from 34 to 46 ml/m^2 ($p<0.01$), and increase in EDV from 75 to 89 ml ($p<0.05$).

These changes in global function corresponded with deterioration of the regional function in the anterior, apical and apico-inferior segments.

Table 6. Thrombolysis group: serial LV hemodynamics in *anterior* infarction

	Successful (n=26)			Unsuccessful (n=6)		
	Acute	p Value	Chronic	Acute	p Value	Chronic
HR bpm	81±12	ns	76±13	87±16	ns	77±15
Ao mmHg	89±12	ns	92± 8	87±16	ns	95±21
EDP mmHg	23± 9	ns	19± 8	18± 7	ns	18±11
EDV ml/m^2	84±21	ns	88±20	75±18	0.05	89±18
ESV ml/m^2	40±15	ns	41±15	34±10	0.01	46±16
EF %	52±10	ns	55±11	54± 7	0.05	49±13
SV ml/m^2	42±11	0.03	48±14	39±10	ns	43±12

Mean±SD

Abbreviations as previously. Values are expressed as means ±SD; Student t-test for paired data.

Table 7. Thrombolysis group: serial LV hemodynamics in *inferior* infarction

	Successful (n=16)			Unsuccessful (n=8)		
	Acute	p Value	Chronic	Acute	p Value	Chronic
HR bpm	82±15	0.02	71±12	85±16	ns	75±12
Ao mmHg	97±10	ns	102±12	88±17	ns	91±25
EDP mmHg	19± 7	ns	18± 5	18± 8	ns	19±12
EDV ml/m^2	70±14	ns	70±22	70±17	0.02	89±21
ESV ml/m^2	30± 9	ns	31±13	32±10	0.01	48±17
EF %	58±10	ns	59± 8	54± 9	0.02	46±14
SV ml/m^2	41±11	ns	43±10	36±10	ns	42±16

Mean ±SD

Abbreviations as previously. Values are expressed as means ±SD; Student t-test for paired data.

Discussion

As shown by our results, recanalization of an occluded coronary artery in the acute phase of a myocardial infarction appears to be associated with preservation of global and regional LV function, when compared to the natural fate of the LV function of patients randomly assigned to conventional treatment.

These results are in agreement with the findings of our previous pilot study (18) where the LV function was assessed sequentially – at the acute and chronic stages – in patients with succesful or unsuccessful recanalization. Similar results have been reported by Rentrop et al. (31), Ganz et al. (14) and Mathey et al. (25). Thereafter several studies (9, 32, 34, 44) were published on the effect of early reperfusion on LV function. From these non-randomised studies it appeared that patients with successful recanalisation had a higher global ejection fraction than those with unsuccessful recanalisation or conventional treatment.

Also, it appeared that the LV damage was less in patients with spontaneous recanalisation demonstrated by the existence of an open infarct vessel at 4–6 weeks after the acute event than in those with an occluded infarct vessel (9). Schwartz et al. (34) demonstrated improvement of the LV function only when recanalisation was achieved within 4 hours. According to Rentrop et al. (32) only some subgroups showed an improved LV function after thrombolysis: those with collaterals, those with incomplete obstruction before intervention and those in whom complete obstruction was permanently recanalised.

Although these studies have aroused great interest, their results have mainly been based on series in which patients with successful thrombolysis were compared with patients in whom the procedure failed. Such analysis carries considerable bias, since patients in whom thrombolysis succeeded are not necessarily similar to those in whom the intervention failed.

This bias can be ruled out only by means of a properly conducted randomized trial and the 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 of patients randomized to special therapy. In this sequence, patients with evolving infarcts 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 (49) for the comparison of a new method of treatment with an accepted mode of therapy.

When analyzing the hemodynamic data on an "intention to treat" basis we found a significant preservation of left ventricular function after thrombolytic therapy when compared to conventional treatment. The results of the four completed randomised trials (1, 19, 20, 22) and the still ongoing trial conducted in the Thoraxcenter

Rotterdam, are conflicting. Khaja et al. (20) found that i. c. streptokinase was more effective than placebo (i. c. infusion of dextrose) in achieving reperfusion. But they detected no improvement of LV function as a result of reestablished coronary flow measured at treatment, at 12 days and at 5 months. Kennedy et al. (19) and Leiboff et al. (22) demonstrated no difference in the radionuclide determined ejection fraction at discharge in patients with anterior or inferior myocardial infarction treated with intracoronary streptokinase or controls. However, it may be argued that the intervention in these studies was instituted rather late. In the study of Khaja et al. (20) the time period between chest pain and infusion of streptokinase was 5.4 hours, and in the study of Kennedy et al. (19) this time period was between 3 and 12 hours in the majority of the patients.

Schwartz et al. (34) clearly demonstrated benefit only in early reperfusion (within 4 hours) but not in late reperfusion (later than 4 hours) which is in agreement with animal experiments. These 3 studies are counter-balanced by the results of the study of Anderson et al. (1) and the preliminary results of our study. Both studies show that i.c. streptokinase appears to have a beneficial effect on the left ventricular function.

However, it should be appreciated that measurement of the global ejection fraction is a rather crude method which may not detect improvement of LV function. More sophisticated techniques are required for analysis of this function. Since only the infarction area is at risk and can potentially benefit from reperfusion, mixing data from areas of the ventricle which may benefit from reperfusion with data from areas which cannot benefit from reperfusion will make it harder to detect any real effect of reperfusion. Determination of changes in regional rather than global ventricular function is now recognized as the proper way to study patients before and after reperfusion (15, 39, 45).

Stack et al. (45) determined regional and global ventricular performance before, 24 hours after, and 16 days after intracoronary streptokinase. All reperfused patients showed improvement of regional shortening in the jeopardized region ($p = 0.01$), but the global ejection fraction showed no improvement or a decrease in half of these patients. The global ejection before streptokinase was increased by compensatory increases of wall motion in the non-infarction regions of the heart, while the global ejection fraction 16 days later was decreased by subsidence of the compensatory increases of wall motion of the non-infarcted regions of the heart. However, when appropriate regional techniques for evaluation of the jeopardized myocardium were utilized, significant salvage of myocardium was indicated by recovery of contractile function in patients who were reperfused during the first 6 hours of myocardial infarction.

Very similar results were shown by Sheehan et al. (39), who utilized computerized measurements of motion along 100 chords around the left ventricle. Regional hypokinesia improved in 41% of patients with reperfusion by streptokinase and subsequent coronary bypass grafting and in 30% of patients with reperfusion by streptokinase alone.

No improvement was seen in patients who did not attain reperfusion. However, the ejection fraction did not discriminate between reperfused and non-reperfused patients. Due to increased motion of the non-infarction regions of the heart, the global ejection fraction was often normal in acute myocardial infarction despite severe regional hypokinesia in the infarction area. Late after infarction, the subsidence of increased motion in the non-infarction regions of the heart often masked significant improvement in regional hypokinesia. These authors concluded that early thrombolysis in acute myocardial infarction results in improved LV function, and regional wall motion must be measured to adequately assess this effect.

Our results show that a significant improvement of regional function in the "infarct zone" is observed in inferior infarction as well as in anterior infarction, although significant changes in regional function of the remote "non-infarct zone" were observed at the acute as well as at the chronic stage (6, 23, 27, 47).

The results of the four published reports on a randomized trial of intracoronary streptokinase in acute myocardial infarction strengthen our opinion that the ultimate benefits of this invasive treatment are yet to be established. The clinical benefits of thrombolytic therapy could not easily be demonstrated. Although dramatic improvements have been reported in a few patients in cardiogenic shock (24), or in patients with complete occlusion of the left main coronary artery (10), the clinical course at the coronary care unit (CCU) of patients with and without thrombolysis was similar (12).

Earlier we reported no differences in early and late mortality, reinfarction, angina or exercise test data between patients assigned to streptokinase treatment and controls (38). At present, 302 patients have been enrolled in the ongoing trial supported by the Interuniversity Cardiology Institute and the conclusions remain similar (41). Actually this finding is not surprising. If indeed the major effect of early recanalization is preservation of LV function and a greater LVEF, then the beneficial effects on mortality will become evident only when large series of patients are studied.

Sanz et al. (33) and de Feyter et al. (8) reported a better one year survival rate after myocardial infarction in patients with higher LVEF, independent of the extent of coronary disease. Similar

data were found in a follow-up study of 214 hospital survivors at the Thoraxcenter (13). Pooling the results of these studies, a relationship between the one year mortality rate and the LVEF could be constructed (Fig. 5).

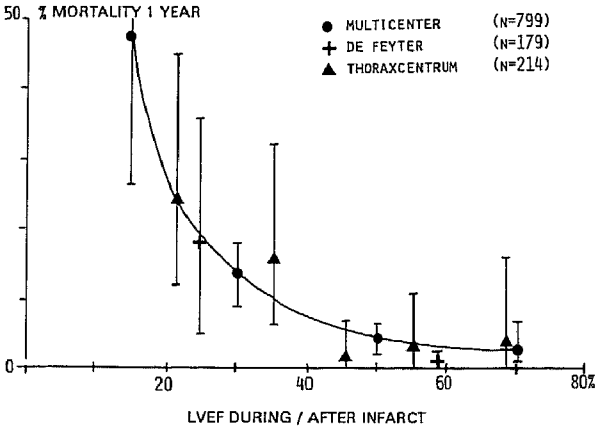

Fig. 5. Relationship between one year mortality and left ventricular ejection fraction at discharge. Data from three different studies (8, 13, 33) were pooled. Vertical bars represent 95% confidence limits.

If these data were applied to the observed improvement of LVEF from 45% in controls versus 55% in patients allocated to thrombolysis, the one year mortality would be reduced from approximately 16% to 10% after thrombolysis, which corresponds to our observations and the data from the Western Washington trial (19). In order to demonstrate this difference in mortality with $p < 0.05$ and a power of 80%, approximately 1800 patients should be enrolled in the study.

The combined analysis of all randomized trials on intracoronary thrombolysis (48) indicates that as yet it has not been resolved whether this method of treatment does indeed improve prognosis in patients with acute myocardial infarction. Accordingly we maintain the view that such invasive treatment should not be generally applied until more follow-up data becomes available. On the other hand the accumulated experience indicates that some patients do benefit from early recanalization. Analysis of subgroups may be used to select those patients who are most likely to benefit from thrombolysis.

Finally, the development of tissue plasminogen activator is likely to reduce the risk of bleeding after thrombolysis (5, 46), which would render this intervention more applicable in clinical practice.

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