Effects of Intracoronary Thrombolysis on Global Left Ventricular Function Assessed by an Automated Edge Detection Technique

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Three hundred and two patients with acute myocardial infarction were enrolled in a randomized multicenter trial to compare conventional treatment with attempted recanalization by intracoronary streptokinase. In a subgroup of patients, the effects of thrombolysis on left ventricular function were evaluated within 48 hr, at 2 wk, and at 3 mo after admission. Global left ventricular ejection fraction (LVEF) was obtained by radionuclide angiography and analyzed with an automatic detection program. Paired data were determined in 160 patients (control 78, thrombolysis 82) within 48 hr and at 2 wk, and in 143 patients (control 71, thrombolysis 72) at 48 hr, 2 wk, and 3 mo. It was shown that LVEF significantly improved in the thrombolysis group as compared with controls both at 2 wk (Δ LVEF thrombolysis 3.9 ± 7.9%, $p < 0.001$ compared with Δ LVEF control 0.6 ± 9.7%, p = N.S.) and at 3 mo (Δ LVEF thrombolysis 3.1 ± 12.4%, $p < 0.05$ compared with Δ LVEF control 2.1 ± 12.2%, p = N.S.). When patients were divided according to infarct site, however, significant improvement at 3 mo was only observed in the patients with anterior infarction (Δ LVEF thrombolysis 5.5 ± 13.1%, $p < 0.05$ compared with Δ LVEF control 3.3 ± 10.4%, p = N.S.). It was shown that acute intervention with intracoronary streptokinase has a potentially favorable and lasting effect on left ventricular function in patients with anterior myocardial infarction. This improvement might be related to the rather rapid administration of thrombolytic therapy with a median time of ~4 hr after onset of symptoms.

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Recent studies have indicated that recanalization of an occluded coronary artery can be achieved in 60–85% of cases of acute myocardial infarction (MI) if intracoronary streptokinase is injected within 6 hr of the onset of chest pain (*1–3*). This rate of recanalization is far higher than the rate found to occur spontaneously (*4,5*).

Although it has been claimed in early studies (*6,7*) that intracoronary streptokinase improves left ventricular function in treated groups as compared with controls, this has not been consistently confirmed by recently performed controlled studies (*8–13*). Moreover, most of the recently published trials failed to show a treatment effect on left ventricular function. The observation of the absence of a treatment effect, however, could be due to different trial designs, to the relatively small sample sizes in these studies, or to the mode of analysis of left ventricular function.

Accordingly, the purpose of this controlled study was to assess the effects of intracoronary streptokinase on global radionuclide left ventricular function in a large randomized multicenter trial. Particular emphasis was placed on the mode of analysis of the radionuclide studies.

MATERIALS AND METHODS

Outline of Study

Between May 1981 and January 1984, the first part of a randomized controlled prospective trial was carried out in four hospitals to compare the effects of intracoronary streptokinase with conventional treatment. In a subset of patients, radionuclide angiography was performed to study the effects of thrombolysis on left

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ventricular function until 3 mo after the acute event. In this study, the main emphasis was placed on the results of radionuclide angiography. Clinical results were mentioned only if they were relevant to the radionuclide data. The overall clinical and angiographic results will be reported separately.

Patient Enrollment

Patients ≤70 yr of age with myocardial ischemic pain of >30 min duration were eligible for participation if they could be randomly assigned to a treatment group within 4 hr after the onset of chest pain. The chest pain had to persist after nitroglycerin therapy and the ECG had to show the following changes in ST segment elevation; 0.2 mV or more in the precordial leads and 0.1 mV in the limb leads. Exclusion criteria were previous treatment with streptokinase, and high risks of bleeding such as recent trauma, cardiopulmonary resuscitation, and hematuria.

Randomization Procedure

Patients were allocated by randomization to the thrombolysis group or to the control group. Patients allocated to the thrombolysis group were asked to give informed consent after randomization. The control group only received conventional therapy without acute angiography.

Coronary angiography was performed as soon as possible after the informed consent. Before angiography, the patient received 5,000 IU i.v. heparin, 100 mg i.v. prednisolone, and 250 mg acetylsalicylic acid. Intravenous lidocaine 2 mg/min and i.v. nitroglycerin were administered if necessary.

Acute Catheterization Protocol

Patients with total coronary artery obstruction received an intracoronary infusion of 4,000 U/min. The infarct-related vessel was visualized in a fixed projection every 15 min. If recanalization occurred, the intracoronary infusion was continued for at least an additional 15 min. The maximum infusion period was 60 min. Patients with initially incomplete obstruction did not receive streptokinase if the severity of the stenosis was estimated to be <50% in luminal diameter. Stenosis of >50% were perfused with streptokinase for at least 15 min. The mean dose of streptokinase was 217,000 U/patient (range 0–375,000).

Subsequent Therapy

All patients, including those in the control groups, were fully anticoagulated with i.v. heparin and were subsequently treated with coumadin until discharge from the hospital. Beta-blockers, nitrates, and calcium-antagonists were not administered routinely within the first 72 hr after random assignment.

Data Acquisition and Analysis

Within 48 hr after admission to the cardiac care unit, radionuclide angiography (RNA) was performed with a mobile gamma camera* interfaced with an IMAC 7400 computer system.† Red blood cells were labeled in vivo after i.v. injection of 15 mCi (555 MBq) technetium-99m. Gated radionuclide angiograms were made in 45–60° left anterior oblique (LAO) view to provide optimal separation of left and right ventricle. A 20% window was used around the 140 keV gamma-peak and data were collected in a matrix of 64 × 64 pixels. Gating was performed with 20 frames/cycle and data were acquired over a period of 8 min. Data were stored on floppy disk. Whenever possible, oral nitrates were discontinued at least 12 hr before the scintigraphic procedure. The RNA studies were repeated after 14 days and after 3 mo. All RNA studies were performed with the same acquisition technique. Global left ventricular ejection fraction (LVEF) was computed by means of an automatic edge-detection program implemented in the IMAC system. The method has the advantage of a low operator interaction and has good reproducibility as previously assessed by our own laboratory (*14*). An LVEF of 50% was considered the lower limit of normal. Since the RNA studies were obtained from one single view, regional wall motion abnormalities were not evaluated in this study. All patients were evaluated blinded to patient identity and treatment assignment. In all patients who had at least one coronary angiogram, the coronary artery responsible for the infarction was determined by correlating angiographic and electrocardiographic data. The infarct-related coronary artery was classified as totally obstructed or patent before intervention and afterwards. Patency was defined as complete filling of the artery within three cardiac cycles. Serial electrocardiograms were evaluated for confirmation of the presence and location of infarction according to standard criteria. At 2 wk, the coronary angiogram was repeated in 50 patients and the infarct related artery proved to be reoccluded in ten patients (20%). Fifteen patients (27%) in the treatment group had acute percutaneous transluminal coronary angioplasty. Early coronary artery bypass grafting was not performed in both groups.

Statistical Analysis

Data analysis was based on the intention to treat principle following original treatment allocation. Only patients with at least two RNA studies were taken into consideration. Student's t-test was used to determine statistical significance from paired data. Data were expressed as the mean ± s.d. and/or median and range. All p values were two-tailed and a p value of <0.05 was considered to be statistically significant.

RESULTS

Patient Characteristics

One hundred and fifty out of a total of 302 patients were assigned to conventional treatment and 152 pa-

tients to thrombolytic therapy. In 160 patients, radionuclide angiography was performed within 2 days after intervention and after 2 wk. Baseline characteristics are shown in Table 1 and were not significantly different among controls (n = 78) and thrombolysis patients (n = 82). The patient characteristics of the total group of 302 patients were very similar to the patients who underwent the paired RNA studies. In both groups, three patients died before the first RNA study.

Radionuclide Angiography

Paired radionuclide data were determined in 160 patients (control 78, thrombolysis 82) within 48 hr and 2 wk (Table 2), and in 143 patients (control 71, thrombolysis 72) at all three times (Table 3). The 48-hr RNA studies showed equal distribution of normal and abnormal (<50%) LVEF values in both groups: 45 (58%) of the control group and 48 (55%) of the thrombolysis group showed an abnormal LVEF. At all three times the thrombolysis group showed increased LVEF values compared with the control group. At 2 wk, a significant increase in LVEF was noticed in the thrombolysis patients (Δ LVEF 3.9 ± 7.9%, $p < 0.001$) compared with the control patients (Δ LVEF 0.6 ± 9.7%, p = N.S.). At 3 mo a significant increase in LVEF was observed in the treatment group (Δ LVEF thrombolysis 3.1 ± 12.4%, $p < 0.05$ compared with Δ LVEF control 2.1 ± 12.2%, p = N.S.).

When patients were divided according to site of infarction, this significant difference was noticed in both the anterior and inferior infarctions at 2 wk. At 3 mo, the significant improvement in LVEF was only observed in the patients with anterior infarction (Δ LVEF thrombolysis 5.5 ± 13.1%, $p < 0.05$ compared with Δ LVEF control 3.3 ± 10.4%, p = N.S.). The patients with inferior infarction did not show significant difference at 3 mo (Δ LVEF thrombolysis 1.2 ± 13.5%, p = N.S. compared with Δ LVEF control 1.5 ± 11.8%, p = N.S.).

The dropoff of patients between 2 wk and 3 mo was mainly due to logistic reasons since only three (4%) patients in the thrombolysis group and two (3%) patients in the control group died in that period.

TABLE 1
Baseline Characteristics of 160 Patients with Acute Myocardial Infarction who Underwent Radionuclide Angiography*

Item	Control	Thrombolysis
No. of patients (pts)	78	82
Age (yr)	55 (35–70)	54 (30–70)
Male (pts)	66 (85%)	67 (82%)
Anterior MI (pts)	33 (42%)	39 (47%)
Inferior MI (pts)	45 (58%)	43 (53%)
Previous MI (pts)	20 (26%)	15 (18%)
Time to random assignment (min)	108 (0–240)	115 (0–240)
Time to infusion (min)	—	243 (100–385)
Total dose of streptokinase (U)	—	217,000 (0–375,000)
Patency of infarct-related artery (pts)	—	65 (79%)

* Values are expressed as absolute numbers with percentages or as median with range.

TABLE 2
Paired Radionuclide LVEF (%) Within 48 hr and at 2 wk

Group	No. of patients	LVEF 48 hr mean ± s.d.	LVEF 2 wk mean ± s.d.
C total*	78	40 ± 13	41 ± 14
T total†	82	44 ± 14	48 ± 14‡
C anterior MI	33	32 ± 11	34 ± 14
T anterior MI	34	36 ± 12	40 ± 13§
C inferior MI	45	47 ± 11	46 ± 11
T inferior MI	48	50 ± 12	54 ± 12**

* C = Control.
† T = Thrombolysis.
‡ $p < 0.001$. (p Values were obtained after comparison with 48 hr studies).
§ $p < 0.01$.
** $p < 0.05$.

DISCUSSION

The results of this controlled, prospective, randomized multicenter trial show that radionuclide LVEF improves over time in patients allocated to thrombolysis. The improvement in LVEF differed significantly from the LVEF values in the control group, which did not show any significant increase in LVEF during the 3 mo follow-up. In particular, in patients with anterior MI this treatment effect was still present at 3 mo.

This indicates a beneficial effect of thrombolysis on left ventricular function already in the early phase of acute MI.

Our data are at variance with most prospective randomized trials of intracoronary streptokinase in acute myocardial infarction (*8,10,12,13*). Even a preliminary study by our own group (*15*) did not show a significant improvement in LVEF. Only Anderson et al. (*9*) reported improvement of left ventricular function after streptokinase infusion. These different findings may be explained by different trial designs, by the sample sizes that were studied, or by the different mode of analysis of left ventricular function.

The Western Washington Trial (*12*) reported no improvement in radionuclide LVEF in the streptokinase group (n = 134) compared with controls (n = 116). In their study, LVEF was determined with a computer-

TABLE 3
Paired Radionuclide LVEF (%) of 143 Patients Who Underwent All Three RNA Studies

Group	No. of patients	LVEF 48 hr mean ± s.d.	LVEF 2 wk mean ± s.d.	LVEF 3 mo mean ± s.d.
C total*	71	38 ± 13	39 ± 15	41 ± 15
T total†	72	43 ± 13	48 ± 14‡	47 ± 14§
C anterior MI	31	30 ± 13	32 ± 17	32 ± 14
T anterior MI	30	37 ± 12	40 ± 12§	44 ± 15§
C inferior MI	40	44 ± 11	44 ± 11	48 ± 12
T inferior MI	42	48 ± 12	53 ± 11**	49 ± 13

* C = Control.
† T = Thrombolysis.
‡ $p < 0.001$. (p Values were obtained by comparison with 48 hr studies).
§ $p < 0.05$.
** $p < 0.01$.

automated method (*16*) as soon as possible after the acute intervention and at 2 wk. However, the absence of a beneficial effect might be due to the difference in time between onset of symptoms and randomization between our study (<4 hr) and the Western Washington Trial (<12 hr). Two randomized studies of Khaja et al. (*8*) and Leiboff et al. (*10*) reported no differences in radionuclide left ventricular function between treatment and control groups. Both studies were too small to detect significant differences in left ventricular function, and the Leiboff study even showed a trend towards a decreased LVEF. In addition, the Khaja study included patients up to 6 hr after onset of symptoms. Leiboff (*10*) did not mention the mode of LVEF analysis, and Khaja (*8*) used an automatic edge detection technique.

A recent study by Rentrop et al. (*13*) also reported a lack of treatment effect on left ventricular function. Their trial design was quite comparable to ours in that they compared a thrombolysis group with an uncatheterized control group, but only 47 patients underwent paired radionuclide LVEF immediately before intervention and on Days 10–14 after the MI. In their study, a manual edge-detection technique was used.

Objective assessment of left ventricular function in the acute phase of MI may be difficult because of changes in left ventricular compliance, blood viscosity, collaterals, and preload and afterload of the left ventricle. This is supported by data of Wackers et al. (*17*) who reported considerable spontaneous variations in radionuclide LVEF during the first 24 hr of acute MI in the individual patient. In our studies, most patients underwent the first RNA study between 24 and 48 hr after entering the trial, when major physiologic changes in left ventricular function are less likely to occur.

The improvement in left ventricular function may be due partly to salvage of myocardium, but is most likely caused by amelioration in regional function of the noninfarcted segments, as has been echocardiographically assessed by Hooghoudt et al. (*18*). In addition, Mathey et al. (*19*) concluded in a nonrandomized study that quantitatively small ventricular function benefits of reperfusion can only be identified by regional wall motion analysis. This may be related to the per-

TABLE 4
Comparison of Different Prospective Randomized Trials on Intracoronary Fibrinolysis in Acute Myocardial Infarction

Study	No. of patients	Time to randomization (hr)	First RNA*	Second RNA	Third RNA	Analysis of global LVEF	LVEF response
Khaja (*8*)	40	6	Day 12	5 mo	—	Automatic	–
Anderson (*9*)	50	4	Day 1	Day 10	—	Not mentioned	+
Kennedy (*12*)	250	12	Day 1–2	Days 12–14	—	Automatic	–
Leiboff (*10*)	55	4	Day 1	Days 10–14	—	Not mentioned	–
Rentrop (*13*)	47	12	Preintervention	Days 10–14	—	Manual	–
This study	160	4	Day 1–2	Days 12–14	3 mo	Automatic	+

* After intervention, unless otherwise noted.

fusion of collateral vessels which do not function prior to reperfusion. However, in the report of Khaja et al. (*8*) regional wall motion analysis showed no group benefit after reperfusion. Our study cannot answer these questions since the presence of collateral vessels was not determined. Moreover, regional wall motion was not analyzed in this study.

It has also been reported by Stack et al. (*20*) and Sheehan et al. (*21*) that offsetting hyperfunction in nonischemic segments tends to normalize global left ventricular function. Therefore, only patients with a markedly depressed left ventricular function might show significant improvement (≥5% absolute EF units) in LVEF. As a result patients with a normal initial LVEF (≥50%) would not benefit from reperfusion. However, our study showed in patients with a normal initial LVEF that at 2 wk 11/34 (32%) patients in the thrombolysis group and only 3/33 (10%) in the control group significantly improved their LVEF ($p < 0.001$, chi-square).

Analysis of Global Radionuclide LVEF

Table 4 shows a comparison between the different randomized trials. In two trials, the means of analysis of radionuclide LVEF was not mentioned. In the study of Khaja et al. (*8*), the Western Washington Trial, and our study an automatic edge detection program was used. In our opinion, automatic edge detection is the only legitimate way for proper analysis of LVEF, since considerable intra- and interobserver variability have been reported with manual analysis (*22,23*). This holds true, in particular, for multicenter trials where uniform analysis of left ventricular function is crucial. Our edge-detection program has been shown to have excellent reproducibility; mean and s.d. of differences were 0.8% and 4.3%, respectively (*14*).

CONCLUSION

In this controlled, randomized study the effects of intracoronary thrombolysis on left ventricular function were studied until 3 mo after the MI. Global LVEF was determined from the RNA studies and analyzed by an automatic edge-detection program. Our study showed a beneficial effect of intracoronary thrombolysis on left ventricular function in patients with acute myocardial infarction. This effect was already noticeable at Day 2 and persisted for 3 mo. In particular, patients with anterior MI showed a significant improvement in left ventricular function which was sustained for at least 3 mo after the acute event. Since patients with anterior infarction have a large risk of clinically deteriorating in the early phase of myocardial infarction, they should potentially benefit from early intervention with intracoronary streptokinase.

Thus, acute intervention with intracoronary streptokinase has been shown to have a potentially favorable and lasting effect on left ventricular function in patients with anterior MI. This improvement is probably related to the relative large group of patients studied and to the rather short entry window of 4 hr, which resulted in a rapid administration of thrombolytic therapy. The application of an automatic edge-detection program for appropriate analysis of left ventricular function appears to be very desirable.

FOOTNOTES

* Siemens AG, Erlangen, FRG.
† CGR, Holland.

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