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Intravenous Streptokinase in Acute Myocardial Infarction (I.S.A.M.) Trial: Serial Evaluation of Left Ventricular Function Up to 3 Years After Infarction Estimated by Radionuclide Ventriculography

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The Intravenous Streptokinase in Acute Myocardial Infarction (I.S.A.M.) trial was a prospective, placebo-controlled, double-blind multicenter trial of high-dose short-term intravenous streptokinase in acute myocardial infarction administered within 6 h after the onset of symptoms. Global and regional left ventricular ejection fractions were determined by radionuclide ventriculography in a subset of 120 patients 3 days, 4 weeks, 7 months, 18 months and 3 years after acute myocardial infarction.

In patients with anterior myocardial infarction, left ventricular ejection fraction was higher in the streptokinase than in the placebo group 3 days after acute infarction (49 ± 14% vs. 40 ± 11%, p = 0.02). This difference of about 10% units in ejection fraction persisted during the 3 year follow-up period. Among streptokinase-treated patients, regional left ventricular ejection fraction was higher within the infarct zone as well as in remote myocardium throughout the follow-up period. Among patients with inferior infarction, no significant differences between the treatment and control groups were demonstrable with respect to global and regional left ventricular ejection fraction.

Thus, intravenous administration of streptokinase within 6 h after the onset of symptoms of acute myocardial infarction preserves left ventricular function over a period of ≥3 years in patients with acute anterior myocardial infarction. It improves regional myocardial function within the infarct zone as well as in remote areas. In patients with acute inferior myocardial infarction, benefit from intravenous streptokinase is of only minor degree.

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Acute myocardial infarction is mostly caused by a thrombotic occlusion of a coronary artery (1,2). Angiographic studies demonstrated that intravenous streptokinase can reopen coronary arteries occluded by a thrombus (3,4). Intravenous administration of streptokinase is therefore an effective way to salvage jeopardized myocardium and to limit infarct size (3,4). Accordingly, large placebo-controlled trials (5–7) comparing the effects of intravenous streptokinase with conventional treatment demonstrated a reduction in mortality, especially in patients with anterior myocardial infarction. Left ventricular function is a powerful predictor of long-term prognosis after myocardial infarction (8–10). Previous studies (11–13) of intravenous streptokinase assessed left ventricular function only within the 1st year after acute myocardial infarction.

In the present study we determined global and regional left ventricular function by radionuclide ventriculography up to 3 years after acute myocardial infarction in a subset of patients from the Intravenous Streptokinase in Acute Myocardial Infarction (I.S.A.M.) trial.

Methods

Study patients. The I.S.A.M. trial was a prospective, placebo-controlled, double-blind multicenter trial investigating the effects of high dose short-term intravenous streptokinase in acute myocardial infarction versus treatment with heparin and aspirin only (14). The primary study end point was a comparison of mortality 21 days after infarction in streptokinase- and placebo-treated patients. From March 1982 to March 1985, 1,741 subjects aged up to 75 years participated. The study design has been published in detail elsewhere (14). In brief, patients were included if they could be treated with the study medication within 6 h after the onset of acute myocardial infarction and had no contraindication to streptokinase therapy. Criteria for evolving acute myocardial infarction were typical clinical symptoms with electrocardiographic ST segment elevations ≥1 mm in the limb leads and ≥2 mm in the chest leads, or both. Informed consent was obtained from all patients included. The study was approved by an independent ethical and review committee.

After randomization, heparin (5,000 IU), aspirin (0.5 g)

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and methylprednisolone (0.25 g) were given intravenously, followed by administration of the study medication, a 60 min infusion of 1.5 million IU of streptokinase or placebo. Treatment was continued with heparin (800 to 1,000 IU/h) for 3 to 4 days followed by phenprocoumon for ≥3 weeks.

In all patients, blood samples were drawn every 2 h for the 1st 30 h and every 4 h for the next 20 h to determine creatine kinase myocardial isoenzyme levels (14). Time-activity curves of creatine kinase were evaluated concerning time to peak activity after the start of treatment to estimate maintenance or early restoration of coronary blood flow. By comparing enzyme release data (14) and angiographically documented rates of reperfusion (1,3,4), a threshold value of ≤11 hours from the start of treatment to peak activity of creatine kinase was chosen as an indicator of maintenance or early restoration of coronary blood flow.

Radionuclide ventriculography. In the subset of 120 patients initially treated at our institution, left ventricular function was assessed by gated equilibrium radionuclide ventriculography 3 days, 4 weeks, 7 months, 18 months and 3 years after acute myocardial infarction. Radionuclide ventriculography was performed after in vivo labeling of autologous red blood cells with 740 MBq (20 mCi) of technetium-99m (15) by using a small field of view Anger camera with a low energy all-purpose parallel hole collimator and a dedicated computer system (IMAC 7300, CGR Koch & Sterzel). Data acquisition was performed in anterior and "best septal" left anterior oblique projections. Each acquisition (5 to 10 min.) consisted of 16 frames spanning 90% of the cardiac cycles. Global left ventricular ejection fraction was calculated with a semiautomatic program based on the isocount-line concept using end-diastolic and end-systolic regions of interest and a left posteroapical region of interest for background correction (16,17). Regional left ventricular ejection fraction was calculated by dividing end-diastolic and end-systolic regions of interest into angular sectors of 45° each (12,17). Anterolateral, apical and inferior walls (five sectors) were analyzed in anterior projection, and septal, apical and posterolateral walls (eight sectors) in left anterior oblique projection. Normal values and data concerning accuracy and reproducibility of these methods have been published in detail elsewhere (16,17).

Statistical analysis. Data are presented as mean values ± SD. Contingency tables were evaluated with use of chi-square analysis, ordered variables by the Mann-Whitney two sample rank test. Multiple comparisons for intraindividual analysis of ejection fraction data were performed according to the distribution-free technique of Wilcoxon and Wilcox (18). Two-sided probability values are reported.

Results

Clinical characteristics (Table 1). Of the 120 patients included in the present study, 60 had been assigned to the streptokinase and 60 to the placebo group. The distribution of selected characteristics at baseline, during the 4 week hospital period and during the 3 year follow-up period is presented in Table 1. With the exception of time from the start of treatment to peak creatine kinase activity, baseline characteristics were distributed homogeneously between the two groups. Further analysis based on the partitioning of chi-square contingency tables revealed that the inhomogeneity in time to peak activity of creatine kinase must be attributed to the higher frequency of early reperfusion in the streptokinase group compared with the placebo group (time to peak activity of creatine kinase ≤11 h vs. >11 h after the start of treatment, $p = 0.002$). During the 4 week hospital period and during the 3 year follow-up period, the frequency of reinfarction, coronary bypass surgery and coronary angioplasty was low in both groups and did not differ between groups.

Table 1. Distribution of Selected Characteristics at Baseline, During the 4 Week Hospital Period and During the Follow-Up Period (from hospital discharge to 3 years)

	Streptokinase (n = 60)	Placebo (n = 60)	p Value
Baseline			
Male	73%	83%	NS
Mean age (yr)	59.9	59.6	NS
Previous infarction	10%	13%	NS
Mean time to treatment (min)	149	151	NS
Infarct location			
Anterior	47%	47%	NS
Inferior	53%	53%	
Time to CK-MB peak activity (after start of treatment)			
≤11 h	55%	31%	
>11 h	27%	60%	
Undefined*	15%	7%	0.005
No data	3%	2%	
Extent of CAD			
1 vessel	34%	40%	
2 vessels	28%	38%	
3 vessels	25%	17%	NS
No angiography	13%	7%	
Hospital period			
Reinfarction	3%	7%	NS
CABG	7%	2%	NS
Coronary angioplasty	2%	2%	NS
Death	7%	3%	NS
Follow-up period			
Reinfarction	0%	0%	NS
CABG	7%	7%	NS
Coronary angioplasty	7%	7%	NS
Death	7%	3%	NS
No radionuclide ventriculography	10%	3%	NS

*no CK-MB curve or no clear CK-MB peak. CABG = aortocoronary bypass surgery; CAD = coronary artery disease; CK-MB = myocardial isoenzyme of creatine kinase; NS = $p > 0.10$.

Global left ventricular function (Table 2). Three days after acute myocardial infarction, left ventricular ejection fraction was reduced in both the streptokinase and the placebo groups ($p < 0.001$, respectively) compared with normal values from our laboratory (65 ± 5%). For the total

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Table 2. Left Ventricular Ejection Fraction From 3 Days to 3 Years After Acute Myocardial Infarction in Streptokinase- and Placebo-Treated Patients

	Streptokinase		Placebo		
	no.	LVEF (%)	no.	LVEF (%)	p Value
Total group					
3 days	46	54 ± 12	55	48 ± 13	0.04
4 wk	47	55 ± 13	53	47 ± 15	0.007
7 mo	50	56 ± 14	55	50 ± 16	0.03
18 mo	51	55 ± 14	52	50 ± 14	0.10
3 yr	46	55 ± 12	50	49 ± 15	0.07
Patients with AMI					
3 days	20	49 ± 14	25	40 ± 11	0.02
4 wk	19	52 ± 15	24	40 ± 15	0.008
7 mo	21	52 ± 14	26	42 ± 17	0.03
18 mo	22	50 ± 15	24	41 ± 13	0.04
3 yr	21	51 ± 13	23	40 ± 15	0.01
Patients with IMI					
3 days	26	58 ± 10	30	56 ± 8	NS
4 wk	28	57 ± 11	29	53 ± 13	NS
7 mo	29	60 ± 13	29	56 ± 12	NS
18 mo	29	59 ± 13	28	57 ± 11	NS
3 yr	25	57 ± 11	26	57 ± 11	NS

AMI and IMI = anterior and inferior myocardial infarction, respectively; LVEF = left ventricular ejection fraction; NS = $p > 0.10$.

group, a difference of 6% ejection fraction units ($p = 0.04$) was observed between streptokinase-treated and control patients. When the two groups were subdivided on the basis of infarct location, left ventricular ejection fraction was higher in the streptokinase group only in patients with anterior myocardial infarction ($p = 0.02$). In both treatment groups, especially in the placebo group, left ventricular ejection fraction was lower in patients with anterior than in those with inferior infarction ($p = 0.03$ streptokinase, $p < 0.001$ placebo group).

Results similar to those of the initial investigation were obtained in follow-up radionuclide ventriculography 4 weeks, 7 months, 18 months and 3 years after acute myocardial infarction (Table 2). In all investigations, left ventricular ejection fraction was between 5% to 8% units higher in the streptokinase than in the placebo group. This difference was predominantly caused by a respective difference of 9% to 12% units in patients with anterior myocardial infarction. Among patients with inferior myocardial infarction, differences between the treatment and control groups in all investigations were only 0% to 4% units ($p > 0.25$).

In a subgroup of 75 patients (35 in the streptokinase and 40 in the placebo group), all five radionuclide determinations of left ventricular ejection fraction (i.e., complete follow-up) were available for the study of the development of left ventricular function within individual patients. With the exception of deaths (0%, $p < 0.001$), the characteristics displayed in Table 1 did not differ between this subgroup and patients with incomplete follow-up. Aside from death, the major reason for incomplete follow-up was patient refusal

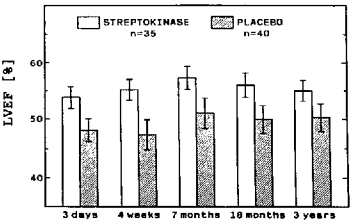

Figure 1. Left ventricular function (mean values ± SEM) from 3 days up to 3 years after acute myocardial infarction in 35 streptokinase- and 40 placebo-treated patients. The data displayed are only from patients with complete follow-up (five radionuclide determinations of left ventricular ejection fraction [LVEF]).

or, in the early studies (3 days, 4 weeks), hemodynamic instability or emergency bypass surgery. Ejection fraction data from these 75 patients (Fig. 1) were consistent with results of analysis of ejection fraction data from all patients (Table 2). That is, there were differences in left ventricular ejection fraction between the streptokinase and the placebo group of 5% to 8% units (although these differences did not reach statistical significance because of the smaller number of patients in the latter group [$0.05 < p < 0.25$, respectively]) and differences of 11% to 14% units ($p < 0.02$, respectively) in patients with anterior myocardial infarction and no significant differences in patients with inferior myocardial infarction.

Intraindividual comparison of data obtained 3 days up to 3 years after acute myocardial infarction revealed the highest values of left ventricular ejection fraction 7 months after acute myocardial infarction in both treatment groups (Fig. 1). Whereas changes between the 5 determinations of left ventricular ejection fraction did not reach statistical significance in the streptokinase group ($p > 0.10$, respectively), left ventricular ejection fraction increased in the placebo group from 4 weeks to 7 months after acute myocardial infarction ($p = 0.02$).

Regional left ventricular function (Fig. 2). In patients with anterior myocardial infarction, regional left ventricular ejection fraction was reduced in most of the 13 sectors with lower values in the placebo group during the total follow-up period. Compared with normal values, differences were greatest in the apical wall and adjacent myocardium. Significant differences between the treatment and control groups ($p < 0.05$) occurred in the infarct area as well as in remote myocardium and were most prominent 4 weeks after acute myocardial infarction (Fig. 2A). In patients with inferior myocardial infarction, regional left ventricular ejection fraction was decreased in both the streptokinase and placebo groups in apical and inferior walls as well as in the adjacent

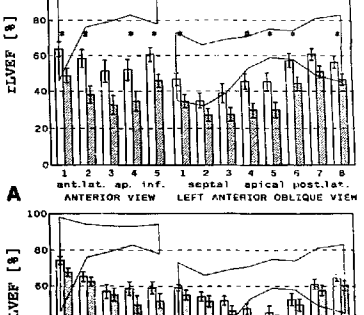

Figure 2. Regional left ventricular ejection fraction (rLVEF) 2 weeks after acute anterior (**A**) or inferior (**B**) myocardial infarction. **A,** 19 streptokinase-treated (**white bars**) and 24 placebo-treated (**hatched bars**) patients. **B,** 28 streptokinase-treated (**white bars**) and 29 placebo-treated (**hatched bars**) patients. Mean values ± SEM are shown. For comparison with normal values from our laboratory (17) the area encompassing ± 1 standard deviation of the normal values is shown between the thin lines. * $p < 0.01$; ≈ $p < 0.05$ comparing the streptokinase and placebo groups. ant.lat. = anterolateral; ap. = apical; inf. = inferior; post.lat. = posterolateral.

parts of the anterolateral and posterolateral walls (Fig. 2B). Compared with patients with anterior myocardial infarction, among patients with inferior infarction differences between the streptokinase and placebo groups were smaller and did not reach statistical significance.

Analyzing only the data obtained from the 75 patients with a complete follow-up concerning intraindividual comparison of regional left ventricular ejection fraction, significant changes occurred only in sectors located within the infarct zone with highest values 7 or 18 months after acute infarction. Among patients with anterior myocardial infarction, regional left ventricular ejection fraction increased in both treatment groups in one sector within the anterolateral wall ($p \leq 0.01$, respectively) and in the streptokinase group in one additional sector within the apical wall ($p = 0.01$). Among patients with inferior myocardial infarction, regional left ventricular ejection fraction increased in both groups within the posterolateral wall, in the streptokinase group in one sector ($p = 0.03$) and in the placebo group in two sectors ($p \leq 0.001$, respectively).

Discussion

Global left ventricular function after streptokinase therapy. The results of the present study using high dose short-term intravenous streptokinase within 6 h after the onset of symptoms of acute myocardial infarction demonstrate a benefit in left ventricular function caused by early thrombolytic therapy. Three days after acute myocardial infarction, global left ventricular ejection fraction was 6% units higher in the streptokinase than in the placebo group (Table 2). Because of the number of patients included (n = 120) and the low frequency of overall mortality (Table 1), this benefit in function could not be correlated with an improved survival (10,19). Subset analysis of ejection fraction data revealed that the benefit for the total group is predominantly caused by a benefit of about 10% units in ejection fraction in patients with anterior myocardial infarction. Patients with inferior myocardial infarction did not differ from control patients. These results are in good agreement with data obtained by Res et al. (20) 2 days after intracoronary administration of streptokinase with a benefit in global left ventricular ejection fraction of 5% units in streptokinase-treated patients with anterior myocardial infarction and an insignificant difference of 1% unit in patients with inferior myocardial infarction.

Anterior versus inferior infarction. The difference between anterior and inferior myocardial infarction concerning benefit in left ventricular function due to thrombolytic therapy most likely can be attributed to the smaller size of inferior compared with anterior infarcts (21). Benefit from coronary reperfusion has been reported (21,22) to be greatest in patients with a large infarct. Additional reasons for a smaller or no benefit in patients with inferior infarction may be a lower rate of infarct-related vessel patency and a higher incidence of collateral vessels (23,24). Furthermore, radionuclide ventriculography in the left anterior oblique projection overestimates the contribution of the anterior myocardial wall and underestimates the influence of the inferior wall because of photon absorption within the cardiac blood pool (16). Underestimation of global left ventricular ejection fraction by 6% to 8% units by radionuclide ventriculography has been reported in patients with an anterior wall aneurysm (16) and acute anterior myocardial infarction (25). However, in acute inferior myocardial infarction, radionuclide determination of global left ventricular ejection fraction seems to be less influenced by the wall motion abnormality. As reported by Kennedy et al. (25), an overestimation of about 1% unit by radionuclide compared with contrast ventriculography can be expected.

After reperfusion, formerly ischemic but non-necrotic myocardium requires several days to recover function (26). Previous studies (2–4) demonstrated an increase in global left ventricular ejection fraction 2 to 3 weeks after acute

myocardial infarction, a time when most randomized trials of intravenous streptokinase assessed left ventricular function (7,27–30). In accordance with our results (Table 2), a benefit in ejection fraction of 6% to 12% units was observed in streptokinase-treated patients with anterior myocardial infarction. In inferior myocardial infarction, differences were smaller (2% to 8% units) and a significant benefit was observed only in some trials (27,30).

Late follow-up results. Left ventricular function in patients treated by thrombolysis has mostly been assessed only within the 1st year after acute myocardial infarction. Within this period a stable benefit has been reported after intracoronary as well as after intravenous streptokinase (11–13,20). Data concerning longer follow-up periods are rare. Blanke et al. (31) reported that over 3 years patients treated by intracoronary streptokinase had a benefit in left ventricular function compared with results in a nonrandomized control group. The findings of the present study—a benefit in left ventricular function in the streptokinase-treated group 3 days after acute myocardial infarction (Table 2) and stability of global left ventricular ejection fraction in this group up to 3 years (Fig. 1)—confirm these data with respect to intravenous streptokinase. Thus, we found that intravenous streptokinase results in a benefit in global left ventricular function that is preserved at least up to 3 years after acute myocardial infarction.

In contrast to our streptokinase group, there was a slight increase in global left ventricular ejection fraction in the placebo group from 4 weeks to 7 months after acute myocardial infarction (Fig. 1). Schelbert et al. (32) similarly observed an increase in global left ventricular ejection fraction in 61% of conventionally treated patients in the late postinfarction period. The presence of ischemic but viable myocardium in the infarct area (33) recovering as a result of development of collateral channels, or late reperfusion, or functional improvement of noninfarcted myocardium (8,34) may explain this finding.

Regional left ventricular function. Determination of global left ventricular ejection fraction is not the most effective way to assess the effects of thrombolysis within the infarct area. Evaluation of regional myocardial function has been reported (8,35) to be more sensitive since dysfunction of the infarct area may be superimposed by hyperkinesia of remote myocardium. In the present study, regional left ventricular ejection fraction was higher in the infarct area as well as in remote myocardium in patients with anterior myocardial infarction in the streptokinase group than in such patients in the placebo group (Fig. 2A). This finding was demonstrable from 3 days up to 3 years after acute infarction. Four weeks after anterior myocardial infarction, Serruys et al. (8) also observed differences between treatment and control groups in both infarcted and noninfarcted areas. Martin et al. (23) and Bassand et al. (29) reported differences only in remote myocardium. Treatment versus control group differences with respect to infarct area are best explained by limitation of infarct size due to early reperfusion (36,37), whereas differences with respect to remote areas may have several mechanisms. In experimental infarction, focal myocardial necrosis and metabolic derangements indicating ischemia have been observed in nonoccluded segments (38). These findings were more evident with permanent occlusion than with reperfusion after 3 hours of occlusion (38). Two weeks after acute myocardial infarction, Martin et al. (23) observed mild hyperkinesia of noninfarcted myocardium in streptokinase-treated patients but not in randomized control patients. This phenomenon was more marked in patients with multivessel disease than in those with single-vessel disease. Martin et al. (23) attributed their findings to the higher rate of infarct-related vessel patency in streptokinase-treated patients, resulting in additional blood flow to noninfarcted areas from the patent infarct vessel as a result of collateral flow.

In contrast to patients with anterior myocardial infarction, among patients with inferior infarction, no differences between the two treatment groups were demonstrable in the present study (Fig. 2B). This result is in accordance with data from similar studies also using radionuclide ventriculography (28,29). However, the majority of trials (8,14,30) employing contrast angiography demonstrated minor dysfunction of the infarct zone in streptokinase- compared with placebo-treated patients. The discrepancy between results obtained with radionuclide and contrast ventriculography may be explained by the higher spatial resolution of the contrast technique and by the difficulty of assessing the inferior myocardial wall by radionuclide determination of regional left ventricular ejection fraction, even when biplane radionuclide ventriculography is used (17).

In previous studies, serial analysis of regional left ventricular function after thrombolysis has been performed up to 6 months after acute myocardial infarction (7,24,26,35). After early reperfusion, improvement of regional wall motion within the infarct area was observed beginning 3 days after infarction (26). In the present study we analyzed regional left ventricular ejection fraction from 3 days to 3 years after acute infarction. During this period, areas with an increase of regional left ventricular ejection fraction were observed in both treatment groups within the infarct zone with the highest values 7 or 18 months after infarction. In noninfarcted areas, regional left ventricular ejection fraction did not change significantly. After coronary artery bypass surgery, Serruys et al. (34) reported an increase of the initially depressed regional shortening fraction in bypassed and nonbypassed regions up to 6 months postoperatively. They attributed this finding to recovery of myocardium from an ischemic injury, a thesis that would also explain the increase in regional left ventricular ejection fraction within the infarct zone observed in the present study.

Limitations of the study. The major limitation of the present study is the high degree of incomplete follow-up, which may influence longitudinal analysis. Although radionuclide ventriculographic studies were performed in 84% of all patients included or 91% of patients alive at the time of investigation, complete follow-up was available in only 75

patients (63%) because of the criterion of the need for five investigations. Although this low frequency of complete follow-up is unsatisfactory, it is at least comparable with that of other studies (13,20,35,36) also using serial evaluation of myocardial function after acute myocardial infarction over follow-up periods ≥3 months. With respect to the characteristics displayed in Table 1, patients with complete and incomplete follow-up differed only in the frequency of death. Restricting analysis to long-term survivors may underestimate the benefit of streptokinase therapy (12,21). However, in the present study, analysis of data only from patients with complete follow-up (Fig. 1) revealed results consistent with results of analysis of data from all patients (Table 2). Therefore the high degree of incomplete follow-up does not seem to be a source of major bias in the final results.

Conclusions. In patients with acute anterior myocardial infarction, high dose short-term intravenous streptokinase administered within 6 h after the onset of symptoms resulted in an improvement of global left ventricular function 3 days after infarction. Regional left ventricular function within the infarct area as well as in remote myocardium was improved, a benefit that was preserved up to 3 years. In patients with inferior myocardial infarction, no significant benefit in global and regional left ventricular ejection fraction due to streptokinase therapy could be demonstrated.

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