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Streptokinase in myocardial infarction: Results of German studies

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Introduction

The year 1965 saw the completion of the first study by the German-Swiss working group on the treatment of acute cases of myocardial infarction with highly purified streptokinase (SK) which had been started in 1962. A second controlled trial was carried out in 1968. None of these studies, nor those of other groups of authors, have been free of errors in their statistical planning and evaluation. In consequence after ten years' fibrinolytic therapy we are still at the stage of contemplating the merits and demerits of multicentre trials rather than that of making concrete recommendations. It is my task to cover as referee the results of three German studies. In two of these studies I participated myself and I have been very kindly authorized by Dr Breddin to refer briefly to the results of the Frankfurt study group (Breddin, 1973).

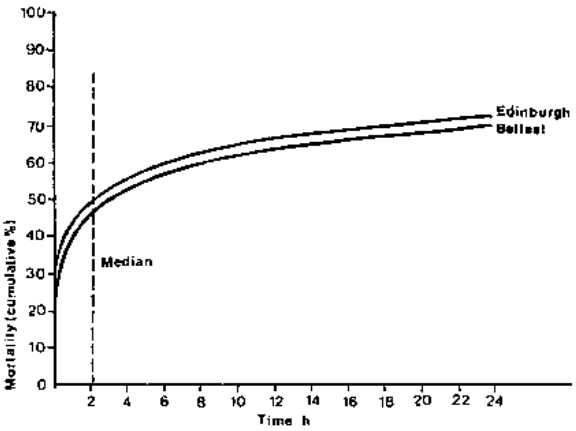

FIG. 1. Cumulative percentage mortality in the first 24 h. after the onset of symptoms of myocardial infarction (from Fulton *et at* Circulation, 39 Suppl. 4. p. 186. (1969).

General clinical results (mortality)

(i) Results of the first German-Swiss study

Let me start by mentioning the most significant error in the first study (Schmutzler, 1966). In 1962 -before the advent of the coronary care units-the view was held that myocardial infarctions very rarely reached the clinic during the first three hours and they were therefore not included in the randomization programme. This was a serious error for two reasons. Firstly, because the mortality is extremely high during the first hours and falls off exponentially, as has been shown by the statistical figures of Fulton, Julian & Oliver (Fig. 1) and other authors. This means that it is in fact during the first phase (some 50 % of the fatal cases occur within the first two hours) that the probability is greatest of finding statistically significant differences between different forms of treatment. The second reason lay in the practical conditions of the trial: in a short time more than 100 patients from this early group had been treated with streptokinase and the working group decided therefore to treat a comparison group with heparin, starting the treatment within three hours of the onset of the symptoms. Since an attempt was made subsequently to balance the groups, which were unequally weighted in terms of numbers, all claim to randomization was lost. As we shall hope to show in the discussion no intended or unintended selection according to degree of severity was obtained in that way. At the start of treatment the groups were statistically uniform with regard to age, sex distribution, location of infarct and age of infarct.

Table I shows the significant fall in the overall mortality and in the mortality between the 2nd

TABLE 1. First German-Swiss Study

Mortality	Streptokinase n=297	Heparin n=261	p
Total hospital mortality			
(40 days)	42 (14,1%)	56 (21,7%)	< 0,05
within 24 hours	16 (5,4%)	14 (5,4%)	n.s.
2nd-40th day	26 (8,7%)	42 (16,1%)	< 0,02

and 40th day after the start of treatment in the patient group, treated with streptokinase. Patients of the control group received only heparin. In order to facilitate comparison with our second group and with the other studies to which reference will be made today, these groups will also be broken down according to the age of the infarct at the start of treatment (Table 2).

Three important points should be stressed here:

1. The unweighted numerical ratio of patients treated with streptokinase and anticoagulants in both groups.
2. The agreement between the two groups in relation to early mortality, a factor requiring very critical examination in view of the errors mentioned above.
3. The difference in the mortality from the 2nd to the 40th day.

(ii) Method (first and second German-Swiss study)

Both the German-Swiss studies covered only infarctions where the symptoms dated back not more than twelve hours at the start of treatment, i.e. at the time of connection of the infusion pump. The treatment lasted 18 hours. The period of greatest mortality (see Fulton) was approximately covered in this way and the connective tissue organization of the necrosis was not inhibited.

It has to be stressed that the diagnosis of myocardial infarct during the first hours is frequently based only on the clinical picture and on electrocardiographic changes which are not yet conclusive. Such patients were only included in the study if the diagnosis could be confirmed within a 12-hour period (from the ECG or from the rise of the serum enzymes). Patients admitted in a moribund state (defined as the state in which no further specific attempt of treatment was possible) were not included in the randomization programme (n=12). Like the patients of uncertain diagnosis (n=47) or with contraindications (n=59) they were evaluated separately.

The following conditions were taken to be contraindications: (1) hypertension with systolic values over 200 mmHg and diastolic values over 120 mmHg, (2) haemorrhagic diatheses, (3) intestinal diseases with increased risk of haemorrhage, (4) frank pulmonary oedema, (5) severe general sclerosis, in particular encephalomalacia, (6) active tuberculosis, (7) liver or renal insufficiency, (8) anticoagulant therapy on admission, (9) previous streptokinase treatment within the past six months. We are aware that some of the conditions in this list are diagnoses involving the danger of a subjective assessment by the doctor at the time of admission. It should be stressed, however, that in the second study the majority of doctors were already convinced of the effectiveness of the streptokinase therapy for acute cases of cardiac infarction and would have been more likely therefore on ethical grounds to decide for rather than against this treatment. This would of course lead to the treatment being loaded with 'bad risk' patients.

In order to avoid any bias in the division of patients into the streptokinase or control groups, the patients were allocated on the alternating series principle. We believe that the alternating roster of reception doctors reduced the possibility of any subjective influence and avoided the disadvantages of other chance distributions in the case of relatively small numbers (climatic factors, weekend and holiday duty, &c.). This is however without doubt a point vulnerable to criticism, the validity of which is nevertheless reduced by the subsequent statistical criteria. Table 3 (Study 2) shows the age and sex distribution. The mean age in the streptokinase group was 58,7 years and in the control group 59,7 years. There was equally no statistical difference between the age and location of the infarctions. There was a good

TABLE 2. First German-Swiss Study

Mortality with respect to treatment and timing of treatment

	Interval between onset of symptoms and infusion							
	0-3 hours				4-12 hours			
	Streptokinase n = 194		Control n = 81		Streptokinase n = 103		Control n = 180	
	No.	%	No.	%	No.	%	No.	%
Total hospital mortality (40 days)	26	13,4	17	21.0	16	15,5	39	21,7
Within 24 hours	10	5,2	4	4.9	6	5,3	10	5,5
2nd-40th day	16	8,7	13	16,9	10	10,3	29	17,1

TABLE 3. Distribution of sex and age

	Streptokinase group				Control group			
			Total				Total	
Age	Male	Female	No.	%	Male	Female	No.	%
30-39	3	1	4	2,9	2	0	2	1,5
40-49	20	2	22	15,9	9	2	11	8,4
50-59	34	6	40	29,0	42	5	47	35,9
60-69	48	10	58	42,0	41	15	56	42,7
70-79	8	3	11	8,0	9	6	15	11,5
80-89	2	1	3	2,2	0	0	0	0,0
Total	115	23	138	100	103	28	131	100
Percent	83,3	16,7	100		78,6	21,4	100	

agreement in the clinical findings on admission, the blood pressure on admission and the administration of various typical preparations (Tables 4, 5 and 6).

Table 7 shows the therapeutic scheme, used by us in the second study. It should be stressed that the control group received during the first 18 hours merely oral anticoagulants. There was a marked deviation from the therapeutic scheme only in 7 patients in the light of coagulation analyses or the streptokinase-resistance test. Activation of the plasma-fibrinolytic system may be held to be proved where in at least one investigation the plasma thrombin-time is more than doubled during the first 18 hours. More complex investigations have been carried out by only a few of our colleagues, who were coagulation specialists. It has to be pointed out, furthermore, that in the case of myocardial infarction no direct proof of the effect of the fibrinolytic therapy is possible, in contrast to arterial and various occlusions of the peripheral system. Unfortunately statistical investigations on large groups are of greater value as evidence than proofs of therapeutic success in the case of individual patients.

TABLE 4. History and clinical findings on admission

	Streptokinase		Control	
	n	%	*n*	%
	138		131	
History:				
Angina pectoris	102	74	86	66
Previous infarction	19	14	20	15
Neither of the above	17		25	
Clinical findings:				
Shock	35	25	31	24
Arrhythmia	43	31	37	28
Hypertension	32	23	32	24
Heart failure	41	30	29	22
(a) Hepatomegaly	31	22	23	18
(b) Pulmonary congestion	28	20	15	11
(c) Edema	8	6	7	5
ECG typical on admission	134	97	124	95
Subsequent ECG typical of infarction	4	3	6	4,5

TABLE 5. Systolic and diastolic blood pressure on admission (mmHg). In 4 cases (3 Sk and 1 control) no measurable blood pressure was present on admission

		Streptokinase group *n*= 138-3	Control group *n*= 131-1
Systolic blood pressure	Mean	136,1	139,3
	S. D.	28,5	29,2
Diastolic blood pressure	Mean	85,3	89,2
	S. D.	21,5	17,4

TABLE 6. Drugs administered

	Streptokinase group *n*=138	%	Control group *n*=131	%
Digitalis	60	43,5	57	43,5
Corticosteroids	10	7,3	5	3,8
Analgesics	104	75,3	104	79,4

(iii) Results of the second study

The comparison of the mortality figures was used as the decisive criterion of therapeutic success in the second study also. Comparing the patients who received immediate administration of streptokinase with those receiving only oral anticoagulants during the first 18 hours, we find in contrast to the first study a weighted numerical ratio between the early and late treatment groups (Table 8). The significance of the differences between the two treatment groups was tested with the chi-square test. This test revealed highly significant differences both for the whole random sample and also for the partial samples of patients, whose treatment was begun up to six hours after the onset of the infarct (Table 8).

On the other hand in the random sample of patients, who were treated 7 or more hours after the onset of the infarct, no significant differences in the mortality were found between the control and streptokinase groups.

TABLE 7. Dosage and duration of treatment with streptokinase and anticoagulants

		Streptokinase group	Control group
Streptokinase (SK):			
Start of infusion		Immediately	Immediately
Initial dose		250.000 I.U.	(Levulose 5% without heparin)
Maintenance dosage/hour	Mean	131.000 I.U.	-
	S. D.	21,030	
Duration of treatment (hrs.)		18 hours	18 hours
Volume of infusion		170 ml.	170 ml.
Heparin:			
Start of treatment		Immediately after the SK infusion	Immediately after levulose infusion
Dosage/hour (I.U.)	Mean	1403 I.U.	1535 I.U.
	S. D.	254	429
Mean duration (hrs.)	Mean	29,4 hours	32,9 hours
	S. D.	5,2	7,1
Treatment less than 20 hrs.		4 patients	None
Treatment more than 48 hrs.		27 "	13 patients
Treatment 20-48 hrs.		99 "	99 "
Phenprocumon			
15 mg		Immediately	Immediately
9 m g		24 hrs. later	24 hrs. later

TABLE 8. (Second Study) Mortality with respect to treatment, timing of treatment and time of death

Interval between onset of symptoms and infusion	Streptokinase group *n*	%	Control group *n*	%	χ^2	d.f.	P <
0-12 hours (all patients)	138	100	131	100	-	-	-
Mortality: Total	20	14,5	34	26,0	9,24	2	<0,01
1 st day	3	2,2	14	10,7			
2nd-40th day	17	12,6	20	17,1			
0-6 hours	102	100	89	100	-	-	-
Mortality: Total	14	13,7	22	24,7	8,24	2	< 0.025
1 st day	3	2,9	13	14,6			
2nd-40th day	11	11,1	9	11,8			
7-12 hours	36	100	42	100	-	-	-
Mortality: Total	6	16,7	12	28,6	0,65	2	n.s.
1 st day	0	0.0	1	2,4			
2nd-40th day	6	16,7	11	26,8			

The causes of death in the two treatment groups are shown in Table 9. The total of the percentage figures for the clinical causes of death is larger than 100%, since in some patients several causes of death have been given equal validity. No statistical difference could be established between the two treatment-groups, although there was a tendency towards the accumulation of congestive heart failure and ventricular fibrillation in the control group.

The authors of the two German-Swiss studies are of the opinion that a control check of the plasma thrombin time is to be regarded as a minimum requirement in the case of a fibrinolytic therapy of more than six hours. Information on the behaviour in the case of short-term fibrinolysis is given in the Frankfurt study.

(iv) Frankfurt study (Breddin, 1973)*

In a non-randomized pilot study the authors treated 134 patients with streptokinase according to the following therapeutic regime. The patients received 250.000 units streptokinase within 30 minutes, followed by 500.000 units during the next

*We are grateful to Professor Breddin (Frankfurt) for kind permission to report the results of his study here.

TABLE 9.

	Streptokinase group (*n* = 138)			Control group (*n* = 131)		
	n 20	Percent	Percent of all patients	n 34	Percent	Percent of all patients
Clinical diagnosis:						
Rupture	3	15	2,2	6	18	4,6
Reinfarction	6	30	4,4	5	15	3,8
Heart failure	5	25	3,6	15	44	11,5
Pneumonia	-	--	--	3	9	2,3
Aneurysm	1	5	0,7	1	3	0,8
Ventr. fibrillation	3	15	2,2	12	35	9,2
Other	4	20	2,9	5	15	3,8
Post mortem findings:	14	100		20	100	
Rupture, aneurysm	4	29		5	25	
Reinfarction	3	21		3	15	
Heart failure	4	29		9	45	
Pneumonia	-	--		1	5	
Other	1	21		2	10	

2-5 hours. After this infusion the patients received 10.000 units heparin followed by 50.000 units heparin/day over a 48 hours period. Conventional oral anticoagulant therapy was administered at the same time.

A control group of 95 patients received initially 12.500 units hepatitis followed after 3 to 4 hours by the same treatment as the streptokinase group. It was found however that a high proportion of severe shock cases were building up in the streptokinase group (41,8 % as against 29,5 %, with a mortality rate of 37,5% compared with 22,1%). The overall mortality rate in the streptokinase group was 18,7 %, compared with 21,1 % in the control group. The reason for this was the appointment of an increasing number of doctors, who had gained the impression that streptokinase was particularly effective in the case of cardiogenic shock. Analysis of the results of this pilot study showed that a short-term lysis period of 3 hours does not involve any increased risk of haemorrhage (only 1 nonfatal haemorrhage occurred, due to an ulcus ventriculi). This led to a first double-blind study being carried out in the years 1969 to 1971 on patients under 70, in which the contra-indications and diagnostic conditions were identical with those in our second study.

Randomization. The trials substance and placebo were made available by the firm Behringwerke AG. The ampoules, which were marked with code letters, contained either 250.000 units Streptase® or a dried protein. It was not possible to distinguish the substance from the placebo externally or after solution. The key to the code was not known to any of the investigators and analysis of the fibrinolytic activity was not carried out at any of the treatment centres, thus ensuring that the conditions for a true double-blind study were observed. The amount of streptokinase administered was identical with that in the pilot study. The heparin dosage was uniform for all patients over the 48 hour period: 5000 units heparin during the first 8 hours, followed by 7500 units/8 hr with a simultaneous start of the oral anticoagulant regimen.

Results of the Frankfurt study

In the double-blind study 102 patients were treated with streptokinase, 13 of whom (12,7%) died. 104 patients received placebo prior to the heparin treatment, 29 of whom (27,9 %) died. This difference is statistically significant (Table 10). The maximum difference in the mortality rate in this study did not occur within the first 24 hours (4,9% compared with

TABLE 10. Frankfurt working group

Mortality	Streptokinase group n = 102	Placebo group n = 104	χ^2	d.f.	P
Total hospital morality	13 (12,7%)	29 (27,9%)	7,271	2	< 0,01
Within 24 hours	5 (4,9%)	9 (8,7%)	0,99	2	n.s.
After 24 hours	8 (8,2%)	20 (21,1%)	4,71	2	< 0,03

8,7%), but after the first day (8,2% compared with 21,1 %). If the patients were classified according to the age of the infarct at the start of treatment the most striking difference was in the group of patients admitted during the first 3 hours.

Further clinical results (German-Swiss working group)

The following results from our own working group represent in comparison with the mortality statistics 'soft data', partly because they are based on the subjective impressions of the patient or the doctor and partly because we do not know exactly how to interpret them in pathophysiological terms. At the time of admission and prior to the start of therapy a number of clinical findings had to be recorded on the test form for each patient, including the clinical diagnoses: shock, arrhythmia, cardiac failure and reinfarction; information from the patient on angina pectoris was also to be noted during the course of the treatment.

Angina pectoris. Table 11 shows that in both treatment groups there was a marked decrease in the incidence of angina during the first 3 days. The reduction in the pain was, however, more marked in the streptokinase group already after 2 hours. This difference was found to be highly significant with a χ^2 value of 30,56 (with a Yates correction) in the case of 8 degrees of freedom.

We found to our regret that the diagnosis 'arrhythmia' was of no value without classification into critical and less important forms or into primary and shock-dependent arrhythmias, and furthermore without an exact ECG recording by means of a tape store or trend recorder.

Shock and cardiac failure. In Table 12 we can make use merely of the columns 'shock symptoms' and 'heart failure'. The state of shock was diagnosed clinically from the known symptoms of moist, cold, grey cyanosed skin, the low or undetectable blood pressure, anuria and cerebral disorientation verging on somnolence.

The incidence and prognosis of cardiogenic shock in myocardial infarction depends very much on the definition of shock which is used. If it is defined clinically in the manner described above, this syndrome will have to include also cases of pure pain shock - improved by alleviation of the pain - and also acute left ventricular failure or inadequate volume flow rate. These cases would not all be included under the haemodynamically correct diagnosis with a cardiac index below 2,0 l/min/m² (Pabst, 1969; Dissmann, 1967, Weil, 1968) - an increased peripheral resistance of 2000 dyn/sec/cm^{-5} and a central venous pressure of more than 25 cm H_20. The prognosis of shock, defined in haemodynamically strict terms, is far worse (a mortality rate of 80-100%) than that found by us. A few authors regard it as absolutely unfavourable (Dissmann, 1967). Our study contributed nothing to the clarification of the question of whether cardiogenic shock with its poor prognosis can be improved by the administration of streptokinase, although we were all very much impressed by the developments in individual cases. The question can only be fully

TABLE 11. Frequency of angina pectoris

	Streptokinase group			Control group		
	Surviving paticnts	Angina pectoris n	Angina pectoris Percent	Angina pectoris Percent	Angina pectoris n	Surviving patients
Before start of infusion	138	124	90	88	115	131
0-2 hours	138	112	81	89	115	130
2-4	138	70	51	65	83	128
4-8	137	32	23	51	62	122
8-16	135	27	20	49	59	120
16-24	135	22	16	46	54	117
24-48	133	16	12	25	29	115
48-72	129	12	9	23	26	113

TABLE *12*

	Streptokinase n= 138		Control n = 131			
Status before therapy	No. of patients	Survived	No. of patients	Survived		P
Shock	35	31 = 89%	31	21	68%	< 0,05
Arrhythmia	43	36 = 86%	37	22	59%	< 0,05
Heart failure	41	31 = 75%	39	16	55%	< 0,05
Re-infarction	19	13 = 57%	20	12	60%	n.s.

clarified by haemodynamic measurements with direct access to the arterial system. We were unable to accept the risk of haemorrhage involved in this procedure.

The significance test revealed that the only clear differences were in the case of the partial random sample for arrhythmia - which we did not wish to use - and for shock (χ^2 = 4,27 with 1 degree of freedom) but not in the case of congestive heart failure. In view of the vagueness referred to above in the clinical diagnoses we only felt justified in publishing this part of the results, because an error of definition must produce the same effect in either group as is in fact shown by the identical frequency of occurrence (Table 12).

Electrocardiographic comparisons. Examination of the electrocardiograms* in the second study was only completed a few weeks ago and the statistical calculation is still pending. The measurements were carried out by a team of 3 doctors, who were not aware of the type of treatment and who checked each other's results on a rectangular system (they merely knew whether the patient had died or survived).

The following parameters were measured:

(a) Q duration, QRS duration, QT duration, Q wave width. In addition the freuency, the maximum STrise in mm and the deepest negative T value in mm.

(b) The reduction and losses in the R-wave during the course of the infarct (the reduction being defined as the minimum fall in the R-amplitude in relation to the initial finding at 0,2 mV) were evaluated in qualitative terms according to the Yes/No principle.

Results

In the case of transmural anterior wall infarctions and with measurement of the maximum ST-rise in V_2 to V_4 up to the third week a higher maximum ST-elevation was found in the control group than in the group treated with streptokinase (Fig. 2). No differences were found in the posterior wall infarction. This result was in agreement with that of the first study (Poliwoda, 1966), in that we were able to show (although only the limb leads were measured with no differentiation according to site of infarction) an earlier regression of the ST-elevation (complete return to the baseline).

In the case of the anterior wall infarction, furthermore, a smaller proportion of R-reductions occurred in the limb leads with the third day after the start of streptokinase treatment, a phenomenon which was noted in the chestwall leads from the second week onwards. The changes were very much less marked second week onwards. The changes were very much less marked in the case of the poste-

*We are indebted to Professor Gillmann for passing the results to us in advance (see Gillmann, 1973).

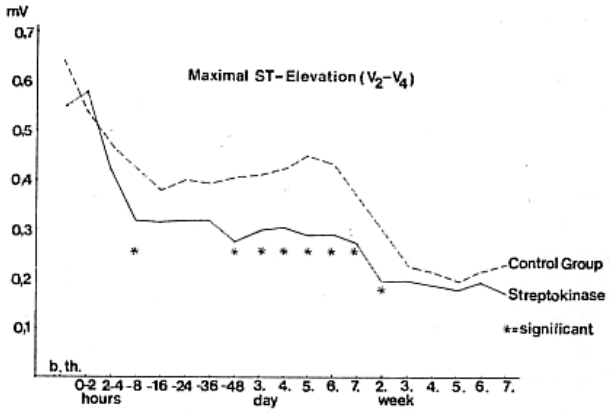

FIG. 2. Maximal ST-elevation.

rior wall infarction, and also in the evaluation of the R-losses alone. No differences were found, moreover, in the Q-wave width and in the lowest terminal values for T-negativity. With the administration of streptokinase there was a striking reduction in the occurrence of a peripheral low voltage (low frontal amplitude) at almost all recording periods in the group of posterior wall infarctions, which was only observed after the 4th week in the anterior wall infarctions. This result duplicated the results in the first study, where the regression of the Q/R ratio was detected earlier in the streptokinase-treated patients in the case of both posterior and anterior wall infarctions (Poliwoda, 1966).

Further results of the first study: significantly earlier start of the regression of the Q-width, the terminal T-negativity and the Q-depth, and also an increased occurrence of the so-called rudimentary infarcts in the streptokinase-treated group (χ^2 = 6,630). In the mathematical-statistical evaluation the curves were smoothed out in accordance with a 3rd-degree polynomial. Four parameters and their dispersion were calculated for the characterization of this polynomial. Highly significant differences were found for all parameters (position at the point of origin, steepness of the curve, bending of the curve, points of inflection and extremes of the curve). These evaluations are going to be done now in the second study.

Serum enzymes. The second German-Swiss study included obligatory examination of the GOT (serum aspartate amino-transferase) and CPK (creatine phosphokinase) enzymes at specified intervals of time. In the case of the GOT enzyme there was a significantly more rapid and higher rise in the enzyme in the streptokinase group (Fig. 3). The differences were significant with a χ^2-value of 13,87 (d.f. = 5) (Praetorius, 1973).

The statistics of these curves were difficult to evaluate. Use was made in principle of the model presentations and the method of pharmacokinetics,

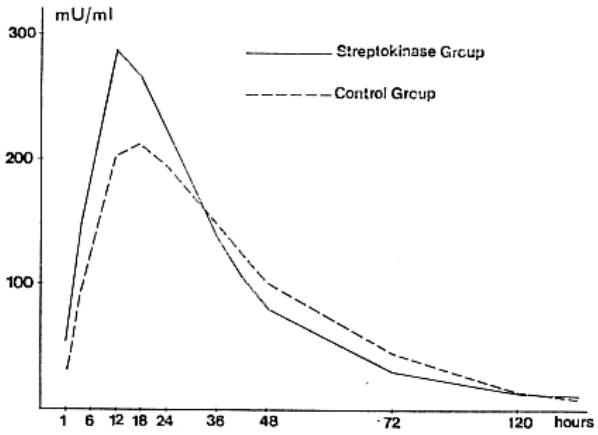

FIG. 3. GOT (Serum).

with the simplifying division of the organism into two compartments (infarct zone and blood circulation). Of the parameters shown in Table 13 K_1 and K_2 are elimination constants, Y_{max} is the enzyme activity peak and A_0, A_1, and A_2 are quantities, dependent on the rate constants and the initial concentration. T_{max} (hours) gives the point in time of the occurrence of the enzyme activity peak. In order to test the differences between the treatment regimens, the calculated parameters of all patients were evaluated according to a Manova.

A similar, although not statistically significant, difference was observed in the CPK enzyme curve. However this result was less susceptible to evaluation since the rapid *in vitro* aging of the enzyme had not been corrected in this study by use of an activated CPK. In the earlier study it was only possible to compare the groups of patients receiving early and late administration of streptokinase, since in the control group insufficient enzyme determinations were available for the evaluation of the curve. There was an earlier and steeper rise in the GOT and CPK activities in the case of the early streptokinase treatment (Praetorius, 1966; Körtge, 1968). A possible hypothesis to explain these findings is that the rapid rise in the enzyme activity is the result of a more rapid washing out of the enzymes from the infarct zone as a result of the improved blood flow.

Complications. Table 14 shows the complications observed in the two German-Swiss studies and in the Frankfurt study. The aim of this table is not a statistical comparison which is not possible. But it should demonstrate that the earlier fear of an increase in serious haemorrhagic complications cannot be confirmed in the case of streptokinase therapy lasting 3 to 18 hours.

Theory of the mechanism of action

The success-rate of streptokinase in the case of myocardial infarction in the view of the authors of these studies, is by no means only dependent on its success in re-opening the coronary occlusion. We believe that further important factors are the improvement in the microcirculation in the area of the terminal capillaries of the peripheral vascular system and of the myocardium. Streptokinase treatment at a medium dosage gives rise to free SK-activator and plasmin activity, resulting in

TABLE 13

GOT.	n	A_0	A_1	A_2	y_{max}	k_1	k_2	t_1	t_2	tmax
Streptokinase group	87	10,5	934,3	899,2	283,8	3,05	1,27	5,5	13,2	12,2
Control group	69	9.0	751,8	735,0	207,1	2,15	1,00	7,8	17,0	16,1

$\chi^2 = 13{,}87$ F = 5 $\chi^2_{5\,\%} = 11{,}07$ k_1, k_2: days^{-1}

t_1, t_2,: half-life period (hrs.)

TABLE 14

Study	German-Swiss I (1966)		German-Swiss II (1973)		Frankfurt (Breddin, 1973)		Total	
Treatment	SK	Hep	SK	Control	SK	Placebo	SK	Controls
No. of patients	n = 297	n = 261	n = 138	n = 131	n = 102	n = 104	n = 537	n = 496
Hemorrhage	9	0	7	2	4	1	20 (3,7%)	3 (0,6%)
Rise in temperature	2	0	2	0	1	0	5	0
Rash	0	0	3	1	1	0	4	1
Embolism	?	?	0	0	?	?	-	-
Reinfarction (1st-40th day)	15	22	10	10	5	8	30	40
Stop of treatment	1	0	3	1	?	?	-	-

Localization of hemorrhage:
Streptokinase: macrohaematuria 5, epistaxis 3, gums bleeding 3, gastrointestinal 3, injection site 7.
Control groups: macrohaematuria 0, epistaxis 0, gums bleeding 0, gastrointestinal 3, cerebral 1.
Heart rupture: In the streptokinase groups 8+3+0 = 11
In the control groups 9+6+3 = 18.

fibrinolysis and fibrinogenolysis. The lowered fibrinogen level reduces the blood viscosity and must therefore by Poiseuille's law cause a reduction in the peripheral resistance, since besides the haemotocrit fibrinogen has been shown to have the greatest influence on the blood viscosity (Begg, 1960; Ehrly, 1970). The question still requires discussion of whether the interaction of all these factors leads to a substantial improvement in the rheological situation in the case of myocardial infarction, thus possibly counteracting cardiogenic shock and also the occurrence of disturbances of the cardiac rhythm.

It is known that the incidence of primary thromboses in myocardial infarction is vigorously disputed. The survival time of the myocardial tissue is in most cases shorter than the time in which the patient can be successfully treated. A number of investigators have found, on the other hand, that the extension of the necrotic area depends on how long the ligature or vascular occlusion continues to exist (whether the occlusion is temporary or final). The classical experiment in regard to the influence of streptokinase on the peripheral area round the infarct comes from the Cliffton group (Nydick, 1961). The fibrinolytic treatment of shock - and not only of cardiogenic shock - has been recently discussed, in particular by Lasch and co-workers in view of the importance of microthrombi in the peripheral circulation.

A striking feature, emerging from the two studies by our working group, is the difference in the mortality rates between the two control groups. It is to be considered whether the absence of any heparin treatment in the first 18 hours in the case of the second study provides the explanation of this difference. It has to be stressed again, however, that the absence of adequate randomization in the first study prevents any exact comparison of the figures.

Conclusions

In the light of the results reported above we believe strongly that in spite of the as yet unresolved scientific contradictions there are strong arguments in favour of administering streptokinase in cases of myocardial infarction within the first 12 hours after the onset of the symptoms. An objective examination of the special question of whether any effect is produced on the haemodynamic picture in the case of cardiogenic shock is in our view at the present time the most important task of clinical research in this sphere.

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