

**THROMBOLYSIS  
AND INTERVENTIONAL CARDIOLOGY;  
EXPERIENCES FROM THE 80's**

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Een sterke vergroting van het oppervlak van een trombus laat  
wat meer in detail het werk van trombolyse zien.  
De anders gladde fibrinedraden krijgen eerst een korrelige  
structuur alvorens in stukken te breken.

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EXPERIENCES FROM THE 80'S**

**TROMBOLYSE  
EN INTERVENTIE CARDIOLOGIE;  
ERVARINGEN UIT DE JAREN '80**

**PROEFSCHRIFT**

ter verkrijging van de graad van doctor  
aan de Erasmus Universiteit Rotterdam  
op gezag van de Rector Magnificus  
Prof. Dr. C.J. Rijnvos  
en volgens besluit van het College van Dekanen.  
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door

**JOHANNES JOSEPHUS REINARDUS MARIA BONNIER**

geboren te Arnhem

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## Preface

# Modern Medical Science is the gentle Art of Rediscovery

Dirk Durrer

In October 1978 I assumed the position of cardiologist at the Catharina Hospital in Eindhoven at the time when the cardiothoracic surgery program began in this hospital. At that time I did not know the number of patients that had to be treated daily. During our fellowship training in cardiology, particularly in a university hospital, there was time to discuss problems with teachers and to consider solutions. In a large non-academic cardiology department like that of the Catharina hospital, the situation is different: quick decisions are necessary.

From 1978 onwards, clinical cardiology changed at such pace that even some universities had difficulty to implement new therapeutic developments such as percutaneous transluminal coronary angioplasty and thrombolysis. In those early years we had a relatively small staff which made it difficult to keep up with these rapid changes. I was in a privileged position, since my colleagues gave me the opportunity to visit leading centres and to learn about new developments and implement them in our daily practice of cardiology. It was necessary to critically assess the clinical value of these developments by continuous monitoring and evaluation of the results.

The fact, that we could start a fellowship program in cardiology in 1980 was of great significance. We considered this a recognition that we were successful in both implementing and critically assessing these new developments. In this thesis aspects of new treatment modalities in modern cardiology are addressed: thrombolysis and percutaneous transluminal coronary angioplasty.

### THROMBOLYSIS

The role of thrombosis in the etiology of acute myocardial infarction was first described by Herrick in 1912.<sup>1</sup> In 1933 Tillett described that Lancefield Group A beta hemolytic streptococci isolated from patients produced a fibrinolytic substance<sup>2</sup>, called streptokinase. Subsequently Sherry proved that the diffusion of streptokinase into the thrombus resulted in lysis of the clot. Streptokinase also activated plasminogen in the systemic circulation which produced fibrinogenolysis and impaired hemostasis.<sup>3-5</sup> The first use of streptokinase for treatment of acute myocardial infarction was

reported by Fletcher in 1958<sup>6</sup>, but the results were inconclusive. The finding that there were only a few complications and a low in-hospital mortality rate in patients treated with intravenous streptokinase led to large-scale studies. Stampfer and Yusuf<sup>7,8</sup> pooled all data from 18 studies, performed between 1963 and 1979, which indicated that there was approximately a 20% reduction in the mortality rate over the subsequent weeks following therapy with intravenous streptokinase for acute myocardial infarction compared with conventional therapy. Nevertheless, thrombolysis was not accepted in medical practice until Rentrop in 1979 demonstrated by angiography, that the intracoronary administration of streptokinase dissolved a coronary artery thrombus.<sup>9</sup> Soon afterwards we began to treat acute myocardial infarction in our hospital with intracoronary streptokinase in selected patients with promising results. However, several practical limitations to this approach became evident. Twenty-four hour availability or stand-by of the catheterization laboratory staff is needed which is both laborious and expensive. After Schröder<sup>10</sup> again advocated the intravenous use of streptokinase in 1985 and others<sup>11</sup> had showed that the results were comparable with those of intracoronary administration, the enthusiasm for intracoronary administration diminished rapidly.

In 1983, the research department of Beecham laboratories introduced a new thrombolytic agent for intravenous use: anisoylated plasminogen streptokinase activator complex (APSAC), now called anistreplase.<sup>12</sup> We concentrated on the use of this drug in our hospital and were the first to investigate anistreplase in patients. The results of the first 13 patients with acute myocardial infarction treated with this thrombolytic agent in our department were reported in 1984.<sup>13</sup> The reperfusion rate tested by angiography was high (92%). This was sufficient reason to continue investigation with this new drug.

We subsequently undertook a study, together with other hospitals in our region, in which we compared anistreplase to streptokinase, in patients with acute myocardial infarction. The first chapter of this thesis presents the results of this trial. In this open multicenter

randomized trial we compared the reperfusion rates produced by intravenous anistreplase with those of intracoronary streptokinase at 90 minutes after dosing, and assessed in both groups the reocclusion rates at 24 hours after dosing. Side-effects, coagulation and fibrinolytic parameters were also studied. In addition we compared both drugs with respect to their effect on major components of the coagulation- and fibrinolytic system and investigated the relations between the systemic lytic state and clinical items as reperfusion, reocclusion and bleeding complications. The results are presented in chapter two.

Since not all patients receiving anistreplase or streptokinase in the trial had successful reperfusion, we investigated a possible explanation for unsuccessful thrombolytic therapy. In chapter three we report the effects of antibodies on reperfusion, reocclusion and haemostatic changes and the depletion of antibodies in response to the drug. In addition the effect of anistreplase on blood- and plasma viscosity, platelet function and any possible influence on the cardiac output during administration of this drug in patients with acute myocardial infarction were studied in more detail (chapter four).

Chapter five deals with the use of nonionic contrast medium and its rheological effect. This contrast medium is often used to investigate patients with myocardial infarction, but its influence on hemorheology and platelet function had not been reported. When a nonionic contrast medium therefore is used during studies in patients with acute myocardial infarction, the influence on blood rheology or platelet function should be taken into account and corrections should be made.

In chapter six the role of PTCA after intravenous streptokinase in acute myocardial infarction is discussed. A discussion on this subject is like the waves in the sea, advancing and receding. Several well designed randomized trials concerning PTCA in myocardial infarction patients have addressed this issue: Erbel et al.<sup>14</sup>, Topol et al.<sup>15</sup> and Simoons et al.<sup>16</sup>, but controversy remains. The benefits and risks of PTCA performed directly or electively after successful or unsuccessful thrombolysis in a selected group of patients are discussed in this chapter.

## **PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY**

The American radiologists Dotter and Judkins proved in 1964 that it is possible to reduce a severe stenosis in an artery by percutaneous angioplasty.<sup>17</sup> They used progressively increasing sizes of catheters to decrease the stenosis and to increase the blood flow in patients with peripheral arteriosclerosis. In Europe Zeitler started to use this method and in 1974 Grüntzig, trained by Zeitler, modified the multiple catheter system of Dotter by developing a distensible double-lumen balloon catheter made of polyvinylchloride, a material of low compliance. When the balloon was inflated it created a circumferential pressure rather

than the axial force of the Dotter technique on the arteriosclerotic plaque. Grüntzig further miniaturized the balloon, tested the technique in human cadaver experiments and in September 1977 performed the first percutaneous transluminal coronary angioplasty (PTCA) in Zürich.<sup>18</sup> This therapeutic tool represented a major breakthrough in the treatment of coronary artery stenosis. In the following years coronary angioplasty was also used to study the acute effects of myocardial ischemia, produced by inflation of the balloon as reported by Serruys in 1986.<sup>19</sup>

In the second part of this thesis several aspects related to the PTCA-procedure are described.

Chapter seven reports the long-term follow-up (8.5 years) of the first 100 patients with a left anterior descending coronary artery lesion treated with PTCA. The results were satisfactory, even though at that time PTCA catheters were rigid and non steerable, in contrast with the current flexible, steerable catheters.

In chapter eight we describe the initial and long-term results of coronary angioplasty and coronary bypass surgery in patients 75 years or older. This is a fast growing group in our society with an increased morbidity. Therefore it is important to make the correct decision as to who should be operated on and who should have PTCA, when medical treatment fails. Results indicated that the complications of PTCA were less than those of surgery, but still there were failures and complications such as acute occlusion and even cardiogenic shock.

Emergency coronary bypass operation is an accepted solution for such PTCA complications but requires close collaboration with cardiothoracic surgeons. Therefore we analyzed the possible risk factors in order to attempt to predict the likelihood of unfavorable outcome (chapter nine).

Since PTCA provokes ischemia during balloon inflation, which can be harmful for the left ventricle, we collaborated with the Cardiochemistry laboratory of the Thoraxcenter in Rotterdam in studies on the effects of intravenous diltiazem and metoprolol during angioplasty of single-vessel coronary artery disease. The goal of both studies was to see if it would be possible to protect the left ventricle against ischemia with these drugs. The results are presented in chapters ten and eleven.

Thus, the two sections of this thesis deal with two new therapeutic approaches in patients with coronary artery disease, which have been introduced in a large cardiology practice of a non-academic centre over the last 10 years. Continuous critical assessment of such a new technology remains mandatory and requires good documentation of indications and results. This requires close collaboration with academic institutions and participation in multicenter clinical trials.

As Pasteur said:  
"Keep your enthusiasm, but let strict verification be its constant companion."

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# Comparison of Intravenous Anisoylated Plasminogen Streptokinase Activator Complex and Intracoronary Streptokinase in Acute Myocardial Infarction

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Hans J.M.L. Hoffmann, MSc, and the Dutch Invasive Reperfusion Study Group\*

**Coronary angiography was used to compare the efficacy of anisoylated plasminogen streptokinase activator complex (APSAC) administered intravenously and streptokinase given by intracoronary infusion in inducing reperfusion in patients with a proven acute myocardial infarction. Forty-two patients received 30 U of APSAC intravenously over 5 minutes and 43 patients received 250,000 IU of streptokinase given via intracoronary infusion over 90 minutes, after occlusion of the infarct-related vessel was demonstrated by angiography. Reperfusion was achieved in 23 (64%) of 36 patients (mean time to reperfusion 46 minutes) treated with APSAC and 25 (67%) of 37 patients (mean time to reperfusion 45 minutes) treated with intracoronary streptokinase, who were angiographically evaluated 90 minutes after the start of treatment. Twenty-four hours after treatment, reocclusion had occurred in 1 (5%) of 22 patients in the APSAC group and in 3 (13%) of 23 patients in the streptokinase group. No major bleeding was observed in either treatment group despite a similar systemic lytic state that lasted for up to 48 hours. Two patients treated with APSAC died after severe left ventricular failure unrelated to therapy. The results indicate that APSAC given intravenously is as effective as streptokinase given intracoronary in producing thrombolysis in acute myocardial infarction. The major advantages of APSAC are its rapid and convenient administration by a single intravenous injection, the low rate of arterial reocclusion and good patient tolerance.**

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\* See Appendix.

The role of coronary thrombosis as an initiator of acute myocardial infarction (AMI) has been well documented and is generally accepted.<sup>1</sup> The beneficial effect of intravenous thrombolytic therapy with streptokinase was demonstrated in a large European multicenter trial,<sup>2</sup> which showed that for successful lysis of coronary artery thrombi patients should receive lytic therapy within 3 to 6 hours of the onset of symptoms of an AMI. The development of coronary catheterization and angiographic techniques, and the realization that standard intravenous infusion rates of streptokinase may have been insufficient to produce thrombolysis and hence salvage of myocardial tissue, led Rentrop et al<sup>3,4</sup> to treat early AMI with direct intracoronary infusions of streptokinase. These investigators were able to demonstrate rapid arterial reperfusion in more than 70% of the patients and their results have been reviewed in detail by Udall.<sup>5</sup> Recently, Vermeer<sup>6</sup> compared intravenous and intracoronary streptokinase therapy in AMI and concluded that the intracoronary route gave better patency rates than the intravenous route. The principal disadvantage of streptokinase is that it has to be administered over 30 to 60 minutes<sup>7</sup> because of a significant incidence of hypotension and because systemic administration of streptokinase is followed by rapid nonspecific degradation by inactivators, thus reducing the delivery of active material to the site of the thrombus. Also, while the intracoronary route is the more effective,<sup>6</sup> the technique is more complicated and may delay further the start of treatment. Research has been directed to the development of better intravenous thrombolytic agents, with properties that would facilitate early treatment of AMI. The properties of the anisoylated plasminogen streptokinase activator complex (APSAC), with its longer fibrinolytic activity and greater resistance to early inactivation, make it particularly suitable for rapid intravenous injection in patients with AMI.<sup>8</sup>

We performed this open, multicentered randomized trial to compare the reperfusion rates produced by intravenous APSAC with those of intracoronary streptokinase at 90 minutes after dosing, and to assess, in both groups, the reocclusion rates at 24 hours after dosing, side effects and coagulation and fibrinolytic parameters.

## METHODS

**Patients:** Eighty-five patients (71 men and 14 women) ranging in age from 36 to 75 years (mean 55) par-

	Therapy		
	APSAC (n = 42)	SK (n = 43)	Total (n = 85)
Male/Female	35/7	36/7	71/14
Mean age (yrs) (range)	55 (37-70)	55 (36-75)	55 (36-75)
Anterior infarct	18	21	39
Inferior infarct	24	22	46
Angiography			
Initial perfusion grade			
0	36	32	68
1	6	11	17
Time from onset of pain to therapy			
Mean (hrs)	2.5	2.3	2.4
≤2.5 hrs	19	26	45
>2.5 hrs	23	17	40

APSAC = anisoylated plasminogen streptokinase activator complex; SK = streptokinase.

Grade 0 (no perfusion)	No antegrade flow beyond the point of occlusion
Grade 1 (penetration without perfusion)	Contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction
Grade 2 (partial perfusion)	Contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel or its rate of clearance from the distal bed, or both, are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel
Grade 3 (complete reperfusion)	Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction. Clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery

ticipated in the study. All patients had been referred to emergency departments within 4 hours of the onset of chest pain caused by AMI. Participating patients had chest pain of at least 30-minute duration and ST-segment elevation of at least 0.1 mV in 1 or more of the standard leads or at least 0.2 mV in 1 or more of the V leads in a 12-lead electrocardiogram. The symptoms were not relieved by sublingual glyceryl trinitrate. If a patient had no contraindications to thrombolytic therapy and informed consent was obtained, a coronary angiography was performed. In case of an occluded infarct-related vessel (TIMI grade 0 or 1), the patients were randomly assigned to treatment with either 30 U of intravenous APSAC or 250,000 IU of intracoronary streptokinase; 42 patients received APSAC and 43 received streptokinase on an open basis. The 2 groups were similar in sex ratio, age, site of infarction and cardiovascular characteristics (Table I). The mean time between onset of pain and start of lytic therapy was

slightly shorter in the streptokinase group (2.3 hours) compared with the APSAC group (2.5 hours).

**Treatment:** APSAC is formulated in a mixture of clinical grade human albumin, D-mannitol and L-lysine (Eminase®, Beecham). It was supplied in vials containing 30 units of APSAC as a sterile off-white powder. Each 30 U dose of APSAC was dissolved in 5 ml of water for injection or physiologic saline and administered intravenously over 5 minutes. Streptokinase was supplied as lyophilized powder in vials containing 250,000 IU of purified streptokinase (Kabikinase®, Kabivitrum). It was administered by intracoronary infusion in physiologic saline at rates between 2,000 and 5,000 IU/min. Ten patients were given intravenous bolus injections of 10,000 IU after each angiographic procedure. The total doses ranged from 64,000 IU in 45 minutes (1 patient) to 500,000 IU in 90 minutes (1 patient). The mean streptokinase dosage was 275,000 IU and the mean time of administration 67 minutes. All patients received 5,000 IU of heparin before catheterization. No additional heparin was given during the thrombolytic therapy. Anticoagulation therapy with heparin was started 4 hours after dosing.

**Angiographic evaluation:** Angiography of the occluded infarct-related coronary artery was carried out by the Judkins technique before the patients were randomized. After the start of lytic therapy, angiography was performed at 15-minute intervals for up to 90 minutes to assess coronary artery reperfusion. The catheter was removed after 90 minutes, but the sheath was left in the peripheral artery for 48 hours to minimize bleeding from the puncture site. Approximately 24 hours after dosing, additional angiograms were performed to assess the degree of reperfusion or to discover if reocclusion had occurred. The degree of perfusion at each angiographic assessment was classified according to the criteria used in the TIMI trial<sup>9</sup> (Table II). The angiograms were read blind by an independent cardiologist. In the postdosing assessments, patients with grades 0 or 1 were considered to show no reperfusion of the infarct-related vessels and those with grades 2 or 3 to show reperfusion.

**Coagulation parameters and fibrinolytic assays:** Blood samples for analysis in the Central Coagulation Laboratory were taken before lytic therapy and at 90 minutes, 12, 24 and 48 hours after therapy to assess fibrinogen concentration (clotting-rate method of Clauss), euglobulin clot lysis time, streptokinase resistance titer and other parameters of fibrinolysis and coagulation. The blood for fibrinogen determinations was collected in tubes with a citrate anticoagulant, to which 0.7 M ε-aminocaproic acid had been added as an inhibitor of in vitro fibrinogenolysis. All samples were processed immediately after collection and plasma was frozen at -70°C for future analysis.

**Adverse effects:** Two deaths occurred, both in the APSAC group. One patient, a 58-year-old man, died of severe left ventricular failure during catheterization. This patient had had an AMI 5 years earlier. The second, a 61-year-old woman, also died of left ventricular failure 2 days after treatment. This patient had shown

		Therapy				p Value
		Intravenous APSAC (n = 42)		Intracoronary SK (n = 43)		
Evaluated		36		37		
Not evaluated		6		6		
	Site of Infarct	Reperfusion (%)	No reperfusion (%)	Reperfusion (%)	No reperfusion (%)	
All evaluated patients	Anterior	9 (60)	6 (40)	13 (72)	5 (28)	NS (p <0.80)
	Inferior	14 (67)	7 (33)	12 (63)	7 (37)	NS (p <0.98)
	Total	23 (64)	13 (36)	25 (68)	12 (32)	NS (p <0.20)
Initial perfusion						
Grade 0	Anterior	7 (54)	6 (46)	8 (62)	5 (38)	
	Inferior	13 (65)	7 (35)	10 (67)	5 (33)	
	Total	20 (61)	13 (39)	18 (64)	10 (36)	
Grade 1	Anterior	2 (100)	—	5 (100)	—	
	Inferior	1 (100)	—	2 (50)	2 (50)	
	Total	3 (100)	—	7 (78)	2 (22)	

NS = not significant. Other abbreviations as in Table I.

		Therapy				p Value
		Intravenous APSAC (n = 42)		Intracoronary SK (n = 43)		
Evaluated		36		37		
Not evaluated		6		6		
Time to treatment after onset of symptoms		Reperfusion (%)	No reperfusion (%)	Reperfusion (%)	No reperfusion (%)	
<2.5 hours		10 (77)	3 (23)	15 (65)	8 (35)	NS
≥2.5 hours		13 (57)	10 (43)	10 (71)	4 (29)	NS
Total		23 (64)	13 (36)	25 (68)	12 (32)	

NS = not significant. Other abbreviations as in Table I.

		Therapy			
		Intravenous APSAC (n = 23)		Intracoronary SK (n = 25)	
Evaluated		22		23	
Not evaluated		1		2	
	Site of Infarct	Reocclusion (%)	No reocclusion (%)	Reocclusion (%)	No reocclusion (%)
All evaluated patients	Anterior	—	8 (100)	2 (17)	10 (83)
	Inferior	1 (7)	13 (93)	1 (9)	10 (91)
	Total	1 (5)	21 (95)	3 (13)	20 (87)

reperfusion of an anterior infarct-related vessel after 90 minutes and early reocclusion had not occurred. There was no evidence that there was a relation between these deaths and the patients' APSAC therapy. Otherwise, only minor adverse events occurred, with 2 patients developing hematoma at the puncture site after APSAC therapy and another showing hypotension of 5-minute duration that resolved after treatment. None of the patients required blood transfusions.

One patient in the streptokinase group had angiography stopped because of vomiting. Another developed hypotension during infusion (infusion was stopped after 45 minutes and a total dose of 96,000 IU of streptokinase). The hypotension disappeared after treatment.

**Statistical analysis:** A 2-tailed chi-square test was used in analyzing the reperfusion data, with  $\alpha = 0.05$  and  $df = 1$ . The Fisher exact test was used to test for possible differences between the group of patients treat-

ed within 2.5 hours and those treated 2.5 to 4 hours. Values obtained from the Fisher exact test were 2-tailed, tested at  $\alpha = 0.05$ . One-factor analysis of variance was performed on coagulation parameters and the results of fibrinolytic assays.

## RESULTS

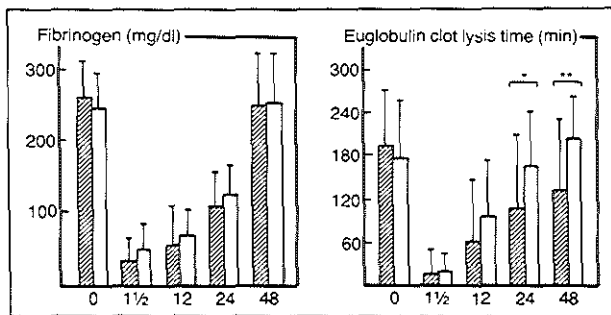
**Angiographic findings:** The findings 90 minutes after the start of lytic therapy were taken as the point for determining whether or not a patient had gained satisfactory reperfusion of the infarct-related vessel, with the angiographic examination 24 hours after therapy carried out to determine if the infarct-related vessel was still patent or if rethrombosis had occurred (Tables III and V).

**Intravenous anisoylated plasminogen streptokinase activator complex:** Thirty-six of the 42 patients who received intravenous APSAC had coronary angiography performed 90 minutes after treatment. Twenty three (64%) of these patients showed reperfusion; 9 (60%) from the group with anterior infarcts and 14 (67%) from the group with inferior infarcts. The mean time to reperfusion was 46 minutes (Table III). All 13 patients who did not show reperfusion at 90 minutes had shown no perfusion (TIMI grade 0) at the pretreatment angiography. Six (46%) of these patients had anterior infarcts and 7 (54%) inferior infarcts. Of the 13 evaluated patients who received APSAC within 2.5 hours of the onset of symptoms, reperfusion was achieved in 10 (77%) patients, compared with 13 (57%) of the 23 patients who were treated between 2.5 hours and 4 hours after the onset of symptoms (difference not significant) (Table IV). One of the 6 patients not assessed at 90 minutes had died of severe left ventricular failure during catheterization. The other 5 patients had shown reperfusion but coronary angiography was discontinued before 90 minutes. In 2 of these patients a percutaneous transluminal coronary angioplasty was performed at 60 minutes and 75 minutes, respectively, after treatment; in the other 3 angiography was stopped for various reasons at 45, 60 and 75 minutes after treatment, respectively.

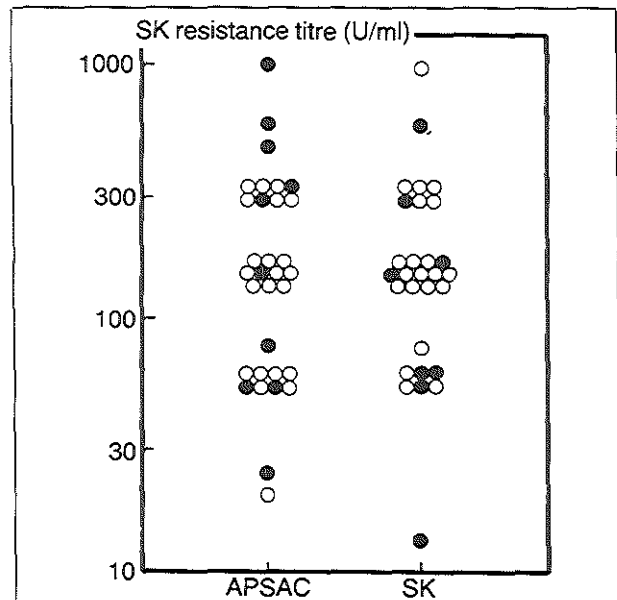
**Intracoronary streptokinase:** Coronary angiography was performed 90 minutes after the start of infusion of streptokinase in 37 of the 43 patients. Twenty-five

(68%) patients showed reperfusion of the infarct-related vessels; 13 (72%) from the group with anterior infarcts and 12 (63%) from the group with inferior infarcts (Table III). The mean time to reperfusion was 45 minutes. Five (42%) of the 12 patients who did not show reperfusion had anterior infarcts and 7 (58%) had inferior infarcts. Ten of these 12 had shown no perfusion (TIMI grade 0) at pretreatment coronary angiography. Fifteen (65%) of the 23 evaluated patients who received streptokinase within 2.5 hours of the onset of symptoms showed reperfusion, compared with 10 (71%) of the 14 patients who were treated between 2.5 hours and 4 hours after the onset of symptoms (difference not significant) (Table IV). Six patients could not be evaluated at 90 minutes. Three of them showed reperfusion at 60 minutes but angiography was not continued; 1 of these patients had angiography discontinued because of vomiting while in the other 2 angiography was discontinued because of other reasons. Two of the patients who were not examined at 90 minutes did not show reperfusion at 60 minutes and 75 minutes, respectively, requiring mechanical clearance by guidewire perforation of the infarct-related vessel followed by percutaneous transluminal coronary angioplasty. One patient was withdrawn from the trial as his age (75 years) was outside the range specified in the protocol ( $\leq 70$  years).

Of the 23 patients in the APSAC group, 22 patients with reperfusion at 90 minutes were reassessed by coronary arteriography after 24 hours. One patient was not reassessed because the procedure failed. Only 1 (5%) patient with an inferior infarct showed reocclusion (Table V). Coronary angiography was performed at 24 hours in 23 of the 25 patients treated with streptokinase who had shown reperfusion at 90 minutes. One of the 2 patients not assessed had undergone percutaneous transluminal coronary angioplasty and the other coronary artery bypass grafting. Three (13%) patients showed



**FIGURE 1.** Course of fibrinogen and euglobulin clot lysis time (mean  $\pm$  standard deviation) in patients treated with intravenous anisoylated plasminogen streptokinase activator complex (hatched bars) and intracoronary streptokinase (clear bars). \*  $p < 0.02$ ; \*\*  $p < 0.005$  by analysis of variance.



**FIGURE 2.** Streptokinase resistance titer in both treatment groups. Note logarithmic ordinate. ○ = reperused; ● = not reperused (at 90 minutes).

reocclusion, 2 of whom had anterior infarcts and 1 an inferior infarct (Table V).

**Coagulation and fibrinolytic assays:** The changes in the most important parameters, plasma fibrinogen concentration and euglobulin clot lysis time, are given in Figure 1. Fibrinogen rapidly decreased in both groups after therapy, reaching minimal levels 90 minutes after the start of therapy. In the APSAC treated patients the mean fibrinogen concentration at this time ( $33 \pm 31$  mg/dl) was lower than that in the patients treated with streptokinase ( $50 \pm 34$  mg/dl) (analysis of variance not significant). Thereafter, fibrinogen levels increased and returned toward pretreatment values between 24 and 48 hours after treatment.

The euglobulin clot lysis time sharply decreased; i.e., total fibrinolytic activity in plasma increased, reaching a minimum 90 minutes after dosing and thereafter gradually increasing in both groups. The euglobulin clot lysis time was significantly lower among patients treated with APSAC, both at 24 hours ( $p < 0.02$ , analysis of variance) and at 48 hours ( $p < 0.005$ , analysis of variance) after lytic therapy, reflecting the sustained fibrinolytic activity of APSAC.

The streptokinase-inhibiting capacity of plasma, measured as streptokinase resistance titer in pretreatment plasma, was identical in both groups (Figure 2): mean 148 U/ml (range 20 to 1,000) in the APSAC treated patients and mean 148 U/ml (range 13 to 1,000) in the patients who received streptokinase. There was no correlation between pretreatment streptokinase resistance titer and occurrence of reperfusion in either group, as indicated in Figure 2. More detailed results of coagulation and fibrinolysis studies in these patients have been published elsewhere.<sup>10</sup>

## DISCUSSION

In nearly 90% of patients, coronary arterial occlusion is likely to be present in the first 4 hours after the onset of symptoms of AMI.<sup>1</sup> However, in an individual patient it is not possible to be certain that occlusion and subsequent reperfusion have occurred unless coronary angiography has been performed before and after lytic therapy.

The importance of thrombolytic therapy in the treatment of AMI has been confirmed by recent studies carried out in Europe and the US using intracoronary streptokinase. In the Western Washington Trial<sup>11,12</sup> a reperfusion rate of 69% was achieved after thrombolytic therapy, although there was no significant difference in patient survival 1 year after therapy between these patients and a control group who received nonthrombolytic therapy. These results are comparable with those of the Interuniversity Cardiology Institute of the Netherlands Study Group,<sup>6</sup> which found an 85% patency rate in infarct-related vessels after thrombolytic therapy and a significantly higher survival rate 1 year after therapy among the patients who received thrombolytic treatment (90 vs 84% in the control group). Simoons et al<sup>13</sup> have noted a similar decrease in mortality rates in-hospital after thrombolytic therapy. Vermeer<sup>6</sup> suggests that the differences in long-term mortality rates be-

tween the Interuniversity Cardiology Institute of the Netherlands Study Group findings and those in the Western Washington Trial are partly attributable to the greater delay between onset of symptoms and start of therapy in the latter trial. The benefits of early thrombolytic therapy have been demonstrated in the GISSI<sup>14</sup> trial ( $1.5 \times 10^6$  U streptokinase by intravenous infusion vs placebo), when a marked reduction in hospital mortality was seen in patients who received thrombolytic therapy within 4 hours of the onset of symptoms, compared with those whose treatment was more delayed. The largest decrease in mortality was seen among patients treated within 1 hour of the onset of symptoms.

The present study shows that 30 U of APSAC by intravenous injection is as effective as 250,000 IU of streptokinase by intracoronary infusion in producing reperfusion in occluded coronary arteries within 90 minutes of treatment. Furthermore, the administration of APSAC as a single intravenous injection in 5 minutes is easier and quicker than intracoronary infusion of streptokinase in patients with AMI because of the delay caused by the catheterization of the patient for the intracoronary procedure.

After streptokinase therapy, fibrinogen decreased to about 22% of pretreatment values, which was close to the values found in other studies on intracoronary streptokinase.<sup>15,16</sup> In the APSAC treated patients there was a marked reduction in fibrinogen to 15% of pretreatment values, a result identical to our earlier findings.<sup>17</sup>

When given in equally effective doses, both drugs systemically activate the fibrinolytic system in most patients (93%) to similar degrees, without causing significant bleeding. The differences in euglobulin clot lysis time between the treatment groups indicate that APSAC has a more sustained fibrinolytic activity than streptokinase. In the present study, reocclusion occurred in more patients treated with streptokinase (3 patients, 13%) than in the APSAC group (1 patient, 5%). However, the small number of patients in this trial should be noted.

We believe that APSAC is well suited for rapid thrombolysis of relatively fresh clots, as evidenced by the 77% of patients in this study treated within 2.5 hours of the onset of symptoms of AMI who showed reperfusion 90 minutes after dosing, compared with 56% of patients whose treatment was more delayed. In contrast, the difference in reperfusion rates between patients who were treated early and those treated late with streptokinase was far less marked.

APSAC can be given successfully and safely as a single intravenous injection. These are advantages that the other known plasminogen activators, which are either hypotensive at high doses or are cleared too rapidly, are not likely to have.

APSAC apparently reduced the incidence of early reocclusion observed by most investigators after thrombolytic therapy with streptokinase in AMI. This can be explained by APSAC's prolonged fibrinolytic activity, resistance to autodegradation and strong fibrin affinity. However, further trials are needed to confirm that the incidence is, indeed, lower.

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## Appendix

### The Dutch Invasive Reperfusion Study Group

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## Systemic Effects of Thrombolytic Drugs in Acute Myocardial Infarction: Comparison of Intravenous APSAC (BRL 26921) and Intracoronary Streptokinase

J. J. M. L. Hoffmann, J. J. R. M. Bonnier, J. B. R. M. De Swart

**SUMMARY.** The systemic effects of intravenous anisoylated plasminogen-streptokinase activator complex (APSAC; BRL 26921; 30 U) and intracoronary streptokinase (250 000 U) were compared in 70 patients with acute myocardial infarction. In 5 patients no signs of a systemic lytic state were observed. In all other patients, significant consumption of coagulation and fibrinolytic factors occurred: fibrinogen levels decreased by 85% in the APSAC group and 78% in the streptokinase-treated patients. For plasminogen the decreases were 68% and 64% and for  $\alpha_2$ -antiplasmin activity >95% and 87% (APSAC and streptokinase, respectively). Fibrin(ogen) degradation products were generated to mean levels of 739 mg/L and 355 mg/L, respectively. Although there was a trend for the lytic state to be more profound in the APSAC-treated patients, no difference with the streptokinase group was observed with regard to bleeding complications or therapeutic efficacy, which was 64% and 68% respectively for APSAC and streptokinase. The total fibrinolytic activity, measured as euglobulin clot lysis time, sustained longer in the APSAC group, which might be the reason for the low reocclusion rate (4.5%) in comparison with the SK group (13%).

**KEYWORDS.** Acyl-enzymes. APSAC. Myocardial infarction. Systemic lytic state. Streptokinase. Thrombolysis.

Acyl-enzymes with plasminogen activator potency constitute a new approach in the field of clinical fibrinolysis.<sup>1,2</sup> Their principle of action is that the acyl form of the enzyme, which is catalytically inactive, will be hydrolysed under physiological conditions according to first-order kinetics. By this spontaneous deacylation an active plasminogen activator is generated in the circulation with a controlled rate, so that a long-acting fibrinolytic activity will be obtained.

Of the acyl-enzymes available, the anisoylated plasminogen-streptokinase activator complex (APSAC; formerly BRL 26921) has been best investigated. From prior investigations in limited numbers of patients with acute myocardial infarction it appears that APSAC is an effective thrombolytic agent.<sup>3-6</sup> Unfortunately, its relative fibrin-selectivity present in animal systems<sup>1,2,7</sup> has not been found in humans, probably because of interspecies differences in plasminogen activation kinetics<sup>2</sup> or in binding to fibrin. Because of its efficacy and its favourable kinetic properties, which allow iv bolus administration,

APSAC is considered as a promising thrombolytic drug. Several clinical trials in patients with acute myocardial infarction are at present in progress in order to assess its value in clinical practice.

Up to now there are no studies published in which APSAC was compared with the standard drug for thrombolytic treatment, namely streptokinase (SK). Therefore we studied 85 patients with acute myocardial infarction in an open, randomised multicentre trial comparing SK (250 000 U by intracoronary infusion) and APSAC (30 U by rapid intravenous injection); this dosis of APSAC contains approximately 1 million units of SK, complexed to plasminogen and inactivated by active-site acylation. The aim of this study was to compare both drugs with respect to their effect on major components of the coagulation and fibrinolytic systems and to investigate possible relations between the systemic lytic state and clinical items as reperfusion, reocclusion and bleeding complications.

### PATIENTS AND METHODS

#### Patients

Eighty five patients with acute myocardial infarction entered the study. There were 14 females and 71 males,

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39 with anterior and 46 with inferior myocardial infarction. The age of the patients ranged from 36 to 70 years, mean age 54.8 years. All patients gave their informed consent for participating in the study, which had been approved by the local ethical committee.

### Study Protocol

In the patients fulfilling the inclusion criteria, angiography was performed to document occlusion of one or more coronary vessels. Then, the patients were randomised to either of two treatment regimens: APSAC (30 U; equivalent on a molar basis to about 1 million U of SK) by single intravenous injection during 2–4 min or SK (250 000 U) by intracoronary infusion for 60 min. Thrombolytic therapy was always started within 4 h from the onset of chest pain. The administration of heparin was allowed as a catheter flush (5000 U by bolus injection) at the insertion of catheters and heparin was mandatory after thrombolytic therapy (1000 U/h as a continuous infusion): in the APSAC-treated patients it started 4 h after starting thrombolytic therapy and in the SK-group as soon as the thrombin time decreased below twice the upper normal limit (usually 3–5 h after starting SK). In all cases heparin infusion was maintained up to 24 h after starting thrombolysis; thereafter oral anticoagulants were given if necessary. Repeat coronary angiograms were made at 15 min intervals during the first 1 h 30 min and 24 h after starting therapy for assessing coronary reperfusion and reocclusion, respectively. The study was carried out by members of the Dutch IRS group (see appendix) in three hospitals in the south-eastern part of the Netherlands.

### Methods

Blood for coagulation and fibrinolysis studies was collected in plastic syringes containing 1/10 volume of 0.1 M sodium citrate (for  $\alpha_2$ -antiplasmin, euglobulin clot lysis time and streptokinase resistance titer determinations) and 0.1 M sodium citrate plus 0.07 M  $\epsilon$ -aminocaproic acid for all other determinations. Blood was centrifuged immediately at 4°C and plasma was snap-frozen and stored at –70°C until testing. All analyses were carried out in the central coagulation laboratory. From 15 patients no or insufficient plasma was available for testing. Fibrinogen concentration was measured with the clotting-rate method (Clauss); prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT) and reptilase time (RT) according to standard methods using commercial reagents. APTTs were measured without and with addition of Polybrene for heparin neutralisation.<sup>8</sup> Serum fibrin/fibrinogen degradation products (FDP/fdp) were estimated semi-quantitatively using a latex agglutination assay (Thrombo-Wellcotest; Wellcome Diagnostics). Plasminogen and  $\alpha_2$ -antiplasmin activities were determined using the chromogenic substrates S-2251 (Kabi) and euglobulin clot lysis time

**Table 1** Patient Characteristics and Outcome of Thrombolytic Therapy. Non-evaluable Patients have been Omitted

	APSAC	SK
Number of patients	36	34
sex (M:F)	30:6	27:7
age, mean $\pm$ SD (y)	54.6 $\pm$ 8.1	54.8 $\pm$ 10.1
Systemic lytic state	33/36 (91.7%)	32/34 (94.1%)
reperfusion	23/33	21/32
no reperfusion	10/33	11/32
No systemic lytic state	3/36 (8.1%)	2/34 (5.9%)
reperfusion	0/3	2/2
no reperfusion	3/3	0/2
Reperfusion	23/36 (63.9%)	23/34 (67.7%)
Major bleeding	None	None
Reocclusion	1/22 (4.5%)	3/23 (13.0%)

(ECLT) according to Nilsson et al.<sup>9</sup> Streptokinase resistance titers in plasma were measured using the technique of Deutsch.<sup>10</sup>

A systemic lytic state was defined as a decrease in fibrinogen concentration after thrombolytic therapy by at least 10% of the pretreatment value.<sup>11</sup>

### Statistics

For statistical evaluation we used analysis of variance, if indicated after logarithmic transformation of the data. P values <0.05 were considered significant.

### RESULTS

The patient characteristics and clinical findings are summarised in Table 1. The composition of the two treatment groups was closely comparable. The efficacy of APSAC, expressed as reperfusion rate at 1 h 30 min was 64%, not significantly different from 68% for SK. The incidence of reocclusion of initially reperfused coronary arteries was 4.5 and 13%, respectively. Minor bleeding from puncture sites occurred frequently in both groups, but major bleeding did not occur in this study and no patient required blood transfusion.

In 5 out of the 70 patients of whom adequate samples were available for testing, no signs of a systemic lytic state could be observed (3 APSAC and 2 SK). In both SK-treated patients, successful reperfusion was achieved, in the 3 others, treated with APSAC, it was not. The data of these 5 patients have been excluded from the statistical analysis. The course of the coagulation parameters of the remaining patients is shown in Figure 1. The pretreatment values were identical in both groups and only slight deviations from the normal range were seen in some patients. After therapy, however, considerable changes became apparent: fibrinogen concentration fell to very low levels, while the Polybrene-APTT, PT (not shown), thrombin time and reptilase time were strongly prolonged during the early post-treatment period.

The nadir of fibrinogen was approximately 15%



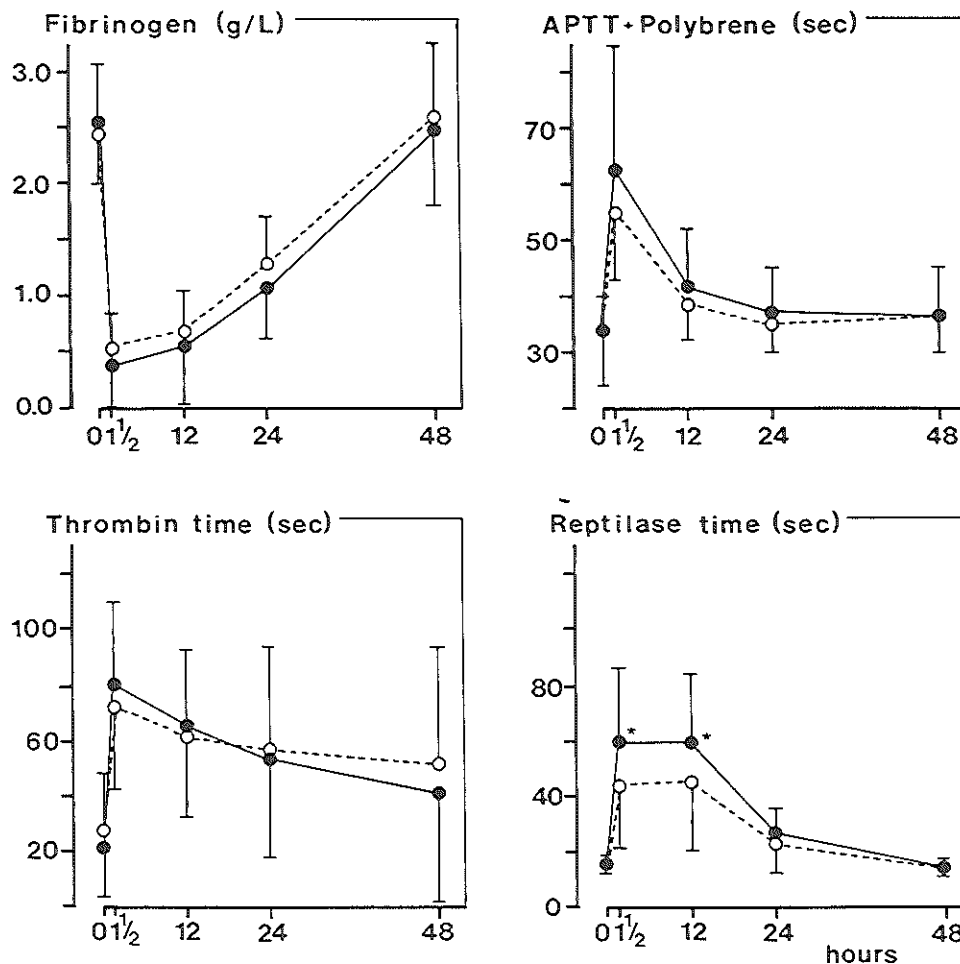


Fig. 1 Course of coagulation parameters during thrombolytic therapy with APSAC (●) and SK (○). Mean  $\pm$  SD is shown. \* $p < 0.05$ .

(APSAC) and 22% (SK) of the respective pretreatment values, and it was normal again at 48 h; the differences between both groups were never statistically significant. The course of the other coagulation parameters was also comparable between the two groups, except significant differences in PT and reptilase time at 1 h 30 min and 12 h post-treatment.

The course of the fibrinolytic parameters is shown in Figure 2. In the APSAC group, significantly more FDP/fdp were generated during therapy than in the SK group. Plasminogen was consumed to about one third its original level in both groups.  $\alpha_2$ -Antiplasmin activity became undetectably low in all but 1 APSAC-treated patients, but in only a part of the patients in the SK-group. The difference in  $\alpha_2$ -antiplasmin at 1 h 30 min was significant ( $p < 0.005$ ) between both groups. The total fibrinolytic activity in euglobulin fractions sharply increased (i.e. ECLT decreased) after therapy and then slowly decreased. The differences in ECLT between both groups at 24 and 48 h were statistically significant ( $p < 0.02$  and  $p < 0.005$ , respectively), indicating that APSAC has a more sustained fibrinolytic effect than SK. The streptokinase-inhibiting activity in plasma, measured as SK-resistance titer (SKRT), was identical in both groups: mean 148

(range 15–1000) U/mL in the APSAC group and mean 148 (range 13–1000) in the SK group. The degree of fibrinolysis as a function of pretreatment SKRT is shown in Figure 3: the correlation coefficient (by linear regression) was 0.173 (not significant).

## DISCUSSION

Although APSAC is much less fibrin-selective in humans<sup>3–6</sup> than in animals,<sup>2,7,12</sup> it might be better suited for clinical usage than SK, due to the possibility of rapid intravenous administration. Then, APSAC should not cause more side effects, mainly systemic lysis, than SK does. These systemic effects of APSAC were the subject of this comparative study with intracoronary SK, which is considered as the standard for thrombolytic treatment of acute myocardial infarction.<sup>13</sup>

A major problem in assessing the coagulation system during thrombolytic therapy is that the fibrinolytic activity will continue in vitro after blood collection, thereby giving falsely low results for fibrinogen and other factors and falsely elevated levels of FDP/fdp.<sup>14</sup> In order to prevent in vitro fibrinolysis to go on,

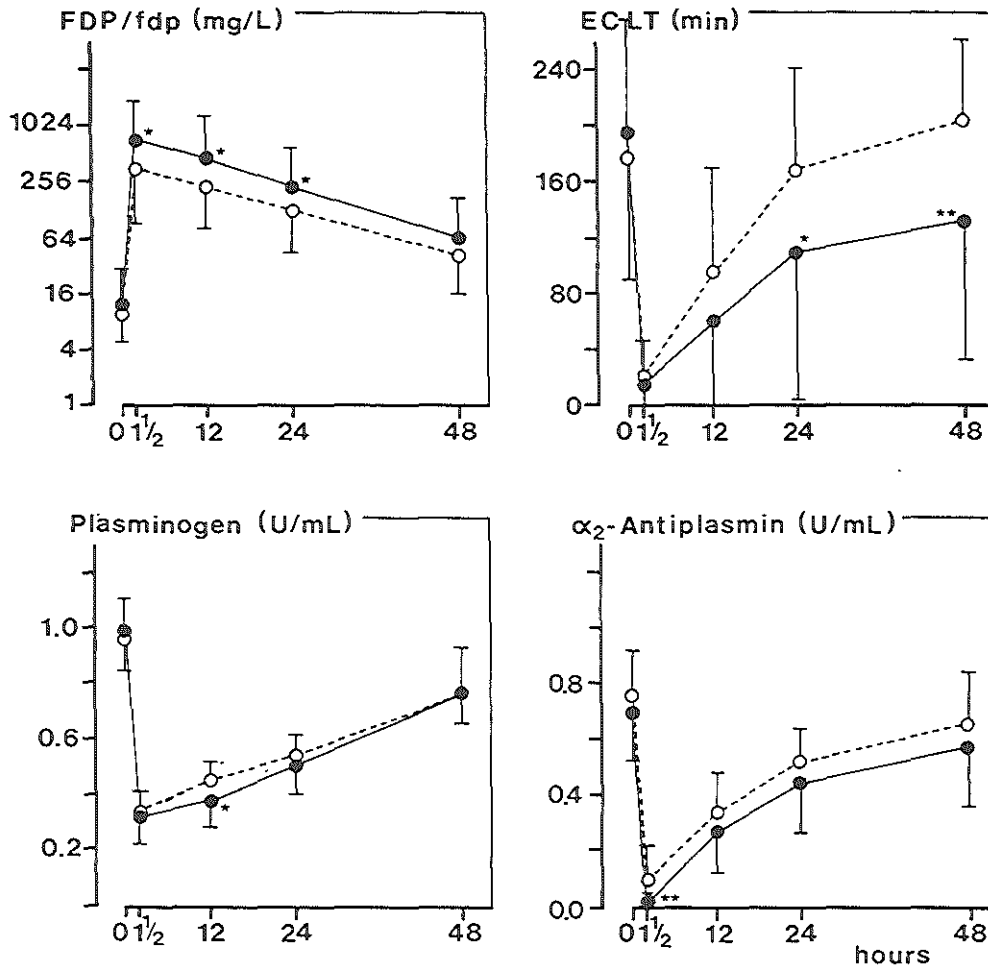


Fig. 2 Course of fibrinolysis parameters during thrombolytic therapy with APSAC (●) and SK (○). Mean  $\pm$  SD is given. \* $p < 0.05$ ; \*\* $p < 0.005$ .

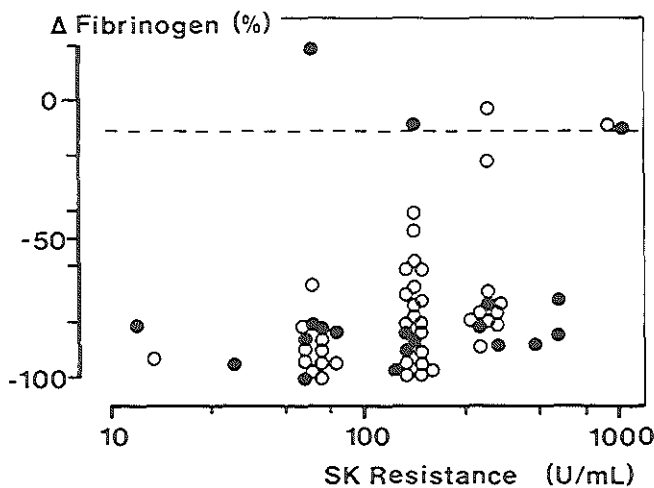


Fig. 3 Change in fibrinogen concentration relative to pre-treatment level, as a function of SK resistance titer (logarithmic scale). Dotted line represents definition of lytic state. Reperfusion (○) and no reperfusion (●) is indicated.

we have collected blood in anticoagulant containing  $\epsilon$ -aminocaproic acid for those determinations, in which this inhibitor had been shown not to interfere (unpublished results). Only  $\alpha_2$ -antiplasmin, euglobulin clot lysis time and streptokinase resistance had to be determined in plain anticoagulated plasma.

After SK therapy, fibrinogen decreased to about 22% of pre-treatment values in our patients (Fig. 1), a value close to that of other studies on intracoronary SK.<sup>15,16</sup> In the APSAC group the fall in fibrinogen was marked, to 15% of baseline values, which is identical with our earlier observations,<sup>5</sup> but clearly lower than in two recent studies on intravenous APSAC.<sup>17,18</sup> This discrepancy is probably caused by the different methods used: we used the Clauss technique, which reflects rapidly coagulable fibrinogen and can be negatively influenced by higher levels of FDP. The methods used by the other authors measure total clottable protein and may include some slowly-coagulable fibrinogen fragments. In any case, all available studies with SK and APSAC, administered

locally or systemically, indicate that after administration of therapeutically effective doses, fibrinogen will fall to low levels, often below 0.5 g/L, but rapidly increases to normal values within 48 h (Fig. 1).<sup>5,6,14-18</sup>

From Figure 1 it is concluded that global coagulation tests provide little, if any additional information during thrombolytic therapy. In order to appreciate the effect of thrombolytic therapy on these global assays without the effect of heparin interfering, we included two heparin-insensitive coagulation assays, the Polybrene-APTT<sup>8</sup> and the reptilase time. Even with these tests the information obtained is limited. As Figure 1 shows, the reptilase time is probably the best global test for monitoring thrombolytic therapy,<sup>6</sup> although fibrinogen concentration alone appears to be sufficient for this purpose.

As a consequence of fibrinogenolysis FDP/fdp increased to very high levels in both treatment groups (Fig. 2). The peak level of FDP/fdp in the APSAC group (739 mg/L) corresponds to about 30% of the pretreatment fibrinogen concentration, a value identical with that found in high-dose (1.5 million U) intravenous SK therapy.<sup>14</sup>

In line with expectations, the ECLT fell extremely after therapy in both groups. In most patients, the clot in the euglobulin preparation dissolved immediately, as has been described by others.<sup>17,18</sup> In the early post-therapy period we found no difference in ECLT between APSAC and SK, but the fibrinolytic activity in the SK group was approximately normal at 24 and 48 h, while in the APSAC group it was still elevated (Fig. 2). This sustained fibrinolytic activity might be speculated to be a factor of importance in preventing early reocclusion. A similar suggestion on a relation between the lytic state and reocclusion has been made by others.<sup>4,17</sup>

Plasminogen activities were identical in both groups throughout therapy; the lowest activity, about 30% of the pretreatment level, is in reasonable agreement with data from studies on APSAC<sup>4,18</sup> and SK,<sup>14</sup> but the minimum was not as low as in our earlier study;<sup>5</sup> the reason for this remains unexplained.

Functional  $\alpha_2$ -antiplasmin decreased to undetectable levels in the majority of patients, both in APSAC and SK (Fig. 2). This is fully in keeping with the concept that fibrinogenolysis only occurs once the plasmin generated has completely exhausted circulating free  $\alpha_2$ -antiplasmin. This process is much better reflected by measurement of  $\alpha_2$ -antiplasmin activity than by an immunological assay.<sup>5</sup> Data on  $\alpha_2$ -antiplasmin during thrombolytic therapy are rather scarce: Walker et al<sup>3</sup> observed a mean decrease to 28% of the baseline value after APSAC in varying doses, but there was no systemic lysis in all of their patients and if it was, not as profound as in our study (mean decrease in fibrinogen: 44%). The results on  $\alpha_2$ -antiplasmin reported by Collen et al<sup>14</sup> in patients treated with high-dose intravenous SK are not easily explained: fibrinogen fell to below 10% of its initial concentration, but  $\alpha_2$ -antiplasmin had decreased to only 24% of its pretreat-

ment activity, while one should expect extremely low levels with such a degree of fibrinogenolysis. The results shown in Figure 1 and 2 indicate only a few statistically significant, but clinically hardly relevant differences between the systemic effects of APSAC and SK, while their clinical efficacy and safety was identical (Table 1). The degree of systemic lysis appeared to be somewhat more profound in the APSAC group, but one should realise that 30 U of APSAC is equivalent to approximately 1 million U of streptokinase.

Table 1 shows a correlation between reperfusion and the occurrence of a systemic lytic state, especially in the case of APSAC, while a truly local effect of SK was observed in two patients who had reperfusion without a systemic lytic state. However, the small number of patients does not allow to draw a firm conclusion on this subject. In agreement with others we found no correlation between presence of systemic lysis and major bleeding complications.<sup>6,18</sup>

The significance of anti-SK antibodies has up to present not been investigated in detail and certainly not so in APSAC therapy. The effect of SK-resistance on systemic lysis is difficult to interpret from the results of Walker et al<sup>3</sup> because of the low number of patients and the wide range of doses applied. Figure 3 indicates that the effects of APSAC may be modulated by anti-SK antibodies: high SK-resistance titers sometimes prevent a systemic lytic state to occur, but there is no significant correlation between these parameters. Reperfusion appears not to be related at all with SK resistance titers, irrespective whether APSAC or SK was the thrombolytic drug administered.

In conclusion, the results of our present investigation can be summarised as follows: when administered in equally effective doses, intravenous APSAC and intracoronary SK both will give rise to systemic activation of the fibrinolytic system in the majority (93%) of patients, to a closely comparable degree, but without the systemic lysis causing significant bleeding. Since early thrombolytic treatment can substantially reduce early mortality from acute myocardial infarction<sup>19</sup> and time-consuming cardiac catheterisation is obviated, intravenous APSAC seems one of the better thrombolytic drugs currently available.

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## APPENDIX

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## Significance of Antibodies to Streptokinase in Coronary Thrombolytic Therapy with Streptokinase or APSAC

J. J. M. L. Hoffmann, R. Fears, J. J. R. M. Bonnier, R. Standring, H. Ferres, J. B. R. M. De Swart

**SUMMARY.** In 61 patients with acute myocardial infarction, who received thrombolytic therapy with intracoronary streptokinase (250 000 U) or intravenous anisoylated plasminogen-streptokinase complex APSAC (30 U), the concentration of IgG antibodies to streptokinase (IgG anti-SK) was measured using a recently developed micro-radioimmunoassay technique. The distribution of IgG anti-SK in the patients was approximately log-normal with a geometric mean of 0.84 µg/ml. The correlation with the streptokinase resistance titer was statistically significant, but there was a wide scatter of individual results.

In both drug regimens a significant correlation was found ( $r = 0.51$  and  $0.67$ ) between degree of systemic lytic state, expressed as residual fibrinogen 1.5 h after dosing, and pretreatment IgG anti-SK, as well as between post-treatment euglobulin clot lysis time and pre-treatment IgG anti-SK ( $p < 0.025$ ). Comparable, angiographically-defined reperfusion rates were obtained for intravenous APSAC (66%) and intracoronary SK (69%). For both APSAC and SK there was no significant difference in initial IgG anti-SK between the patients who achieved reperfusion and those who did not. However, the rarity of patients with very high antibody levels in this study precludes a definitive conclusion on reperfusion success in such patients. There was no correlation between time at which sustained reperfusion was achieved (mean interval 45 min for APSAC and 47 min for streptokinase) and baseline IgG anti-SK levels. The incidence of side effects of APSAC and SK was too low to examine in relation with antibody levels.

The time course of changes in IgG anti-SK during the first 48 h after therapy was independent of drug regimen and pre-treatment antibody level. The maximum decrease in IgG anti-SK concentration after dosing was approximately 1.0 µg/ml. This is less than the amount expected by stoichiometric binding of APSAC with antibody and indicates that APSAC might be poorly bound by antibodies to streptokinase.

Although concurrent studies *in vitro* demonstrate that IgG anti-SK can bind and at high concentrations even cause some loss of activity for a streptokinase-containing thrombolytic agent, the present clinical results show that the reperfusion response in our population of patients was not significantly affected by IgG anti-SK at therapeutic doses of intravenous APSAC or intracoronary SK, while the systemic lytic state was significantly influenced by anti-SK antibodies.

**KEYWORDS.** Anti-streptokinase antibodies. Intravenous APSAC. Acute myocardial infarction. Reperfusion. Intracoronary streptokinase. Streptokinase resistance. Systemic lytic state.

More than 40 years after the discovery of the fibrinolytic properties of streptokinase (SK), renewed interest in thrombolytic agents has arisen after the demonstration that SK could effectively restore the blood flow in occluded coronary arteries of patients with acute myocardial infarction.<sup>1</sup> It recently became evident that early thrombolytic treatment with SK significantly

reduced the mortality in such patients,<sup>2,3</sup> but reperfusion trials indicate that 20–30% of the patients fail to respond to thrombolytic treatment.<sup>1</sup> The reasons for this failure are largely unknown.

Some authors have explained at least part of the therapeutic failures of SK by high levels of antibodies to SK in those patients.<sup>4,5</sup> It is known that following infections with streptococci and after administration of SK, antibodies to streptococcal proteins are formed<sup>6,7</sup> which are capable of reacting with SK and neutralising its potency to activate the fibrinolytic system.<sup>4,8</sup> However, absence of systemic fibrinolytic activity is not necessarily identical with failure to lyse

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coronary thrombi, although there may be a relationship in some patients.<sup>9-11</sup> So, adequate evidence from clinical studies that antibodies to SK can prevent successful dissolution of thrombi is currently not available in the literature, certainly not concerning thrombolytic therapy in acute myocardial infarction.

Most authors who reported measurements of anti-SK activity in blood or plasma have relied upon the streptokinase resistance test (SKRT) or some modification of it.<sup>6,7,12</sup> However, this functional assay of total SK inhibiting capacity is not specific for antibodies to SK, since it also measures other inhibitors, such as antiplasmin.<sup>7</sup> Moreover, the SKRT cannot be carried out in samples containing SK; therefore, studies on antibodies to SK during thrombolytic therapy have been impossible. Recently a sensitive radioimmunoassay has been described which does not have these disadvantages.<sup>13</sup>

We now present results obtained using this assay in a recent randomised comparative study on intravenously administered anisoylated plasminogen-streptokinase activator complex (APSAC; BRL 26921), a novel thrombolytic agent,<sup>14</sup> and intracoronary SK in acute myocardial infarction.<sup>15,16</sup> Overall, these drug regimens achieved comparable reperfusion rates (64% for APSAC and 68% for SK) and the aim of the present study was to investigate the significance of anti-SK antibodies in the clinical response (reperfusion and haemostatic changes). In addition, data are presented on the course of IgG anti-SK concentrations during the first 48 h after thrombolytic treatment with APSAC or SK. Thus, the study was intended to assess the effects of antibodies on short term events as reperfusion, reocclusion and haemostatic changes and the depletion of antibodies in response to drug, but not to examine the induction of an anamnestic response and other long term effects.

## PATIENTS AND METHODS

### Patients

The Dutch Invasive Reperfusion Study<sup>15</sup> is an open, randomised, multicentre trial comparing i.v. APSAC and i.c. SK in patients with acute myocardial infarction. Eighty five patients were recruited, but the present analysis is confined to 61 patients from whom sufficient plasma for measurement of SKRT and IgG anti-SK was available. These 61 patients were in no respect different from the entire study group. There were 50 male and 11 female patients with a mean age of 54.8 years (range 37-70 years). Thirty two of them were treated with APSAC and 29 with SK. Each patient had given his or her informed consent prior to entering the study, which had been approved by our ethical committee.

### Study Protocol

After angiographical demonstration of coronary

artery occlusion, the patients were randomised to thrombolytic treatment with either APSAC (30 U by a 5 min intravenous injection) or SK (250 000 U over 60 min by intracoronary infusion). Administration of the thrombolytic drugs was always started within 4 h (mean 2.3 h) from the onset of chest pain. Heparin was given, when necessary, as a catheter flush (5000 U i.v.) and then as a continuous i.v. infusion (1000 U/h), from about 4-24 h after initiating thrombolytic therapy.

Vascular patency was assessed by coronary angiography every 15 min for 1.5 h. All angiograms were read independently by two investigators in a 'blind' fashion and classified on a 4-class scale, according to the definitions used in the TIMI trial.<sup>17</sup> Reperfusion was assumed if at 1.5 h a sustained change from class 0 or 1 to class 2 or 3 had occurred. Reocclusion was assessed by coronary angiography at 24 h (range 18-30 h) after starting thrombolytic therapy.

## Methods

Blood for coagulation studies was collected before and 1.5, 12, 24 and 48 h after therapy.<sup>16</sup> In all patients pre-treatment plasma was used for measuring SKRT and IgG anti-SK; moreover, in 22 patients IgG anti-SK was determined also in post-treatment plasma samples. SKRT was performed as described by Deutsch and Fischer.<sup>7</sup> The assay of IgG anti-SK was carried out according to Moran et al.<sup>13</sup> Briefly, 25  $\mu$ l of appropriately diluted patient plasma was pipetted into the wells of a microtitre plate. Then 25  $\mu$ l of <sup>125</sup>I-labelled SK dilution (approximately 100 ng SK/ml) was added to each well and after 3 h incubation at ambient temperature, the IgG anti-SK/<sup>125</sup>I-SK immunocomplexes were precipitated by adding 50  $\mu$ l of a Protein A-Sepharose suspension (50 g/l) in buffer. The plate was continuously agitated for 1 h and centrifuged (10 min; 1000 rpm). The supernatant was removed and the precipitate washed 6 times. Finally, each well was cut loose from the plate and counted for radioactivity. The results were expressed in  $\mu$ g SK bound per ml plasma ( $\mu$ g/ml).

Inhibition of fibrinolytic activity *in vitro* in a model system was measured using a semi-purified IgG preparation. Sera containing high anti-SK binding levels were obtained from individuals previously treated with APSAC and IgG-enriched serum fractions were prepared by salt-fractionation. The fibrinolytic activity of a range of concentrations of SK and APSAC was measured by the fibrin plate assay using a range of anti-SK antibody concentrations. The inhibition (%) was calculated by measuring the amount of activator required to produce an equivalent lysis area in the presence of antibody as that produced in the absence. Thus, the inhibition by a range of antibody concentrations over a range of activator concentrations was quantified and a plot made of relative inhibition versus fold excess of antibody (that is, ratio of antibody to antigen).

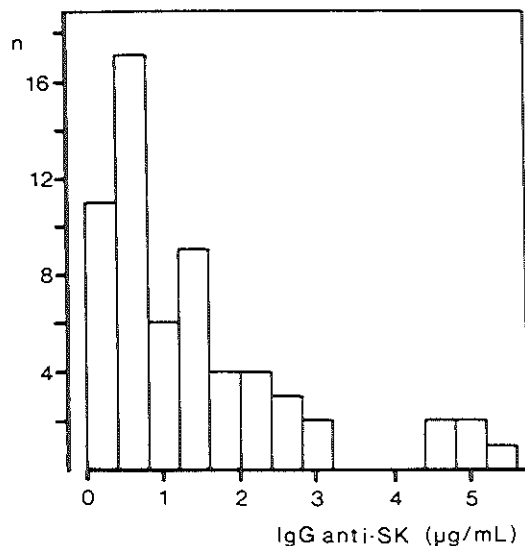


Fig. 1 Histogram of the distribution of IgG anti-SK concentrations in a population of patients with acute myocardial infarction (total  $n = 61$ ).

### Statistics

Standard methods were used for the statistical evaluation of the results, as indicated in the results section. In case of non-normal distributions, the data were transformed prior to testing. Significance was assumed at  $p$  values  $< 0.05$ .

## RESULTS

### Distribution of IgG Anti-SK in Patients

The distribution of pre-treatment IgG anti-SK concentrations in our population of patients with acute myocardial infarction is shown in Figure 1. The arithmetic mean was  $1.39 \mu\text{g/ml}$  and the geometric mean, after logarithmic transformation of the data,  $0.84 \mu\text{g/ml}$ . The tenth and ninetieth percentile values were  $0.21$  and  $2.67 \mu\text{g/ml}$ , respectively. There was no difference in IgG anti-SK between the patients who were treated with i.v. APSAC and i.c. SK ( $p > 0.5$ ; Student  $t$ -test).

The level of IgG anti-SK appeared to be dependent on age: younger patients had significantly higher levels than older ones ( $p < 0.02$ ; linear regression). The highest values of IgG anti-SK ( $4.7$ – $5.5 \mu\text{g/ml}$ ) were found in 5 patients whose mean age was only 44.4 years as compared to a mean age of 55.7 years in the other patients, whose IgG anti-SK concentration was below  $3.0 \mu\text{g/ml}$  ( $p < 0.005$ ; Student  $t$ -test). There was no sex-dependent difference apparent in our population.

The relation between IgG anti-SK and SKRT, both in pre-treatment plasma, is demonstrated in Figure 2. When calculated from log-log regression analysis, the coefficient of correlation was statistically significant ( $r = 0.43$ ;  $p < 0.001$ ; 95% confidence limits of  $r$ :  $0.18$ – $0.61$ ). However, a very wide scatter of data in individual patients was obvious.

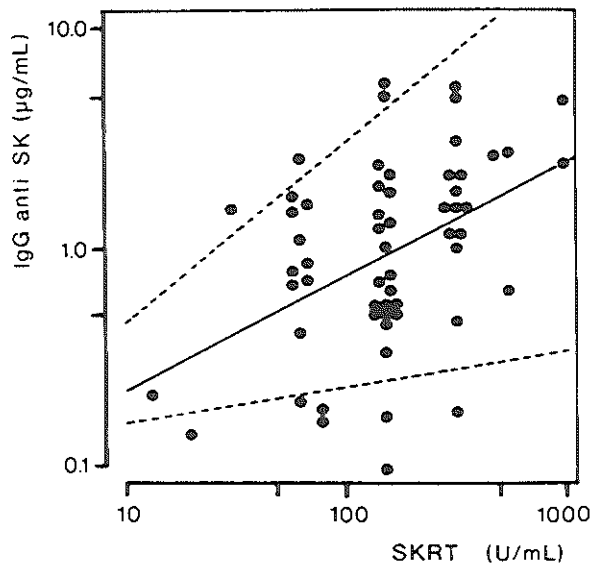


Fig. 2 Relationship between IgG anti-SK and SKRT in pre-treatment plasma. Correlation coefficient  $r = 0.43$  ( $p < 0.001$ ). Dotted lines represent 95% confidence interval of regression. Note logarithmic scale of both axes.

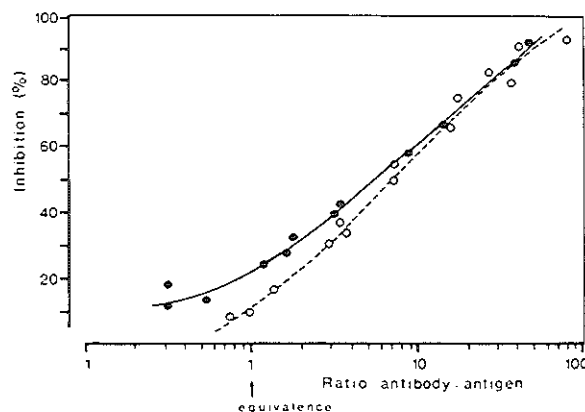


Fig. 3 Effect of IgG antibodies to SK on in vitro fibrinolytic activity of APSAC (○) and SK (●) in a fibrin plate assay.

### Inhibition of Fibrinolytic Activity in vitro

Results from the fibrin plate assay, comparing the inhibition of fibrinolytic activity of SK and APSAC by partially purified preparations of IgG anti-SK, are shown in Figure 3. At an antibody:antigen ratio of 1.0 (equivalence), SK was rather more inhibited than was APSAC. At excess antibody levels, the inhibition of SK and APSAC became similar, but for both agents a large excess of antibody was required to produce an appreciable inhibition of fibrinolytic activity in the fibrin plate.

### IgG Anti-SK and the Systemic Lytic State

Figure 4 shows the degree of systemic lysis, expressed as residual fibrinogen at 1.5 h, as a function of pre-treatment IgG anti-SK. In both groups the best fit of

correlation was described by a linear regression function. The coefficient of correlation was 0.51 ( $p < 0.005$ ; 95% confidence limits:  $0.19 < r < 0.73$ ) in the APSAC group (Fig 4A) and 0.67 ( $p < 0.001$ ; 95% confidence limits:  $0.41 < r < 0.83$ ) in the SK group (Fig. 4B), respectively. On the contrary, the relation between SKRT and residual fibrinogen was not significant, neither in the patients treated with i.v. APSAC ( $r = 0.10$ ; n.s.), nor in those treated with i.c. SK ( $r = 0.19$ ; n.s.).

The relationship between pre-treatment IgG anti-SK and euglobulin clot lysis time (ECLT) at 1.5 h after initiation of therapy, was also assessed. In both therapy regimens, the post-dosing ECLT became very short (10–20 min) in the majority of patients. More prolonged ECLT's were nearly exclusively found amongst those patients with a relatively high pre-treatment antibody level (Table), although of those 5 patients with the highest pre-treatment IgG anti-SK, only 2 patients (both receiving SK) demonstrated a substantially prolonged ECLT at 1.5 h.

### IgG Anti-SK and Reperfusion

The distribution of pre-treatment IgG anti-SK according to whether successful reperfusion was achieved or not, is shown in Figure 5. For both APSAC and SK there was no significant difference

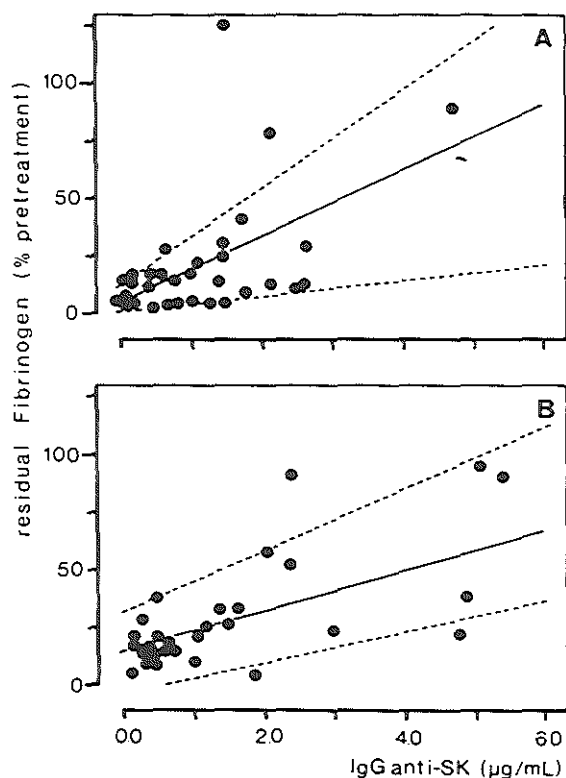


Fig. 4 Degree of systemic lysis, expressed as residual fibrinogen at 1.5 h after dosing, as a function of pre-treatment IgG anti-SK in patients treated with i.v. APSAC (A) or i.c. SK (B). Coefficients of correlation 0.51 (A) and 0.67 (B), respectively (both  $p < 0.005$ ). The 95% confidence limits are represented by dotted lines.

Table Euglobulin clot lysis time (ECLT) at 1.5 h in patients with low and high pre-treatment IgG anti-SK levels.

Treatment	n	Baseline IgG anti-SK ( $\mu\text{g/ml}$ )	ECLT (min) (mean $\pm$ SEM)	
i.v. APSAC	23	$\leq 2.0$	$10.4 \pm 0.4$	*
	5	$> 2.0$	$57.2 \pm 35.3$	
i.c. SK	20	$\leq 2.0$	$16.0 \pm 3.9$	**
	8	$> 2.0$	$82.5 \pm 32.2$	

\*  $P < 0.025$  and \*\*  $p < 0.005$  by Wilcoxon signed rank test

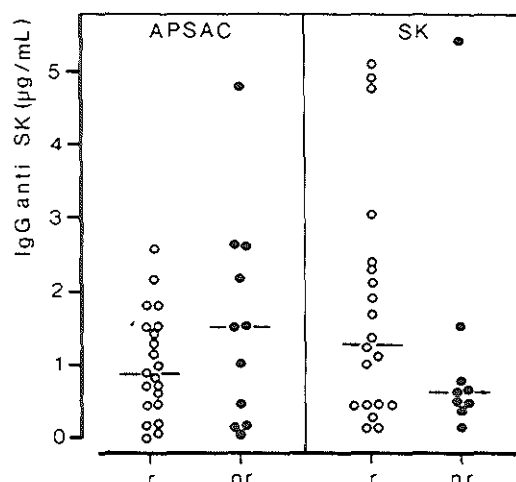


Fig. 5 Distribution of pre-treatment IgG anti-SK concentrations in both patients groups relative to reperfusion success: r = reperfused, nr = not reperfused at 1.5 h. Median values are indicated by horizontal lines.

(Mann-Whitney U-test) in pre-treatment IgG anti-SK between the groups of patients who reperfused and those who did not. Also, there was no statistically significant correlation between pre-treatment IgG anti-SK concentration and time to sustained reperfusion for those patients who reperfused within the 90 min study period:  $r = 0.20$  (n.s.; linear regression analysis) for APSAC and  $r = 0.17$  (n.s.) for SK. We also found no significant difference in reperfusion rate between patients with high and low SKRT, irrespective of the type of drug given (not shown).

In the entire group of patients studied, reocclusion of an initially reperfused coronary artery at 24 h was documented in only 4 cases: one patient had been treated with i.v. APSAC and 3 with i.c. SK. In 3 of these 4 patients plasma was available for measuring pre-treatment IgG anti-SK; the concentrations were  $1.54 \mu\text{g/mL}$  (APSAC) and  $1.10$  and  $1.39 \mu\text{g/mL}$  (SK) respectively. Adverse side-effects were mild and of low incidence: hypotension, vomiting and haematomas<sup>15</sup> and so it was impossible to investigate a relationship with anti-SK levels.

### IgG Anti-SK after Therapy

The course of IgG anti-SK during the first 2 days after



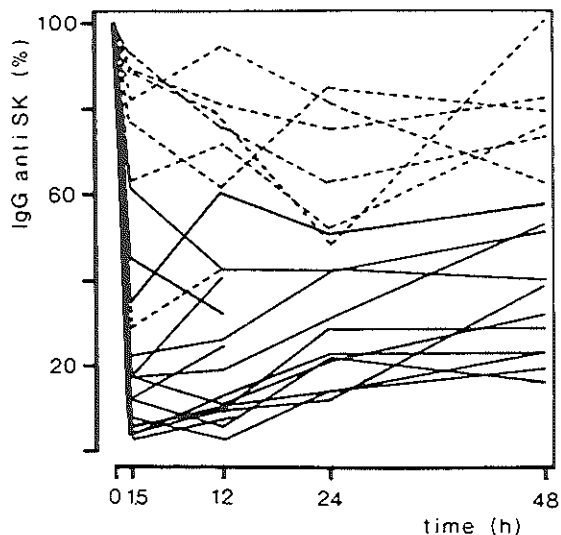


Fig. 6 Course of IgG anti-SK concentrations after thrombolytic therapy in patients with pre-treatment levels above (---) and below (—) 2.0 µg/ml. Differences between both groups were significant ( $p < 0.001$ ) at all post-treatment moments.

treatment was determined in 22 patients, 11 of whom had received APSAC and 11 SK. There was no difference between these two groups with respect to change in IgG anti-SK concentration: in all patients it decreased significantly ( $p < 0.001$ ; paired t-test) immediately after therapy, remained more or less constant up to 24 h and began to rise slowly on the second day. However, within both groups, two entirely different patterns emerged, when the proportional decrease in IgG anti-SK was calculated (Fig. 6): in 14 patients (8 APSAC, 6 SK) there was a considerable decrease to only 17% of baseline on the average, while in the remaining patients (3 APSAC, 5 SK) the mean residual IgG anti-SK concentration was still 70% of baseline. This significant difference was closely related to the patients' pre-treatment antibody level: the former pattern was confined to patients with IgG anti-SK concentrations  $< 2.0$  µg/ml, while 7 of the 8 patients exhibiting the latter pattern had IgG anti-SK levels above this value.

Upon plotting the post-treatment IgG anti-SK value as a function of the pre-treatment level, as shown in Figure 7, it became clear that up to a baseline level of approximately 1.0 µg/ml nearly all IgG anti-SK had disappeared after therapy, but in patients with initial concentrations above this value, the depletion in IgG anti-SK was independent of pre-treatment level and amounted to approximately 1.0 µg/ml. This was observed for the APSAC-treated patients as well as for those who had received i.c. SK (Fig. 7).

## DISCUSSION

High reperfusion rates can often be achieved with current regimens of thrombolytic agents, but reasons for failure in approximately 1 in 4 patients are not usually

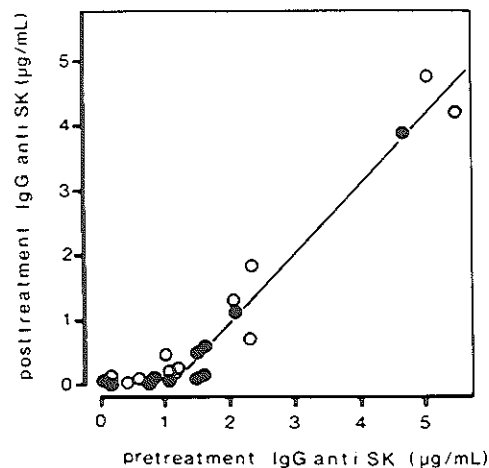


Fig. 7 Post-treatment IgG anti-SK as a function of pre-treatment concentration in patients treated with i.v. APSAC (O) or i.c. SK (●). Slope of regression line 1.03 and intercept on x-axis 1.06 µg/ml ( $r = 0.98$ ).

clear.<sup>1</sup> Resistance to lysis may be related to location, age and composition of the thrombus, but also, perhaps, to variations in the circulating level of substrate and inhibitors. One of the theoretical explanations for the failure of SK-containing thrombolytic drugs is the inactivation by antibodies to streptococcal proteins. Reports on the role of anti-SK in thrombolytic therapy are scarce and are predominantly confined to older studies in patients with deep venous thrombosis or thrombophlebitis, who were treated with intravenous SK.<sup>4,5,8</sup> Moreover, in the few patients with acute myocardial infarction described, the effect of anti-SK on systemic lysis rather than on reperfusion was reported.<sup>4</sup> It is highly questionable whether such results can be extrapolated to intracoronary SK therapy or to reperfusion in acute myocardial infarction. Only two recent reports on anti-SK in acute myocardial infarction thrombolysis are available. The study by Rothbard and colleagues, describing 15 patients receiving i.c. SK, showed no correlation between anti-SK, measured as SKRT, and presence of lytic state or between SKRT and reperfusion; however, the patient with the highest SKRT in their study did not show systemic lysis or reperfusion.<sup>11</sup> Lew et al described a single patient who failed to develop a systemic lytic state and did not reperfuse after high dose i.v. SK<sup>18</sup>; this patient had an extremely high anti-SK antibody titer, measured using a semiquantitative electrophoresis method. Thus, there is no convincing evidence that anti-SK antibodies can prevent coronary reperfusion within a normal population. In the present report we describe the relevance of antibodies to SK, measured using a new and specific assay for IgG anti-SK, in patients with acute myocardial infarction who were treated with intravenous APSAC or intracoronary SK. Only short term effects, e.g. on reperfusion success and the systemic lytic state, were examined in this study; we did not investigate the longer term effects such as the anamnestic rise in anti-

bodies<sup>6</sup> and the consequences thereof for possible re-treatment.

The distribution of IgG anti-SK concentrations in our patient population was most probably log-normal (Fig. 1), which is in agreement with that in healthy volunteers.<sup>13</sup> Since the distribution of SKRT is also known to be log-normal,<sup>8</sup> the statistical correlation of IgG anti-SK and SKRT is not surprising. However, the inconsistencies amongst individuals described by Moran et al.<sup>13</sup> were also present in our patients (Fig. 2) hence there is a poor association between SKRT and IgG anti-SK concentration for the individual patient.

The mean concentration of IgG anti-SK in our patients (1.4 µg/ml) is comparable with a mean of 0.9 µg/ml, found in a small group of patients in Scotland,<sup>19</sup> but much lower than in English volunteers, being approximately 3.3 µg/ml.<sup>13</sup> Similar geographical differences have been reported for SKRT and are postulated as resulting from differences in exposure to streptococcal infections.<sup>4,5</sup> The age-dependence in IgG anti-SK (higher levels in younger subjects) has not been reported previously, but might also account for the difference between the mean values in Dutch and Scottish patients compared to English volunteers. In the present study none of the 5 younger patients exhibiting higher levels had a history of recent infection, but 1 had been treated with intracoronary SK 2 years previously.

We evaluated the potential influence of IgG anti-SK in a model system *in vitro*. Although the fibrin plate method provides an insight into the effect of antibodies on fibrinolytic activity, it requires an incubation time of 24 h and it is possible that antibody exchange could occur, leading to overestimation of the inhibition. Our results *in vitro* suggest that for the antibody:antigen ratio expected in a normal population of patients receiving thrombolytic therapy for acute myocardial infarction, the inhibition of SK might be rather greater than that of APSAC, but for both drugs the net inhibition is small (Fig. 3). For example, for APSAC there might be 10% inhibition of the dose at an IgG anti-SK concentration of 3.3 µg/ml, i.e. above the ninetieth percentile in the current study. Although *in vitro* methods can only provide a partial estimate of what might happen *in vivo*, our use of a specific assay for IgG anti-SK allows a more precise prediction of the role of antibody in the response to SK-containing thrombolytic agents than has been possible previously.<sup>20</sup>

When the clinical response to *i.v.* APSAC and *i.c.* SK therapy was examined, there was a statistically significant relationship found between pre-treatment IgG anti-SK concentration and residual fibrinogen (at 1.5 h post-dosing) in both groups (Fig. 4). This is consistent with the correlations noted previously between SKRT and systemic lysis in patients receiving intravenous SK,<sup>4,5,8,20</sup> but not after intracoronary SK.<sup>11</sup> It is most likely that increasing levels of antibody bind and inactivate increasing proportions of the SK-containing plasminogen activators administered and

thus modulate the circulating fibrinolytic activity and the development of the systemic lytic state. These *in vivo* results are comparable with the *in vitro* results described above (Fig. 3) and those of Matsuo et al.<sup>21</sup>

It is also interesting to note the correlation between pre-treatment IgG anti-SK and post-dosing ECLT (Table). Since post-treatment ECLT is mainly determined by the residual levels of fibrinogen and plasminogen as well as by the circulating amount of plasminogen activator, where present, the relationship between IgG anti-SK and ECLT presumably reflects the same process as the correlation between IgG anti-SK and residual fibrinogen. However, it is also conceivable that because APSAC is cleared much slower from the circulation than SK-plasminogen, the contribution of APSAC to the ECLT at 1.5 h is still considerable and therefore that in the APSAC group the ECLT is less dependent on pre-treatment IgG anti-SK than in the SK group. In addition we feel that caution must be advised in interpreting this correlation because under the acidification conditions involved in measuring ECLT, we cannot exclude the possibility that not all complex is precipitated or the possibility that the complexes may dissociate.

With regard to thrombolytic efficacy, when the patients' response to APSAC and SK was examined there was found to be no significant correlation between pre-treatment anti-SK concentration and reperfusion success. Because patients with high IgG anti-SK levels were rare in our population, any possible effect of high antibody concentrations on reperfusion remains to be established using larger groups of patients.

In the patients in whom successful recanalisation was achieved there was no correlation found between pre-treatment IgG anti-SK level and time at which sustained reperfusion was achieved, neither for SK (mean interval 47 min), nor for APSAC (mean interval 45 min). Furthermore, we found no statistically significant correlation between residual fibrinogen at 1.5 h and time interval to sustained reperfusion. This finding contrasts with a recent study<sup>22</sup> using 750 000 U of SK *i.v.*, where both high residual fibrinogen concentration and delayed reperfusion were attributed to a high pre-treatment antibody level. The difference between our results and this conclusion<sup>22</sup> might be explained by an augmented delivery of the thrombolytic drug to the thrombus or to a suboptimal dose of SK used in the previous study. Furthermore, Lew et al employed only a semiquantitative estimate of anti-SK concentration and recognised reperfusion by non-angiographic criteria.<sup>22</sup>

The very small number of patients who reoccluded within 24 h does not permit any conclusions to be drawn. However, it would be improbable that IgG anti-SK would affect reocclusion; the 3 reoccluded patients had only averaged IgG anti-SK levels, even in comparison with those who reperfused successfully without reocclusion. Reocclusion beyond 24 h after dosing would be very unlikely, since there will be no

longer SK or APSAC in the circulation by that time, in view of the half-life of the drugs.

The course of IgG anti-SK after administration of the thrombolytic drug is compatible with binding of antibody to SK or APSAC and clearance of the complexes, as has been suggested by others.<sup>4,8,18</sup> Somewhat surprisingly, it was found that the clearance of antibody-SK and antibody-APSAC complexes apparently became saturated at approximately 1.0 µg/mL IgG anti-SK (Fig. 7) and thus gave rise to two different patterns of antibody depletion (Fig. 6), depending on the pre-treatment IgG anti-SK concentration. In theory, the dose of SK applied in the present study (250 000 U) should deplete IgG anti-SK by about 0.8 µg/ml, assuming a normal plasma volume.<sup>13</sup> Thus, in the SK-treated patients, the results are compatible with the theoretical calculation. On the contrary, the quantity of SK complexed in the dose of APSAC applied, would theoretically be expected to deplete IgG anti-SK by more than 3.0 µg/ml, since 30 U of APSAC is equivalent to approximately 1 million U of SK on a molecular basis. In fact, APSAC depleted IgG anti-SK to the same level as occurred in the SK group, thus to only 25% of the theoretical value. These data on decrease in IgG anti-SK after APSAC are similar to those from the only other report available on this subject.<sup>19</sup> In that study, 6 patients were treated with i.v. APSAC (30 U) and from the data an average depletion of IgG anti-SK of 0.80 µg/ml can be derived, similar to the mean in our APSAC group (0.90 ± 0.42 µg/ml). Only partial disappearance of IgG anti-SK after APSAC therapy might be explained by circulation of antigen-antibody complexes after dosing if the clearance process was saturated. However, we searched for such complexes in plasma taken 1.5 h after dosing, using an immunoblotting technique, but without success (R. Standring, unpublished result). The steric conformation of the APSAC molecule may also be important. For example the plasminogen moiety or the anisoyl-group might render the SK part less accessible for antibody binding than in the unmodified SK molecule.

In conclusion, although the degree of systemic lysis (residual fibrinogen) was shown to correlate with pre-treatment IgG anti-SK, most patients could still be defined as exhibiting a systemic lytic state after treatment with SK or APSAC. Whether or not APSAC is relatively protected from binding to and inhibition by IgG anti-SK, it is concluded from the present results that such antibodies, at least in the range studied here, have little effect on the reperfusion success in a normal population of patients with acute myocardial infarction who are treated with therapeutic doses of intravenous APSAC or intracoronary SK.

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# Effects of anistreplase on blood viscosity and platelet function in patients with acute myocardial infarction

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## Summary

The effect of thrombolysis on viscosity and platelet function *in vivo* is not exactly known. Reduction in viscosity could be beneficial in acute myocardial infarction by facilitating myocardial blood flow. Effect on platelet function could cause reocclusion or bleeding. The present study was performed in order to assess the effects of anistreplase (APSAC: anisoylated plasminogen streptokinase activator complex), 30 U intravenously, on these parameters in ten patients with acute myocardial infarction not receiving any anti-platelet drug therapy. We measured platelet aggregation, plasma and blood viscosity and cardiac output.

There was a rapid and significant decrease of 13 percent in plasma viscosity at 90 minutes, parallel to a 97 percent decrease in fibrinogen. Blood viscosity at high and low shear rates was significantly decreased, reaching the lowest value after 24 hours, due to the reduction in plasma viscosity and haematocrit. Platelet aggregation rapidly decreased within 30 minutes and fully recovered after 24 hours in most patients; it showed hyper-aggregation at 48 hours, which disappeared after one week. No correlation was found between cardiac output and blood viscosity (high and low shear rate), plasma viscosity, or fibrinogen concentration. Whether there would be a beneficial effect from reduced viscosity due to thrombolytic therapy during acute myocardial infarction needs further investigation.

**Keywords:** thrombolytic therapy – blood viscosity – platelet function – platelet aggregation – acute myocardial infarction

## Introduction

In the last decade several clinical trials have clearly demonstrated that early administration of a thrombolytic agent to patients with acute myocardial infarction significantly reduces mortality and morbidity.<sup>1-7</sup> The reduction in mortality is similar for several thrombolytic agents used, such as streptokinase anisoylated plasminogen streptokinase activator complex (anistreplase) and tissue-type plasminogen activator (alteplase).

Anistreplase is a combination of streptokinase and plasminogen with an anisoyl group reversibly placed within the catalytic centre of the plasminogen moiety. In the circulation anistreplase is de-acylated at a controlled rate. This produced a more sustained fibrinolytic activity compared to streptokinase, which might be an advantage with respect to reocclusion rates. It can be given as an intravenous injection over 4 to 5 minutes.

The lack of success of thrombolytic therapy in a considerable percentage of acute myocardial infarction patients indicates that the underlying mechanisms responsible for recanalization, preservation of left ventricular function and improved survival are still not clearly understood. Factors such as early and late reocclusion,

platelet activation and effect on blood flow still require further research.

In this pilot study some of these factors were addressed in more detail, namely: the effect of anistreplase on blood and plasma viscosity, platelet function and any possible influence on the cardiac output during administration of this drug to patients with acute myocardial infarction.

## Patients and methods

### Patients

Between April and December 1990 ten patients with an acute first myocardial infarction, who were not receiving any antiplatelet drugs such as aspirin or dipyridamol, were treated with anistreplase (table 1).

### Methods

After establishing the diagnosis of acute myocardial infarction by the usual inclusion and exclusion criteria and excluding the use of aspirin or other anti-platelet drugs for ten days before admission, anistreplase (30 U.) was slowly given intravenously over five minutes. The lytic thera-

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Table 1

Patients characteristics		
<i>patients</i>		
sex (male/female)	9/1	
age (yrs) mean ± SD	60.0 ± 6.4	(range 50-68)
weight (kg)	74.4 ± 10.5	(range 53.0-84.3)
height (m)	1.75 ± 0.04	(range 1.70-1.78)
history of AMI	none	
location of infarction anterior/inferior	1/9	
<i>infarct-related vessel</i>		
RCA	8	
RDA	1	
CX	1	
time chest pain to alteplase (hrs)	2:23 ± 1:03	(range 1:10 - 4:15)
days in hospital	13.8 ± 5.2	(range 8 - 24)

py was started within four hours after onset of symptoms. Patency of the infarct related coronary artery was assessed by angiography after 60, 75 and 90 minutes and again after 48 hours; left ventriculography was also performed after 60, 90 minutes and 48 hours.

Cardiac output was measured by thermol dilution technique after 90 minutes and 48 hours. Intravenous heparin was started three hours after the administration of anistreplase. The dosage was adjusted according to the activated partial thromboplastin time (target value: 2-3 time baseline). Blood was collected before administering anistreplase and at regular intervals over the next two days, for laboratory examination through a venous catheter or by venepuncture. An additional sample was taken after 7-9 days, prior to discharge from hospital. Blood and plasma viscosity were determined at low (1,3 s<sup>-1</sup>) shear rate (representing small venules) and high (128,5 s<sup>-1</sup>) shear rate (representing arteries and large veins). Shear rate can be

Fig. 1. Mean blood viscosity, measured at both high (128.5 S<sup>-1</sup>) and low (1.3 S<sup>-1</sup>) shear rates and corrected for hematocrit, at critical time points. The differences with pretreatment are indicated by an asterisk (\* P < 0.05; n=8-10).

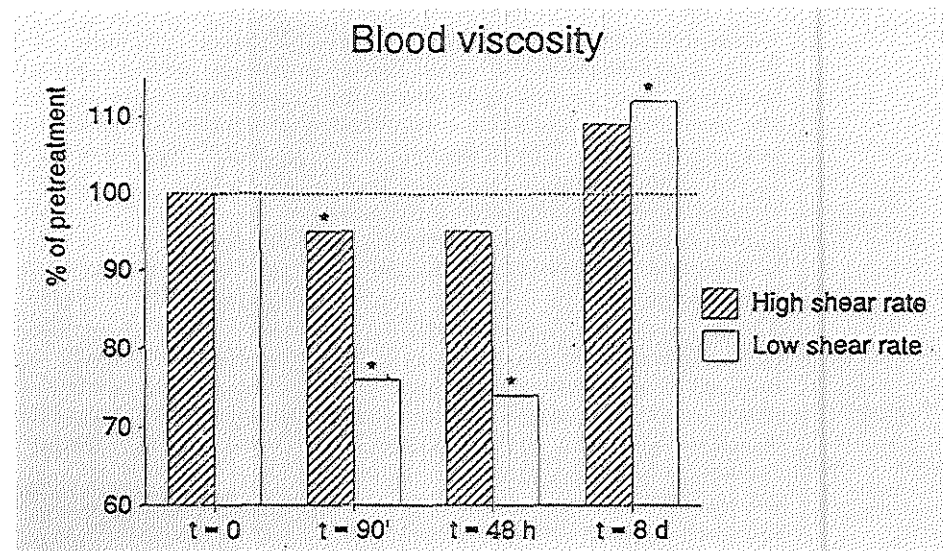


Table 2

Angiographic characteristics				
<i>TIMI grading</i>	60 min.	75 min.*	90 min.*	48 hrs*
0 (no perfusion)	2	-	-	-
1 (penetration)	-	-	-	-
2 (partial perfusion)	1	2	-	-
3 (normal perfusion)	7	7	9	9
<i>diameter of stenosis</i>				
< 50%	1	1	1	-
50-70%	-	-	-	4
70-90%	3	4	4	3
90-100%	5	3	3	2
filled collateral	1	1	1	-

\* One patient excluded after 60 min. because of PTCA.

defined as the velocity gradient over fluid.<sup>8</sup> Platelet aggregation in platelet rich plasma was measured in an optical aggregometer using ADP as inducer.

Statistical analysis

Statistical evaluation of the data was performed using paired and unpaired Student's t-test, considering p values <0,05 as significant. For measurements of a normal distribution, mean ± SD is given and in case of abnormal distribution, median and range, unless stated otherwise.

Results

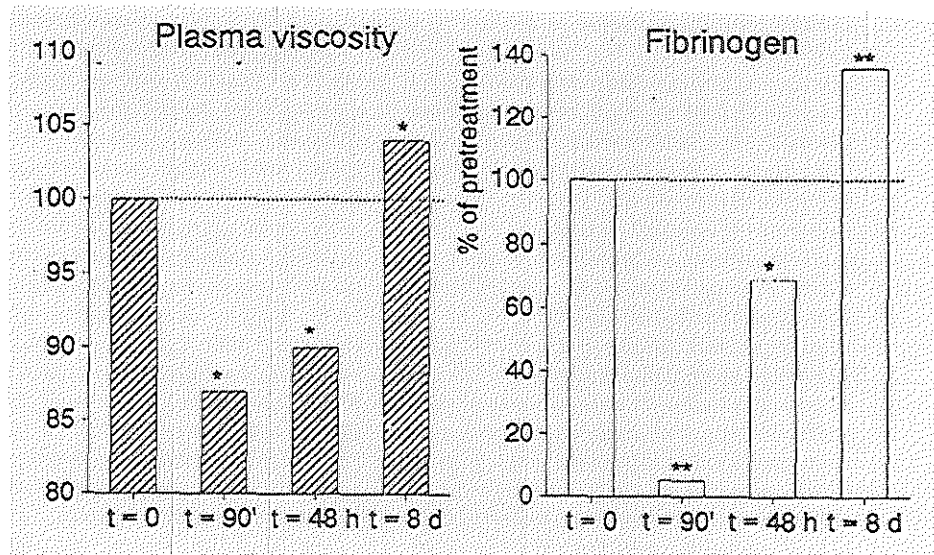
Infarct characteristics

The angiographic results are shown in table 2. Protocol violation occurred in one patient, in whom PTCA was performed after 60 minutes. It is interesting to note that in this small series all patients had reperfusion, while none had reocclusion, within 48 hours.

Viscosity

Fig. 1 gives a graphic representation of the values found for blood viscosity at high

Fig. 2. Course of mean plasma viscosity and plasma fibrinogen, relative to pretreatment values (\*  $P < 0.05$  and \*\*  $P < 0.01$ ;  $n=6-10$ ).



and low shear rates, with correction for the hematocrit which showed no difference. This correction had to be done because hematocrit is the most important factor influencing blood viscosity especially under low shear conditions occurring in partially or completely occluded vessels during acute myocardial infarction.

Fig. 2 shows plasma viscosity and fibrinogen values. There was a rapid and significant decrease in plasma viscosity during the first 48 hours, associated with a marked decrease in fibrinogen concentration. After eight days viscosity in blood, plasma and fibrinogen levels were within normal range.

#### Platelet aggregation

Fig. 3 shows effects on ADP-induced platelet aggregation. A biphasic response in ex vivo platelet aggregation was observed after anistreplase. After an immediate inhibition for 6-12 hours, full recovery of the platelet aggregation was attained within 24 hours. Then a phase of hyper-aggregation became apparent, lasting for at least

24-48 hours after the administration of anistreplase. This effect disappeared after one week.

#### Cardiac output

Table 3 shows cardiac output after 90 minutes and 48 hours. There was no relation between cardiac output and either blood viscosity (high shear rate), blood viscosity (low shear rate), plasma viscosity or fibrinogen concentration (Pearson's correlation coefficient  $r < 0.51$ ).

#### Discussion

Several large-scale clinical trials have demonstrated that all thrombolytic agents administered to patients with acute myo-

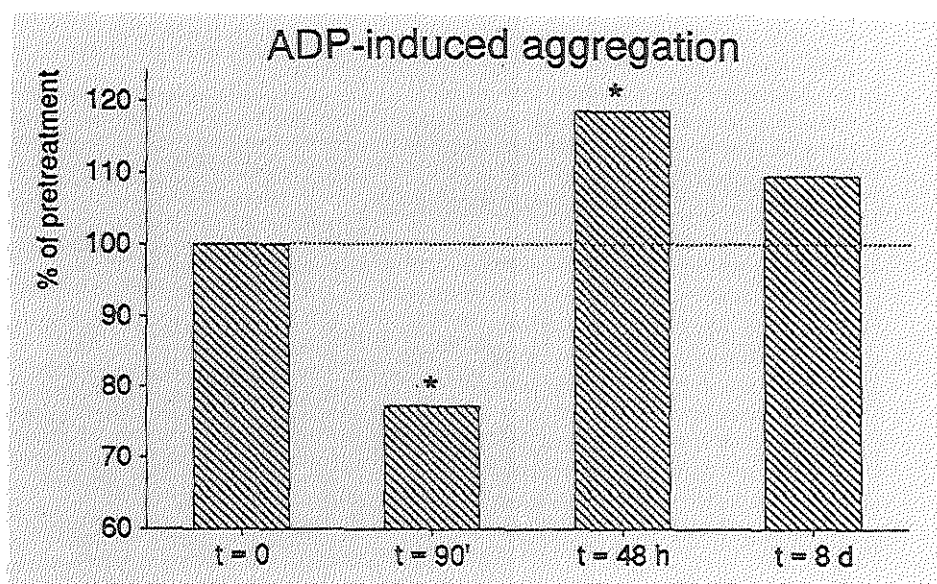
Table 3

#### Cardiac output

Cardiac output (l/min):

	mean $\pm$ SD range
90 min.	6.49 $\pm$ 2.04 (4.1 - 10.2)
48 hrs	4.91 $\pm$ 1.16 (3.5 - 6.0)

Fig. 3. Mean platelet aggregation, induced with 2.4  $\mu$ M ADP at different times. Difference with pretreatment is indicated (\*  $P < 0.05$ ;  $n=6-10$ ).



cardial infarction reduce mortality and morbidity.<sup>1-7</sup>

There are still possible mechanisms for improved survival that have not been studied. We examined three factors which may improve survival: namely the effect of anistreplase on blood viscosity, platelet function and cardiac output.

The importance of blood and plasma viscosity in acute myocardial infarction was first described by Chmiel et al. in 1973:<sup>9</sup> after their publication a few authors focused solely on the role of viscosity.<sup>10, 12</sup> Jan et al. concluded in a well documented study on blood viscosity in patients with acute myocardial infarction who received no thrombolytic therapy, that the increased viscosity at the onset was mainly due to high hematocrit, and the subsequent increase in viscosity, which peaked at about the fourth day, resulted from elevation of plasma fibrinogen. This impaired the rheological properties of blood, especially in the coronary microcirculation distal to the occluded vessel. Because oxygen supply to myocardial tissue is greatly dependent on this blood rheology, at least a part of the myocardial damage can be attributed to increased viscosity.<sup>13</sup>

In our study we investigated the role of anistreplase in patients receiving this drug during their acute myocardial infarction. These patients had a significantly decreased blood and plasma viscosity, as well as fibrinogen levels, which may be responsible for a reduced myocardial workload and oxygen consumption.

Moriarty et al. studied patients with acute myocardial infarction receiving streptokinase, and found similar findings to ours for anistreplase, although he did not know if this contributed to preservation of myocardial function and improved survival.<sup>14</sup> GISSI-2,<sup>6</sup> ISIS-3<sup>7</sup> and the Bassand study<sup>15</sup> show no difference between the effects of streptokinase, anistreplase and alteplase on mortality. As we know, alteplase does not influence viscosity and has only a very small effect on fibrinogen levels; it also gives a higher initial patency and a higher reocclusion rate. Therefore the net effect on mortality is probably the same for the three thrombolytic agents. A possible benefit of lowering viscosity therefore requires further investigation.

Since the research by De Wood et al. the role of thrombus formation in the pathogenesis of acute myocardial infarction is well established.<sup>16</sup> We use agents which induce lysis of fibrin in thrombus but the role of platelets in this process has not been thoroughly investigated. Some studies however demonstrated platelet aggregation in patients with unstable angina pectoris and evolving myocardial infarction.<sup>17-21</sup>

The available literature on the effects of

thrombolytic therapy on platelet function yields highly conflicting data.<sup>3, 22-27</sup> In our study we found a biphasic response in *ex vivo* platelet aggregation, an immediate inhibition lasting about 6-12 hours, followed by a phase of hyper-aggregation during day 1 and 2 after thrombolysis. This hyper-aggregation may play a role in a higher reocclusion rate of the infarct related vessel. As known from the literature, PTCA during acute myocardial infarction has a higher reocclusion rate compared to this procedure in stable angina pectoris. This may be the explanation of this phenomenon.<sup>28</sup> Our hypothesis that there is a correlation between viscosity and cardiac output (measured at 90 minutes and after 48 hours, because we expected on theoretical grounds the largest difference) was not confirmed. Although it seems that cardiac output after 90 minutes was higher than after 48 hours, the difference was not statistically significant, probably because of the small number of patients.

The beneficial effect of reduced viscosity during acute myocardial infarction still requires further investigation. Additional research is also needed to establish the role of platelets in patients treated with the thrombolytic agent anistreplase.

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## HEMORHEOLOGICAL EFFECTS OF A NONIONIC CONTRAST MEDIUM: AN EX VIVO STUDY

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### ABSTRACT

Blood and plasma viscosity were measured in 10 patients, before and after administration of the nonionic contrast medium Iopromide for coronary angiography. In all patients the hematocrit dropped markedly; the mean ( $\pm$ SD) value decreased from  $0.425 \pm 0.036$  to  $0.386 \pm 0.037$  ( $p < 0.001$ ). The mean blood viscosity also decreased significantly, in a dose-dependent way; this effect could be entirely explained by the change in hematocrit. Plasma viscosity remained constant despite the high viscosity of the contrast medium. The drop in hematocrit was caused by the volume of the contrast medium plus a shift of water from extravascular spaces to plasma, due to the high osmolarity of the contrast agent. The contrast medium studied is unlikely to cause clinically relevant late effects on blood rheology other than hemodilution.

### INTRODUCTION

Intravascular radiodiagnostic procedures are associated with the administration of sometimes considerable volumes of contrast media (CM) to patients. CM are iodinated derivatives of benzoic acid which are used in highly viscous, hyperosmolar solutions (1,2). With regard to its chemical nature, a CM can be either an ionic or a nonionic molecule. Most ionic CM are extremely hyperosmolar, while the nonionic CM have a much lower osmolarity, but still higher than plasma. All CM are known to cause adverse reactions, which are partially related to their osmolarity and thus the nonionic CM generally display less toxic side-effects than ionic agents do (1,2).

One of the adverse reactions of CM is their ability to induce red cell aggregation, at least *in vitro* and again nonionic CM appear to have the milder effects (2-5). The *in vivo* significance of red cell aggregation due to CM is supposed to be limited or even absent, because the red cells would be rapidly disaggregated under the shear conditions in blood, flowing in the

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**KEY WORDS:** Blood viscosity - contrast agents - hematocrit - hemorheology - Iopromide - plasma viscosity

vessels (4,5). To our best knowledge there are no published data supporting this assumption.

Another effect of CM, also at least *in vitro*, is due to their high osmolality; they cause a pronounced shift of water from the red cells to plasma, which leads to a decrease in hematocrit, a decrease in mean red cell volume and a decline in red cell fluidity by stiffening of the red cell membranes (6). All these factors contribute to whole blood viscosity but their net effect on blood viscosity *in vivo* is entirely unpredictable, because some of these factors are highly variable or even impossible to measure (6).

Since there are very few reports concerning the effects of CM on *ex vivo* hemorheology, we designed a study for documenting the rheological effects of Iopromide, a nonionic CM, in patients receiving a relatively large dose of CM during diagnostic coronary angiography.

## PATIENTS AND METHODS

### **Patients**

We studied 10 patients, 1 female and 9 males, with a mean age of 54.7 y (range 30-75 y), who underwent coronary angiography for angina pectoris or coronary artery disease. Just before angiography, blood was collected for measuring baseline rheological parameters. During the procedure, the cardiologist determined the amount of CM necessary for each individual patient. The CM used was the nonionic, low osmolar Iopromide (Ultravist-300<sup>®</sup>; Schering AG, Berlin, FRG). The mean duration of the angiographic procedure was 31.7 min (range 20-65 min) and immediately after completion, another blood sample was taken from all patients.

### **Methods**

Blood for rheology measurements was collected into evacuated, siliconized glass tubes containing liquid K<sub>3</sub>-EDTA (final concentration 1.5 mg/mL; 4.00 mL blood to 0.045 mL of anticoagulant, a dilution by 1.1%; Monoject<sup>®</sup>, Sherwood, Ireland). Rheological testing was always performed within 1 hour from venepuncture; meanwhile the samples were kept at ambient temperature (19-22 °C). All viscosity determinations were carried out at 37.0 °C in a Couette-type rotational viscosimeter (Contraves LS-30; Contraves AG, Zürich, Switzerland), according to the ICSH recommendations (7), at two different shear rates: 1.3 s<sup>-1</sup> (low) and 128.5 s<sup>-1</sup> (high), respectively. Standardized blood viscosity, corrected to an hematocrit of 0.45, was calculated using the formula described by Matrai *et al* (8). Hematocrit was measured in an automated impedance-type cell counter (Model S+; Coulter Inc., Hialeah, Fl., USA), which was calibrated with fresh blood from normal subjects against the microhematocrit reference method. Total protein and albumin concentrations in plasma were determined using standard biochemical methods (biuret and bromocresol green, respectively).

Statistical evaluation was done using the two-sided paired t-test or Spearman's rank correlation test, regarding p values < 0.05 as significant.

## RESULTS

The mean volume of CM administered to our patients was 152 mL, ranging between 110 and 260 mL. The osmolality of Iopromide was 616 ± 8 mmol/kg (mean ± SD; n = 3) and its viscosity at 37 °C was 4.94 ± 0.09 mPa.s (n = 4).

Before angiography, the rheological parameters of all 10 patients were within the reference ranges ruling in our laboratory. In all patients the hematocrit decreased significantly after angiography (Table I), as did the native blood viscosity, measured at low and high shear rates. The decrease in high-shear blood viscosity was significantly correlated with the dose of CM administered (r = 0.86; p < 0.01 by Spearman's rank test). The relationship between low-shear blood viscosity or hematocrit and the CM dose did not reach statistical significance. The viscosity of plasma did not change and neither did the calculated standardized (i.e. corrected to

hematocrit 0.45) blood viscosity. The concentrations of total protein and albumin in plasma decreased by approximately 12% of the baseline value, which was highly significant (Table I).

When CM was added to whole blood *in vitro*, there was a gradual, small but significant increase in high shear blood viscosity (from 0 to 5% v/v CM: 4.36 to 4.51 mPa.s at 128.5 s<sup>-1</sup>; p=0.01), and a decrease in low-shear blood viscosity (mean 17.7 to 14.2 mPa.s at 1.3 s<sup>-1</sup> from 0 to 5% CM). The mean hematocrit dropped slightly, but the decrease did not reach statistical significance if corrected for the dilution with CM (results not shown). As expected, the viscosity of plasma, to which 5% (v/v) of CM had been added, significantly increased from 1.40 ± 0.03 to 1.51 ± 0.01 mPa.s (p < 0.01).

TABLE I  
Rheological Parameters before and after Angiography with CM.  
Mean ± SD is given; n=10

parameter	baseline	after CM	p
hematocrit (L/L)	0.425 ± 0.036	0.386 ± 0.037	< 0.001
plasma viscosity (mPa.s)	1.37 ± 0.11	1.35 ± 0.21	NS*
plasma total protein (g/L)	72.6 ± 3.0	64.3 ± 3.9	< 0.001
plasma albumin (g/L)	45.7 ± 3.6	40.8 ± 3.8	< 0.001
<b>at high shear rate (128.5 s<sup>-1</sup>)</b>			
native blood viscosity (mPa.s)	4.50 ± 0.44	3.89 ± 0.38	0.03
standardized blood viscosity (mPa.s)	4.83 ± 0.22	4.67 ± 0.46	NS
<b>at low shear rate (1.3 s<sup>-1</sup>)</b>			
native blood viscosity (mPa.s)	15.2 ± 3.7	10.9 ± 1.9	< 0.001
standardized blood viscosity (mPa.s)	17.3 ± 3.0	15.7 ± 2.9	NS

\*NS : not significant

## DISCUSSION

Despite the notion that intravascular CM may influence blood rheology because all CM are highly viscous solutions, surprisingly few literature has been published on this subject. The available studies almost exclusively focused on the *in vitro* effects of ionic and nonionic CM on red cell morphology and red cell aggregation (2-6). Some authors believe that the aggregation phenomenon is unimportant for the *in vivo* situation (4) and that it is unlikely to pose any threat to the patient (5). However, evidence for this from clinical studies is lacking and yet such studies are necessary because it is impossible to estimate the effects of CM on blood rheology by simple *in vitro* experiments.

The results from the present study indicate that the fall in native blood viscosity after CM administration depends largely if not entirely upon the decrease in hematocrit. After correction to a standard hematocrit of 0.45, the change in blood viscosity, both at low and at high shear rate, was very small and of no statistical significance (Table I). Indirectly, this means that red cell aggregation by CM is unlikely to be of clinical relevance, at least some time after CM administration (4,5). A similar decrease in blood viscosity has been described by Acciavatti *et al.*, who observed a small lowering of blood viscosity, only at high shear (150 s<sup>-1</sup>), after giving 100 mL of the nonionic CM Iopamidol to patients (9). These authors were unable to make any hypothesis on a possible effect of CM on red blood cells. Acute effects of CM on red cell rheology were not investigated in this study and neither in the present one. This leaves the possibility that CM can affect red cell rheology immediately after injection; probably, such effects would be rapidly reversible.

The lack of a significant change in plasma viscosity after 30 min is in agreement with a previous study in which 80 mL of the ionic and high-osmolar CM diatrizoate was given without

any effect on serum viscosity (10). Apparently this can be explained by a balance between increase in plasma viscosity due to the CM's own viscosity (see *in vitro* results) and a concomitant decrease in viscosity as a consequence of hemodilution (see below).

The above results all indicate that the hematocrit is the parameter of central importance in this study. The change in hematocrit must have been caused by at least two factors: the volume of CM and the osmolarity of CM. If only the volume of CM administered (mean 152 mL) was of influence, a 3% decrease in hematocrit would have been expected in the average patient with an estimated blood volume of 5.0 L (2.1 L red cells plus 2.9 L plasma). From the total protein and albumin concentrations in plasma before and after CM, it can easily be inferred that the mean plasma volume increased with about 350 mL (or 12%), which is far more than the volume of CM used. This difference is explained by a shift of extravascular water to the plasma space in order to compensate for the much higher osmotic pressure of CM as compared with plasma osmolarity. A similar phenomenon has been described *in vitro*, where the water shifted from the red cells to plasma (6). In our study we unfortunately did not record red cell volumes and therefore we cannot give an opinion on a possible loss of water from red blood cells *in vivo*. However, if such a loss would have been present, it was of very limited size (about 2% of red cell volume), since there was hardly any difference between the mean hematocrit observed after CM (0.386; see Table I) and the value expected on the basis of the decrease in plasma protein concentrations (0.397, on the average). Anyhow, the shift of water from red cells to plasma *in vivo* was considerably smaller than found *in vitro* (6); of course in the latter case there was no other source of water available for compensating the high osmotic pressure induced by CM.

Some limitations of our study have to be mentioned. Because there were no blood samples taken immediately after giving the CM, conclusions regarding any acute effects on blood rheology are not justified. Such acute effects might be expected in view of the very high local concentrations of CM, close to the site of injection. Further, we had no opportunity to directly measure parameters of red cell aggregation or fluidity and our conclusions based on indirect measures need to be interpreted with some caution.

In conclusion, it has been shown that all hemorheological changes observed about 30 min after the administration of the nonionic CM Iopromide, can be explained by hemodilution due to the high osmolarity and the volume of the CM. It is unlikely that by this time other effects of CM on blood rheology are of clinical importance.

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## Value of immediate angioplasty after intravenous streptokinase in acute myocardial infarction

To improve reperfusion, immediate percutaneous transluminal coronary angioplasty (PTCA) was considered after intravenous streptokinase (0.75 to 1.5 million U) was administered to 98 patients with acute myocardial infarction less than 4 hours after the onset of chest pain. Thirty-four culprit arteries were occluded (group A); 42 arteries were patent with residual stenosis of more than 70% (group B). Twenty-two patients had residual stenosis of less than 70% (group C); eight of these had severe disease of the remaining vessels. Group C patients were either treated conservatively or underwent bypass surgery. Immediate PTCA was attempted in 74 patients (32 in group A, 42 in group B) and was successful in 68 (92%). Emergency bypass surgery for acute occlusion after PTCA was required in two patients. Follow-up averaged 23 months (range, 16 to 47 months). Asymptomatic occlusion recurred in three patients. Restenosis occurred in five patients: four had early restenosis (one in group A, three in group B) and one had late restenosis (group B). These arteries were successfully redilated. Late reinfarction occurred in two patients. They were treated with intravenous urokinase and repeat PTCA. Elective bypass surgery was performed in three patients because of recurrent angina. They had severe three-vessel disease as revealed by control angiography. The mortality rate was 2.7% (two patients; one in group B had early reinfarction, and one patient in group A died suddenly after 17 months). Eighty-five percent of patients treated with PTCA alone remain free of symptoms. This approach has a high success rate and low morbidity and mortality rates. Long-term results are superior to thrombolysis alone. (*AM HEART J* 1990;119:786.)

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It is now well established that the earlier thrombolytic therapy is given in patients with acute myocardial infarction (AMI), the more myocardial tissue and function can be preserved.<sup>1-10</sup> Intravenous streptokinase (SK) is widely accepted as a rapid, convenient, and easy means of administration. Thrombolytic therapy, however, is not always effective or successful in restoring blood flow.<sup>11, 12</sup> A significant residual stenosis usually remains at the site of initial occlusion after successful thrombolysis.<sup>13</sup> This can result in an unfavorable clinical course with recurrent ischemic events or myocardial infarction.<sup>14-16</sup> Percutaneous transluminal coronary angioplasty (PTCA) has been used to open occluded coronary arteries, to

restore blood flow when thrombolytic therapy fails, and to dilate vessels with severe residual stenosis after thrombolytic therapy.<sup>14-17</sup> Combined thrombolytic therapy and PTCA could be very effective in achieving optimal perfusion; however, the procedure is longer and the risk of acute occlusion after angioplasty is higher than when PTCA is used for stable angina. We report our early and late results of the combined use of intravenous SK and PTCA.

### METHODS

The study population consisted of 98 patients who were admitted to the coronary care unit of the Catharina Hospital within 4 hours after the onset of symptoms of AMI. Diagnosis was based on acute typical chest pain that lasted for more than 30 minutes and was unrelieved by sublingual nitroglycerin and persistent ST segment elevation of more than 2 mm in two or more leads. Exclusion criteria included cardiogenic shock (defined as sustained systolic pressure of 90 mm Hg or less that lasted for 1 hour or more), recent SK therapy, previous coronary artery bypass surgery, bleeding diathesis, recent surgery, recent cerebrovascular accident,

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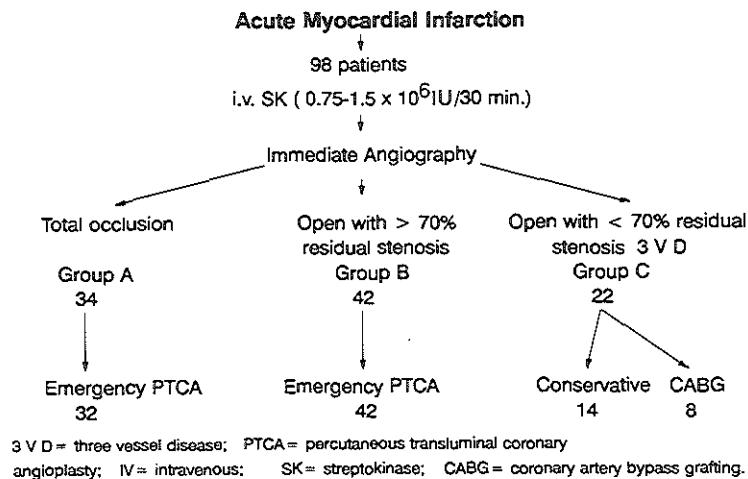


Fig. 1. Treatment regimen.

recent prolonged cardiopulmonary resuscitation, age greater than 75 years, significant hepatic disease, and pregnancy.

**Treatment regimen** (Fig. 1). After informed consent was obtained, patients received intravenous nitroglycerin (0.3 to 5.0 mg/hr). They were then given premedication that consisted of 12 mg dexamethasone, and after this 0.75 to 1.5 million units SK was infused intravenously over 30 minutes. Meanwhile, arrangements were made to transport each patient to the catheterization laboratory for emergency angiography. After placement of vascular sheaths, 5,000 U heparin was administered. A pacing catheter was positioned in the right ventricle. Selective arteriography of the infarct-related artery was performed in multiple views, followed by visualization of the other coronary artery. Bi-plane left ventriculography was performed in the 30-degree right anterior oblique and 60-degree left anterior oblique projections. Global and regional left ventricular performance was analyzed with a VAX computer (Digital Equipment Corp., Maynard, Mass.). Patients with complete occlusion of the infarct-related artery were considered for emergency mechanical reperfusion and angioplasty. Patients with 70% or more residual stenosis were also considered for immediate PTCA.

**Definitions.** The determination of the patency of the infarct-related artery was made according to the classification of the Thrombolysis in Myocardial Infarction (TIMI) trial.<sup>18</sup> As defined by the TIMI study group, TIMI grade 0 = "no perfusion" with no antegrade flow beyond the point of occlusion; TIMI grade 1 = "penetration without perfusion," contrast fails to opacify the coronary bed distal to the obstruction; TIMI grade 2 = "partial perfusion," contrast filling or clearance is delayed but there is complete opacification of the distal coronary bed; and TIMI grade 3 = "complete perfusion," showing a normal pattern of contrast filling clearance. Vessels that show TIMI grade 0 or grade 1 flow were considered to be occluded. Angiographic exclusion criteria for PTCA were defined as left

main stem stenosis, less than 70% stenosis of a single vessel, severe disease of the remaining vessels ( $\geq 70\%$  stenosis), and distal coronary occlusive lesions unsuitable or not amenable for PTCA.

## RESULTS

The baseline characteristics of the 98 study patients are listed in Table I. They were divided into three groups according to the degree of stenosis of the infarct-related coronary artery after the administration of intravenous streptokinase: group A (34 patients) had totally occluded infarct-related vessels, group B (42 patients) had patent infarct-related vessels with residual stenosis of more than 70%, and group C included patients with residual stenosis of less than 70% with TIMI grade 3 flow, of whom eight had severe disease of the remaining vessels. The median age was 54 years, and 78.5% of the patients were men. The median time from onset of pain to administration of SK was 2.1 hours, whereas the median time from onset of pain to PTCA was 2.8 hours. The angiographic data of patients are shown in Table II. Eighty-three percent of the patients had one-vessel disease; 5% had two-vessel disease; 10% had three-vessel disease. In 2% of the patient population it was not possible to define the site of the lesion in the culprit artery. Patients in group C were either treated conservatively (14 patients) or underwent coronary artery bypass grafting (eight patients). Thirty two patients in group A and 42 patients in group B underwent immediate coronary angioplasty (total = 74 patients).

The results of coronary angioplasty are summarized in Table III. Angioplasty was attempted immediately after intravenous infusion of SK and angiog-

**Table I.** Patient characteristics

	Group A	Group B	Group C
No. of patients	34	42	22
Mean age (yr)	54.7	53.5	56.1
Range (yr)	(34-72)	(40-72)	(25-76)
Sex ratio (M:F)	26:8	34:8	17:5
Previous MI	2	4	1
Congestive heart failure	0	0	0
Obstruction of IRA after SK (%)	100	> 70-99	< 70 + 3 VD
Time from onset of pain to SK (hr)	2.37 (1.1-4.3)	2.11 (1.0-3.3)	1.96 (1.3-3.3)
Time from onset of pain to PTCA (hr)	2.91 (2.2-5.6)	2.78 (2.1-5.3)	—

SK, Streptokinase; PTCA, percutaneous transluminal coronary angioplasty; 3 VD, three-vessel disease; MI, myocardial infarction; IRA, infarct-related artery.

**Table II.** Angiographic data

	Group A	Group B	Group C	Total
Infarct location				
Anterior	16	19	9	44
Inferior	18	23	13	54
Infarct-related artery				
LAD	16	19	9	44
LC	6	2	4	12
RCA	12	21	9	42
Extent of coronary disease				
None	0	0	2	2
One-vessel	31	39	11	81
Two-vessel	2	2	1	5
Three-vessel	1	1	8	10
LVEDP (mm Hg)	18.2	15.6	16.1	
Range	(8-24)	(5-30)	(4-25)	
LV Ejection fraction (%)	54.8	56.2	56.9	
Range	(37-69)	(49-63)	(51-62)	

LAD, Left anterior descending; LC, left circumflex artery; RCA, right coronary artery; LV, left ventricular; EDP, end-diastolic pressure.

raphy in 74 patients in groups A and B. PTCA was successful in 68 patients (92%). PTCA was attempted in 32 of the 34 group A patients and was successful in 28 (87.5%). Inability to cross the occlusion (three patients) or a guiding problem (one patient) were the causes of failure. PTCA was not performed in two patients because the sites of occlusion were considered unsuitable. PTCA was attempted in all patients in group B (42) but was successful in 40 (95%).

**Complications during PTCA.** Acute reocclusion occurred in two patients (group B); they underwent emergency bypass surgery. Two patients had ven-

tricular tachycardia and fibrillation; both were successfully defibrillated. One patient had transient atrial fibrillation. Another patient had severe transient hypotension that responded to inotropic therapy. The early and late follow-ups of both groups are shown in Table IV. One patient died 5 days after the procedure because of reinfarction and sustained ventricular tachycardia followed by asystole. Four patients (three in group B, one in group A) had recurrent angina. They were found to have restenosis and underwent successful repeat PTCA. Coronary angiography was repeated before discharge in all patients in whom initial PTCA was successful (68). Asymptomatic reocclusion was found in two patients (group B).

**Long-term follow-up.** All patients were seen at the outpatient clinic regularly for 16 to 47 months (mean = 23 months). They were evaluated clinically and by routine exercise testing on a bicycle ergometer. Thirty-seven symptom-free patients consented to have routine repeat angiography after 6 months. Thirty-six were found to have patent vessels with residual stenosis (<50%); one had total occlusion with collaterals (group A). Recurrent angina due to restenosis occurred in one patient (group A). The vessel was successfully redilated. Three patients (two in group A, one in group B), in whom angina developed, had restenosis of the infarct-related vessel but were found to have severe three-vessel disease and underwent elective coronary bypass surgery. One patient (group A) died suddenly after 17 months. Fourteen patients (group C) made uneventful recoveries and are free of symptoms at follow-up. An invasive regimen to maintain myocardial perfusion during hospitalization was also followed after discharge. Patients who had late infarction with reocclusion of the infarct-related artery were treated with thrombolytic agents followed by PTCA. Patients with angina and severe three-vessel disease underwent coronary artery bypass surgery. With the application of this policy, 63 out of 74 patients (85%) who underwent PTCA after thrombolysis remained improved (Canadian Cardiovascular Society classes I and II) during follow-up.

## DISCUSSION

Limitation of myocardial infarct size by salvaging ischemic myocardial tissue in the area that undergoes necrosis is the most important aim in the management of patients with acute myocardial infarction in order to preserve cardiac function and improve prognosis. Intravenous SK has been approved as a standard treatment for AMI because of the ease and rapidity of administration<sup>19, 20</sup> and its efficacy in reducing mortality.<sup>21</sup> However, regardless of the route

of administration, recanalization may not occur. In addition, SK has no effect on an underlying severely stenotic lesion. The presence of severe residual stenosis increases the incidence of reinfarction and/or postinfarction angina.<sup>13, 22-25</sup> In our patient series, a patent infarct-related vessel after administration of intravenous SK was present in 64 patients (65%); this is similar to the outcome of other studies.<sup>26-29</sup> Thus many of these patients achieved early reperfusion, most probably as a result of the thrombolytic agent, but, as expected, most of the recanalized infarct-related arteries had high-grade residual stenosis (77.5%). PTCA was successful in 68 of the 74 patients (92%) in whom it was attempted. The success rate was high both in patients with totally occluded arteries (87.5%) and in those with significant residual stenosis (95.2%). The presence of a systemic lytic state did not adversely affect the outcome of PTCA, as other studies have also shown.<sup>14, 15</sup>

The present study shows that a therapeutic intervention for the treatment of AMI that combines administration of intravenous SK and emergency angioplasty is effective in achieving a high level (85%) of early and sustained coronary perfusion. Patients who were treated with this regimen had a very low rate of cardiac complications (including death) at both short-term and long-term follow-up. The effectiveness of a combined medical and mechanical recanalization in increasing coronary reperfusion and in improving left ventricular function has already been reported.<sup>29-31</sup> In a recently published study of 342 patients with AMI, who were treated with the same regimen as in our study, Stack et al.<sup>30</sup> reported a significant number of interventional complications and an 11% in-hospital mortality rate. The better results obtained in our study group are due to the following differences. First, we excluded from our series patients in cardiogenic shock. Second, the mean interval between onset of pain and performance of PTCA in our series was  $\leq 3$  hours in contrast to 4.5 hours in the other series. Conceivably, as a result of a shorter ischemic time, the mean global left ventricular ejection fraction of our patients was 10% higher than in the patients reported on by Stack et al.<sup>30</sup> It has been demonstrated that the duration of ischemia before reperfusion is achieved is of paramount importance in the determination of myocardial salvage and in the clinical outcome of patients with AMI.<sup>5, 19, 25</sup> In spite of the encouraging results achieved with a combination of thrombolysis and PTCA, the role and timing of angioplasty in the management of AMI is still a matter of controversy. A recent study<sup>32</sup> that compared immediate angioplasty with delayed elective angioplasty showed no advantages of immediate angioplasty. However,

Table III. Results of PTCA

	Group A	Group B
Successful PTCA	28/32 (87.5%)	40/42 (95.2%)
Severity of stenosis in initial CAG (mean) (%)	100	95
Stenosis after PTCA (mean) (%)	40	30

PTCA, Percutaneous transluminal coronary angioplasty; CAG, coronary arteriography.

Table IV. Early and late outcome in the PTCA patients groups

Outcome	Group A (N = 32)		Group B (N = 42)	
	Early	Late	Early	Late
Death	—	1	1	—
Emergency CABG	—	—	2	—
Elective CABG	—	2	—	1
Asymptomatic reocclusion	—	1	2	—
Late MI (reocclusion)	—	1	—	1
Restenosis requiring emergency PTCA	1	1	3	—

PTCA, Percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; MI, myocardial infarction.

among the patients who were selected for elective angioplasty (7 days), 18% had recurrent ischemia (most of which occurred within 24 hours of admission) that required crossover to urgent PTCA, and the global ejection fraction was significantly improved in the immediate PTCA group.

These findings indicate that after successful intravenous thrombolysis, careful monitoring of patients is mandatory for consideration of angioplasty if ischemia recurs. In another recently published multicenter study,<sup>33</sup> the authors recommended that immediate coronary angioplasty after thrombolysis should not be performed as a routine procedure in all cases, and they claimed that this had no additional benefit over thrombolysis alone. However, it should be noted that the combination of recombinant tissue plasminogen activator and coronary angioplasty was not addressed in this study. This combination may be the cause of the high acute and early reocclusion rate, which may differ from treatment with SK followed by PTCA, because of the long-acting systemic effect of SK.

**Limitation of the study.** The number of patients in our study was small, and there was no control group. However, the data from this study compare favorably

with the results from recently published randomized trials.<sup>14-17,30</sup> Furthermore, the good long-term prognosis in our series could be related to the large number of patients with one-vessel disease rather than to early and maintained perfusion of the culprit vessel.

**Conclusions and recommendations.** This study has shown that early administration of intravenous SK in AMI followed by emergency angioplasty is feasible and safe. This strategy is associated with a high reperfusion rate, a low mortality rate, and low recurrence of cardiac events at both short-term and long-term follow-up. Early reperfusion is the main goal in treating patients with evolving myocardial infarction. An intravenous thrombolytic agent should be administered as soon as possible, preferably before hospitalization. Careful monitoring for ischemia is also required. Angiography can be postponed only when clinical signs of reperfusion have appeared, such as sudden relief of chest pain and normalization of the ST segment. Further studies should be directed to identification of patients at high risk of re-occlusion after successful thrombolysis so that timely angiography and subsequent angioplasty or coronary bypass surgery can be performed.

The authors express their appreciation to Mrs. G. Odenthal and Mrs. M. v.d. Broek for their secretarial assistance.

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# Long-term follow-up of 100 patients with left anterior descending artery lesions treated with percutaneous transluminal coronary angioplasty

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**KEY WORDS:** Percutaneous transluminal coronary angioplasty, long-term follow-up, left anterior descending artery.

*In order to analyse late outcome, we reviewed the data on the first 100 patients who underwent percutaneous transluminal coronary angioplasty (PTCA) of the left anterior descending artery (LAD) in our institution. Their ages ranged between 40.0 and 82.3 years (mean 66.6, males 75%, females 25%). All patients were treated with the non-steerable system between September 1980 and February 1983, and followed up for 6.2–9.6 years (mean 8.5 years).*

*The primary success rate was 73%. We were unable to cross the lesion in 19%, and 8% of the patients required emergency bypass surgery because of acute occlusion or dissection. Elective bypass surgery was required in 18% of the patients. The clinical restenosis rate was 22%. Risk factors in this patient group were: smoking 66%; hypertension 37%; elevated serum cholesterol 32% and diabetes mellitus in 7%. After an initially successful PTCA, 12 out of 73 patients required a second PTCA of the same vessel because of restenosis and three, PTCA of a new lesion in another vessel because of recurrence of angina. Fifty-four patients were asymptomatic during the follow-up period of 8.5 years. Ninety-four of the 100 patients are still alive.*

*Canadian Heart Association anginal classification of the study group was: class 0: 80 patients; class I: 11 patients; class II: three patients; class III and IV: no patient. Six patients died, there were four non-cardiac deaths because of cancer; one patient died 24 h after a myocardial infarction as a result of cardiogenic shock and ventricular septal rupture and one died suddenly 6 years after the initial PTCA.*

*Thus, PTCA of the LAD is a safe procedure with excellent long-term results during an average 8.5 years' follow-up. More than half of the patients are totally asymptomatic after the initial PTCA.*

## Introduction

The clinical value and use of PTCA<sup>[1]</sup> is judged by its long-term effect on symptoms, the need for medication, return to work and the cost of medical care. In this article we will review the clinical outcome of our initial experience with percutaneous transluminal coronary angioplasty (PTCA) of the left anterior descending artery (LAD) in order to evaluate its long-term benefit. We will compare our results with those of the National Heart, Lung and Blood Institute PTCA Registry and the first 169 patients who underwent PTCA by Andreas Gruntzig<sup>[2]</sup> in Zurich between 1977 and 1980.

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## Methods

### PATIENT POPULATION

The first 100 patients (75 men and 25 women) aged 40.0–82.3 years, (mean 66.6 years) with a stenosis in the LAD anatomically suitable for PTCA participated in this evaluation. All patients had angina pectoris Canadian Heart Association class III or IV in spite of adequate medical therapy.

### DILATATION EQUIPMENT

The guiding catheter used in this initial patient group was a 9-F left Judkins polyurethane catheter made by Schneider Medintag, Zurich, or a 9-F El Gamal catheter when the orifice of the left main coronary artery was high and the left Judkins did not provide adequate engagement.

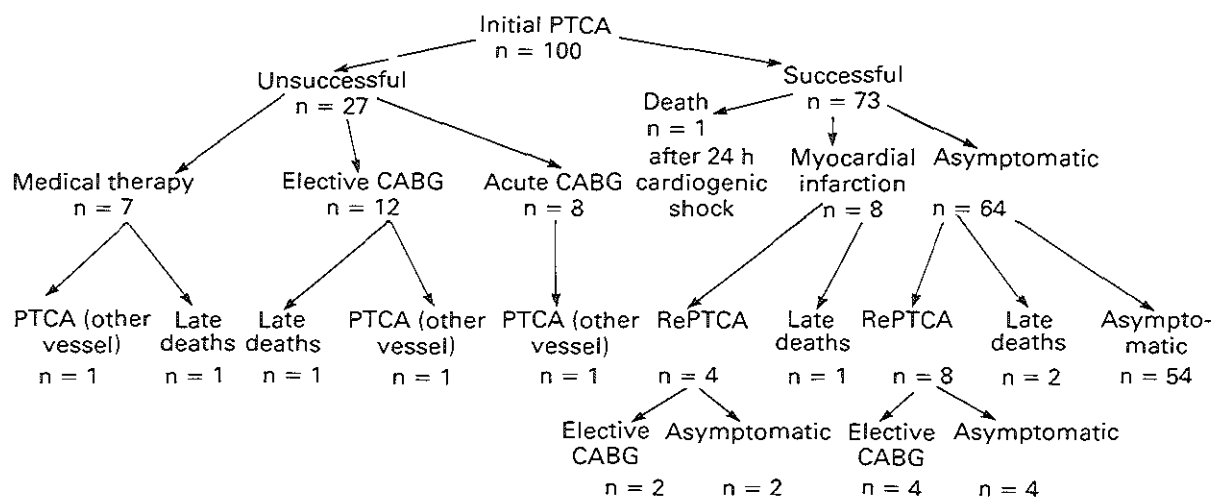


Figure 1 Follow-up data in 100 patients who underwent PTCA of the LAD. CABG: coronary artery bypass grafting.

The balloon dilatation catheter used in this study was the Gruntzig DG and DJ Schneider, Zurich. Neither are steerable, that is, the dilatation catheters did not allow directional control. Only shaping the short wire at the tip of the balloon and turning it facilitated entry into the vessel and across the stenosis. The diameters used were 2.0, 3.0 or 3.7 mm. A Myler temporary pacemaker catheter was positioned in the pulmonary artery in all patients.

#### MEDICATION

All patients routinely received 10 000 U heparin during the procedure, as well as calcium-channel blockers, nitrates and dextran. After the procedure aspirin or coumarin, dipyridamole and calcium-channel blockers were given for 6 months.

#### RISK FACTORS

66% of all patients were smokers; 37% had systemic hypertension; 37% had elevated serum cholesterol and 7% suffered from diabetes mellitus.

#### Results

The acute results and follow-up data of our first 100 patients, who underwent PTCA of the LAD between September 1980 and February 1983, are shown in Fig. 1. Early and late mortality are summarized in Table 1. PTCA was successful in 73 patients and failed in 27 patients. After an initial successful PTCA, one patient died after 24 h in cardiogenic shock after ventricular septal rupture. He had undergone PTCA during evolving acute

Table 1 Mortality after PTCA

#### A Cardiovascular

1 patient 24 h after PTCA during acute myocardial infarction with ventricular septal rupture  
1 patient suddenly after 6.2 years, at home

#### B Non-cardiovascular

1 kidney tumour after 5.9 years  
1 carcinoma of the stomach after 3.2 years  
1 carcinoma of the rectum after 7.4 years  
1 carcinoma of the pancreas after 2.1 years

myocardial infarction. Eight patients had a myocardial infarction after apparently successful PTCA (cardiac enzymes were elevated at least twice the normal value). Three of these patients remained asymptomatic; four patients underwent repeat PTCA within 6 months because of restenosis. Subsequently, two remained asymptomatic and two underwent CABG. There was one late death, after 3.2 years, from carcinoma of the stomach.

In the 64 patients initially asymptomatic after PTCA, restenosis occurred in eight within 2.3–5.2 months (mean 4.5 months), who underwent a second PTCA. Subsequently four of these patients underwent elective CABG because of recurrence of angina but four remained asymptomatic. There were two late deaths, one patient died suddenly at home after 6.2 years and one died of a kidney tumour after 5.9 years. Fifty-four out of the 64 patients initially asymptomatic remained asymptomatic and required no further treatment during long-term follow-up.



Of the 27 patients in whom PTCA was initially unsuccessful, seven were treated conservatively. At follow-up a single patient later underwent successful PTCA of the circumflex artery, and there was one late mortality, after 2.1 years, as a result of carcinoma of the pancreas. Twelve patients underwent elective CABG. A single patient had successful PTCA of the right coronary artery after 5.2 years and another died of carcinoma of the rectum after 7.4 years. Eight patients underwent emergency CABG because of acute occlusion or dissection of the vessel during PTCA. Four developed acute myocardial infarction with moderate elevation of cardiac enzymes while four patients did not develop peroperative myocardial infarction. Subsequently a single patient had successful PTCA of the right coronary artery after 4.7 years. Ninety-two per cent of all patients had repeat coronary angiography at 6 months. All patients underwent exercise stress testing on a bicycle ergometer and were re-evaluated between November 1988 and February 1989. The follow-up period ranged from 6.2 to 9.6 years (mean 8.5 years). Sixteen patients had mild disease in another vessel that did not require intervention at the time of the initial PTCA. Ninety-four patients are alive after a mean follow-up of 8.5 years. Eighty patients are in Canadian Heart Association anginal class 0, 11 patients in class I, and three in class II. There are no patients in class III or IV.

### Discussion

Though our cohort is relatively small, the results of our first 100 patients who underwent PTCA of the LAD with the non-steerable system demonstrate the safety of the procedure. The six late deaths were unrelated. The long-term follow-up is excellent even though 26 patients underwent coronary artery bypass grafting, eight acute and 18 elective. Eighty patients remain asymptomatic, in 54 cases, after initial PTCA alone.

In comparison with the initial 169 patients reported by Gruntzig<sup>[2]</sup>, in whom other vessels as well as the LAD were dilated, 83 out of the 133

patients with successful PTCA were in functional class 0, and no patients were in class III or IV after 1 year.

The PTCA Registry<sup>[3]</sup> has reported similar figures, as has the group from the Mayo Clinic<sup>[4]</sup>. Restenosis occurred in 22% in our series, while Gruntzig reported 31% and the PTCA Registry 33.6%. However, in the PTCA Registry 72% of the initially successful patients remained improved after 4 years and did not require further interventions. The annual mortality rate in their patients with PTCA and single-vessel disease was less than 1% per annum.

### Conclusions

Although patients who had PTCA required many interventions during the first 6 months, such as re-PTCA because of restenosis and coronary artery bypass grafting, subsequent interventions and clinical events were rare. Interventions were considered safe since there was no mortality. Thus the long-term outcome after PTCA is excellent in patients with left anterior descending artery stenosis. More than 50% of the patients remained totally asymptomatic after the initial PTCA, after a mean follow-up of 8.5 years.

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# Initial and long-term results of coronary angioplasty and coronary bypass surgery in patients 75 years or older

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## ABSTRACT

**Objective** – To evaluate the clinical outcome after percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) in patients 75 years or older who underwent either procedure between 1980 – 1987 in our institution.

**Patients and methods** – Ninety three patients, between 75–89 years, suffering from angina pectoris, all in class III or IV C.C.S., out of whom 79 patients (85%) had three vessel disease underwent PTCA, while 81 patients 75 – 89 years, all in class III or IV C.C.S., out of whom 62 patients (77%) had three vessel disease, underwent CABG. Follow-up: after PTCA 8.2 years, after CABG 8.3 years.

**Results** – Primary success rate in 93 PTCA patients was 84% (78 patients). In 72% of patients only one vessel was dilated in spite of the fact that three vessel disease was present.

There were 4 major cardiac events: 2 emergency bypass operations and 2 deaths. Other complications were: myocardial infarction in 3 patients and CVA in 1 patient. It was impossible to dilate the lesion in seven patients (5 underwent elective CABG, 2 were treated conservatively). Median hospital stay was 4.3 days. In 81 CABG patients 53 (63%) made an uneventful recovery.

Death occurred in 6 patients; 24 patients developed other complications: CVA in 2 patients, myocardial infarction in 8 patients, 10 patients needed a re-thoracotomy and 4 patients required prolonged ventilation because of adult respiratory distress syndrome. Median hospital stay was 14.2 days.

During follow-up after PTCA there were 8 deaths. Three patients suffered a non-fatal myocardial infarction, two patients required elective CABG and 10 patients underwent repeat PTCA because of recurrence of severe angina. Four patients had recurrence of mild angina medically treated. Sixty-four patients were free of angina without any complications (69%). During

follow-up after CABG, there were 8 deaths. One developed a non-fatal myocardial infarction; 6 patients required PTCA and 3 had recurrence of mild angina during follow-up received medical treatment. Thus 57 patients were free of angina without other complications (70%). Actuarial survival after PTCA was 92% after 10 years and 91% after CABG (excluding four deaths after emergency CABG for complications of coronary angiography).

**Conclusions** – PTCA is a safe procedure in elderly patients.

Dilatation of the culprit lesion relieves symptoms. The complication rate is lower and the hospital stay is significantly shorter when compared to CABG ( $p < 0.05$ ). Long-term follow-up did not show a significant difference between PTCA and CABG. Therefore PTCA is preferable in patients 75 years or older, when the culprit lesion is suitable for PTCA.

## INTRODUCTION

The population is ageing and the percentage and number of patients 75 years or older is increasing. In this patient population a conservative medical management is often chosen for those suffering from ischemic heart disease. However when symptoms are not adequately relieved, the options for revascularization should be considered. A number of reports have documented the efficacy of PTCA in elderly people [1–18], but also CABG can be performed in this group with increasing safety [18–28]. In this observational study we report our experience between 1980 and 1987 in patients 75 years or older, who underwent PTCA or CABG.

## PATIENTS AND METHODS

Between September 1980 and December 1987, 3142 patients underwent PTCA in our institution. Ninety three patients were 75 years or older (3%). In the same period 3657 patients underwent CABG, of whom 81 patients (2%) were 75 years or older.

Follow-up was available up to June 1991 for all patients. Information was obtained from the referring physician, from the patients at out-patient visits, or by telephone.

\* Submitted for publication.

## PROCEDURE

PTCA was performed via the femoral artery in 98% of the cases. In the majority (72%) an "over the wire" balloon system was used. Angioplasty was considered successful, when the stenosis was reduced to less than fifty percent of the luminal diameter, without major complications (myocardial infarction, cerebrovascular accident, emergency coronary artery bypass surgery or death). Ten thousand units of heparin were given at the onset of the procedure and 5000 units at the end. Aspirin, 250 mg intravenously, was given after the procedure, if the patient was not already receiving the drug before PTCA. In addition during a six month period after PTCA 300 mg dipyridamole per day and 80 mg Aspirin were prescribed. Up to 1985 a calcium entry blocker was also prescribed. Complete revascularization was not necessarily the goal in these elderly patients undergoing PTCA. In CABG patients, however, complete revascularization was performed if possible. Cardiopulmonary bypass with moderate hypothermia and crystalloid cardioplegia was used. Postoperatively all patients received Aspirin 300 mg daily or coumadin up till 1984, combined with 300 mg dipyridamole a day for at least one year. After 1984 the combination of 80 mg Aspirin combined with 300 mg dipyridamole daily was prescribed routinely to all patients.

## STATISTICAL ANALYSIS

Continuous variables are expressed as median  $\pm$  standard deviations. Student's t-tests were performed to determine whether there was a significant difference between mean values.

## RESULTS

The age range for PTCA patients was 75 – 89 years (median 80), for CABG patients 75 – 84 years (median 77) (table 1). Fifty eight percent (54 patients) in the PTCA group were males, and 66% (53 patients) in the group that underwent CABG. There were no differences in smoking habits, hypertension, diabetes, anginal classification, prior myocardial infarction or prior CABG. There was also no difference in severity of coronary artery disease: 85% of the PTCA patients had three vessel disease while 77% of the CABG patients had three vessel disease. No difference was found in left ventricular ejection fraction, angiographically determined, in both groups. There were only a few patients with very poor left ventricular function in either group. In total 122 vessels were dilated in the PTCA group (table 2): left anterior descending artery or a graft to the left anterior descending artery in 66 patients (54%), left circumflex coronary artery in 24 patients (20%), right coronary artery in 22 patients (18%), diagonal branch in 7 patients (6%). An unprotected left mainstem was dilated in 3 patients (2%). These 3 patients had class IV angina and were not suitable candidates for CABG. One vessel was dilated in 67 patients (72%), two vessels in 23 patients (25%) and three vessels in 3 patients (3%). In the CABG group 3 patients (4%) had a single distal anastomosis; 15 patients (19%) had two distal anastomoses; 12 patients

Table 1.

Clinical profile of 174 patients, 75 years of age and older undergoing coronary angioplasty or coronary artery bypass graft surgery.

	PTCA (n=93)	CABG (n=81)
Male	54	53
Female	39	28
Mean age	80	77
Smoking history,		
former	17	14
current	37	31
Hypertension	47	40
Diabetes	5	3
Anginal class (CCS)		
0	—	—
I	—	—
II	0	2
III	43	37
IV	50	42
Prior MI	36	30
Prior CABG	9	13
Diseased vessels		
1	4	3
2	10	16
3	79	62
LVEF		
> 45%	69	62
25–45%	22	18
< 25%	2	1

Abbreviations:

PTCA= percutaneous transluminal coronary angioplasty  
 CABG= coronary artery bypass grafting  
 LVEF= left ventricular ejection fraction  
 MI = myocardial infarction;  
 n = number of patients  
 n.s = not significant

Table 2.

Extent of procedure in ninety three patients undergoing percutaneous transluminal coronary angioplasty and eighty one patients undergoing coronary artery bypass grafting.

	PTCA (n=93)	CABG (n=81)
one vessel/distal anastomosis	67 (72%)	3 (4%)
two vessels/distal anastomoses	23 (25%)	15 (19%)
three vessels/distal anastomoses	3 (3%)	12 (15%)
four or more distal anastomoses	—	51 (62%)

Abbreviations:

As in Table 1.

(15%) had three distal anastomoses and 51 patients (62%) 4 distal anastomoses or more (table 2). Complete revascularisation was performed more frequently in the surgical patients as compared to PTCA patients in whom in the majority of cases only the culprit lesion was dilated.

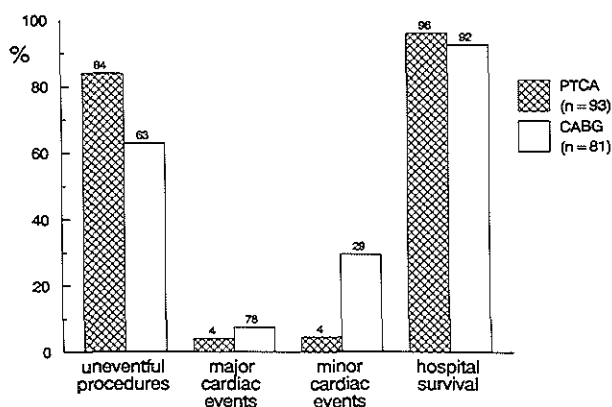
Median follow-up after PTCA was 8.2 years, range 3.5 – 10.9 years and after CABG 8.3 years, range 3.5 – 11.2 years.

## PERIPROCEDURAL RESULTS

PTCA was successful in 78 out of 93 patients (84%). In 7 patients it was impossible to cross the lesion: 5 patients underwent CABG on an elective basis and 2 were treated conservatively.

There were four major complications: two deaths and two emergency CABG. One patient underwent PTCA during cardiogenic shock after an acute myocardial infarction. The stenosis was adequately dilated, but the patient died within 24 hours from progressive shock. The second patient developed dissection of the left main coronary artery, induced by the guiding catheter and died during the procedure. CABG was uncomplicated without myocardial infarction in the 2 emergency procedures. In addition there were 4 other complications: one patient had a cerebrovascular accident, but recovered without residual symptoms and three patients suffered a myocardial infarction in the first 24 hours after PTCA. Hospital survival for the whole PTCA group was 96% (91 patients). The median hospital stay was 4.3 days (2–15 days).

CABG was uneventful in 53 out of 81 patients (63%). There were 6 deaths, all procedure related. Four died during emergency surgery from evolving myocardial infarction as a result of complications during coronary angiography elsewhere. Two other patients sustained a myocardial infarction during the operation and died on the second and third day after the procedure respectively. In addition 24 patients developed non-fatal complications within 30 days including two cerebrovascular accidents, which recovered uneventfully. Eight patients had an uncomplicated myocardial infarction, ten patients required re-thoracotomy because of excessive bleeding and 4 patients required prolonged ventilation (more than 3 days) because of adult respiratory distress syndrome. Hospital survival was 92% (75 patients). The median hospital stay was 14.2 days (8–53 days). Figure 1 shows an overview of the initial results of PTCA and CABG.



**Fig. 1** Initial results of percutaneous transluminal coronary angioplasty and coronary artery bypass grafting in 174 patients, 75 years or older.

## LONG-TERM FOLLOW-UP

Follow-up was available in all patients. Table 3 shows the late outcome of these patients.

In the PTCA group median follow-up was 8.2 years (3.5–10.9 years). Actuarial survival was 92% after 10 years. There were 8 late deaths: 2 sudden cardiac deaths after 3 and 6 years and 6 non-cardiac from cancer. Three patients had a non-fatal myocardial infarction. Elective coronary bypass surgery was performed in 2 patients because of recurrence of angina and repeat PTCA was performed in 10 patients. Thus in the PTCA group 68 patients (76%) had event free long-term survival. Four of these patients had angina pectoris C.C.S. class II or III which was treated conservatively, so 64 patients (70% of the initially surviving group) were free of angina.

**Table 3.** Outcome of patients 75 years or older after successful percutaneous coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG).

	PTCA (n=93)	CABG (n=81)
Median hospital stay (days)	4.3	14.2 p < 0.05
In hospital deaths	2	6*
Late, cardiac deaths	2	3
Late, non-cardiac deaths	6	5
Survival	83 (89%)	67 (83%)
Follow-up (10 years)	92%	91%
Non-fatal MI	3	1
Survival no MI	80	66
Elective CABG (PTCA group)	2	–
Survival no MI or (re) CABG	78	66
Repeat PTCA (PTCA group)	10	–
PTCA (CABG group)	–	6
Survival no MI, CABG or PTCA	68	60
Recurring angina	4	3
Survival no MI, CABG or PTCA and angina free	64 (70%)	57 (76%)

Abbreviations:

As in Table 1.

\* Four patients were operated on an emergency base after complicated coronary angiography elsewhere

In the CABG group median follow-up was 8.3 years (3.5–11.2 years). Actuarial ten year survival was 91% (excluding the four early deaths during emergency surgery). There were 8 deaths: one patient died after a myocardial infarction after 5.4 years and two patients died suddenly at 2.4 and 6.8 years after operation.

while 5 patients died from cancer. Only 1 patient had a non-fatal myocardial infarction. Elective PTCA was performed in 6 of the patients who had prior CABG because of recurrence of angina.

Thus in the CABG group 60 patients (80%) had event free long-term survival. Three of these patients had angina pectoris C.C.S. class II-III and were treated conservatively, thus 57 patients (76% of the initial group) survived free of angina.

Figure 2 shows the total survival calculated by the Kaplan-Meier method<sup>32</sup> for all patients 75 years or older, who underwent PTCA or CABG. The four patients referred to our institution for emergency bypass surgery, due to complications during coronary angioplasty elsewhere, and died, are not included. There is no statistical difference between both groups.

## DISCUSSION

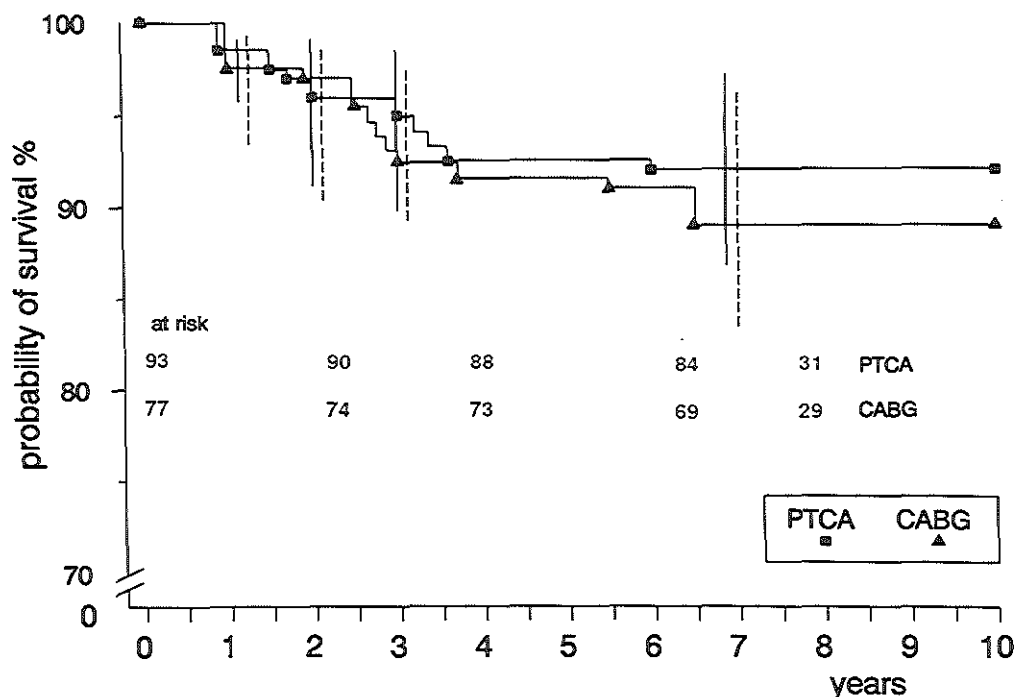
Patients of 75 years or older form a considerable and rapidly growing part of our population. In 1995 the number of elderly citizens (> 65 years) in The Netherlands will increase to two million and it is calculated that in 2030 one million Dutch citizens will be 75 years or older. Already more than fifty percent of patients admitted to the department of cardiology of the Thoraxcenter in Rotterdam in 1990 are older than 65 years.<sup>33</sup> Cardiovascular disease remains the main cause of morbidity and mortality in this group<sup>29</sup> and an increasing number of elderly patients unresponsive to medical therapy for angina pectoris will be referred for PTCA or CABG.

CABG in this patient population is associated with an increased mortality and morbidity.<sup>18-28</sup> In a recent review of the influence of age on the results of coronary

artery surgery, Weintraub et al.<sup>27</sup> reported the highest mortality in the group of patients 80 years or older, followed by the group of 70-79 years. Wound infection and neurological events were higher in these groups, compared to younger patients. In contrast several reports indicate that the results of PTCA in elderly patients are comparable to those obtained in younger patients<sup>30</sup>, although other authors report lower success rates and increased morbidity.<sup>12</sup> Thus PTCA may be an attractive alternative to surgery.<sup>1-17, 31</sup>

The PTCA and CABG results, in this retrospective study are similar to those published in the literature. The percentage of complications, tended to be higher in the CABG group. Furthermore the hospital stay after CABG was significantly longer. Late outcome was excellent in both groups, although there was a trend towards more cardiac events necessitating repeated interventions after PTCA to achieve similar late outcome. It is interesting to note that mortality during follow-up in both groups was mainly due to cancer and not to coronary artery disease. Another observation from this study was that dilating the culprit lesion in the majority of PTCA patients appeared sufficient to achieve a similar late outcome as the completely revascularized CABG patients. So in selected cases dealing with the culprit lesion only in patients selected for PTCA is often sufficient. It is not always necessary to operate on patients with three vessel disease to achieve freedom from angina and long-term survival.

A point of criticism of this study is the selection of patients, since it was a non-randomized series and it was not recorded in detail why PTCA was done in a certain cohort of patients and CABG in the other group (indication bias).



**Fig. 2** Kaplan Meier curve of total survival time [■ PTCA ▲ CABG] for patients 75 years or older, who underwent PTCA or CABG. Vertical lines are 95% confidential intervals. The numbers indicate patients 'at risk'. Four patients had complications during coronary angiography elsewhere and were referred for emergency bypass surgery. They died during the procedure and are not included in the curve.

In conclusion, PTCA and CABG in patients 75 years or older can be performed with an acceptable incidence of complications. In the elderly, dilatation of the culprit lesion often provides adequate symptomrelieve in the majority of patients selected for PTCA. The complication rate for PTCA was lower and the hospital stay was shorter compared to CABG. These observations suggest, that PTCA in patients 75 years or older is preferable to CABG, when the culprit lesion is suitable for PTCA. If the culprit lesion is not identified or unsuitable for PTCA, CABG can be performed with an acceptable result.

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# Acute myocardial ischaemia and cardiogenic shock after percutaneous transluminal coronary angioplasty; risk factors for and results of emergency coronary bypass

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**KEY WORDS:** Acute myocardial ischaemia, cardiogenic shock, PTCA, risk factors, emergency CABG.

Between 1 September, 1980 and 1 January, 1989, 4142 patients underwent percutaneous transluminal coronary angioplasty (PTCA). We retrospectively studied the 155 [3.7%; 119 males, mean age 53.4 years, (range 33–78 years) and 36 females, mean age 59.6 years (range 40–74 years)] who required urgent coronary artery bypass grafting (CABG) (Group I) and a select control group of 155 patients, in whom PTCA was performed without complications (Group II).

Before PTCA, 14 Group I and 42 Group II patients had angina Class II, and 78 Group I and 49 Group II patients had angina class IV ( $\chi^2$ -test,  $P < 0.05$ ). There were 445 complications in the 155 group I patients: 303 (68%) early (during PTCA) and 141 (32%) late (within 24 h). On arrival in the operating room 126 patients were stable; five were in cardiac arrest and 19 in cardiogenic shock (AS-group; 24 patients). In the AS-group and control group, respectively, angina Class II occurred in 2/24 (8.3%) and 42/155 (27.1%) patients, angina Class IV in 14/24 (58.3%) and 49/155 (31.6%) ( $P < 0.05$ ), single-vessel disease in 8/24 (33.3%) and 85/155 (54.8%), triple-vessel disease in 7/24 (29.2%) and 23/155 (14.9%) ( $P < 0.05$ ); elective PTCA in 11/24 (45.8%) and 92/155 (59.4%), urgent PTCA in 12/24 (50%) and 48/155 (30.9%) ( $P < 0.05$ ), PTCA of the left anterior descending artery (LAD) in 18/24 (75%) and 86/166 (51.8%), PTCA of the right coronary artery in 2/24 (8.3%) and 47/166 (28.3%) ( $P < 0.05$ ).

Angina pectoris Class IV, triple-vessel disease, urgent PTCA and PTCA of the LAD were risk factors for development of cardiac arrest/cardiogenic shock after PTCA.

Of the 155 Group I patients, four (2.6%) died. The myocardial infarction rate was 62/155 (40%). Of the 24 AS-group patients, the myocardial infarction rate was 10/24 (41.7%), although the time to revascularization was significantly shorter (median 103 min; range 73–185 min) than in the 126 patients who were in good condition preoperatively (median 135 min; range 80–235 min) (Wilcoxon's rank sum test,  $P < 0.001$ ).

## Introduction

Eleven years after the introduction of percutaneous transluminal coronary angioplasty (PTCA) by Grüntzig *et al.* in 1977<sup>[1]</sup>, a Task Force of the American College of Cardiology/American Heart Association (Subcommittee on PTCA) formulated internationally recognized guidelines for the procedure<sup>[2]</sup>, thus emphasizing the rapid acceptance of this method for revascularization of jeopardized myocardium. In the Special Report of the Sub-

committee is underscored the importance of weighing beforehand the likelihood of a successful PTCA against the likelihood of failure and the risk of complications (abrupt vessel closure, morbidity, mortality and restenosis).

Despite the enthusiasm for the benefits of PTCA there is concern for the hazardous aspects of the method: 'Although there is a tendency to categorize angioplasty procedures as having low, moderate or high risk, situations do occur in low risk procedures that lead to catastrophic complications'<sup>[3]</sup>. The retrospective study presented here, based on data from more than 4000 consecutive patients

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Table 1 Number of procedures from 1 September, 1980–1 January, 1989

Year	PTCA (n)	Emergency CABG after PTCA	
		(n)	(%)
1980	20	0	0
1981	86	9	10.5
1982	144	15	10.4
1983	217	19	8.7
1984	328	22	6.7
1985	595	26	4.4
1986	779	23	2.9
1987	992	24	2.4
1988	981	17	1.7
Total	4142	155	

PTCA = percutaneous transluminal coronary angioplasty;  
CABG = coronary artery bypass grafting.

undergoing PTCA in one institution, concentrates on the potentially lethal sequelae of PTCA, on their possible prevention and on the results of their surgical treatment.

## Materials and Methods

### DEFINITIONS

*Angina Pectoris* (AP) was graded according to Canadian Cardiovascular Society Classes I, II, III and IV<sup>[4]</sup>. PTCA's were classified as *elective* (according to the waiting list), *urgent* (within 48 h of diagnostic cardiac catheterization), and *emergency* (as an extension of the initial diagnostic catheterization). *Complications of PTCA* leading to emergency CABG were denoted *early* when they occurred during PTCA and *late* when they occurred within 24 h of the start of the procedure. The *types of dilated lesions* were morphologically classified, according to Rösch and Rahimtoola<sup>[5]</sup>, as *short* (< 5 mm long), *concentric or eccentric; tubular* (5–20 mm long), *regular, irregular or with ulcerating plaque*, and *diffuse* (> 20 mm long).

### MATERIALS AND METHODS

From 1 September, 1980 to 1 January, 1989 in the Catharina Hospital in Eindhoven, PTCA was performed in 4142 patients. An emergency operation was necessary in 155 of these patients (3.7%). The complication rate decreased from 10.5% in 1981 to 1.7% in 1988 (Table 1).

From the introduction of PTCA to our institution in 1980, the data on every candidate for

Table 2 Operations in 155 patients of group I

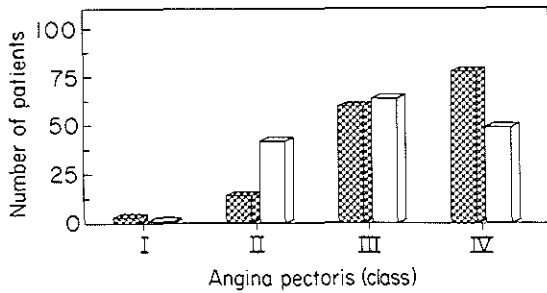
Operation	Patients	
	(n)	(%)
No history of previous CABG	152	98.1
History of previous CABG	3	1.9
Total	155	100
of which		
CABG I	61	39.4
II	62	40
III	17	11
IV	12	7.7
V	3	1.9
Total	155	100

CABG = coronary artery bypass grafting. I–V = number of grafts.

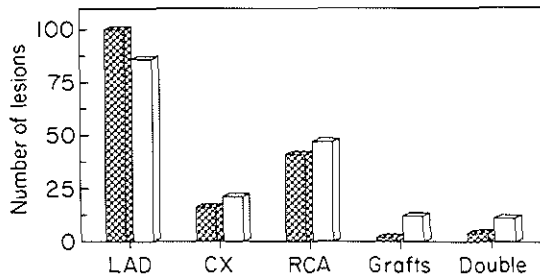
PTCA have been formally discussed by a cardiologist and a surgeon. A surgical team stood in readiness for every PTCA performed.

In addition to our study group (I) we studied a select control group (group II) of 155 patients, in whom PTCA was performed without complications. The control group was selected from the PTCA Patient Registry using the patient immediately following each patient who needed operation, of the same sex and the same age ( $\pm 4$  years). In groups I and II the mean ages of the men were, respectively, 53.4 years (range 33–78 years) and 54.8 years (range 34–76 years), of the women, 59.6 years (range 40–74 years) and 58.9 years (range 44–74 years), and of all patients 54.8 years (range 33–78 years) and 55.7 years (range 34–76 years). In the 155 patients of group I a history of previous coronary surgery was absent in 152 patients and present in three. Usually one or two venous bypasses were constructed (Table 2). In no case was the internal thoracic artery used as bypass graft in these often critically ill patients. The mode of myocardial protection during operation was intermittent cross-clamping in 38 patients, crystalloid cardioplegia in 97 patients and (in the last 2 years) blood cardioplegia in 20 patients, according to Buckberg's protocol of reperfusion strategy<sup>[6]</sup>.

'Time to revascularization' was designated the time elapsed between notification by the cardiologist that a complication necessitating emergency operation had occurred to the moment after completion of both distal and proximal anastomoses. In



**Figure 1** Indications for percutaneous transluminal coronary angioplasty in 155 patients of group I (▨, surgical group) and 155 patients of group II (□, control group). Angina pectoris was graded according to the Canadian Cardiovascular Society classification.



**Figure 2** Distribution of dilated vessels in 155 patients of Group I (▨, surgical group) and 155 patients of Group II (□, control group). LAD=left anterior descending coronary artery, CX=circumflex coronary artery, RCA=right coronary artery.

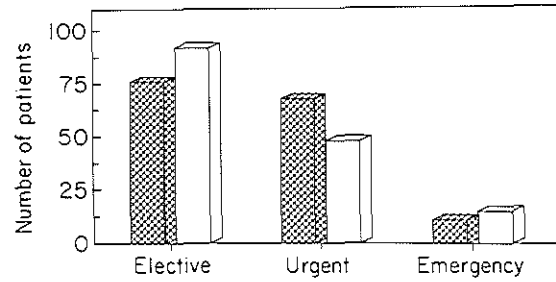
the cases where blood cardioplegia was used, this included up to 20 min of warm regional reperfusion. Perioperative myocardial infarction was considered to be present when the postoperative ECG, 12 h after the operation, showed new Q-waves and simultaneously an elevation of the serum-level of glutamic oxaloacetic transaminase (GOT) to at least twice normal.

To analyse the statistical significance of the data the  $\chi^2$ -test, the Z-norm test and Wilcoxon's rank sum test were used.

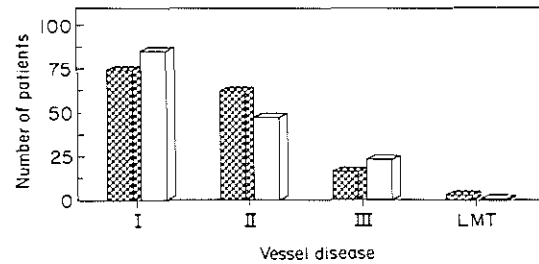
## Results

The indications for PTCA in group I (surgical group) and in group II (control group) are depicted in Fig. 1. Only 14 patients were AP Class II in group I, compared with 42 in group II; on the other hand, there were 78 patients with AP Class IV in group I compared with only 49 in group II ( $\chi^2$ -test,  $P < 0.05$ ).

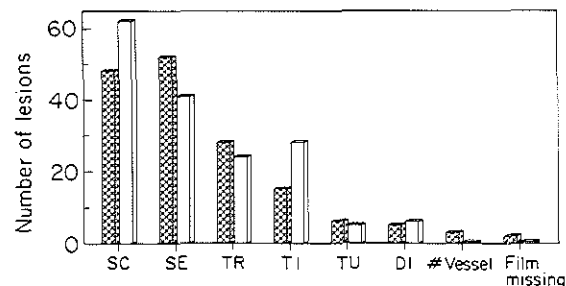
Figure 2 shows the distribution of dilated vessels in groups I and II; it is significantly different ( $\chi^2$ -test,  $P < 0.05$ ), but the difference in this distribution is



**Figure 3** Classification of percutaneous coronary angioplasty in 155 patients of Group I (▨, surgical group) and 155 patients of Group II (□, control group). For explanation, see text.



**Figure 4** Distribution of coronary artery disease in 155 patients of Group I (▨, surgical group) and 155 patients of Group II (□, control group). I=single-vessel disease, II=double-vessel disease, III=triple-vessel disease, LMT=left main trunk lesion.



**Figure 5** Types of dilated lesions in 155 patients of group I (▨, surgical group) and 155 patients of Group II (□, control group). SC=short concentric, SE=short eccentric, TR=tubular regular, TI=tubular irregular, TU=tubular with ulcerating plaque, DI=diffuse, # = obstructed. For explanation see text.

mainly caused by the small number of PTCAs in grafts and double PTCAs.

Figures 3–5 show the respective distributions of classification of PTCA, of coronary artery disease and of types of dilated lesions in groups I and II. In none of these variables was there a significantly different distribution between groups. The

Table 3 Complications of percutaneous transluminal coronary angioplasty in 155 patients of group I, leading to emergency coronary artery bypass grafting, and in 155 patients of group II

Complication	Early (during PTCA)				Late (within 24 h)				Total			
	Group I		Group II		Group I		Group II		Group I		Group II	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Persistent chest pain	62				48		5		110		5	
ECG changes indicative of myocardial ischaemia	62				45		2		107		2	
Inability to cross	30		4		1				31		4	
Inability to dilate	26		4		2				28		4	
Spasm	6		3		2				8		3	
Dissection	59		25		13				72		25	
Perforation with haemopericardium	2								2			
Occlusion	1								1			
Asystole	27				27		3		54		3	
Ventricular tachy- cardia/fibrillation	5								5			
Cardiogenic shock	7		2						7		2	
Total	14				3				17			
	303	68	38	79	141	32	10	21	445	100	48	100

PTCA = Percutaneous transluminal coronary angioplasty.

complications of PTCA in the 155 patients of group I, leading to emergency operation, and in the 155 patients of group II are listed in Table 3. In group I there were 445 complications, 303 (68%) early and 141 (32%) late; in group II there were 48 complications, 38 (79%) early and 10 (21%) late. In 34 patients of group I and in three patients of group II, the late complication was documented by recatheterization.

In Fig. 6 the type of stenosis and the type of concomitant complications are indicated. Most complications of all types of lesions were early. Early dissection was prominent, especially in tubular regular lesions (43%). Similar numbers of occlusions were early and late, in all types of lesion (Fig. 7).

On arrival in the operating theatre, 126 of the 155 group I patients were stable. Five had a cardiac arrest and needed continuous cardiopulmonary resuscitation, 19 were in cardiogenic shock and needed intermittent resuscitation (24 patients, AS-group — arrest or shock). In five patients the condition was not documented.

The postoperative cardiac complications are listed in Table 4. Myocardial infarction occurred,

overall, in 40% of cases, and in the patients with intermittent crossclamping, crystalloid cardioplegia and blood cardioplegia the incidence was 39.4%, 42.2% and 30%, respectively. There was no relation of myocardial infarction rate to the mode of operative myocardial protection (Z-norm test). In the 24 patients of the AS-group, myocardial infarction occurred in 10 (41.7%) cases; although the time to revascularization was significantly shorter in these patients (median 103 min, range 73–185 min) than in the 126 patients who arrived in the operating room in good condition (median 135 min, range 80–235 min) (Wilcoxon's rank sum test,  $P < 0.001$ ), this did not result in a lower myocardial infarction rate.

The non-cardiac complications are given in Table 5. The pulmonary complications were acute respiratory distress syndrome, necessitating prolonged mechanical ventilation, and airway infection and atelectasis, necessitating bronchoscopy.

Four patients died: 2.6% (Table 6). Three of them had AP Class IV preceding PTCA and had urgent PTCA for this. Three were in cardiogenic shock when they arrived in the operating room and notwithstanding cardiopulmonary resuscitation

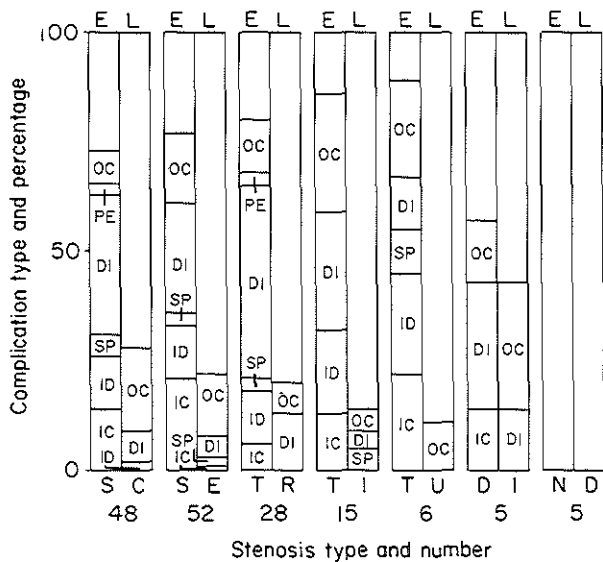


Figure 6 Type of stenosis and type of complication in 155 patients of group I (surgical group). Stenoses: SC=short concentric, SE=short eccentric, TR=tubular regular, TI=tubular irregular, TU=tubular with ulcerating plaque, DI=diffuse, ND=not documented. Complications: E=early, L=late, IC=inability to cross, ID=inability to dilate, SP=spasm, DI=dissection, PE=perforation, OC=occlusion.

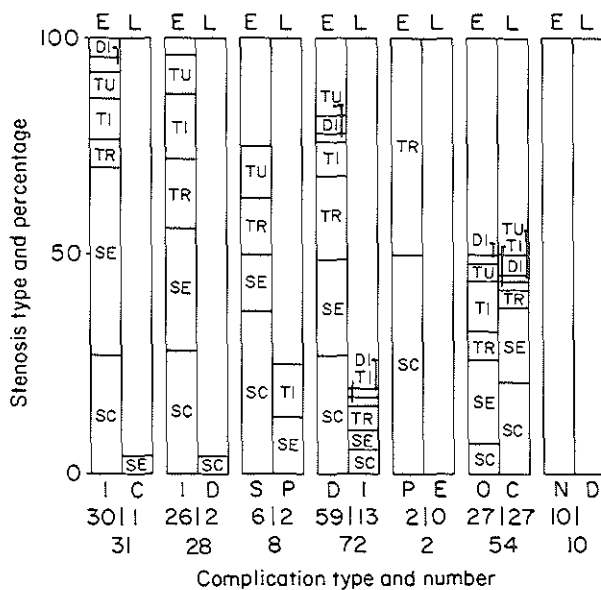


Figure 7 Type of complication and type of stenosis in 155 patients of Group I (surgical group). Abbreviations as in Fig. 6.

and the use of IABP in two patients, they all developed a lethal perioperative myocardial infarction.

In the group of 24 patients arriving in the operating room in cardiac arrest or cardiogenic shock (AS-group) we studied the following vari-

ables, probably contributing to the development of these pathological states. In the AS-group there were 11/24 (45.8%) patients with a history of previous myocardial infarction compared with 53/155 (34.2%) in the control group (statistically non-significant difference;  $\chi^2$ -test,  $P > 0.05$ ). The following factors however were of importance (Figs 8, 9). In the AS-group there was a low incidence of AP Class II (2/24; 8.3%) vs the control group (42/155; 27.1%) and a high incidence of AP Class IV (14/24; 58.3%) vs the control group (49/155; 31.6%) ( $\chi^2$ -test,  $P < 0.05$ ). Single-vessel disease was seen only in 8/24; 33.3% of patients in the AS-group and in 85/155; 54.8% in the control group, as opposed to triple-vessel disease, which occurred in 7/24; 29.2% of the AS-group and in only 23/155; 14.9% of the control group ( $\chi^2$ -test,  $P < 0.05$ ). Elective PTCA was performed in 11/24 patients; 45.8% in the AS-group and in 92/155; 59.4% in the control group; urgent PTCA however was performed in 12/24; 50% of cases in the AS-group and in only 48/155; 30.9% in the control group ( $\chi^2$ -test,  $P < 0.05$ ). Finally, PTCA of LAD occurred more frequently in the AS-group (18/24; 75%) than in the control group (86/166; 51.8%) and PTCA of RCA occurred less frequently in the AS-group (2/24; 8.3%) than in the control group (47/166; 28.3%) ( $\chi^2$ -test,  $P < 0.05$ ).

Thus AP-class IV, triple-vessel disease, urgent PTCA and PTCA of LAD were risk factors for the development of cardiac arrest/cardiogenic shock after PTCA. In the 24 patients of the AS-group no risk factor was present in one patient, one risk factor in seven patients, two risk factors in five, three in ten patients and four in one patient. Among the four patients who died, one risk factor was present in one, two risk factors in two and three risk factors in one.

## Discussion

Early in our experience with PTCA, we realized that a clear understanding of which patients were predisposed to acute myocardial ischaemia after PTCA, was lacking. In recent years, several authors have addressed this question<sup>[7-10]</sup>. Vlietstra stated that: 'the major risks of PTCA are myocardial infarction and death, usually a consequence of coronary artery thrombotic occlusion or dissection<sup>[9]</sup>'. He adds: 'When one considers the risk of mortality in patients with stable angina having percutaneous transluminal coronary angioplasty, the assumption generally made is that the observed mortality

Table 4 Postoperative cardiac complications in 155 patients of group I

Complication	Patients	
	(n)	(%)
New low output	5	3.2
Ventricular tachycardia/ventricular fibrillation	19	12.3
Atrioventricular block (pacemaking)	2	1.3
New Q-waves and SGOT $\geq 2$ N ( $> 60$ U ml <sup>-1</sup> )	62	40.0
Any of the above	70	45.2

SGOT = Serum glutamic oxaloacetic transaminase.

Table 5 Postoperative non-cardiac complications in 155 patients of group I

Complication	Patients	
	(n)	(%)
Bleeding (resterotomy)	6	3.9
Wound infection	3	1.9
Pulmonary	11	7.1
Renal (dialysis)	3	1.9
Liver	3	1.9
Sepsis	2	1.3
Cholecystitis	1	0.6
Intestinal obstruction	1	0.6
Incarcerated hernia	1	0.6
Any of the above	26	16.7

directly reflects procedure related mortality. This assumption is not true when dealing with very ill patients (e.g. patients with cardiogenic shock). For them, the observed mortality is the net result of the hazards and benefits imposed by the underlying illness, and the treatments that have been used. Under these circumstances, the effects of treatment might only become evident when there is comparison with the outcome in a control group<sup>[9]</sup>. The obvious drawback of a retrospective study of patients undergoing PTCA and emergency operation from 1980–1989 is that in this period rapid developments have taken place in the indications for, the technique and procedure of PTCA and in methods of myocardial protection, once acute myocardial ischaemia has occurred. This makes cohorts of earlier years incomparable with those of later years. However the inclusion in the study of a time-matched control group makes it possible to draw certain conclusions.

From 1981 to 1988 in our institution, the incidence of PTCA leading to emergency CABG

decreased from 10.5% to 1.7%; overall it was 3.7%. This is in accordance with data in other published large series<sup>[11–15]</sup>.

For this stepwise improvement two factors seem important: increased operator experience and improvement of technology; an increasing understanding of when PTCA is indicated may also have contributed. Holmes *et al.* found that despite a higher risk patient population in the cohort of patients undergoing PTCA between 1985–1987 vs the 1977–1981 cohort, the overall complication rate in the recent cohort was either unchanged or decreased from that in the earlier cohort<sup>[16]</sup>. Regarding early (during PTCA) and late (< 24 h) occlusion we saw exactly 50% early and 50% late occlusion. It underscores the message of Page *et al.*<sup>[17]</sup> that the risks of PTCA do not end when the patient leaves the catheterization laboratory and that 'Patients with a severe intimal dissection and a significant amount of myocardium at risk should be monitored closely and sent immediately to surgery if ischaemic symptoms occur'<sup>[18]</sup>.

In a detailed account of risk factors for acute closure after coronary angioplasty and the associated in-hospital cardiac mortality, given by Ellis *et al.*<sup>[7,8]</sup>, clinical variables associated with increased procedural mortality were age > 65 years, female gender, a history of hypertension, diabetes, prior myocardial infarction, prior bypass surgery, multi-vessel disease, left main coronary disease, a large area of myocardium at risk, impairment of left ventricular function, and collateral vessels that supply significant areas of myocardium and originate distal to the segment to be dilated.

Our finding that angina Class IV carries a higher risk of acute myocardial ischaemia than lower AP classes is in accordance with the findings of others. De Feyter *et al.* concluded that coronary angioplasty for unstable angina can be performed with a

Table 6 Postoperative mortality in 155 patients of group I

Age (years), sex	Previous myocardial infarction	AP Class IV	Vessel disease	PTCA	Complication of PTCA	ACBG plus	Perioperative myocardial infarction	Other complications
56, M	-	+	I	LAD/UR	Chest pain; ECG changes	IABP	+	Renal, Pulmonary
60, M	+	+	II	CX/UR	Inability to cross; shock	IABP	+	
67, F	-	-	II	LAD/EL	Occlusion; shock		+	Incarcerated hernia
69, M	-	+	II	RCA/UR	Occlusion; shock	CPR	+	Renal

M = Male, F = female, - = absent, + = present, UR = urgent, EL = elective, LAD = left anterior descending coronary artery, CX = circumflex coronary artery, RCA = right coronary artery, ECG = electrocardiographic, ACBG = aorto-coronary bypass grafting, CPR = cardiopulmonary resuscitation, IABP = intra-aortic balloon pumping.

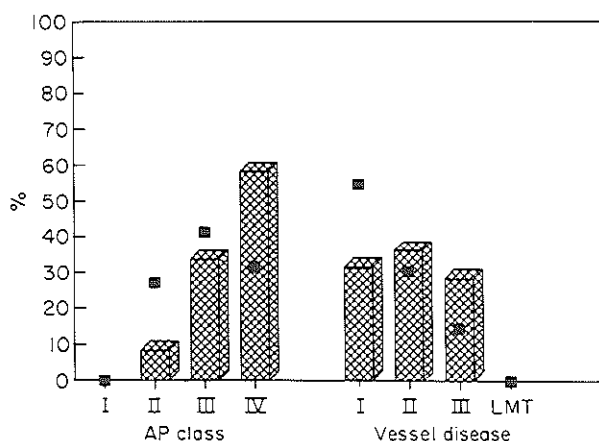


Figure 8 Incidence of factors contributing to development of cardiac arrest/cardiogenic shock in 24 patients (AS-group) of Group I. LMT = left main trunk lesion. ▨ = arrest/shock (n = 24); ■ = control group (n = 155).

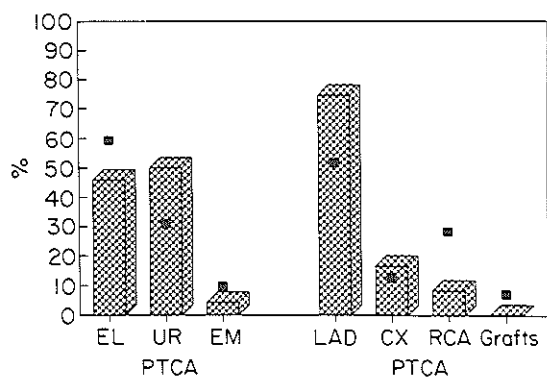


Figure 9 Incidence of factors contributing to development of cardiac arrest/cardiogenic shock in 24 patients (AS-group) of group I. PTCA = percutaneous transluminal coronary angioplasty, EL = elective, UR = urgent, EM = emergency, LAD = left anterior descending coronary artery, CX = circumflex coronary artery, RCA = right coronary artery, ▨ = arrest/shock (n = 24); ■ = control group (n = 155).

high initial success rate but at an increased risk of major complications<sup>[19]</sup>. In cases of unstable angina, Di Marco *et al.* reserve PTCA for patients with single-vessel disease and no evidence of previous myocardial infarction<sup>[20]</sup>.

Our results showed that the morphological type of lesion, as classified by Rösch and Rahimtoola<sup>[5]</sup> was not a determinant of complications of PTCA necessitating emergency surgery. It should be added that this classification was not devised to this end. The lesion-specific classification of types A, B and C, as proposed by the ACC/AHA Task Force<sup>[2]</sup> appears to take into account better the uniquely technical aspects of PTCA for risk stratification, but must stand the test of time.

Study of the subset of 24 patients who arrived in the operating room in the haemodynamically very unstable state of cardiac arrest or cardiogenic shock, candidates for 'desperate' operation according to Page<sup>[17]</sup>, gave valuable information. The risk factors identified were: AP Class IV; triple-vessel disease; urgent PTCA; and PTCA of LAD. In the presence of one or more of these risk factors, the cardiologist should be aware of the increased possibility of a serious complication after PTCA and take this into account in his choice of invasive procedure.

Only one of the 24 AS-group patients was free of risk factors and none of the four patients who died was free of risk factors. We cannot suggest, however, that the absence of risk factors implies a PTCA without the possibility of a serious complication; our data confirm that the occurrence of complications after PTCA remains unpredictable. Thus we should not refrain from surgical standby.

Our finding of 2.6% postoperative death is roughly in accordance with other published studies of emergency revascularization for complications of PTCA<sup>[11-15]</sup>.

Von Segesser and Turina point to the fact that myocardial infarction can be prevented in a substantial proportion of patients when revascularization is performed within 1 h of coronary occlusion<sup>[18]</sup>. The relatively good results in the 24 patients in cardiac arrest/cardiogenic shock may be partly explained by their shorter mean revascularization time vs patients who arrived in the operating room in good condition. As in Page's experience<sup>[17]</sup>, the surgical team moves faster in these cases, the patient usually being on cardiopulmonary bypass within 20 min. It was our experience that we lost valuable time by installing IABP and by the more complicated transport of the patient to the operating room as a consequence. Nowadays we prefer the rapid institution of cardiopulmonary bypass.

We thank the cardiologists who referred patients for PTCA for their permission to include data on their patients. We thank the anaesthesiologists, the collaborators of the Heart Catheterization Laboratory, the Department of Extra Corporeal Circulation and the nursing staff for very effective action. The advice of Prof. Dr J. Lubsen and the statistical calculations by Drs A. P. M. Schellekens are gratefully acknowledged. We also thank Mrs Mara Siemonsma for fine secretarial assistance and Mr Guy van Dael for the illustrations.

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# Myocardial Protection by Intravenous Diltiazem During Angioplasty of Single-Vessel Coronary Artery Disease

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**The possible cardioprotective effect of diltiazem during ischemia caused by percutaneous transluminal coronary angioplasty was tested. Electrocardiograms and myocardial lactate, hypoxanthine and urate production were determined in 26 patients with a stenosis in the left anterior descending artery without angiographically demonstrable collaterals. Measurements took place before angioplasty, after each of 4 occlusions and 15 minutes after the last balloon inflation. Patients were randomly given placebo or DL-diltiazem (0.4 mg/kg as a bolus intravenously, followed by an infusion of 15 mg/hr). During angioplasty the ST-segment elevation for the anterior wall leads V<sub>2</sub>, V<sub>4</sub> and V<sub>6</sub>, and the intracoronary lead was similar for both groups, as was lactate release. Diltiazem significantly reduced cardiac hypoxanthine release immediately after angioplasty from 63 to 88% (p < 0.05). The drug diminished urate production after the last dilatation by 82% (p < 0.05). In conclusion, intravenous infusion of diltiazem reduced cardiac adenosine triphosphate breakdown during angioplasty as shown by diminished hypoxanthine and urate production. In contrast, diltiazem was unable to attenuate ST-segment elevation and lactate release.**

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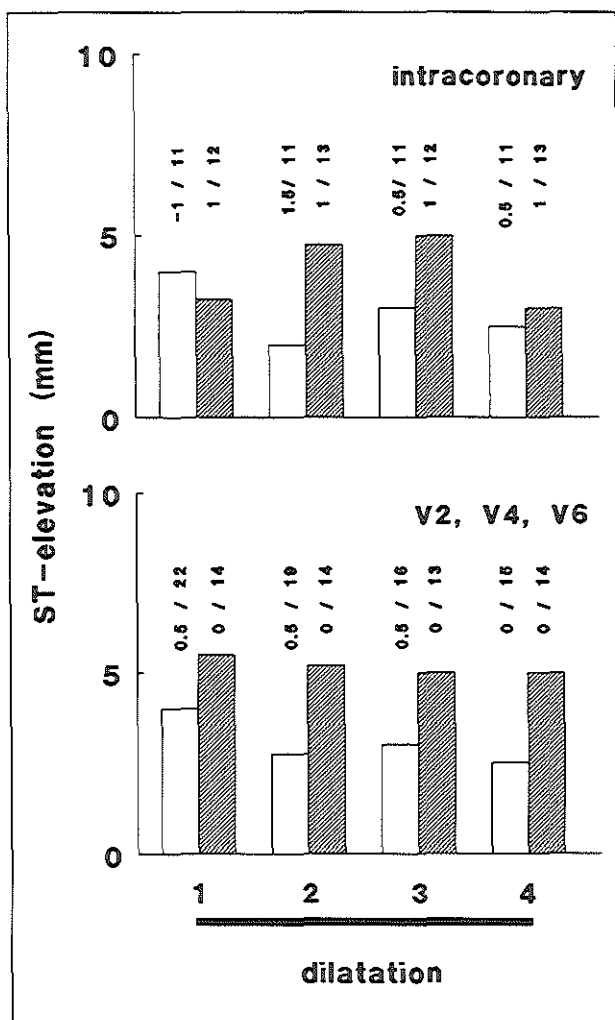
In the last decade, calcium antagonists have proven to be effective in the treatment of many cardiovascular disorders. A few of these drugs, including diltiazem, have been successful in the management of angina pectoris. One of the advantages of diltiazem is its ability to delay ischemic ventricular arrhythmias.<sup>1</sup> In addition, calcium antagonists may improve the protection afforded by potassium-cardioplegia for heart surgery.<sup>2</sup> They may also be useful for local cardioplegia during coronary angioplasty.<sup>3-8</sup> Diltiazem delayed the onset of pacing-induced ischemia.<sup>9,10</sup> In isolated hearts and open-chest animals, diltiazem<sup>11-15</sup> and other calcium antagonists<sup>14,16-19</sup> exert an energy-sparing effect during ischemia. In this study, we tested whether diltiazem could minimize adenosine triphosphate-breakdown during angioplasty and thus serve as a potential cardioprotective agent during the procedure.

## METHODS

**Patients:** The study involved 26 patients with 1-vessel coronary artery disease undergoing percutaneous transluminal coronary angioplasty. The following characteristics were observed for each patient. Coronary artery disease was limited to an isolated proximal stenosis <1 cm in the left anterior descending artery (narrowing >70%) and no collateral filling was seen angiographically in the region supplied by this artery. There was no history of previous myocardial infarction, and nitrates were not required during the dilatation procedure (Table I). Antiplatelet drugs (including aspirin) and other cardioactive medications except short-acting nitrates were discontinued  $\geq 48$  hours before the procedure. With the exception of heparin, no drugs were given before completion of data acquisition. This research project was approved by the institutional committee on patient research. All patients gave informed consent before the study, and no complications related to the protocol were observed.

**Coronary angioplasty:** A normal El Gamal diagnostic 7Fr catheter (Cordis) was introduced through the right femoral vein in the great cardiac vein. Its position was confirmed with the injection of a small volume of nonionic contrast medium (Isopaque Coronar 370). An 8Fr guiding catheter was introduced percutaneously and advanced to the aortic root through the right fem-

	Placebo Group (n = 13)	Diltiazem Group (n = 13)
Age (yrs). average	58	58
Range	43-72	37-74
Sex: M/F	10/3	11/2
Patients in CCS		
Grade II	4	4
Grade III	7	6
Grade IV	2	3
Average severity of stenosis (%)		
Before angioplasty	79	82
After angioplasty	37	35
Average ejection fraction (%)	64	66
Mean aortic pressure during transluminal occlusion (mm Hg)	102	97
Mean heart rate during transluminal occlusion (beats/min)	74	68
None of the differences reached significance at $p < 0.05$ . CCS = Canadian Cardiovascular Society.		



**FIGURE 1.** Effect of diltiazem on ST-segment elevation during angioplasty, measured with the intracoronary lead (*top*) and the precordial leads (*bottom*). Bars indicate the median values, ranges are given above the columns. Open bars = placebo; hatched bars = diltiazem. No significant effects

oral artery. The left anterior descending artery was visualized by injection of contrast medium after the first blood samples had been taken. Then, the angioplasty balloon (Advanced Cardiovascular System Inc.) was introduced. Coronary angioplasty was performed according to Simpson et al.<sup>20</sup> using a steerable guidewire (Advanced Cardiovascular System, high torque floppy, 0.014 inch). Balloon diameters were 3.0 or 3.5 mm. The maximal inflation pressures ranged from 6 to 12 atmospheres. For each patient, the dilatations were sustained for 90 seconds or until the onset of chest pain. In each patient, 4 consecutive dilatations were performed, with a 5 minute recovery between inflations. Control coronary angiography was then performed.

**Sampling:** Great cardiac venous and femoral arterial blood samples, taken before, immediately after each deflation and 15 minutes after the procedure, were treated as previously described.<sup>21</sup>

**Lactate and purine analysis:** In the deproteinized samples, lactate was determined enzymatically.<sup>22</sup> In addition, the adenine nucleotide catabolites hypoxanthine and urate were assayed by high-performance liquid chromatography,<sup>23</sup> as modified by Huizer et al.<sup>21</sup> Urate was detected at 290 nm.

**Electrocardiograms:** These were monitored from the precordial leads V<sub>2</sub>, V<sub>4</sub> and V<sub>6</sub>, and from the intracoronary lead, using the guidewire placed in the left anterior descending artery. Each lead was calibrated before the procedure (10 mm = 1 mV). Maximal ST elevation at the end of each inflation was measured 0.80 second after the J point, with the T-wave-P-wave interval as the isoelectric line.

**Experimental regimen:** The patients were randomly assigned to treatment with placebo or diltiazem (double-blind). Five minutes before the first dilatation, and immediately after data collection at rest, they received either DL-diltiazem (0.4 mg/kg intravenously [Lorex]), or solvent, as a bolus over 5 minutes, followed by a continuous infusion of either 15 mg/hr diltiazem or solvent. Plasma diltiazem was determined with the methodology described for verapamil.<sup>24</sup>

**Statistical analysis:** Results are given as median and range, unless indicated otherwise. Nonparametric statistical methods were used: for within-group analysis the Wilcoxon signed rank test, for between-group analysis the Mann-Whitney rank sum test. A  $p$  value  $< 0.05$  was considered statistically significant.

## RESULTS

**Clinical characteristics:** The clinical characteristics of the study groups assigned to diltiazem or placebo are listed in Table I. Age, Canadian Cardiovascular Society grade, severity of the stenosis in the left anterior descending artery and left ventricular ejection fraction in the 2 groups were comparable. Inflation time (approximately 80 seconds), inflation pressure (approximately 9 atmospheres) and pain symptoms (in 10 or 11 of 13 patients) during the 4 consecutive inflations were comparable in the 2 groups. Cross-sectional area of the stenosis before and after coronary angioplasty was similar in both groups (approximately 80 and 35%, respectively). The baseline values of lactate, hypoxanthine and

Sampling Site	Treatment	No.	Lactate Concentration (mM)					
			Pre	Dilatation				Post
				1	2	3	4	
Arterial	Placebo	13	0.68 (0.41-1.54)	0.65 (0.41-1.48)	0.64 (0.44-1.57)	0.63 (0.38-1.61)	0.57 (0.38-1.54)	0.56 (0.38-1.85)
Arterial	Diltiazem	13	0.73 (0.43-0.99)	0.66 (0.40-0.91)	0.69 (0.36-0.93)	0.66 (0.39-0.84)	0.67 (0.39-0.86)	0.64 (0.34-0.91)
Venous	Placebo	13	0.53 (0.37-1.65)	1.54 (0.90-2.56)	1.45 (0.62-2.34)	1.48 (0.81-2.67)	1.50 (0.74-2.93)	0.59 (0.29-1.71)
Venous	Diltiazem	13	0.60 (0.34-0.86)	1.47 (0.54-2.39)	0.94 (0.45-2.32)	1.37 (0.41-2.51)	1.05 (0.43-3.24)	0.69 (0.35-0.98)

No. = number of observations. Median values are given with ranges in parentheses. No significant effects of treatment were observed.

Sampling Site	Treatment	No.	Hypoxanthine Concentration ( $\mu$ M)					
			Pre	Dilatation				Post
				1	2	3	4	
Arterial	Placebo	11	0.60 (0.23-0.96)	0.41 (0.07-0.63)	0.33 (0.07-0.79)	0.25 (0.05-0.55)	0.20 (0.05-0.79)	0.15 (0.02-0.48)
Arterial	Diltiazem	12-13	0.70 (0.25-1.60)	0.31 (0.11-0.87)	0.34 (0.08-0.84)	0.29 (0.09-0.52)	0.24 (0.06-0.54)	0.16 (0.08-0.49)
Venous	Placebo	11	0.41 (0.11-0.97)	0.94 (0.44-5.20)	1.30 (0.16-2.33)	1.31 (0.33-2.07)	1.04 (0.33-2.41)	0.42 (0.03-0.93)
p Value				0.017	0.017	0.023	0.017	
Venous	Diltiazem	13	0.31 (0.09-0.85)	0.42 (0.17-2.52)	0.33 (0.10-4.89)	0.43 (0.06-5.58)	0.37 (0.05-3.13)	0.18 (0.03-0.65)

No. = number of observations. Median values are given with ranges in parentheses. Where differences between placebo and diltiazem were statistically significant, p values are given.

Sampling Site	Treatment	No.	Urate Concentration ( $\mu$ M)					
			Pre	Dilatation				Post
				1	2	3	4	
Arterial	Placebo	13	236 (192-449)	224 (185-457)	234 (179-481)	220 (177-455)	212 (174-469)	225 (168-462)
Arterial	Diltiazem	12-13	246 (138-347)	244 (136-352)	240 (131-351)	226 (128-358)	243 (126-348)	238 (115-348)
Venous	Placebo	13	242 (188-495)	221 (181-481)	217 (182-478)	230 (178-480)	238 (174-512)	221 (173-469)
Venous	Diltiazem	13	244 (144-342)	250 (131-356)	251 (130-351)	251 (130-352)	247 (128-359)	238 (124-348)

No. = number of observations. Median values are given with ranges in parentheses. No significant effects of treatment were observed.

urate were similar for both groups (Tables II through IV).

**Electrocardiographic measurements:** No ST-segment or T-wave abnormalities were observed before angioplasty. Figure 1 shows the actual degree of ST-segment elevation during each occlusion. Electrocardiographic measurements taken from the intracoronary lead and the anterior wall leads V<sub>2</sub>, V<sub>4</sub> and V<sub>6</sub> show that ST elevation tended to be smaller in the placebo group, but the differences were not significant. Some patients did not develop ST-segment elevation during transluminal occlusion. Although they did not show any

collaterals on pretreatment coronary arteriography, it is possible that they developed collaterals during balloon occlusion. ST-segment depression during occlusion was observed on only 1 occasion.

**Lactate release:** The arterial lactate concentrations were not affected by diltiazem (Table II). After angioplasty great cardiac venous lactate increased 2- to 3-fold ( $p < 0.01$ ) in both the placebo and diltiazem groups. Figure 2 shows the arteriovenous difference of lactate at control and after each balloon dilatation. Patients in both groups produced lactate immediately after the balloon deflations. Treatment with diltiazem tended to

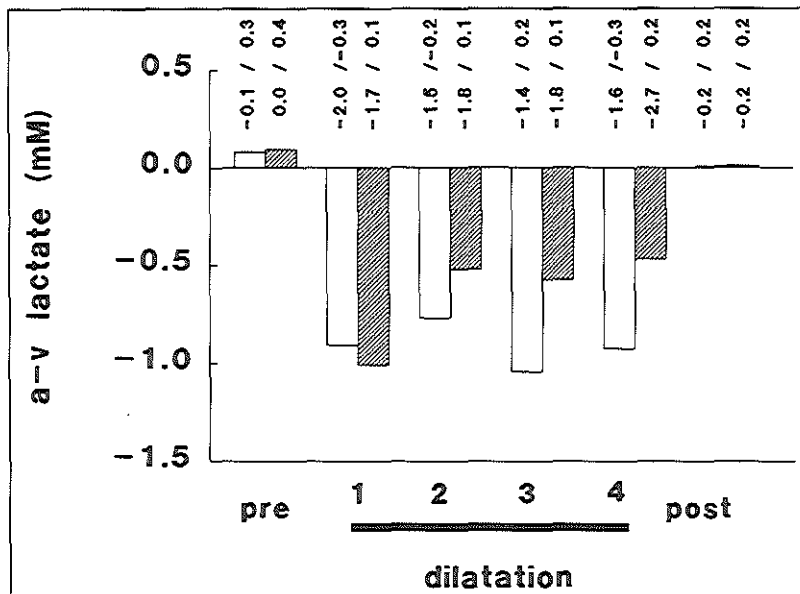


FIGURE 2. Effect of diltiazem on lactate uptake by the heart. Immediately after angioplasty, lactate production was noted, as the great cardiac venous concentration exceeded the arterial one. Bars indicate the median values, ranges are given above the columns. Open bars = placebo; hatched bars = diltiazem. No significant effects of treatment were found. a = arterial; v = venous.

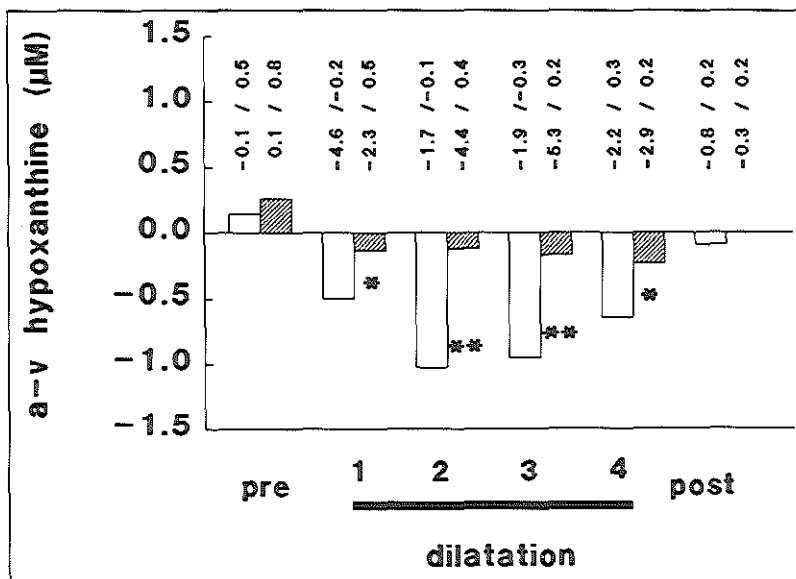


FIGURE 3. Effect of diltiazem on hypoxanthine uptake by the heart. Immediately after angioplasty, hypoxanthine production was noted, as the great cardiac venous concentration exceeded the arterial one. Bars indicate the median values, ranges are given above the columns. Open bars = placebo; hatched bars = diltiazem. Treatment with diltiazem lowered hypoxanthine production after each dilatation significantly. \* p < 0.05; \*\* p < 0.01. Abbreviations as in Figure 2.

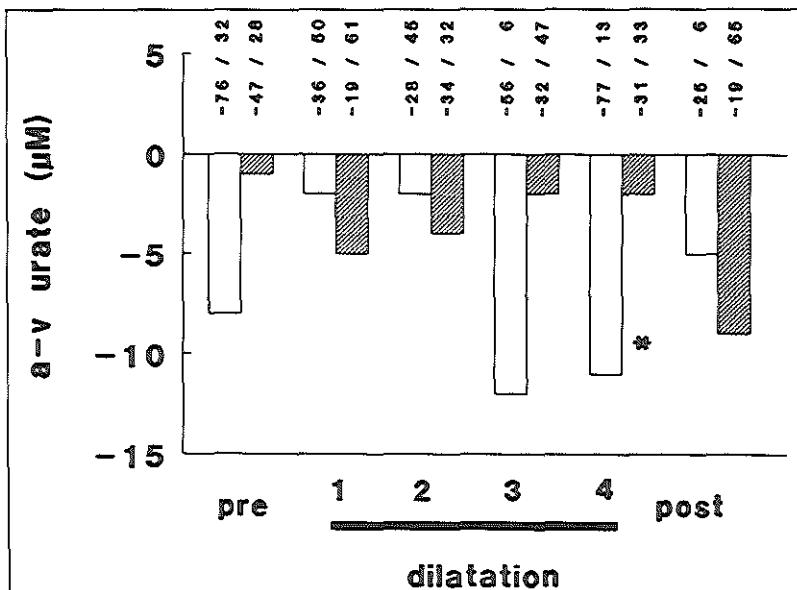


FIGURE 4. Effect of diltiazem on urate production by the heart. Bars indicate the median values, ranges are given above the columns. Open bars = placebo; hatched bars = diltiazem. Treatment with diltiazem significantly reduced the urate production found immediately after the last dilatation. \* p = 0.047. Abbreviations as in Figure 2.

reduce lactate production after angioplasty was performed ( $p > 0.05$ ).

**Hypoxanthine metabolism:** The hypoxanthine concentrations are listed in Table III. Diltiazem did not affect the arterial values. In the placebo group, the great cardiac venous hypoxanthine concentrations increased 3- to 5-fold ( $p < 0.01$ ) after each dilatation. In contrast, only a minor increase was observed in diltiazem-treated patients (Table III). In these patients venous hypoxanthine was lower ( $p \leq 0.02$ ) than that in the placebo group. Figure 3 shows the effect of placebo and diltiazem on hypoxanthine production by the heart. Samples taken directly after the 4 occlusions showed 63 to 88% lower hypoxanthine production in the diltiazem group than in the placebo group ( $p < 0.05$ ).

**Urate release:** Diltiazem had no significant effect on the arterial and venous urate concentrations (Table IV). Figure 4 shows the effect of placebo and diltiazem on urate production by the heart. At rest and directly after the first 3 dilatations, there were no significant differences between the groups. Only immediately after the fourth dilatation was urate release smaller ( $p = 0.047$ ) in the diltiazem group.

**Diltiazem levels:** The plasma concentrations of diltiazem, measured 5 minutes after the last deflation, varied widely (132 to 4,730  $\mu\text{g/liter}$ , median 902).

## DISCUSSION

**Electrocardiographic data:** We did not detect a statistically significant effect of diltiazem treatment on ST-segment changes during coronary angioplasty. The changes tended to be larger in the diltiazem group. In contrast, several investigators<sup>5,7,8</sup> observed that severity and time to onset of ischemic ST- and T-wave changes during coronary angioplasty were significantly reduced after treatment with this drug. In other studies, the administration of diltiazem has also been shown to reduce ST-segment elevations due to pacing-induced ischemia in dogs<sup>9</sup> as well as in man.<sup>10</sup> We cannot explain the discrepancies between our results and these reports.

**Lactate production:** In this study, diltiazem tended to reduce the amount of lactate produced by the heart subjected to coronary angioplasty. However, this effect was not statistically significant. Hanet,<sup>4</sup> Werner<sup>6</sup> and their co-workers reported a significant reduction in lactate production with other calcium antagonists used intracoronarily. Remme et al<sup>10</sup> observed that diltiazem could attenuate significantly lactate production induced by rapid atrial pacing.

**Hypoxanthine and urate release:** After ischemia the human heart releases hypoxanthine due to adenosine triphosphate catabolism. This has been demonstrated during pacing stress testing,<sup>23,25</sup> coronary angioplasty<sup>26</sup> and heart surgery.<sup>2,27</sup> In our study, hypoxanthine production was also obvious after each balloon deflation. Diltiazem could diminish this production. Based on animal studies,<sup>11-15</sup> it seems unlikely that the drug influenced purine uptake/release independent of adenosine triphosphate hydrolysis. An interesting aspect of the present investigation is the production of urate (Figure 4).<sup>27</sup> This could be partly suppressed by diltiazem. The

appearance of urate indicates that the human heart contains xanthine oxidoreductase. This enzyme exists in the heart in a number of species,<sup>28</sup> but its presence in human heart is controversial.<sup>29,30</sup> We cannot exclude that the enzyme could be active in the intact human heart, generating free radicals in its oxidase form.

**Diltiazem levels:** We are puzzled by the large variation in plasma diltiazem concentrations. The same phenomenon has been noted in other clinical trials (W.J. Remme, personal communication). Whether distribution or metabolism of the drug varies greatly from patient to patient is not known. We did not see a correlation between diltiazem blood level and suppression of, for example, hypoxanthine release.

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## Effect of Intravenous Metoprolol Given During Angioplasty in Patients with Single-Vessel Coronary Artery Disease

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**In a double-blind, randomized, placebo-controlled trial, the possible cardioprotective effect of metoprolol during ischemia caused by percutaneous transluminal coronary angioplasty was tested. Electrocardiograms, hemodynamics and myocardial metabolism were studied in 27 patients with a stenosis in the left anterior descending coronary artery. Measurements took place before angioplasty, after each of 4 1-minute occlusions and 15 minutes after the last balloon deflation. Patients were randomly given placebo or metoprolol (15mg as a bolus intravenously, followed by an infusion of 0.04mg/kg per hour). At the end of the procedure, the rate• pressure product had decreased by 15% (NS) and 23% ( $p = 0.001$ ) in the placebo and metoprolol group, respectively. This was mainly due to similar decreases in heart rate. Metoprolol tended ( $p = 0.060$ ) to reduce time to recovery of precordial and intracoronary ST-segment elevation due to angioplasty. Chest pain was lower in the treated group, but the effect was not statistically significant. Lactate, hypoxanthine and urate release immediately after deflation was similar in both groups. Metoprolol reduced the arterial plasma hypoxanthine concentration throughout the procedure, by about 30% ( $p \leq 0.02$  vs. placebo).**

**Thus, intravenous infusion of metoprolol tended to attenuate chest pain and ST-segment elevation, but failed to affect cardiac lactate and oxypurine release. It did, however, reduce significantly the arterial hypoxanthine concentrations during angioplasty, possibly indicating that the  $\beta$ -blocker inhibits extracardiac adenosine-triphosphate catabolism.**

Running head: Metoprolol during Angioplasty

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**B**eta-blockers protect against unstable angina and reduce the risk for myocardial infarction and sudden death.<sup>1-6</sup> In isolated hearts propranolol exerts an energy-sparing effect during ischemia.<sup>7,8</sup> A beta-blocker, administered intravenously or intracoronarily, protects against ischemia during acute coronary occlusion in man.<sup>9,10</sup> Bonnier et al. showed recently that a calcium entry blocker, diltiazem, could reduce oxypurine production from high-energy phosphates, induced by percutaneous transluminal coronary angioplasty (PTCA). In the present study, published in abstract form<sup>12</sup>, we tested whether metoprolol could further attenuate ischemic injury during this procedure, e.g., by diminishing adenosine-triphosphate breakdown.

### EXPERIMENTAL

**Study population:** The trial involved 27 patients with 1-vessel coronary artery disease undergoing PTCA. They all showed an isolated proximal stenosis <1 cm in the left anterior descending artery (narrowing >80%), without demonstrable collaterals. Beta-blocker treatment was discontinued  $\geq 1$  week before the procedure; other cardioactive drugs were withheld 48 hours before the study. With the exception of heparin, no drugs were given during the study before completion of data acquisition. The institutional committee on patient research approved the project. All patients gave informed consent before the study; they did not suffer protocol-related complications.

**Coronary angioplasty:** The procedure has been described in detail before.<sup>11</sup> Briefly, a diagnostic catheter was introduced in the great cardiac vein. A guiding catheter was introduced percutaneously and advanced to the aortic root. The left anterior descending artery was visualized with contrast medium after the first venous and arterial samples were taken. Then PTCA was performed using a standard balloon catheter over the guide-wire, with maximal inflation pressures ranged from 6 to 12 atmospheres. For each patient, the dilatations were sustained for 60 seconds, regardless of chest pain; 4 consecutive dilatations were done, with  $\geq 5$  minutes between each inflation, and followed by control coronary angiography.

**Sampling:** Great cardiac venous and femoral arte-

rial blood samples, taken before, immediately after each deflation and 15 minutes after the procedure, were processed as previously described.<sup>13</sup>

**Lactate and purine analysis:** In the deproteinized samples, lactate was determined enzymatically.<sup>14</sup> In addition, the adenosine-triphosphate catabolites hypoxanthine and urate were assayed by high-performance liquid chromatography<sup>15</sup>, as modified by Huizer et al.<sup>13</sup> Hypoxanthine and urate were detected at 254 and 290 nm, respectively.

**Electrocardiograms:** These were monitored from the precordial leads V<sub>2</sub>, V<sub>4</sub> and V<sub>6</sub> and the intracoronary lead, and analyzed as described before.<sup>11</sup>

**Experimental regimen:** The patients were randomly treated with placebo or beta-blocker (double-blind). After baseline arterial and venous samples had been taken, 3 loading doses of 5 mg (5 ml) of a racemic mixture of S- and R-metoprolol tartrate (Seloken<sup>R</sup>, Astra) or placebo (5 ml saline) were rapidly injected intravenously at 2-minute intervals. Then the first dilatation took place. The bolus injections were followed by a continuous infusion of metoprolol 0.04 mg/kg per hour (or placebo) after the second balloon deflation. (For continuous use the drug was diluted with saline to 0.1 mg/ml.) Plasma metoprolol was determined gas chromatographically with electron capture detection.<sup>16</sup>

**Pain:** At the end of each inflation, patient's chest discomfort was scored with Borg's new pain-scale.<sup>17</sup>

**Statistical analysis:** The statistical package for social science (SPSS-X) was used for data analysis. Adequacy of metoprolol dosing was evaluated by comparing the post-PTCA heart-rate and double-product values with baseline data (Student's t-test). ECG variables and arteriovenous differences were expressed as changes from baseline before being subject to multivariate analysis. Analysis of variance with repeated measurements was used, with treatment and time as variables. Student's t-test was used for the between-group analysis, except for the comparison of the chest-discomfort rating scale (Mann-Whitney 2-sample test). Unless otherwise stated, results are given as mean  $\pm$  standard error.  $p < 0.05$  was considered significant.

## RESULTS

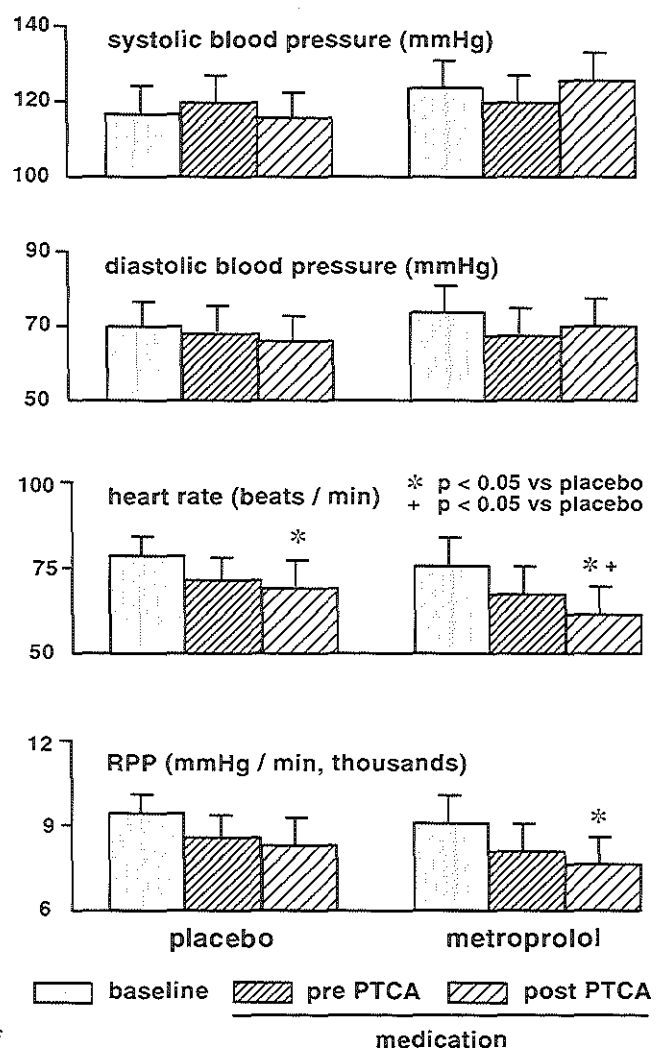
**Clinical characteristics:** The study population was relatively homogeneous; for example, age and severity of the stenosis in the left anterior descending artery (Table 1), and ejection fraction of the left ventricle (not shown) in the 2 groups were comparable. The disease of all patients was classified as Grade III of the Canadian Cardiovascular Society. They experienced angina pectoris only during exercise and received anti-anginal therapy.

Inflation time, inflation pressure and pain symptoms during the 4 consecutive inflations were comparable in the metoprolol group (average 59.8 seconds, 11 out of 12 patients with pain) and the placebo group (average 60.2 seconds, all 15 patients with pain). Cross-sectional area of the stenosis before and after coronary angioplasty decreased by about 85% in both groups (Table 1). The baseline values of plasma lactate, hypoxanthine and urate were similar for both groups.

**TABLE 1** Clinical Characteristics of the Study Groups

Variable	Placebo Group n=15	Metoprolol Group n=12
Age (yrs), Average $\pm$ SE	59 $\pm$ 2	57 $\pm$ 2
Range	46-75	42-72
Sex: MF	12/3	10/2
Essential hypertension	1	1
Hyperlipidemia	0	1
Smokers (presently)	6	8
Irregular heart rhythm	0	2
Diabetes mellitus	1	0
Severity of stenosis (%)		
Before angioplasty	93.0 $\pm$ 0.8	92.5 $\pm$ 1.3
After angioplasty	15.6 $\pm$ 0.7	15.3 $\pm$ 1.3

None of the differences reached significance at  $p < 0.05$ .

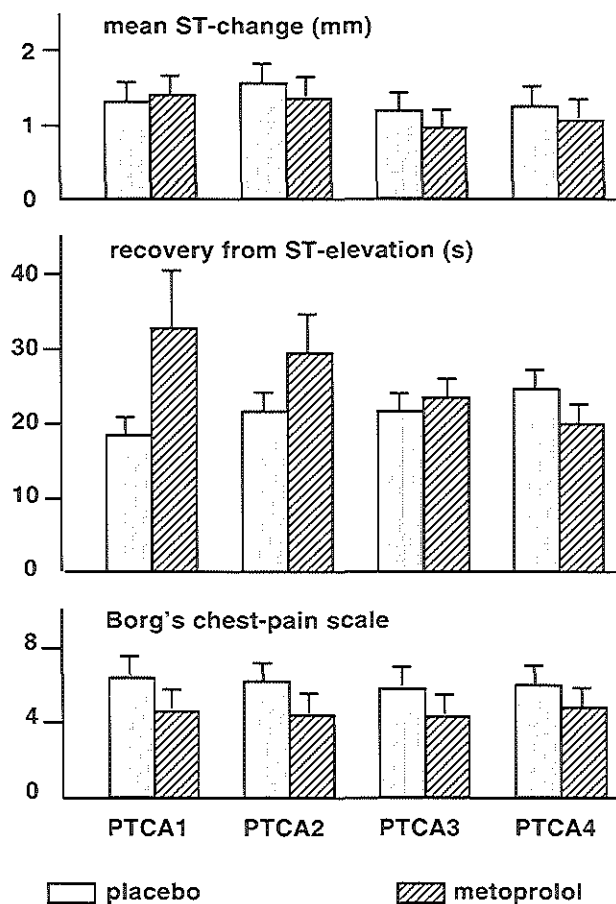


**FIGURE 1.** Hemodynamics before medication, after the bolus injections, and 15 minutes after the last deflation. Metoprolol treatment (n = 12) induced a larger decrease in heart rate than placebo treatment (n = 15) did; however, the drop in rate-pressure product (RPP) did not differ significantly between the groups.

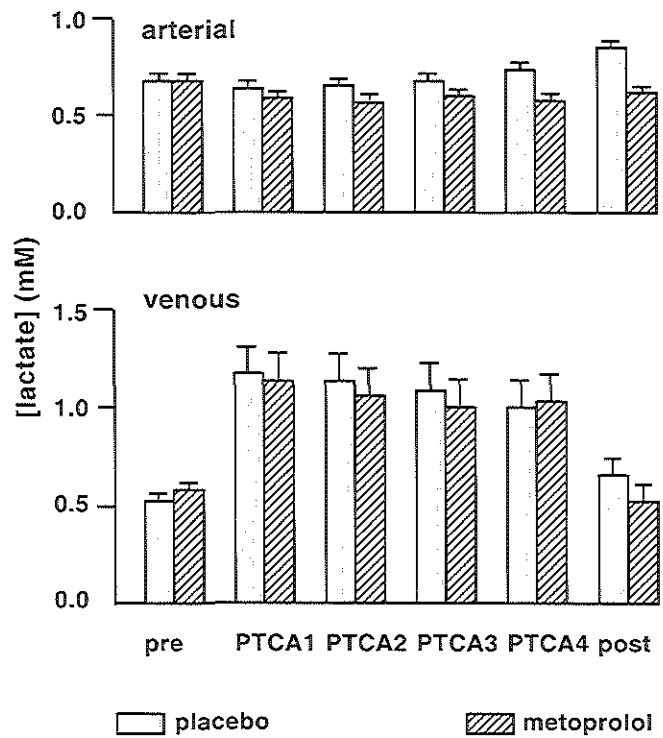


**Hemodynamics:** Systolic and diastolic blood pressure did not change significantly throughout the procedure (Figure 1). In the placebo group, heart rate decreased 15% 15 minutes after the last deflation ( $p = 0.007$  versus baseline); in the metoprolol group, heart rate dropped by 23% ( $p < 0.001$  versus baseline,  $p = 0.03$  versus placebo). The rate-pressure product fell significantly only in the latter (by 23%,  $p = 0.001$ ). Metoprolol did not influence this variable significantly in comparison with placebo (Figure 1).

**Electrocardiographic measurements:** No statistically significant differences were found between the treatments for the ST-segment changes (as the mean of the anterior wall leads  $V_2$ ,  $V_4$  and  $V_6$ , Figure 2). The absolute intracoronary and peak ST-segment changes, as well as for the time to onset of the ST-changes, showed similar results. A trend ( $p = 0.060$ ) in reduction in time to recovery of ST-changes with metoprolol compared to placebo was found (Figure 2): The time to recovery of ST-elevation – initially somewhat higher in the metoprolol group – decreased under the influence of the drug, and increased in the placebo group.



**FIGURE 2.** Effect of metoprolol on precordial ST-segment changes, recovery of ST-elevation, and chest pain during angioplasty. The pain scale is in arbitrary units: 0 = no pain, 10 = extremely strong pain. No significant effects of metoprolol treatment were found, although there was a trend ( $p = 0.060$ ) in favor of the drug in time to recovery of ST-elevation.  $n = 9-15$ .

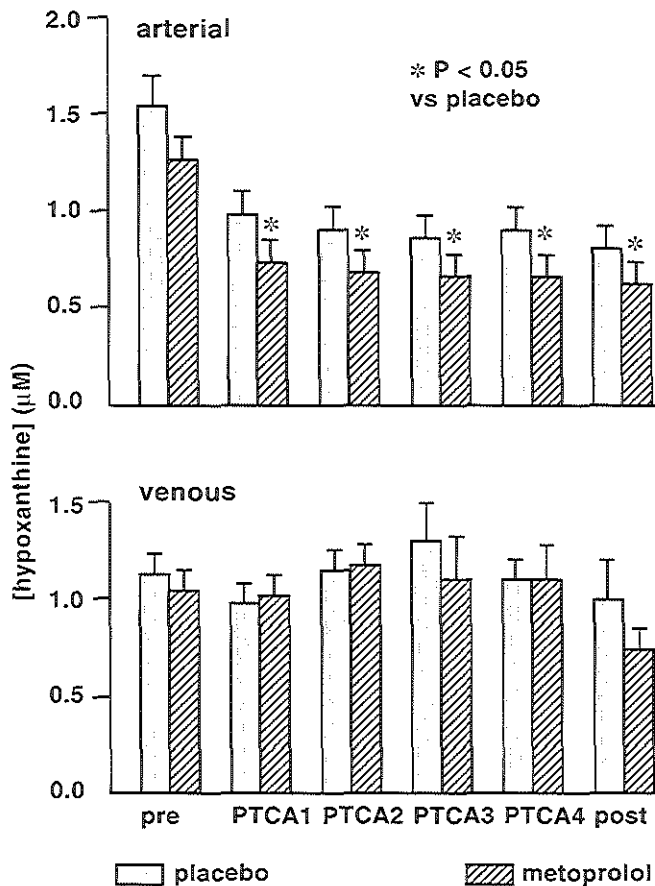


**FIGURE 3.** Effect of metoprolol on lactate metabolism of the heart. Drug treatment started after collection of baseline data. Immediately after angioplasty, lactate production was noted, as the great cardiac venous concentrations exceeded the arterial ones. No significant effects of metoprolol treatment were found.  $n = 12-15$ .

**Chest pain:** The groups did not differ statistically with regard to pain experienced during balloon inflation. However, for the metoprolol group consistently less pain was scored than for the placebo group (Figure 2).

**Lactate metabolism:** The arterial lactate concentrations were lower in the metoprolol group than in the placebo group, but the drug did not significantly affect them ( $p = 0.059$ , Figure 3). The same was true for the great cardiac venous lactate concentrations after angioplasty, which doubled in both groups. Also the arteriovenous difference in lactate was comparable between the groups.

**Hypoxanthine metabolism:** The arterial and venous concentrations of hypoxanthine are given in Figure 4 on page 66. In both groups, the arterial concentrations fell after the first deflation and remained low. After each dilatation, the arterial hypoxanthine concentrations in the metoprolol group were about 30% lower than in the placebo group ( $p \leq 0.02$ ). The great cardiac venous levels remained more or less constant during the study. The groups showed no significant differences in venous hypoxanthine concentrations or hypoxanthine production due to PTCA.



**FIGURE 4.** Effect of metoprolol on arterial and great cardiac venous hypoxanthine concentrations. Treatment with  $\beta$ -blocker lowered the arterial concentration during the procedure significantly. However, cardiac hypoxanthine production due to angioplasty was not significantly influenced.  $n = 12-15$ .

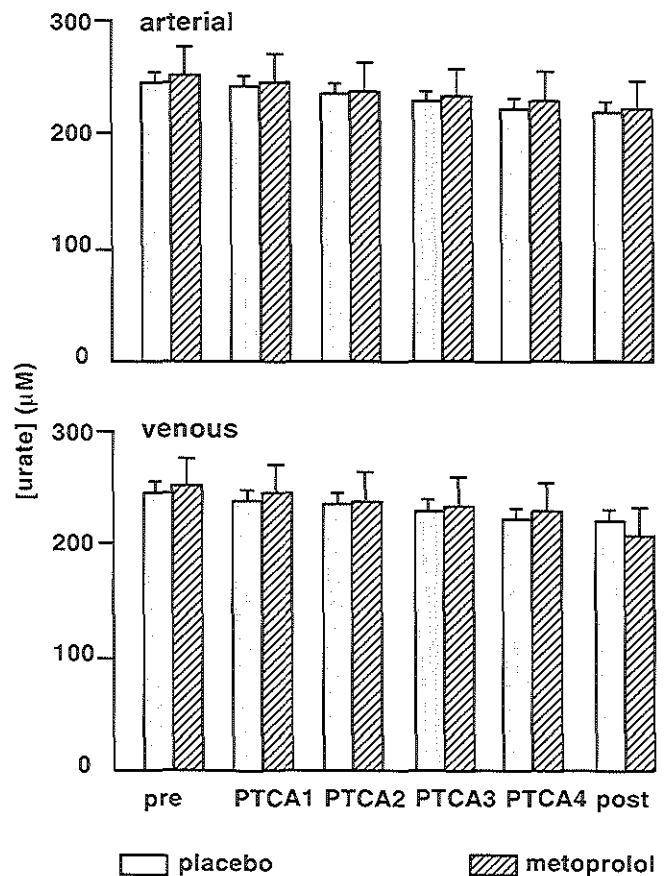
**Urate release:** Metoprolol had no significant effect on the arterial and venous urate concentrations, nor on urate production by the heart (Figure 5). Only 30% of the hearts produced (small amounts of) urate before PTCA, in contrast to the majority of hearts (usually 70%) after each deflation.

**Metoprolol levels:** The plasma concentrations of metoprolol, measured 5 minutes after the last deflation, varied relatively little ( $164 \pm 18$  nM).

## DISCUSSION

**Metoprolol dosing:** The plasma levels measured at the end of the procedure were within the therapeutic range for metoprolol.<sup>18</sup> We observed the expected drop in heart rate and double product (Figure 1), indicating that the drug suppressed partially the beta-adrenergic system of the patients. The time-effects found with some variables is perhaps due to metoprolol accumulation in cardiac tissue.<sup>19</sup>

**ECG changes and chest pain:** The leads used included those optimal for monitoring ischemia of the area perfused by the left anterior descending coronary artery.<sup>20</sup> We did not detect a statistically significant effect of metoprolol treatment on ST-segment changes



**FIGURE 5.** Effect of metoprolol on urate production by the heart. The drug did not affect the arterial and great cardiac venous urate concentrations, nor their difference across the heart.  $n = 12-15$ .

or chest pain during coronary angioplasty (Figure 2). However, the ST-segment changes and chest pain tended to be smaller in the metoprolol group. Labovitz et al.<sup>21</sup> recently observed some decrease of duration and extent of maximal ST-segment elevation during angioplasty by ultrashort-acting beta-adrenergic blockade. Metoprolol administration is highly effective in reducing ambulatory ischemia as evidenced by angina pectoris during daily life.<sup>22</sup>

**Lactate production:** Metoprolol was without effect on cardiac lactate metabolism (Figure 3). The drug tended to reduce the arterial lactate levels, which is in line with the reduction of arterial hypoxanthine (vide infra).

**Oxypurine metabolism:** After ischemia, the human heart releases hypoxanthine due to adenosine-triphosphate catabolism. This has been demonstrated during an atrial pacing stress test<sup>15,23</sup>, during coronary angioplasty<sup>11,24</sup>, and during open-heart surgery.<sup>25</sup> In contrast to earlier work<sup>11,24</sup>, coronary occlusion did not influence venous hypoxanthine. Still the arteriovenous difference became negative, because the arterial levels fell. The difference with earlier work, the relatively short balloon inflation time, could explain the discrep-

ancy. Metoprolol reduced the arterial hypoxanthine concentrations during the procedure (Figure 4). This could indicate that beta-blockade attenuates extracardiac adenosine-triphosphate breakdown. We speculate that beta-blockade leads to less anginal attacks<sup>22</sup> (cf. tendency in Figure 2) by lowering the plasma levels of the hypoxanthine precursor adenosine<sup>26</sup> (see also ref.8).

The appearance of urate (cf. ref.27) indicates that the human heart contains xanthine oxidoreductase. In line with in vitro observations<sup>28</sup>, perfusion of explanted human hearts with hypoxanthine shows little production of xanthine and urate in comparison to several other species.<sup>29</sup> Harrison et al.<sup>30</sup> demonstrated recently that xanthine oxidase, purified from human milk, has little affinity for its normal substrate(s). However, it has considerable reduced-nicotinamide-adenine-dinucleotide oxidase activity; this generates free radicals. Hopefully future investigations will reveal whether or not human heart contains this xanthine oxidase (the desulpho form).

**Conclusions:** (i) Metoprolol tended to attenuate chest pain and ST-segment changes due to coronary angioplasty. (ii) Cardiac lactate, hypoxanthine and urate release were similar in both groups. (iii) The drug lowered the arterial hypoxanthine concentration, possibly indicating that beta-adrenergic-blockade reduces extracardiac adenosine-triphosphate catabolism.

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## Summary and general discussion

The first part of this thesis deals with clinical and pathophysiological aspects of thrombolysis.

A comparison of intravenous anisoylated plasminogen streptokinase activator complex (APSAC or anistreplase) with intracoronary streptokinase for the treatment of patients with an acute myocardial infarction is presented in chapter one. Intravenously administered anistreplase appeared equally effective as streptokinase given intracoronary in lysing the thrombus responsible for acute myocardial infarction. The advantage of anistreplase would be its rapid and convenient mode of administration by single bolus intravenous injection over 5 minutes. The findings of our study were confirmed by Anderson et al.<sup>1</sup> and Relikvan Wely et al.<sup>2</sup> Earlier studies indicated that administration of intracoronary streptokinase is more efficient to recanalize the infarct-related coronary artery than intravenous streptokinase (60%–75% versus 45–60%).<sup>3–6</sup> So it could be expected that intravenous anistreplase might be superior to intravenous streptokinase. In the AIMS study<sup>7</sup> a 50% reduction in mortality was observed after treatment with anistreplase, compared with placebo. This difference was greater than the 25% relative mortality reduction after intravenous streptokinase in the GISSI-1<sup>8</sup> and ISIS-2<sup>9</sup> studies, although the confidence intervals overlapped. The absolute reductions in mortality in these studies were: AIMS: mortality anistreplase versus placebo: 6 versus 12%; difference (95% CI) –6% (–9 to –3%); GISSI-1: mortality streptokinase IV versus control: 11 versus 13%; difference (95% CI) –2% (–3% to –1%); ISIS-2: mortality streptokinase IV versus placebo: 9 versus 12%; difference (95% CI) –3% (–4 to –2%). However more recently Anderson et al. directly compared intravenous anistreplase with intravenous streptokinase in 370 patients and observed no differences neither in early patency nor in infarct size nor in hospital mortality.<sup>10</sup> Furthermore in the ISIS-3<sup>11</sup> mega-trial no differences were found in mortality and morbidity between anistreplase and streptokinase and r-tPA (alteplase®) all administered intravenously. The lack of survival difference in spite of superior early patency after r-tPA and anistreplase in comparison with streptokinase led to considerable discussion and confusion. White<sup>12</sup> in-

dicated that although patency after 90 minutes for r-tPA is superior, no differences are apparent between various thrombolytic agents after 3 hours or 24 hours. He questioned the influence of very early patency on infarct size and clinical outcome. Others have indicated that the r-tPA regimen used in GISSI-2 and ISIS-3 was not optimal, particularly because no immediate anticoagulation with intravenous heparin was achieved (ECSG-6).<sup>13</sup>

Unfortunately the discussion on the choice of thrombolytic drugs has been dominated by financial issues, and the use of streptokinase was advocated mainly because of considerable difference in price. If this price difference would become less important, other factors should also be considered. For example, anistreplase can be given as a bolus intravenous injection over 5 minutes, while streptokinase has to be administered via an intravenous infusion over a one hour period. Therefore anistreplase can be used more easily in the ambulance as done in the EMIP study.<sup>14</sup> When a bolus injection of anistreplase is administered, or a streptokinase infusion is given, the thrombolytic effect persists for 48 hours. On the other hand the action of alteplase stops immediately after its infusion is discontinued. This might result in a higher reocclusion rate after alteplase, unless a high level of anticoagulation is maintained. However Anderson et al.<sup>15</sup> in the TEAM-3 trial found no difference between anistreplase and alteplase in mortality and morbidity. Thus it remains uncertain whether the prolonged lytic state is indeed clinically significant. In contrast with streptokinase and anistreplase, alteplase does not produce any allergic reactions or drop in bloodpressure. In wider perspective, the difference in price, should not be exaggerated because the costs of the thrombolytic drug are only a fraction of the total costs of treatment of a myocardial infarction.<sup>16</sup> Pharmacological differences and ease of use should be considered. Particularly streptokinase and anistreplase should be avoided in patients with a reinfarction, because of development of anti-streptokinase antibodies when the patient was previously treated with streptokinase or anistreplase.

It is possible that in some patients a combination of thrombolytic drug may provide a more optimal result.

An example of such a regimen is the KAMIT trial, where a combination of alteplase and streptokinase compared with streptokinase alone improved coronary patency, without excessive bleeding complications.<sup>17</sup> This is currently under investigation in the GUSTO trial, where the effectiveness of four different regimens is compared: streptokinase with aspirin and delayed subcutaneous heparin as in ISIS-3, and alteplase, streptokinase and the combination of alteplase and streptokinase, all with aspirin and intravenous heparin are investigated. The dose of intravenous heparin is adjusted to APTT measurements.

It is now appreciated that the study of a single thrombolytic drug should be changed to studies of drug regimens or strategies. Further drug regimens may include newer drugs as hirudine (an antithrombotic drug) or antiplatelet drugs (IIb-IIIa receptorblocking agents)<sup>18</sup>, which might improve further reperfusion and prevent reocclusion.

Chapter two gives insight into the systemic effects of anistreplase and intracoronary streptokinase. We studied the major components of the coagulation and fibrinolytic process and looked for the relation between the systemic lytic state and clinical events such as reperfusion, reocclusion and bleeding complications. Both intravenous anistreplase and intracoronary streptokinase gave rise to a similar degree of activation of the fibrinolytic system, which became apparent in 93% of the patients. In this small patient cohort, there were no significant bleeding complications. In the Anderson study<sup>1</sup>, where a larger group of patients was studied, intravenous anistreplase caused less bleeding complications than intracoronary streptokinase. This probably reflects the increased bleeding risk after vascular access and angiography.

The third chapter addresses the significance of antibodies to streptokinase in relation to coronary thrombolytic therapy both with streptokinase and anistreplase. There is a possibility that patients undergoing thrombolytic therapy for acute myocardial infarction have had a streptococcus infection in the past. If subsequently streptokinase or streptokinase related anistreplase is used, their effect may be mitigated by the presence of antibodies. Similarly antibodies can be induced by previous treatment with anistreplase or streptokinase for an acute myocardial infarction, which limits the use of these components for the treatment of reinfarction. The aim of our study was to investigate whether antibodies are responsible for failure to restore reperfusion when these drugs are used. In eight patients who received streptokinase on two occasions, because treated reinfarction White observed allergic reactions in four patients.<sup>19</sup> In patients where alteplase was readministered no allergic reactions were observed. Unfortunately antibodies were not measured in this study. In our patients without preceding streptokinase or anistreplase infusions, we did not find IgE antibodies and did not observe any allergic reactions.

Furthermore reperfusion rate appeared not to be related to IgG antibodies to streptokinase, although the

systemic state was significantly influenced by such anti-streptokinase antibodies. Large series are required to determine whether increased IgG antibody levels tend to reduce the efficacy of streptokinase and anistreplase. Also the increased risk of late complications such as serum sickness and Guillain-Barré syndrome, which are occasionally seen after initial treatment<sup>20,21</sup> should be investigated. Therefore streptokinase and anistreplase are a good choice for the first infusion in patients with myocardial infarction, but for reinfarction alteplase, saruplase (Pro-urokinase) and urokinase, are probably better alternatives.

In chapter four we report a study on the influence of intravenous anistreplase on blood viscosity and platelet function in patients with acute myocardial infarction. We found a rapid and significant decrease of plasma- and blood-viscosity, which paralleled the decrease in plasma fibrinogen. Platelet aggregation rapidly decreased and fully recovered within 24 hours, which was followed by a state of hyperaggregation after 48 hours. This effect disappeared after one week. The phase of hyperaggregation might induce reocclusion, particularly if PTCA has been performed, which may result in extensive intravascular damage.<sup>20</sup>

The results of the study on the rheological effects of a nonionic contrast medium in vivo are discussed in chapter five. In the management of patients with acute myocardial infarction, contrast medium may be injected for various reasons. This study was performed to investigate the influence of nonionic contrast medium on rheology and platelet function. We found that nonionic contrast has a beneficial effect mainly by causing hemodilution. This can be concluded from the observation that blood viscosity decreases together with a marked fall in hematocrit while there was no change in plasma viscosity. The fall in hematocrit is caused by the added volume of the contrast medium plus a shift of water from the extravascular space to the plasma as a result of the high osmolarity of the nonionic contrast agent. Nonionic contrast had no effect on platelet aggregation.<sup>23</sup>

In chapter six we addressed the value of immediate PTCA after intravenous streptokinase in acute myocardial infarction.

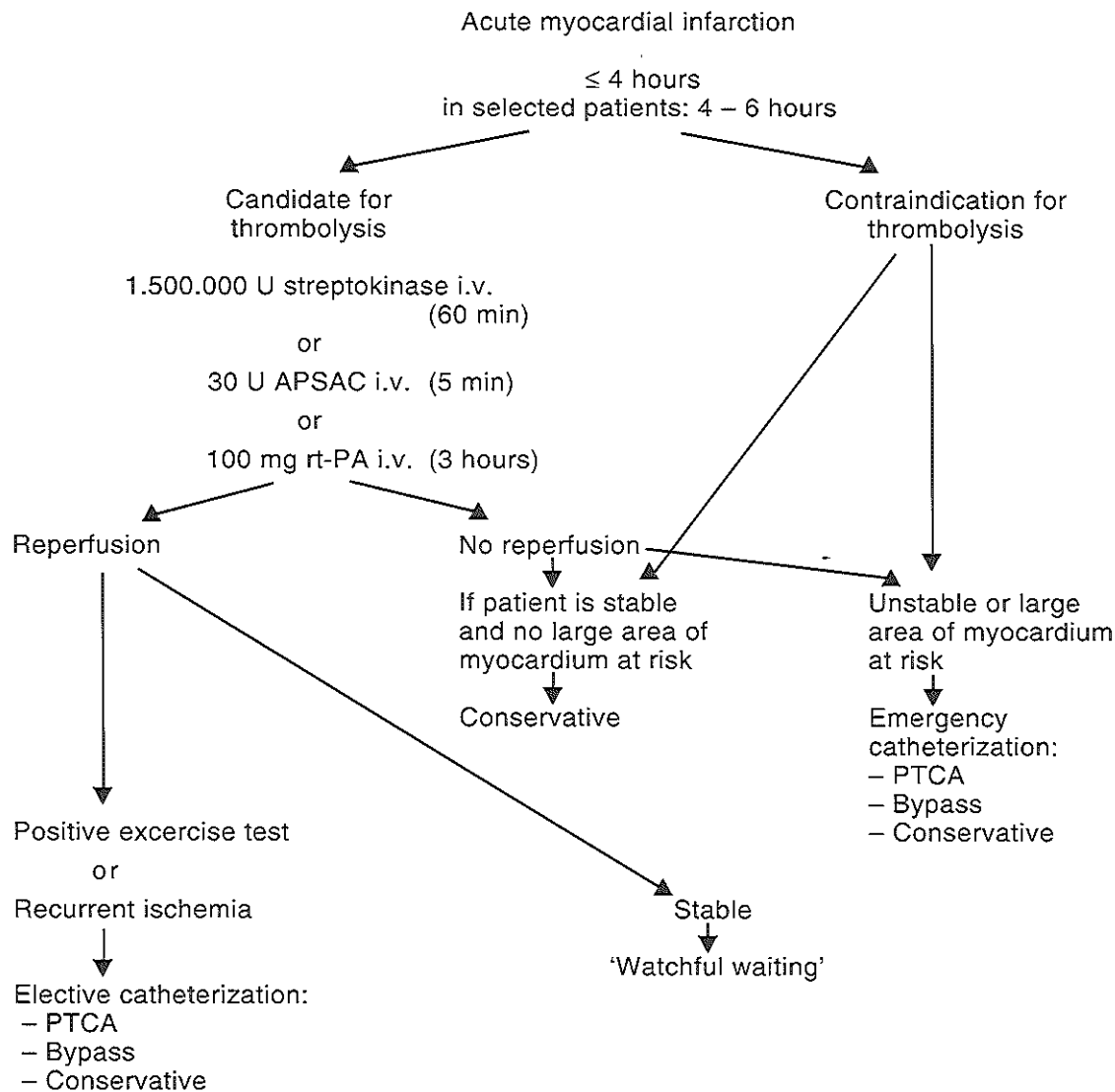
In this observational study patients were divided into three groups immediately after thrombolysis and angiography: patients with total occlusion; patients with an open vessel with > 70% residual stenosis and patients with an open vessel with < 70% residual stenosis in the infarct related vessel. In 28 out of 32 patients (87%) with total occlusion in spite of thrombolytic therapy, PTCA of the occluded vessel was successful. In those with an open vessel after thrombolysis, PTCA was effective in 40 out of 42 patients (95%)! During long-term follow-up (mean 23 months) one patient out of the group with totally occluded vessels after thrombolysis required re-PTCA and two underwent elective coronary bypass surgery. Furthermore one patient had an asymptomatic reocclusion, one had

a late myocardial infarction and one patient died suddenly after 17 months. In the ESCG-5, TAMI-1 and TAMI-2<sup>24,25,26</sup>, rescue PTCA appeared less satisfactory: mortality figures were respectively 7%, 4% and 3% and reocclusion occurred in 17%, 9% and 15%. The lower rate of reocclusion in our experience might be explained by the fact that we used streptokinase, while alteplase or urokinase were used in the ESCG-5 and the TAMI studies. It may be postulated that the systemic effect after streptokinase protects the patient against reocclusion. Furthermore we treated a selected group of patients and not all of the patients who arrived with a myocardial infarction got thrombolysis.

The role of PTCA in acute myocardial infarction remains controversial<sup>22</sup> in spite of several randomized trials.<sup>24,27,28</sup> More recently it has been proposed to perform direct PTCA, without thrombolysis in patients with evolving myocardial infarction. This would prevent activation of the coagulation sequence as induced by thrombolytic drugs.<sup>22</sup> In an ongoing trial Zijlstra et al.<sup>29</sup> now compare direct coronary angioplasty versus intravenous streptokinase in acute myocardial infarction.

From the preliminary results they concluded, that direct PTCA results in a higher patency rate, better preserved left ventricular function, and that there is less recurrent ischemia. More data are required, however, before this procedure can be recommended in clinical practice. In his thesis on thrombolysis and coronary angioplasty for acute myocardial infarction, H.Bosker<sup>30</sup> presented recommendations which were similar to those reached in the TIMI II-B<sup>27</sup> and the ESCG-5 studies.<sup>24</sup> He concluded that some subsets of patients may benefit from early PTCA: patients in cardiogenic shock, patients with a large anterior wall infarction and patients with a large area of myocardium at risk.

The approach we presently follow is summarized in the diagram and based on the experience gathered from our own studies and literature.<sup>22-31</sup> It should be appreciated, that such a scheme is oversimplified and that many other factors may play a role and contribute to the decisions in clinical practice.



Decision making diagram in patients with acute myocardial infarction.

This approach can be explained as follows:

**Timeframe:** Most patients with an acute myocardial infarction arrive or are admitted to the hospital within 4 hours. In general patients in the Netherlands arrive earlier compared with GISSI-2, ISIS-2 and ISIS-3. For example thrombolytic therapy in our study described in chapter one was started at an average of 2.4 hours after the onset of symptoms and in the study by the Interuniversity Cardiology Institute patients were entered in the hospital after a median of 90 minutes.<sup>31</sup> In contrast in Andersons study<sup>1</sup> conducted in the USA, treatment started after an average of 3.3 hours, which is approximately one hour later. The more rapid treatment in our study may be related to the short travel distances within The Netherlands. Furthermore it is possible that educational programmes, can help patients to recognize the symptoms of a heart attack earlier.

In GISSI-1<sup>18</sup> no benefit of thrombolytic therapy was observed after a treatment delay exceeding 9 hours. Similarly the EMERAS study, did not show any benefit in mortality from thrombolytic therapy after 6 hours.<sup>32</sup> Therefore we limit thrombolysis to patients admitted within 4–6 hours after onset of symptoms, even though ISIS-2 suggested some benefit of late therapy in a subset of patients.

**Reperfusion:** In our practice reperfusion was assessed without coronary angiography on the basis of clinical judgement including the general condition of the patient, disappearance of chest pain and recovery of the ST-segment in the electrocardiogram. It is possible that in the future continuous ST-segment monitoring will make this decision easier.<sup>33,34</sup>

**'Unstable':** Coronary angiography is considered in 'unstable' patients with recurrent pain, new electrocardiographic changes, sweating, bloodpressure drop or excessive bloodpressure elevation.

**Exercise test:** A submaximal exercise test is performed in stable patients before they leave the hospital. A positive test (ischemic ST-segment changes on the electrocardiogram during exercise with or without angina) is an indication for elective coronary angiography to assess whether PTCA or CABG should be offered. This decision depends on the extent of disease.<sup>27</sup> In our experience only 5%–10% of all patients treated with a thrombolytic agent need urgent CABG or PTCA because of instability.

The majority of patients can be managed with an initially 'conservative' approach. Of these patients 15%–30% will need PTCA or CABG at a later stage, as demonstrated in the TIMI-II study<sup>27</sup> and our own data. In 1991 27 patients (7%) out of 360 patients with an acute myocardial infarction required urgent interventions and 48 (13%) underwent an elective intervention.

In the second part of the thesis various aspects of PTCA are discussed.

The initial- and long-term results of the first 100 patients, who underwent PTCA for left anterior descending artery stenosis in our department are described in chapter seven. Although ultimately most patients may require bypass surgery, the majority in our study did not need surgery over an average follow-up of 102 months, despite the fact that 'restenosis' (defined as an increase of the luminal diameter stenosis of the dilated lesion above 50%) occurred in 22% of the patients. More than half of the patients remained asymptomatic and led a completely normal life after an average follow-up of 102 months. It is also noteworthy that all these patients undergoing a first PTCA procedure, were discharged from the hospital within 2 days and that none needed to be readmitted for anginal symptoms. In several large ongoing trials in which PTCA is compared with CABG (BARI: bypass angioplasty randomized investigation; CABRI: coronary angioplasty bypass randomized investigation, and others<sup>35</sup>) the cost/benefit aspect and quality of life aspects of both procedures will be investigated.

Chapter eight deals with symptomatic coronary artery disease in a population of 75 years or older. This is an increasing proportion of patients in our society. If the symptoms cannot be sufficiently controlled by medical treatment, the question arises what the optimal management for those patients should be: PTCA or CABG? Data in chapter eight indicate that PTCA gives very good results and in most patients may be preferable to coronary bypass surgery. Indeed our results show less major complications (4% in PTCA versus 7% in CABG), as well as a lower rate of other complications (4% in PTCA versus 30% in CABG) and a shorter hospital stay (4.3 days versus 14.2 days). PTCA of the culprit lesion alone was performed in 75% of all patients. At long-term follow-up, there was no difference in outcome between the PTCA and CABG patients. A point of criticism of this study is the selection of the patients, since it was a non-randomized series, and it is not recorded why PTCA was done in certain patients and CABG in the others (indication bias). An interesting observation was the fact that after a successful PTCA or CABG, late mortality in this group mainly resulted from non cardiac disease (cancer).

Factors which increase the risk of complications of the PTCA procedure and the results of emergency coronary bypass surgery in patients after failed PTCA are discussed in chapter nine. Although some groups of patients can be identified with increased risk during PTCA, it should be appreciated that even in 'low risk' patients unexpected complications occur, therefore also in these patients the risk is not negligible. The number of patients who are candidates for PTCA is increasing rapidly. In 1980 in our institution 20 patients underwent PTCA; in 1991 the number of interventions has increased to 1199 !!! In order to cope with these volumes it has been proposed to conduct low risk PTCA without immediate surgical standby. In fact, in Germany PTCA is already done on a large scale with surgical 'standby' in another remote hospital. Similar



practice is emerging in the United Kingdom.<sup>36</sup> This tendency seems to become more accepted by some cardiology groups. Apparently, in Germany and in the UK the number of centres performing cardiac surgery was not sufficient to accommodate the required number of PTCA procedures. In order to achieve some level of surgical standby a system of rapid transportation (ambulance, helicopter) to cardiac surgical centres was arranged. Recently this situation has somewhat improved, because several new centers started with cardiac surgery. The safety of remote PTCA has also improved through the development of 'bail out' coronary stenting, which allows to operate patients with PTCA complications on an elective basis.<sup>37</sup> However this approach should be investigated on a large scale, before it will be accepted in general practice.

In spite of new technical developments we believe, that remote PTCA should not be accepted in The Netherlands for several reasons. First of all we have sufficient cardiac surgical centres which are well distributed over the whole country. Thus, it is always possible to send a candidate for PTCA to a centre with surgical facilities. Secondly, there is (still) enough capacity for performing more PTCA's in the established centres. The waiting-lists do not result from lack of capacity but from budgetary restrictions. In several registries, it had been shown that large centres performing PTCA have higher primary success rates and less complications than centres where limited numbers of procedures are being done.<sup>38,39</sup> Finally it should be appreciated there are no reliable predictors which allow to identify the patient who is at low or high risk of complications during the PTCA procedure. In their recent 'Guidelines for percutaneous transluminal angioplasty', the American Heart Association and the American College of Cardiology classify the coronary lesions in types A, B and C.<sup>40</sup> This classification is only of limited help in predicting complication risk, because even in type A lesion, which has a high success rate and low risk of acute complications, such complications occur in some patients. Thus surgical standby during PTCA is still mandatory in all patients.

The study described in chapter ten was initiated to test the idea that the calcium-antagonist diltiazem could have a local cardioplegic effect during the PTCA procedure. This hypothesis was based on experimental evidence that diltiazem is able to delay the occurrence of pacing induced myocardial ischemia.<sup>41</sup> The administration of the drug before the intervention would thus potentially allow longer balloon inflations which might improve the PTCA results<sup>42</sup>, while the negative effects of ischemia would be avoided. However, it appeared that intravenous infusion of diltiazem did not reduce ST-segment elevation and lactate release<sup>43</sup>, although cardiac adenosinetriphosphate breakdown during angioplasty was reduced.

Subsequently we studied the effect of the beta-blocker metoprolol given intravenously during PTCA in patients with single-vessel coronary artery stenosis (chapter eleven). We found a tendency towards less

chest pain and a reduction of precordial ST-segment elevation which suggests that the degree of ischemia was reduced. This was not confirmed by the metabolic measurements since there was no effect on cardiac lactate, hypoxanthine and urate release immediately after deflation of the balloon. Metoprolol did, however, reduce the arterial plasma hypoxanthine level throughout angioplasty by about 30% ( $p < 0.02$  versus placebo). A possible explanation for this finding is that the beta-blocker metoprolol inhibits extracardiac adenosinetriphosphate catabolism, but not the cardiac adenosinetriphosphate catabolism. Again our results were inconclusive. This may be explained by the fact that balloon inflation to induce ischemia was limited to 60 seconds, instead of 90 or 150 seconds as in other investigations.<sup>44,45</sup>

It should be appreciated that it has not been established which medication should be given during and after PTCA. To reduce thrombotic complications administration of aspirin or other equivalent antiplatelet agents is mandatory.<sup>46</sup> The value of dextran is still unknown.<sup>47,48,49</sup> More powerful antiplatelet agents such as monoclonal antibodies are under investigation. Prolonged postprocedural heparinization may be useful in high risk PTCA patients.<sup>50</sup> It should be appreciated that patient response to heparin is highly variable. The standard '10,000' U heparin bolus injected before PTCA leads to activated clotting time (ACT)  $< 300$  sec. (what has been associated with thrombus formation) in 5% of patients with stable angina and in up to 15% of patients with unstable angina pectoris.<sup>51</sup> Nitrates are helpful in the event of occurrence of coronary spasm, but are not necessary in most patients.<sup>52</sup> The role of calcium channel blockers as diltiazem has been advocated to allow longer balloon inflations and prevent ischemia. This is probably only a theoretical benefit. Serruys et al.<sup>53</sup> showed that nifedipine intracoronary, when the left anterior descending artery was occluded during PTCA, reduces the contractile and mechanical function of the anterior wall of the left ventricle by a 'regional cardioplegic' effect, but increased the post-stenotic flow. Nifedipine prevents the metabolism of the ischemic cardiac cells from becoming anaerobic during transluminal occlusion for periods lasting up to 90 sec. Halpern et al.<sup>54</sup> showed a similar but less pronounced effect after diltiazem. Piessens et al.<sup>43</sup> reported reduction of ST-segment elevation and lactate release after infusion of diltiazem. This was, however, not shown in our study described in chapter 10, although we found a reduction of cardiac adenosinetriphosphate breakdown. Thus diltiazem may serve as a potential cardioprotective agent. Serruys<sup>55</sup> showed a similar effect for nifedipine. It should be appreciated that in spite of some beneficial effect of calcium channel blockers demonstrated in these studies it still needs to be proven whether it is indeed beneficial to locally treat the myocardium with a calcium antagonist immediately before PTCA. The role of calcium channel blockers during coronary spasm, occasionally seen during PTCA is well established.<sup>56,57</sup> Nevertheless in our study where half of the patients did not get calcium

channel blockers, no spasm was observed. It is possible that the new soft PTCA balloon material gives less stimuli to provoke spasm, in contrast with the old rigid catheters. The use of beta-blockers to prevent ischemia during PTCA is discussed extensively by Zalewski et al.<sup>45</sup> and Feldman et al.<sup>44</sup> They found a reduction in the degree of myocardial injury, judged by the extent of ST-segment elevation during occlusion of the left anterior descending artery and less pain during balloon inflation. We, however, could not confirm these findings in our study with metoprolol (chapter 11). So the benefit of using this drug during PTCA needs further investigation.

In this thesis some aspects of thrombolysis and interventional cardiology are discussed. Our aim was to optimize these new treatment modalities after their implementation in a nonacademic institution. We believe, that it remains mandatory to assess the results of such interventions in clinical practise, especially when these are still in an evolutionary phase. Continuous critical assessment of our medical practice is most essential in improving our therapeutic decisions to the benefit of our patients.

As Willem Einthoven said:

"The truth is all that matters, and what you and I think is inconsequential."

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# Samenvatting

Dit proefschrift behandelt twee onderwerpen die in de afgelopen jaren het karakter van de klinische cardiologie en meer bepaald de behandeling van patienten met coronarialijden sterk hebben beïnvloed.

Deel een behandelt de trombolyse van het acute hartinfarct en deel twee behandelt de interventie cardiologie.

Sedert de herintroductie van trombolyse als behandeling bij het acute hartinfarct in 1979 door P. Rentrop is door vele grote studies bewezen dat het geven van een tromboliticum een verbeterde overlevingskans geeft. Aanvankelijk werd streptokinase intracoronair toegepast, hetgeen omslachtig is en 24 uur per dag standby van de catheterisatiekamer vereist.

In onze kliniek vergeleken wij daarom het tromboliticum APSAC (anisoylated plasminogen streptokinase activator complex, anistreplase) een middel dat intraveneus in 5 minuten als een bolus gegeven kan worden met intracoronair toegediende streptokinase.

De resultaten, beschreven in hoofdstuk 1, laten zien dat intraveneus toegediende anistreplase even effectief is als intracoronair toegediende streptokinase, anistreplase heeft echter voordelen: de snelle toedieningsvorm, de lage reocclusie en de goede verdraagzaamheid door de patiënt.

Hoofdstuk 2 behandelt de effecten van intracoronair toegediende streptokinase en intraveneus toegediende anistreplase op het stollingsmechanisme. Er bleek vrijwel geen verschil te zijn. Slechts de totale fibrinolytische activiteit gemeten door de euglobuline-clotlystijd bleek langer te duren. Dit is mogelijk de verklaring voor de lagere reocclusie in de anistreplase groep, vergeleken met reocclusie in de streptokinase groep.

In hoofdstuk 3 wordt nagegaan of circulerende antilichamen tegen streptokinase in het bloed bij trombolytische therapie met streptokinase en anistreplase verantwoordelijk zijn voor het feit, dat niet bij 100% van de patienten reperfusie wordt bereikt. In deze studie konden we niet aantonen, dat reperfusie beïnvloed wordt door IgG antilichamen, wanneer streptokinase en anistreplase in een therapeutische dosering worden

toegepast. Wel werd de systemische lyse duidelijk beïnvloed door de antilichamen zonder echter de reperfusie te beïnvloeden.

In hoofdstuk 4 wordt ingegaan op het effect van anistreplase op de viscositeit van het bloed en bloedplaatjesfunctie. Verondersteld wordt dat een reductie van viscositeit gunstig kan zijn omdat het bloed beter zou kunnen doorstromen. We vonden dat inderdaad de viscositeit zowel in plasma als bloed significant afnam samen met een daling van het fibrinogeengehalte. Bovendien vonden we dat er na de fase van inhibitie van plaatjesaggregatie één tot twee dagen later een fase van hyperaggregatie ontstaat. Dit is mogelijk een verklaring voor de minder goede resultaten van PTCA enkele dagen na trombolyse. Nader onderzoek is noodzakelijk om deze hypothese te toetsen.

In hoofdstuk 5 worden de rheologische effecten in het bloed behandeld van een "non-ionisch" contrastmiddel dat wordt gebruikt tijdens catheterisatie. We vonden een duidelijke verlaging van de bloedviscositeit door een daling van de haematocriet. De plasmaviscositeit bleef gelijk ondanks de hoge viscositeit van het contrast. De haematocrietdaling wordt deels veroorzaakt door het volume van het contrast en door een verschuiving van water van de extravasculaire ruimte naar het plasma, als gevolg van de hoge osmolariteit van het contrastmiddel. Dus, uit rheologisch oogpunt, is een "non-ionisch" contrastmiddel uiterst geschikt omdat het hemodilutie geeft en dus de circulatie bevordert.

In hoofdstuk 6 komt een controversieel onderwerp aan de orde: het nut van percutane transluminale coronair angioplastiek (PTCA) van de verantwoordelijke stenose voor het hartinfarct na trombolyse. De studie is niet gerandomiseerd en de getallen zijn relatief klein. Het blijkt dat de patienten in onze kliniek die een PTCA ondergingen het goed deden. De patienten die een afgesloten vat hadden vóór de PTCA deden het zelfs beter dan degenen die een open vat hadden en dus geen PTCA nodig hadden omdat de vernauwing in het vat na trombolyse minder dan 70% was. Het is niet mogelijk uit dit niet gerandomiseerd onderzoek conclusies te trekken. Men kan zich echter wel afvragen of de

afwezigheid van een ernstige stenose na behandeling bij deze patiënten niet een rol speelt.

In deel 2 van dit proefschrift wordt ingegaan op verschillende aspecten van de interventie cardiologie.

In hoofdstuk 7 worden de lange termijnresultaten besproken van de eerste 100 patiënten die in ons ziekenhuis een PTCA van de ramus descendens anterior ondergingen. Het blijkt dat na de eerste behandeling meer dan de helft na 8,5 jaar geen angina pectoris heeft en geen dokter meer heeft geraadpleegd voor hartklachten. Dus PTCA is een uitstekende behandelingsmethode.

Hoofdstuk 8 behandelt de korte- en lange termijnresultaten van patiënten die vijfenzeventig jaar of ouder waren en die of een PTCA of een bypassoperatie ondergingen vanwege medicamenteus niet te behandelen angineuze klachten. Ofschoon dit geen gerandomiseerd onderzoek is, kunnen toch enkele belangrijke conclusies worden getrokken. PTCA blijkt bij oudere patiënten een veilige procedure te zijn. Ongeacht de uitgebreidheid van het coronariairlijden blijkt dilatatie van de laesie, verantwoordelijk voor de klachten, voldoende. De peri-procedurele complicaties zijn minder vergeleken met patiënten die een kransvatomleidingsoperatie ondergingen. In onze optiek verdient PTCA daarom de voorkeur boven bypasschirurgie bij deze categorie patiënten, wanneer de laesie, verantwoordelijk voor de klachten, kan worden vastgesteld.

Hoofdstuk 9 behandelt de uitkomst van patiënten die vanwege een PTCA met een complicatie een spoed bypassoperatie dienden te ondergaan. Uit deze studie

bleekt eens te meer dat adequate chirurgische standby van groot belang is. De mortaliteit van alle patiënten die een spoedoperatie ondergingen vanwege een mislukte PTCA bedroeg 2,6%, ondanks het feit dat 24 patiënten in cardiogene shock waren toen ze werden geopereerd. Snelheid van handelen na een PTCA met complicaties is van levensbelang!

Hoofdstukken 10 en 11 behandelen het effect van intraveneus diltiazem en metoprolol (een beta-receptor blokker) op myocardischemie veroorzaakt door het opblazen van de ballon tijdens PTCA. In samenwerking met het Cardiochemisch laboratorium van het Thoraxcentrum van de Erasmus Universiteit in Rotterdam werden diverse metaboliëten gemeten zoals lactaat, hypoxanthine en uraat. Verder werd het ECG continu geregistreerd. We vonden dat diltiazem de cardiale adenosinetri-fosfaatafbraak reduceert tijdens PTCA, wat blijkt uit een verminderde productie van uraat en hypoxanthine, diltiazem had echter geen invloed op de lactaat-productie en ST-segment afwijkingen.

Voor metoprolol gold dat het mogelijk de pijn op de borst tijdens PTCA verminderde en dat er minder ST-segment elevatie optrad, maar dat het geen invloed had op de lactaat en oxypurine uitstorting. Het had wel invloed op de arteriële hypoxanthineproductie, wat er mogelijk op duidt dat metoprolol het extracardiale adenosinetri-fosfaat catabolisme beïnvloedt.

Dit proefschrift geeft antwoord op een aantal vragen betreffende nieuwe behandelingsmethoden uit de klinische praktijk en draagt bij aan de discussie over een aantal controversiële onderwerpen. Duidelijk is dat zowel in de trombolysen als in de interventie cardiologie nog vele vragen onbeantwoord blijven.

# Curriculum vitae

Hans Bonnier was born on the 4th of December 1941 in Arnhem.

He received his medical degree from the University of Nijmegen in 1971 and his certificate in cardiology after his training in the Thoraxcenter in Rotterdam (chief: Prof. P.G. Hugenholtz) and a training period of 6 months at the University of Alabama in Birmingham, USA, in the department of Prof. John Kirklin and Prof. Thomas James, in 1977.

Since October 1978 he has worked at the Catharina Hospital in Eindhoven as a staff member of the department of cardiology.

Since 1980 he has worked in the field of interventional cardiology and thrombolysis.

He has written several articles on these subjects and participated as course director in several interventional courses in- and outside Europe.

He has participated in the past and is presently participating in several international trials.

At present he is the President of the working group on interventional cardiology of the Dutch Society of Cardiology and a member of several committees.

He is married with Henriette and has 2 children: Cecile and Marieke.