PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY IN ACUTE ISCHEMIC SYNDROMES

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Percutane Transluminale Coronaire Angioplastiek bij Acute Ischemische Syndromen

PROEFSCHRIFT

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus Prof. Dr. A.H.G. Rinnooy Kan
en volgens besluit van het College van Dekanen

De openbare verdediging zal plaatsvinden op
woensdag 14 september 1988 om 14.00 uur

door

Haryanto Suryapranata

geboren te Pangkalpinang (Indonesië)

PROMOTIECOMISSIE

Promotor	:	Prof. Dr. J.R.T.C. Roelandt
Overige leden	:	Prof. P.G. Hugenholtz Prof. Dr. A.V.G. Bruschke Dr. P.D. Verdouw
Co-promotor	:	Dr. P.W. Serruys

Financial support by the Netherlands Heart Foundation and Medtronic for the publication of this thesis is gratefully acknowledged.

My roots lie in China starting with Chu Liong, Chu - dynasty 1131 B.C., at the time that the emperor decreed that every man must have a family name and a wife.

The Yap family tree

To my parents

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ACKNOWLEDGEMENTS

First of all, I am grateful to Prof. PG. Hugenholtz and Prof. JRTC. Roelandt who enabled me to work in the stimulating atmosphere of the Thoraxcenter. Their continuing support and encouragement are deeply appreciated.

I would like to thank the other members of my dissertation Committee, Prof. AVG. Bruschke and Dr. PD. Verdouw, for their constructive guidance and willingness.

My deepest gratitude goes to Patrick Serruys for being both my friend and teacher. It has been a great privilege for me to be involved in his research activities. In fact, he introduced me to clinical research and his enthusiasm and intellect have been a source of inspiration and stimulation for all these years.

I would like to convey my deepest appreciation to Pim de Feyter for his indispensable role in preparing this thesis. His invaluable scientific criticisms and ideas have had a decisive influence which have enabled this work to become a reality. Words are not sufficient to express my gratitude.

I am also grateful to Marcel van den Brand, from whom, together with Patrick Serruys and Pim de Feyter, I have had the privilege and confidence to learn the technique of coronary angioplasty. It is a source of personal pleasure for me to know that I am able to have his continued support and friendship.

For the warm and friendly atmosphere and the profesional support of all the other cath.lab members, I wish to express my thanks to: Laetitia Bautz, Kevin Beatt, Ad den Boer, Gini van Bruggen, Nico Bruining, Margot van Dooren, Sylvia Espigares, Peter Frederik, Ingrid Huizing, Ingrid van Kessel, Jurgen Ligthart, Marie-angèle Morel, Ronald van der Perk, Marjo de Ronde, Roel de Ruiter, Linda Souhuwat, Gert-Jan Tanis, Jan Tuin, Susan Veldhof, Jan Verploegh, Nico Vogelaar, Linda de Vroed, Inge Zorn and Felix Zijlstra.

There are many other colleagues and friends who have contributed in one way or another. To them I offer my appreciation; in particular to: Aida Azar, Jantine van den Berg, Prof. E. Bos and his staff, Ron van Domburg, Cor van Dijk, Marianne Eichholtz, Myriam van Elst, Paolo Fioretti, Rene Geuskens, Peter-Paul Kint, Koos Lubsen, Hans Luijten, Simon Meij, Max Patijn, Maarten Simoons, Cees Slager, Jan Tijssen, Frank Vermeer, Johan Verroste, William Wijns, Cees Zeelenberg, and all members of the Working Group on Thrombolytic Therapy in Acute Myocardial Infarction of the Netherlands Interuniversity Cardiology Institute.

I am particularly grateful to Anja van Huuksloot, Gusta Koster-Wijker and especially to Claudia Sprenger de Rover, for the excellent secretarial assistance in preparing so many versions of the individual papers and this thesis.

Above all, I am most grateful to my parents for their love and moral support and for allowing me the opportunity to journey "so far". Finally, I owe a great debt to my wife Lieve and our children for enduring my selfish endeavours during all these years, especially to little Franciska who by her natural charm has tried to keep me from working.

OVERVIEW

Acute myocardial ischemic syndromes are apparently related to the underlying pathophysiology leading to the clinical instability. Depending on the completeness and the duration of blood deprivation, different clinical syndromes result, such as sudden death, acute transmural infarction, nontransmural infarction, or unstable angina. Recent clinical, angiographic, and pathologic studies have emphasized the important pathophysiologic link between unstable angina, acute myocardial infarction, and early postinfarction angina.

The term unstable angina is used for prolonged episodes of myocardial ischemia at rest in the absence of detectable myocardial necrosis. However, in the acute situation, when a patient presents with chest pain and electrocardiographic signs of ischemia, the distinction between unstable angina and myocardial infarction is often difficult. The uncertainty of outcome in a specific patient forces one to provide maximal treatment. The prime goal of any intervention in this situation must primarily be the preservation or early restoration of antegrade flow in the ischemia-related artery, in order to resolve myocardial ischemia and to prevent (further) myocardial necrosis, and so to improve both short- and long-term mortality and morbidity. Despite the latest substantial improvements in surgical techniques, cardioplegia, anaesthesia, and postoperative care, there is still no consensus as to the safety of surgery in the management of these subsets of patients. As an attractive alternative to coronary artery bypass surgery, percutaneous transluminal coronary angioplasty would logically play an important role in the management of patients with acute myocardial ischemic syndromes.

In chapter II of this thesis, the immediate and two-year follow-up results of coronary angioplasty in 200 consecutive patients with unstable angina are described. Furthermore, clinical, electrocardiographic, angiographic and angioplasty related variables are analyzed to identify predictors for unfavorable early and late outcome. The results indicate that coronary angioplasty for unstable angina can be performed effectively with a high initial success rate and an excellent long-term prognosis.

However, the procedural complications are definitely more frequent in this setting than with elective angioplasty. The reasons for the relatively high complication rate are again apparently related to the underlying pathophysiology leading to the clinical instability such as plaque fissuring with platelet aggregation and formation of a partial or even intermittent occlusive thrombus. These processes will lead to a critical reduction in myocardial blood supply and coronary

angioplasty, designed to enlarge the stenosed lumen, may effectively interrupt this process. On the other hand, coronary angioplasty itself may cause further injury of the already ulcerated intima and may have the potential to intensify the ongoing thrombogenic process in some of the patients with acute ischemic syndromes. This may lead to an increased frequency of abrupt closure of the artery during the procedure. This is a strong argument for adjunctive therapy with thrombolytic agents in the acute stage of the disease. Therefore, intracoronary streptokinase was adopted to the procedure in those patients with abrupt reclosure of the artery immediately after dilatation. The results of this additional strategy are discussed in chapter III.

In addition to the fact that coronary angioplasty can be performed effectively in patients with unstable angina, analysis of the global and regional left ventricular function further demonstrates the benefit of correcting these obstructive lesions, as shown in chapter IV.

Limitation of myocardial infarct size through salvage of ischemic myocardium in the region undergoing necrosis is the major goal in the management of patients with acute myocardial infarction. The concept of limiting infarct size by early recanalization has been proven in clinical practice to be effective and the beneficial effects of thrombolytic agents in acute myocardial infarction on infarct size, left ventricular function and patient survival have been convincingly shown. However, the very efficacy of this initial treatment has created a new problem: the management of patients with residual stenosis whose ischemic symptoms persist after thrombolysis. In order to maintain the initial benefit achieved by thrombolysis, it is necessary to deal with the underlying obstruction. Coronary angioplasty may play a valuable role in attaining these goals.

The role of coronary angioplasty immediately following thrombolysis in acute myocardial infarction is shown in chapters V and VI. Chapter V describes our experience with coronary angioplasty immediately after intracoronary streptokinase in 115 consecutive patients with acute myocardial infarction. The aim of the study described in chapter VI was to investigate whether immediate angioplasty after thrombolysis provided additional benefit in the preservation of regional myocardial function in the infarct zone by reviewing the results of the Netherlands multicenter trial of thrombolytic therapy in which selected patients underwent angioplasty. Preservation of global and regional left ventricular function with low mortality rate and other major cardiac events suggest that immediate coronary angioplasty after thrombolysis can be safely used to provide complete reperfusion in the setting of acute myocardial infarction and, in some patients, reperfusion may need to be supplemented by additonal revascularization procedure such as

angioplasty in order to optimize the chances of obtaining full functional recovery.

However, current available data on the use of coronary angioplasty are conflicting and no clear answers as yet have emerged about the additional value of angioplasty in acute myocardial infarction. The precise role, timing, and rationale for coronary angioplasty in acute myocardial infarction is still unsettled and requires further evaluation.

The high incidence of recurrent myocardial infarction and unstable angina in patients with non-Q wave myocardial infarction call for some prophylactic measure to prevent further loss of myocardium, for one might postulate that these patients are left with an "incomplete infarction" with an area of the myocardium "at risk" and might therefore benefit from revascularization of the relevant artery. The short- and long-term results of 114 consecutive patients treated with coronary angioplasty for severe angina after a non-Q wave myocardial infarction are described in chapter VII. The high initial success rate and the low incidence of subsequent death and late recurrent myocardial infarction, as well as the sustained symptomatic benefit suggest that coronary angioplasty is an effective initial treatment strategy in patients with angina after a non-Q wave myocardial infarction.

Chapter VIII analyzes the serial global and regional left ventricular function in patients undergoing coronary angioplasty early after a non-Q wave myocardial infarction. The results demonstrate not only that repeated ischemic attacks early after a non-Q wave myocardial infarction may lead to prolonged regional myocardial dysfunction, but more importantly, that this "stunned" myocardium has the potential to achieve normal contraction after successful coronary angioplasty.

Coronary angioplasty has now obtained a definitive place in the management of acute myocardial ischemic syndromes. The results of the present thesis show not only that coronary angioplasty can be performed safely and effectively in the management of patients with acute myocardial ischemic syndromes, but also that myocardial function may recover after successful coronary angioplasty. Research should be increased to further improve the technique, to accurately define the indications for and to study the extent (single-vessel versus multivessel dilatation) and the timing of dilatation in this group of acutely ill patients.

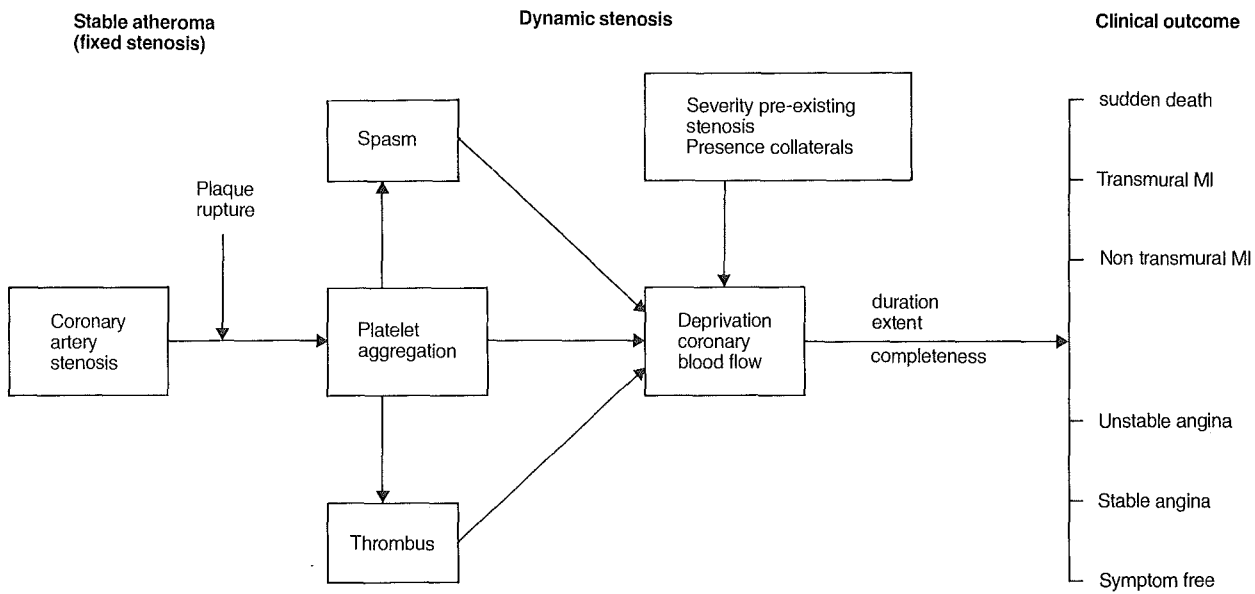
CHAPTER I

INTRODUCTION

Acute myocardial ischemic syndromes encompass the clinical entities of unstable angina, acute myocardial infarction, and early postinfarction angina. Similarities as well as differences compound the various clinical presentations. Clinically there may be considerable overlap between the groups. Additionally, it is common for a patient who presents with one clinical coronary syndrome to evolve either suddenly or at a later date to another syndrome.

Although our understanding of the pathophysiology of acute myocardial ischemic syndromes is incomplete, recent studies allow a better understanding of precipitating mechanisms leading to clinical presentation of our patients with acute ischemic syndromes. In the past few years there has been increasing clinical, angiographic, and pathologic evidence to suggest that the acute changes that initially occur in the coronary artery endothelium are similar in these patients with acute ischemic syndromes (1-15). It has become evident that the endothelial ulceration that occurs adjacent to an atherosclerotic plaque, the subsequent platelet adhesion and aggregations, and eventually thrombosis are the important underlying processes in acute ischemic syndromes. Several recent studies have emphasized this important pathophysiologic link between unstable angina, acute myocardial infarction and early postinfarction angina. The data which implicate these processes comes from a variety of sources, including careful histological studies (2,3) postmortem coronary angiography (4), antiplatelet studies in unstable angina (5,6) and thrombolysis in acute myocardial infarction (7,8), surgical findings following acute coronary occlusion (9), identification and recognition of specific morphology both angiographically (9-12) and angioscopically (13), and platelet activity studies (14,15).

The underlying culprit in coronary artery disease is the atherosclerotic coronary artery plaque. A stable atherosclerotic plaque develops neovascularization at its base. These vessels are fragile and may rupture with bleeding into plaque. The acute ischemic syndromes are initiated by injury to this atherosclerotic plaque. The initial stimulus that leads to ulceration of the endothelium overlying an atherosclerotic plaque has not yet been identified. Rheologic, hemodynamic and vasomotor stresses may initiate and propagate plaque damage, leading to further luminal narrowing. Plaque injury exposes circulating blood elements such as platelets to collagen and atherosclerotic debris within the plaque.


Stable atheroma
(fixed stenosis)
Dynamic stenosis
Clinical outcome
Spasm
Severity pre-existing
stenosis
Presence collaterals
Plaque
rupture
sudden death
Transmural MI
Non transmural MI
Coronary
artery
stenosis
Platelet
aggregation
Deprivation
coronary
blood flow
duration
extent
completeness
Unstable angina
Stable angina
Thrombus
Symptom free

Interaction at the damaged vessel wall with circulating catecholamines and local release of platelet-derived vasoconstrictor and thrombogenic substances such as thromboxane A2, leucotrienes, histamine and serotonin, or an imbalance of these relative to vasodilating and antithrombotic such as prostacyclin, endothelial-dependent relaxant factor and plasminogen activator, can lead to intraluminal thrombus, stenosis, constriction or coronary spasm (16-19). An immediate decrease in coronary flow or distal platelet emboli may lead to acute transient ischemia, subsequent malignant ventricular arrhythmias and sudden cardiac death. This process may stabilize because of endogeneous thrombolysis with or without subsequent expansion of the plaque leading to stable angina. Whether this new remodeled plaque is more prone to future injury is unknown. However, since blood flow is related to the fourth power of the coronary diameter, small changes in lumen diameter may worsen ischemia. Furthermore, critical lesions seem to have a high propensity to progression to total occlusion (20-23). These mechanisms may ultimately lead to a partially or totally occlusive thrombus or the thrombus may fragment either acutely or chronically with peripheral embolization. Other factors such as the severity of pre-existing stenosis, the extent of collateral circulation, the perfusion pressure, the intensity of anti-adhesion, deaggregation and vasodilation forces, and endogeneous thrombolysis will also influence the changes in coronary blood flow. In a complex interplay the balance between these competing forces determines whether the mass of the formed thrombus is partially or totally occlusive, or whether its presence is transient or permanent. Depending on the completeness and the duration of blood deprivation (a product of both intraluminal event and the available collateral flow), different clinical syndromes result, such as sudden death, acute transmural infarction, non-transmural infarction, or unstable angina (Fig. 1).

In unstable angina, the process is limited to endothelial ulceration, platelet aggregation and thrombus formation, which may be intermittent, or more permanent in the presence of an adequate collateral supply (2,3,10,13,24). Myocardial infarction is related to the same process but with the formation of a totally occlusive thrombus. When the balance between intracoronary thrombus and antithrombotic natural and pharmacologic factors lean toward continued thrombus formation, persistent total coronary occlusion leading to acute myocardial infarction may occur (1,10,24-27). If the coronary artery remains occluded for a long period (more than 15 minutes), then myocardial necrosis will occur. If very early clot lysis occurs or an adequate collateral supply is present infarction will be smaller (non-Q wave myocardial infarction) and if not or late clot lysis occurs, infarction will be larger (Q wave myocardial infarction) (9,28). In a

patient with non-Q wave infarction, rethrombosis and reocclusion often occur, leading to repeat myocardial infarction affecting the same myocardial region (28,29).

The term unstable angina is used for prolonged episodes of myocardial ischemia at rest (chestpain with electrocardiographic changes) in the absence of detectable myocardial necrosis. In retrospect, when the symptoms have subsided, unstable angina can be distinguished from myocardial infarction by the lack of elevation of serum cardiac enzymes. However, in the acute situation, when a patient presents with chest pain and electrocardiographic signs of ischemia, the distinction between unstable angina and myocardial infarction is often difficult. Treatment of patients in this situation is facilitated by the fact that the initial goal of therapy is the same: to resolve myocardial ischemia and to prevent (further) myocardial necrosis. In practice this means the preservation or early restoration of antegrade flow in the ischemia-related artery.

Percutaneous transluminal angioplasty, to widen the lumen of a stenotic vessel by means of an intravascular catheter, was first performed by Dotter and Judkins in 1964 (30). This technique proved effective in peripheral arteries. However, it took until 1977 before Gruentzig used this method, to dilate the coronary arteries of conscious man (31). In the ten years since the beginning of coronary angioplasty, this technique has expanded from a curiosity to a major therapeutic alternative for patients needing revascularization. Subsequent improvements in equipment and technique have established coronary angioplasty as a major treatment mode for stable angina in patients with single vessel disease. Recently, the initial restricted indications have been widened to include dilatation of complex lesions, multivessel lesions and vein grafts. As an attractive alternative to coronary artery bypass surgery, percutaneous transluminal coronary angioplasty would logically play an important role in the management of patients with acute myocardial ischemic syndromes. The advantages of coronary angioplasty over coronary artery bypass surgery in these critically ill patients are that the intrinsic risk of major surgery and anesthesia can be avoided, it is easy and rapid to implement, and there is a reduction of hospital stay and costs.

The present thesis describes our experience with coronary angioplasty in the management of patients with acute ischemic syndromes. The efficacy of coronary angioplasty in patients with unstable angina pectoris is described in chapters II-IV; chapters V and VI deal with the results of coronary angioplasty immediately following thrombolysis in patients with acute myocardial infarction; and finally, the role of coronary angioplasty in the management of patients with angina pectoris after a non-Q-wave myocardial infarction is discussed in chapters VII and VIII.

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CHAPTER II

CORONARY ANGIOPLASTY FOR UNSTABLE ANGINA: IMMEDIATE AND LATE RESULTS IN 200 CONSECUTIVE PATIENTS WITH IDENTIFICATION OF RISK FACTORS FOR UNFAVORABLE EARLY AND LATE OUTCOME

ABSTRACT

Two hunderd patients (164 men ; mean age 56 years, range 36 to 74) with unstable angina (chest pain at rest, associated with ST-T changes) underwent coronary angioplasty. In 65 patients with multivessel disease, only the "culprit" lesion was dilated. The initial success rate was 89.5% (179 of 200 patients). At least one major procedure-related complication occurred in 21 patients (10.5%): death in 1, myocardial infarction in 16, and urgent surgery in 18. All patients were followed-up for 2 years. There were 5 late deaths, 8 late non-fatal myocardial infarctions and angina pectoris recurred in 52 patients. The restenosis rate was 32% (51 of 158) in the patients with initial successful angioplasty who had repeat angiography. At 2-year follow-up after attempted coronary angioplasty in all 200 patients, the total incidence rate of death was 3% (1 procedure-related and 5 late deaths), of non-fatal myocardial infarction 12% (16 procedure-related and 8 late after angioplasty), and 13% (26 patients) were still symptomatic although they had improved in functional class. Multivariate analysis showed that variables indicated an increased risk a) for major procedure-related complications were: ST-segment elevation, persistent negative T wave and stenosis more than 65% (odds ratio 3.7, 3.7 and 3.3, respectively); b) for angiographic restenosis were: presence of collaterals, ST-segment depression, multivessel disease, left anterior descending coronary artery stenosis, and history of recent onset of symptoms (odds ratio: 2.2, 2.0, 1.9, 1.9, and 0.54, respectively); and c) for late coronary events (recurrence of angina, late myocardial infarction or late death) were: multivessel disease, total occluded vessel and ST-segment elevation (odds ratio 3.7, 2.8 and 0.44, respectively). Thus, coronary angioplasty for unstable angina can be performed with a high initial success rate, but at an increased risk of major complications. The prognosis is favorable after initial successful coronary angioplasty.

INTRODUCTION

The general term unstable angina is used to encompass patients who present with a wide variety of symptoms,

electrocardiographic changes, coronary anatomy and left ventricular function (1-3). This explains the wide divergence in prognosis reported by several studies (2,3). A subgroup of patients with unstable angina, who have chest pain at rest associated with electrocardiographic changes, have a poor short- and long-term prognosis (4-7). These patients must be considered as a different subgroup from the patients with new onset or progressive angina, who have a prognosis that is only slightly worse than that of patients with chronic stable angina pectoris (8-10). Management of unstable angina pectoris has evolved progressively and recently, coronary angioplasty has been shown to be a relatively safe and effective treatment for unstable angina (11-20).

In this study, we describe the immediate and 2-year follow-up results of coronary angioplasty in 200 consecutive patients with chest pain at rest associated with electrocardiographic changes. Furthermore, clinical, electrocardiographic, angiographic and angioplasty related variables were analyzed to identify predictors for a) major complications during attempted coronary angioplasty, or b) restenosis, recurrence of angina, late myocardial infarction or late death after initial successful coronary angioplasty.

PATIENTS AND METHODS

During the period from January 1983 to January 1985, a total of 2887 patients were admitted to our coronary care unit. Of these, 442 patients were considered to have unstable angina pectoris. Unstable angina was defined as chest pain at rest lasting for at least 15 minutes, associated with documented electrocardiographic ST-T changes and no subsequent signs of cardiac necrosis (cardiac enzyme increase less than twice normal and no development of a pathologic Q wave). Patients were treated with a combination of nitrates, beta-blockers, Calcium-antagonists and heparin. They all underwent coronary angiography. Patients with refractory unstable angina underwent either emergency coronary angioplasty or bypass surgery. Elective angioplasty or surgery was performed in stabilized patients if they had persisting exertional angina detected either clinically or with exercise testing.

Patients were selected for surgery if they had multivessel disease with one or more critical stenoses supplying a large area of viable myocardium in addition to the ischemia-related vessel or if they had left main stem disease. Selected for coronary angioplasty were patients with single or multivessel disease in whom the culprit lesion was technically suitable for angioplasty (21).

The culprit lesion in cases with multivessel disease was identified by the localization of electrocardiographic ST-T

changes during chest pain. Electrocardiographic changes in leads I,AVL, and V_1-V_6 were related to lesions of the left anterior descending artery and changes in leads II,III, AVF with either the right coronary artery or the left circumflex artery. Furthermore, certain angiographic characteristics (such as severity and morphology of the lesion, the presence of an intracoronary thrombus and degree of antegrade filling) served as an aid in the detection of the culprit lesion.

Table I: Extent of coronary artery disease and the details of management of patients with unstable angina

		extent of coronary artery disease				
Unstable angina	n	0V	1V	2V	3V	LM
Refractory to pharmacologic treatment						
emergency PTCA	114	0	78	24	12	0
emergency CABG	87	0	3	16	45	23
Initially stabilized with pharmacologic treatment						
elective PTCA	86	0	57	19	9	1
elective CABG	73	0	4	13	49	7
pharmacologically	82	14	11	24	25	8
Total number of patients	442	14	153	96	140	39

PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary aorta bypass grafting LM = left main coronary artery; 0,1,2,3 V = 0,1,2,3 vessel disease, respectively.

Twohundred patients (164 men, 36 women) with a mean age of 56 (range 36 to 74) years underwent coronary angioplasty and comprise the study group. Single vessel disease was present in 135 patients and multivessel disease in 65 patients. The mean global left ventricular ejection fraction was 0.59±0.10. The extent of coronary artery disease and the actual management of these patients are shown in table I. The characteristics of the undilated segments of the 65 patients with multivessel disease undergoing dilatation of only the culprit lesion are shown in table II. Patients were categorized into three groups according to their history:
a) recent onset unstable angina, defined as chest pain for the first time within 1 month prior to coronary angioplasty;
b) worsening angina, defined as chronic stable angina that had progressed to chest pain at rest; and
c) early postinfarction unstable angina, defined as occurrence of a myocardial infarction within one month prior to coronary angioplasty.

The documented electrocardiographic ST-T changes associated with chest pain at rest were classified, in ranking order of severity, as follows:
1) transient ST-segment elevation (at least 0.1 mV) during chestpain with return to (nearly) normal or to the ST-segment level that existed before the onset of chest pain at rest;
2) transient ST-segment depression (at least 0.1 mV) during chestpain with return to (nearly) normal or to the ST-segment level that existed before the onset of chest pain at rest;
3) development of permanent negative T waves (at least 0.1 mV) during or after disappearance of chest pain at rest without documented ST-segment elevation or depression;
4) transient minimal ST-T changes: ST-segment elevation or depression (less than 0.1 mV), minimal T wave inversion (less than 0.1 mV), pseudonormalization of T wave, T wave amplitude increase or decrease during chestpain.

Table II: Characteristics of non-dilated coronary stenoses in 65 patients with multivessel disease and PTCA of the culprit lesion only

	UNDILATED LESIONS PER PATIENT	
	1 lesion	2 lesion
Number of undilated lesions	44	42
Technically suitable for CABG	41	36
Technically suitable for PTCA	22	18
Non-dilated LAD	6	2
Non-dilated RCA/CX	38	40
Stenosis to infarcted myocardium	15	6

PTCA = percutaneous transluminal coronary angioplasty; CABG = Coronary aorta bypass grafting; LAD = left anterior descending coronary artery; RCA = right coronary artery; CX = left circumflex artery.

Coronary Angiography

Coronary angiograms were obtained in multiple views, including hemiaxial projections. A consensus of two angiographers was used to evaluate the coronary angiograms. The degree of coronary obstruction was assessed with the use of a caliper system and was given in percentage of luminal diameter. The length of the lesion was measured in relation to the length of the inserted balloon. A lesion was considered long if it was greater than 1 cm. Lesions were categorized into concentric lesions (symmetric, hourglass coronary

narrowings) and eccentric lesions (asymmetric narrowings). Collateral circulation was considered present when they were angiographically visible. For this study, only the presence of collateral circulation to the ischemia related vessel was noted. An intracoronary thrombus was defined as 1) contrast medium staining at the site of an abrupt occlusion of the vessel or 2) the presence of an intracoronary filling defect (22).

Coronary Angioplasty

Coronary angioplasty was performed with a steerable dilatation system. A 7F pacing electrode catheter was positioned in the right atrium. At the beginning of the procedure, heparin 100 mg and acetylsalicylic acid 250 mg were administered intravenously and low molecular weight dextran was infused slowly. Electrocardiogram and aortic pressure were monitored continuously. To prevent coronary spasm, intracoronary nifedipine or isosorbide dinitrate was given (23). Initial balloon inflation pressure was 2.0 atmospheres, with subsequent inflations ranging to 12 atmospheres. Inflation was maintained according to electrocardiographic changes, degree of blood pressure drop or induced pain; it never lasted longer than 60 seconds. Balloon inflations were repeated until there was a significant reduction in the transstenotic pressure gradient and a reduction in the severity of the obstruction as judged from repeat angiograms made immediately after the dilatation. Coronary angioplasty was considered to be successful if a reduction in the severity of the obstruction to less than 50% luminal diameter narrowing was obtained or if the transstenotic gradient index was reduced to less than 0.30 (mean proximal pressure minus mean distal pressure divided by mean aortic pressure). Furthermore, it was required that acute ischemic symptoms were completely relieved and that no progression to myocardial infarction or death had occurred (24). All procedures were carried out with cardiac surgical team on standby.

Coronary intimal dissection was defined according to the National Heart, Lung, and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry (25) by 1) the presence of angiographically evident intimal damage producing an intraluminal filling defect; 2) extraluminal extravasation of contrast material; and 3) linear luminal density or luminal staining.

The diagnosis of a (peri)procedural myocardial infarction was determined by the development of a new pathologic Q wave (0.03 msec) or typical increase in cardiac enzymes (more than twice normal level).

After the procedure, all patients were monitored for 24 hours in the coronary care unit where electrocardiograms and

enzyme levels were measured. They were discharged after 2-3 days, and treatment with nifedipine (40-60 mg daily) and acetylsalicylic acid (500 mg daily) was maintained for 6 months.

Follow-Up

Clinical follow-up information was obtained either by personal interview, by information obtained from the referring physician or by questionaire. Patients were evaluated for the occurrence of death, myocardial infarction or recurrence of angina pectoris. The majority of the patients underwent exercise testing with thallium 201 scintigraphy and repeat angiography.

Patients performed symptom-limited exercise on a bicycle ergometer with stepwise increments of 10 Watts every minute. The three orthogonal leads XYZ of the Frank lead system were recorded. An ischemic response was defined as at least a 0.1 mV ST-segment depression, 0.08 seconds after the J point. The maximum workload achieved was expressed as a percentage of the normal workload predicted for age, sex and height. Thallium 201 exertional scintigraphic imaging was performed in the anterior and left anterior oblique 45° and 65° views, immediately after injection of 1.5 mCi of thallium 201 at peak stress. The post-exercise images were obtained four hours later. Images were obtained using a Searle Phogamma V camera and processed with computer interface as described previously (26). Defects with redistribution were considered to represent exercise induced ischemia. Persistent defects without redistribution were considered to represent scars.

Repeat angiograms were obtained in multiple views, including hemiaxial views for the left coronary artery. Restenosis was defined as an increase of the luminal diameter stenosis of the dilated lesion above 50%.

Data Analysis

The following four (ontoward) outcome events were defined: 1) major procedure-related complications (death, myocardial infarction, or urgent bypass surgery); 2) procedure-related death or myocardial infarction; 3) late coronary event (recurrence of angina pectoris, myocardial infarction, or death within one year); and 4) restenosis (at least 50% narrowing of the dilated artery at repeat angiography. The 'late coronary event' outcome was defined only for patients with initial successful angioplasty. The outcome event 'restenosis' was defined only for patients with initial successful angioplasty who subsequently underwent repeat angiography.

We used a composite logistic prediction function to determine which pre-treatment characteristics were independently related to the risk for each of the above (ontoward) outcome events. Of the clinical characteristics, we considered sex, age, history of angina, presence of previous myocardial infarction, and the presence of refractory versus stabilized symptoms. The electrocardiographic data included the presence of ST-segment displacement of at least 0.1 mV, T-wave inversion of at least 0.1 mV, and minor ST-segment displacement or T-wave inversion. The angiographic data included site and severity of the lesion, length and eccentricity of the lesion, the presence of multivessel disease, the extensiveness of collateral flow, the presence of an intracoronary thrombus, and the global ejection fraction. Procedural characteristics were also involved in the construction of the risk model for 'late coronary event' and in that for 'restenosis'; these included duration of inflation, maximal inflation pressure, the occurence of a dissection, and the postdilation transstenotic pressure gradient.

In univariate analysis, the relation between predictors (e.g. sex) and outcome was expressed as a relative risk (or risk ratio) - that is, as the ratio of the rate of the respective outcome event observed in patients belonging to one category relative to that observed in the other category. For instance, the risk associated with gender is the rate of the outcome event in males divided by that in females. Continuous variables were dichotomized. The 95% confidence limits of the relative risk estimates are also given (27). If the 95% confidence interval does not contain the value 1, the association of the predictor and outcome is statistically significant at the 5% level.

The objective of multivariate logistics analysis was to find the combination of characteristics that predicted (unfavorable) outcome as accurately as possible. As a general principle, indicator variables were used. These are variables that assume the value of 1 if the property considered is present and 0 if absent. The BMDP package was used which selects stepwise predictor variables based on the maximum likelihood ratio (MLR). This provides a measure of significance and has an asymptotic chi-square distribution. Thus, variables were included into the model if they led to a substantial improvement of the log-likelihood (p value less than 0.10), or if their removal led to a substantial decrease (p value less than 0.15). Forward selection and backward elimination of the variables into the model yielded the same models. The regression coefficients have a direct epidemiologic implication: each coefficient represents the log

Table III: Initial and 1-year results of coronary angioplasty for unstable angina in different subsets

		major complication						cumulative incidence of coronary events after successful angioplasty					
		total	death	MI	acute surgery	success rate		death		MI		AP	
	N					%	(N)	6M	1 yr	6M	1 yr	6M	1 yr
All patients	200	21	1	16	18	90	(179)	2	2	3	5	37	47
Refractory	114	11	1	8	9	90	(103)	1	1	2	4	20	24
Stabilized	86	10	0	8	9	88	(76)	1	1	1	1	17	23
Recent onset AP	85	10	0	7	9	88	(75)	0	0	0	0	10	16
Changing pattern	81	9	1	7	7	89	(72)	2	2	2	4	17	20
Post-MI AP	34	2	0	2	2	94	(32)	0	0	1	1	10	11
ST-elevation	58	8	0	7	6	86	(50)	0	0	1	1	9	9
ST-depression	33	2	1	1	1	94	(31)	0	0	1	2	7	8
Negative T-wave	55	8	0	6	8	85	(47)	0	0	1	1	11	14
Minor ST-T	54	3	0	2	3	94	(51)	2	2	0	1	10	16
Single vessel	135	15	0	11	12	89	(120)	0	0	2	3	17	24
Multi vessel	65	6	1	5	6	91	(59)	2	2	1	2	20	23
LAD/LM *	135	12	0	9	10	91	(123)	2	2	1	2	27	34
RCA/CX *	65	9	1	7	8	86	(56)	0	0	2	3	10	13

MI = myocardial infarction; AP = angina pectoris; * see tables I and II.

odds of unfavorable outcome controlling for the other variables in the model. Its antilogarithm is the relative risk for the property considered. As an example, if the regression coefficient for ST-elevation is 1, its antilogarithm (e^1) is 2.7. This means that the risk of unfavorable outcome within one year for patients with ST-elevation is 2.7 times as high as that for patients who had no ST-elevation. In fact, the coefficients concern relative odds, which are a good approximation for the relative risk, since the frequency of unfavorable outcome is relatively low.

Table IV: Univariate analysis of variables to predict immediate and late unfavorable outcome

	n	Risk Ratio	95% CI
Procedure-related complications (death, MI, acute surgery)			
stenosis more than 65%	110	2.6	1.0 - 6.7
Coronary events at 1-year (death, MI, recurrent angina)			
worsening angina	73	1.4	0.9 - 2.2
previous MI	67	1.5	1.0 - 2.4
ST-elevation	53	0.6	0.3 - 1.0
ST-depression	30	1.4	0.8 - 2.2
stenosis more than 65%	93	1.4	0.9 - 2.3
total occlusion	16	1.9	1.0 - 3.0
MV-disease	58	2.3	1.5 - 3.7
collaterals	30	1.5	0.9 - 2.5
Angiographic restenosis			
ST-depression	28	1.5	0.9 - 2.3
total occlusion	14	1.7	0.9 - 2.7
MV-disease	51	1.6	1.0 - 2.5
collaterals	29	1.6	1.0 - 2.4
dissection	40	1.4	0.9 - 2.1

Only the significant variables are tabulated. CI = confidence interval; MI = myocardial infarction; MV = multivessel.

RESULTS

Initial Success Rate and Major Procedure-Related Complications

The overall initial success rate was 89.5% (179 of 200 patients). A major complication (death, myocardial infarction or urgent surgery) occurred in 10.5% (21 of 200 patients). The initial success rate and major complication rate for the relevant clinical subsets are tabulated in table III. The results of univariate analysis are presented in table IV. The majority of the analyzed variables were insignificant. The significant risk factors using multivariate analysis of variables predictive for an increased risk of a major complication and procedure-related myocardial infarction are shown in table V.

Table V: Risk factors to predict procedure-related major complications, restenosis and coronary events at 1 year

Risk factor	Coefficient	S.E.	O.R.	95% CI
	procedure-related major complication (death, MI, and urgent surgery)			
ST-elevation	1.3	0.63	3.7	1.1 -12.6
persistent neg. T-wave	1.3	0.63	3.7	1.0 -13.1
stenosis more than 65%	1.2	0.54	3.3	0.93- 6.9
constant	-3.7	0.67	-	-
	procedure-related myocardial infarction			
ST-elevation	1.2	0.71	3.3	0.84-13.4
persistent neg. T-wave	1.2	0.73	3.3	0.84-13.4
constant	-3.3	0.59	-	-
	angiographic restenosis			
collaterals	0.77	0.44	2.2	0.92-5.1
ST-depression	0.68	0.45	2.0	0.82-4.8
multivessel disease	0.66	0.37	1.9	0.94-4.0
LAD-stenosis	0.64	0.41	1.9	0.86-4.2
worsening AP or post-MI AP	0.62	0.38	1.6	1.3 -5.7
constant	-2.0	0.49	-	-
	coronary events at 1 year (recurrent AP, MI and late death)			
multivessel disease	1.3	0.36	3.7	1.8 -7.5
total occlusion	1.0	0.56	2.8	0.94-8.4
ST-elevation	-0.82	0.42	0.44	0.2 -1.0
constant	-1.3	0.26	-	-

For abbrevations see tables I-IV.

Table VI: Clinical follow-up after attempted coronary angioplasty in 200 patients with unstable angina

Follow-up	6 months	6-12 months	12-24 months
	successful PTCA (n=179)		
late death	2	0	2
new myocardial infarction	3	2	2
recurrent Angina	37 (20)	10 (3)	3 (1)
Repeat PTCA	18 (11) (3*)	3	2 (1) (1*)
Bypass surgery	8 (5)	3 (1)	1 (1*)
Pharmacologic therapy	11 (4)	7 (2)	0
	unsuccessful PTCA (n=21)		
late death	0	1	0
new myocardial infarction	0	1	0
recurrent Angina Pectoris	2	0	0

( ) patients with multivessel disease; * new stenosis at non-dilated site; PTCA = percutaneous transluminal coronary angioplasty.

Table VII: Cumulative incidence of major coronary events (death, myocardial infarction), bypass surgery, repeat PTCA, and functional class at initial attempt and at 6, 12 and 24 months

	inital attempt	6 months	12 months	24 months
N	200	199	197	196
death	1	3	4	6
MI	16	19	22	24
CABG	18	26	29	30
Repeat PTCA	-	18	21	23
Functional class*				
I	0	178	170	168
II	0	17	22	22
III	86	2	4	4
IV	114	0	0	0

* New York Heart Association; MI = Myocardial infarction; CABG = Coronary aorta bypass grafting; PTCA = Percutaneous transluminial coronary angioplasty.

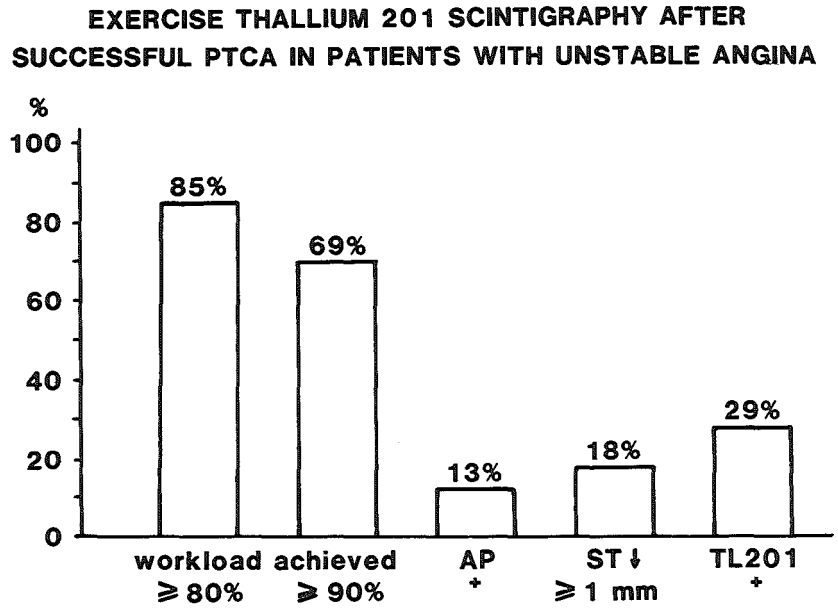

Fig. 1. Workload achieved > 80% or > 90% predicted for age, sex and height.
AP+ : exercise induced angina pectoris;
ST ↓ : exercise induced ischemic ST-segment depression;
TL 201 + : reversible perfusion defect.

Clinical Follow-Up and Angiographic Stenosis

The data from clinical follow-up after successful and unsuccessful coronary angioplasty are shown in table VI. The majority of coronary events occurred within 6 months after the procedure. The total need for bypass surgery (acute and elective) at 1 year was 14% and at 2 years 15% (table VII). The total incidence of myocardial infarction (either procedure-related or late, or both) at 1 year was 11% and at 2 years 12%. The total incidence of death at 1 year was 2% and at 2 years 3%. At 1-year follow-up, 85% of all the patients were in New York Heart Association functional class I, 11% in class II and 2% in class III (table VII).

Exercise testing and thallium 201 scintigraphy following successful angioplasty were performed in 157 and 146 patients respectively, 1.7±3.8 months after the procedure. Twenty-two patients did not perform an exercise test because of physical handicap in 5, death in 2, refusal in 1 and in 14 patients the cause was unknown. The majority of the patients achieved a workload of more than 80% of the predicted value and experienced no angina during the test. A reversible thallium perfusion defect could be induced in 29% of the patients (fig. 1).

A repeat angiogram was performed in 158 patients, 5.1±4.8 months after successful angioplasty. Twenty-one patients were not recatheterized because of death in 2, late myocardial infarction in 1, relative contraindication in 3 and refusal in 15 patients. Of the latter group, 4 patients had recurrent angina. Angiographic restenosis was present in 32% (51 of 158 patients). Nine patients (18%) with restenosis did not experience angina. The results of univariate analysis are presented in table IV. The majority of the analyzed variables were insignificant.

The significant risk factors using multivariate analysis of variables predictive for late coronary events or angiographic restenosis after a successful procedure are shown in table V. Multivessel disease was shown to be a rather strong predictor for late coronary events. This was mainly due to the persistence of undilated lesions.

Dilatation of Only the Culprit Lesion in Multivessel Disease

The initial success rate and major complication rate were comparable in patients with single vessel disease and dilatation of that particular lesion (89% and 11%, respectively) and in patients with multivessel disease and dilatation of the culprit lesion only (91% and 9%, respectively). The angiographic restenosis rate was comparable in patients with culprit lesion dilatation and multivessel disease to that in patients with single vessel disease

COMPARISON OF EXERCISE THALLIUM 201 SCINTIGRAPHY AFTER DILATATION OF CULPRIT LESION IN PATIENT WITH MULTIVESSEL DISEASE AND PATIENTS WITH SINGLE VESSEL DISEASE

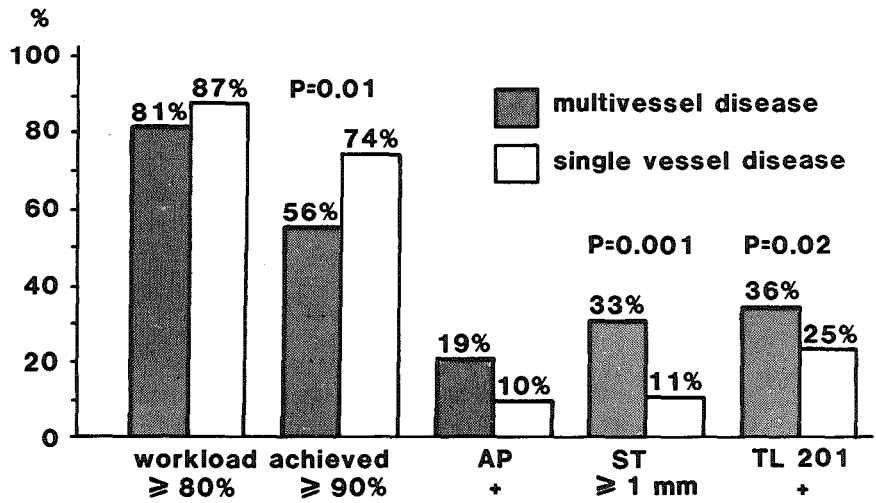

Fig. 2. For abbreviations see figure 1.

(18/51:35% versus 33/107:31%).

Persistent or recurrent angina was significantly more frequent in patients with incomplete revascularization than in those with complete revascularization at 6 months and 1 year, 17/135 (13%) versus 20/65 (31%) at 6 months and 24/135 (18%) versus 23/65 (35%) at 1 year, as shown in tables III and VI. In patients with dilatation of the culprit lesion and multivessel disease, the maximal work capacity achieved during stress testing was less, while the occurrence of exercise induced ischemic ST-segment depression and reversible perfusion defect was more frequent than in patients with single vessel disease and dilatation of that particular lesion (fig. 2).

DISCUSSION

Immediate and Late Results of Coronary Angioplasty for Unstable Angina

Patients described as having unstable angina as originally advocated by Conti and associates (1) can be divided into three subgroups: a) recent onset angina; b) progressive effort angina with a deteriorating clinical pattern superimposed on chronic stable angina; and c) episodes of prolonged ischemic pain at rest. Patients belonging to subgroups a and b have a reasonably good prognosis with most patients having a satisfactorily initial response to medical therapy (8-10). These patients can usually be evaluated for myocardial revascularization on an elective basis. In this study, we reserved the term unstable angina for patients belonging to subgroup c; that is, patients with prolonged episodes of chest pain at rest. The prognosis for this subgroup is worse, especially if ischemic symptoms persist (4-7). We believe that immediate control of ischemia with stepwise intensification of pharmacologic treatment is the cornerstone in managing these patients. If despite this tailored pharmacologic approach patients continue to have attacks of ischemia, prolongation of what must be regarded as ineffective treatment should be avoided and an attempt at myocardial revascularization, either acute bypass surgery, or acute angioplasty, should be institituted without delay, in an attempt to prevent progression to myocardial infarction and so to improve prognosis.

In our study, the initial success rate of coronary angioplasty was 90%, and the major complication rate was 10%. This is comparable to the recently reported initial success rates of 70% to 93%, and major complication rates of 3% to 12% (14-20). The procedure-related death rate was low (0.5%) and

compared favorably with reported death rates of 0% up to even 5.4% (14-20). The procedure-related myocardial infarction rate was 8% and the need for acute surgery was 9%, which are within the range of 4% to 12% and 1.5% to 12%, respectively, reported by others (14-21). Our results and those reported by others (14-21) reveal a high level of major complications of coronary angioplasty in patients with unstable angina. This major complication rate is definitely higher than the rate of 3% to 4% reported for coronary angioplasty in patients with stable angina (28,29). The reasons for this high major complication rate may be related to the clinical instability of these patients, and more specifically the higher frequency of complicated lesions (severe, eccentric lesions) due to a different underlying pathology and an increased risk of abrupt closure due to the formation of an acute occlusive thrombus (30). A thrombus may form more readily since unstable angina is related to plaque fissuring with denudation of the intima, adhesion and aggregation of platelets and partial (non)-occlusive thrombus formation (31-34). In such a milieu, intracoronary instrumentation or balloon trauma may easily lead to a total occlusive thrombus.

After initial successful angioplasty the prognosis is excellent with a low number of deaths (1% at 1 year and 2% at 2 years) and a low occurence of late myocardial infarction (3% at 1-year and 4% at 2-year follow-up). This is in keeping with other reports (14-20).

The results of electrocardiographic exercise testing and thallium 201 scintigraphy, performed approximately 2 months after an initial successful angioplasty, indicated good functional recovery and absence of evidence of ischemia in the majority of the patients.

Angiographic restenosis occurred in 32% of the patients within 6 months of the procedure. The angiogram was repeated in 88% of all patients with successful coronary angioplasty, so that this study fairly accurately reflects the actual restenosis rate and is only minimally biased by the refusal of asymptomatic patients to undergo a second angiogram. This rate does not appear to be higher than the restenosis rate of 25% to 30% for stable angina (35,36), although it has been suggested that the restenosis rate in unstable angina is somewhat higher (12,35,36). At 1-year follow-up the recurrence rate of angina after an initial successful angioplasty was 26%; the majority occurring within 6 months after the procedure.

Thus, at 1-year follow-up of all the 200 patients who had an attempted coronary angioplasty, 4 patients (2%) died (1 procedure-related and 3 late deaths), 22 patients (11%) sustained a nonfatal myocardial infarction (16 procedure-related and 6 late), 26 patients (13%) were, although they had experienced some improvement, still symptomatic (New York Heart Association class II and III), and

170 patients (85%) were symptom-free. However, to achieve this result, bypass surgery was necessary in 29 (15%) patients (18 acute surgery and 11 late, elective surgery) and 21 (11%) patients underwent repeat coronary angioplasty.

Predictors of Early and Late Unfavorable Outcome

In an attempt to improve patient selection for coronary angioplasty and to identify high risk patients, univariate and multivariate analysis was performed on potential clinical and angiographic predictors of a major complication. It has been suggested that unstable angina per se is a risk factor for early (37) and late unfavorable outcome (12,35,36). In patients undergoing elective angioplasty, major complications were shown to be associated with patient-related variables: female gender (38-41), patients older than 60 years (40), multivessel disease (38), angina more than 6 months (40), prior coronary bypass surgery (40); and with lesion-related variables: eccentricity (38-40, 42), calcified lesion (38-40), lesion length (38-40,42), "complicated" lesion (43), intracoronary thrombus (44), and vein graft lesion (40). In our study, which differs from the above cited studies in that only patients with unstable angina were analyzed, we found that the changes of the electrocardiogram during an ischemic attack (ST-segment elevation or persistent negative T waves) and the severity of the stenosis were associated with an increased risk of a major procedure-related complication. Transient ST-segment elevation is thought to reflect transmural ischemia and is associated with more severe ischemia than ST-segment depression which represents subendocardial ischemia (45). The development of new T wave inversion, which persists, may be related to minimal cell necrosis not detected by current enzyme measurement techniques and represents severe coronary artery stenosis (46). These patients are known to have a poor overall prognosis (46,47). We could not establish a relation between the presence of intracoronary thrombus detected angiographically and an increased risk of major complications as have others (44). However, this is not surprising since angiography is a very insensitive method for detecting intracoronary thrombus. Careful postmortem sectioning (30-32) and angioscopic examination (34) of the coronary arteries have shown that plaque rupture and thrombus formation almost invariably occur in patients with unstable angina and have established the role of thrombus in the pathogenesis of this condition.

Angiographic restenosis after coronary angioplasty (12,35,36) has been shown to be associated with patient-related variables: male (35), diabetes (48-50), duration of angina less than 2 months (35,36,49,50), variant angina (51), multivessel disease (52), smoking (49,50) , hypercholestero-

lemia (49,50); lesion-related variables: total or greater than 90% occlusion (35,36,50,52,53), left anterior descending coronary lesion (36,52), vein graft stenosis (35,54,55); and procedure-related variables: no dissection (36), greater than 30% residual stenosis (36), greater than 15 mmHg residual pressure gradient (35,36).

In our study, we found a higher angiographic restenosis in patients with angiographically visible collaterals to the dilated vessel, multivessel disease, left anterior descending coronary stenosis, and with transient ST-segment depression during an ischemic attack. Coronary events at 1 year including recurrent angina pectoris, late myocardial infarction or late death were associated with multivessel disease and total occlusion. Multivessel disease was a risk factor due to the persistence of undilated coronary artery lesions.

Dilatation of Only the Culprit Lesion in Multivessel Disease

The foremost consideration in the acute treatment of unstable angina must be the preservation of myocardial function. Coronary angioplasty of only the "culprit lesion" in patients with refractory unstable angina and multivessel disease has been shown to be an effective therapeutic alternative to coronary bypass surgery (21,56). Improvement in myocardial function has been demonstrated using this strategy (57). This approach was used because multiple dilatations in these unstable patients may increase the risk of major complications and there is a risk of performing unnecessary dilatations because of the difficulty in assessing the significance of any additional stenosis in the acute setting. The initial success rate and major complication rate of coronary angioplasty in patients with single vessel disease and dilatation of that particular vessel were comparable to those with multivessel disease and dilatation of only the culprit lesion. The angiographic restenosis rate was higher, although not statistically significant, in patients with multivessel disease compared to those with single vessel disease. However, recurrent or persistent angina pectoris at 6 months follow-up was significantly higher in patients with multivessel disease (31%) than in patients with single vessel disease (13%). Incomplete dilatation was also associated with increased occurrence of stress-induced angina pectoris, significant ST-segment depression, reversible perfusion defect, and reduced exercise tolerance.

We believe that angioplasty of the culprit lesion in patients with unstable angina and multivessel disease should be regarded as an initial treatment strategy in those whose symptoms do not respond adequately to pharmacologic treatment. In most patients, this approach will have a longterm success, but in some further dilatations or even bypass surgery will be

required, so that this strategy does not provide a definitive longterm treatment in all patients. However, the subsequent interventions can be performed on a more elective basis with less risk. This strategy warrants further evaluation in a randomized controlled study.

CONCLUSION

The initial success rate of coronary angioplasty in patients with unstable angina is 90%. The hazards of dilatation in patients with unstable angina are high and clearly exceed the hazards of dilatation in those with stable angina. The total major complication rate in patients with unstable angina is about twice of that in patients with stable angina. No strong single or set of predictors of unfavorable outcome has been identified, but the procedure appears to be more hazardous in patients who have chest pain at rest associated with transient ST-segment elevation or who develop persistent negative T waves.

After an initially successful procedure, the prognosis is excellent with a low late death rate and a low late myocardial infarction rate. The angiographic restenosis rate or angina at 6 months is approximately 30% and therefore appears comparable with that obtained in patients with stable angina. However, these results apply to selected patients with predominantly single vessel disease and well preserved left ventricular function.

At present, it seems reasonable to consider such patients for coronary angioplasty, although the risks of the procedure in this acute setting are relatively high. However, the alternative, coronary bypass surgery in these patients, is also associated with a rather high complication rate (58-62). Currently, randomized trials comparing the results of coronary angioplasty and surgery in patients with unstable angina are lacking. There is a compelling need for randomized trials to compare the results of both strategies and to provide definitive answers on the relative merits of both treatment strategies.

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CHAPTER III

CORONARY ANGIOPLASTY IN PATIENTS WITH UNSTABLE ANGINA PECTORIS: IS THERE A NEED FOR THROMBOLYSIS?

ABSTRACT

Management of unstable angina has evolved progressively and recently, coronary angioplasty has been shown to be an effective treatment strategy for unstable angina. However, the procedure-related major complication rate is higher when compared to angioplasty in stable angina. The underlying pathophysiology may explain this higher complication rate. Rupture of an atherosclerotic plaque associated with thrombus formation is frequent in the pathogenesis of unstable angina. These processes lead to a critical reduction in myocardial blood supply, and coronary angioplasty may effectively interrupt this process. On the other hand, coronary angioplasty itself may cause further injury of the already ulcerated intima and may have the potential to intensify the ongoing thrombogenic process and may lead to an increased frequency of abrupt closure of the artery during the procedure. Therefore, intracoronary streptokinase was adopted to the procedure in those patients with abrupt closure of the artery immediately after dilatation in order to attempt to improve the immediate result. Coronary angioplasty was attempted in 200 consecutive patients with unstable angina. Initial success in crossing the obstructed artery was achieved in 196 patients. Of these, however,an abrupt closure immediately after dilatation occurred in 21 patients, of whom 12 were treated additionally with intracoronary streptokinase and success was achieved in 9 patients without evidence of necrosis or emergency bypass surgery. Of the remaining 9 patients, 4 were successfully re-dilated with a larger size balloon, 4 underwent urgent surgery (1 death post-operatively) and 1 was treated conventionally. Final success was achieved in 188 patients (94%) without evidence of myocardial necrosis, emergency surgery, or death. These beneficial results suggest that in some cases coronary angioplasty may need to be supplemented by additional intracoronary thrombolysis in order to improve immediate outcome by avoiding urgent surgery and procedure-related myocardial infarction.

INTRODUCTION

The clinical syndrome of unstable angina causes great concern to clinicians because of the perceived high risk of

progression to myocardial infarction or cardiac death (1,2). Only limited information is available on the merits of pharmacological treatment, bypass surgery, or coronary angioplasty from controlled randomized trials in these patients. Management of unstable angina has evolved despite this lack of trial data, and recently, coronary angioplasty had been shown to be relatively safe with significant symptomatic relief. However, the major complication rate (myocardial infarction, emergency bypass surgery, and inhospital mortality) is rather high when compared to patients with stable angina (3-5). In an early series of 200 patients with unstable angina (3), we reported that coronary angioplasty can be performed with a high initial success rate (89.5%), but at an increased risk of major procedure-related complications (10.5%). The reasons for this relatively high complication rate are apparently related to the underlying pathophysiology leading to the clinical instability and an increased risk of abrupt closure after attempted angioplasty due to the formation of an acute occlusive thrombus (6,7). The present study was therefore undertaken to investigate whether additional thrombolytic therapy in case of abrupt vessel closure could improve the immediate results of coronary angioplasty in patients with unstable angina pectoris.

PATIENTS AND METHODS

Between January 1986 and December 1987, coronary angioplasty was attempted in 200 consecutive patients with unstable angina pectoris. They represented 20% of our total coronary angioplasty population during the study period. All were treated intensively with beta-blockers, calcium antagonists, intravenous nitroglycerin and heparin. Patients were selected for angioplasty if the ischemia-related lesion was suitable for dilatation. The stenotic artery was considered to be ischemia-related in patients with single vessel disease, while in patients with multi-vessel disease the ischemia-related artery was determined by correlation with documented resting ST segment changes, as described previously (3).

Unstable angina pectoris was defined as symptoms of angina at rest lasting for at least 15 minutes associated with ST-T changes without evidence of further myocardial necrosis, as defined by either cardiac enzyme elevation (creatinine kinase twice of the normal value) or development of new pathologic Q waves. Intracoronary thrombus was defined as a definite contrast filling defect or contrast staining during angiography in at least 2 orthogonal views by at least 2 angiographers. In addition, patients with ischemia-related occluded vessel were considered to have thrombus.

Coronary angioplasty was performed with preformed guiding catheters, steerable dilating balloon catheters, and a pneumatic inflation device. A 7 French pacing electrode catheter was positioned in the right atrium. Before the procedure, heparin 10.000 U and acetylsalicylic acid 250 mg were administered intravenously. Two electrocardiographic leads and aortic pressure were monitored continuously. Initial balloon inflation pressure was 2 atmospheres with subsequent inflations ranging to 12 atmospheres. All procedures were carried out with cardiac surgical team on standby. The current study differs from the previous one (3) in the management of acute complication during angioplasty. In case of abrupt vessel closure after angioplasty, emergency recanalization was attempted by repeat dilatation using the same or a larger size balloon. If this approach failed, acute surgery was performed in those patients with major coronary dissection, while intracoronary streptokinase was given to those patients in whom abrupt occlusion was presumably due to acute thrombosis. After the procedure, all patients were followed for 24 hours in the coronary care unit, where electrocardiograms and cardiac enzyme levels were monitored. A peri-interventional myocardial infarction was diagnosed if either new pathologic Q waves developed or an abnormal cardiac enzyme elevation was documented.

Angioplasty was considered successful when a reduction of the severity of the obstruction to less than 50% luminal diameter narrowing was achieved with abolition of acute ischemic symptoms and without progression to myocardial infarction, emergency surgery or death. Only the ischemia-related vessel was dilated in the majority of the patients with multivessel disease (60 out of 80 patients). The clinical and angiographic characteristics are shown in table I.

Table I: Clinical and angiographic characteristics

n	200
Age (median, yr)	59 (range 29-83)
Male	148 (74%)
Time from angiography to PTCA (median, days)	2 (range 0-75)
Postinfarction unstable angina	94 (47%)
Previous CABG/PTCA	39 (20%)
Single vessel disease	120 (60%)
Double vessel disease	56 (28%)
Triple vessel disease	24 (12%)
Single vessel dilatation	180 (90%)
Multi vessel dilatation	20 (10%)
Angiographic evidence of thrombus	43 (22%)
Total/functional occlusion	29 (15%)

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

RESULTS

In the 200 patients who underwent coronary angioplasty for unstable angina pectoris, 221 lesions were dilated (115 in left anterior descending, 49 in left circumflex, 48 in right coronary artery and 9 in bypass graft). Single-vessel dilatation was performed in 180 patients, including 25 multilesion dilatations in the same artery. Double artery dilatation was performed in 19 patients and triple artery dilatation in 1.

Technical failure to cross the lesion occurred in 4 patients in whom the artery was found to be occluded at the time of attempted angioplasty; 3 of these underwent elective coronary bypass surgery and 1 was treated conservatively. While the obstructed artery could be crossed and dilated in 196 patients. Of these, however, an abrupt closure immediately after attempted dilatation occurred in 21 patients (11%). This was presumably due to occlusive thrombus in 12 patients who were therefore treated with 250,000 units of intracoronary streptokinase, and success was achieved in 9 of these patients without evidence of further necrosis or emergency surgery. Major coronary dissection was observed in 4 patients who underwent emergency bypass surgery. Of the remaining 5 patients, in whom the mechanism of abrupt occlusion was uncertain, 4 were successfully re-dilated using a larger size balloon and 1 was treated conservatively (table II). From these 21 patients with abrupt closure after attempted angioplasty, 12 had angiographic evidence of intracoronary thrombus prior to angioplasty.

Peri-interventional myocardial infarction, defined by either cardiac enzyme elevation or new Q waves, was documented in 6 patients, of whom 4 underwent emergency bypass surgery with 1 death postoperatively (table II).

Table II: Management and outcome of patients with acute reclosure during the procedure

	n	myocardial infarction
Re-dilatation*	4	0
Intracoronary (IC) streptokinase	10	1
IC streptokinase + acute surgery	2	1
Acute surgery	4	3**
Conservative	1	1
Total	21	6

* prolonged inflations with a larger size balloon.
** 1 patient died post-operatively.

Thus, from these 200 patients who underwent coronary angioplasty for unstable angina, final success in dilating the obstructed artery was achieved in 188 patients (209 lesions) without evidence of myocardial necrosis, emergency surgery, or death.

These results show high initial success rate of coronary angioplasty in patients with unstable angina pectoris with lower major complication rate when compared with the results of our previous study (3) in which thrombolytic therapy was not applied in case of acute closure during the procedure (table III).

Table III: Clinical data and major complications compared to previous reported results (3)

	Previous data	Present data
n	200	200
Males (%)	82	74
Age (yr)	56	59
Previous infarction (%)	37	47
Multivessel disease (%)	33	40
Multivessel dilatations (%)	0	10
Total occlusion (%)	13	15
Intracoronary thrombus (%)	15	22
Abrupt vessel closure (%)	11.5	10.5
Initial success rate (%)	89.5	94
Major complications* (%):	10.5	4
Death (%)	0.5	0.5
Myocardial infarction (%)	8	3
Emergency surgery (%)	9	3

* Either death, myocardial infarction, or emergency surgery. Thrombolytic therapy had not been used in our previous reported study (3).

DISCUSSION

Coronary angioplasty, as an alternative to bypass surgery, has recently been shown to be effective in the treatment of unstable angina pectoris (3,8-23) with initial success rate up to 91% and low procedure related death (up to 2%). However, these results are obtained in selected patients with predominantly single vessel disease and well preserved left ventricular function, and the results should be interpreted with this in mind. Nevertheless, the rate of major complication (procedure related myocardial infarction and emergency surgery) is rather high and varies between 8% to 13%

(3,8-23); although Meyer et al (13) reported a lower complication rate. This complication rate of angioplasty in patients with unstable angina pectoris is definitely higher than the complication rate (3% to 4%) reported for angioplasty in those with stable angina pectoris (4,5).

Table IV: Results of fibrinolytic or anticoagulant treatment in patients with unstable angina

Study	n	Treatment	Angiographic evidence of lysis (%)
Vetrovec et al.(37)	13	IC SK	77
Mandelkorn et al.(28)	9	IC SK	44
Shapiro et al.(38)	18	IC SK	67
			Clinical outcome
Lawrence et al.(39)	20	IV SK (24 hr) + coumadin	5% Sudden death (6 months)
	20	coumadin	40% Sudden death/MI (6 months)
Telford & Wilson(40)	100	heparin + atenolol	3% MI (7 days)
	114	placebo or atenolol	15% MI (7 days)
Gold et al.(41)	24	IV tPA or placebo	40% reduction in recurrent ischemia (7 days)
Topol et al.(42)	40	IV tPA or placebo	Improved pacing threshold to ischemia (7 days)

IC = intracoronary; IV = intravenous; SK = streptokinase; tPA = tissue plasminogen activator; MI = myocardial infarction.

The reasons for this high complication rate are apparently related to the underlying pathophysiology. Almost all patients with unstable angina pectoris have a high grade fixed coronary stenosis (24,25) and on top of this fixed stenosis other dynamic conditions may also play a role, such as plaque fissuring with platelet aggregation, increased vasomotor tone, and formation of a partial or even intermittent occlusive thrombus (26-30). Evidence derived from postmortem pathologic studies (29,30), from postmortem coronary arteriography (31), from serial coronary

arteriography (25,32,33), from lysis of intracoronary thrombi (34), from surgery during acute coronary syndromes (35), and from intraoperative angioscopy (36) has confirmed the importance of coronary thrombosis. Further clinical evidence to support the role of intracoronary thrombus comes from the observation that thrombolytic therapy in patients with unstable angina did lyse the thrombus in a considerable number of patients (table IV) (28,37-42). In addition, the role of platelets in intracoronary thrombus is also shown by the reduction of the incidence of mortality and nonfatal myocardial infarction after administration of aspirin in patients with unstable angina (43,44).

The formation of an intracoronary thrombus is an active, dynamic process. Identification of such a thrombus with angiography depends on the timing of the angiogram after the acute event, the size of the intracoronary thrombus at the time of the angiogram, the severity of illness in the populations studied, and the angiographic criteria used for identification (28,45-48). The angiographic presence of an intracoronary thrombus is reported to be between 1% and 52% (table V). Angiographic criteria probably underestimate the frequency of thrombosis in patients with unstable angina pectoris since a mural (nonocclusive) thrombus superimposed on an atherosclerotic plaque cannot always be identified with currently available techniques. In a pilot study using intraoperative angioscopy, intracoronary thrombi that were undetectable on review of coronary angiograms were detected in 7 of the 10 patients with unstable angina (36).

Table V: Angiographic evidence of intracoronary (IC) thrombus

Study	n	IC thrombus n	IC thrombus %	Time between acute event and angiography
Holmes et al.(45)	1202	16	1	less than 3 months (2A)
Vetrovec et al.(46)	129	8	6	less than 1 month (2A)
Mandelkorn et al.(28)	9	4	44	less than 2 months (3)
Capone et al.(47)	119	44	37	less than 14 days (2A)
Capone et al.(47)	44	23	52	less than 24 hours (2A)
Zack et al.(48)	83	10	12	less than 3 months (1,2A, 2B)

( ) = definition of intracoronary (IC) thrombus: 1) occlusive thrombus; 2) nonocclusive thrombus, A) intraluminal defect, B) intraluminal staining; 3) reduction in severity of stenosis after streptokinase infusion.

Several studies have emphasized the important pathophysiologic link between unstable angina and non-Q wave myocardial infarction (29,30,49-52). In unstable angina, the pathophysiologic process is limited to endothelial ulceration, platelet aggregation and thrombus formation, which may be intermittent, or more permanent in the presence of an adequate collateral supply. Myocardial infarction is related to the same process but with the formation of a totally occlusive thrombus. When the balance between intracoronary thrombus and antithrombotic natural and pharmacologic factors lean toward continued thrombus formation, persistent total coronary occlusion leading to acute myocardial infarction may occur. If the coronary artery remains occluded for a long period (more than 15 minutes), then myocardial necrosis will occur. If very early clot lysis occurs with or without embolization to the distal coronary bed, or if an adequate collateral supply is present, infarction will be limited (non-Q wave myocardial infarction), whereas it will be extended (Q wave myocardial infarction) when no or late clot lysis occurs. In addition, in a patient with non-Q wave infarction, rethrombosis and reocclusion often occur, leading to repeat myocardial infarction affecting the same myocardial region (52).

These data suggest that rupture of an atherosclerotic plaque with associated thrombus formation is frequent both in the pathogenesis of unstable angina and myocardial infarction. These processes will lead to a critical reduction in myocardial blood supply and coronary angioplasty, designed to enlarge the stenosed lumen, may effectively interrupt this process and may normalize myocardial blood flow. However, coronary angioplasty may act as a two-edged sword, because angioplasty itself may cause further injury to the plaque and the already ulcerated intima (53), which has the potential to intensify the ongoing thrombogenic process. This may lead to an increased frequency of abrupt total occlusion during the procedure.

The reported incidence rates of abrupt closure after attempted angioplasty vary between 2 and 12% (7,11,54,55). The management of this serious complication has changed over the past ten years and remains controversial. There was a time when all patients with acute occlusion underwent emergency surgery. In earlier reported series (56-58), emergency surgery was performed in 5 to 13% of the patients in whom angioplasty was attempted. More recent reports show a decline in emergency coronary bypass surgery to 2%, along with an increase in the frequency of myocardial infarction without surgery (59). About 40-60% of patients who have emergency surgery after angioplasty have evidence of myocardial infarction, despite prompt operation, and mortality rates range from 0-6.4% (57-62).

Identification of factors associated with increased occlusion rates might be of great value in optimizing patient selection and developing treatment strategies for preventing this complication. Although the extent of myocardial ischemia resulting from acute occlusion usually may be predicted from the patient's diagnostic angiogram, the occurence of abrupt occlusion is not foreseeable. However, in the patients presented here, there was a correlation between the presence of intracoronary thrombus before angioplasty and the subsequent development of complete coronary artery occlusion after attempted angioplasty. In patients with pre-existing intracoronary thrombus, abrupt occlusion occurred in 28% (12/43) compared with 6% (9/157) in those without angiographic evidence of intracoronary thrombus. This finding is consistent with other reports (7,63). This leads us to believe that the mechanism of occlusion in this series was an ongoing thrombogenic process, while coronary spasm as an alternative cause of abrupt occlusion was unlikely since intracoronary nitroglycerine and nifedipine were routinely administered. In addition, the use of intensive anticoagulant therapy: intravenous heparin 2-4 days prior to the procedure and routine premedication with intravenous aspirin (250 mg) combined with heparin (10.000 U) during the dilatation did not prevent abrupt vessel occlusion from occurring either during dilatation or immediately after what appeared to be successful dilatation. This is consistent with other clinical and experimental reports (7,63-65), showing that platelet thrombus deposition occurred despite continuous heparin use.

Since thrombolytic therapy combined with coronary angioplasty has been widely and safely used in the setting of acute myocardial infarction, it would be justified to apply this rescue strategy in our unstable patients with abrupt vessel occlusion after angioplasty. Therefore, since 1986 emergency redilatation (with the same or an oversized balloon) or intracoronary thrombolysis or combination of both have been adopted as a treatment of this complication. Intracoronary streptokinase was given in our patients in whom abrupt closure of the coronary artery immediately after dilatation was presumably due to acute thrombosis. Out of the 4 cases with major coronary dissection who underwent emergency surgery, 3 had myocardial infarction. In contrast, only 2 out of 12 patients who received intracoronary streptokinase had evidence of myocardial infarction. These findings compare favorably with those of our previous series (table III), suggesting that in some cases thrombolytic therapy may improve immediate outcome of angioplasty in unstable angina by avoiding urgent surgery and procedure-related myocardial infarction. However, because this was a retrospective study we can only speculate about the reasons for the improvement in the result. Subtle but nevertheless potentially important factors that may have contributed to the improved results include: increased

operator experience, the exclusive use of better X-ray equipment and advanced angioplasty systems, optimization of balloon size, longer observation period in the catheterization laboratory after dilatation, and less stringent criteria for repeat dilatation when the arterial segment appeared to be hazy on the angiogram. Although all of these procedural modifications may be exerting a favorable influence on the outcome of dilatation, we believe that thrombolytic therapy itself has led to the more effective resolution of acute complications that occur during attempted angioplasty.

Recent published randomized placebo-controlled trials of rtPA in unstable angina further confirm the potential of fibrinolytic therapy in this setting, particularly in patients with angiographic evidence of intracoronary thrombus (41,42). However, Ambrose et al (66) recently reported that intracoronary streptokinase was usually ineffective in reducing the percent stenosis of the angina-producing vessel, measured quantitatively, in patients with unstable angina and non-Q wave myocardial infarction. Besides, there may have been no thrombus present at the time of angiography due to spontaneous lysis or due to heparin therapy, it is possible in some patients with unstable angina that the thrombus deposited at the site of plaque disruption is already organized within the coronary artery at the time of clinical presentation (30) and therefore is resistant to short infusions of streptokinase. To achieve thrombolysis, it may be necessary to give the thrombolytic therapy within hours of onset of unstable symptoms. Furthermore, results of a small randomized placebo-controlled trial of rt-PA in unstable angina (41) have shown that a prolonged (12 hours) infusion of rtPA with heparin effectively lyses thrombus and leads to stabilization of the clinical syndrome when compared with heparin alone. In this randomized trial, angiographic evidence of intracoronary thrombus was detected in 73% of placebo-treated and none in the rtPA-treated patients. A highly significant correlation was observed between the presence of thrombus and recurrent angina. However, bleeding was observed in 67% of the rtPA-treated patients and none in the placebo group.

In our institution thrombolysis has been used as a treatment of complication and not as a primary or preventive therapy. The reason for this, is that, it will be not justified and maybe unsafe to treat preventively all patients with unstable angina, since only 10% of the patients will present with acute complications. Secondly, that the haemorrhagic risks inherent to the thrombolytic therapy using either specific clot lysing agents or systemic fibrinolytic agents are not negligible and therefore may not be imposed to this population as a whole.

Future studies should be directed towards the place of thrombolytic therapy in the management of patients with unstable angina, especially in those refractory to

pharmacologic therapy. Firstly, thrombolytic therapy as a cool-off strategy. Secondly, as a preventive strategy in order to avoid acute complication during coronary angioplasty. And finally, as a rescue strategy in case of abrupt vessel occlusion during attempted angioplasty. At present, we are conducting a double blind randomized trial of intravenous rtPA versus placebo in patients with unstable angina refractory to pharmacologic therapy who will undergo coronary angioplasty within 24 hours. Until further information becomes available we would propose the following practical approach. Patients with unstable angina should initially receive prompt management with stepwise intensification of pharmacologic therapy including antiplatelet drug and anticoagulation with heparin in an attempt to achieve stability. Early angiographic and revascularization is indicated if this approach fails and ischemic episodes continue in spite of maximal medical management. Coronary angioplasty is indicated when the stenosis, technically suitable for dilatation, is found to be responsible for the unstable state. An intravenous thrombolytic agent should be given prior to angioplasty in patients with angiographic evidence of intracoronary thrombus. In case of abrupt vessel occlusion during attempted angioplasty, intracoronary streptokinase and redilatation should be carried out.

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CHAPTER IV

EFFECTS OF SUCCESSFUL PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY ON GLOBAL AND REGIONAL LEFT VENTRICULAR FUNCTION IN UNSTABLE ANGINA PECTORIS

ABSTRACT

Sixty-eight patients (58 men, 10 women, mean age 56.3 years, range 31 to 72) with unstable angina pectoris, either initially stabilized with or refractory to optimal pharmacologic treatment, were studied to determine whether regional dysfunction due to stunning of the myocardium caused by attacks of chest pain at rest could be improved with percutaneous transluminal coronary angioplasty (PTCA). Patients were included in the study if they had successful single vessel PTCA, no angiographic restenosis, no reocclusion or late myocardial infarction and 2 serial left ventriculograms of sufficient quality to allow automated contour analysis before and after PTCA. Global ejection fraction increased significantly (from 56% to 60%; $p = 0.05$) only after successful dilatation of a stenosis of the left anterior descending coronary artery. Analysis of regional wall displacement showed significant improvement of regional wall motion in the areas supplied by the dilated vessel of either the left anterior descending, the left circumflex or the right coronary artery. Thus, regional myocardial dysfunction, due to stunning of the myocardium in patients with unstable angina improves after successful PTCA.

INTRODUCTION

Profound and prolonged myocardial ischemia that does not progress to necrosis may stun cardiac muscle and produce functional, metabolic and structural changes (1-3). In patients with unstable angina, abnormalities in regional resting cardiac wall motion may be a result of prolonged attacks of transient ischemia. Regional myocardial dysfunction has been shown to improve after restoration of an adequate blood flow in animal experiments (4-6), after coronary bypass surgery (7-10) and after coronary artery reperfusion in acute myocardial infarction, either by clot lysis or direct percutaneous transluminal coronary angioplasty (PTCA)(11-13).

This study determines whether regional myocardial dysfunction due to stunning of the myocardium caused by attacks of transient ischemia at rest can be improved with successful PTCA in patients with unstable angina.

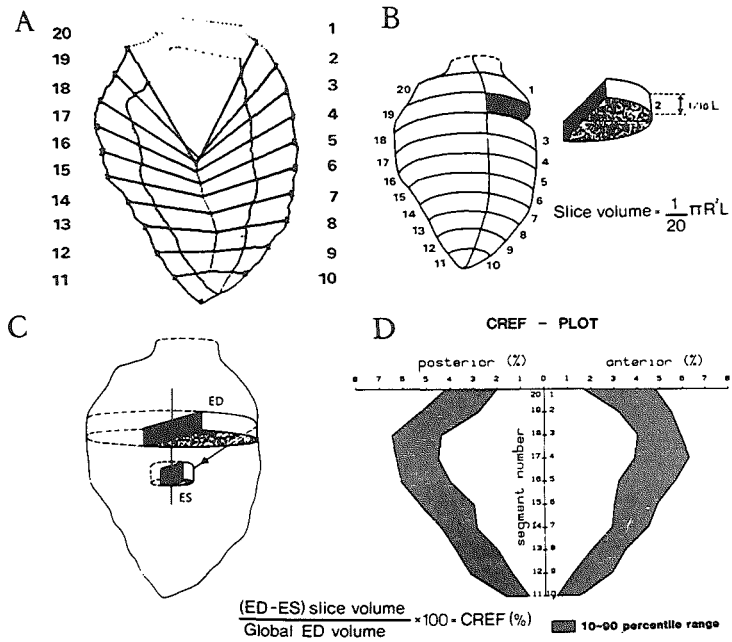

Figure 1. A, example of the computer output showing the end-diastolic (ED) and end-systolic (ES) contours of the 30° right anterior oblique left ventriculogram. Systolic regional wall displacement was determined along a system of 20 coordinates on the pattern of actual endocardial wall motion in normal persons and generalized as a mathematic expression amenable to automatic data processing. [15-18] B, the left ventricular end-diastolic cavity is seperated into 20 half-slices. The volume of each half slice is computed according to the given formula, where R = radius and L = left ventricular long-axis length. C, the regional contribution to global ejection fraction (CREF) is determined from the systolic decrease of volume of the half slice that corresponds to a particular wall segment. The systolic volume change is mainly a consequence of the decrease of radius (R) of the half slice. When normalized for end-diastolic volume, the systolic segmental volume change was considered as a parameter of regional pump function. During systole this parameter expresses quantitatively the contribution of a particular segment to global ejection fraction. The sum of the values for all 20 segments equals the global ejection fraction. D, shaded zones represent the 10th to the 90th percentille area of CREF values in normal persons. On the x axis, the CREF values of the anterior and inferoposterior wall areas are displayed (%), while on the y axis the segment numbers of the anterior wall (1-10) and of the inferoposterior wall (11-20) are depicted. The segmental CREF values in the anterobasal (segments 1 to 5), anterolateral (segments 5 to 9), apex (segments 9 to 12), inferoapical (segments 12 to 16) and posterobasal (segments 16 to 20) wall regions were analyzed.

METHODS

Between February 1983 and June 1985, 150 patients with unstable angina pectoris underwent PTCA. Unstable angina pectoris was defined as chest pain at rest lasting for at least 15 minutes, accompanied by electrocardiographic ST-T changes and no subsequent signs of myocardial necrosis. Sixty-eight patients (58 men, 10 women, mean age 56.3 years, range 31 to 72) who fulfilled the following criteria were selected for this study: successful single artery dilatation in patients with unstable angina pectoris; no angiographic restenosis, reocclusion or late reinfarction during follow-up; and serial left ventriculograms of sufficient quality to allow automated contour analysis before PTCA and at follow-up catheterization.

Thirty-two percent of patients had had a myocardial infarction; 19% had collaterals to the infarct-related vessel. The mean number of documented attacks of pain was 2.8 ± 2 and the mean time between the last attack of pain and the left ventriculogram before PTCA was 43 ± 48 hours. Treatment consisted of a combination of intravenous nitroglycerin, beta-adrenergic receptor antagonists and calcium antagonists. Fourty-four patients (65%) who underwent emergency PTCA were refractory to treatment. Initial stabilization was achieved in 24 patients (35%), but they remained symptomatic on slight exertion. These patients underwent elective PTCA.

PTCA was performed with a steerable balloon catheter system. In patients with multivessel disease only the ischemia-related vessel was dilated (14). PTCA was considered successful if the severity of obstruction was reduced to less than 50% of the luminal diameter, with abolition of acute ischemic symptoms and no progression to myocardial infarction or death.

After discharge, treatment with nifedipine, 40 to 60 mg daily and acetylsalicilic acid, 500 mg daily, was continued for a period of 6 months. Sixty-three of the 68 patients underwent exercise thallium-201 scintigraphy at a mean of 2.8 months (range 1 to 4) after PTCA. Patients performed symptom-limited exercise on the bicycle ergometer with stepwise increments of 20 Watts every minute. The 3 orthogonal leads XYZ of the Frank lead system were recorded. An ischemic response was defined as at least 0.1 mV of ST-segment depression of 0.08 second after the J point. The maximal workload achieved was expressed as a percentage of the normal workload predicted for age, sex and body length. Thallium exertional scintigraphic imaging was performed in the anterior, left anterior oblique 45° and 65° views, immediately after injection of 1.5 mCi of thallium-201 at peak stress. Postexercise images were recorded 4 hours later. Images were obtained using a Searle Phogamma V camera. Defects with redistribution were considered to represent reversible ischemia.

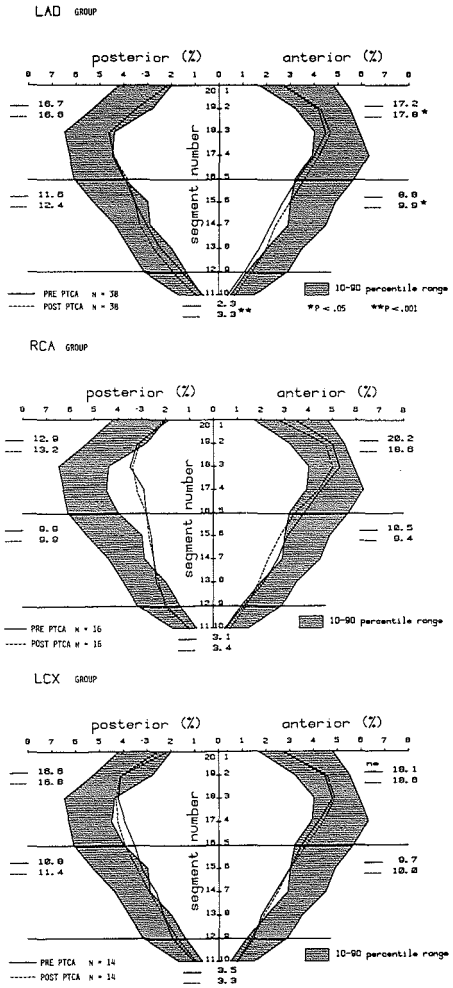

Figure 2. Left ventricular regional wall motion in 38 patients with a stenosis of the proximal left anterior descending (LAD) coronary artery, in 16 patients with a stenosis of the right coronary artery (RCA), and in 14 patients with a stenosis in the left circumflex coronary artery (LCX) before and after percutaneous transluminal coronary angioplasty (PTCA).

All patients underwent follow-up catheterization a mean of 3.1 ± 2 months after PTCA. A restenosis was defined as an increase of the luminal diameter stenosis of the dilated lesion of more than 50%.

Analysis of Global and Regional Left Ventricular Function

The coronary angiograms were recorded before left ventricular (LV) angiograms. Global and regional LV function were studied from the 30° right anterior oblique LV cineangiogram using an automated hardwired endocardial contour detector linked to a minicomputer. This method of analysis has been described in detail (15-18). Figure 1 shows an example of computer output showing the end-diastolic and end-systolic contours of the left ventriculogram and system of coordinates along which segmental wall displacement is determined.

The inter- and intra-observer variability of automated assessment of global and regional LV performance ranged between 1.6 and 2.3% standard error of the estimate for global ejection fraction; and for summed regional contribution to ejection fraction anterobasal, anterolateral, apex, inferoapical and posterobasal segments, respectively, between 0.4 and 2.3% standard errors of the estimate.

Statistics

Results are expressed as mean ± standard deviation. Statistics were determined with 2 tailed Student t-test. A p value of less than 0.05 was considered statistically significant.

RESULTS

Global and regional LV function before and after PTCA were analyzed for all patients and grouped according to the dilated vessel (Tables I and II, Figure 2). Global ejection fraction was significantly improved in patients who underwent PTCA of the left anterior descending artery due to a decrease in end-systolic volume, whereas no significant change in serial global LV function was observed in patients with PTCA of the right or left circumflex coronary artery (Table I). Computer- assisted regional wall motion analysis showed improvement in motion of the initially abnormal segments in all three subsets of patients, whereas the regional wall motion decreased to a small extent in initially normal segments (Figure 2, Table II).

The results of thallium-201 scintigraphy are shown in figure 3. Most of the patients had no signs of myocardial ischemia with a normal exercise tolerance.

Table I: Global left ventricular hemodynamics before (B) and after (A) successful PTCA

	All patients (n = 68)		Left anterior descending coronary artery (n = 38)		right coronary artery (n = 16)		left circumflex coronary artery (n = 14)	
Variables	B	A	B	A	B	A	B	A
HR bpm	72±12	71±12	74±12	70±10	73±13	73±18	68±13	70±10
MAP mmHg	98±17	108±16**	99±18	109±19**	89±10	103±11**	106±16	110±13
EDP mmHg	21±7	19±7	21±8	18±6	19±6	19±8	22±7	20±6
EDV ml/m^2	75±16	77±18	74±15	74±18	74±18	79±22	77±18	79±14
ESV ml/m^2	32±14	30±15	32±13	28±12*	32±16	35±21	29±12	31±12
SV ml/m^2	43±10	46±11	42±11	46±11*	43±8	44±12	47±12	48±9
EF %	57±12	59±11*	56±12	60±10**	56±13	54±14	59±11	60±11

* p value less than 0.05; ** p value less than 0.005.
EDP = end-diastolic pressure; EDV = end-diastolic volume; EF = global ejection fraction. ESV = end-systolic volume; HR = heart rate; MAP = mean arterial pressure; SV = stroke volume.

Table II: Analysis of the regional wall motion before (B) and after (A) successful PTCA

	left anterior descending coronary artery (n = 38)		right coronary artery (n = 16)		left circumflex coronary artery (n = 14)	
	B	A	B	A	B	A
Total analyzed segments	760	760	320	320	280	280
Total number of abnormal segments	322	137	116	75	104	48
Abnormal segments/patients	9±5	4±3*	7±4	5±5**	7±5	3±4*
Sum of abnormal CREF value(%)	17±8	23±10**	10±6	13±7*	16±8	20±11*
Sum of normal CREF value (%)	41±18	40±18*	46±18	41±17*	43±18	40±18

* p value less than 0.05, ** p value less than 0.001
CREF = regional contribution to global ejection fraction (see fig. 1).

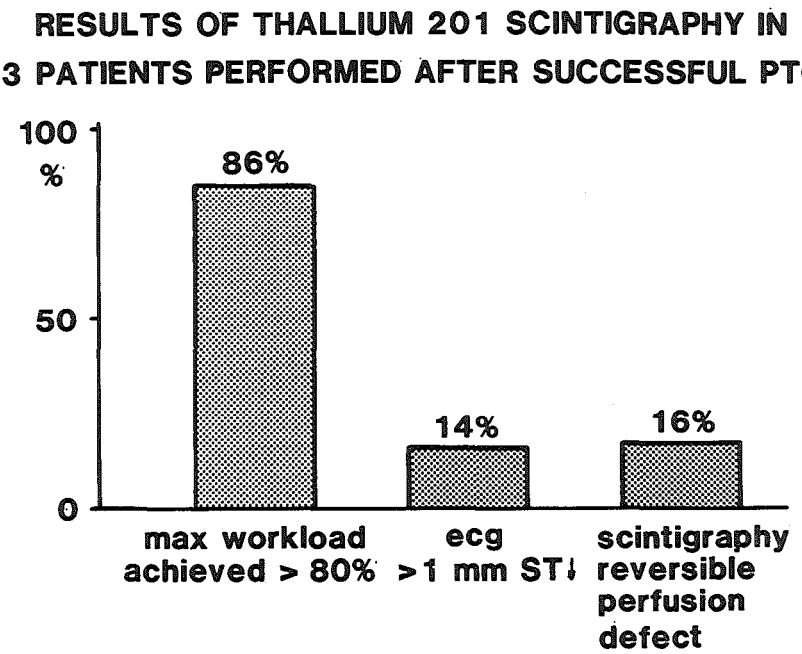

Figure 3. Results of exercise thallium-201 scintigraphy in 63 patients after successful percutaneous transluminal coronary angioplasty. ecg = electrocardiogram

DISCUSSION

In patients undergoing successful PTCA, anatomic improvement correlates well with elimination of angina (19), improved function on atrial pacing (20) and conventional exercise testing (21-23), improved perfusion with myocardial scintigraphy (21,22) and radionuclide ventriculography (24), and restoration to a nearly normal coronary flow reserve (25).

The myocardium is capable of recovering function lost as a result of ischemia after adequate reperfusion. Whole or partial recovery may occur after successful coronary artery bypass surgery (9,10,26-28).

In this study, we demonstrated that successful PTCA was accompanied by improvement in global LV function in patients with dilatation of a lesion of the left anterior descending coronary artery and by significant improvement of LV regional wall motion in the initially impaired regional segments of the areas perfused by the left anterior descending, circumflex and right coronary arteries. The improvement (left anterior descending group) or maintenance (right coronary artery and left circumflex groups) of LV global ejection fraction was primarily due to improvement of the initially abnormal regional wall motion, even after the disappearance of the compensatory actions of the initially enhanced function of the non-ischemic segments.

Limitations

Myocardial dysfunction as a result of prolonged ischemia may improve spontaneously when the ischemic attacks resolve spontaneously either as part of a natural healing process or as a result of pharmacologic therapy (29). Ideally, the effects of PTCA on LV function should be determined in a randomized controlled study, but it is difficult to justify this type of study in our group of patients due to severity of the disease. We believe that the normalization of antegrade flow after PTCA, evidenced by repeat angiography and no signs of ischemia in most of the patients who underwent exercise thallium-201 scintigraphy, is the main reason for the observed recovery of myocardial function.

Differences in pharmacologic treatment before and after PTCA, in particular the use of beta-adrenergic blockade before PTCA, may also play a role in the observed difference of LV function. However, we have shown that regional wall motion improved selectively in the areas that received better blood supply after PTCA rather than in the ventricle as a whole.

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CHAPTER V

CORONARY ANGIOPLASTY IMMEDIATELY AFTER THROMBOLYSIS IN 115 CONSECUTIVE PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

ABSTRACT

Between September 1981 and May 1986, coronary angioplasty immediately after intracoronary thrombolysis was attempted in 115 patients with acute myocardial infarction. The present study describes our experience with this combined procedure. Primary success was achieved in 102 patients (89%). Before discharge, 79 of these patients agreed to be restudied angiographically. The infarct-related vessel was still patent in 71 patients (patency rate of 90%). Sequential left ventricular angiograms of adequate quality sufficient to allow automated analysis were obtained in 58 patients. Global ejection fraction improved significantly from 52 ± 10% to 55 ± 9% ($p = 0.01$) from the acute to the chronic stage. In patients with anterior infarction, the increase in global ejection fraction was primarily the result of significant improvement of the regional myocardial function of the infarct zone. No significant changes in global and regional myocardial function could be seen in patients with inferior infarction. However, when patients in whom the infarct-related vessel was reoccluded at follow-up angiography are excluded from analysis, the global and regional myocardial function did improve significantly irrespective of the location of the infarct. Median clinical follow-up of 20 (range 4 to 50) months resulted in an overall mortality rate of 4%. Preservation of global and regional left ventricular function with a low mortality rate suggests that immediate coronary angioplasty after thrombolysis can be safely used to provide reperfusion in the setting of acute myocardial infarction and that this combined procedure may be the optimal mode of therapy. Further randomized studies are warranted to precisely define the role of coronary angioplasty in acute myocardial infarction.

INTRODUCTION

Limitation of myocardial infarct size through salvage of ischemic myocardium is the major goal in the management of patients with acute myocardial infarction. Several methods for re-establishing blood flow during acute myocardial infarction in an attempt to prevent or reduce cell necrosis have generated particular interest.

Since the first clinical demonstration by Rentrop et al (1), we and many others have demonstrated that rapid recanalization can be achieved by intracoronary infusion of streptokinase in approximately 80% of patients (2-12). However, a frequent finding after recanalization is severe residual coronary stenosis that may restrict antegrade flow and limit the recovery of regional left ventricular function. Therefore, additional interventions, such as coronary bypass surgery and coronary angioplasty, have been advocated in this setting to improve this incomplete restoration of flow and maximize myocardial salvage (13-15).

The present study describes our experience with angioplasty immediately after intracoronary thrombolysis as primary therapy in the management of selected patients with acute myocardial infarction.

METHODS

Between September 1981 and May 1986, a total of 4400 patients were admitted to the coronary care unit of the Thoraxcenter; of these patients, 1100 had an acute myocardial infarction. Intracoronary thrombolytic therapy was given to 243 patients. Coronary angioplasty immediately after thrombolysis was attempted in 115 patients with acute myocardial infarction, and these patients formed our study population. Patients selected were less than 70 years of age and had no history of hemorrhagic diathesis or previous cerebral vascular accident. All patients had chest pain of less than 4 hours duration at the time of admission and had ST-segment elevation typical of myocardial infarction on their electrocardiogram. Informed consent was obtained from all patients. Immediately after admission, an infusion of nitroglycerin was started and as soon as possible the patients were transferred to the catheterization laboratory. Prophylactic lidocaine (2 mg/min) was given intravenously. Pre-treatment was similar for all patients and was aimed at the rapid achievement of an optimal hemodynamic state by means of light sedation and by controlling the heart rate between 60 and 90 bpm and systolic blood pressure between 100 and 140 mmHg. Complications such as left ventricular failure or rhythm disturbances were treated appropriately. The combination of hypotension (systolic pressure below 90 mmHg) and sinus tachycardia (heart rate over 100 bpm) led to temporary exclusion. If the hemodynamic condition of the patient improved quickly, inclusion in the study was still possible.

Clinical Characteristics

Clinical data for all patients are shown in table I. When patients were subdivided into 2 groups based on the location of the infarct (51 patients with inferior and 64 with anterior infarction), all data were distributed evenly, including a history of previous myocardial infarction and previous bypass surgery. Similarly, maintenance therapy and hemodynamic state at the time of admission were the same in both groups.

Table I: Baseline characteristics

characteristics	anterior infarction	inferior infarction	total
n	64	51	115
Male/female	54/10	42/9	96/19
Median age (yr)	55	57	56
Previous infarction	11	8	19
Previous bypass surgery	2	3	5
Previous PTCA	1	1	2
History of angina:			
less than 4 weeks	22	14	36
more than 4 weeks	12	15	27
Therapy before admission:			
beta-blocker	18	11	29
nitrates	15	10	25
Ca-antagonist	14	8	22
anti-coagulant	6	3	9
diuretics	7	3	10
digitalis	1	0	1
none	38	33	71
Killip Class II/III/IV	7/2/3	10/3/1	17/5/4
Single/double/triple VD	41/14/9	33/11/7	74/25/16
Initial EF (%)	51±10	55±10	52±10
Peak CK (U/L)	960±701	947±738	955±709

PTCA = percutaneous transluminal coronary angioplasty;
VD = vessel disease, EF = global ejection fraction;
CK = creatinine phosphokinase.

Intracoronary Thrombolysis and Coronary Angioplasty

Initial coronary angiography and administration of intracoronary streptokinase were performed as previously described (2-4,15-19). Briefly, intracoronary perfusion with

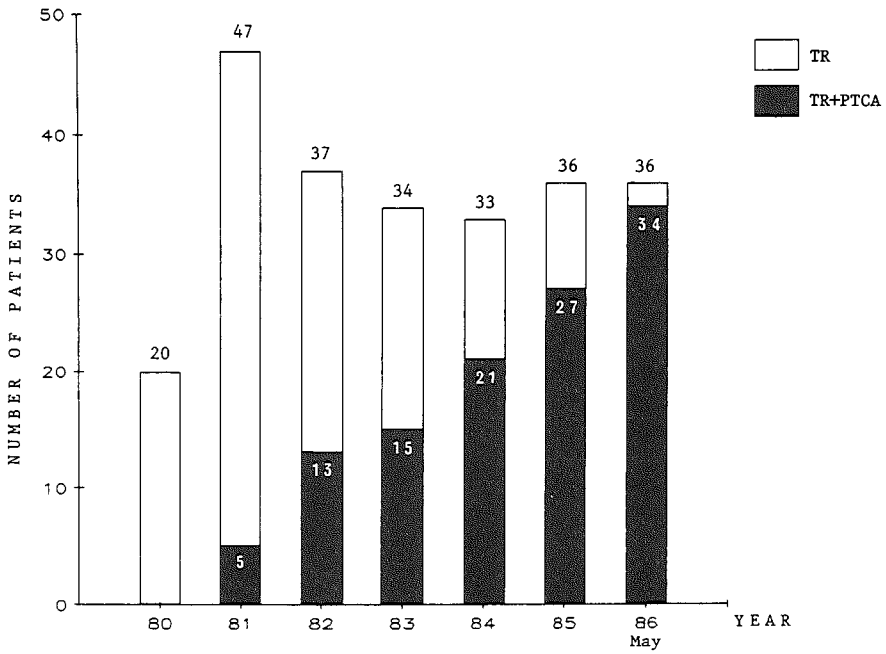

Fig. 1. Breakdown of 243 patients treated with thrombolytic therapy since 1980. Increasing number of patients receiving additional percutaneous transluminal coronary angioplasty (PTCA) is shown (n = 115). TR, Thrombolytic therapy; TR (+) PTCA, thrombolytic therapy immediately followed by coronary angioplasty.

streptokinase was carried out at a rate of 4000 units/minute to a maximum of 250,000 units. Coronary angiography was repeated every 15 minutes until the vessel was patent or until chest pain had disappeared. Coronary angioplasty was performed after thrombolysis when the residual stenosis was 60% or more and when the procedure was judged to be technically and organizationally feasible. The increasing number of patients receiving additional coronary angioplasty is shown in figure 1. In fact, for the year 1986, analyzed until May, all but 2 patients were treated with additional coronary angioplasty immediately after thrombolysis. Successful dilatation was defined as an improvement in the diameter stenosis from more than 60% to less than 50% and restenosis as a return to more than 50%. Left ventriculography in the right anterior oblique projection was performed at the end of the procedure. All patients received heparin followed by acenocoumarol at least until they were discharged from the hospital. In addition, nifedipine, 10 mg 6 times daily, and, aspirin, 500 mg, were given to all patients. From the patients who agreed to follow-up catheterization, coronary and left ventricular angiography were performed before they were discharged.

Analysis of Global and Regional Left Ventricular Function

Global and regional left ventricular function was studied in the 30° right anterior oblique view by means of an automated hardwired endocardial contour detector linked to a mini-computer (20). For each analyzed cineframe, left ventricular volume was computed according to Simpson's rule. After the end-diastolic and end-systolic frames were identified, stroke volume, global ejection fraction and total cardiac index were computed. In figure 2A, examples of the end-diastolic and end-systolic contours of the left ventriculogram, as displayed by the analysis system, are shown. Systolic regional wall displacement was determined along a system of 20 coordinates on the pattern of actual endocardial wall motion in normal individuals (21) and generalized as a mathematical expression amenable to automatic data processing (22,23). For each segment, segmental volume was computed from the local radius (R) and the height of each segment (1/10 of left ventricular long-axis length (L) according to the formula: $1/20\ \Pi R^2L$). When normalized for end-diastolic volume, the systolic segmental volume change was considered as a parameter of regional pump function (fig. 2,B and C). During systole this parameter expresses quantitatively the contribution of a particular segment to global ejection fraction, termed regional contribution to global ejection fraction (CREF) (22). It follows that the sum for all segments equals the global ejection fraction. The cross-hatched zones in figure 2D represent the segmental CREF values between the

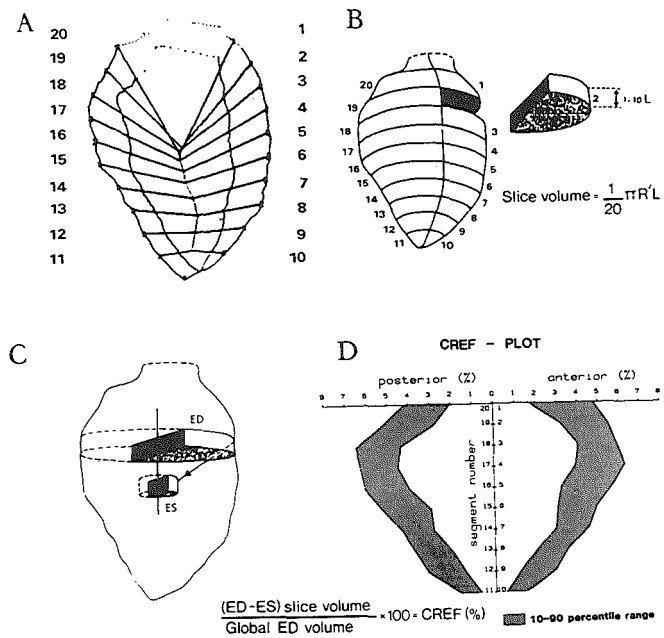

Fig. 2. A, Example of computer output showing end-diastolic and end-systolic contours of 30-degree right anterior oblique left ventriculogram. Systolic regional wall displacement was determined along a system of 20 coordinates on pattern of actual endocardial wall motion in normal individuals and generalized as mathematical expression amenable to automatic data processing. [20-23]. B, Left ventricular end-diastolic cavity divided into 20 half slices. Volume of each half slice is computed according to given formula. R, radius; L, left ventricular long-axis length. C, Regional contribution to global ejection fraction (CREF) is determined from systolic decrease of volume of half slice corresponding to particular wall segment. Systolic volume change is mainly consequence of decrease of radius (R) of half slice. When normalized for end-diastolic volume, systolic segmental volume change was considered a parameter of regional pump function. D, Shaded zones represent tenth to ninetieth percentile areas of CREF values in normal individuals. On the X axis CREF values of anterior and inferoposterior wall areas are displayed (%); on the y axis segment numbers of anterior wall (1-10) and inferoposterior wall (11-20) are shown. Segmental CREF values in anterobasal (segments 1-5), anterolateral (segments 5-9), apex (segments 9-12), inferoapical (segments 12-16) and posterobasal (segments 16-20) wall regions were analyzed.

tenth and ninetieth percentiles, as determined from 20 normal individuals. The segmental CREF-values in the anterobasal (segments 1 to 5), anterolateral (segments 5 to 9), apical (segments 9 to 12), inferior (segments 12 to 16) and posterobasal (segments 16 to 20) wall regions were analyzed.

Clinical Follow-Up

All patients were followed at the outpatient clinic for at least one year after admission, and survival status was assessed for all patients at six month intervals. Recurrent myocardial infarction, angina pectoris, cardiac failure, bypass surgery, and percutaneous transluminal coronary angioplasty were recorded.

Statistical Analysis

Data are expressed as mean ± SD. Paired Student t tests were applied to the hemodynamic data.

RESULTS

Since September 1981, we have attempted coronary angioplasty of the infarct-related vessel in 115 patients (fig. 3); in 102 of them the infarct-related vessel was successfully dilated (primary success rate of 89%). In 13 patients, attempted angioplasty was unsuccessful; one patient died of cardiogenic shock during the procedure and 4 other patients underwent coronary artery bypass surgery 1 to 27 (mean 9) days after the initial procedure. Of the remaining 8 patients, 2 subsequently developed stable angina (New York Heart Association class II) controlled by pharmacologic treatment and 6 were asymptomatic. Follow-up angiography was performed in 4 patients in whom the attempted angioplasty was unsuccessful. An occluded infarct-related vessel was found in 2 patients, one of whom was asymptomatic at follow-up, whereas the infarct-related vessel was still patent in 2 other patients, one of whom underwent coronary artery bypass surgery and one who was asymptomatic at follow-up. Of the 102 successfully treated patients, 4 patients died 59 (range 7 to 120) days after the initial procedure, 8 subsequently developed a non-fatal recurrent infarction, 10 underwent elective bypass surgery 87 (range 21 to 231) days after the initial procedure, and 8 underwent successful repeat coronary angioplasty 6.5 (range 0.5 to 30) months after the initial procedure. Of the remaining patients, 17 subsequently developed stable angina (New York Heart Association class II) that was controlled by pharmacologic treatment and 55 were

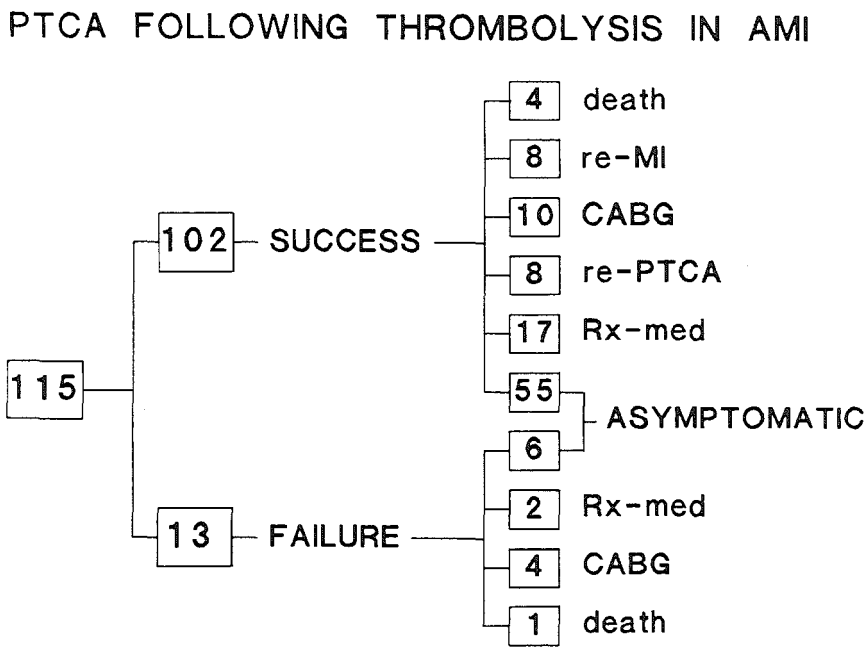

Fig. 3. Short- and long-term follow-up in 115 consecutive patients undergoing coronary angioplasty immediately after thrombolysis. re-MI, Recurrent myocardial infarction; CABG, coronary artery bypass graft; re-PTCA, repeat coronary angioplasty; Rx-med, controlled by pharmacologic treatment.

asymptomatic and were receiving no antianginal therapy at follow-up.

Before discharge, 79 of 102 patients who underwent successful angioplasty agreed to be restudied angiographically. In 71 patients the infarct-related vessel remained patent. On the other hand, 8 stenotic lesions that had been successfully recanalized and dilated at the acute stage were found to be reoccluded at the time of follow-up angiography before discharge. This observation suggests a reocclusion rate of 10% (8 of 79) when recanalization is immediately followed by angioplasty. Among these 8 patients with reocclusion, one died during the hospital stay as a result of recurrent infarction with cardiogenic shock, 2 subsequently developed non-fatal recurrent infarction, 3 had residual angina controlled by pharmacologic treatment, and 2 were asymptomatic. Patient population, infarct-related vessel, and primary success and reocclusion rates at follow-up are shown in figure 3 and table II.

Table II: Angiographic data

			Follow-up angiography after initially successful PTCA		
IRV	attempted PTCA	primary success	n	re-occlusion	re-stenosis
LM	2	2	2	0	1
LAD	58	53	40	1	6
LCX	12	10	8	1	3
RCA	40	35	29	6	5
Bypass graft	3	2	0	0	0
Total	115	102	79	8	15

IRV = infarct-related vessel; PTCA = percutaneous transluminal coronary angioplasty; LM = left main coronary artery; LAD = left anterior descending coronary artery; LCX = left circumflexus; RCA = right coronary artery.

Global and Regional Left Ventricular Function

Sequential left ventricular angiograms of sufficient quality to allow automated contour analysis were obtained from 58 patients (25 with inferior and 33 with anterior infarction). The global ejection fraction increased significantly ($p = 0.01$) from 52 ± 10% to 55 ± 9%. The significant increase in end-diastolic volume was accentuated by the inclusion of patients with reocclusion of the infarct-

Table III: Global left ventricular hemodynamics

		All (n=58)			without reocclusion (n=50)			with reocclusion (n=8)		
		A	P value	C	A	P value	C	A	P value	C
HR	bpm	85±14	0.00001	74±13	84±14	0.00004	74±13	88±13	0.07	72±15
MAP	mmHg	89±13	0.01	95±13	91±13	0.02	96±13	82±11	0.03	90±13
EDP	mmHg	20±8	ns	18±7	20±8	ns	18±7	17±7	ns	19±7
EDV	ml/m^2	79±17	0.05	85±20	80±17	ns	82±18	71±15	0.008	104±26
ESV	ml/m^2	38±11	ns	39±14	38±11	ns	36±12	33±11	0.006	55±22
SV	ml/m^2	41±12	0.0005	46±11	42±12	0.007	46±12	38±9	0.02	49±7
EF	%	52±10	0.01	55±9	52±10	0.002	56±9	54±10	0.01	49±8

Sequential changes in global left ventricular hemodynamics in patients in whom the left ventriculogram of adequate quality was obtained at acute (A) and at follow-up catheterization before discharge (C). Values are expressed as mean ± standard deviation; Only P values less than 0.1 are tabulated. HR = heart rate; MAP = mean aortic pressure; EDP = end-diastolic pressure; EDV = end-diastolic volume; ESV = end-systolic volume; SV = strokevolume; EF = global ejection fraction; ns = not significant.

related vessel after initially successful angioplasty. When these patients with reocclusion are excluded from analysis, the end-diastolic volume did not change significantly, as shown in table III.

Figure 4 shows the sequential changes in regional myocardial function from the acute to the chronic stage in the patients in whom left ventriculography was performed at the time of acute and follow-up catheterization. In patients with anterior infarction, the increase in global ejection fraction (from 51 ± 10% to 55 ± 10%; $p = 0.05$) was primarily due to a significant improvement in regional contribution to ejection fraction of the infarct zone, as shown in figure 4. In contrast, in the group of patients with inferior infarction, the regional contribution to ejection fraction of the infarct zone remained unchanged. However, when patients in whom the infarct-related vessel was found to be reoccluded at follow-up angiography are excluded from analysis, the regional myocardial function of the infarct zone did improve significantly irrespective of the infarct location as shown in figure 5.

Clinical Follow-Up

Results of median clinical follow-up of 20 months after admission (range 4 to 50 months) are shown in table IV. The survival rate was 96%, and infarct location did not affect longterm survival (mortality rate of 5% versus 4%). In addition, incidences of non-fatal recurrent infarction (7%), bypass surgery (12%), and repeat PTCA (7%) were also low in this study population. Among the remaining 80 patients, 19 had stable angina (New York Heart Association, class II), 12 with anterior and 7 with inferior infarction.

Table IV: Clinical follow-up (median of 20 months)

	Anterior infarction	Inferior infarction	All
Mortality	3 (5%)	2 (4%)	5 (4%)
Recurrent infarction	2 (3%)	6 (12%)	8 (7%)
Bypass surgery	10 (16%)	4 (8%)	14 (12%)
Repeat-PTCA	4 (6%)	4 (8%)	8 (7%)
Angina NYHA class II	12 (19%)	7 (14%)	19 (17%)
Without symptoms	33 (52%)	28 (55%)	61 (53%)
Total	64	51	115

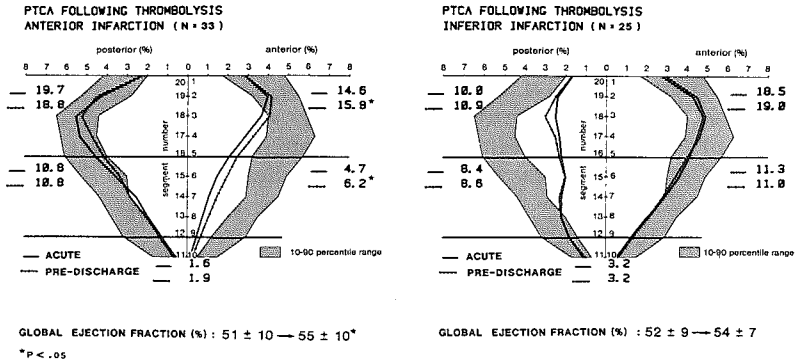

Fig. 4. Sequential changes in regional contribution to global ejection fraction from acute (at admission, solid line) to predischarge (dotted line) stage in patients with anterior (left-sided) and inferior (right sided) infarction treated by combined procedure of intracoronary thrombolysis and angioplasty. In patients with anterior infarction, significant increase in global ejection fraction was primarily due to significant improvement in regional myocardial function of infarct zone (anterior, segment 1 to 10) even after disappearance of compensatory actions of initially enhanced function of noninfarct zone (posterior). In group of patients with inferior infarction, regional myocardial function of infarct zone remained unchanged.

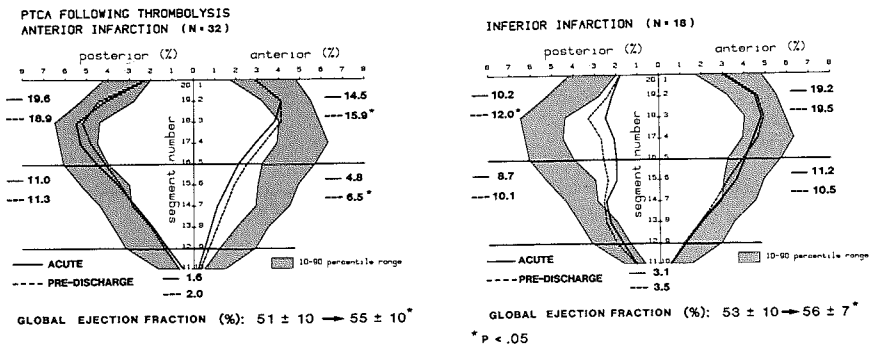

Fig. 5. Sequential changes in regional myocardial function as shown in Fig. 4, after exclusion of patients in whom infarct-related vessel was found to be reoccluded at follow-up angiography before discharge.

DISCUSSION

The present study reports our experience with angioplasty immediately after intracoronary thrombolysis in the management of patients with acute myocardial infarction. As our study was not randomized and did not include a control group, we can make no definitive statements about the effects of angioplasty on early death and other major cardiac events, and the results should be interpreted with this in mind.

Although the current results might be biased by the selection of those patients who were hemodynamically stable and in whom it was judged to be technically and organizationally suitable for angioplasty, the findings are in agreement with earlier observations that the recovery of regional function is greatest in patients with the lowest residual stenosis after the intervention (4,24-27).

Serial left ventricular angiograms of sufficient quality to allow automated contour analysis were available for 58 of the 115 patients (50%) in this study. The lack of serial ventriculograms of all subjects is another limitation of this study. To investigate possible selection bias, we compared these 58 patients with 57 patients from whom no serial contrast ventriculograms were obtained and found no difference between groups (table V). Although these data are reassuring, they do not definitely exclude selection bias.

Table V: Characteristics of patients with (A) and without (B) sufficient serial left ventricular angiograms

characteristics	A (n=58)	B (n=57)	total (n=115)
Male/female	51/7	45/12	96/19
Median age (yr)	56	56	56
Anterior/inferior infarction	33/25	31/26	64/51
No therapy before admission	37	34	71
Killip class II/III/IV	9/2/1	8/3/3	17/5/4
Previous infarction/CABG/PTCA	14	12	26
Single/double/triple VD	36/17/5	38/8/11	74/25/16
Peak CK (U/L)	850±596	1123±845	955±709
Recurrent infarction	5	3	8
CABG/repeat-PTCA	12	10	22
Mortality	3	2	5

CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; VD = vessel disease; CK = creatinine phosphokinase.

Primary Success and Late Patency

In this series, the primary success rate for angioplasty immediately after thrombolysis was 89% and was similar or even more favorable when compared with other reports (26-35) in which the range was 65% to 91% (table VI). This implies that this combined procedure can be safely used to provide reperfusion in the setting of acute myocardial infarction. Although many studies have shown that rapid recanalization can be achieved by intracoronary thrombolysis with a reperfusion rate comparable to that of the combined procedure (intracoronary thrombolysis followed by additional angioplasty), analysis of serial global and regional left ventricular function demonstrated the benefit of correcting these residual obstructive lesions (13,26,36,37). This approach seems rational if an isolated occlusion is only minimally opened with streptokinase, since it is these residual high-grade stenoses that are the most likely to reocclude (15,29,38,39). Reocclusion during the hospital stay occurred in 10% of patients in whom initially successful angioplasty was performed after thrombolysis; this is in accordance with our earlier observation (15) and those of other investigators (table VI). According to other reports (15,28,29,38,39), reocclusion is dependent on the degree of luminal narrowing after reperfusion. More recently, this was confirmed by Erbel et al (27), who reported a reocclusion rate of 7% in patients after successful angioplasty, 32% after unsuccessful angioplasty with high-grade residual stenosis, and 20% after successful thrombolysis alone. Serruys et al (15) showed a reocclusion rate of 6% in patients undergoing additional angioplasty after thrombolysis and 17% in patients undergoing thrombolysis alone. These results suggest that reperfusion may need to be supplemented by additional revascularization procedures, such as coronary bypass surgery and angioplasty, and any intervention should not be postponed, since reocclusion rate is highest in the first 5 days after thrombolysis (27) and any reduction in perfusion may impede myocardial recovery.

Global and Regional Left Ventricular Function

In many of the previous randomized trials (5-12), successful reperfusion with intracoronary thrombolysis alone did not bring about an improvement in global left ventricular function. In a recently published report of a randomized trial, Erbel et al (27) also found no significant changes in global ejection fraction, even in those patients treated with additional angioplasty after intracoronary thrombolysis. In contrast, our study shows that successful reperfusion with angioplasty was associated with a significant improvement in

Table VI: Uncontrolled studies on coronary angioplasty after thrombolysis in acute myocardial infarction: primary success, angiographic re-occlusion and in-hospital mortality rates

study		attempted PTCA after lysis (n)	primary success (%)	Before dischange: angiographic re-occlusion (%)	Before dischange: mortality rate (%)	Before dischange: global/regional LV function
Meyer et al	1982(14)	21	81	8*	5	-
Gold et al	1984(32)	28	71	15	9	-
Yasuno et al	1984(31)	25	72	33	?	+
Papapietro et al	1985(33)	18	72	25	6	-
Holmes et al	1985(30)	29	72	23	7	-
Erbel et al	1985(34)	46	74	3	?	?
Kitazume et al	1986(35)	22	91	10	5	-
Thoraxcenter	1986	115	89	10	3	+

* Angiographic follow-up at 6 months.

global left ventricular function. This was in agreement with the data from a randomized trial of intracoronary streptokinase versus coronary angioplasty, recently published by O'Neill et al (26). On the other hand, both randomized trials (26,27) showed significant improvement in regional myocardial function of the infarct zone after coronary angioplasty; a finding consistent with ours.

The initial ejection fraction was found to be higher in patients with inferior compared to anterior myocardial infarction (40). Timmis et al (41) showed that patients with an initial global ejection fraction of less than 50%, who were successfully treated with intracoronary streptokinase, had significant gains in left ventricular function at follow-up catheterization before discharge regardless of infarct location, whereas those with an initial global ejection fraction of more than 50% did not. In the present series, the initial global ejection fraction in patients with inferior infarction was higher (55 ± 10%) compared to those with anterior infarction (51 ± 10%) but did not reach statistical significance (table I). This lack of difference may be due to the fact that patients were selected on the basis of them having a clinically stable hemodynamic state before they underwent any invasive investigation and treatment, which also explains the high proportion of patients in Killip classes I and II. The significant increase in global ejection fraction in the present study was primarily the result of a significant improvement in the regional myocardial function of the infarct zone in the group of patients with anterior infarction, as shown in figure 4. Whereas in the group of patients with inferior infarction this improvement did not occur. This finding is in accordance with other reports (27). A possible explanation for the lack of improvement in inferior wall myocardial function might be the disproportionately high incidence of reocclusion in those patients with a lesion of the right coronary artery. When patients with reocclusion of the dilated artery are excluded from analysis, the regional wall motion of the infarct zone improved significantly irrespective of the infarct location, as shown in figure 5. This is in accordance with previous studies that have shown that failure of recanalization or reocclusion after initially successful recanalization of an occluded vessel is associated with poor improvement in regional myocardial function (4).

A higher mortality rate was found in patients with anterior infarction (19%) compared to those with inferior infarction (5%)(42). The overall mortality rate of 4% in our patient population, with an in-hospital mortality rate of 3%, was similar, or even more favorable, when compared to other reports (table VI). The fact that patients with anterior infarction treated by intracoronary thrombolysis followed by angioplasty had a low mortality rate (5%) and was similar to those with inferior infarction (4% mortality rate) again

suggests that reperfusion may need to be supplemented by additional revascularization procedures to optimize the chances of obtaining full functional recovery. The additional value of immediate angioplasty in preserving global and regional left ventricular function and limiting infarct size may help to explain the observed reduction in the mortality rate and other major cardiac events. On the other hand, the need for acute revascularization in patients with inferior infarction is still open to discussion.

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CHAPTER VI

VALUE OF IMMEDIATE CORONARY ANGIOPLASTY FOLLOWING INTRACORONARY THROMBOLYSIS IN ACUTE MYOCARDIAL INFARCTION

ABSTRACT

A total of 533 patients with acute myocardial infarction of less than 4-h duration were enrolled in the multicenter randomized trial of intracoronary thrombolysis compared to conventional treatment. In two of the five participating centers, an additional coronary angioplasty immediately after thrombolysis was attempted in 46 patients. According to the treatment allocation and early and late patency of the infarct-related vessel, patients were subdivided into three groups: conventionally treated (group A); successful coronary angioplasty following thrombolysis with persistent patent infarct-related vessel (group B); and late patency of the infarct-related vessel postthrombolytic therapy without angioplasty (group C). The highest global ejection fractions were observed in group B (54±10%) and group C (55±13%), while the lowest ejection fraction was found in group A (47±14%). The sequential changes in global ejection fraction from the acute to the chronic stage was + 4% ($p = 0.05$) in group B, while no significant changes could be demonstrated in group C. Furthermore, in the group successfully treated by angioplasty, the improvement in global ejection fraction was more pronounced and persisted up to three months after the intervention. This was supported by analysis of regional myocardial function of the infarct zone (+ 16% improvement, $p = 0.01$). The long-term clinical follow-up (median 24 months) of the patients successfully treated by combined procedure of thrombolysis and angioplasty (group B) was most favourable with a lower incidence of re-infarction (6%), and late coronary bypass surgery (13%) and/or (re)-percutaneous transluminal coronary angioplasty (3%) was performed less frequently.
These results suggest that reperfusion may need to be supplemented by additional revascularization procedures in order to optimize the chances of obtaining full functional recovery and so to improve the prognosis.

INTRODUCTION

Since the first study by Rentrop et al (1), we and many others have demonstrated that rapid recanalization can be achieved by intracoronary streptokinase in approximately 80%

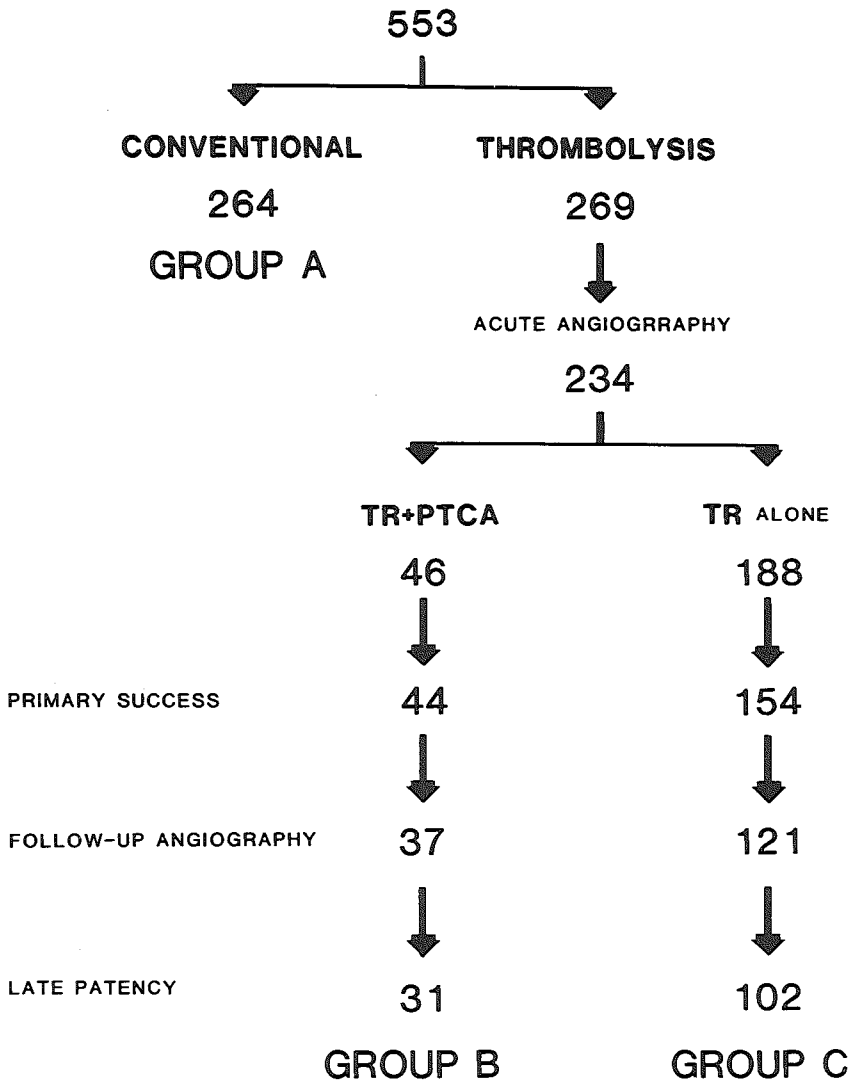


Fig. 1. Flow chart. TR, thrombolysis; PTCA, percutaneous transluminal coronary angioplasty.

of patients (2-5). The large multicenter trial conducted by the Interuniversity Cardiology Institute in the Netherlands has documented that early recanalization is associated with a limitation of infarct size, preservation of left ventricular function, and improved survival when compared to conventional treatment (6-8). However, a frequent finding after recanalization is severe recurring or residual coronary stenosis which may restrict antegrade flow and limit the recovery of regional left ventricular function. Therefore, additional interventions, such as coronary angioplasty, have been advocated in this setting to improve this incomplete restoration of flow and maximize myocardial salvage (4,9-22).

The aim of this study was to investigate whether immediate angioplasty after thrombolysis indeed provided additional benefit in the preservation of regional myocardial function in the infarct zone by retrospectively reviewing the results of the Netherlands multicenter trial of thrombolytic therapy (6-8) in which selected patients underwent angioplasty.

PATIENTS AND METHODS

Between June 1981 and March 1985, 533 patients with an acute myocardial infarction were enrolled in a multicenter randomized trial of intracoronary thrombolysis compared to conventional treatment; 264 patients were allocated to conventional and 269 to thrombolytic therapy. The initial protocol (23-26) was modified in two ways: the first was as a result of data which suggested that reocclusion of the coronary artery occurred predominately in patients with severe residual stenosis (4,12,15,16). It was therefore decided to proceed to immediate coronary angioplasty in such patients at two of the five participating centers (predominately the Thoraxcenter, Rotterdam). This combined procedure was performed in 46 out of 269 patients allocated to thrombolysis (fig. 1). The second change (January 1984) was to introduce intravenous streptokinase (500,000 U) at the time of admission to hospital (6-8,27-29). During the study period consecutive patients up to the age of 70 years with chest pain and ECG signs of typical myocardial infarction, who arrived within four hours of the onset of symptoms, were admitted to the trial, as described in previous reports (6-8,23-26,30-34).

As the object of this study was to assess the additional value of a successful coronary angioplasty as compared to successful thrombolysis alone, the study population was retrospectively divided into three groups:

group A: patients allocated to conventional treatment (n=264);

group B: patients recanalized by coronary angioplasty following thrombolysis with persistent patency of the infarct-related vessel at follow-up angiography (n=31);

group C: patients recanalized by thrombolysis without angioplasty with subsequent late patency of the infarct-related vessel (n=102).

Patients with persistent occlusion in spite of attempted recanalization procedures (n=36) and patients with initial patency after recanalization in whom the infarct-related vessel was found reoccluded at follow-up angiography (n=25) were excluded from analysis in this study. The necessary angiographic data was unobtainable in the remaining 75 patients; the recanalization procedure could not be performed in spite of allocation to thrombolysis (n=35), or the late patency of the infarct-related vessel could not be evaluated (n=40).

Electrocardiographic Assessment (31,32)

ST-segment elevation of at least 0.1 mV in one or more extremity leads, 0.2 mV in one or more precordial leads, or at least 0.2 mV ST-segment depression in one or more precordial leads compatible with posterior infarction were analyzed. The sum of ST-segment elevation on the ECG was defined for anterior infarcts as the sum of ST-segment elevation in leads I, aVL, V1-V6 and for inferior infarcts as the sum of ST-segment elevation in I,II,III, AVL, AVF, V5, V6 and ST-segment depression in V1-V4.

Measurement of Serum Alpha-Hydroxybutyrate Dehydrogenase

Serum alpha-hydroxybutyrate dehydrogenase levels were determined on admission, every 12 hours for the first two days and then every 24 hours until 5 days after admission. Cumulative release of alpha-hydroxy butyrate dehydrogenase (HBDH) in the first 72 hours was calculated from these data as described earlier (33,35). In two of the 5 participating hospitals total lactate dehydrogenase was measured instead and converted to alpha-hydroxybutyrate dehydrogenase by exchange of standards.

Intracoronary Thrombolysis and Coronary Angioplasty

Initial coronary angiography and the administration of intracoronary streptokinase was performed as previously described (6-8). Briefly, intracoronary streptokinase was carried out at a rate of 4,000 units per minute to a maximum of 250,000 units. Coronary angiograms were repeated every 15 minutes. Coronary angioplasty was attempted in 46 patients in whom it was judged to be technically and organizationally feasible. It was carried out only when the residual stenosis

was 60% or more after thrombolysis. Successful dilatation was defined as an improvement in the diameter stenosis from greater than 60% to less than 50%. Left ventriculography was performed at the end of the procedure. From the patients who agreed to follow-up catheterization, coronary and left ventricular angiography were obtained both in the control and the thrombolysis-treated group, either before discharge or 4-8 weeks after the acute phase.

Radionuclide Angiography

Radionuclide angiography was carried out at the bedside on the first or second day after admission and repeated before hospital discharge and at three months. Gated images were obtained with 20 frames in each heart cycle after in vivo labelling with 15 mCi Technetium 99m. Data were analyzed by a fully automated computer program on a DEC-gamma 11 or an ADAC system (36), or with a MDS or a Philips data analysis system.

Analysis of Global and Regional Left Ventricular Function

Global and regional left ventricular function was studied from the 30° right anterior oblique view using an automated hardwired endocardial contour detector linked to a mini-computer. This method of analysis has been described in detail previously (37-40). Figure 2 shows examples of the end-diastolic (ED) and end-systolic (ES) contours of the left ventriculogram as well as the segmental contribution to the global ejection fraction, as displayed by the analysis system.

Clinical Follow-Up

All patients were followed at the outpatient clinic for at least one year after admission and survival status was assessed at six month intervals. Recurrent myocardial infarction, angina pectoris, cardiac failure, bypass surgery and coronary angioplasty were recorded.

Statistical Analysis

Data are expressed as mean ± SD. Paired or unpaired Student t tests were applied to the hemodynamic data whenever appropriate.

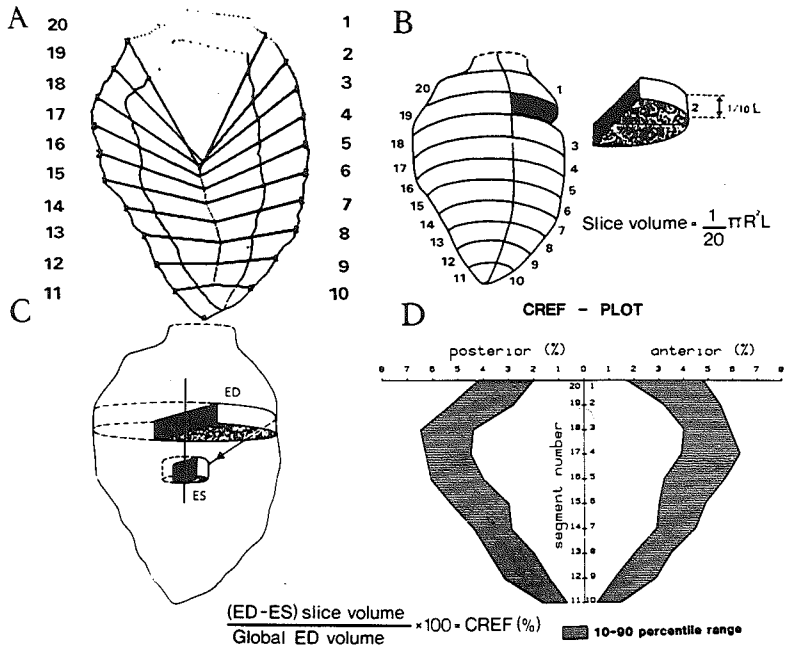


Fig. 2. A: Example of the computer output showing the end-diastolic (ED) and end-systolic (ES) contours of the 30° RAO left ventriculogram. Systolic regional wall displacement was determined along a system of 20 coordinates on the pattern of actual endocardial wall motion in normal individuals and generalized as a mathematical expression amenable to automatic data processing [38-40]. B: The left ventricular end-diastolic cavity is divided into 20 half-slices. The volume of each half-slice is computed according to the given formula; R is radius and L is left ventricular long axis length. C: The regional contribution to global ejection fraction (CREF) is determined from the systolic decrease of volume of the half slice which corresponds to a particular wall segment. The systolic volume change is mainly a consequence of the decrease of radius (R) of the half-slice. When normalized for end-diastolic volume, the systolic segmental volume change was considered as a parameter of regional pump function. D: The shaded zones represent the 10th-90th percentiles area of CREF values in normal individuals. On the x-axis the CREF values of the anterior and inferoposterior wall areas are displayed (%), while on the y-axis the segment numbers of the anterior wall (1-10) and of the inferoposterior wall (11-20) are depicted.

Table I. Results of acute and late angiography

	Acute angiography		Follow-up angiography: Patent (0)		occluded (●)		adequate LV angiography
Controls (n=264)			106		99		174
Thrombolysis (n=269):	without PTCA	with PTCA	without PTCA	with PTCA	without PTCA	with PTCA	
35 no angiography	35	0	13	0	9	0	14
65 0 - 0	52	13	36	10	3	0	36
133 ● - 0	102	31	66	21	16	6	91
36 ● - ●	34	2	11	0	8	0	17

In spite of allocation to thrombolysis, angiography could not be performed in 35 patients. Out of 234 patients who underwent acute angiography, 65 had a patent infarct-related artery and in 169 this artery was occluded. Recanalization was achieved in 133 patients. Ultimately the infarct-related artery remained occluded in 36 out of 234 patients who underwent angiography and at least one attempt at recanalization (15%), while the artery was open at time of study or became recanalized in 198 patients (85%). The median time between onset of symptoms and angiographic documentation of a patent infarct-related vessel for the entire thrombolysis group was 200 minutes, ranging from 55 to 375 minutes.The late patency rates in the control group and thrombolysis group were respectively 52% (106/205) and 79% (157/199) ($p = 0.0001$). The reocclusion rate in patients recanalized by intracoronary streptokinase was 20% (22 out of 109 patients), while late occlusion in the patients with a patent infarct-related vessel at first angiogram was 6% (3 out of 49 patients).

RESULTS

Early and Late Angiographic Findings

Table I shows the results of early and late angiography. Coronary angioplasty was attempted in 46 patients and was successful in 44 patients, including 5 patients with occluded vessel after intracoronary streptokinase in whom subsequent mechanical perforation and angioplasty was performed. Table II details the angiographic data concerning the infarct-related vessel, primary success, and the reocclusion rate. The patients with a persistent patent infarct-related vessel with angioplasty (group B) and without (group C) and patients allocated to conventional treatment (group A) formed our study population (fig. 1).

Table II: Angiographic data

IRV	attempted PTCA	primary success	angiographic follow-up after successful PTCA	reocclusion
LAD	29	27	23	1
LCX	2	2	2	1
RCA	15	15	12	4
Total	46	44 (96%)	37 (84%)	6 (16%)

IRV	attempted TR alone	primary success	angiographic follow-up after successful TR alone	reocclusion
LM	1	1	0	-
LAD	75	61	50	5
LCX	36	31	24	5
RCA	74	60	46	8
Bypass	2	1	1	1
Total	188	154 (82%)	121 (79%)	19 (16%)

IRV = infarct-related vessel; PTCA = percutaneous transluminal coronary angioplasty; TR = thrombolysis; LM = left main coronary artery; LAD = left anterior descending coronary artery; LCX = circumflexus; RCA = right coronary artery.

Table III: Baseline Characteristics

	Controls (group A)	TR + PTCA (group B)	TR alone (group C)
N	264	31	102
Female	41 (16%)	4 (13%)	18 (18%)
Age (yr; mean ± SD)	55 ± 8	57 ± 8	55 ± 10
Anterior infarction	116	22	50
Previous infarction	60 (23%)	8 (26%)	12 (12%)
Previous CABG	8 (3%)	0	1 (1%)
Time to admission (median, min)	90	95	90
Sum of ST elevation (median, mm)	12	14	12

Baseline characteristics of the three subdivided groups: TR+PTCA= recanalization with angioplasty following thrombolysis with late patency; TR alone = recanalization following thrombolysis alone with late patency; CABG = coronary bypass surgery.

Baseline Data

The baseline data were distributed evenly, including the median time delay for hospital admission, infarct location, history of previous myocardial infarction and previous bypass surgery (Table III).

Global and Regional Left Ventricular Function

Acute angiography (at admission) was performed only in patients allocated to thrombolysis, while late angiography (before discharge or at 4-8 weeks) was performed in the thrombolysis as well as in the control group.

The global left ventricular volume data determined from contrast angiography are presented in table IV. At the chronic stage, the highest global ejection fractions were observed in patients with persistent patent infarct-related vessel after thrombolysis either with (group B, 54±10%) or without (group C, 55±13%) angioplasty, while the lowest ejection fraction was found in the control group (group A, 47±14%).

In table IV, the sequential changes in global ejection fraction from the acute to chronic stage are also shown. In the angioplasty group (group B), the global ejection fraction improved significantly by 4.2% ($p = 0.05$), while no significant change in global ejection fraction could be demonstrated in the subset of patients undergoing successful

Table IV: Left ventricular volumes

	Controls (A)	TR + PTCA (B)	TR alone (C)
EDV 2	95 ± 37 (n=180)	80 ± 21§ (n=29)	82 ± 32 § (n=86)
Δ EDV	-	-0.4 ± 19 (n=24)	9 ± 23* (n=43)
ESV 2	53 ± 31 (n=177)	38 ± 14§ (n=27)	39 ± 24 § (n=80)
Δ ESV	-	-3.4 ± 14 (n=23)	5 ± 13* (n=40)
EF 2	47 ± 14 (n=174)	54 ± 10§ (n=27)	55 ± 13 § (n=79)
Δ EF	-	4.2 ± 9* (n=23)	-0.5 ± 8 (n=40)

EDV, ESV, EF = enddiastolic volume, endsystolic volume, ejection fraction at chronic (2) stage; Δ EDV, Δ ESV, Δ EF = sequential change in enddiastolic volume, endsystolic volume and ejection fraction from acute to chronic stage where both were available; See also table III. Values are expressed as mean ± SD; Student t test for unpaired and paired (Δ) data. §p = 0.005 versus controls; *p = 0.05 acute versus chronic.

Table V: Regional myocardial function of the infarct zone

CREF-IZ		Controls (group A)	TR + PTCA (group B)	TR alone (group C)
Anterior infarction	n	69	20	40
Antero-basal	%	12.2	15.7	13.7
Antero-apical	%	4.4	6.0	5.8
Apex	%	1.1	1.8	1.9
Inferior infarction	n	105	7	39
Apex	%	2.6	3.0	3.6
Infero-apical	%	6.9	10.7	10.8
Infero-basal	%	10.8	14.4	13.5

Regional contribution to global ejection fraction (%) of the infarct zone (CREF-IZ) at follow-up angiography.
Antero-basal = segments 1 - 5; Antero-apical = segments 5 - 9; Apex = segments 9 - 12; Infero-apical = segments 12 - 16; Infero-basal = segments 16-20. See also table III and figure 3.

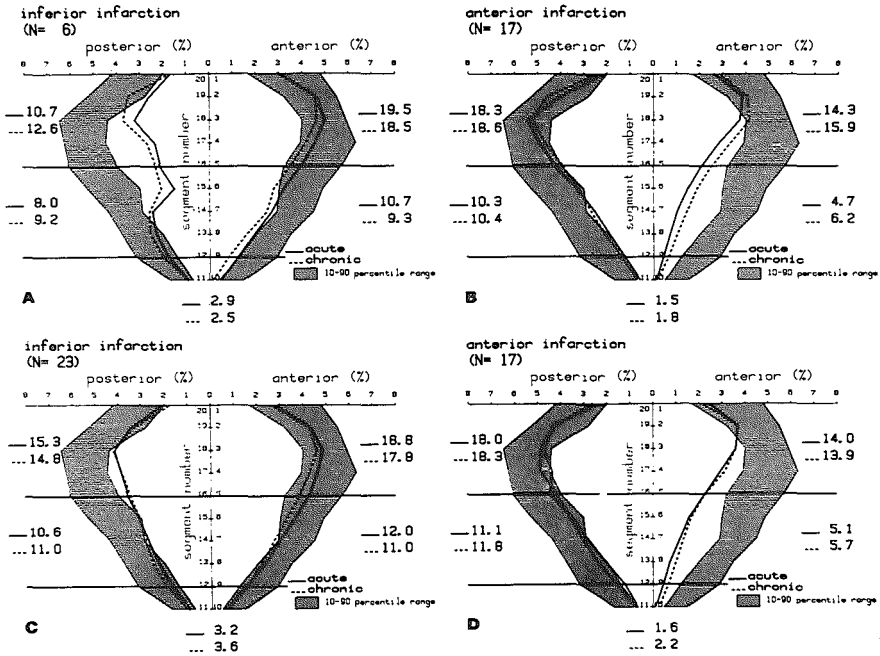
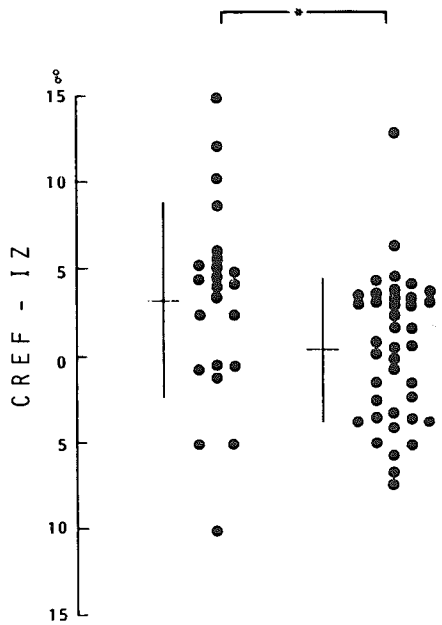


Fig. 3. Sequential changes in regional contribution to global ejection fraction from the acute (at admission, solid line) to the chronic (before discharge, dotted line) stage in patients with inferior (left sided) and anterior (right sided) infarction treated by a combined procedure of thrombolysis and angioplasty (A and B) as well as treated by thrombolysis alone (C and D). The improvement in global ejection fraction of patients treated by angioplasty following thrombolysis was due to significant improvement of the regional myocardial function of the infarct zone even after the disappearance of compensatory actions of the initially enhanced function of the noninfarct zone.



	TR + PTCA	TR alone
	n = 23	n = 40
Δ (%) CREF	+ 16%**	+ 2%
global EF	51±10→55±9*	57±12→57±12

*p <0.03 **p <0.01

Fig. 4. Sequential changes (%) in regional contribution to global ejection fraction (CREF) of the infarct zone (anterior = segment 1 to 10; inferior = segment 11 to 20) from the acute to the chronic stage in the patients in whom both angiograms were available. In the group of patients successfully treated by thrombolysis followed by angioplasty with late patency (TR + PTCA), the significant increase in global ejection fraction (from 51% to 55%, p = 0.03) was primarily due to a 16% improvement in regional contribution to ejection fraction of the infarct zone. In the group of patients with persistent patent infarct related vessel after thrombolysis without angioplasty (TR alone), the regional contribution to ejection fraction of the infarct zone remained unchanged.

thrombolysis without angioplasty (group C). Similar trends were observed in the regional myocardial function of the infarct zone (table V).

Figures 3 and 4 show the sequential changes in regional myocardial function from the acute to the chronic stage in the patients in whom the left ventriculogram was performed at the acute as well as at a follow-up catheterization. In the angioplasty group (group B), the significant improvement in global ejection fraction was primarily due to a 16% increase in regional myocardial function of the infarct zone, as shown in figures 3 and 4. In the group of patients with persistent patent infarct-related vessel after thrombolysis without angioplasty (group C), the regional myocardial function of the infarct zone remained unchanged.

Radionuclide Angiography

Left ventricular ejection fraction as determined by radionuclide angiography at the acute stage (days 1-3), before discharge (days 10-20), and at three months are presented in table VI. Paired analysis of the sequential changes in global radionuclide ejection fraction from days 1-3 to days 10-20 and from days 1-3 to three months, respectively, showed a significant improvement in the patients with persistent patent infarct-related vessel after thrombolysis with or without angioplasty (groups B and C), and this was most marked when intracoronary thrombolysis was followed by angioplasty (group B). No significant changes in radionuclide ejection fraction could be detected in patients treated conventionally. These data are in agreement with the contrast angiographic findings.

Table VI: Radionuclide Angiography

	Controls (A)	TR + PTCA (B)	TR alone (C)
RNAEF 1	43 ± 14 (n=200)	40 ± 15 (n=26)	47 ± 14$^{\S\pounds}$ (n=90)
RNAEF 2	44 ± 15 (n=172)	49 ± 16 (n=49)$_{\S}$	51 ± 15§§ (n=85)
RNAEF 3	45 ± 15 (n=144)	56 ± 14§ (n=17)	52 ± 15§§ (n=78)
Δ EF 2 - 1	0.9 ± 11 (n=141)	10 ± 7** (n=18)	4 ± 9** (n=76)
Δ EF 3 - 1	1.7 ± 13 (n=115)	9 ± 14* (n=14)	3 ± 12 (n=68)

RNAEF = Radionuclide ejection fraction (%) at day 1-3 (1), day 10-20 (2) and at 3 months (3); ΔEF = sequential change in radionuclide ejection fraction. $^{\S}p = 0.05$ and $^{\S\S}p = 0.005$ versus controls; $^{\pounds}p = 0.05$ versus TR + PTCA; *p = 0.05 and **p = 0.005 acute versus chronic. See also tables III and IV.

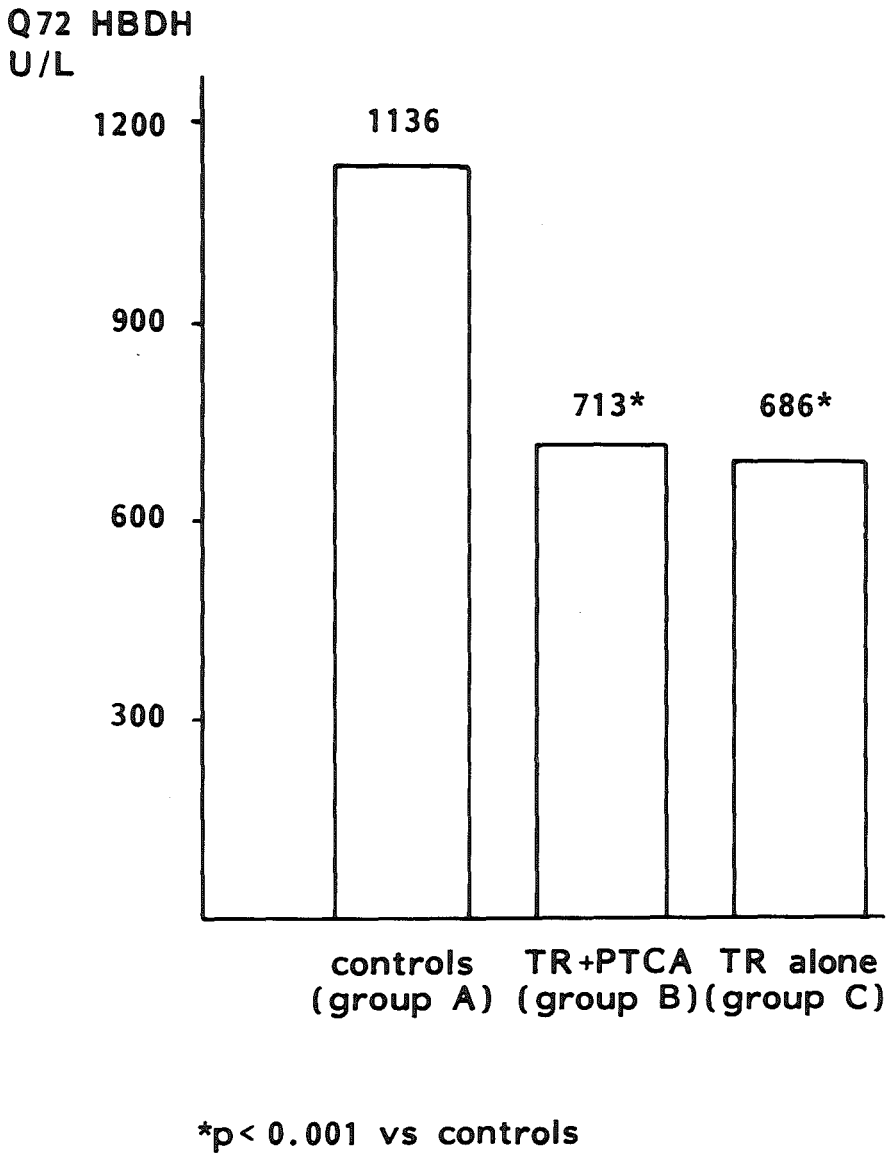


Fig. 5. Median cumulative serum alpha-hydroxybutyrate dehydrogenase release in the first 72 hours after onset of symptoms (Q72 HBDH).

Enzymatic Infarct Size

Enzymatic infarct size was estimated by cumulative HBDH release in the first 72 hours after onset of symptoms. As shown in figure 5, the median cumulative HBDH release in the control group (1136 U/L) was significantly higher than in the two other groups.

Long-Term Follow-Up

Median clinical follow-up of 24 months in all subsets of patients are presented in table VII. The clinical follow-up of patients treated by thrombolysis and angioplasty was most favourable when the patency of the infarct-related vessel could be demonstrated prior to discharge (group B). These patients had a low reinfarction rate (6%); late coronary bypass surgery (13%) and/or (re)-PTCA (3%) was performed less frequently than in the other groups, while only 1 patient died. Conversely, the incidence of late reinfarction was 21% in the group treated by thrombolysis alone.

Table VII: Long-term clinical follow-up (median 24 months)

	Controls (A) n = 264	TR + PTCA (B) n = 31	TR alone (C) n = 102
Re-infarction	17 (6%)	2 (6%)	21 (21%)
CABG	33 (13%)	4 (13%)	14 (14%)
(Re)-PTCA	13 (5%)	1 (3%)	14 (14%)
Death	46 (17%)	1 (3%)	2 (2%)

See table III.

DISCUSSION

There have been many clinical trials of the efficacy of thrombolytic therapy in achieving reperfusion. However, the efficacy of thrombolysis in randomized trials has varied widely in several studies (41-48). Our data from the multicenter randomized trial (6-8) and the data from the GISSI study (49) have shown the beneficial effects of early thrombolysis in acute myocardial infarction. However, the very efficacy of this initial treatment has created a new problem: how to manage the patients with residual atheromatous lesions whose ischemic symptoms persist after thrombolysis, and who may constitute up to half of the patients treated. In order to

maintain the initial benefit achieved by thrombolysis, it is necessary to deal with the underlying obstruction. Percutaneous transluminal coronary angioplasty or surgery may play a valuable role in attaining these goals.

Limitations of the Study

Although the data from this study support the results from recently published randomized trials (54,55), there are limitations to the study, and the results should be interpreted with this in mind. The group of patients undergoing angioplasty following thrombolysis was relatively small because of the selection criteria and the fact that recruitment for this group occured predominantly in one of the participating centers. Although randomization would have been desirable, this would have further reduced the number of patients in this group. However, retrospective matched analysis on the basis of lesions suitable for coronary angioplasty show similar results (unpublished data from the Data Processing Center, Interuniversity Cardiology Institute in the Netherlands).

Reocclusion

The rationale behind the decision to perform angioplasty immediately after thrombolysis was to augment perfusion, reduce infarct size, and improve left ventricular function as well as to prevent re-occlusion. Although we have been able to demonstrate a favourable influence of angioplasty on left ventricular function and recurrent myocardial infarction, it is clear that the procedure does not influence the rate of reocclusion before discharge (Table II). This seems to be due to the disproportionately high incidence of reocclusion in those patients with a right coronary artery lesion. Why lesions in this artery should be susceptible to reocclusion is open to speculation.

Preservation of Left Ventricular Function and Need for Regional Assessment

Although the present study shows that rapid recanalization can be achieved by intracoronary thrombolysis alone with a reperfusion rate comparable with the combined procedure (intracoronary thrombolysis followed by additional angioplasty), analysis of serial global and regional left ventricular function demonstrated the additional benefit of correcting the residual obstructive lesions. Global left

ventricular ejection fraction was measured by contrast and radionuclide angiography (tables IV and VI). Both methods showed higher ejection fractions at the follow-up study when recanalization had been successful either with (group B) or without (group C) additional angioplasty. This finding is supported by analysis of regional wall motion and enzymatic infarct size measurement. Furthermore, in the group successfully treated by angioplasty, the improvement in global ejection fraction was more pronounced and persisted up to three months after the intervention.

In most studies published thus far, the assessment of global ejection fraction has prevailed since it is relatively easily obtainable. In fact, increased motion of the non-infarcted regions of the heart, often kept the global ejection fraction within normal limits despite severe regional hypokinesia in the infarction area. Therefore, analysis of left ventricular wall motion in the area at risk, which potentially should benefit most from reperfusion, must be carried out in order to detect any real benefit of reperfusion (8,50-53). In this study, the regional contribution to global ejection fraction of the infarct zone was most improved in the group of patients successfully treated by thrombolysis followed by angioplasty. In this subset of patients, global ejection fraction increased significantly ($p = 0.03$) from 51% to 55% from the acute to the chronic stage, an improvement primarily resulting from a 16% increase in the regional contribution to ejection fraction of the infarct zone (figures 3 and 4). This finding was in accordance with the results of recently published randomized trials (54,55). These results suggest that in some patients, reperfusion may need to be supplemented by additional revascularization procedures, such as angioplasty, in order to optimize the chances of obtaining full functional recovery. The additional value of immediate angioplasty in preserving left ventricular function and limiting infarct size might help to explain the observed reduction in one year mortality and other major cardiac events. The present study shows that intracoronary streptokinase combined with coronary angioplasty can be safely used to provide reperfusion in the setting of acute myocardial infarction.

The high survival rate, the lower incidence of reinfarction, as well as the preserved regional and global left ventricular function in the subgroup successfully treated with thrombolysis and coronary angioplasty suggests that this combination may be the optimal mode of therapy for selected patients.

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APPENDIX: PARTICIPATING CENTERS AND COLLABORATORS

Thoraxcenter, Erasmus University and University Hospital Dijkzigt, Rotterdam: Marcel JBM van den Brand, MD, Pim J de Feyter, MD, Paolo Fioretti, MD, Paul G Hugenholtz, MD, Patrick W Serruys, MD, Maarten L Simoons, MD, Haryanto Suryapranata, MD, William Wijns, MD.
Department of Cardiology, Free University, Amsterdam: Machiel J van Eenige, MSc, Jan CJ Res, MD, Jan P Roos, MD, Freek WA Verheugt, MD, Frans C Visser, MD, Ernst E van der Wall, MD.
Department of Cardiology, Zuiderziekenhuis, Rotterdam:
Diederik CA van Hoogenhuyze, MD, X Hanno Krauss, MD, Dick ACM Kruyssen, MD, Willem J Remme, MD, Cock J Storm, MD.
Department of Cardiology, St. Annadal University Hospital, Maastricht: Frits WHM Bär, MD, Simon HJG Braat, MD, Pedro Brugada, MD, Karel den Dulk, MD, Wim T Hermens, MSc, Mercedes Ramentol, MD, Hein JJ Wellens, MD, Geert M Willems, MSc, Chris de Zwaan, MD.
Department of Cardiology, University Hospital, Leiden:
Berend Buis, MD, Jos G Engbers, MD, Arnoud van der Laarse, PhD.
Data processing Center, Thoraxcenter, Erasmus University Rotterdam: Aida J Azar, M.P.H., Brenda Bos, Sophie van der Does, Ron T van Domburg, MSc, Gerrit A van Es, MSc, Jacobus Lubsen, PhD, Jan P van Mantgem, MD, Karel J de Neef, MD, Max Patijn, MSc, Juan Planellas, MD, Jan GP Tijssen, MSc, Frank Vermeer, MD, Anneke A Wagenaar, Inge CJ Zorn.

CHAPTER VII

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY FOR ANGINA PECTORIS AFTER A NON-Q-WAVE ACUTE MYOCARDIAL INFARCTION

ABSTRACT

Despite initially favorable prognosis in patients with non-Q-wave acute myocardial infarction (AMI), long-term mortality in this subset of patients appears to be similar to or even greater than that in patients with Q-wave AMI. The relatively poor late prognosis is primarily due to a high incidence of unstable angina and recurrent AMI. Between January 1982 and January 1987, 114 patients with suitable coronary narrowing underwent percutaneous transluminal coronary angioplasty (PTCA) for angina pectoris (present either at rest or during mild exertion, and despite optimal pharmalogic therapy), a median of 31 (range 2 to 362) days after a non-Q-wave AMI. Success was achieved in dilating the obstructed artery in 98 patients (113 of the 129 dilated arteries). Emergency bypass surgery was performed in 7 patients. Mean clinical follow-up of 20 (range 3 to 59) months was obtained in all patients and revealed no deaths. Of the 98 patients with successful PTCAs, 6 (6%) developed a non-fatal recurrent AMI and 62 (63%) were asymptomatic. However, recurrent angina affected 31 patients (32%) and was treated by repeat PTCA (n = 18), coronary bypass surgery (n = 5) or pharmacologic therapy (n = 8). At follow-up, 74% of the patients (73/98) were asymptomatic after a successful PTCA, and if necessary a repeat PTCA, without incidence of recurrent AMI, coronary bypass surgery or death. The high initial success rate, low incidence of subsequent death and late recurrent AMI and sustained symptomatic benefit suggest that PTCA is an effective initial treatment strategy in these selected patients.

INTRODUCTION

The clinical course of patients with non-Q-wave acute myocardial infarction (AMI) has been a subject of interest. Natural history studies have suggested that, compared with Q-wave AMI, non-Q-wave AMI is associated with less necrosis, better left ventricular function and lower in-hospital mortality. Despite this more favorable initial prognosis, long-term survival for patients with non-Q-wave AMI appears to be similar to or even less than that in patients with Q-wave AMI (1-13). The relatively high mortality rate of patients

with non-Q-wave AMI seems to be related to unstable angina or subsequent recurrent AMI in the same area (1-10) and may be preventable if recurrent AMI can be averted with revascularization.

The present study describes the short-and long-term results of consecutive patients treated with percutaneous transluminal coronary angioplasty (PTCA) for severe angina after a non-Q-wave AMI.

METHODS

The study population consisted of 114 patients with a non-Q-wave AMI who underwent PTCA between January 1982 and January 1987. All had symptoms of angina, either at rest or during mild exertion, despite optimal pharmacologic therapy. They represented 8% of our total PTCA population during the study period. Non-Q-Wave AMI was defined in this study as prolonged chest pain compatible with AMI, associated with electrocardiographic ST-segment and T-wave abnormalities without progression to pathologic Q waves, but with abnormal elevation of the creatinine kinase level (at least twice of the normal value) before any intervention. Post-infarction angina was considered unstable if it occurred at rest lasting for at least 15 minutes and was associated with electrocardiographic manifestations of myocardial ischemia without evidence of further myocardial necrosis.

Patients were selected for PTCA if the ischemia-related lesion was suitable for dilatation. The selection was based only on symptoms and coronary anatomy, and was not influenced by left ventricular function. PTCA was considered successful when a reduction of the severity of the obstruction to less than 50% luminal diameter narrowing was achieved with abolition of acute ischemic symptoms and without progression to AMI, emergency surgery, or death. PTCA was performed a median of 31 (range 2 to 362) days after non-Q-wave AMI; 53% of the procedures were performed within 30 days of AMI. Clinical and angiographic data are summarized in table I. After the procedure, patients were monitored for 24 hours in the medium care unit. They were treated with nifedipine 60 mg daily and acetylsalicylic acid 500 mg daily over a period of 6 months.

All patients were followed at the outpatient clinic. Survival status, recurrent AMI, angina pectoris, cardiac failure, bypass surgery and PTCA were recorded. The majority underwent symptom-limited exercise on the bicycle ergometer with stepwise increments of 20 Watts every minute. The orthogonal leads XYZ of the Frank lead system were recorded. An ischemic response was defined as at least a 0.1 mV ST-segment depression, occurring 0.08 seconds after the J point. The maximum workload achieved was expressed as a percentage of the normal workload predicted for age, sex and height.

Table I: Clinical and angiographic data

Number of patients	114
Male/female	88/26
Age (median, yr)	57 (range 31-74)
Previous CABG/PTCA	2/9
Anterior/Inferior non-Q AMI	73/41
Peak CK enzyme level (median, U/liter)	357 (range 206-972)
Stable/unstable angina pectoris	61/53
Therapy before procedure:	
- triple therapy (NTG i.v.)*	97 (35)
- double therapy	17
Median time from AMI to PTCA (days)	31 (range 2-362)
Single/double/triple vessel disease	75/33/6
Total occlusion	22
Single-vessel dilatation	100
Multivessel dilatation	14
Initial global ejection fraction (%)	58±8 (range 32-71)

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CK = creatinine phosphokinase (normal value less than 100 U/liter); PTCA = percutaneous transluminal coronary angioplasty. * Optimal pharmacologic therapy consisted of betablocker, calcium antagonist and nitrates, including 35 patients who needed intravenous nitroglycerin (NTG i.v.)

RESULTS

From the 114 patients who underwent PTCA for angina after a non-Q-wave AMI, 129 lesions were dilated. Single-vessel dilatation was performed in 100 patients, including 16 multilesion dilatations in the same artery. Double artery dilatation was performed in 13 patients and triple artery dilatation in 1 (table II). Success was achieved in dilating the obstructed artery in 98 patients (113 lesions).

Table II: Angiographic results

PTCA artery	N	Primary success
Left anterior descending	78	70 (90%)
Right	31	27 (87%)
Left circumflex	20	16 (80%)
Total	129	113 (88%)

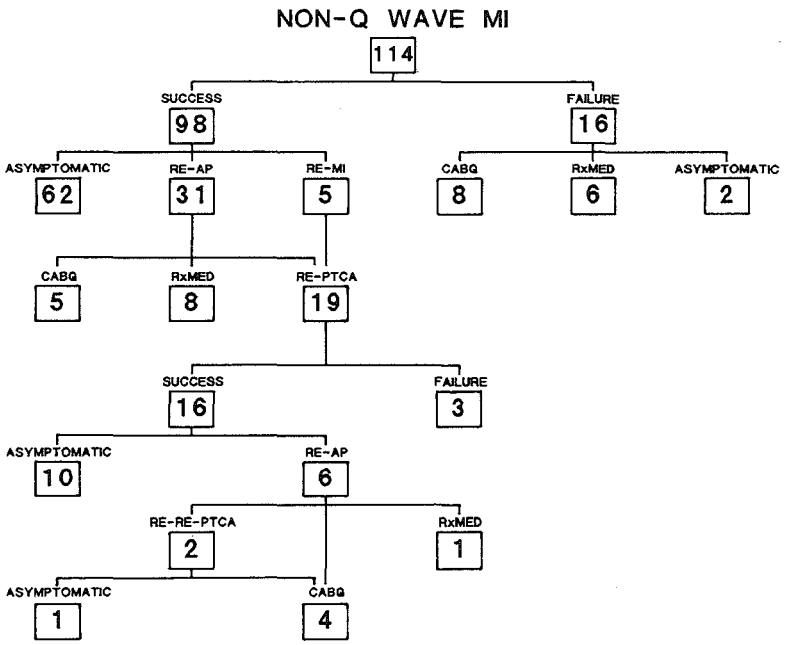

Figure 1. Short- and long-term (mean, 20 months) clinical follow-up in 114 patients undergoing coronary angioplasty (PTCA) for severe angina (AP) after a non-Q-wave myocardial infarction (MI). CABG = coronary artery bypass grafting; Rx Med = controlled by pharmacologic treatment.

Figure 1 shows the clinical outcome of all patients. In 16 patients, the attempted PTCA was unsuccessful: in 9 because the artery was occluded, in 5 because the stenosis could not be crossed with either the guide wire or balloon catheter, and in 2 because of abrupt closure or major dissection. Peri-interventional AMI, defined by either cardiac enzyme elevation or new Q waves, was documented in 5 patients, of whom 3 underwent emergency bypass surgery.

Of the 98 successfully treated patients, 62 were asymptomatic and 5 developed a non-fatal recurrent AMI (1 of them underwent an urgent PTCA). Thirty-one patients developed recurrent angina and of these, 5 underwent an elective bypass surgery 168 (range 7 to 534) days after the initial procedure, 8 were controlled by pharmacologic therapy, and 18 underwent a repeat PTCA 120 (range 1 to 300) days after the initial procedure. Success was achieved in re-dilating the artery in 16 patients.

Results of electrocardiographic exercise testing were available in 71% (70 of 98) of the patients, 8 (range 1 to 49) months after initially successful PTCA (fig. 2). The mean maximum workload achieved, predicted for age, sex and height, was 98% (range 54 to 131%).

Clinical follow-up was obtained in all patients, at a mean interval of 20 (range 3 to 59) months, and is summarized in table III. If coronary artery bypass surgery, recurrent AMI, death or recurrent angina requiring pharmacologic therapy were to be considered events, 74% of the patients would be considered event-free at 20 months after successful PTCA, whereas if any cardiac recurrence, including repeat PTCA, were to be considered events, only 63% of patients would be event-free at 20 months (fig 3).

Table III: Mean clinical follow-up of 20 (range 3 to 59) months

	initial success (n = 98)	failure (n = 16)
Death	0	0
Emergency CABG	0	7
AMI related to PTCA	0	5
Late recurrent AMI	6	0
Repeat PTCA	13	0
Repeat PTCA + CABG	6	0
Late CABG	5	1
Pharmacologic therapy	8	6
Event-free	62	2

Abbreviations as in table I.

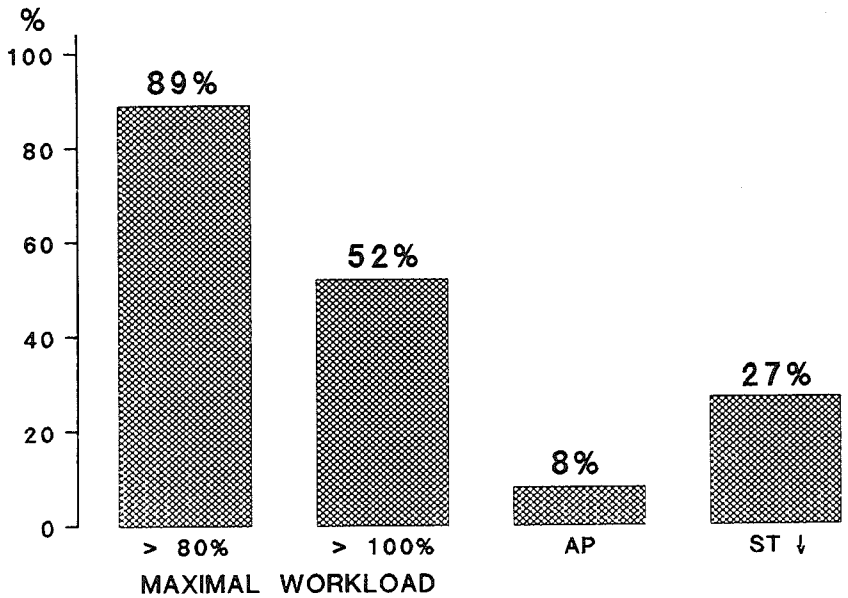

Figure 2. Results of electrocardiographic exercise testing (n = 70), 8 (range 1 to 49) months after initially successful PTCA. A maximum workload of > 80% and > 100% predicted for age, sex and height was achieved in 89% and 52% of the patients, respectively. The majority of the patients (92%) were symptom-free during the test; an ischemic ST-segment depression was documented in 27%.

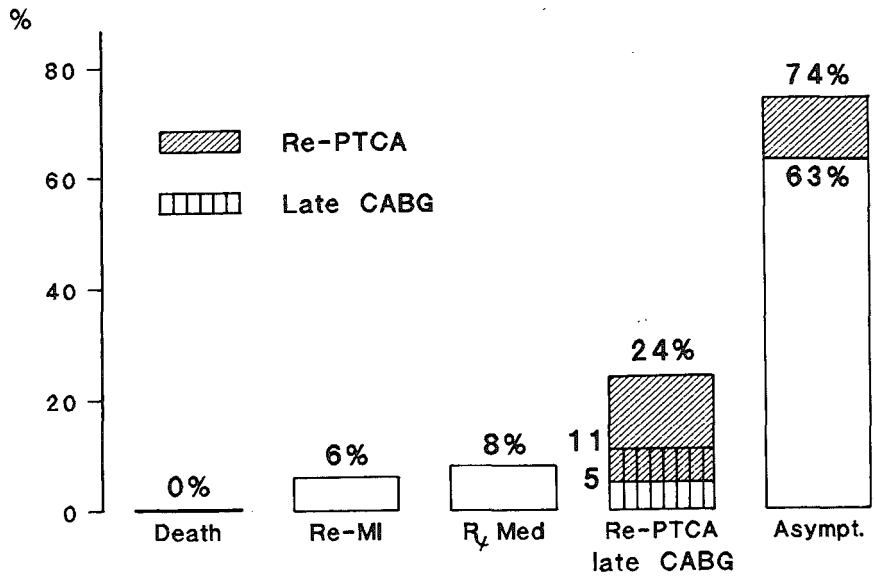

Figure 3. If coronary artery bypass surgery (CABG), recurrent myocardial infarction (re-MI), death or recurrent angina requiring pharmacologic therapy (Rx Med) were to be considered events, 74% of the patients would be considered event-free (Asympt.) at 20 months after initially successful angioplasty, whereas if any cardiac recurrence, including repeat coronary angioplasty (Re-PTCA) were to be considered an event, only 63% of patients would be event-free.

DISCUSSION

The reported incidence of non-Q-wave AMI varies between 20 and 36% of all AMIs (1,3,5,12). Although non-Q-wave AMI and Q-wave AMI (as classified by electrocardiographic results) cannot always be anatomically differentiated (4,14), it seems likely that they differ clinically, physiologically and prognostically, as discussed by Spodick (15). Despite the initially limited area of myocardial necrosis and favorable short-term prognosis for patients with non-Q-wave AMI, several studies show substantial late morbidity and mortality rates in these patients (1-13). Despite marked improvement in pharmacologic therapy, the reported incidence of recurrent AMIs remains high at 6 to 86% and is associated with a poor prognosis (1,4-6,10,16-20). Maisel et al (5) reported a high mortality, both early and late, for patients with subsequent extension following a non-Q-wave AMI. In-hospital mortality rate in this subset of patients was 43%, while in those with Q-wave AMI was 15%. The one-year cumulative survival rates for patients with Q versus non-Q-wave AMI without extension were similar: 82% and 84%. For those with extension, however, one-year survival rates were 66% and 35%, respectively. This finding was supported by others (1,3,10,18,21).

Several investigators suggest that coronary bypass surgery or PTCA is feasible and safe for patients with angina after non-Q-wave AMI (22-25). Our present results indicate not only that PTCA can be performed safely and effectively in this subset of patients, but also that the incidences of late recurrent AMI (6%) and cardiac death (0%) are lower than expected. However, recurrent angina occurred in 32% of our patients after successful PTCA, a percentage similar to that reported for stable angina (26). All patients were satisfactorily treated by repeat PTCA, coronary bypass surgery or pharmacologic therapy. These findings are comparable with the general results of the total PTCA population during the same period, perhaps because PTCA was performed in half of the patients more than 1 month after non-Q-wave AMI, thus hindering any significant distinction betwwen them and an average PTCA population. However, the time delay from non-Q-wave AMI to PTCA did not affect the outcome, despite the fact that unstable angina was more frequent among the patients treated within 30 days than those treated more than 30 days, as shown in table IV.

Among the 22 patients with a totally occluded artery at the time of PTCA, attempted recanalization was successful in only 13 (success rate of 59%), and of these, repeat PTCA or coronary bypass surgery or both was necessary in 6. Of the 9 unsuccessful cases, 3 underwent emergency bypass surgery, 5 had residual angina controlled by pharmacologic therapy and 1 was asymptomatic. When these patients with a totally occluded artery were excluded, the primary success rate became 92%.

Table IV: Time delay from non-Q-wave AMI to PTCA

	patients treated less than 30 days	patients treated more than 30 days
Number of patients	60	54
Anterior AMI	67%	60%
Unstable angina	72%	18%
Initial success rate	85%	85%
Emergency CABG	7%	5%
AMI related to PTCA	5%	4%
Late recurrent AMI	5%	5%
Repeat PTCA/late CABG	23%	22%

Abbreviations as in table I

These findings suggest that when the artery is occluded, the benefits of PTCA after a non-Q-wave AMI are limited, even when recanalization is initially successful.

Limitations of this study include the fact that it was uncontrolled and involved only patients with non-Q-wave AMI with recurrent anginal symptoms and anatomy suitable for PTCA. In fact, most patients had a single-vessel disease with relatively small to moderate enzymatic infarct size and might be expected to have a favorable outcome. However, these patients constituted a high-risk subgroup because of the presence of ongoing angina, which implied that the cardiac event was not yet complete and suggested that more aggressive invasive management could have improved clinical status and the condition of the myocardium.

The high initial success rate and the low incidence of subsequent death and late recurrent AMI, as well as the sustained beneficial effect, suggest that PTCA is an effective initial treatment strategy in patients with angina after a non-Q-wave AMI.

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CHAPTER VIII

RECOVERY OF REGIONAL MYOCARDIAL DYSFUNCTION FOLLOWING SUCCESSFUL CORONARY ANGIOPLASTY EARLY AFTER A NON-Q-WAVE MYOCARDIAL INFARCTION

ABSTRACT

More agressive therapy has been suggested for patients who sustain a non-Q wave myocardial infarction (MI) because of the frequency of subsequent unstable angina, recurrent MI and high mortality rate, when compared to patients with Q wave MI. Furthermore, repeated ischemic attacks early after a non-Q wave MI may lead to prolonged regional myocardial dysfunction. The present study was undertaken to investigate whether, in patients with angina early after a non-Q wave MI, the regional myocardial dysfunction of the infarct zone could be improved by successful coronary angioplasty. Between 1981 and 1986, coronary angioplasty was attempted in 61 patients within 30 days (mean 15 ± 8) of a non-Q wave MI. All patients were symptomatic with 72% having unstable angina prior to angioplasty. The primary success rate was 86%. There were no deaths in this series during a mean follow-up of 20 months. Sequential global and regional left ventricular function were assessed before and 6 months after successful angioplasty. The global ejection fraction increased significantly from 60 ± 9 to 67 ± 6% ($p=0.0003$). This significant increase in the global ejection fraction was primarily due to a significant improvement in the regional myocardial function of the infarct zone, even after subsidence of the compensatory hypercontractility of regions remote from the infarction.
The results of the present study show not only that repeated ischemic attacks early after a non-Q wave MI may lead to prolonged regional myocardial dysfunction, but more importantly, that this depressed myocardium has the potential to achieve normal contraction after successful coronary angioplasty.

INTRODUCTION

The reported incidence of non-Q wave myocardial infarction (MI) varies between 20 and 36% of all acute MI (1-5) and seems to be increasing (6) probably as a result of therapeutic interventions employed before or during the acute symptomatic phase of MI that may minimize the extent of acute myocardial damage. Although non-Q wave MI and Q wave MI as classified by electrocardiographic results cannot always be

anatomically differentiated (7,8), it seems likely that they differ clinically, physiologically and prognostically as discussed by Spodick (9). In particular, non-Q wave MI is generally associated with smaller amounts of myocardial necrosis, better left ventricular function and a lower incidence of in-hospital mortality when compared with Q wave MI. Despite these initially favorable features, evidence has accumulated that long-term mortality in these patients is similar to or even greater than that in patients with Q wave MI. The relatively high mortality rate of patients with non-Q wave MI seems to be related to unstable angina or subsequent recurrent MI in the same area (1-3,7,10-15) and may be prevented if recurrent MI can be averted with revascularization. These findings have understandably led some to recommend more agressive evaluation and treatment strategies for survivors of non-Q wave MI. The results of recently published data suggest that coronary angioplasty is an effective initial treatment strategy in patients with angina after a non-Q wave MI (16,17).

Transient reduction in coronary blood flow may lead to prolonged post-ischemic ventricular dysfunction (18,19). Repeated ischemic attacks early after a non-Q wave MI may aggravate regional myocardial dysfunction. The aim of this study was therefore to determine whether in patients with angina early after a non-Q wave MI, the regional myocardial dysfunction could be improved by coronary angioplasty.

PATIENTS AND METHODS

The study population consisted of 61 patients who underwent early coronary angioplasty between January 1982 and January 1987 for angina, either at rest or during submaximal exercise despite optimal pharmacologic therapy, within 30 days (mean 15 ± 8, range 2 to 30 days) after a non-Q wave MI. They represented 5% of our total coronary angioplasty population during the study period. All patients were symptomatic with 72% having unstable angina prior to angioplasty. Non-Q wave MI was defined in this study as prolonged chest pain compatible with acute MI, associated with electrocardiographic ST-segment and T-wave abnormalities without progression to pathologic Q-waves, but with abnormal elevation of the creatinine kinase level (at least twice of the normal value) before any intervention. Post-infarction angina was considered unstable if it occurred at rest lasting for at least 15 minutes, associated with electrocardiographic manifestations of myocardial ischemia without evidence of further myocardial necrosis. Patients were selected for coronary angioplasty if the ischemia-related lesion was suitable for dilatation. The selection was based only on the symptoms and the coronary anatomy and was not influenced by left ventricular function.

Angioplasty was considered successful when a reduction of the severity of the obstruction to less than 50% luminal diameter narrowing was achieved with abolition of acute ischemic symptoms without progression to MI, emergency surgery, or death. Restenosis was defined as a return of the diameter stenosis to more than 50% at follow-up. Clinical and angiographic data are summarized in table I.

After the procedure, patients were monitored for 24 hours in the medium care unit. They were treated with nifedipine 60 mg daily and acetylsalicylic acid 500 mg daily over a period of 6 months. All patients were followed at the outpatient clinic. Survival status, recurrent MI, angina pectoris, cardiac failure, bypass surgery and coronary angioplasty were recorded. Follow-up coronary and left ventricular angiography as well as exercise thallium-201 scintigraphy were obtained in the patients with initially successful angioplasty.

Table I: Clinical characteristics

n	61
Male/female	44/17
Age (median, yr)	57 (range 31-75)
Previous CABG	1
Previous PTCA	2
Anterior/Inferior non-Q MI	41/20
Peak CK enzyme level (median, U/l)	387 (range 230-972)
Stable angina pectoris	17
Unstable angina pectoris	44
Median time from MI to PTCA (days)	15 (range 2-30)
Single/double/triple vessel disease	44/13/4
Total occlusion	10
Single-vessel dilatation	57
Multivessel dilatation	4

CABG = coronary artery bypass graft; PTCA = percutaneous transluminal coronary angioplasty; MI = myocardial infarction; CK = creatinine phosphokinase.

Quantitative Analysis of Left Ventricular and Coronary Angiography

Global and regional left ventricular function was studied from the 30° right anterior oblique projection using an automated hardwired endocardial contour detector linked to a mini-computer. This method of analysis has previously been described in detail (20-24). The analysis of regional left ventricular function was based on automated, high resolution, frame to frame edge detection of left ventricular contour.

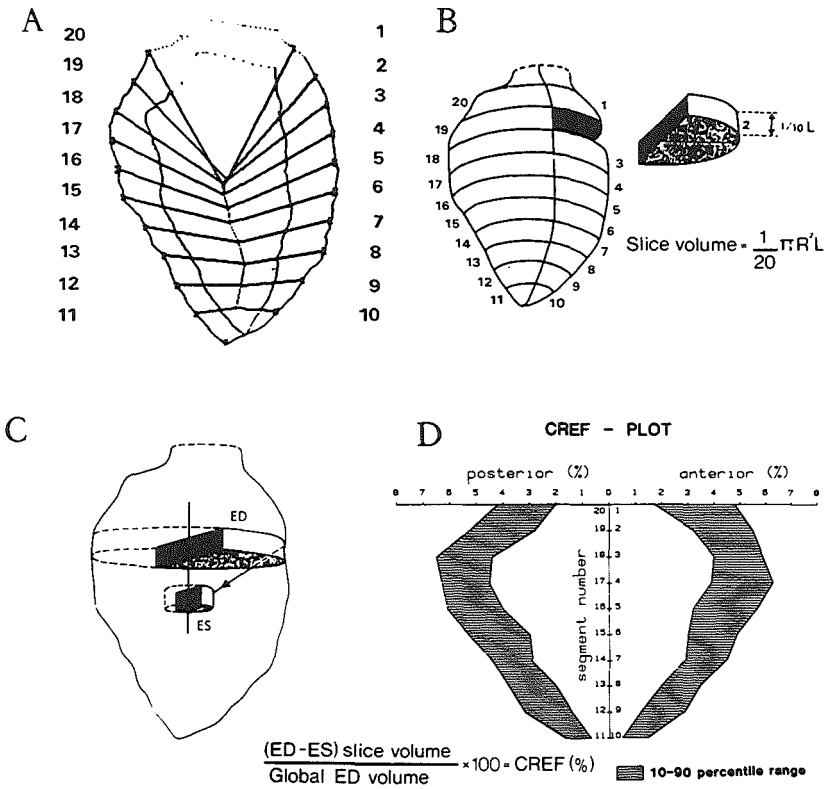

Figure 1. A. Example of the computer output showing the end-diastolic and end-systolic contours of the 30° RAO left ventriculogram. Systolic regional wall displacement was determined along a system of 20 coordinates on the pattern of actual endocardial wall motion in normal individuals and generalized as a mathematical expression amenable to automatic data processing (20-24). B. The left ventricular end-diastolic cavity is divided into twenty half slices. The volume of each half slice is computed according to the given formula, R is radius and L is left ventricular long axis length. C. The regional contribution to global ejection fraction (CREF) is determined from the systolic decrease of volume of the half slice which corresponds to a particular wall segment. The systolic volume change is mainly a consequence of the decrease of radius (R) of the half slice. When normalized for end-diastolic volume, the systolic segmental volume change was considered as a parameter of regional pump function. D. The shaded zones represent the 10th - 90th percentiles area of CREF values in normal individuals. On the X-axis the CREF values of the anterior and infero-posterior wall areas are displayed (%), while on the y-axis the segment numbers of the anterior wall (1-10) and of the infero-posterior wall (11-20) are depicted.

This system allows fast and reliable acquisition of single left ventricular contour, every 20 ms, all over a complete cardiac cycle. Figure 1 shows examples of the end-diastolic and end-systolic contours of the left ventriculogram as well as the segmental contribution to the global ejection fraction, as displayed by the analysis system.

Quantitative analysis of the dilated coronary segment before and after angioplasty procedure and at follow-up coronary angiography were carried out with the computer-assisted Coronary Angiography Analysis System (CAAS), which has been described in detail previously (25,26).

Exercise Thallium-201 Scintigraphy

Patients performed symptom-limited exercise on the bicycle ergometer with stepwise increments of 20 watts every minute. The 3 orthogonal leads X Y Z of the Frank lead system were recorded. An ischemic response was defined as at least a 0.1 mV ST-segment depression, occurring 0.08 sec after the J point. The maximum workload achieved was expressed as a percentage of the normal workload predicted for age, sex and height. Thallium scintigraphic imaging was performed in the anterior, 45 and 65 degree left anterior oblique views, immediately after injection of 1.5 mCi of thallium-201 at peak stress. The post-exercise images were obtained 4 hours later. Images were obtained with a Searle Phogamma V Camera and processed with computer interface as previously described (27). Defects with subsequent redistribution were considered to represent exercise-induced ischemia. Persistent defects without redistribution were considered to represent infarcted myocardium.

Statistics

Data are expressed as mean ± SD. Paired Student t tests were applied whenever appropriate. A p value of less than 0.05 was considered significant.

Table II: Angiographic data

PTCA artery	n	Primary success
Left anterior descending	40	34 (85%)
Right	13	11 (85%)
Left circumflex	11	10 (91%)
Bypass graft	1	1 (100%)
Total	65	56 (86%)

RESULTS

From the 61 patients who underwent coronary angioplasty for angina after a non-Q wave MI, 65 lesions were dilated (table II). Success was achieved in dilating the obstructed vessel in 52 patients (56 lesions). Clinical follow-up was obtained in all patients, at a mean interval of 20 (range 3 to 59) months, and summarized in table III. In 9 patients, the attempted angioplasty was unsuccessful: in 5 because the vessel was found to be occluded at the time of attempted angioplasty, in 3 because the stenosis could not be crossed either with the guide wire or balloon catheter, and in 1 because of major dissection. Of these 9 failure cases, 4 underwent an emergency coronary bypass surgery, 4 were controlled by pharmacologic treatment, and 1 became asymptomatic.

Table III: Mean clinical follow-up of 20 (range 3 to 59) months

	Acute	Late
Death	0	0
Recurrent MI	3	3
CABG	4	4
Repeat PTCA	-	10*
Pharmacologic therapy	-	8
Asymptomatic	-	34

* 2 patients underwent subsequent bypass surgery; abbrevations as in table I.

Of the 52 successfully treated patients, 33 were asymptomatic and 2 had developed a non-fatal recurrent MI, one of whom underwent urgent coronary angioplasty. Seventeen patients developed recurrent angina and of these, 4 underwent elective bypass surgery, 77 (range 7 to 256) days after the initial procedure, 4 were controlled by pharmacologic therapy, and 9 underwent repeat coronary angioplasty 108 (range 1 to 210) days after the initial procedure. Success was achieved in re-dilating the vessel in 8 patients. Of these, 7 patients were asymptomatic during the clinical follow-up and 1 underwent elective bypass surgery after a third dilatation. In 2 patients the second dilatation was unsuccessful; 1 underwent emergency bypass surgery and 1 developed a non-fatal recurrent MI. Furthermore, if coronary artery bypass surgery, recurrent MI, death or recurrent angina requiring pharmacologic therapy are considered events, 77% of the patients were event-free at 20 months after successful

angioplasty, while if any cardiac recurrence, including repeat coronary angioplasty, are considered events, only 63% of patients were event-free at 20 months (fig 2).

Follow-Up Angiography

Follow-up coronary angiography was obtained in 46 patients (88%) at a mean of 5.1 (range 2 to 8) months after initially successful coronary angioplasty. Restenosis occurred in 16 patients (35%): 2 were asymptomatic, 10 underwent repeat coronary angioplasty, 2 underwent elective bypass surgery and 2 were controlled by pharmacologic therapy. No restenosis was observed in 4 patients with recurrent angina after initially successful angioplasty, but all had triple vessel disease requiring either coronary bypass surgery (n = 2) or pharmacologic treatment (n = 2).

Computer-assisted quantitative analysis of the dilated coronary artery before and after the angioplasty procedure and at a follow-up were available in 37 patients who underwent an initially successful angioplasty (71%). The diameter stenosis was 69±11% before angioplasty, 32±9% immediately after angioplasty, and 34±12% at a follow-up angiography.

Table IV: Global left ventricular hemodynamics (n = 36)

	Before PTCA	Follow-up	P-value
HR bpm	70 ± 12	70 ± 17	ns
MAP mmHg	82 ± 12	85 ± 9	ns
EDP mmHg	23 ± 10	19 ± 8	ns
EDV ml/m^2	73 ± 17	71 ± 15	ns
ESV ml/m^2	29 ± 12	24 ± 6	0.006
SV ml/m^2	44 ± 12	47 ± 11	0.08
EF %	60 ± 9	67 ± 6	0.0003
CI $L/min/m^2$	3.0 ± 0.8	3.1 ± 0.8	ns

Sequential changes in global left ventricular hemodynamics in the patients undergoing successful coronary angioplasty in whom adequate quality left ventriculogram was performed before the initial procedure as well as at a follow-up angiography (6 months). HR = heart rate; MAP = mean aortic pressure; EDP = end-diastolic pressure; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; EF = global ejection fraction; CI = cardiac index; PTCA = percutaneous transluminal coronary angioplasty.

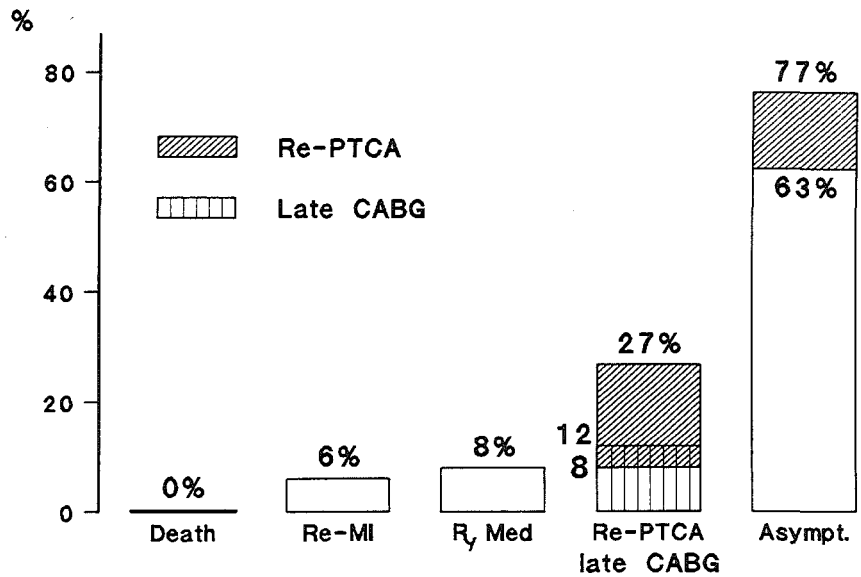

Figure 2. If coronary artery bypass surgery (CABG), recurrent myocardial infarction (re-MI), death or recurrent angina requiring pharmacological therapy (R/Med) are considered events, 77% of the patients were event-free (Asympt.) at 20 months after initially successful angioplasty, while if any cardiac recurrence, including repeat coronary angioplasty (Re-PTCA) is considered an event, only 63% of patients were event-free.

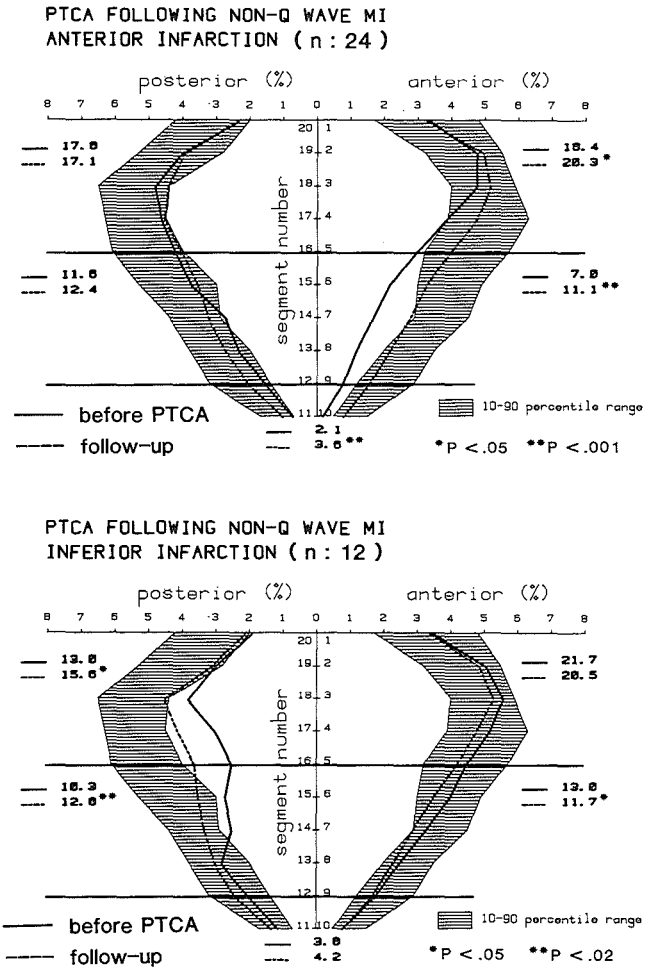

Figure 3. Sequential changes in regional contribution to global ejection fraction from the acute (before angioplasty, solid line) to the chronic (at 6 months, dotted line) stage in patients with anterior and inferior non-Q wave Myocardial infarction, undergoing successful coronary angioplasty. The initially depressed regional myocardial function of the infarct zone has the potential to achieve normal contraction after adequate reperfusion with coronary angioplasty, resulting in a significant increase in global ejection fraction even after the disappearance of compensatory actions of the initially enhanced function of the non-ischemic zone.

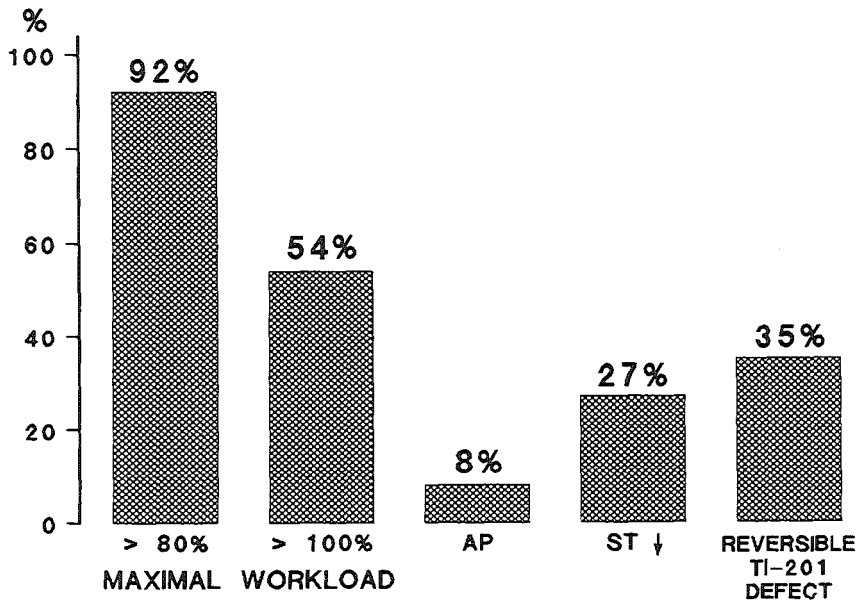

Figure 4. Results of exercise thallium-201 scintigraphy (n = 37), 4.5 (range 1-11) months after initially succesfull angioplasty. A maximum workload of > 80% and > 100% predicted for age, sex and height was achieved in 92% and 54% of the patients, respectively. The majority of the patients (92%) were symptom-free during the test; ST-segment depression was documented in 27%, and a reversible thallium-201 perfusion defect in the area supplied by dilated vessel was observed in 35% of the patients.

Quantitative Analysis of Global and Regional Left Ventricular Function

Sequential left ventricular angiograms, before and 6 (range 2 to 8) months after initially successful coronary angioplasty, of adequate quality sufficient to allow automated contour analysis were obtained in 36 patients undergoing successful coronary angioplasty (69%). Table IV shows the sequential changes in the global left ventricular function before coronary angioplasty and at follow-up angiography. The global ejection fraction increased significantly from 60±9% to 67±6% ($p=0.0003$), and this was due to a significant decrease in end-systolic volume from 29±12 to 24±6 ml/m^2. This significant increase in the global ejection fraction was primarily due to a significant improvement in the regional contribution to ejection fraction of the infarct zone, as shown in figure 3.

Exercise Thallium-201 Scintigraphy

Electrocardiographic exercise testing and thallium-201 scintigraphy was obtained in 37 patients (71%), 4.5 (range 1 to 11) months after an initially successful angioplasty (fig 4). A maximum workload of more than 80%, predicted for age, sex, and height, was achieved in 92% of the patients. Ninety-two percent of the patients were symptom-free during exercise; ischemic ST-T segment depression was induced in 27%, and a reversible thallium-201 perfusion defect in the area supplied by dilated vessel was documented in 35% of the patients.

DISCUSSION

The pathophysiologic basis of the apparent greater clinical instability after non-Q wave MI and the reason for loss of the initial prognostic advantage may be related to the degree of potentially jeopardized myocardium. Patients with non-Q wave MI appear to have more residual myocardial mass at risk as determined by exercise scintigraphy (4,11) for subsequent ischemia or necrosis. This hypothesis has been supported by several studies that found greater rates of angina, recurrent MI and sudden death among hospital survivors of non-Q wave MI than among those with Q wave MI (7,12,28-32). These findings support the concept of myocardial salvage through recanalization to prevent further loss of myocardium, for one might postulate that these patients are left with an "incomplete MI" with an area of the myocardium "at risk", and might therefore benefit from revascularization of the relevant artery. As coronary angioplasty might be an attractive option

in the management of these patients, the present study reports not only that coronary angioplasty can be performed safely and effectively in patients with angina early after a non-Q wave MI, but also that myocardium is capable of recovering function after successful coronary angioplasty.

In most studies, the assessment of global ejection fraction has prevailed since it is relatively easily obtainable. Although there was significant improvement in global ejection fraction in our patients, the crucial question remains whether these differences can be ascribed to the salvage of previously jeopardized myocardium in the area supplied by dilated vessel. Therefore, analysis of left ventricular wall motion in the area at risk, which potentially should benefit most from correcting the residual stenosis, must be carried out in order to detect any real benefit of correcting the obstructive lesion. In fact, increased motion of the non-ischemic regions may keep the global ejection fraction within normal limits despite severe regional hypokinesia in the ischemic area. As this compensatory augmented motion in the non-ischemic area usually subsides chronically, the global ejection fraction has proved to be an unreliable and insensitive measure of assessing either the severity of hypokinesia in an ischemic region or the effect of therapeutic interventions in salvaging function. Here again, regional wall motion must be analyzed to adequately assess this effect.

Many wall motion models have been proposed to approximate actual endocardial motion; this reflects the problems investigators have had in establishing a geometric frame work from which to judge whether the motion of the endocardial contour is normal or abnormal (33). All these methods assess wall motion in terms of extent of shortening at specific points on an axis reference system, although it is highly unlikely that a particular endocardial site coincides with one of these axes during the entire cardiac cycle. The wall motion analysis system we used is based on the motion pattern of small irregularities at the left ventricular endocardial border (endocardial landmarks) that can be detected in the contrast cineangiogram with the automated endocardial outlining system (20,21). This endocardial landmark pathway has been investigated in 23 normal human left ventricles and validated in pigs with metal endocardial markers inserted with a percutaneous, retrograde, transvalvular approach (22-24). This wall motion analysis is unaffected by the translation and rotation of the heart, thus permitting an actual study of the segmental wall motion and derived variables.

Experimental studies (34) have shown that restriction of flow during reperfusion results in relative underperfusion of, and continued ischemia in, the subendocardium. Whole or partial reversal of the myocardium dysfunction occurs after successful coronary artery bypass surgery (35-39). The results

of the present study show not only that repeated ischemic attacks early after a non-Q wave MI may lead to prolonged regional myocardial dysfunction, but more importantly, that this "stunning" of the myocardium is capable of recovering function and has the potential to achieve normal contraction after a successful coronary angioplasty. In this study, global ejection fraction increased significantly from 60 ± 9 to 67 ± 6%, an improvement primarily due to a significant improvement of the regional contribution to ejection fraction of the infarct zone even after subsequently subsidence of compensatory actions of the initially enhanced function of the non-ischemic zone (fig 3). These results suggest that in some patients reperfusion may need to be supplemented by additional procedure such as angioplasty in order to optimize the chances of obtaining full functional recovery. The additional value of angioplasty in preserving left ventricular function might help to explain the observed low mortality rate and other major cardiac events.

On the other hand, these results might be biased by the selection of patients, the fact that it was uncontrolled and involved only patients with non-Q wave MI with both recurrent anginal symptoms and anatomy suitable for coronary angioplasty. Furthermore, myocardial dysfunction as a result of prolonged ischemia might improve when the ischemic attacks resolve spontaneously either as part of a natural healing process or as a result of pharmacologic therapy (40,41). Therefore, randomization would have been desirable. However, it is difficult to justify this type of study in our patients population since these patients constitute a high-risk subgroup because of the presence of ongoing angina, either at rest or during submaximal exercise, despite optimal pharmacologic therapy. The incidence of angina recurring after acute MI varies from 18 to 57% (1,7,11,29,32,42-44). Such early post MI angina carries a poor short-and long-term prognosis (1,7,11,28-30,44-46). Although differences in pharmacologic treatment before and after angioplasty procedure may also play a role in the observed difference of left ventricular function, the present study shows that the regional wall motion improved selectively in the areas supplied by dilated artery rather than in the ventricle as a whole.

We believe that the normalization of the antegrade flow after coronary angioplasty, evidenced by repeat angiography, and the sustained symptomatic benefit with no signs of ischemia in the majority of the patients undergoing exercise Thallium-201 scintigraphy, is the main reason for the observed recovery of myocardial function.

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CHAPTER IX

GENERAL COMMENTS AND CONCLUSIONS

Coronary angioplasty has been shown to be an effective mode of therapy to enlarge the lumen diameter of stenosed coronary artery. The indications for coronary angioplasty in coronary artery disease have been widely expanded and so has the total number of angioplasty procedures. As coronary angioplasty might be an attractive option in the management of patients with acute myocardial ischemic syndromes, the present thesis shows not only that coronary angioplasty can be performed effectively in patients with acute ischemic syndromes, but also that global and regional left ventricular function can be improved after successful coronary angioplasty. However, these results may be biased by the selection of the patients and the fact that it is uncontrolled and involves only patients with anatomy suitable for coronary angioplasty.

Coronary Angioplasty for Unstable Angina Pectoris

Unstable angina pectoris is, by definition, an unstable state leading either to improvement or to culmination into myocardial infarction or death (1,2). Patients described as having unstable angina as originally advocated by Conti et al (3) can be further divided into 3 subgroups: a) recent onset angina pectoris; b) progressive effort angina with a deteriorating clinical pattern superimposed on chronic stable angina; and c) prolonged episodes of ischemic chest pain at rest. The first 2 groups of patients have a reasonably good prognosis and satisfactorily initial response to medical therapy (4-6). These patients can usually be evaluated for myocardial revascularization on an elective basis. Unstable angina is defined in this thesis as chest pain at rest lasting for at least 15 minutes associated with reversible electrocardiographic ST-T changes without clinical, electrocardiographic and enzymatic evidences of further myocardial necrosis. The prognosis for this subset of patients has been shown to be significantly worse, especially if ischemic symptoms persist (7-10). This is the more so when optimal pharmacologic treatment with beta-blockers, nitrates and calcium-antagonists have proven to be inadequate (8,10).

Since the causes of unstable angina are multifactorial (11-14) and within the same patients different pathophysiological mechanisms may occur at different times and in succession, it will be difficult to decide what optimal

therapy for that particular stage of the disease at that particular moment in time for that patient consists of. The uncertainty of outcome in a specific patient forces one to provide "maximal" treatment. Therefore, the management of unstable angina pectoris is first of all directed toward the relief of acute ischemia and secondly to the prevention of progression to myocardial infarction and we believe that immediate control of ischemia with stepwise intensification of pharmacologic treatment is the cornerstone of the management of these patients. If despite this tailored pharmacologic approach patients continue to have ischemic attacks, prolongation of what must be regarded as ineffective treatment should be avoided and a more definitive attempt at myocardial revascularization should be instituted without delay, in order to prevent progression to myocardial infarction and so to improve prognosis.

Despite the latest substantial improvements in surgical techniques, cardioplegia, anaesthesia, and postoperative care, there is still no consensus as to the safety of surgery in the management of this subsets of patients and many centers continue to manage these patients medically. Acute surgery in those patients still carries a substantial risk with perioperative mortality rate varying from 1.8% to 7.7% and the incidence of perioperative myocardial infarction varying between 1% and 16.7% (15-19). In fact, in a recently published randomized prospective study (20), patients with unstable angina pectoris had similar outcomes whether they received pharmacologic therapy alone or surgical therapy. Coronary angioplasty, as an initial alternative to bypass surgery, has been shown to be effective for the treatment of patients with unstable angina either stabilized or refractory to optimal pharmacologic treatment (21-30) (table I). The reported lower success rates of 63 to 76% were achieved with the non-steerable dilatation catheters. The more recent results were achieved with the more advanced steerable dilatation system and may therefore reflect the current state of the art. However, the initial success rate of coronary angioplasty in unstable angina remains lower than the rate of more than 90% achieved nowadays in patients with stable angina pectoris. This is mainly due to the higher complication rate in patients with unstable angina undergoing coronary angioplasty (table I).

The reasons for this high major complication rate are related to the underlying pathophysiology leading to clinical instability and an increased risk on abrupt closure due to the formation of an acute occlusive thrombus (12-14,31-38). Although these data suggest that intracoronary thrombus is often present in patients with this acute coronary syndrome, only a few studies have examined the role of thrombolytic therapy (12,39-46). Recently published randomized trials of thrombolysis in unstable angina further confirm the potential

Table I: Coronary angioplasty for either initially stabilized or refractory unstable angina

	n	Success rate %	Major complication rate			Coronary events after successful angioplasty			mean Follow-up months
			death %	MI %	acute surgery %	death %	MI %	AP %	
Stabilized UA									
Faxon 1983 (21)*°	442	63	0.9	8	-	1.7	1.5	18	18
Quigley 1986 (22)	25	81	4	12	12	0	0	32	18
de Feyter 1987 (23)	71	87	0	10	12	2	2	23	12
Steffenino 1987 (24)	89	90	0	5	5	0	1.5	23	10
Refractory UA									
Williams 1981 (25)*	17	76	0	0	6	0	0	8	10.5
Meyer 1983 (26)*	50	74	0	4	2	0	0	36	6
de Feyter 1985 (27)	60	93	0	7	7	2	0	13	9
Timmis 1987 (28)	56	70	5.4	7.1	12.5	3.3	3.3	39	6
Plokker 1988 (29)	469	88	1	4.9	3	1.5	0.1	21	19.3
Sharma 1988 (30)	40	88	0	0	12	0	0	34	11

* use of a non-steerable dilatation system
° the majority of the patients were initially stabilized
UA = unstable angina pectoris; MI = myocardial infarction; AP = angina pectoris.

benefit of thrombolytic therapy in this setting (43,44), although it is associated with a relatively high incidence of bleeding (43). Thrombolysis has been used in our patients as a treatment of abrupt vessel occlusion during coronary angioplasty and not as a primary or preventive therapy. The reason for this is, firstly, that it will be not logic to treat preventively all patients with unstable angina, since only 10% of these patients presented with acute complication. Secondly, that the haemorrhagic risks inherent to the thrombolytic therapy using either specific clot lysing agents or systemic fibrinolytic agents are not negligible and therefore may not be imposed to this population as a whole. This strategy has lead to the improved immediate outcome of coronary angioplasty for unstable angina by avoiding urgent surgery and procedure-related myocardial infarction (chapter III). This clinical observation does not pretend to answer the question whether thrombolytic agent should be used as part of the therapeutic arsenal for unstable angina in order to cool-off the clinical instability, but the reported experience should be viewed as a rescue strategy during angioplasty of which value should be prospectively assessed in a randomized fashion.

Furthermore, future studies should be directed toward defining subgroups of patients with unstable angina who will most likely benefit from thrombolytic therapy and toward the design of therapeutic schemes associated with a reduced bleeding frequency.

After initial successful coronary angioplasty the prognosis is excellent, with a low incidence of late mortality (up to 3%) and a low occurrence of late nonfatal myocardial infarction (up to 3.5%), while the angiographic restenosis rate and recurrence of angina after an initial successful coronary angioplasty appears to be comparable to those of patients with stable angina (21,26).

We believe that coronary angioplasty is an effective treatment with a high initial success rate but with an increased risk of major complications in patients with either refractory or initially stabilized unstable angina. However, it should be appreciated that current results are obtained from selected groups of patients, those with predominantly single vessel disease and well preserved left ventricular function. To expand the potential use of coronary angioplasty as an alternative to coronary artery bypass surgery in patients with unstable angina and multivessel disease, dilatation of only the "culprit" lesion has been recommended as an initial approach to stabilize the patient's condition (46,47). This strategy is successful in the majority of the patients. However, it is associated, not unexpectedly, with a higher occurrence of angina pectoris after the procedure, which may necessitate later elective coronary artery bypass surgery or elective coronary angioplasty of other vessels (47).

Coronary Angioplasty in Acute Myocardial Infarction

Limitation of myocardial infarct size through salvage of ischemic myocardium in the region undergoing necrosis is the major goal in the management of patients with acute myocardial infarction in order to preserve cardiac function and to improve prognosis. The concept of limiting infarct size by early recanalization of occluded coronary artery in acute myocardial infarction has been proven in clinical practice to be effective and the beneficial effect of thrombolytic agents in acute myocardial infarction on infarct size, left ventricular function, clinical course and patient survival has been convincingly shown (48-54). Such therapy, however, is usually associated with an increased rate of early postinfarction angina and reinfarction (50,55-57). Coronary angioplasty has been applied as an effective treatment in the management of patients with acute myocardial infarction since 1982 (55). In fact, there are 3 different strategies that involve angioplasty during acute myocardial infarction. Firstly, to perform an immediate angioplasty without any thrombolytic agent on board; secondly, to perform immediate angioplasty but in conjunction with a thrombolytic agent; and thirdly, to perform, for some logistic limitations or for clinical indications, a socalled delayed angioplasty following thrombolysis. The advantages and disadvantages of these different strategies are listed in tables II-IV.

Table II: Immediate coronary angioplasty without preceding thrombolysis

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advantages:
- optimizes antegrade flow
- potentiates mechanically the natural lysis phenomenon
- avoids the bleeding complications of thrombolytic therapy
- applicable to patients with contra indication for thrombolytic therapy
- economizes time and money by combining a single diagnostic and therapeutic laboratory session.

disadvantages:
- potentially risk in the setting of an acute myocardial infarction
- "blind procedure": uncertainty as to the distal anatomy and the proper size of balloon to be used
- dislocation of thrombotic material
- sudden reperfusion with reperfusion damage (0_2 and Ca^{++} paradox?)
- no alteration of thrombogenic state
- logistics of staffing and maintaining an interventional laboratory around the clock.

Table III: Immediate coronary angioplasty after initial thrombolysis

advantages:
- more gradual reperfusion
- better delineation of the stenotic lesion and the distal anatomy prior to intervention
- rationale for intervention based on critical evaluation of the residual stenosis
- informed choice of the balloon size.

disadvantages:
- delay in achievement of optimal antegrade flow
- dilatation of a "recanalized" lesion may be complicated by a total occlusion
- uncertainty as to the degree of completion of the lytic process
- loss of time and money in exchanging therapeutic equipment for intervention
- staffing and maintenance of an interventional laboratory around the clock

Table IV: Delayed coronary angioplasty after lysis

advantages:
- elective procedure in optimal conditions after more comprehensive clinical assessment
- availability of surgical back up on a non-emergency basis
- persistent lytic state may have resulted in further (and even complete) thrombolysis

disadvantages:
- potentially risk for intercurrent reocclusion
- additional cost and patient discomfort due to need for a second procedure
- Interventional risk exposure in "asymptomatic" patients without scientific validation of benefit.
- Surgical emergency in patients with persisting lytic state and recent myocardial damage.

Table V: Success rate of immediate coronary angioplasty in acute myocardial infarction

	n	success rate %
Without thrombolysis		
Hartzler 1983 (58)	12	92
Pepine 1984 (59)	8	100
Holmes 1985 (60)	26	85
O'Neill 1986 (62)	29	83
Rutherford 1986 (63)	222	91
Marco 1987 (64)	43	95
Topol 1987 (65)	11	82
Rothbaum 1987 (61)	151	87
After succesful lysis		
Meyer 1982 (55)	21	81
Serruys 1983 (66)	18	100
Gold 1984 (67)	12	75
Yasuno 1984 (68)	25	72
Papapietro 1985 (69)	11	82
Erbel 1985 (70)	46	74
Holmes 1985 (60)	15	73
Erbel 1986 (71)	69	65
Kitazume 1986 (72)	16	88
Suryapranata 1987 (73)	46	96
Topol 1987 (65)	15	100
Suryapranata 1988 (74)	115	89
Stack 1988 (75)	216	90
After failed lysis		
Gold 1984 (67)	16	69
Holmes 1985 (60)	14	71
Papapietro 1985 (69)	7	57
Prida 1986 (76)	18	83
Kitazume 1986 (72)	6	83
Fung 1986 (77)	13	92
Topol 1987 (65)	6	83

The initial results of coronary angioplasty with or without thrombolysis are listed in table V (55,58-77). From these studies it appears that coronary angioplasty is a safe and effective therapy in the management of patients with acute myocardial infarction. However, the precise role, the timing and patient selection for coronary angioplasty in acute myocardial infarction is still unsettled and requires further evaluation.

The value of coronary angioplasty during thrombolytic therapy has recently been analyzed in several randomized trials (65,71,78-80). The results summarized in table VI indicate that immediate angioplasty did not lead to further limitation of infarct size, nor to further preservation of global left ventricular function, although Erbel et al (71) reported some further improvement in regional myocardial function of the infarct zone after successful angioplasty in a subgroup of patients with anterior infarction. In addition, the number of patients with reocclusion in spite of immediate angioplasty is disturbingly high, particularly in patients treated with rt-PA and angioplasty. The higher tendency to reocclude after rt-PA might in part be related to the "thrombus specificity" of rt-PA. Remnants of thrombus material, together with the endothelial trauma caused by angioplasty and subintimal bleeding may lead to higher tendency of thrombosis, whereas early re-thrombosis after coronary angioplasty in patients treated with streptokinase may be prevented by the depletion of fibrinogen and other coagulation factors due to streptokinase. Hospital mortality was somewhat lower after immediate angioplasty in the German study (71) but was higher, although not significantly, in the other major trials (65,78-80) (table VI). Additional early revascularization was less frequently necessary after immediate angioplasty. Furthermore, Guerci et al (81) reported the results of a smaller sized randomized, prospective double-blind placebo controlled trial of intravenous rt-PA with subsequent random assignment of patients to undergo or not undergo delayed-elective angioplasty (72 hours). Their data show that early intravenous rt-PA and delayed angioplasty is beneficial in acute myocardial infarction. Most recently published studies comparing a strategy of immediate angioplasty with delayed-elective angioplasty showed no advantages over immediate angioplasty (table VI). However, among the patients assigned to elective angioplasty (7 days), 18% had definite recurrent ischemia (most of which occurred within 24 hours of admission) requiring crossover to an emergency procedure (79), whereas the remaining patients had the procedure as planned at the seven-day point. These findings suggest that after successful intravenous thrombolysis, the elective angioplasty strategy requires careful monitoring for recurrent ischemia, with early angiography and consideration of angioplasty when ischemia occurs.

Future studies should be directed toward defining a subgroup of patients with acute myocardial infarction who will most likely benefit from coronary angioplasty after thrombolysis. More specifically, to identify the high risk group of patients with persistent occlusion of the infarct-related vessel despite early thrombolysis and to predict accurately the risk of reocclusion. Likewise, there is no single reliable marker of reperfusion available and there

Table VI: Coronary angioplasty following thrombolysis in acute myocardial infarction: results of major randomized trials

	German trial(71) iv + ic STK*		European trial(78) iv rt-PA		TAMI**(79) iv rt-PA		TIMI-IIA***(80) iv rt-PA	
	immediate PTCA	-	immediate PTCA	-	immediate PTCA	elective PTCA	immediate PTCA	delayed PTCA
n	83	79	183	184	99	98	195	194
Attempted PTCA (%)	83	-	93	-	100	52	72	55
Time to intervention (hrs)	3.7	2.8	3.3	-	±4.5	-	1.8	32.7
Patency rate after intervention (%)	86	90	91	-	91	92	84	93
Additional PTCA/CABG (%)	-	-	5	7	20	32	15.4	7.7
Re-infarction/re-occlusion(%)	14	20	5	8	11	13	6.7	3.1
Hospital death (%)	7	14	7	3	4	1	7.7	5.2
Change in global EF	-	-	-	-	-	-	-	-
Change in regional EF	anterior	-	-	-	+	+	-	-

* intravenous and intracoronary (iv + ic) streptokinase (STK) and in case of occluded vessel mechanical recanalization.

** excluded for coronary angioplasty (PTCA): occluded infarct vessel, lesion less than 60%, left main stem disease or otherwise not amenable for PTCA.

*** only patients with patent infarct vessel, judged amenable for PTCA

CABG = coronary artery bypass surgery; EF = ejection fraction.

are no angiographic parameters which allow accurate prediction of reocclusion. Furthermore, even the acute assessment of regional wall motion will not tell us the viability of the myocardium at risk. At present, we are conducting a randomized trial of early intravenous rtPA alone versus early intravenous rtPA followed by delayed-elective coronary angioplasty.

Emergency angioplasty without thrombolytic therapy should probably be performed in patients who develop coronary occlusion during or after diagnostic catheterization, in whom mechanical recanalization could be performed without any delay. Furthermore, emergency angioplasty may be offered to those patients who are likely to benefit from thrombolytic therapy, but in whom such therapy cannot be performed because of enhanced risk of bleeding.

Coronary Angioplasty for Early Postinfarction Angina

The recurrence of angina after sustained myocardial infarction but still during the hospitalization period is reported to be between 18-57% and is considered to have a poor short- and long-term prognosis (82-87). The incidence of early nonfatal reinfarction in patients with early postinfarction angina ranges between 19-34% (82,83). Reinfarction in these patients is therefore a serious complication as it carries an

Table VII: Incidence of non-Q wave myocardial infarction (NQMI)

Reference	n	NQMI	%
Abbott 1973 (90)	230	78	35
Madias 1974 (91)	104	43	41
Rigo 1975 (92)	159	48	31
Genovese 1976 (93)	500	22	4
Cannom 1976 (94)	188	40	21
Rothkopf 1979 (95)	43	10	23
Fabricius 1979 (96)	276	98	36
Thanavaro 1980 (97)	745	124	17
Mahony 1980 (98)	635	141	22
Marmor 1981 (83)	200	58	29
BHAT Trial 1982 (99)	3837	806	21
Krone 1983 (100)	593	94	16
Coll 1983 (101)	458	28	6
Maisel 1985 (102)	1253	227	22
Connolly 1985 (103)	1221	353	29
Theroux 1986 (104)	448	157	35
Boden 1986 (105)	538	194	36
Gibson 1986 (89)	241	87	36
Huey 1987 (106)	150	35	23
Goldberg 1987 (107)	2451	882	36

Table VIII: Non-Q wave myocardial infarction (NQMI): incidence of reinfarction (RE-MI) and mortality

Reference	NQMI	RE-MI %	Mortality % Early	1-YR	2-YR	5-YR
Abbott 1973 (90)	78	-	23	-	-	-
Madias 1974 (91)	43	-	9	-	-	-
Rigo 1975 (92)	48	-	13	-	19	-
Madigan 1976 (87)	50	-	2	-	-	-
Cannom 1976 (94)	40	-	8	-	33	-
Kossowsky 1976 (108)	35	35	11	-	-	-
Szklo 1978 (109)	283	-	18	-	28	-
Fabricius 1979 (96)	98	-	-	-	-	49
Rothkopf 1979 (95)	10	20	-	-	-	-
Poehllman 1980 (110)	50	13	8	-	-	-
Thanavaro 1980 (97)	124	-	3	-	-	-
Hutter 1981 (88)	67	57	9	-	-	52
Marmor 1981 (83)	58	43	12	-	-	-
Hollander 1984 (111)	38	18	-	-	21	-
Maisel 1985 (102)	277	8	8	12	-	-
Connolly 1985 (103)	353	-	6	-	-	-
Zema 1985 (112)	28	-	4	-	-	-
Gibson 1986 (89)	87	18	-	9	-	-
Gibson 1986 (113)	576	7	4	-	-	-
Goldberg 1987 (107)	882	-	12	15	21	41

inhospital mortality of 20-36% versus 9-13% for patients without reinfarction (83,85). The one year survival rate was 76% for those with reinfarction versus 91% for those without reinfarction (85). Particularly non-Q wave infarctions have shown to be associated with a higher incidence of recurrent infarction (83,87-89). Tables VII and VIII summarize the incidence and outcome of patients with non-Q wave myocardial infarction (83,87-113).

The problems of definitive therapy and the timing of therapy are more difficult. The high incidence of recurrent myocardial infarction and unstable angina in patients with non-Q wave myocardial infarction call for some prophylactic measure to prevent further loss of myocardium. One might postulate that these patients are left with an "incomplete myocardial infarction" with an area of the myocardium "at risk", and might therefore benefit from revascularization of the relevant artery.

The first reports (114-121) of patients undergoing surgical revascularization early after myocardial infarction noted an increased operative mortality compared to that of

Table IX: Coronary angioplasty for early postinfarction unstable angina (within 30 days after MI)

	n	success rate %	major complication rate death %	MI %	acute surgery %	Coronary events after successful angioplasty death %	MI %	AP %	mean Follow-up months
de Feyter 1986 (129)	53	89	0	8	8	0	4	26	9
Holt 1986 (130)	69	80	2	-	12	0	4	24	21
Gotlieb 1987 (131)	47	91	2	4	2	3	3	18	16.3
Safian 1987 (132)*	68	87	0	1.5	1.5	0	2	41	17
Hopkins 1988 (133)	54	81	0	0	4	0	2	25	11
Suryapranata 1988 (134)*	60	85	0	5	7	0	5	23	20

* post non-Q wave myocardial infarction

other patients undergoing revascularization months or years after myocardial infarction. Patients treated surgically within the first 7 days after myocardial infarction experienced twice the mortality of those treated surgically after 8 to 30 days and more than threefold the mortality of those treated surgically more than 30 days after myocardial infarction (119). However, several investigators (122-124) have demonstrated that surgical intervention is feasible and safe early in the course of non-Q wave myocardial infarction with the incidence of perioperative myocardial infarction between 1% to 10.7%, incidence of in-hospital death between 1.9 to 3.6%, late death in 1% and angina-free survival between 68 to 96% during follow-up period of 15 to 29 months. Despite the substantial improvement in surgical techniques and postoperative care associated with the consequent lower mortality and better long-term results (125-128), there is still no consensus as to the safety of surgery in the early post myocardial infarction phase and many centers continue to manage these patients medically. Accordingly, current strategy for the management of patients with early postinfarction angina is aimed at delaying surgery to such a time when it can be performed with the least inherent risks. However, in patients with severe recurrent angina, the situation may demand an early intervention.

Coronary angioplasty in this situation has been shown to be an attractive alternative to surgical revascularization (129-132) (Table IX). However, the procedural complications are definitely more frequent in this setting than with elective coronary angioplasty. A complication resulting in a myocardial infarction occurred in up to 8% and acute surgery was required in up to 12% of the patients (Table IX). This relatively high complication rate in postinfarction angina may be related to the state of "activity" of the ischemia producing lesion. Intracoronary instrumentation may for a variety of reasons induce total vessel obstruction with resulting re-infarction. The available data suggest that coronary angioplasty performed early after acute myocardial infarction is an effective procedure in a subset of patients who have preserved but jeopardized left ventricular function, predominant single vessel disease, and an anatomy suitable for coronary angioplasty. However, it remains to be determined whether the same benefits can be achieved in patients with early postinfarction angina and multivessel disease, or in those who have reduced left ventricular function.

CONCLUSION

Recent randomized studies aimed at establishing the merits of current pharmacologic treatment, current bypass surgery and coronary angioplasty in the management of patients

with acute myocardial ischemic syndromes are lacking. Until further information becomes available we would propose the following practical approach. Patients with unstable angina or early postinfarction angina should initially receive prompt management with stepwise intensification of pharmacologic therapy in an attempt to achieve stability. Early angiography and revascularization is indicated if this approach fails and ischemic episodes continue in spite of "maximum" medical management. Coronary angioplasty is indicated when a stenosis, technically suitable for dilatation, is found to be responsible for the unstable state. The decision in favour of coronary angioplasty in patients with single vessel disease is easy to make. In the presence of multivessel disease some uncertainty remains. Patients with left main stem disease or severe multi-vessel disease should be scheduled for coronary artery bypass surgery. However, in selected patients with multivessel disease one might prefer dilatation of the ischemia related vessel only, as opposed to total revascularization by multiple dilatations or bypass surgery, since this can be performed faster and so reduce hospital stay. Furthermore, thrombolytic therapy in patients with unstable angina to reduce or treat complications during coronary angioplasty needs further study.

Management of patients with an evolving myocardial infarction should aim at early reperfusion. Intravenous administration with an effective thrombolytic agent should begin as soon as possible, preferably before hospitalization. The available data on the use of coronary angioplasty are conflicting and no clear answers as yet have emerged about the additional value of angioplasty in acute myocardial infarction. Current data indicate that patients with acute myocardial infarction should be considered for delayed-elective angiography and revascularization only when ischemia recurs. While immediate coronary angioplasty with or without thrombolysis should not be recommended as a routine procedure in all patients, it should be restricted to those with a remaining severe stenosis or those with contraindications for thrombolytic therapy. This approach would allow for first lytic treatment in community hospitals and for transfer of selected patients for delayed-elective evaluation and revascularization procedures to well-equipped centers without inflicting undue strain and costs on the medical system. In these patients an elective procedure would allow for more careful evaluation and decision making and is likely to result in a higher success rate than immediate angioplasty. However, it should be appreciated that this recommendation is obtained from studies in which the combination of rt-PA and coronary angioplasty is used. This combination may be the cause of the high acute and early reocclusion rate, which could be less if the combination of streptokinase and coronary angioplasty is used, due to the longacting systemic effects of streptokinase.

Coronary angioplasty has now obtained a definitive place in the treatment of acute myocardial ischemic syndromes. Research should be increased to further improve the technique, to accurately define the indications for and to study the extent (single vessel versus multivessel dilatation) and the timing of dilatation in this group of acutely ill patients. Furthermore, restenosis and reocclusion rates are currently disappointingly high and pose a serious problem which needs to be resolved, either by better pharmacologic approach or possibly by introduction of a prosthesis such as intravascular stents (133).

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De klinische uitingen van acute ischemische hartziekten zijn een direct gevolg van de onderliggende pathofysiologische mechanismen. Afhankelijk van de mate en duur van de verminderde myocardiale doorbloeding kunnen verschillende klinische syndromen, zoals plotse dood, acuut transmuraal infarct, acuut niet transmuraal infarct of onstabiele angina pectoris optreden. Recente klinische, angiografische en pathologische studies hebben de gemeenschappelijke pathofysiologische kenmerken van de mechanismen die ten grondslag liggen aan onstabiele angina pectoris, acuut myocard infarct en postinfarct angina pectoris aangetoond.

Onstabiele angina pectoris is gedefinieerd als perioden van myocard ischemie in rust, zonder daaropvolgende tekenen van necrose. Wanneer een patient zich presenteert met klachten van pijn op de borst gepaard gaande met electrocardiografische tekenen van ischemie, kan het onderscheid tussen onstabiele angina pectoris en acuut myocard infarct echter moeilijk zijn. De onzekerheid over het uiteindelijke beloop bij de individuele patiënt noopt tot het geven van de optimale therapie. Het doel van interventies in deze acute situatie is het behoud of herstel van een adequate bloedstroom, teneinde ischemie op te heffen en (verdere) necrose te voorkomen met het uiteindelijke doel de morbiditeit en mortaliteit op korte en lange termijn te verbeteren. Ondanks verbeteringen in chirurgische techniek, cardioplegie, anesthesie, en post-operatieve zorg, bestaat er nog steeds geen consensus over de rol van acute coronaire bypass chirurgie bij deze groep patiënten. De percutane transluminale coronaire angioplastiek is een aantrekkelijk alternatief voor acute coronaire bypass chirurgie bij de behandeling van patiënten met acute ischemische syndromen.

In hoofdstuk II van dit proefschrift worden de resultaten van coronaire angioplastiek op korte en lange termijn beschreven bij een groep van 200 opeenvolgende patiënten met onstabiele angina pectoris. Tevens worden hierin klinische, electrocardiografische, angiografische en aan de angioplastiek gerelateerde variabelen geanalayseerd, teneinde onafhankelijke risicofactoren voor complicaties te kunnen identificeren. De resultaten tonen aan dat coronaire angioplastiek bij geselecteerde patiënten met onstabiele angina pectoris een effectieve behandeling is met een goede prognose op de lange termijn.

Anderzijds moet er op gewezen worden dat complicaties in deze acute omstandigheden vaker optreden dan bij een electief uitgevoerde angioplastiek voor stabiele angina pectoris. De oorzaak hiervan is de andere pathofysiologie gekenmerkt door geruptureerde plaque met neiging tot thrombus vorming. Hierdoor kan een kritische reductie van de myocardiale

bloedvoorziening optreden. Coronaire angioplastiek kan in deze acute situatie het gestenoseerde lumen vergroten en aldus dit proces onderbreken. Soms geeft coronaire angioplastiek echter aanleiding tot een dusdanige beschadiging van de reeds geulcereerde intima, waardoor het bestaande thrombogene proces verder versterkt wordt. Dit kan leiden tot een acute afsluiting gedurende of kort na de procedure. Dit is een argument om ten tijde van de procedure additionele therapie in de vorm van een thrombolyticum te geven. Daarom werd bij patiënten met een acute occlusie kort na de ballondilatatie, intracoronair streptokinase toegediend. De resultaten van deze behandelingsstrategie worden besproken in hoofdstuk III.

Naast het feit dat coronaire angioplastiek op veilige en effectieve wijze toegepast kan worden bij patiënten met onstabiele angina pectoris, toont de analyse van de globale en regionale linker ventrikel functie verder het nut aan van ballondilatatie bij deze patiënten, zoals beschreven wordt in hoofdstuk IV.

Het belangrijkste doel van de behandeling van patiënten met een acuut myocardinfarct is de beperking van de infarctgrootte. Het concept om de infarctgrootte te beperken door vroegtijdige recanalisatie middels thrombolytica is in de klinische praktijk effectief gebleken. Het gebruik van thrombolytica in de acute fase van het myocardinfarct heeft echter een nieuw probleem gecreëerd: hoe behandelt men patiënten met een reststenose na thrombolyse indien ischemische symptomen blijven bestaan? Teneinde het gunstige effect van thrombolyse te behouden, kan het noodzakelijk zijn om de residuele stenose ook adequaat te behandelen middels coronaire angioplastiek.

De rol van coronaire angioplastiek onmiddellijk na thrombolyse bij het acute myocardinfarct wordt besproken in hoofdstukken V en VI. Hoofdstuk V beschrijft onze ervaringen met coronaire angioplastiek toegepast onmiddellijk na intracoronaire streptokinase bij 115 opeenvolgende patiënten met een acuut myocardinfarct. Het doel van de studie beschreven in hoofdstuk VI was om te onderzoeken of coronaire angioplastiek direct na thrombolyse een additionele waarde heeft bij het behouden van de regionale ventrikel functie in het infarctgebied. Hierbij werd gebruik gemaakt van de resultaten van de "Nederlandse Multicenter Thrombolyse Studie", waarin een deel van de patiënten coronaire angioplastiek ondergingen. De aangetoonde verbetering van de globale en regionale linker ventrikel functie, tesamen met de lage mortaliteit en morbiditeit, suggereren dat angioplastiek direct na thrombolyse veilig toegepast kan worden om complete reperfusie in de acute fase van het myocardinfarct te verkrijgen. Deze additionele revascularisatie procedure kan bij sommige patiënten noodzakelijk zijn om de kansen op volledig functioneel herstel te optimaliseren.

Desalniettemin, de thans beschikte gegevens over het gebruik van coronaire angioplastiek bij het acute myocardinfarct zijn tegenstrijdig en tot op heden bestaat er nog geen duidelijkheid over de plaats van de angioplastiek in deze situatie. Verder onderzoek is vereist om de exacte role en het optimale tijdstip van coronaire angioplastiek bij het acute myocardinfarct nader te bepalen.

Het frequent voorkomen van een recidief myocardinfarct en onstabiele angina pectoris na een non-Q-myocardinfarct vraagt om profylactische maatregelen teneinde verder verlies van myocardweefsel te voorkomen. Het is aannemelijk dat bij deze groep patiënten een deel van het myocard nog steeds "bedreigd" is na een onvolledige infarcering. De korte en lange termijn resultaten van 114 opeenvolgende patiënten behandeld middels coronaire angioplastiek vanwege ernstige angina pectoris na non-Q-myocardinfarct worden beschreven in hoofdstuk VII. Het hoge succespercentage, de lage mortaliteit en morbiditeit, suggereren dat coronaire angioplastiek een effectieve behandeling is bij patiënten met angina pectoris klachten na een doorgemaakt non-Q-myocardinfarct.

In hoofdstuk VIII wordt de globale en regionale linker ventrikel functie beschreven bij patiënten die coronaire angioplastiek ondergaan in de vroege fase na een non-Q-myocardinfarct. De resultaten tonen niet alleen aan dat herhaalde aanvallen van ischemie na een non-Q-myocardinfarct aanleiding kunnen geven tot langdurige myocardiale dysfunctie, maar dat dit "stunned" myocard zich weer kan herstellen na succesvolle coronaire angioplastiek.

Coronaire angioplastiek heeft inmiddels een belangrijke plaats ingenomen bij de behandeling van acute ischemische hartziekten. De resultaten beschreven in dit proefschrift tonen niet alleen aan dat coronaire angioplastiek op veilige en effectieve wijze toegepast kan worden bij deze groep patiënten, maar bovendien dat de linker ventrikel functie in staat is zich te herstellen na een succesvol uitgevoerde dilatatie. Nader onderzoek is echter noodzakelijk om deze behandelingswijze verder te ontwikkelen, de juiste indicatie en het beste tijdstip van deze interventie te bepalen, en de rol van multipele coronaire dilataties te evalueren bij deze groep acuut zieke patiënten.

CURRICULUM VITAE

June 24, 1951	: born in Pangkalpinang, Bangka (Indonesia)
1966 - 1969	: Senior highschool, Canisius College Jakarta, Indonesia
1970 - 1973	: Pre-clinical medical studies, Trisakti University Jakarta, Indonesia
1973 - 1977	: Medical Faculty, Catholic University Leuven, Belgium
June 30,1977	: Graduated and awarded Doctor of Medicine, Surgery, and Obstetrics by Catholic University Leuven, Belgium
July 1, 1977	: Awarded Certificate for passing course in Tropical Diseases by Tropical Institute of Antwerp, Belgium
1977 - 1982	: Specialist training in Internal Medicine, St. Lucas General Hospital, Brugge, Belgium (Dr. A. Hongenaert)
1982 - 1985	: Specialist training in Cardiology, Thoraxcenter, Academic Hospital Dijkzigt, Rotterdam, The Netherlands (Prof. P.G. Hugenholtz)
1985	: Internal Medicine I, Academic Hospital Dijkzigt, Rotterdam (Prof. Dr. M.A.D.H. Schalekamp)
January 1, 1986:	Awarded qualification and certification as cardiologist
1986 - 1988	: Senior cardiologist, Cardiac Catheterization Laboratory, Thoraxcenter, Academic Hospital Dijkzigt, Rotterdam
Current position	: Clinical head of the Cardiac Catheterization Laboratory, Thoraxcenter, Academic Hospital Dijkzigt, Rotterdam