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Late recurrent ischaemia in infarct patients with a normal predischarge exercise test after thrombolysis

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We investigated the prognostic value of normal predischarge exercise test in 109 patients after myocardial infarction treated with i.v. thrombolysis within 4 h. In 29 of these 109 patients, elective PTCA or bypass surgery was performed for prognostic reasons after coronary angiography; 80 patients were treated conservatively with drug therapy. Recurrent postinfarct angina early after hospital discharge was the reason in 4 of 80 for PTCA or bypass surgery. Twenty-three of the remaining 76 conservatively treated patients developed recurrent ischaemia during long-term follow-up of 12·0 ± 6·2 months, including one patient with reinfarction.

Late recurrent ischaemia during long-term follow-up was observed in one third of the conservatively treated patients with a normal predischarge exercise test, although a high percentage (30%) of patients in this subgroup had been treated with PTCA or bypass surgery mainly for prognostic reasons. Predischarge exercise test is therefore of limited value for detection of still viable myocardium at risk of further ischaemic events after acute myocardial infarction and thrombolysis.

Introduction

Systemic thrombolysis in acute myocardial infarction with recanalization of the infarct-related coronary artery results in an improved myocardial function and survival[1–6]. Thrombolysis is therefore an established method of active treatment in the early stage of acute myocardial infarction. However, the subsequent management of these patients is controversial.

While early diagnostic and therapeutic intervention during the first 24–48 h is not advantageous because of more frequent bleeding complications and a higher reocclusion rate[7–9], a rational risk stratification remains to be defined. There are still no reliable non-invasive methods to establish and measure the salvage of initially jeopardized myocardium by thrombolysis. Risk stratification and indication for invasive and expansive diagnostic procedures like coronary angiography or thallium-201 scintigraphy are frequently based on the results of the predischarge exercise test[10,11], just as in patients with conservatively treated myocardial infarction.

We therefore investigated the long-term follow-up of patients after thrombolytic treatment of acute myocardial infarction and its relationship to the results of the predischarge exercise test.

Patients and methods

This analysis includes all patients who have received thrombolytic therapy for acute myocardial infarction in one of the eight hospitals of the Zurich Study Group of Thrombolysis for Acute Myocardial Infarction between 1986 and 1988. The participating hospitals were: Triemli Hospital Zurich, University Hospital Zurich, Waid Hospital Zurich, Limmattal Hospital Zurich, Kantonsspital St Gallen, Kantonsspital Winterthur, District Hospital Uster and District Hospital Wetzikon.

PROTOCOL

Patients were considered eligible for thrombolysis if they were below the age of 70 years, complained of typical chest pain of <3–4 h duration and showed ST-elevation in two leads of the electrocardiogram typical of acute transmural myocardial ischaemia, in one lead at least measuring ≥ 2 mm

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and persisting after oral or intravenous nitroglycerin. The exclusion criteria were: haemorrhagic diathesis; uncontrolled hypertension (systolic blood pressure ≥ 200 mmHg, diastolic blood pressure ≥ 120 mmHg), previous arterial punction or i.m. injection without possibility of local compression; peptic ulcer disease, history of gastrointestinal or urogenital bleeding in the past 3 months; history of stroke within the past 6 months; surgery in the past 6 weeks; arrhythmias requiring immediate transvenous pacing; cardiopulmonary resuscitation with external cardiac massage; any severe disease that would exclude the patient in the opinion of the treating physician.

THROMBOLYTIC THERAPY

Thrombolytic therapy was performed with either streptokinase 1·5 Mio I.U. i.v. or with rt-PA in a total dose of 100 mg i.v.

POST-FIBRINOLYTIC TREATMENT

Immediately after thrombolysis intravenous heparin therapy was started, followed by oral anticoagulation for at least 6 months (1986 to 1987). Starting in 1987 patients received acetylsalicylic acid 500 mg i.v., additionally, instead of oral anticoagulants, aspirin 100–300 mg day^{-1} was prescribed. The concomitant medication was left to the treating physician.

CORONARY ANGIOGRAPHY

According to the uniform management every patient underwent coronary angiography if he did not show any contraindication for a possibly succeeding invasive therapy. Coronary angiography was performed preferentially during the same hospital stay, but not earlier than 72 h after thrombolytic therapy.

EXERCISE TEST

For risk stratification, a submaximal exercise test (bicycle ergometry or treadmill exercise test) was performed according to the guidelines of the European Society of Cardiology[12] before hospital discharge. Horizontal or down-sloping ST-segment depression of ≥ 1 mm, decrease in systolic blood pressure of ≥ 10 mmHg and angina were considered typical signs of ischaemia. If a secondary preventive therapy with beta-blocker and aspirin had been installed during hospitalization this therapy remained unchanged for exercise test.

LONG-TERM FOLLOW-UP

In a limited pilot group a follow-up telephone call was made to 36 patients after $20·5 \pm 5·7$ months. Patients (n = 132) who received thrombolysis thereafter were controlled prospectively by each centre. Information was collected as to recurrent myocardial infarction, presence of angina (New York Heart Association classification), congestive heart failure, invasive therapy (PTCA, bypass surgery) and to medication; further a clinical examination and a symptom-limited exercise test was performed.

DATA COLLECTION

The complete patient data were sent to a central registry for statistical analysis. To evaluate statistical significance the chi-square-test and the two-tailed Fisher's exact test were used.

Results

PATIENT POPULATION AND FOLLOW-UP

195 patients hospitalized with acute myocardial infarction from 1986 to 1988 in the intensive care units of the eight participating hospitals received i.v. thrombolytic therapy.

Six of the 195 patients (3%) died in hospital. No predischarge exercise test was performed in 16 patients with unstable angina who instead received early coronary angiography and invasive therapy. Five patients could not be tested for non-cardiac reasons. Thus, 168 patients underwent submaximal predischarge exercise testing.

Sixteen of 168 patients were lost to follow-up (15 with a normal predischarge exercise test, one with exercise-induced ischaemia). Among 152 patients given the predischarge exercise test long-term follow-up was made after $12·0 \pm 6·2$ months (range 3–31 months, median 12 months). The characteristics of these 152 patients are shown in Table 1.

TIME OF PREDISCHARGE EXERCISE TEST

The predischarge exercise test was performed $15·8 \pm 6·0$ days after myocardial infarction. The mean hospital stay was $17·5 \pm 6·4$ days.

FOLLOW-UP OF PATIENTS WITH ISCHAEMIA DURING PREDISCHARGE EXERCISE TEST

From the 43 patients with ischaemic signs in the predischarge exercise test, 27 (63%) were treated invasively; 16 (37%) did not qualify for PTCA or coronary artery bypass grafting (CABG) because of

Table 1 Characteristics of patients with predischarge exercise test and known follow-up

Patient characteristics	total	ischaemia	no ischaemia
Number of patients (n)	152	43	109
Age (years; mean ± SD)	57·0 ± 8·2	55·8 ± 7·0	57·5 ± 8·6
Male:female	11:1	42:1	8:1
Infarct localization ant:inf/post (%)	46:54	41:59	49:51
Coronary angiography (%)	85	93	82
Vessel patency (%)	83	80	84
Predischarge exercise test (days; mean ± SD)	15·8 ± 6·0	16·2 ± 5·4	15·6 ± 6·2
Hospitalization (days; mean ± SD)	17·5 ± 6·4	18·8 ± 6·4	17·0 ± 6·3
Follow-up (months)	12·0 ± 6·2	12·8 ± 6·2	11·6 ± 6·2

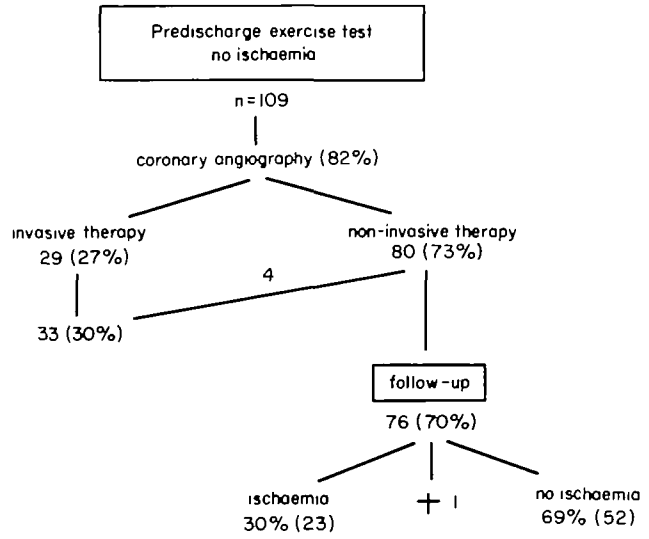

Figure 1 Primary therapy and follow-up of 109 patients without ischaemia at predischarge exercise test.

unfavourable coronary anatomy and/or prohibitive left ventricular function; one of the patients had died during the follow-up period with recurrent myocardial infarction, four patients were still suffering from angina NYHA class II–III, and one patient showed exercise-induced silent myocardial ischaemia despite antiischaemic drug treatment.

FOLLOW-UP RESULTS OF PATIENTS WITH ISCHAEMIA DURING PREDISCHARGE EXERCISE TEST (FIG. 1)

In the group of patients without ischaemia during predischarge exercise test (n = 109), primary invasive treatment was chosen in 29 patients (27%) for prognostic reasons (left main coronary artery stenosis, three-vessel disease with impaired left ventricular function; residual high-grade stenosis of the infarct-related coronary artery with preserved regional contractility). Four additional patients received coronary angiography and invasive therapy as they developed postinfarct angina soon after hospital discharge. Among the remaining 76 patients at follow-up, 30% (n = 23) showed recurrent myocardial ischaemia: in one patient reinfarction occurred, 20 patients complained of angina NYHA class II–III, in two patients signs of ischaemia were present only during a symptom-limited exercise test. One patient with left ventricular aneurysm and therapy-resistant ventricular tachycardia had died.

Table 2 Drug therapy at 1-year follow-up in patients with normal predischarge exercise test and primary conservative therapy

Drug therapy	Ischaemia at follow-up present n = 23	absent n = 52
Antianginal therapy	19 (83%)	40 (77%)
Beta blockers	11 (48%)	23 (44%)
Ca-antagonists	7 (30%)	17 (33%)
Nitrates	10 (43%)	10 (19%)
Molsidomine	3 (4%)	2 (38%)
Platelet aggregation inhibitors	6 (26%)	23 (44%)
Anticoagulants	11 (47%)	11 (21%)

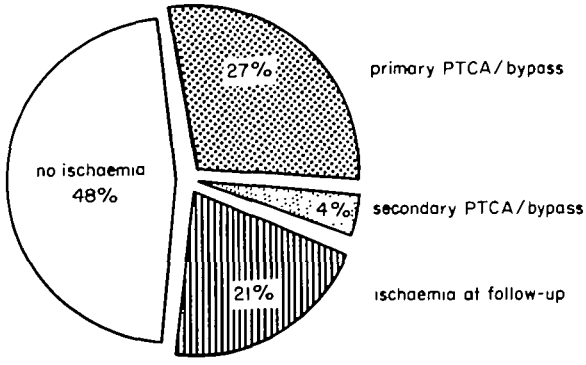

Figure 2 Normal predischarge exercise test (n = 109): final results of follow-up after 1 year.

No signs of ischaemia were present in 52 patients (69%).

DRUG THERAPY AT FOLLOW-UP

The drug therapy given to non-invasively treated patients with a normal predischarge exercise test is summarized in Table 2.

Discussion

Thrombolytic therapy in acute myocardial infarction aims at early re-establishment of coronary reperfusion and salvage of myocardium. After successful thrombolysis, mortality rate has been shown to be significantly reduced. There are, however, controversies as to the preferable post-thrombolytic strategy. The results from recent trials like TAMI and TIMI II favour elective angioplasty instead of an immediate invasive procedure[7,9,13]. As the comparison between the randomly assigned invasive and conservative strategy in the TIMI II trial showed no significant differences in reinfarction and death rate after short-term follow-up (maximum 42 days), 'watchful waiting' was recommended after thrombolysis and restriction of coronary angiography to patients with either spontaneous postinfarct angina or to patients with ischaemia developing during predischarge exercise test[13].

In the present investigation coronary angiography was, according to a uniform protocol, performed in every patient who had received thrombolysis. A prognostic indication such as left main coronary artery stenosis, three-vessel disease with impaired left ventricular function or residual high-grade stenosis of the infarct-related coronary artery with preserved regional contractility, was the reason for primary invasive therapy in 27% of the 109 patients with normal predischarge exercise test (Fig. 2). A further 4% of patients underwent angioplasty or bypass surgery early after hospital discharge because of recurrent severe postinfarct angina. Despite this high initial rate of CABG and PTCA, recurrent ischaemia was observed after 1 year of follow-up in 21% of the patients with a normal predischarge exercise test; a surprisingly high

percentage considering that 83% of these patients were still taking antianginal drugs—half of them beta-blockers (Table 2). Only 48% of patients remained free of symptomatic or silent ischaemia at exercise; they were taking anti-ischaemic medication in 77% (beta-blocker therapy and platelet aggregation inhibitors in 44% each).

Considering our results, doubts must arise about the significance of predischarge exercise test recommended for risk stratification in patients with thrombolytic therapy for acute myocardial infarction: in all our patients without contraindication for a succeeding invasive therapy coronary angiography was performed (85%) and, according to the coronary lesions, one fourth of the patients with initially normal predischarge exercise test received an invasive procedure for prognostic reasons. In addition to early recurrent ischaemia in 4%, late recurrent ischaemia developed in 21% of the remaining patients. Submaximal predischarge exercise testing, which was performed in our study according to the guidelines of the European Society of Cardiology[12], showed identical predictive accuracy to symptom-limited postdischarge exercise testing in patients 6 weeks after conservatively treated myocardial infarction[14]. However, similar investigations have not been performed in patients after thrombolytic treatment for acute myocardial infarction.

An important factor contributing to late recurrent ischaemia after thrombolysis is the problem of stunned myocardium which may persist for weeks and months[15,16]. In a recent study Weiss *et al.* showed that by quantifying viable myocardium with thallium-201 scintigraphy before and after thrombolysis, the ratio of salvaged to initially jeopardized myocardium is predictive of exercise-induced ischaemia; this ratio was found to be inversely related to the severity of the residual coronary stenosis[17]. Whereas exercise-induced ischaemia was recognized with radionuclide study in 64%, it was identified at treadmill exercise electrocardiography with significant ST-depression or angina in only 35%, thus confirming the low sensitivity and predictive accuracy of exercise testing for detecting residual ischaemia in patients after thrombolysis. This finding concurs with our data and is further supported by the results of the TIMI II Study[18], in which among patients randomly assigned to conservative therapy, 22·0% and 16·5% required PTCA and/or bypass surgery, respectively, because of recurrent myocardial ischaemia developing within 1 year of follow-up.

An accurate, highly sensitive and cost-effective method to detect residual ischaemia of viable myocardium in patients after thrombolytic therapy for acute myocardial infarction, is not yet available: bicycle ergometry and treadmill exercise testing are not sensitive enough; thallium-201 scintigraphy is somewhat superior to submaximal predischarge exercise testing in detecting myocardial ischaemia[19], however, compared with parallel examination with positron emission tomography, which identifies metabolically active tissue, it does not reach 100% accuracy and still underestimates the extent of salvaged myocardium[20–22].

Considering the generally good prognosis for survival and reinfarction after thrombolysis, the significance of late recurrent ischaemia in an even longer observation period remains unclear. In our opinion, risk stratification should include exercise testing and generously performed coronary angiography, at least until the role of coronary angiography after acute myocardial infarction and thrombolysis has precisely been established, to identify low-risk patients who might be discharged from hospital early[23] and high-risk patients who should be treated invasively without delay. Such a strategy should save costs in the long term.

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