

Safety and Efficacy of Thrombolysis for Acute Myocardial Infarction in Patients with Prolonged Out-of-Hospital Cardiopulmonary Resuscitation

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Thrombolysis has become an established therapy in reducing infarct size and mortality in patients with acute myocardial infarction. Cardiopulmonary resuscitation often is considered a contraindication for thrombolytic therapy.^{1,2} Published reports reveal that 10 to 21% of patients with acute myocardial infarction need defibrillation, precordial thump and cardiocompression.³⁻⁵ The exclusion of patients who have had cardiopulmonary resuscitation from thrombolytic therapy is not based on randomized studies. The safety of thrombolytic therapy was already established in patients who were resuscitated for a short time in 2 studies.^{5,6} We hypothesize that patients with acute myocardial infarction with an early but prolonged circulatory arrest may benefit greatly from thrombolytic therapy because of the short interval from time of infarction to the arrival in the hospital, and because of the larger area at risk.⁷ To study the safety and effectiveness of thrombolytic therapy we retrospectively studied patients with acute myocardial infarction and prolonged cardiopulmonary resuscitation. We compared data from groups of patients who were and were not treated with thrombolytic therapy.

Between 1989 and 1992 we reviewed patients with an acute myocardial infarction by electrocardiographic or enzymatic criteria, or both, who underwent ≥ 5 minutes of cardiopulmonary resuscitation before hospital admission. Patients who were treated with thrombolysis first and later needed cardiopulmonary resuscitation were excluded from our study. From our data base we found 69 patients who fitted our inclusion criteria: 33 patients were (group I) and 36 were not (group II) treated with thrombolysis. The treating physician decided whether or not a patient was treated with thrombolysis. Retrospectively, coma was not a contraindication for thrombolysis. Group I consisted of 29 men and 4 women (mean [\pm SD] age of 62 ± 12 years [range 40 to 82]) and group II consisted of 20 men and 16 women (mean [\pm SD] age 69 ± 13 years [range 33 to 90]). We analyzed the following parameters: age, gender, medical history, size and site of myocardial infarction, duration of cardiopulmonary resuscitation, defibrillation, artificial ventilation, used medication such as inotropic and antiarrhythmic therapy, neurologic deficit, complications of cardiopulmonary resuscitation such as rib fractures, rib contusions and/or organ lacerations, bleeding, hemoglobin changes during admission, in-hospital mortality and cause of death.⁸ In case of neurologic damage a computed tomography scan was recorded to ex-

clude cerebral hemorrhage and infarction. The course of the neurologic damage was followed by electroencephalography.

Table I lists baseline characteristics. Except for older age and lower male/female ratio of the patients in group II, both groups were highly comparable.

Table II shows the clinical outcome. The reason for cardiopulmonary resuscitation was in most cases the occurrence of ventricular fibrillation. In group II there were more patients with bradyarrhythmias. Eight of 33 patients (24%) in group I needed inotropic support at some instance after admission because of pump failure, versus 28 of 36 patients (78%) in group II. Additional antiarrhythmic treatment consisting of lidocaine, propafenone or amiodarone was needed in 6 of 33 patients (18%) in group I versus 12 of 36 patients (33%) in group II. Enzyme levels did not differ significantly between the 2 patient groups. Also, percent hemoglobin decrease did not differ significantly between both groups.

After cardiopulmonary resuscitation, rib fractures were diagnosed in 2 patients in group I and 1 in group II. In group II, 1 patient was diagnosed as having a rib contusion. In the patients treated with thrombolytic therapy no cardiopulmonary resuscitation-related bleeding accidents occurred. In this group, 1 patient with a remote history of gastric ulceration had hematemesis and died of hypovolemic shock. At autopsy the bleeding was located in the stomach. No relation was found to cardiopulmonary resuscitation procedures. In group II, 1 patient had nonfatal bleeding from the puncture site of the Swan-Ganz catheter. No hemorrhagic stroke was encountered.

Table II lists mortality figures. Neurologic death was similar in both groups. However, cardiac death was much less in group I: in 4 patients the cause of death was related to myocardial infarction: 2 patients had pump failure, 1 had therapy-refractory arrhythmias and 1 had an electromechanical dissociation. One patient died of severe digestive tract bleeding, confirmed by autopsy. Autopsy was also performed in 5 of 12 other deceased group I patients; none had bleeding related to cardiopulmonary resuscitation. In group II, the cause of death in 14 patients was related to myocardial infarction: 12 patients died of pump failure and 2 patients were found to have a electromechanical dissociation. One patient died of septic shock.

In 1980, a National Institutes of Health Consensus Conference on thrombolytic therapy considered cardiopulmonary resuscitation a relative contraindication for thrombolytic therapy.¹ The American College of Cardiology and American Heart Association also advised cardiopulmonary resuscitation to be a relative contraindication for thrombolytic therapy.²

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	Thrombolysis (group I— n = 33)	No thrombolysis (group II— n = 36)
Risk factors		
Hypertension (diastolic pressure > 90 mm Hg)	12	5
Diabetes mellitus	5	5
Hypercholesterolemia (> 6.8 mmol/L)	4	2
Smoking	11	7
Family history of coronary disease	3	1
Unknown	7	16
History		
Old myocardial infarction	14	13
Angina pectoris	6	5
Other cardiac diseases	8	12
Other diseases	9	9
Unknown	3	0
Localization of myocardial infarction		
Inferior	14	16
Right ventricle	4	0
Posterior	0	5
Anteroseptal	13	13
Anterolateral	9	9
Reason for resuscitation		
Ventricular fibrillation	28	26
Bradycardia	8	12
Electromechanical dissociation	1	3
Other	1	5
Number of defibrillations		
Mean	2.8	2.5
Median	1	2
Range	0–24	0–11
Maximal energy delivered (J)		
Mean	1,003	1,144
Median	360	720
Range	0–8,000	0–3,800
Duration of resuscitation (min)		
Mean	20.7 ± 19.2	23.5 ± 14.6
Median	10	20
Range	5–80	5–60

Tenaglia et al⁵ compared 2 groups of patients with acute myocardial infarction, 1 with and 1 without cardiopulmonary resuscitation. However, they excluded patients with a resuscitation procedure lasting >10 minutes. No resuscitation-related complications, e.g., instance tamponade and organ rupture or lacerations were seen.⁸ Furthermore, they found that bleeding, measured from a decline in hemoglobin, the lowest hematocrit and the amount of packed cells needed for treatment did not differ in both groups. Scholz et al⁶ studied 43 of 590 patients with acute myocardial infarction who were treated with thrombolysis and who needed prolonged cardiopulmonary resuscitation. In 22 patients thrombolytic therapy was given during or immediately after cardiopulmonary resuscitation as in our study. The mean (±SD) duration of cardiopulmonary resuscitation in this group was 36 ± 32 minutes (range of 4 to 120). They did not find any difference in bleeding complications

	Thrombolysis (group I— n = 33)	No Thrombolysis (group II— n = 36)
Stay in intensive care (days)		
Mean	4.3 ± 5.9	5.6 ± 9.0
Median	2	3
Range	1–28	1–46
Artificial ventilation	17	33
Laboratory results		
Peak creatine kinase (U/L)	2,818 ± 2,510	1,897 ± 2,115
Peak creatine kinase-MB (U/L)	131.6 ± 86.3	117.4 ± 133.2
Peak lactate dehydrogenase (U/L)	883 ± 369	1,152 ± 971
Admission hemoglobin (mmol/L)	8.8 ± 1.0	7.9 ± 1.4
Percent hemoglobin decrease	12.7 ± 10.6	10.3 ± 5.4
Neurologic damage		
Total	17	19
Coma	9	16
Stroke	1	1
Myoclonias	2	2
Seizure	1	0
Memory disturbances	4	0
In-hospital mortality		
Total	13	24
Death within 1 day	6	16
Death between 2 and 7 days	5	5
Death after 7 days	2	3
Cardiac deaths	4	14
Neurologic deaths	7	7
Death by bleeding	1	0
Death by sepsis	0	1
Other causes of death	1	2

when comparing the groups with and without thrombolytic therapy. In the resuscitated group, 8 bleeding complications were seen (3 at the puncture site, 2 in the gastrointestinal tract, 1 in the urogenital tract, and 2 patients had a decline in hemoglobin without any localization of bleeding). None was related to the cardiopulmonary resuscitation procedure despite the fact that rib fractures were found in 17 patients.

Published reports have shown that the mortality rate is high in patients needing prolonged cardiopulmonary resuscitation. We found an overall in-hospital mortality of 54%. We observed similar in-hospital neurologic morbidity and mortality in both groups. This is related to the anoxia time before and during cardiopulmonary resuscitation and we did not expect this to be different in both groups. A much lower cardiac mortality was noted in the treated group than could be expected by the known mortality reduction of thrombolytic therapy. Clinical manifest bleeding could be detected in only 1 patient in this group. This bleeding complication could not be related to the cardiopulmonary resuscitation procedure. In patients with rib fractures we did not see clinical manifest bleeding. It would be interesting to know whether angioplasty instead of thrombolysis would have had a better outcome with fewer complications in patients in our study. In most clinics the delay before angioplasty is longer than that before thrombolysis. Eckman et al⁹ stated that direct angioplasty has an overall mortality similar to that of thrombolytic therapy, but they do not compare these therapies in their study. Patients with a contraindication to thrombolytic therapy may benefit from mechanical revascularization.

Although limited by its retrospective character and the fact that group II was slightly older and had a lower male/female ratio than group I, we found that prolonged cardiopulmonary resuscitation (>20 minutes) by itself does not have to be a contraindication to thrombolytic therapy. Furthermore, although there were no differences in neurologic outcome, we observed a reduction in cardiac morbidity and mortality. We think randomized prospective studies must be undertaken to investigate the effect of thrombolytic therapy in patients with acute myocardial infarction and prolonged cardiopulmonary resuscitation. Also, a comparison of advantages and disadvantages of mechanical revascularization with thrombolytic therapy in these group of patients needs to be undertaken.

1. Sherry S, Bell WR, Duckert FH, Fletcher AP, Gurewich V, Long DM, Marder VJ, Roberts H, Salzman EW, Sasahara A, Verstraete M. Thrombolytic therapy in

thrombosis: a National Institutes of Health Consensus Development Conference. *Ann Intern Med* 1980;93:141-144.

2. Gunnar RM, Passamani ER, Bourdillon PDV, Pitt B, Dixon DW, Rapaport E, Fuster V, Reeves TJ, Karp RB, Russell RO Jr, Kennedy JW, Sobel BE, Klocke FJ, Winters WL Jr. Guidelines for the early management of patients with acute myocardial infarction. *J Am Coll Cardiol* 1990;16:249-292.

3. Wilcox RG, Olsson CG, Skene AM, von der Lippe G, Jensen G, Hampton JR. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction. *Lancet* 1988;2:523-530.

4. Kennedy JW, Ritchie JL, Davis KB, Fritz JK. Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. *N Engl J Med* 1983;309:1477-1482.

5. Tenaglia AN, Califf RM, Candela RJ, Kereiakes DJ, Berrios E, Young SY, Stack RS, Topol EJ. Thrombolytic therapy in patients requiring cardiopulmonary resuscitation. *Am J Cardiol* 1991;68:1015-1019.

6. Scholz KH, Tebbe U, Hermann C, Wojcik J, Lingen R, Chemnitz JM, Brune S, Kreuzer H. Frequency of complications of cardiopulmonary resuscitation after thrombolysis during acute myocardial infarction. *Am J Cardiol* 1991;69:724-728.

7. Volpi A, Maggioni A, Franzosi MG, Pampallona S, Mauri F, Tognoni G. In-hospital prognosis of patients with acute myocardial infarction complicated by primary ventricular fibrillation. *N Engl J Med* 1987;317:257-261.

8. Krisner JF, Fire EG, Davis JH, Nagel EL. Complications of cardiac resuscitation. *Chest* 1987;92:287-291.

9. Eckman MH, Wong JB, Salem DN, Pauker SG. Direct angioplasty for acute myocardial infarction. A review of outcomes in clinical subsets. *Ann Intern Med* 1992;117:667-676.

Frequency of Hypothyroidism in Adults with Serum Total Cholesterol Levels >200 mg/dl

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In this study, we determined the frequency and severity of increased thyrotropin (TSH) levels in patients with varying ranges of total cholesterol to assess the importance of hypothyroidism as a secondary cause of dyslipidemia.

A hospital data base, *ClinQuery*, was used retrospectively to examine patients admitted to the Beth Israel Hospital from 1987 to 1991 who had cholesterol levels measured within the first 48 hours of admission ($n = 6,713$; 61% male, mean age 57 years).¹ Among these inpatients, a subset had TSH levels measured ($n = 1,094$; 41% male, mean age 64 years); 771 had high-density lipoprotein (HDL) cholesterol levels measured. Between 1988 and 1991, the database enabled the determination of patients with increased TSH levels who were receiving concurrently a lipid-altering agent (niacin, cholestyramine, gemfibrozil or lovastatin) or thyroid hormone replacement therapy, or both.

To determine the incidence of TSH abnormalities in patients being screened for hypercholesterolemia, we prospectively determined TSH levels in 292 consecutive, general outpatients who had cholesterol and HDL cholesterol levels measured. For 10 of 11 patients with increased TSH levels (1 specimen had insufficient serum), thyroxine (T4) levels were determined.

All cholesterol measurements were obtained with a COBAS BIO centrifugal analyzer (Roche Diagnostic Systems, Nutley, New Jersey) using a standard, enzymatic assay (Abbott Laboratories, North Chicago). Increased cholesterol was defined as >200 mg/dl. HDL cholesterol was determined with the same procedure after magnesium phosphotungstate precipitation (Sigma Diagnostics, St. Louis).

TSH levels were determined using 2 noncompetitive immunoassays. For phase I (retrospective study), the DELFIA system (Pharmacia Diagnostics, Fairfield, New Jersey) was used. For phase II (prospective study), the STRATUS system (Baxter Diagnostics, Deerfield, Illinois) was used. T4 levels were determined using the DELFIA immunoassay (Pharmacia Diagnostics). All immunoassays were determined as specified by the manufacturers.

To establish concordance of the 2 TSH methods, a small correlation study was performed. For 26 specimens, the regression line was: STRATUS = (1.13 DELFIA) + 0.1 ($r^2 = 0.997$). An in-house, reference range study for DELFIA suggested an upper limit of 5 that would correspond by this equation to a STRATUS value of 5.8, which is comparable to the manufacturer's suggested upper limit of 6.2. For this study, we used as our thresholds 5 for DELFIA and 7 for STRATUS (the latter was increased from 5.8/6.2 to enhance the specificity of an increased TSH).

The limits for the cholesterol ranges were set arbitrarily within the *ClinQuery* system as <200, 200 to 250 and >250 mg/dl. To maintain consistency, the same ranges were used for the prospective analysis.

All statistical analyses, except comparison of the frequency of increased TSH levels for different cholesterol

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