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Strategies for pre-hospital thrombolysis: an overview

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Improvement in survival as a result of thrombolytic therapy in patients with myocardial infarction is determined by the delay between coronary occlusion and reperfusion. Treatment at home can reduce this delay, provided that appropriate patients can be identified. Different strategies for pre-hospital thrombolysis have been developed.

Most studies require ECG confirmation of evolving myocardial infarction. In many, the ECG is interpreted by a physician in the ambulance. Others transmit the ECG to a remote physician or use computer analysis of an ECG made 'on the spot', A few studies use no ECG criteria at all.

The pooled data show that with physician interpretation, 723 patients in 14 studies could be treated within 103 min after onset of symptoms (range 60–138 min) with a time gain of 51 min (range 30–74 min), compared with thrombolytic treatment after hospital admission. The therapeutic delay was 93 ± 45 min (SD) with time gains of 62 and 86 min in two studies with ECG transmission (61 patients). In another study using computer analysis, ambulance nurses were able to treat 300 patients within 102 ± 63 min after onset of symptoms, resulting in a time gain of 48 ± 2 min. Without ECG confirmation, cardiologists accompanying the ambulance could administer thrombolysis within 83 ± 4 min after onset of symptoms with a time gain of 45 min in one study. The diagnostic accuracy of this last approach was 42%.

With each of the four approaches, patients can be treated within approximately 100 min after onset of symptoms, resulting in a time gain of 45 min or more. Both the therapeutic delay and the time gain depend on local circumstances. Although the omission of an ECG makes the procedure somewhat faster, this results in a large number of unjustified treatments (58%). The choice of approach in a given city or area will have to depend on the local organization of both prehospital and hospital care.

Introduction

Early thrombolysis is important for salvage of myocardial tissue in acute myocardial infarction. The process of necrosis evolves in the first hours after coronary artery occlusion. During this period, the area of necrosis expands gradually at the cost of jeopardized, but still salvageable, myocardial cells. Many studies have shown a distinct relationship between the timing of thrombolysis and final outcome in terms of left ventricular function and survival[1-6].

Important factors determining the time lapse between coronary occlusion and initiation of thrombolytic therapy (therapeutic delay) are transportation of the patient to hospital and diagnosis and preparation of treatment after arrival in hospital. These time intervals depend on local circumstances, but travel times of half-an-hour and in-hospital delays of one hour are not exceptional[7-9]. Selection of patients at home or on the scene and initiation of thrombolytic therapy prior to transportation to hospital could lead to substantial time gains, provided a feasible, fast and safe procedure is available.

Strategies for pre-hospital thrombolysis

Many pre-hospital thrombolysis projects have been started throughout the world, of which 17 have reported their experiences. Although in some studies, thrombolysis administration is only based on patient history and clinical picture, the general opinion is that the presence of a large jeopardized zone of myocardium must be proven by means of an ECG to identify the patients with the most favourable benefit-risk ratio. Three approaches are available for obtaining an interpretation of an ECG made 'on the spot'. If a physician skilled in ECG diagnosis is present, he/she can provide interpretation of an ECG. However, a physician with these qualifications is not always available and a general practitioner has only limited experience in reading an ECG; in many countries there are no doctors in the ambulance. Ambulances staffed with doctors (often called Mobile Intensive Care Units rather than ambulances) provide advanced care alongside an ambulance system for basic care with personnel at a lower level of training; thus the ambulance with the physician on board may not be the one to arrive at the patient.

Another way to obtain an ECG diagnosis is to transmit the ECG to a remote physician (for instance at a hospital or at the Central Dispatch) for analysis. The development of the cellular phone and digital transmission techniques has overcome some of the drawbacks associated with the use of land phone lines and analogue transmission of the ECG signal, and facilitates establishing the connection and interference-free transmission. Computer analysis of an ECG made 'on the scene' could provide rapid ECG interpretation without a physician

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being present. The results obtained with the different approaches have been summarized in Table 1.

The most common approach is ECG interpretation by an ambulance-based physician (a total of 723 patients treated in 14 studies)[10–22]. This method results in treatment 103 min after onset of symptoms (mean of 14 studies), ranging from 60 to 138 min. The average time gain is 51 min with a range of 30 to 74 min. The rate of unjustified treatments, when mentioned, ranges from 0 to 4%.

The reported experience with ECG transmission is limited. So far only two groups have reported their results, including one pilot study consisting of only four patients[23,24]. The interval between onset of symptoms and start of thrombolysis was not reported in this small study. The second, larger study with 59 patients demonstrated a therapeutic interval of 93 min with a standard deviation (SD) of 45 min. Claimed time gains were 86 min in the first small study and 62 min in the larger one.

The only pre-hospital thrombolysis study depending solely on computerized ECG interpretation is the REPAIR study in Rotterdam, the Netherlands[25]. During a 3-year period 300 patients were treated within 102 ± 63 min (SD) after onset of symptoms by ambulance nurses, resulting in a time gain of 48 ± 2 min, compared with thrombolytic treatment after arrival in hospital in similar patients. There were six unjustified treatments (false-positive rate 2%), five of which were due to noise. One patient was treated based upon a previous ECG, recalled from the computer memory. These false-positive results of computer analysis could have been prevented by proper use of the ECG equipment, including a visual check of the ECG quality before accepting the result of the computer analysis, resulting in a specificity of 100%. These observations are confirmed by the MITI study group in Seattle, Washington, who observed that their computer algorithm was more accurate in recognizing myocardial infarction than the remote physician at the central dispatch.

There is also one report of pre-hospital thrombolysis without ECG criteria. The results of this TEAHAT study, carried out in Göteborg, Sweden, are comparable to those of the other approaches, with a therapeutic interval of 83 ± 3·5 min and a time gain of 45 min[26]. Although the decision to give thrombolysis was made by a cardiologist accompanying the Mobile Intensive Care Unit, only 42% of 59 patients treated outside hospital had a confirmed diagnosis of acute myocardial infarction.

In all pre-hospital studies, complications during transportation were rare and mostly limited to arrhythmias.

All approaches seem to give comparable results with respect to the therapeutic interval and the reported time gains. These parameters are strongly influenced by local factors, such as patient education, the time window used in the selection procedure, the time needed for transportation to hospital and the organization of both pre-hospital and hospital care. In almost all studies the time gain is calculated by subtraction of the interval between onset of symptoms and start of thrombolytic treatment in a group of patients treated before hospital admission, from the same interval in a group of patients treated after arrival in hospital. In order to make a valid comparison between the efficiency of the different procedures for selection and treatment, comparison of the intervals between arrival of the ambulance team and start of thrombolysis is necessary. Few studies report this interval. Comparison of the available data suggests that on-site computer interpretation provides the best compromise between speed and reliability (Table 2).

The average time between ambulance arrival and start of thrombolysis was 38 min in the physician-based studies[10–13]. This ranged from 25 min in Jerusalem[10] to delays from 45 to 54 min in three French studies with Mobile Intensive Care Units with anaesthesiologists[11–13]. The reason for the longer delays in these French studies was the necessity of extensive consultation with the hospital before the decision to give thrombolysis was made.

Sherrid realized treatment within 47 min after arrival, using ECG transmission for obtaining ECG interpretation[24]. As already mentioned, this study included only four patients. With more experience in patient selection, ECG transmission and preparation of the treatment, this interval would probably decrease. A disadvantage of this system is the time needed to establish the connection and to reach the consulting physician. Even in the ideal situation of a physician on-call 24 h a day at the Central Dispatch, this takes 7 min, with a total decision time of 18 min after arrival, as was observed by Weaver in Seattle during Phase 1 of the MITI trial[25]. The experience with ECG transmission is limited at this moment, so its exact value cannot be evaluated yet.

With computerized ECG analysis, ambulance nurses in Rotterdam were able to administer alteplase in 300

Table 1 Results of the different strategies for prehospital thrombolysis

ECG approach	N	Symptom onset thrombolysis	Time gain
Physician interpretation	14	103 min (60–138)	51 min (30–74)
ECG transmission	2	93 ± 45 min	74 min (62–86)
Computer analysis	1	102 ± 63 min	48 ± 2 min
No ECG	1	83 ± 3·5 min	45 min

Reported intervals between onset of symptoms and start of thrombolytic treatment of the claimed time gain of the different strategies. N = number of studies. Values with standard deviations (SD), ranges within parentheses.

Table 2 Intervals between ambulance arrival and start of thrombolytic treatment

ECG approach	Arrival ambulance, start thrombolysis
Physician interpretation	43 min (25–54)
ECG transmission	47 min
Computer analysis	21 ± 9 min
No ECG	18 min

Reported intervals between arrival of the ambulance and start of thrombolytic treatment of the different approaches. Values with standard deviations (SD), ranges within parentheses.

patients within 21 min after arrival[26]. The decision to give thrombolysis was made 10 min after arrival, while insertion of an intravenous line and the preparation of the infusion took another 11 min. The interval between ambulance arrival and start of thrombolysis gradually decreased from 26 to 18 min with increasing experience. The number of failures to insert an intravenous line decreased from 10 to 4% (Fig. 1). One observed advantage of this 'stand-alone' approach was its flexibility. In a number of cases the decision to give thrombolysis was made during the ambulance ride, mostly because the development of new symptoms or ECG changes during transportation necessitated re-assessment of the patient.

Without ECG confirmation of myocardial infarction the cardiologists in the TEAHAT study needed 18 min for selection and treatment[27].

Early thrombolysis: pre-hospital or after arrival in the hospital?

A considerable part of the time gain by prehospital thrombolysis represents time gained because in-hospital delays are avoided. Our experience in Rotterdam indicates that the procedures after arrival in hospital required an additional 28 min, while the total time gain was 48 min. The residual 20 min are saved because of the time needed to prepare the patient for transportation (9 min) and the time needed to drive to the hospital (11 min). Delays in initiation of thrombolytic therapy of more than 80 min after arrival in hospital have been reported by others[7–9]. Therefore, it is argued, one should aim at reducing in-hospital delays to reach early thrombolysis, rather than initiate thrombolytic treatment prior to hospital admission. Indeed, considerable time gain can be reached by improving the procedures for decision and treatment in hospital. Thrombolysis can be administered earlier in the Emergency Department rather than in the Coronary Care Unit, with reported time gains of approximately 35 min[8,18,28]. Another possibility is to admit cardiac patients directly to the Coronary Care Unit, avoiding busy Emergency Departments. It is obvious that the time gain obtainable in a hospital depends on the efficiency of the existing

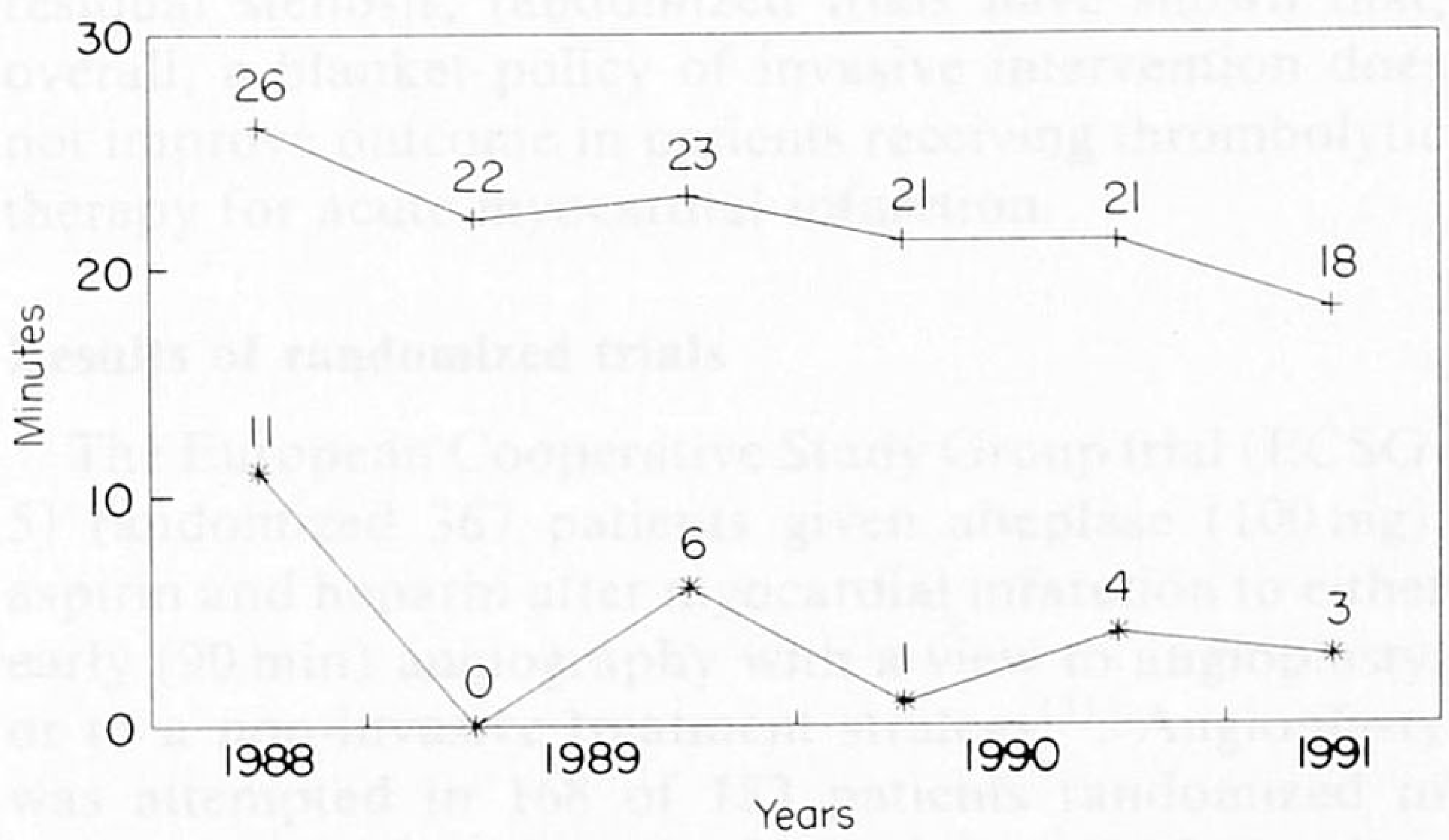

Figure 1 The interval between ambulance arrival and start of thrombolytic treatment in min (+) and the percentage of patients in whom it was impossible to insert an intravenous line (*) per half year, from the second half of 1988 until the second half of 1991.

organization. Nevertheless, even in comparison with the 'fastest' hospital in Rotterdam with a average 'door-to-drug' time of 28 min, almost half-an-hour can be gained by pre-hospital thrombolysis. Additional time can be gained with pre-hospital treatment, especially in situations with longer travel times or in hospitals where a physician is not immediately available. In order to enhance the benefits of thrombolysis by earlier treatment, one should aim at early thrombolysis for all patients by introduction of pre-hospital thrombolytic treatment for patients transported to the hospital by ambulance and reduction of in-hospital delays for other patients. The latter will require considerable effort and money and will not be feasible in many hospitals.

Conclusion

All available strategies for pre-hospital thrombolysis allow fast and safe initiation of thrombolytic treatment, and substantial time gains can be reached depending on local circumstances. Pre-hospital thrombolysis by ambulance-based physicians and by ambulance nurses with computerized ECG interpretation give comparable results. The number of unjustified treatments is acceptable with both methods. The exact value of ECG transmission has yet to be established, but the realization of the connection, the transmission of the ECG and acquisition of a response will always take some time, especially when the remote physician is a busy cardiologist or cardiology resident.

Pre-hospital thrombolysis without ECG confirmation adds little to the time gain, but greatly increases the number of unjustified treatments, even when the decision is made by cardiologists. This emphasizes the necessity of an ECG for selecting appropriate patients.

An ideal method for implementing pre-hospital thrombolysis does not exist. The choice of approach depends on the local organization of both pre-hospital and hospital care. When a physician skilled in ECG diagnosis is not available, computerized ECG analysis on the spot or ECG transmission makes pre-hospital selection and treatment by ambulance nurses or paramedics possible.

Although the procedures for in-hospital thrombolysis can be considerably improved to reduce in-hospital delays, pre-hospital thrombolysis will result in additional time gain, myocardial salvage and patient benefit. Procedures developed for use outside hospital, such as ECG diagnosis on the spot or transmission of an ECG by telephone or telefax could also be of value if applied in Emergency Departments or Coronary Care Units where a physician is not immediately available. If with the same procedures a diagnosis can be made before the patient is transported to the hospital (e.g. total AV block or myocardial infarction), the hospital could be alerted to ensure rapid treatment.

References

[1] Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI), Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986; 1: 397–401.

[2] The I.S.A.M. Study Group, A Prospective Trial of Intravenous Streptokinase in Acute Myocardial Infarction. New Engl J Med 1986; 314: 1465–71.

[3] Vermeer F, Simoons M, Bär F *et al.* Which patients benefit most from early thrombolytic therapy with intracoronary streptokinase? Circulation 1986; 74: 1379–89.

[4] ISIS-2 (Second International Study of Infarct Survival) Collaborative Group, Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17187 cases of suspected myocardial infarction. The Lancet, 13 August 1988: 349–60.

[5] Kennedy J, Martin G, Davis K *et al.* The Western Washington Intravenous Streptokinase in Acute Myocardial Infarction Randomized Trial. Circulation 1988; 77: 345–52.

[6] Van de Werf F vd, Arnold AER. Intravenous tissue type plasminogen activator and size of infarct, left ventricular function and survival in acute myocardial infarction. Br Med J 1988; 297: 1374–9.

[7] Sharkey S, Brunette D, Ruiz E *et al.* An analysis of time delays preceding thrombolysis for acute myocardial infarction. JAMA 1989; 262: 3171–4.

[8] MacCallum A, Stafford P, Jones C *et al.* Reduction in hospital time to thrombolytic therapy by audit of policy guidelines. Eur Heart J 1990; 11: 48–52.

[9] Kereiakes D, Weaver W, Anderson J *et al.* Time delays in the diagnosis and treatment of acute myocardial infarction: A tale of eight cities. Am Heart J 1990; 120: 773–80.

[10] Weiss AT, Fine DG, Applebaum D *et al.* Prehospital coronary thrombolysis, a new strategy in acute myocardial infarction. Chest 1987; 92: 124–8.

[11] Castaigne A, Hervé C, Duval-Moulin A *et al.* Prehospital use of APSAC: results of a placebo-controlled study. Am J Card 1989; 64: 30A–33A.

[12] Sauval P, Artigou J, Cristofini P *et al.* Fibrinolyse préhospitalière par rt-PA dans l'infarctus aigu du myocarde. Arch Mal Coeur 1989; 82: 1957–61.

[13] Cazaux P, Leclerq G, Vahanian A *et al.* Thrombolyse intraneineuse par l'activateur tissulaire du plasminogène (rt-PA) à la phase préhospitalière dans l'infarctus myocardique aigu. Arch Mal Coeur 1989; 82: 1967–71.

[14] Martens U, Lange-Braun P, Langer R *et al.* Systemische Frühlyse des akuten Myokardsinfarkts. Dtsch Med Wschr 1987; 112: 910–14.

[15] Barbash G, Roth A, Hod H *et al.* Improved Survival but not Left Ventricular Function with Early and Prehospital Treatment with Tissue Plasminogen Activator in Acute Myocardial Infarction. Am J Card 1990; 66: 261–6.

[16] Villemant D, Barriot P, Bodenan P *et al.* At home thrombolysis and myocardial infarction, a real saving of time. Eur Heart J 1988; 103: 394 (abstr).

[17] Bippus P, Haux H, Schröder R. Praehospital intravenous streptokinase in evolving myocardial infarction: a randomized study about feasibility, safety, and time gain. Eur Heart J 1988; 103: 395 (abstr).

[18] Nicholas J, Higginson JDS, McBoyle D. Early Intervention in myocardial infarction with streptokinase at home and in accident and emergency department. Eur Heart J 1988; 212: P1198 (abstr).

[19] Burke E, McAleer B, McElhinney K *et al.* Comparative one year mortality in patients treated with thrombolytic treatment at home and in the coronary care unit. Br Heart J 1989; 61: 72 (abstr).

[20] Picart N, Bossaert L, Renard M *et al.* A Belgian multicenter study of prehospital thrombolysis with eminase (APSAC) in acute myocardial infarction. Eur Heart J 1989; 10: 123: 618 (abstr).

[21] Schofer J, Büttner J, Geng G *et al.* Pre-hospital thrombolysis in acute myocardial infarction. Am J Card 1990; 66: 1429–33.

[22] Kokott N, Rutsch W, Berghöfer G *et al.* Pre-hospital treatment with IV rt-PA in acute myocardial infarction. Eur Heart J 1990; 11: 356: P1972 (abstr).

[23] Hooghoudt T, Hertzberger D, Hulst R, Couvée J. Pre-hospital thrombolysis is feasible, safe and reduces time to treatment considerably. Eur Heart J 1990; 11: 356: P1974 (abstr).

[24] Sherrid M, Greenberg H, Marsella R *et al.* A pilot study of paramedic-administered, prehospital thrombolysis for acute myocardial infarction. Clin Card 1990; 13: 421–4.

[25] Bouten M, Simoons M, Hartman J. Snellere behandeling van het acute myocardinfarct door behandeling met alteplase (rt-PA) vóór opname. Ned Tijdschr Geneesk 1990; 50: 2434–8.

[26] Weaver W, Eisenberg M, Martin J *et al.* Myocardial infarction triage and intervention project-phase I: patient characteristics and feasibility of prehospital initiation of thrombolytic therapy. JACC 1990; 15: 925–31.

[27] Risonfors M, Gustavsson G, Ekström L *et al.* Prehospital thrombolysis in suspected acute myocardial infarction: results from the TEAHAT study. J Int Med 1991; 229 (Suppl 1): 401–7.

[28] Verheugt FW, Funke Küpper AJ, Sterkman LG, *et al.* Emergency room infusion of intravenous streptokinase in acute myocardial infarction: Feasibility, safety and hemodynamic consequences. Am Heart J 1989; 117: 1018–21.