Thrombolysis in acute myocardial infarction
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Chapter II

Time as a determinant for success of thrombolytic therapy

1. Introduction

Time between onset of symptoms and initiation of treatment is a major determinant for outcome of therapy in patients with MI. During the last decades attempts have been made to shorten this period as much as possible. Already in the 1960s, reduction in prehospital mortality was achieved by the introduction of ambulances equipped with a battery-operated DC defibrillator and a registrar or houseman, a so-called mobile intensive-care unit (Pantridge, 1967; Mathewson, 1985). Initially, attention was focused on the early treatment of life threatening arrhythmias. Subsequently, it was shown in animals that cell death following coronary occlusion is a time-dependent wavefront-like progressive phenomenon (Reimer, 1979). Reasons why valuable time was sometimes lost before initiation of therapy were elucidated and strategies to circumvent this were developed. This became of major importance in the context of thrombolytic therapy, when time is a primary determinant for success. This will be shown in this chapter.

2. Time-loss between onset of symptoms and initiation of therapy

2.1. Delay by the patient

The major contribution to the time-loss before initiation of treatment is the patients’ delay. This delay was shown to have a skewed distribution with a median and mean of 2 and 10 hours, respectively (Rawles, 1988). Factors influencing the patients’ delay are age, education level and race. Older patients wait longer before calling for help, and blacks wait longer than whites. Educated people are less likely to use the emergency system for symptoms of chest pain (Schaeffer, 1989; Weaver, 1991; Kelly, 1991). Reasons for delay by the patient are, among others, the idea that the pain will subside, insufficient severity and doubt about the cardiac origin of the pain (Ho, 1988). In addition, variations in sensitivity to body sensations and emotions appear to play an important role in treatment seeking behavior (Kenyon, 1991).

2.2. Delay by the doctor and emergency crew

Doctor’s delay, both inside and outside the hospital, depends on the patients’ age, the duration of chest complaints and the site where the call came from. The median and mean value of the delay time in the settings of a) CCU, b) general ward, and c) home amount to 10 to 16 minutes, 15 to 20 minutes, and 20 to 35 minutes, respectively. It had been suggested that elements of the doctor’s behavior may be at a subconscious or instinctive level. The urgency of response is likely to depend on the perceived anxiety content of the message (Rawles, 1988).

Ambulance response times are short, for instance an average of 12 minutes in Cardiff (Wales, UK) and 7 minutes in Nottingham (UK) (McCabe, 1991; Rowley, 1992). In The
Netherlands these figures are comparable. This might be expected, because, according to the Dutch law, an ambulance must be present within 15 minutes after dispatch (Bouten, 1992). There is a striking difference in delay of hospital admission between patients who choose to call a general practitioner compared to those who choose to call an emergency ambulance. If a general practitioner referred the patient to the hospital, median delay was 247 minutes, compared with 100 minutes when the patient called an ambulance directly (Rowley, 1992). This difference remained unchanged between 1982-84 and 1989-90 (Gray, 1993).

2.3. Delay in transport to hospital

Ambulance transportation time in most industrialized countries is of a short duration. Ambulances have priority in traffic and are well identified. In a medium sized town without regular traffic jams, a major gain in time in this link of the chain is not likely. In rural areas, as well as in a metropole, the situation may be different, but even then the loss of time due to transport is limited. In the Nottingham registry, the median time from the patient’s call for the ambulance to its hospital arrival was 29 minutes (Rowley, 1992).

2.4. Delay in the emergency room and/or CCU

In a University hospital participating in the TIMI trial, patients waited for an average (±SD) of 20±18 minutes before the initial ECG was made following their arrival in the emergency department. After confirmation of MI, an additional 70±40 minutes elapsed before commencement of thrombolytic therapy (Sharkey, 1989). This shows that even inside the hospital valuable time is lost before thrombolysis is started.

3. Strategies to reduce the time from onset of symptoms to treatment

3.1. Prehospital and in-hospital delay

Reports on the effect of media campaigns showed that the delay time by the patient before presentation in an emergency room of a city hospital can be reduced, although at the cost of a temporary increase in the number of patients with non-cardiac chest pain (Herlitz, 1989; Blohm, 1992). An effort in a rural community was, however, less successful (Moses, 1991a). Short prehospital delay results in increased eligibility and likelihood of receiving thrombolytic therapy (Goldberg, 1992). In an attempt to shorten transport time to hospital, some investigators even used a helicopter to transfer patients with suspected MI. Only in extraordinary situations time might be saved using this approach (Bellinger, 1988).

It has been attempted to shorten the first phase of delay in the hospital by prehospital 12-lead ECG recording and subsequent telephone transmittance to the emergency department (Grim, 1987; Karagounis, 1990). This approach has not been generally adopted. Efficiency measures and initiation of thrombolytic therapy in the emergency room, instead of the CCU, could lead to a substantial decrease of the delay from 70 to 34 minutes in patients with MI (Verheugt, 1989; MacCallum, 1990; Moses, 1991b). This was called the "fast-track" admission strategy (Pell, 1992). Recently, the potential to save time in the
emergency room was confirmed by the observation that the median time between arrival at hospital to start of thrombolytic therapy, the so called "door-to-needle-time", was 31 minutes for patients who received thrombolytic therapy in the emergency room versus 80 minutes for those who were treated in the CCU (Birkhead, 1992).

Finally, strategies can be designed to accelerate the diagnosis of MI in patients with an atypical history and/or a non-diagnostic ECG. In these situations enzymatic proof by assessment of creatine kinase isoforms or troponin can sometimes be helpful to establish the diagnosis of MI quickly (Jaffe, 1986; Abendschein, 1988, Katus 1989, 1991; Adams, 1993). In addition, the plasma-myoglobin concentration may also be valuable in the establishment of MI. As early as 1 hour after MI, serum concentrations exceeding the normal range have been found. Its peak activity is after 4-12 hours (Stone, 1983). By using a quick myoglobin latex-agglutination test during the first 4-12 hours after onset of symptoms, it was possible to rule out MI within a few minutes (Endert, 1987; Mair 1991, 1992). Early enzymatic confirmation of MI will eventually lead to reduction in time before thrombolytic therapy is administered.

3.2. Prehospital thrombolysis

Already at an early stage, investigators have tried to initiate thrombolysis in the prehospital setting (Koren, 1985). In a small sample size they showed that patients with MI who were treated at home showed a better ventricular performance compared to those who were treated inside the hospital. Subsequent reports on prehospital thrombolysis came from a) the European myocardial infarction project (EMIP), b) the Grampian region early anistreplase trial investigators (GREAT), c) the reperfusion in acute infarction Rotterdam trial (REPAIR), and d) the myocardial infarction triage and intervention study (MITI).

Patients participating in the EMIP trial who were randomly assigned to the prehospital treatment received anistreplase from a physician a median of 55 minutes earlier than those who were treated after arrival in the hospital. This was associated with a nonsignificant 13% reduction in overall mortality at 30 days. However, death from cardiac causes was significantly less in the prehospital treated patients compared to the in-hospital treated patients (8.3 vs 9.8%; reduction in risk 16%; p=0.049) (The European Myocardial Infarction Project Group, 1993). In GREAT, patients with suspected MI living in country towns and villages in Great Britain, received in a randomized design prehospital or in-hospital anistreplase therapy from the general practitioner. The median time anistreplase was administered at home was 101 minutes after the onset of symptoms, whereas hospital administration occurred with a median delay of 240 minutes. Three months mortality rate from all causes of death was 8.0% and 15.5% for early and late receivers of anistreplase, respectively (p=0.04) (GREAT Group, 1992). The 1-year mortality from all causes in home and hospital treated patients was 10.4 and 21.6%, respectively (Rawles, 1993). In the REPAIR trial 9052 patients were screened by the staff of the ambulance which did not include a doctor. Eligible patients underwent on-site ECG recording whereafter, on the basis of the abnormalities, a computer-program suggested a treatment strategy (Kudenchuk, 1991). Only 226 patients (2.5%) were treated with rt-PA. Prehospital treated patients saved 47 minutes compared with in-hospital treatment (Bouten, 1992). The MITI investigators reported a 33 minutes decrease in the interval between symptom onset to
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In the clinical phase, there were no significant differences in mortality, ejection fraction or infarct size. A secondary analysis of time to treatment and outcome showed that therapy initiated within 70 minutes of onset of symptoms was associated with significantly lower mortality (1.2% vs 8.7%), smaller infarct size (4.9% vs 11.2%) and higher ejection fraction (53% vs 49%) than treatment initiated after a longer period (Weaver, 1993a).

Based on the documented delay in each link of the chain from onset of chest pain to CCU admission, we designed the Groninger ambulance study. Our study was comparable to the GREAT trial with the addition of remote ECG confirmation of threatening MI. We also used anistreplase in preference to SK because this could be administered i.v. in 5 minutes and therefore was considered convenient for domiciliary use.

Our study was discontinued after screening of 350 patients and inclusion of 7 patients (2%). As discussed in appendix 1, we were disappointed with the time consuming procedure and the logistical problems associated with remote ECG assessment. Due to these problems we did not gain but even lost time in the enrollment of patients. A silicon-rubber mat with electrodes mounted upon the patient’s chest, and a computer suggesting the treatment strategy, as was performed in the REPAIR study, is probably quicker (Bouten, 1992). Furthermore, we were discouraged by the low inclusion rate. This, however, was also low in the REPAIR and MITI trial, 226/9052 (2.5%) and 360/8863 (4%), respectively (Bouten, 1992; Weaver, 1993a). Some characteristics and results of the aforementioned studies are summarized in Table 1.

4. Strategies to accelerate reperfusion by different dosage schemes and new agents

Different dosage schemes and new thrombolytic agents may reduce time between initiation of thrombolytic treatment and time to reperfusion, thereby enhancing its ultimate success. Whereas in the early days of thrombolytic treatment the duration of infusion was very long, currently short term strategies are under investigation. It became evident in several studies that the efficacy of 100 mg rt-PA, infused in 90 minutes, rather than in 3 hours, was superior compared to the standard regimen. Ninety-minutes patency rates as high as 85% have been reported (Neuhaus, 1989; Neuhaus, 1992; Carney, 1992; Wall, 1992; GUSTO Angiographic Investigators, 1993). This modified rt-PA regimen was called "front-loaded" because of an initial bolus of 15 mg instead of the earlier practiced 10 mg. In contrast, rapid infusion of SK has been associated with hypotension (Lew, 1985a), or a less beneficial outcome compared to rt-PA administration (Taylor, 1993). Thus, optimal dosing of rt-PA may lead to a more rapid restoration of flow which eventually results in a reduction of mortality and morbidity. This appears not to be applicable to treatment with SK.

Another way to enhance early reperfusion is the use of newer thrombolytic agents such as pro-urokinase or staphylokinase. Pro-urokinase or recombinant single chain urokinase-type plasminogen activator (rscu-PA or saruplase), is a fibrin dependent thrombolytic agent (Gurewich, 1984; Pannell, 1986) whose use was associated with earlier reperfusion, a higher patency rate, and fewer bleeding than treatment with SK (PRIMI, 1989); the reocclusion rate was only 1.5% (Weaver, 1993b). Staphylokinase, a small protein
Table 1  Characteristics and results of five prehospital studies indicated by their acronym.

<table>
<thead>
<tr>
<th></th>
<th>Patients (screened/enrolled)</th>
<th>Drug (active/reference)</th>
<th>Doctor (on the spot)</th>
<th>ECG (confirmed MI)</th>
<th>Time (gain in seconds)</th>
<th>Mortality reduction (time)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMIP</td>
<td>-/5469</td>
<td>ani/P</td>
<td>yes</td>
<td>yes (S)</td>
<td>55 (M)</td>
<td>no (1 mo)</td>
</tr>
<tr>
<td>GREAT</td>
<td>-/311</td>
<td>ani/P</td>
<td>yes</td>
<td>no</td>
<td>139 (M)</td>
<td>yes (3 mo)</td>
</tr>
<tr>
<td>REPAIR</td>
<td>9052/226</td>
<td>rt-PA/ref</td>
<td>no</td>
<td>yes (S)</td>
<td>47 (m)</td>
<td>NA</td>
</tr>
<tr>
<td>MITI</td>
<td>8863/360</td>
<td>rt-PA/P</td>
<td>no</td>
<td>yes (R)</td>
<td>33 (M)</td>
<td>no (dis)</td>
</tr>
<tr>
<td>GAS</td>
<td>350/7</td>
<td>ani/P</td>
<td>no</td>
<td>yes (R)</td>
<td>-24 (m)</td>
<td>NA</td>
</tr>
</tbody>
</table>

- = unknown; ani = anistreplase; rt-PA = alteplase; P = placebo; ref = historical reference population of 220 patients; M = median, m = mean; S = on the spot; R = remote (hospital), mo = month(s), dis = discharge, NA = not applicable

References: EMIP (The European Myocardial Infarction Project Group, 1993), GREAT (GREAT Group, 1992), REPAIR (Bouten, 1992), MITI (Weaver, 1993a), GAS (Groningen Ambulance Study, appendix 1)
produced by certain strains of staphylococcus aureus, has been known since 1948 to have fibrinolytic properties (Lack, 1948). In contrast to SK, staphylokinase appears to be more efficient in platelet-rich thrombi and less immunogenic and allergenic (Collen, 1993a). Recombinant staphylokinase was recently given to 5 patients with MI of whom 4 showed reperfusion within 40 minutes (Collen, 1993b). These promising results need further confirmation.

5. Conclusions

Factors determining the time between symptoms of coronary occlusion and reperfusion of the occluded vessel have been extensively studied. This has led to a number of strategies all aimed at the reduction of this interval. The main emphasis has been put on prehospital thrombolytic therapy and measurements to increase in-hospital efficiency.

With respect to prehospital thrombolytic therapy problems have emerged related to a) ECG-confirmation of MI, b) the diagnostic and practical skills of the ambulance staff and c) the responsibility issue related to the absence of a physician. Using strict selection criteria only a minority of patients with symptoms of chest pain have been eligible outside the hospital. The reduction of the delay in time will depend on the early establishment of the diagnosis but, as was shown in our study, that was not always easy. Until now, a reduction in mortality as a result of prehospital initiation of treatment was reported in only one study. Therefore, one must remain critical with respect to this approach especially in a situation where rapid transportation to the hospital is possible (Fox, 1990; Wilcox, 1990; Petch, 1991; Gemmill, 1993).

It is well known that valuable time can be lost after the patient’s arrival in the hospital. Therefore, it is essential that in-hospital procedures gain in efficiency in order to start thrombolysis as soon as possible after the diagnosis has been established, preferably in the emergency department. Furthermore, strategies should be introduced to speed up the time necessary for confirmation of MI in patients with a atypical history and/or a non-diagnostic ECG. Further studies may tell us whether newer thrombolytic agents or revised dosing schemes of currently available thrombolytic drugs can accelerate reperfusion, thereby further enhancing success.

Finally, one comment should be made which may seem paradoxical in the context of this chapter. So far, the maximum time limit for onset of symptoms to initiation of thrombolytic therapy in patients with MI has been 6 hours. Recently a study has been published which indicated that patients with symptoms for more than 6 but less than 12 hours may also benefit from thrombolytic treatment (LATE, 1993; Gil, 1993), although this was not confirmed by another study (EMERAS, 1993). Delayed successful thrombolytic therapy may be beneficial due to other mechanisms than by salvaging ischemic myocardium such as a) improved healing of infarcted tissue, b) prevention of ventricular remodeling, c) perfusion of hibernating myocardium and d) increased electrical stability (Shah, 1991; Kim, 1993). Thus, although time is an essential determinant for success of thrombolytic treatment, one should not apply currently used time limits too strictly.