Thrombolysis after acute myocardial infarction: Are Canadian physicians up to the challenge?

Editorial

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Abstract

ACUTE MYOCARDIAL INFARCTION (AMI) evolves as a time-dependent wave front of ischemia when the abrupt rupture of an unstable fatty plaque initiates coronary thrombosis. The prospect of salvaging potentially viable myocardial tissue has led to the development of reperfusion strategies using thrombolytic agents. The efficacy of thrombolytic therapy is determined in large measure by the speed with which it is initiated. It is therefore vital to minimize the "door-to-needle" time once a patient with AMI arrives at the emergency department. In this issue (see pages 497 to 505) Dr. Jafna L. Cox and associates report that Canadian centres participating in the GUSTO-I trial were significantly slower to initiate thrombolytic therapy than their US counterparts. In this editorial Cox and associates' report is reviewed against the background of similar trials, and strategies to minimize delays in the initiation of thrombolytic therapy are suggested.

Résumé

L'INFARCTUS AIGU DU MYOCARDE (IAM) évolue sous forme d'un front d'ondes d'ischémie temporel lorsque la rupture brutale d'une plaque lipidique instable provoque une thrombose coronaire. La possibilité de sauver du tissu du myocarde qui pourrait être viable est à l'origine de la mise au point de stratégies de reperfusion au moyen d'agents thrombolytiques. L'efficacité de la thérapie thrombolytique dépend en grande partie de la rapidité à laquelle elle est mise en oeuvre. C'est pourquoi il est vital de réduire au minimum le temps écoulé entre l'arrivée et l'administration du traitement lorsqu'un patient atteint d'un infarctus aigu du myocarde arrive au service d'urgence. Dans le présent numéro (voir pages 497 à 505), le Dr Jafna L. Cox et ses collaborateurs signalent que les centres canadiens qui ont participé à l'étude GUSTO-I ont pris beaucoup plus de temps à mettre en oeuvre la thérapie thrombolytique que leurs homologues des États-Unis. Dans cet éditorial, on évalue le rapport du Dr Cox et de ses collaborateurs dans le contexte d'études cliniques semblables et l'on suggère des stratégies afin de réduire au minimum les retards dans la mise en oeuvre de la thérapie thrombolytique.

Modern reperfusion techniques using thrombolysis and angioplasty are the practical application of basic pathologic principles articulated 20 years ago by Reimer and Jennings,[1] who demonstrated the "wavefront phenomenon" of ischemic cell death in acute myocardial infarction (AMI). After the occlusion of a coronary artery, necrosis begins in the subendocardium and moves outward through ischemic but still viable myocardium. The volume of viable tissue is large soon after the cessation of blood flow but diminishes rapidly as the necrosis expands toward the subepicardium. Although the injury is reversible in the first 15 to 20 minutes of ischemia, over the next 3 to 6 hours the wave front of permanent injury expands outward. At its leading edge are injured myocytes that could be rescued by the timely restitution of blood flow. The cell-saving restoration of blood flow is a realistic objective, given the battery of thrombolytic and antithrombotic agents, adjuvant drugs, angioplasty balloons and intracoronary stents that can be summoned to the purpose. We should remember that the prompt administration of acetylsalicylic acid (ASA) is the most expedient way to initiate this process.

Danger of delayed reperfusion

The study reported in this issue by Dr. Jafna L. Cox and associates for the Canadian GUSTO Investigators (see pages 497 to 505) extends their previous experience[2] and reaffirms the extreme importance of early treatment with thrombolytic agents after AMI. Lost time is wasted myocardium. The legacy of delayed reperfusion is impaired ventricular function, more heart failure and reduced survival. It is only a slight exaggeration to paraphrase Vince Lombardi's aphorism on winning: "Early reperfusion isn't everything, it's the *only* thing."

Cox and associates report that Canadian centres participating in GUSTO-I were significantly slower than their US counterparts to initiate thrombolytic therapy for patients with AMI: the median "door-to-needle" time in Canadian and US hospitals was 85 and 66 minutes respectively. Unless Canadian physicians have discovered a way to confound the pathophysiology of myocardial infarction, this tardiness condemns our patients to higher rates of morbidity and death.

Cox and associates' findings are consistent with those of most researchers with respect to a direct correlation between delay to therapy and reduced survival.[1–4] In the GUSTO-I trial[2] the modest advantage of accelerated tissue plasminogen activator (tPA) therapy over streptokinase therapy was of a lesser magnitude than the effect of time to treatment. Among patients who received tPA therapy within 2 hours after the onset of symptoms, 4.3% died; among those who received tPA more than 6 hours after symptom onset, 10.4% died.[2] As a general rule, the earlier the treatment is started and the higher the risk of death, the greater the benefit of thrombolytic therapy.[1–4]

Sources of delay

How do we account for the extra 20 minutes taken to initiate therapy in Canadian centres compared with their US counterparts? Although other studies have addressed the problem of treatment delay,[5,6] the data presented by Cox and associates do not allow us to identify contributing factors. We can only speculate about such factors. How many patients were treated in community as opposed to academic hospitals? Was thrombolytic therapy started in the emergency room or in a coronary care unit? Was therapy initiated by primary care physicians or by specialists? To what extent did the consent process and enrolment in the trial contribute to delays? Cox and associates do report, however, that concern about the risks of therapy may have accounted for delays in certain groups such as older women and patients with hypertension or tachycardia.

Because patients who presented more than 6 hours after the onset of symptoms were excluded from the GUSTO-I trial, no information is available about the outer time limit of effective treatment. However, a number of factors may affect the window of opportunity for reperfusion therapy. The residual flow of blood through collateral arteries can extend myocardial viability to days or weeks in some patients.[7] Certain clinical signs — persistent "stuttering" chest pain and evolving electrocardiographic changes with ST segment elevation — suggest the persistence of salvageable myocardium. Delayed reperfusion may be useful in such cases.

Although thrombolytic therapy achieves the best results when initiated within 4 hours after the onset of pain, the ISIS-2 investigators[4] reported a smaller but sustained benefit for patients treated within 5 to 24 hours. The odds reduction for death from vascular causes was 53% among patients who received streptokinase and ASA up to 5 hours after pain onset and 33% among those who received these agents 5 to 24 hours after pain onset.

The GISSI investigators[3] obtained poor results for thrombolytic treatment initiated 6 hours or more after symptom onset. No significant difference in mortality rates was found between patients who received streptokinase and those who received placebo between 6 and 12 hours after symptom onset. Late thrombolytic therapy was examined more closely by the LATE Study Group[8] in a trial involving 5711 patients who received either alteplase or placebo between 6 and 24 hours after symptom onset. A trend to better 35-day survival was found among patients treated with alteplase within 24 hours, and for those treated within 12 hours the 35-day mortality showed a relative reduction of 25.6%. The LATE investigators concluded that the outer limit for initiating treatment with alteplase should be extended to at least 12 hours.

Strategies to minimize delay

Cox and associates' findings affirm the fundamental importance of early thrombolytic therapy to reduce morbidity and death after AMI. With a median door-to-needle time of 85 minutes, Canadian centres have been less efficient than they should be. We must develop a greater sense of urgency if we are to reduce the door-to-needle time to less than 30 minutes, as recommended by the Emergency Cardiac Care Coalition in 1996.[9]

Canadian hospitals can help to reduce delays in the initiation of therapy by adopting the following strategies.

- Recognize AMI as a medical emergency.
- Perform and interpret electrocardiography in the emergency department. Have a machine handy; do not wait for the technician.
- Have practical guidelines in place for the use of thrombolytic agents.

- Educate staff to ensure a coordinated and prompt response to patients with chest pain.
- Keep thrombolytic agents on site and initiate therapy at the point of first contact. Do not cause further delay by transferring the patient to a coronary care unit.
- Avoid having to call a consultant or specialist before starting treatment. The authority to initiate treatment should reside with the primary care physician in the emergency department.
- Periodically audit door-to-needle times and rectify sources of delay.

Summary

An AMI is a medical emergency no less urgent than serious traumatic injury. A delay in reperfusion treatment condemns potentially viable myocardial tissue to death, and an uncertain fate lurks for the owner of that damaged heart. Wonderful tools are at our disposal to restore coronary blood flow quickly. We no longer have to passively contemplate the inexorable advance of the wave front of necrosis so elegantly described by Reimer and Jennings 2 decades ago.

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