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State-of-the-Art Paper

Total Ischemic Time

The Correct Focus of Attention for Optimal ST-Segment Elevation Myocardial Infarction Care

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Currently accepted standards for gauging quality of care in the treatment of ST-segment elevation myocardial infarction (STEMI) mainly focus on shortening the time to treatment after the patient arrives at the hospital. But this narrow focus fails to consider the substantial duration of myocardial ischemia that exists prior to hospital arrival, and the large number of deaths that occur during the prehospital period. The time from symptom onset until reperfusion occurs is one estimate of total ischemic time. Several experimental studies and now human clinical studies have confirmed that infarct size and mortality are strongly correlated with the total ischemic time, and much less so with its subintervals like door-to-balloon time. This review will discuss the importance of total ischemic time in STEMI. (J Am Coll Cardiol Intv 2011;4:599–604) © 2011 by the American College of Cardiology Foundation

Myocardial infarction is the leading cause of mortality in the United States and the developed world (1). The current benchmarks for the treatment of ST-segment elevation myocardial infarction (STEMI) mainly focus on shortening the time to treatment after the patient has arrived at the hospital. This focus fails to consider the large number of deaths with STEMI that occur before patients even reach the hospital. There is substantial evidence regarding the benefits of early reperfusion and the detrimental effects of late reperfusion in patients with STEMI (2–5). The information regarding the need for early intervention for STEMI is not new and has been discussed at length for decades.

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Animal Data

In 1977, Reimer et al. (6) described the wave front phenomenon of myocardial infarction propagation. In their experiments with circumflex artery ligation in dogs, the area of necrosis was compared with the area at risk when the artery was occluded for 40 min, 3 h, and 6 h. At 40 min of occlusion, 45% of the myocardium at risk was irreversibly injured, but fully 55% of the myocardium at risk was salvageable. However, by 3 h of occlusion, the salvageable area was down to 33%, and by 6 h, only 16% remained salvageable (Fig. 1). Clearly, any benefit of reperfusion is time-dependent from the first moment of occlusion.

Mortality With Fibrinolysis

Clinical observations in STEMI patients receiving fibrinolytic therapy also support the above-mentioned critical importance of early reperfusion (7,8). The European Myocardial Infarction Project Group (9) found that there were 15 more

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lives saved at 30 days per 1,000 patients treated because of 1-h earlier treatment. In the analysis of Boersma et al. (10), which included over 50,000 patients from 22 randomized trials, the greatest impact of fibrinolysis was seen when it was administered within the first 2 h of symptom onset. In patients presenting within just 1 h of symptom onset, there were 65 fewer deaths per 1,000 patients treated when compared with patients with longer duration of symptoms. Both animal and clinical data support the notion that shortening the duration of infarct artery occlusions can lead to smaller infarct sizes and lower mortality. However, this relationship is not linear and most of the benefit of reperfusion is seen within the first 2 h of occlusion (Fig. 1). Boersma et al.'s analysis (10) in humans almost exactly replicates the findings of Reimer et al. (6) in experimental animals. These data regarding the relation between time delay to reperfusion and mortality appear to be extremely solid.

Abbreviations and Acronyms

CI = confidence interval

FAST-PCI = fibrinolytic acceleration of ST-segment elevated myocardial infarction treatment coupled with urgent culprit artery revascularization

MSI = myocardial salvage index

MVO = microvascular obstruction

OR = odds ratio

PCI = percutaneous coronary intervention

PHF = pre-hospital fibrinolysis

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

Mortality With Primary Percutaneous Coronary Intervention

The relationship between delayed treatment of STEMI and worsened outcomes is not limited only to the patients treated with fibrinolysis (3–5,11). In almost 1,800 patients treated with primary angioplasty, De Luca et al. (4) described the relationship between ischemic time and 1-year mortality. In their study, for every 30-min delay before reperfusion, the relative mortality risk increased by 7.5%. Cannon et al. (12), in a 27,000 patient cohort, suggested that the door-to-balloon time was associated with mortality more than the symptom-onset-to-balloon time. However, it must be recognized that almost one-half of the patients in this study had very long door-to-balloon times of >2 h, which would correspond to prolonged symptom-onset-to-balloon times of 3 to 4 h. The median door-to-balloon time was 1 h 56 min (symptom-onset-to-balloon time ~3 to 4 h) and the mortality 6.1% fits nicely on the curve from De Luca et al. (5). It should also be noted that, in observational studies, patients who died before reaching the hospital would not be included in analyses of STEMI intervention outcomes and, thereby, would introduce a survivor bias in studies that were based on patients evaluated only after hospital arrival (13).

Magnetic Resonance Imaging Data for STEMI and Early Reperfusion

Similar to the observations of Reimer et al. (6) and other experimental investigations, Tarantini et al. (14) were able to demonstrate that there was a direct and continuous relationship between ischemic time, transmural necrosis, and severe microvascular obstruction (MVO), as assessed by contrast-enhanced magnetic resonance. In their study of 77 patients with STEMI, for each 30 min of treatment delay, there was a 37% increase in the risk of transmural necrosis and a 21% increase in the risk for severe MVO. One other important finding in this study was that if they were able to demonstrate the presence of normal blood flow in the infarct-related artery at the time of percutaneous coronary intervention (PCI), this was associated with lower rates of transmural necrosis and severe MVO, suggesting that re-establishing some coronary flow before reaching the cardiac catheterization laboratory could be beneficial. These results, in part, also can explain why the CAPTIM (Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction) study patients who presented within the first 2 h of symptom onset benefited from pre-hospital fibrinolysis when compared to a transfer-only strategy for primary PCI (15).

Using magnetic resonance imaging, Francone et al. (16) reported the impact of PCI delay on myocardial salvage and infarct size in 70 STEMI patients. They separated the patients into 4 groups by quartiles of time from symptom onset to PCI: ≤90 min, >90 to 150 min, >150 to 360 min, and >360 min. The mean time in the ≤90-min group was 1.0 ± 0.1 h. The myocardial salvage percentage was highest in the ≤90-min group and declined sharply for the other groups. This was also true for the extent of MVO. Severe MVO was detected in 6 of 19 patients treated within 90 min of symptoms, but in 14 of 17 patients treated after 6 h of symptoms. There were also increases in left ventricular end-diastolic volume and end-systolic volume in the later reperfused groups.

Eitel et al. (17) analyzed 208 patients who underwent PCI for STEMI and calculated a myocardial salvage index (MSI) described as (area of zone at risk − area of infarct zone)/(area of zone at risk). The median salvage index in their study was 48. At 6-month follow-up both the mortality and the cumulative event rates were significantly lower in patients who had a salvage index higher than the median MSI of 48. The MSI was highest within the first 2 h of symptoms. There was a significant inverse correlation of MSI and duration of symptoms before treatment ($r = -0.330$, $p < 0.001$) (Fig. 1). In this study, the strongest predictors of myocardial salvage were complete resolution of ST-segment elevation (beta = 0.31, $p < 0.001$), time from symptom onset to reperfusion (beta = −0.23, $p = 0.002$), anterior myocardial infarction (beta = 0.22, $p = 0.004$), and

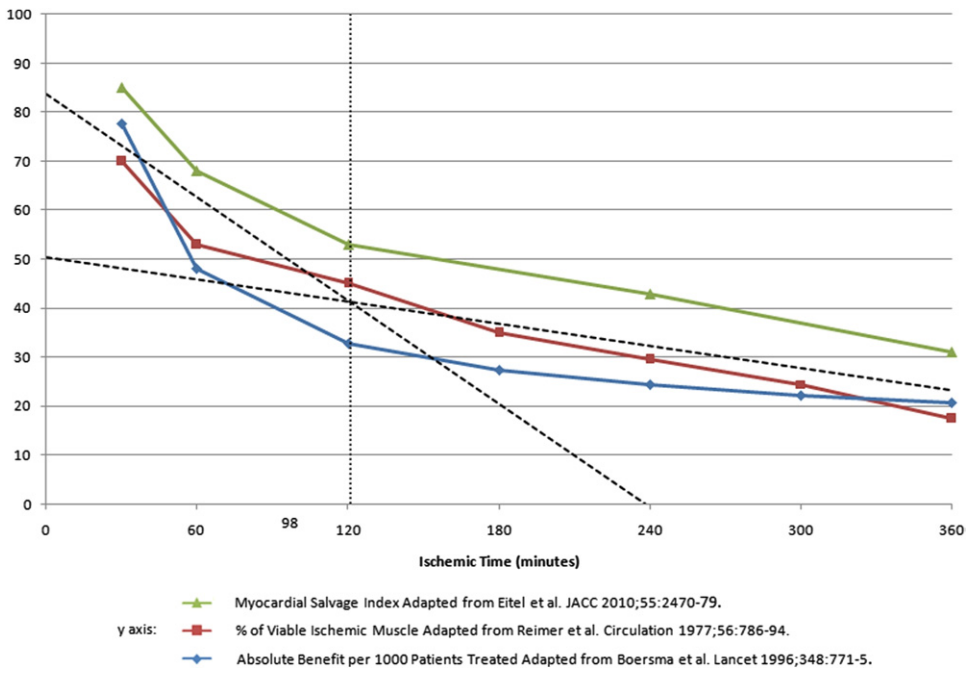

Figure 1. Effects of Total Ischemic Time on Infarct Size and Clinical Outcomes

The experimental animal data, human magnetic resonance imaging data, and human lives saved data all fall on essentially the same lines. The dotted lines are linear fits to the group of data points in the first 2 h and a separate fit to the data points beyond 2 h. The intersection at about 120 min of ischemic time defines a cutpoint for optimal outcomes. Figure produced by Ashley Gunter and Jimmy Yee.

TIMI (Thrombolysis In Myocardial Infarction) flow grade before PCI ≥2 (beta = 0.16, p = 0.03). At 6 months, there were 10 cardiac deaths in the group with salvage index below the median, and only 1 death in the group with salvage index above the median (mortality 9.6% vs. 1%, p = 0.003). The major adverse cardiac events rate at 6 months was also significantly higher in the MSI < median group (22.1% vs. 2.9%, p < 0.001). By contrast, door-to-balloon time was not a predictor of myocardial salvage in this study. Ejection fraction and MVO were also not predictive of 6-month major adverse cardiac events. Thus, the salvage index was the strongest indicator of major adverse cardiac events and the time from symptom onset to reperfusion was one of the strongest predictors of MSI in this study. To put studies for STEMI outcomes into perspective, one should take into account that the patients who have survived the first 3 h of myocardial infarction would have already had >60% transmural infarction, a 40% chance of having severe MVO, and would have survived the highest risk portion of the infarction timeline (14).

Shortening the Time to Treatment From Symptom Onset

Several important time intervals need to be considered in the treatment of STEMI patients. The first interval is the time from arterial occlusion to symptoms. There is a certain period that elapses between the occlusion of the infarct-related artery and the development of chest pain or similar symptoms of myocardial infarction (18).

The second interval is the time from the onset of symptoms to the 911 call. This period depends on the ability of the patient to realize the seriousness of the problem and his/her level of awareness. Certainly, we need to increase the public awareness for the early recognition of the signs and symptoms of STEMI. We will also need to discourage the use of personal or family means of transportation to the emergency department instead of the emergency medical services.

The third interval is the time from the 911 call to the arrival of medical help. The ultimate duration of this interval involves the performance of emergency medical services systems and STEMI systems of care as described by Ting et al. (19), Nallamothu et al. (20), and Henry et al. (21). Currently, even in the best centers using standard order sets, a single phone call system, and a central communication system for rapid transfers and bypassing emergency department evaluation, the in-hospital mortality of patients with STEMI treated with a primary PCI strategy is 5.7% to 6.6% and the 30-day mortality is around 7% (22). By contrast, we and others have shown that pre-hospital

fibrinolysis in STEMI patients followed immediately by urgent culprit artery revascularization can decrease both in-hospital and 30-day mortality and major adverse cardiac events (23–26). In the series of Danchin et al. (25) in France, the median time from symptom onset to hospital admission was 3.6 h for pre-hospital fibrinolysis (PHF), 3.5 h for in-hospital fibrinolysis, 3.2 h for primary percutaneous interventions, and 12 h for no reperfusion therapy. In-hospital mortality was 3.3% for PHF, 8.0% for in-hospital fibrinolysis, and 6.7% for primary percutaneous interventions. One-year survival was 94%, 89%, and 89%, respectively. In a multivariate analysis of predictors of 1-year survival, PHF was associated with a 0.49 relative risk of death (95% confidence interval [CI]: 0.24 to 1.00; $p = 0.05$). In patients with PHF admitted in ≤3.5 h, in-hospital mortality was 0% and 1-year survival was 99% (25). In the FAST-MI (French Registry of Acute ST-Segment Elevation or Non–ST-Segment Elevation Myocardial Infarction) study from France in which 18% of the patients had pre-hospital fibrinolysis, the mortality of patients who had fibrinolysis followed by immediate PCI was 3.9% (27).

In our area, using the STEMI systems of care and the implementation of a strategy of fibrinolytic acceleration of ST-segment elevated myocardial infarction treatment coupled with urgent culprit artery revascularization (FAST-PCI), we were able to decrease mortality by almost one-half without paying a penalty in terms of increased bleeding (23). Our results almost exactly overlap with those of Danchin et al. (25). Mortality was 3.8% with our FAST-PCI compared with 6.4% in primary PCI patients. The 30-day relative mortality risk reduction with FAST-PCI was 0.542 ($p = 0.0151$). The beneficial effect of pre-hospital fibrinolysis is particularly pronounced when it can be initiated within 2 h of symptoms as shown by Bonnefoy et al. (15). In their study, patients randomized to pre-hospital fibrinolysis within 2 h of symptoms had a 30-day mortality of 2.2% when compared with 5.7% with primary PCI. Cardiogenic shock was also less frequent with fibrinolysis than with primary PCI in this group of patients.

The randomized trials with pre-PCI fibrinolysis to date have not been properly designed to detect any reduction in total ischemic time. In the FINESSE (Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events) trial, the median time to balloon was 2.2 h in all patients and the symptom onset to first bolus of reteplase was 165 min. Only 60% of the FINESSE patients were treated within 3 h from the symptom onset and of those who were treated within 3 h, there was a trend toward more clinical benefit with reteplase and abciximab combination treatment (28). None of the patients had pre-hospital fibrinolytic administration. The FINESSE study showed that the in-hospital administration of full-dose reteplase with abciximab bolus before urgent PCI in non–low-risk patients with STEMI did not have an additional benefit over primary PCI. When the trial data were reanalyzed, the high-risk patients (TIMI flow grade risk score ≥3), presenting to a spoke hospital with symptom onset to balloon time <4 h fared better with combination-facilitated PCI (hazard ratio: 0.45, $p = 0.009$) (29).

Another large trial for pre-PCI fibrinolysis was the ASSENT-4 (Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction) trial, which has been criticized for: 1) not administering early antiplatelet therapy; 2) the use of glycoprotein IIb/IIIa inhibitors was not permitted in the facilitated-PCI group, except for bailout situations; and 3) the use of clopidogrel was limited to the stented patients at the time of cardiac catheterization (30). Although the overall results were negative for facilitated PCI with full-dose fibrinolysis in the ASSENT-4 study, patients in that trial who received fibrinolysis early in the ambulance had better outcomes (30). When the data from this trial was reanalyzed and the patients were restratified according to the time to treatment and by enrollment site, patients in the pre-hospital facilitated group had the shortest delay in treatment and lowest mortality (31). In the MITI II (Myocardial Infarction Triage and Intervention Project) trial, the patients treated "very early" (within 70 min of symptom onset) with pre-hospital fibrinolysis had lower mortality (1.2% vs. 8.7%) and smaller infarct size (32). In a meta-analysis of pre-hospital fibrinolysis, it was shown that the time to reperfusion treatment was almost an hour shorter with pre-hospital administration when compared with the patients with in-hospital treatment, and all-cause mortality was significantly reduced (33).

Four other recent trials have proved the safety and effectiveness of fibrinolytics followed by urgent PCI. GRACIA 1 (Randomized Trial Comparing Stenting Within 24 Hours of Thrombolysis Versus Ischemia-Guided Approach to Thrombolysed Acute Myocardial Infarction With ST Elevation) compared the outcomes with early post-fibrinolysis cardiac catheterization to a conservative, ischemia-driven catheterization strategy (34). At 1 year, patients in the early invasive group had fewer primary endpoint events (9% vs. 21%, $p = 0.0008$) and a reduced rate of death or reinfarction (7% vs. 12%, $p = 0.07$). There were no differences in major bleeding or vascular complications.

In TRANSFER-AMI (Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction), all STEMI patients received fibrinolytic therapy and were randomized to either standard treatment or to immediate transfer for PCI within 6 h. Catheterization was performed in 88% of standard treatment patients at a median of 32.5 h after randomization, and in 98.5% of the routine early PCI patients at a median of 2.8 h after randomization. At 30 days, the primary endpoint was less frequent in early PCI patients (11.0% vs. 17.2%, $p = 0.004$). Very importantly, there were no differences between the groups in the incidence of major

bleeding (35). The CARRESS in AMI (Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction) trial (36) used half-dose reteplase and abciximab. Patients were either immediately transferred for PCI or it was performed only as clinically indicated for rescue. The primary outcome was reduced in the immediate-PCI group (4.4% vs. 10.7, p = 0.004). This trial suggested that in a selected group of patients the combined use of half-dose reteplase and abciximab followed by transfer for urgent PCI could be safe and effective. In the NORDISTEMI (Norwegian Study on District Treatment of ST-Elevation Myocardial Infarction) trial (37), the median transfer distance was 158 km, and the median transfer time was 130 min. The composite of death, reinfarction, or stroke at 12 months was significantly reduced in the early invasive fibrinolysis + transfer group compared with the conservative group (6% vs. 16%, p = 0.01). There were no significant differences in the bleeding rates. Borgia et al.'s recent meta-analysis (34), which included the above-mentioned trials, showed that the routine early coronary intervention after fibrinolysis was associated with a decrease in the combined endpoint of death or reinfarction (odds ratio [OR]: 0.65, 95% CI: 0.49 to 0.88; p = 0.004) and a decrease in the recurrent ischemia (OR: 0.25, 95% CI: 0.13 to 0.49; p < 0.001). This was achieved without an increase in major bleeding and/or the benefits were maintained at 6 to 12 months of follow-up. This study is interesting because the benefit is seen in these post-lytic PCI patients even though the lytic therapy to PCI time was between 80 and 1,000 min. As a result, we agree with Drs. Henry and Larson that the paradise is not lost, but rather renamed or redefined (38).

Conclusions

STEMI patients with long ischemic times have very little myocardium left for salvage. Their mortalities are the highest regardless of the method of reperfusion. Trials that compared different reperfusion strategies that have similar ischemic times (generally long) have failed to show any difference in mortality. As illustrated by Figure 1, experimental animal infarct size, number of lives saved clinically, and human cardiac magnetic resonance imaging infarct size data all fall on the same curve with respect to ischemic time. Quite clearly, ischemic times <120 min provide the most benefit. Even in Denmark, with short transfer distances, there was a significant system delay in the treatment of STEMI patients (39). The patients that were transported directly to the PCI center had a median delay in treatment of 172 min and the patients that were transferred from a local hospital had a median system delay of 240 min. One-half of the patients had a system delay >120 min (28% of the direct transports and 65% of the transferred) (39). To achieve the goal of total ischemic time <120 min will likely require pre-hospital diagnosis and initiation of reperfusion immediately at the scene by trained emergency medical services providers acting under protocol, coupled with urgent infarct artery PCI after the patient is transported.

There still has been no randomized trial in the United States using pre-hospital fibrinolysis and urgent culprit artery revascularization, compared with primary PCI, to shorten the total ischemic time. We have placed our faith on the primary PCI route only, attempting to reduce door-to-balloon times, and ignoring, for the most part, the pre-hospital phase of myocardial infarction. The time has come for us not to ignore the findings of Reimer et al. (6), Francone et al. (16), Eitel et al. (17), and many others, and to focus on the total ischemic time rather than focusing on just one of its components. The goal should be to get rid of all the unnecessary steps in the care of STEMI patients and develop the systems of care with the focus of decreasing the total ischemic time. Therefore, we suggest a randomized trial designed to cut down the total ischemic time to <120 min, using pre-hospital electrocardiogram followed by activation of the cardiac catheterization laboratory by the emergency department physician confirming STEMI on the received electrocardiogram. Reduced-dose fibrinolytic therapy would be initiated in the ambulance, coupled with urgent transfer to a primary PCI center for immediate PCI.

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