Time Delays to Reperfusion: a Health Care Issue

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Primary angioplasty (PTCA) is the best reperfusion strategy for ST-segment elevation myocardial infarction (STEMI); however, in the real world, implementing it in due time and proper form involves a minority of candidates to reperfusion.

In their work, published in this issue of the Revista, García Escudero, et al. (1) analyze the time delays in performing both direct and rescue PTCA in STEMI and the different intervals to reperfusion, and its probable causes. The main merit of this work is to show evidence from the real world in our community, and to compare it with the evidence reported in other experiences.

IMPORTANCE OF TIME TO REPERFUSION

When analyzing the evidence from randomized studies, Gersh and Anderson (2) presented a curve that relates time to reperfusion to reduction in mortality and extent of myocardial salvage (Figure 1). The figure shows that the first 2 hours are critical. Then there is an abrupt descent of the survival curve that normalizes in a plateau, 4 hours after AMI onset. It is interesting to observe that during the first 2 hours of evolution, 80% of the compromised myocardium is viable, and only 2 hours later, 20% of the myocardium can be salvaged. Therefore, the first hours are critical for a prompt reperfusion strategy that allows to recover most part of the myocardium at risk. In this context, delays in administering the best strategy available—instead of possible—at time zero may be harmful. By contrast, in late infarction (> 4 hours), time is not so important; in this case, the optimal revascularization strategy (PTCA) that allows to recover most of the little viable muscle that remains will be the one preferred.

However, in a review of 22 randomized studies on PTCA versus thrombolysis (TL) in about 7,000 STEMI patients, Boersma et al. (3) reported that PTCA was superior in all the intervals analyzed, both in very early and late infarctions, and therefore, time seemed less relevant in cases of direct PTCA. However, when reviewing the outcomes of this analysis in detail, we found out that while PTCA was superior to TL in all the intervals, the highest mortality reduction occurred in early-treated infarctions. In this regard, when analyzing the PTCA delay (door-to-balloon time minus door-to-needle time), the authors noticed that the PTCA benefit was maximum in those centers with no more than 35 minutes delay. Therefore, while PTCA is superior to TL regardless of the time passed, the sooner it is performed the higher the benefit is, since delays—especially in very early myocardial infarctions—may neutralize a great deal of its benefit.

In this regard, and (4) based on the data of almost 30,000 myocardial infarctions provided by the United States National Registry of Myocardial Infarction, McNamara et al. proved that, out of 1,000 treated patients, 6.3 died for each 15 minute delay, beginning 90 minutes of door-balloon time up to 150 minutes. This reinforces the importance of immediate myocardial reperfusion with any procedure used.

Two trials with slightly different outcomes—but, in my opinion, with substantial similarities—show evidence in line with what precedes. In the CAPTIM trial, (5) a strong trend was observed toward lower mortality with pre-hospital TL, compared with direct PTCA in myocardial infarction with < 2 hours after the events.

Fig. 1. Relationship between time-line from symptoms onset in myocardial infarction to reperfusion, mortality reduction, and amount of myocardial salvage. [Modified from Gersh. (2)]
symptom onset, whereas mortality was similar in later myocardial infarction. At the same time, in PRAGUE-2 Study, (6) mortality after a month was significantly lower with direct PCTA than with in-hospital TL in myocardial infarctions with > 3 hours after symptoms onset, whereas mortality was similar in early myocardial infarction.

These trials aim at obtaining greater benefits in very early myocardial infarction with faster reperfusion, whereas in cases of later infarctions, the best results will be obtained with the optimal reperfusion strategy.

WHAT HAPPENS IN THE REAL WORLD?

Nallamothu et al. (7) analyzed transport time for primary PCTA in 4,278 myocardial infarction patients in the National Registry of Myocardial Infarction, comparing them with those in the randomized trials: the total door-to-balloon time was 180 minutes (twice the accepted time of 90 minutes), whereas it was 74 minutes in randomized trials. Thus, less than 5% of myocardial infarction patients were treated within a door-to-balloon time < 90 minutes. This shows there are difficulties in the real world when the time of acting immediately comes, according to recommendations for primary PCTA.

In the study by García Escudero, et al., medical care time (from patient’s arrival at the referring center to balloon inflation) was 200 minutes; the transfer time from referring center to receiving center was 31 minutes; whereas delay time to balloon inflation at receiving center was 35 minutes. These data fit in with the previous experience, but they specifically make evident more delay in the referring center, since both the transport to the receiving center and the procedure took place within a reasonable period of time. This specific delay makes it easy to implement remedial actions; it is more difficult when delays occur in the different intervals, from consultation to delays in transport and at the receiving center. Thus, these findings are not applicable to all the situations. Reliable information from each center and region must be available in order to identify and correct those delays.

On the other hand, the so-called patient time (from symptoms onset to arrival at the first center) was 80 minutes; so it is quite an early consultation. However, the SAC survey, (8) which analyzed the median of patients admitted for myocardial infarction between 1987 and 2005, showed that even though consultation time decreased, it was not below a median of 4 hours for the last analyzed period. Therefore, the excellent data about consultation time provided by García Escudero, et al. may not be applied to all centers that admit myocardial infarction patients. Therefore, there is an additional point to solve in order to shorten the time to reperfusion in the real world.

When analyzing delay times for myocardial infarction treatment with TL or PCTA, with data from the French registry (FAST-MI), Danchin et al. (9) reported a time of 57 minutes from consultation to reperfusion for TL patients, and of 170 minutes for PCTA patients. PCTA value is quite similar to the one provided by García Escudero, et al.

In other matters, the 90 minutes door-balloon time out of the average of myocardial infarctions in the National Registry of Myocardial Infarction—which states the time beyond which PCTA outcomes do not exceed TL outcomes—can be modified according to clinical variables of infarction, such as precociouslyness, localization and age. This was confirmed by Pinto, et al. (10) on 192,509 myocardial infarct patients in the United States National Registry of Myocardial Infarction. Thus, in cases of early anterior (extensive) myocardial infarction (< 2 hours after symptoms onset) and in patients aged < 65 years (low risk of hemorrhage), the acceptable door-balloon time should not exceed 40 minutes, with no loss of the PCTA benefit over the TL. At the opposite extreme, the door-balloon time in an elderly patient with late and non-anterior myocardial infarction may be 180 minutes.

Again, time plays a key role; so much so that, in very early myocardial infarction (< 2 hours), adequate door-balloon time is half that of the established time of 90 minutes, whereas it can be extended even more in later infarction.

HOW TO SOLVE THIS PROBLEM?

The difficulties in achieving adequate times for the optimal PCTA reperfusion strategy boosted the use of facilitated angioplasty, which aimed at obtaining better outcomes through pharmacological preparation (TL or TL + Iib-IIIa) that would allow patient to under PTCA in better conditions. However, both the ASSENT-4 (11) and FINESSE (12) trials did not show favorable outcomes: the first trial was suspended due to greater mortality rate, reinfarction, culprit vessel occlusion, and hemorrhagic complications in facilitated PTCA, whereas in the second trial, no differences between both treatments were observed. Therefore, the facilitated PCTA is not superior to the direct one; in consequence, it must be discarded as an alternative treatment.

An explanation of these outcomes, especially those of ASSENT-4, stated that PCTA had been performed very close (< 90 minutes) to drug therapy, and that this was not the hypothesis that had generated the concept of facilitated PCTA. This fact, together with the almost irremediably difficulty of shortening door-balloon time in the real world, motivated the proposal of drug therapy followed by PCTA beyond 2 hours, that is, a form of later facilitated PCTA generically called pharmaco-invasive strategy. In this regard, CARESS-in-AMI Study (13) included high risk myo-
cardiac infarction patients under 75 years of age, treated with $\frac{1}{2}$ dose reteplase + abciximab, and referred to: 1) immediate PCTA (pharmacoinvasive strategy), and 2) conservative treatment. There were no differences regarding death, reinfarction or hemorrhages, and the pharmacoinvasive strategy reduced only the refractory ischemia. A positive aspect of the study is the selective inclusion due to high clinical risk. The negative point is that drug therapy for patients with facilitated TL did not prove superior to conventional TL treatment.

The GRACIA-2 Study (14) evaluated TL followed by PCTA within 3 hours versus direct PCTA within 3 hours. The pharmacoinvasive strategy did not show differences in death or hemorrhages, but it did show more myocardial reperfusion. However, this was due to a great extent to prior TL treatment, so the additional PCTA benefit was low. On the other hand, direct PCTA was performed later than the recommended times, what made it difficult to draw conclusions.

In so doing, the new pharmacoinvasive strategies seem to be safer than facilitated PCTA strategies, but their benefits are not clear as far as superiority compared to conventional strategies is concerned.

So how can delays to myocardial reperfusion be improved, since they are as stated by García Escudero et al.– a real medical-care problem? Some considerations may help to achieve this goal:
- Shorten times to reperfusion, especially for PCTA.
- For myocardial infarctions < 3 hours, administer the available reperfusion strategy without delay.
- For myocardial infarctions > 3 hours, PCTA < 90 minutes or otherwise TL. Patient transport for PCTA should be only for patients selected according to their clinical risk, because of those well known problems of infrastructure and delays in the real world.

In order to achieve these goals, educational programs for physicians and for the community should be implemented, as well as an organization of administrative remedies and the contribution of health care policies. Nevertheless, achieving these goals will be more difficult if there is no on-site information about the reality of myocardial infarction treatment in our community. Unvaluable works like that of García Escudero, et al. will undoubtedly contribute to improve the outcomes of STEMI treatment.

**BIBLIOGRAPHY**


