Reperfusion Strategies in Acute Infarction

Javier Ortigosa Aso and Lorenzo Silva Melchor

Servicio de Cardiología, Hospital Puerta de Hierro, Madrid, Spain

Since the late 1980s, fibrinolysis has been the reperfusion therapy most frequently used in patients with ST-segment elevation acute infarction. However, during the last decade, primary percutaneous coronary intervention (PCI) has become the strategy of choice because, by comparison with fibrinolysis, it associates with significantly lower rates of reinfarction (3% vs 7%), 30-day mortality (5% vs 7%), and hemorrhagic stroke (0.5% vs 1%).[1,2] Nobody doubts primary PCI is the best reperfusion therapy available when performed by an experienced interventional cardiologist shortly after the onset of symptoms. American and European clinical practice guidelines recommend primary PCI is used within 90 minutes of the patient presenting in emergency room.[3,4] Delays in administering fibrinolytics and in performing primary PCI associate with increased mortality ("time is muscle"). Each 30-minutes' delay in performing primary PCI means a 7.5% increase in 1-year mortality.

Analysis of all randomized studies comparing fibrinolysis and primary PCI found the benefits to mortality of primary PCI over fibrinolysis diminished as the delay in primary PCI increased by comparison with fibrinolysis.[5] This delay is the difference between door-to-balloon and door-to-needle time (DB-DN). Both strategies benefit mortality to the same extent at 62 minutes DB-DN.[5] The guidelines recommend 30 minutes door-to-needle and 90 minutes door-to-balloon, giving 60 minutes DB-DN.[3] The US NRMI register,[6] which analyzes "real-world" data, found the benefit to survival of primary PCI over fibrinolysis disappears when DB-DN time was 114 minutes (110 minutes in Betriu et al[7] and 120 minutes in Boersma[2]). Moreover, when the benefit to mortality of PCI over fibrinolysis disappeared, DB-DN time varied considerably with patient characteristics.[6] It was <60 minutes in patients <65 years with previous infarction presenting at ≤2 hours following the onset of symptoms but it was almost 3 hours in patients >65 years, with no previous infarction, presenting at >2 hours following the onset of symptoms. The explanation for these findings seems simple: in previous infarctions there is more ischemic but viable myocardium that can be saved with early reperfusion; at ≤2 hours the occlusive coronary thrombus is easier to treat with fibrinolytics; finally, in patients <65 years, fibrinolytics reduce the risk of cerebral hemorrhage. Therefore, it seems logical to conclude that when choosing the reperfusion therapy (primary PCI or fibrinolysis) DB-DN time should be taken into account together with patient characteristics – age (>65 or <65 years), infarction location (anterior or not), and time lapse since the onset of symptoms (<2 or >2 hours).[6]

The benefit of the fibrinolytic diminishes substantially when administration is delayed. If it is administered at ≤1 hour (the "golden hour"), it saves 65 lives per 1000 patients treated, almost twice as many as when it is applied in the second hour (37 lives per 1000 patients treated). In patients attended at ≤2 hours following the onset of symptoms, fibrinolysis achieves excellent results, equivalent, if not better than those of primary PCI. The PRAGUE-2 study reported 30-day mortality in patients treated with streptokinase at ≤3 hours was similar to that of patients treated with primary PCI.[8] The CAPTIM study reported 30-day mortality in patients treated at ≤2 hours with tPA was less —but was not statistically significant— than that of those treated with primary PCI, with a statistically significant reduction in incidence of shock.[9] The French USIC 2000 register reported 0% inhospital mortality and 99% 1-year survival in patients receiving pre-hospital fibrinolysis and admitted at ≤3.5 hours.[10] Among patients treated with fibrinolysis at ≤1 hour, 25% are discharged without evidence of myocardial necrosis (aborted infarction). In pre-hospital fibrinolysis, the thrombolytic can be administered around 1 hour earlier than in inhospital fibrinolysis, which substantially reduces mortality (absolute reduction 1.7%; odds ratio [OR]=0.83 [0.7-0.98]).

Given such favorable data on pre-hospital fibrinolysis, the prospective RIKS-HIA register[11] found a significantly lower association between primary PCI and 30-day and 1-year mortality than for pre-hospital fibrinolysis. In patients treated at ≤2 hours following the onset of symptoms, survival rates with primary PCI remained greater –but were not statistically significant– than with

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Correspondence: Dr. J. Ortigosa Aso.
Servicio de Cardiología. Hospital Puerta de Hierro.
San Martín de Porres, 4. 28035 Madrid. España.
E-mail: fjortigosa1@hotmail.com

fibrinolysis. Pre-hospital fibrinolysis associated with 3 0-day and 1-year mortality significantly less than inhospital fibrinolysis did.[11] Obviously, a register provides less scientific evidence about the superiority of a specific treatment than a randomized study or a metaanalysis of randomized studies do because variables not included in the analysis can influence treatment choice and results. However, we emphasize that the RIKS-HIA register included 7 times more patients treated with pre-hospital fibrinolysis than CAPTIM (the only randomized study to date) did,[9] and 17 times more than USIC 2000.[10] The statistical value of these studies is too low and they report very high rates of urgent and early PCI in patients treated with fibrinolysis. Furthermore, they were conducted in 1997-2000, when primary PCI results were worse than they are today.

In the present issue of *Revista Española de Cardiología*, Rosell-Ortiz et al,[12] on behalf of the Spanish Out-of-Hospital Fibrinolysis Evaluation Project group (PEFEX), analyze out-of-hospital management of patients with acute infarction, highlighting out-of-hospital fibrinolysis. Their data are of great interest as they come from the out-of-hospital context and their sample is wide-ranging and highly representative. They include 2372 patients with acute infarction attended out-of-hospital between 2001 and 2004. Reperfusion therapy was administered to 59.1% of patients (out-of-hospital fibrinolysis in 19.7%, inhospital fibrinolysis 35.8%, and primary PCI 3.6%). Urgent PCI was used in 5.5% of patients and programmed PCI in 11.8%. The authors conclude that out-of-hospital fibrinolysis is performed safely and reduces inhospital and 1-year mortality in the "real world." However, the low 30-day mortality of patients treated with out-of-hospital fibrinolysis (3.9%) in their study is partly because it was used at a very early stage in a low-risk patient group. Note that out-of-hospital fibrinolysis was performed at ≤2 hours in 68% of patients who received it, although it is unclear why the treatment was not used with many other patients seen at ≤2 hours. The high percentage of patients (6.7%) with ≥1 episodes of ventricular fibrillation –which exceeds figures reported in other series– is remarkable.

Simple strategies have been identified that reduce door-to-balloon time in patients undergoing primary PCI.[13] The most effective are: *a)* the physician first attending the patient and making the diagnosis activates the interventional cardiology team without consulting the cardiologist; *b)* the entire team is activated with a single call from the switchboard; *c)* the duty team reaches the hospital within 20 minutes; *d)* the duty cardiologist is physically present; and *e)* each week, emergency room physicians and interventional cardiologists are informed of the door-to-balloon times of patients treated recently. The time saved with each of these strategies is 8-19 minutes. The price paid is the occasional but infrequent false alarm or inappropriate activation of the interventional cardiology team, (Bradley reported a mean of 2 false alarms over 6 months).

Decisions about which reperfusion therapy (primary PCI or fibrinolysis) to apply in a specific patient should be taken by the out-of-hospital emergency services or the inhospital emergency room physician who first attends the patient and diagnoses acute infarction. This decision should comply with the healthcare area protocol on reperfusion therapy agreed by clinical cardiologists, interventional cardiologists, emergency room and out-of-hospital emergency service physicians, and primary care physicians. In defining the protocol, they should take into account the geographic characteristics of the area (distances, traffic conditions, etc), interventional cardiology resources, and healthcare transport.

Choice of reperfusion therapy should be individualized and based on: *a)* the time lapse following the onset of symptoms; *b)* estimated DB-DN time for the individual patient and occasion; *c)* patient age; *d)* infarction location; and *e)* risk of intracranial hemorrhage with the fibrinolytic. In general, if >3 hours have passed since the onset of symptoms, the hospital interventional cardiology team should be alerted directly and the patient transferred to interventional cardiology without going through emergency room, to avoid delays in performing primary PCI. If, on the contrary, <3 hours have passed since the onset of symptoms, DB-DN time should be estimated. If >2 hours have passed, pre-hospital fibrinolysis should be initiated; if <2 hours have passed, primary PCI is the better option. As an exception to this rule, in younger patients with previous infarction or extensive infarction of <2 hours' evolution, a probable DB-DN time of ≤1 hour should be required and, failing this, pre-hospital fibrinolysis should be initiated. In patients contraindicated for fibrinolysis or with cardiogenic shock, primary PCI should always be the treatment of choice.

In a healthcare area with at least 1 hospital with a cardiac catheterization laboratory, it seems illogical that mobile intensive care units should transport patients with acute infarction to hospitals without a laboratory. With the data available, it only seems rational to establish a protocol of always referring these patients to a hospital with a laboratory to perform primary PCI, urgent PCI (in patients in whom fibrinolysis is unsuccessful), or elective coronary angiography in patients in whom fibrinolysis has achieved reperfusion. Fibrinolysis does not achieve reperfusion (persistence of pain and/or <70% resolution of ST-segment elevation at 90 minutes) in 40%-50% of patients; moreover, 10%-20% of successfully reperfused patients experience reocclusion of the artery. Urgent PCI is preferable to repeat fibrinolysis in these patients. Patients reperfused with a fibrinolytic benefit from systematic use of coronary angiography during hospitalization.[14] Patients who are stable following primary PCI, urgent PCI, or elective coronary angiography (with or without PCI) can be transferred to the referring hospital for further hospitalization.

When patients attend the emergency room of a hospital without an interventional cardiology laboratory and <3 hours have passed following the onset of symptoms, they should be transferred to a center with a laboratory for primary PCI if estimated DB-DN time is <2 hours. If not, they should be treated with inhospital fibrinolysis. Therapy received by patients treated in a hospital with a cardiac catheterization laboratory differs notably from that received by patients in a hospital without one. The strongest predictor of delay in performing primary PCI is the need for patient transfer from a hospital without a laboratory to a hospital with one.[5] Although several studies have shown a significant, ≤42% reduction in mortality, reinfarction, and ictus in patients transferred for primary PCI versus fibrinolysis in situ,[15] we would stress that in all these studies transfer time was <3 hours, and frequently <90 minutes, which is not at all common in the real world.

A combined reperfusion strategy (facilitated PCI) with initial pharmacologic treatment to achieve early but partial reperfusion followed as soon as possible by PCI to complete and ensure sustained reperfusion, can conceptually prove very attractive. Facilitated PCI with the administration of fibrinolytic, glycoprotein IIb/IIIa inhibitors (GP), or both, followed by immediate PCI, has been proposed as a reperfusion strategy preferably applied in patients presenting soon after the onset of symptoms, in whom it is assumed that primary PCI can be delayed. Two wide-ranging studies with clinical objectives have compared facilitated and primary PCI. The ASSENT-4 PCI study[16] compared facilitated PCI with tenecteplase with primary PCI. Enrolment was stopped when only 1666 patients of the projected 4000 had been included, due to an increase in 30-day mortality with facilitated PCI. Only 19% of patients included were enrolled in the pre-hospital context. At 90 days, the rate of combined primary outcome (death, heart failure, and cardiogenic shock) was significantly greater in the facilitated PCI group although no significant differences were found in any individual component of the primary outcome. Rates of ictus and intracranial hemorrhage were significantly greater in the facilitated PCI group but this did not completely explain the excessive 30-day mortality in this group. We should stress that lower mortality was found in patients randomized to facilitated PCI in the ambulance and that the mean time between administration of the fibrinolytic to performing PCI was only 97 minutes. Patients undergoing facilitated PCI were not administered clopidogrel or heparin, which may explain the low TIMI 3 flow achieved with the fibrinolytic. The FINESSE study (reported at the 2007 European Society of Cardiology Congress) compared facilitated PCI with (half-dose) reteplase plus abciximab or abciximab only with primary PCI in patients with acute infarction in whom estimated time to PCI was 1-4 hours. At 90 days, no differences were found between strategies in the combined primary outcome of overall mortality, readmission for heart failure, ventricular flutter or cardiogenic shock. Nor were there significant differences in overall mortality or in any of the individual components of the primary outcome. The strategy of facilitated PCI with reteplase plus abciximab associated with significantly greater (but not statistically significant) rates of major and minor bleeding and of intracranial hemorrhage. The negative results of both studies do not currently support the application of facilitated PCI. The bad results of facilitated PCI in these studies are believed to be due to late administration of the fibrinolytic and early performance of PCI in the facilitated PCI group. Hope remains that future studies can demonstrate the validity of facilitated PCI based on pre-hospital, early administration of the fibrinolytic in areas where PCI is delayed by >3 hours.

One objective of Spain's 2004-2007 plan for ischemic heart disease is to construct a network to facilitate extending the use of primary PCI, although it recognizes that implementing PCI as a routine treatment for the entire population entails substantial logistic and technical limitations. In Spain, 5102 primary PCIs were performed in 103 hospitals in 2005. This means that only 12.5% of patients with acute infarction admitted were treated with primary PCI.[17] The autonomous regions of Galicia and Murcia have successfully constructed networks that put primary PCI, performed on time, by expert interventional cardiologists, within the reach of all inhabitants and should serve as an example for the implementation of similar healthcare networks in the other Spanish regions. One key aspect, as indicated in the plan, is that attention to acute infarction centers on the patient. This obliges representatives of the different healthcare levels (out-of-hospital medical attention, emergency room, clinical cardiology, interventional cardiology) to coordinate their efforts, something they are frequently reluctant to do.

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