Point of view

The rationale for facilitated percutaneous coronary intervention: philosophical speculation, methodological problem or practical need?

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If we take a close look at the development of philosophy what would surely strike us, as happens with all sciences, is the intrinsically conflictual nature of its history. Indeed, every step of its history has been marked by two duelers fighting over a series of decisive questions.

In his existence man is obliged to choose only one of the many possibilities that are placed in front of him at a time. The limits within which he is obliged to act force him to exclude all the other avenues if he wants to be effective and free, but this *Aut-Aut* risks making him renounce to something positive in what he has discarded[1].

Nowadays, the two dominant, but alternative, approaches, in the management of acute ST-elevation myocardial infarction (STEMI) are primary percutaneous coronary intervention (PCI) and fibrinolytic therapy. Each approach has seen significant advances during the last several decades that have translated into improved survival rates and the achievement of the goals of reperfusion therapy: to achieve rapid and optimal restoration of flow in the infarct-related vessel, and to maintain this initial result in the long term.

Fibrinolytic therapy is the most widely applied first-line therapy for acute myocardial infarction and its effect on mortality has been conclusively demonstrated in randomized controlled trials involving thousands of STEMI patients[2-4]. Despite the widespread availability and ease of fibrinolytic administration, this strategy is limited by unacceptable rates of intracerebral hemorrhage, ineffective reperfusion, and reinfarction. Moreover, the benefit of thrombolysis is extremely time-sensitive[2,5], but when treatment is established within the first 2 hours after symptom onset, survival dramatically increases[5]. This finding has also been demonstrated by the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial[6], which was set up to compare prehospital thrombolysis and primary PCI in patients with STEMI and did not demonstrate any difference in the combined endpoint of death, reinfarction, and disabling stroke at 30 days between the two groups.

Primary PCI, on the other hand, is more reliable in restoring normal epicardial blood flow[7,8], and several trials have proved its benefits in terms of mortality (from 60 min to 12 hours after symptom onset). Unfortunately, particularly in Italy, PCI is not available in all centers[9,10] and often there are intrahospital times much longer than what reported in the literature, reducing its time-dependent benefits. Consistent with these considerations, recent studies and clinical trials[11,12] suggest that the time since symptom onset should be taken into consideration when one selects reperfusion therapy. A meta-analysis by De Luca et al.[13] showed that, in patients with STEMI treated by primary PCI, the symptom-onset-to-balloon time, but not the door-to-balloon time, is related to mortality, particularly in non-low-risk patients and a symptom-onset-to-balloon time > 4 hours was identified as an independent predictor of 1-year mortality.

These considerations could spontaneously lead one to hypothesize new strategies combining a precocious pharmacological approach with a delayed mechanical-induced coronary patency in order to reduce the time delay in the STEMI setting[14].

Preliminary non-randomized studies combining pharmacological and mechanical approaches have demonstrated improved epicardial and microvascular function, thus rendering these strategies complementary and no longer alternative.

In its broadest terms, this new strategy (facilitated PCI) uses a combination of IIb/IIIa inhibitors, unfractionated heparin, and/or reduced-dose fibrinolytic therapies before primary PCI. The philosophy of this approach is to open the time frame to early PCI patients, which means allowing more patients to receive an intervention during the early phases of PCI, independent of geographical and logistic barriers. In fact, such a strategy potentially takes advantage of the wide availability and speed of pharmacological agents in opening arteries whilst also taking advantage of the further improvements in flow and lower rates of reocclusion associated with PCI. The rapidity and ease of administration provided by pharmacological agents will allow for more prompt and reliable restoration of a TIMI grade 3 flow and reduce the adverse events related to delays in transfer for primary PCI. The benefits of PCI would include the restoration and maintenance of complete perfusion as well as early risk stratification.

On the other hand, early randomized trials did not show a clinical benefit for routine angioplasty performed after full-dose fibrinolysis because of increased mortality rates, most probably due to hemorrhage in the vasa vasorum and abrupt closure. Other complications included bleeding, reinfarction, and emergency coronary artery bypass grafting.

The Plasminogen-Activator Angioplasty Compatibility Trial (PACT) study[15] compared primary PCI to half-dose alteplase followed by immediate angiography and angioplasty if needed. With increased operator experience and the use of stents, this strategy was found to be safe with no observed differences in stroke or major bleeding. The early left ventricular function was similar in both treatment groups, but the importance of the early restoration of arterial patency was demonstrated once more. Convalescent ejection fractions were the highest with a patent artery and a TIMI grade 3 flow on arrival at the catheterization laboratory (62.4%) or when consequent to angioplasty within 1 hour of bolus (62.5%) compared to those who had a delayed restoration of TIMI grade 3 flow (58%) ($p = 0.0001$). The TIMI 14[16-18], GUSTO V[19], Strategies for Patency Enhancement in the Emergency Department (SPEED)[20], and Integrilin and Low-Dose Thrombolysis in Acute Myocardial Infarction (INTRO-AMI)[21] trials each examined certain combinations of alteplase, reteplase, or streptokinase with abciximab or eptifibatide during acute myocardial infarction. Primary PCI was discouraged in these trials. In the largest trial, GUSTO V[19], 16 588 patients were randomized to full-dose reteplase or half-dose reteplase with full-dose abciximab within the first 6 hours of acute myocardial infarction, and only 7% of patients underwent facilitated PCI. These trials demonstrated higher TIMI grade 3 flow rates in those treated with combination therapy compared to full-dose thrombolytics, with lower composite endpoints of death, reinfarction, and urgent revascularization.

The benefit impact of IIb/IIIa inhibitors as adjunctive therapy to stenting on the efficacy of myocardial reperfusion and the outcome of patients with STEMI has been recently reinforced by the Abciximab-Carbostent Evaluation trial (ACE) which randomized 400 patients with acute myocardial infarction to undergo infarct-related artery stenting alone or stenting plus abciximab[22]. The incidence of death, reinfarction, target vessel revascularization and stroke at 1 month was lower in the abciximab group than in the stent only group (4.5 and 10.5% respectively, $p = 0.023$), and randomization to abciximab was independently related to the risk of the primary endpoint (odds ratio 0.41, 95% confidence interval 0.17 to 0.97, $p = 0.041$). At 6 months, the cumulative difference in mortality between the groups increased (4.5 vs 8%), and the incidence of the composite of 6-month death and reinfarction was lower in the abciximab group than in the stent only group (5.5 and 13.5% respectively, $p = 0.006$)[22].

The results of ACE need to be placed in the context of the four previous trials which showed conflicting results: ReoPro and Primary PTCA Organization and Randomized Trial (RAPPORT)[23], Intracoronary Stenting and Antithrombotic Regimen-2 (ISAR-2)[24], Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up (ADMIRAL)[25], and Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC)[26]. The ISAR-2 trial[24], based on a sample of 401 patients, showed a benefit of abciximab in terms of a reduction in the composite endpoint of death, reinfarction, and target vessel revascularization at 1 month (5.0 vs 10.5%, $p = 0.038$), but this benefit was no longer evident at 12 months. The ADMIRAL trial[25], based on a sample of 300 patients, showed a significant reduction in the composite endpoint of death, reinfarction, and urgent target vessel revascularization at 1 month, and this benefit was maintained at 6 months (7.4 vs 15.9%, $p = 0.02$). On the contrary, the CADILLAC trial[26], the largest study based on a sample of 2082 patients, did not confirm the benefit of abciximab at the primary endpoint timing of 6 months. In fact, in this latter trial, at 6 months there were more deaths and reinfarctions, albeit not statistically significant, among the stent-abciximab group compared with the stent control group. The reason why this occurred, leading to particular confusion in this field, needs to be addressed. The study showed a strong

benefit of coronary stenting, as compared with coronary angioplasty, with or without abciximab, and no adjunctive benefit of abciximab in the stenting arm (primary endpoint rate 11.5% in the stenting only group [n = 512] and 10.2% in the stenting plus abciximab group [n = 524]). Interestingly, the 30-day composite endpoint for CADILLAC was 6.8% in the control arm, but in each of the other four trials it exceeded 10%, reflecting the risk of the control cohorts in each trial[26]. The low risk observed in CADILLAC was not only driven by the clinical exclusion criteria but also by the multiple angiographic exclusion criteria eliminating the anatomically difficult cases that would have benefited most from the drug[27].

As in Hegelian dialectics, the result of the contradiction, i.e. the movement of opposites, is the synthesis of a third moment which overcomes and resolves the conflict on a higher level conciliating a more comprehensive truth over and above the truth of two opposite poles, thesis and antithesis. The synthesis is a new thesis that brings into play another dialectical movement, generating in this way a process of historical and continuous intellectual development. Therefore, it is preferable to obtain a synthesis between more opportunity; this *Et-Et* maintains the diversity but recovers the best that opportunity itself can offer[28]. Even the philosopher Jean-Jacques Rousseau had expressed the same concept in the metaphor of two hunters[29]. Two hunters organize a deer hunt. The two have different roles. One has to push the deer towards the trap, the other has to kill it. During the hunt, one of the hunters notices a rabbit in shooting range and decides to hunt this easier prey. With this metaphor, Rousseau wanted to remind us that the refusal to collaborate necessarily brings with it, in different societies, the acceptance of inferior results. From his point of view it is necessary to encourage people to collaborate. But this can only be achieved with a fair and just distribution of the prey and the imposition of objectives able to satisfy and improve the condition of those collaborating; otherwise, inferior interests would prevail.

As advances are made in both the pharmacological and the interventional management of STEMI, permutations of the two strategies cannot presently be recommended because we are still awaiting the results of ongoing evaluation in randomized clinical trials. The benefits of facilitated PCI in the setting of STEMI seen in small trials and subgroups remain to be confirmed in larger clinical trials which are better designed to detect differences in mortality: Addressing the Value of Facilitated Angioplasty After Combination Therapy or Eptifibatide Monotherapy in Acute Myocardial Infarction (ADVANCE MI), Assessment of the Safety and Efficacy of a New Thrombolytic Regimen-4 (ASSENT-4), Grupo de Análisis de la Cardiopatía Isquémica Aguda-2 (GRACIA-2), Faster Fibrinolytic and Aggrastat for ST-Elevation Resolution (FINESSE) and Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS). If any strategy proves promising in trials at high volume centers with experienced operators, the results will need to be confirmed in the community setting.

Nowadays, our goal is to optimize the management of STEMI patients using all available tools in every different context. The idea of associating powerful pharmacological therapies that precede mechanical reperfusion could be a winner and guarantee the synergism necessary to overcome the therapeutic passivity of the unavoidable delay related to the transport for primary PCI. Only by collaborating would it be possible to achieve results.

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