EuroIntervention 2011;7:415-419

AMI on the move

Marco Valgimigli, MD, PhD

Cardiology Department, University of Ferrara, Italy

"…these special feelings won't ever fade
'cause I knew from the start
you put a move on my heart…"
Tamia Hill

The primary task for a cardiologist is, indeed, to "put a move on the heart", or preferably to "keep it moving". So it is probably not a coincidence that the practice of cardiologists, especially interventional cardiologists, must be extremely dynamic. The speed with which evidence accrues in this field is impressive and, most importantly, the capability for interventional cardiologists to keep up with the pace and transfer new treatment strategies into successful working algorithms is likewise remarkable. The advent of primary PCI as mainstay reperfusion strategy in patients with ST-segment elevation myocardial infarction has revolutionised the treatment of this critically ill condition. As a natural consequence, the logistics of medical and para-medical personnel both inside and outside hospitals has been greatly affected.

Therefore, the truth today is… the revolution in terms of optimal management of STEMI patients has simply just started!

What we do in the STEMI setting is of great value providing we understand both the cellular pathway we want to modulate by treatment and that we accomplish this chosen treatment on time. It is for these reasons that the integrated analysis of these four papers on STEMI published in this issue of the EuroIntervention[1-4] provides a great opportunity to understand what direction the field of AMI treatment is heading towards.

Growing evidence suggests that patients with STEMI should not be transported to get an EKG done at the nearest hospital facility, but vice-versa, that it is better for the EKG to be brought to the patient. This revised pre-hospital pathway saves time –and consequently patients' myocardium– as was shown by Ortolani and colleagues[1]. This fast-track diagnostic modality gives the patient direct access to the care he or she needs, pinpointing the exact location where he/she needs to go: the catheterisation laboratory, without any additional and avoidable dangerous intersections. For STEMI patients, the ideal emergency room should be located locally, and not within the hospital. This is the number one strategy in providing the best care available in a timely manner.

Easy to say, but not so easy to implement. The province of Bologna has a great record, and noteworthy history within Italy, for the optimal management of patients with STEMI via an integrated out-of-hospital network. Yet, even here, the proportion of STEMI patients being triaged in the pre-hospital setting increased from 12% in 2003 to up to only 41% in 2007[1].

Great move but please keep it moving along!

This also underlies the difficulty of integrating different hospital systems as well as, sometimes, various pre-hospital transfer services. This task may require more political finesse rather than more medical skills. Therefore, our mission is also to sensitise policy-makers about this important goal, and to work together to make it happen.

There is abundant literature on the role of door-to-balloon (D2B) in STEMI patient outcomes. Even the decision to either perform or not to perform pre-hospital lysis should, at least in part, depend on a forecast of final D2B time[5].

But, has the time come to revise the concept of D2B time?

The paper by Ortolani et al again emphasises the central role of the EKG, more than that of the "door"[1]. Getting inside the door of an establishment to receive an EKG is an essential waste of time. Even more so if that door belongs to a non-primary PCI capable hospital, which would then lead to even additional delays in (re) transferring the patient to the right hospital. Indeed, the door-in door-out (DIDO) time has been recently shown to greatly impact final D2B time in patients who need re-transferring[6]. Therefore, it is increasingly evident that the "door" component of the delay should

**Corresponding author: University of Ferrara, Cardiovascular Institute, Arcispedale S. Anna Hospital, Corso Giovecca 203, 44100 Ferrara, Italy. E-mail: vlgmrc@unife.it*

PCR online

DOI: 10.4244/EIJV7I4A68

ideally be avoided. The first timing to monitor is the delay from the emergency call to the EKG. The second time-frame would be the interval from the EKG to reperfusion. It is interesting to note as well that the balloon component of the D2B terminology could be improved today. Lesion pre-dilatation is the moment in which distal embolisation most frequently occurs in STEMI patients. A more contemporary sequencing of intervention is vessel wiring, thrombus aspiration and direct stenting. Hence the question becomes when the clock should stop ticking in this modern treatment scenario, provided conventional balloon inflation could be avoided?

Not only should the EKG move towards the patient, similarly effective and safe antithrombotic treatment[2] should do so as well. This is the topic of an extensive and never-ending debate[7-9], and yet, negative and positive studies should not exclude themselves as in algebra. Investigators and clinicians should go beyond the plain conclusions of each independent study and try to contextualise the results of each into the proper clinical scenario in which the study findings were generated.

With that respect, the On-TIME 2 study[7] has the great value of reconciling the apparently contrasting evidence on the use of glycoprotein IIb/IIIa inhibitors in STEMI generated by recent or less recent literature[8,9].

The ON-TIME 2 study shows that in the very first hours of STEMI onset, when myocardial stunning is still prevailing on necrosis, and rich-in-platelet thrombus is occluding coronary circulation, glycoprotein IIb/IIIa inhibition is of great value and may save lives[10,11]. This benefit is on top of any aspirin and 600 mg clopidogrel loading doses. The paper by Heestermans et al[2] suggests that this benefit is such that it may at least partially compensate for the delay in transportation of the patient to the primary PCI facility centre. This message is potentially extremely critical, it is a message however, as the authors acknowledge, that suffers from the same limitations of the main ON-TIME 2 paper, i.e., the study is unfortunately not powered for a clinical endpoints. Even if many previous studies have clearly shown a strong association between ST segment elevation resolution and outcomes, in order to convince the sceptical medical community, a study powered for clinical events is essential. Even more so, type I and type II errors are not corrected for in this sub-study. Therefore, this interesting study can be considered as hypothesis generating. Is a relatively long infusion of tirofiban truly needed to improve outcomes in STEMI patients being transferred to a primary PCI centre? That is what the analysis of ST segment elevation resolution before and after intervention would suggest. Yet, if we look at overall mortality at 30 days, I am not fully convinced that a relatively long infusion duration of tirofiban is the key. Relatively speaking, mortality is reduced by 66% in patients receiving infusion duration of less than 55 minutes (the median duration of drug infusion) and by 58% in patients receiving longer infusion duration. Are long infusions truly needed?

As the main On-TIME 2 paper shows[11], I am still convinced that the most relevant covariate in driving the benefit of glycoprotein IIb/IIIa inhibition is the delay of treatment with respect to the onset of symptoms more than the duration of infusion once therapy has been started[10].

Yet, there is a distinct value in this analysis which should not be dismissed.

To carry out de-thrombotic action, even a potent intravenous drug takes time. Starting a glycoprotein IIb/IIIa inhibitor at the time of stenting may be too late to significantly affect the coronary environment in which stents are placed. Similarly, the use of a glycoprotein IIb/IIIa inhibitor at a later stage, when myocardium necrosis is predominant and therefore true myocardium at risk is negligible, the clock cannot be set back to help rescue microcirculatory damage8, 9. In other words, there may be a specific therapeutic window for glycoprotein IIb/IIIa inhibition which has been captured or missed depending on the patient population and study designs, thus explaining the apparently contradictory results of many studies addressing the role of glycoprotein IIb/IIIa inhibitors in STEMI patients.

It may be sad to learn all these lessons in 2011, when glycoprotein IIb/IIIa inhibition seems to have reached the end of its life span and when it is hard to believe that companies will still invest resources in randomised studies. Let us hope that at least future intravenous potent antiplatelet agents, which are still in the development phase, such as cangrelor or elinogrel, may continue where glycoptein IIb/IIIa inhibitors have stopped.

Provided the STREAM study will be positive[12], the outstanding question for the future will be whether lysis, potent intravenous antiplatelet agents, or a combination of both in patients who are at low risk for bleeding or still nothing should be implemented in early presenter STEMI patients who need to be transferred to a primary PCI centre.

Future treatments should also aim at modulating new therapeutic targets.

The paper by Muller and colleagues[3] provides an interesting snapshot into several distinct molecular pathways, which appear to be selectively up-regulated at the site of myocardial infarction.

This study investigated the whole blood gene expression of genes belonging to the family of critical signalling pathways involved in the pathogenesis of plaque rupture and thrombosis in acute myocardial infarction.

The findings of this paper[3] highlights the induction of transcripts belonging to the chemokine family, in particular CCL2 (MCP-1), CCL18 and CXCL12 (SDF-1), which are genes involved in the cell-cell or cell-extracellular matrix interaction family, namely FN1 (fibronectin 1), CDH5 (VE-cadherin) and SPP1 (osteopontin), as well as APOE (apolipoprotein E), at the site of occlusion during myocardial infarction. As currently none of these molecular pathways are targeted by drugs, this study emphasises how little our pharmacological armamentarium affects the process of injury repair and healing once myocardial necrosis has occurred.

The futuristic study from Aalst[3] is perfectly counterbalanced by the paper by Delewi et al from The Netherlands[4]. Accelerated idioventricular rhythm is frequently accompanying myocardial reperfusion, either obtained by lysis or percutaneously. While the mechanisms behind this electrical phenomenon are not completely understood, for the first time this study has addressed its haemodynamic consequences.

The authors found that accelerated idioventricular rhythm following reperfusion is associated with marked reduction in both systolic and diastolic blood pressure, irrespective of infarct-related artery. This reduction in blood pressure was associated with only a very modest increase in heart rate during accelerated idioventricular rhythm, which emphasises the importance of the atrial contraction especially in the acute phase of a myocardial infarction to preserve myocardial pre-loading and finally systemic haemodynamics.

Where are we heading from here?

The key word appears more and more to be "anticipation". The arrival in-door of the patient should be anticipated via a well-established pre-hospital network system. Reperfusion may be anticipated via the initiation of a potent yet safe antiplatelet agent such as tirofiban, new molecular targets mediating healing have been identified allowing the hopes that myocardium remodelling may be one day modulated upfront. Finally, the knowledge of the haemodynamic consequence of reperfusion, which includes, but it is clearly not restricted to accelerated idioventricular rhythm, allows a correct anticipation of the clinical scenario in which coronary recanalisation is carried out.

AMI on the move. Move to treat AMI.

Conflict of interest statement

The author has no conflict of interest to declare.

References

1. Ortolani P, Marzocchi A, Marozzini C, Palmerini T, Saia F, Taglieri N, Alessi L, Nardini P, Bacchi Reggiani ML, Guastaroba P, De Palma R, Grilli R, Picoco C, Gordini G, Branzi A. Pre-hospital ECG in patients undergoing primary percutaneous interventions within an integrated system of care: reperfusion times and long-term survival benefit. *EuroIntervention*. 2011;7:449-457.

2. Heestermans T, de Boer MJ, van Werkum JW, Mosterd A, Gosselink AT, Dambrink JH, van Houwelingen G, Koopmans P, Hamm C, Zijlstra F, ten Berg JM, van 't Hof AWJ. Higher efficacy of pre-hospital tirofiban with longer pre-treatment time to primary PCI: protection for the negative impact of time delay. *EuroIntervention*. 2011;7:442-448.

3. Muller O, Delrue L, Hamilos M, Vercauten S, Ntalians A, Trana C, Mangiacapra F, Dierickx K, De Bruyne B, Wijns W, Behfar A, Barbato E, Terzic A, Vanderheyden M, Bartunek J. Transcriptional fingerprint of human whole blood at the site of coronary occlusion in acute myocardial infarction. *EuroIntervention*. 2011;7:458-466.

4. Delewi R, Remmelink M, Meuwissen M, van Royen N, Vis M, Kock KT, Henriques JPS, de Winter RJ, Tijssen JGP, Baan Jr J, Piek JJ. Acute haemodynamic effects of accelerated idioventricular rhythm in primary percutaneous coronary intervention. *EuroIntervention*. 2011;7:467-471.

5. Ector H, Lancellotti P, Roberts WC, Wenger NK, Moss AJ, Smith ER, Borer JS, Eagle KA, Freedman J, Krum H, Lang C, Remme WJ, Piper HM, White CJ, Loscalzo J, Marbán E, Sobel BE, Roberts R, Rahimtoola SH, Camm AJ, Van de Werf F, Swedberg K, Timmis AD, Stone KS, Zipes DP, Iosselani DG, Taylor AJ, Rosen MR, Grines CL, DeMaria AN, Narula J, King SB 3rd, Wagner GS, Saksena S, Pearlman AS, Bodnar E, Emery RW, Cohn LH, van der Wall EE, Abdulla RI, Lesch M, Alfonso F, Ekroth R. A statement on ethics from the HEART Group. *JACC Cardiovasc Imaging*. 2008;1:410-2.

6. Wang TY, Nallamothu BK, Krumholz HM, Li S, Roe MT, Jollis JG, Jacobs AK, Holmes DR, Peterson ED, Ting HH. Association of door-in to door-out time with reperfusion delays and outcomes among patients transferred for primary percutaneous coronary intervention. *JAMA*. 2011;305:2540-7.

7. Van't Hof AW, Ten Berg J, Heestermans T, Dill T, Funck RC, van Werkum W, Dambrink JH, Suryapranata H, van Houwelingen G, Ottervanger JP, Stella P, Giannitsis E, Hamm C; Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) 2 study group. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet*. 2008;372:537-46.

8. Ellis SG, Tendera M, de Belder MA, van Boven AJ, Widimsky P, Janssens L, Andersen HR, Betriu A, Savonitto S, Adamus J, Peruga JZ, Kosmider M, Katz O, Neunteufl T, Jorgova J, Dorobantu M, Grinfeld L, Armstrong P, Brodie BR, Herrmann HC, Montalescot G, Neumann FJ, Effron MB, Barnathan ES, Topol EJ; FINESSE Investigators. Facilitated PCI in patients with ST-elevation myocardial infarction. *N Engl J Med*. 2008;358:2205-17.

9. Mehilli J, Kastrati A, Schulz S, Frungel S, Nekolla SG, Moshage W, Dotzer F, Huber K, Pache J, Dirschinger J, Seyfarth M, Martinoff S, Schwaiger M, Schömig A; Bavarian Reperfusion Alternatives Evaluation-3 (BRAVE-3) Study Investigators. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation*. 2009;119:1933-40.

10. Heestermans T, van 't Hof AW, ten Berg JM, van Werkum JW, Boersma E, Mosterd A, Stella PR, van Zoelen AB, Gosselink AT, Kochman W, Dill T, Koopmans PC, van Houwelingen G, Zijlstra F, Hamm C. The golden hour of prehospital reperfusion with triple antiplatelet therapy: a sub-analysis from the Ongoing Tirofiban in Myocardial Evaluation 2 (On-TIME 2) trial early initiation of triple antiplatelet therapy. *Am Heart J*. 2010;160:1079-84.

11. ten Berg JM, van 't Hof AW, Dill T, Heestermans T, van Werkum JW, Mosterd A, van Houwelingen G, Koopmans PC, Stella PR, Boersma E, Hamm C; On-TIME 2 Study Group. Effect of early, pre-hospital initiation of high bolus dose tirofiban in patients with ST-segment elevation myocardial infarction on short- and long-term clinical outcome. *J Am Coll Cardiol*. 2010;55:2446-55.

12. Armstrong PW, Gershlick A, Goldstein P, Wilcox R, Danays T, Bluhmki E, Van de Werf F; STREAM Steering Committee. The Strategic Reperfusion Early After Myocardial Infarction (STREAM) study. *Am Heart J*. 2010;160:30-5 e1.