ny

Should we reserve mechanical thrombectomy to patient with short (or long) ischemic time? A critical view at the data

"Whereas time-to-treatment time reduction is widely accepted as beneficial, the potential benefit deriving from routine thrombectomy in STEMI patients, and the relationship between time-to-treatment and effectiveness of thrombectomy, is still debated."

Giovanni Luigi De Maria
Heart Centre, Oxford University Hospitals, Oxford, UK

Adrian P Banning
Heart Centre, Oxford University Hospitals, Oxford, UK

Italo Porto
Author for correspondence:
Interventional Cardiology Unit,
Cardiovascular and Neurologic
Department, San Donato Hospital,
52100 Arezzo, Italy
italo.porto@gmail.com

Primary percutaneous coronary intervention (PPCI) is established as the routine treatment for patients presenting with ST elevation myocardial infarction (STEMI) [1]. However, even though there has been a reduction in mortality and morbidity, the interventional cardiologist still has to deal with cases in which myocardial perfusion is impaired despite the apparently successful restoration of epicardial coronary artery patency. This condition, commonly (although somewhat mistakenly) known as 'no reflow,' is related to mechanical and functional coronary microcirculatory impairment during or soon after PPCI [2–4].

The understanding of no reflow pathogenesis has significantly improved over the last decade and we now know that it can be considered as the result of a complex network of many factors, including ischemia injury, distal embolization (DE), reperfusion injury and individual susceptibility [3]. All these four elements are potential targets for therapeutic actions in order to prevent, to treat and to minimize the impact of no reflow. While several pharmacological and nonpharmacological strategies are starting to be tested in the clinical arena [5–7], the main currently available instruments against no reflow mainly rely on the reduction of ischemic injury (by shortening ischemic time) and on the prevention of DE, by means of mechanical thrombus aspiration, after the substantial failure of distal protection devices in the STEMI setting [2].

Since the first observation of the wavefront phenomenon of myocardial ischemic cell death in the 1970s [8], an overwhelming amount of evidence has shown that shortening symptoms-to-balloon (or, more correctly, time-to-treatment) time, is associated to better myocardial reperfusion, lower infarct size, improved myocardial salvage and better prognosis [1,9–10], although a 'ceiling' effect might be present [11]. In this regard, Tarantini et al. showed a 37% increase in the risk of transmural necrosis and 21% increase in the risk of microvascular obstruction occurrence for each 30 min of treatment delay [9]. Interestingly, myocardial salvage trend with time is not linear, with the most of myocardium at risk 'rescuable' within the first few hours after symptoms onset [9].

Whereas time-to-treatment time reduction is widely accepted as beneficial, the potential benefit deriving from routine thrombectomy in STEMI patients, and the relationship between time-to-treatment and effectiveness of thrombectomy, is still debated. The controversy has become particularly evident over the last year since the TASTE trial [12,13] results presentation at Transcatheter Cardiovascular Therapeutics 2013 conference. This large study questioned the promising results of the previous, single-center TAPAS trial, which had previously suggested a prognostic benefit at 1 year for thrombectomy. These new TASTE data have reopened the debate on the real usefulness of thrombus aspiration and DE prevention in general [2].

A relatively underexplored topic is the possible interaction between time-to-treatment and the effectiveness of thrombus aspiration. In other words, given the curvilinear shape of myocardial salvage – should thrombus aspiration (and more generally speaking DE prevention) be suggested only in earlier presenters? Alternatively is it more likely to be helpful in late presenters with more organized thrombus or in both?

In pre-TASTE era, we described, in an individual patient's data pooled analysis of three prospective randomized trials (REMEDIA, PIRHATE and Export study), a significant interaction (p = 0.04) between time-to-treatment (categorized as <3 h, >3 h to <6 h and >6 h to <12 h) and thrombus aspiration, in terms of achievement of effective myocardial reperfusion, defined as combination of ST resolution and myocardial blush grade ≥ 2 [14]. In TASTE a less strict stratification according to time-to-treatment (above or below 2 h), resulted in a similar effectiveness of thrombus aspiration in both groups, although the overall significance was lost due to sample size reduction (hazard ratio 0.95 [0.69–1.30] vs 0.94 [0.44–1.99], respectively) [12].

These data can be seen in contrast with those reported by Napodano *et al.*, who reported a significant increase in infarct size and microvascular obstruction extension at cardiac magnetic resonance only in early comers (time-to-treatment <3 h) with DE compared with those without DE [15]. No detrimental effect of DE was observed in late comers. The authors thus postulated that thrombectomy should mainly be reserved to early presenters, as coronary microcirculation might be already irreversibly compromised in those with high ischemic time. However, angiographically visible DE only (the so-called macroembolization, when particles in the range of millimeters travel through the epicardial circulation during angiographic cine loop filming) was measured in this study, not taking into account the possible clinically relevant implications of microembolization (embolization of particles under the resolution power of angiography) as well as bio-humoral DE [16,17].

In our opinion, the pathophysiology of plaque instability and the strict correlation between ischemic time and DE must both be considered to reflect the complex relationship between time and effectiveness of prevention of DE.

Firstly, histopathological analysis of the composition of thrombotic material retrieved during thrombus aspiration in PPCI has revealed that thrombi are older than 24 h in nearly 50% of cases [18] and, notably, Rittersma *et al.* described a 9% of thrombi older than 5 days [19]. Additionally, older thrombotic material has been typically associated to longer ischemic time, worse progno-

sis, increased oxidative and inflammatory activity and, importantly, to pre-PPCI spontaneous DE [20–22].

These observation are extremely important and have four crucial implications: plaque instability is not always an 'out of the blue' event, but in nearly half of cases is a dynamic, 'chronic' but also evolving phenomenon leading finally to vessel occlusion; there is a clear mismatch between the true ischemic time, starting in the exact moment in which plaque instability phenomenon begins, and patient's referred ischemic time, which starts with symptoms onset; studies analyzing interaction between DE and ischemic time have taken so far into account only procedural DE and not spontaneous, pre-PPCI DE, which is extremely relevant in pathophysiology of STEMI; older thrombi might have a higher detrimental effect to an already damaged coronary microcirculatory bed.

Thus, we believe that thrombus aspiration and more in general DE prevention is warranted not only in early comers in order to protect a viable and relatively 'healthy' coronary microcirculation, but also in late comers in which procedural DE can represent the 'coup de grace' to an already compromised coronary microcirculation. This is particularly true as even patients labelled as early comers may actually be late presenters. Premising that every effort should be done in order to achieve a time to treatment as short as possible, this is why thrombectomy and DE prevention in general should be suggested in all STEMI comers with evidence of conspicuous thrombotic burden and favorable coronary anatomy, irrespectively of the measured ischemic time.

Thrombus aspiration and DE prevention are thus not 'a matter of time' and in such regard, even if no randomized controlled trials have been specifically designed to address this issue, thrombus currently remains routine practice in both American and European STEMI guidelines [23,24].

Of course, we need to look with extreme attention to the upcoming TOTAL trial expected to be completed in 2015 [25]. This will be the third big study on thrombus aspiration after TAPAS and TASTE, and hopefully it will be able to solve some of the persisting debate left by these two contrasting trials.

Financial & competing interests disclosure

References

1   De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. *Circulation* 109, 1223–1225 (2004).

2   De Maria GL, Patel N, Kassimis G, Banning AP. Spontaneous and procedural plaque embolisation in native coronary arteries: pathophysiology, diagnosis, and prevention. *Scientifica (Cairo)* 2013, 364247 (2013).

3   Niccoli G, Burzotta F, Galiuto L, Crea F. Myocardial no-reflow in humans. *J. Am. Coll. Cardiol.* 54, 281–292 (2009).

4   Porto I, Niccoli G. No reflow: what's in a name? *Curr. Pharm. Des.* 19, 4517–4518 (2013).

5   Remote Preconditioning Trialists' Group, Healy DA, Khan WA *et al.* Remote preconditioning and major clinical complications following adult cardiovascular surgery: Systematic review and meta-analysis. *Int. J. Cardiol.* 176, 20–31. (2014).

6   Venugopal V, Hausenloy DJ, Ludman A *et al.* Remote ischaemic preconditioning reduces myocardial injury in patients undergoing cardiac surgery with cold-blood cardioplegia: a randomised controlled trial. *Heart* 95, 1567–1571 (2009).

7   Hausenloy DJ, Yellon DM. Remote ischaemic preconditioning: underlying mechanisms and clinical application. *Cardiovasc. Res.* 79, 377–386 (2008).

8   Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. 1. Myocardial infarct size vs duration of coronary occlusion in dogs. *Circulation* 56, 786–794 (1977).

9   Tarantini G, Cacciavillani L, Corbetti F *et al.* Duration of ischemia is a major determinant of transmurality and severe microvascular obstruction after primary angioplasty: a study performed with contrast-enhanced magnetic resonance. *J. Am. Coll. Cardiol.* 46, 1229–1235. (2005).

10   De Luca G, van't Hof AW, de Boer MJ *et al.* Time-to-treatment significantly affects the extent of ST-segment resolution and myocardial blush in patients with acute myocardial infarction treated by primary angioplasty. *Eur. Heart J.* 25, 1009–1013 (2004).

11   Menees DS, Peterson ED, Wang Y *et al.* Door-to-balloon time and mortality among patients undergoing primary PCI. *N. Engl. J. Med.* 369, 901–909 (2013).

12   Frobert O, Lagerqvist B, Olivecrona GK *et al.* Thrombus aspiration during ST-segment elevation myocardial infarction. *N. Engl. J. Med.* 369, 1587–1597 (2013).

13   Lagerqvist B, Fröbert O, Olivecrona GK *et al.* Outcomes 1 year after thrombus aspiration for myocardial infarction. *N. Engl. J. Med.* 371, 1111–1120 (2014).

14   De Vita M, Burzotta F, Porto I *et al.* Thrombus aspiration in ST elevation myocardial infarction: comparative efficacy in patients treated early and late after onset of symptoms. *Heart* 96, 1287–1290 (2010).

15   Napodano M, Peluso D, Marra MP *et al.* Time-dependent detrimental effects of distal embolization on myocardium and microvasculature during primary percutaneous coronary intervention. *JACC Cardiovasc. Interv.* 5, 1170–1177 (2012).

16   Porto I, De Maria GL, Pieroni M, Bolognese L, Crea F. Mechanisms, prevention and treatment of distal embolization. *Curr. Pharm. Des.* 19, 4576–4585 (2013).

17   Porto I, Biasucci LM, De Maria GL *et al.* Intracoronary microparticles and microvascular obstruction in patients with ST elevation myocardial infarction undergoing primary percutaneous intervention. *Eur. Heart J.* 33, 2928–2938 (2012).

18   Kramer MC, van der Wal AC, Koch KT *et al.* Histopathological features of aspirated thrombi after primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction. *PLoS One.* 4, e5817 (2009).

19   Rittersma SZ, van der Wal AC, Koch KT *et al.* Plaque instability frequently occurs days or weeks before occlusive coronary thrombosis: a pathological thrombectomy study in primary percutaneous coronary intervention. *Circulation* 111, 1160–1165 (2005).

20   Kramer MC, van der Wal AC, Koch KT *et al.* Presence of older thrombus is an independent predictor of long-term mortality in patients with ST-elevation myocardial infarction treated with thrombus aspiration during primary percutaneous coronary intervention. *Circulation* 118, 1810–1816 (2008).

21   Yunoki K, Naruko T, Inoue T *et al.* Relationship of thrombus characteristics to the incidence of angiographically visible distal embolization in patients with ST-segment elevation myocardial infarction treated with thrombus aspiration. *JACC Cardiovasc. Interv.* 6, 377–385 (2013).

22   Yunoki K, Naruko T, Sugioka K *et al.* Erythrocyte-rich thrombus aspirated from patients with ST-elevation myocardial infarction: association with oxidative stress and its impact on myocardial reperfusion. *Eur. Heart J.* 33, 1480–1490 (2012).

23   O'Gara PT, Kushner FG, Ascheim DD *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol.* 61, e78–e140 (2013).

24   Steg PG, James SK, Atar D *et al.* ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur. Heart J.* 33, 2569–2619 (2012).

25   Jolly SS, Cairns J, Yusuf S *et al.* Design and rationale of the TOTAL trial: a randomized trial of routine aspiration ThrOmbecTomy with percutaneous coronary intervention (PCI) versus PCI ALone in patients with ST-elevation myocardial infarction undergoing primary PCI. *Am. Heart J.* 167, 315–321.e1 (2014).