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EDITORIAL COMMENT

Aspiration thrombectomy: Just another piece of the puzzle – Intuitive, but not sufficient☆

Trombectomia aspirativa: apenas mais uma peça do *puzzle*. Intuitiva, mas não suficiente

Ricardo Seabra Gomes

Instituto do Coração, Carnaxide, Portugal

Thrombotic occlusion of a coronary artery was identified over 30 years ago as the pathophysiological mechanism of myocardial infarction (MI). In 1979, Rentrop et al.[1] first reported successful reperfusion by recanalizing an occluded coronary artery with a guidewire and directly infusing streptokinase. The following year, DeWood et al.[2] demonstrated spontaneous regression of occlusive thrombi in some patients undergoing coronary angiography within 24 hours of symptom onset of MI.

Preventing the formation of thrombi in chronic coronary disease, or dissolving them and proceeding to early recanalization in the acute phase of MI, then became the main therapeutic goal in reducing mortality.

For years, fibrinolysis, initially intracoronary and later intravenous, dominated treatment of the acute phase of MI. Following progressive advances in percutaneous coronary intervention (PCI), randomized studies and meta-analyses established primary angioplasty as the treatment of choice to achieve better and faster coronary recanalization and to reduce mortality. At the same time, various antithrombotic agents, particularly anticoagulants and antiplatelets, were developed and tested as an adjunctive therapy in the acute phase of MI, both for fibrinolysis and, more recently, in primary angioplasty, in an effort to improve and maintain coronary reperfusion and to reduce complications.

A recognized limitation of primary angioplasty is microvascular obstruction, known as the no-reflow phenomenon, consisting of reduced myocardial perfusion at the microvascular level despite recanalization of the epicardial coronary artery. This can be due to endothelial damage, vasospasm, inflammation, reperfusion injury to myocytes, or distal embolization of thrombotic material or plaque fragments. Diminished myocardial perfusion is associated with larger infarct size, greater left ventricular remodeling and higher mortality. It thus appears equally important to rapidly

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E-mail addresses: seago@esoterica.pt, sgomes@institutocoracao.com

obtain normal epicardial flow and adequate myocardial perfusion.

It is therefore intuitive to think that mechanical thrombus removal before PCI would be one way to reduce distal embolization and microvascular obstruction. However, various early studies using distal protection devices or mechanical thrombus aspiration (TA) did not demonstrate clinical benefit. Manual TA is now the most commonly used technique. It is simple and safe, and is ''reasonable'' and ''should be considered'' during PCI in the American[3] and European[4] guidelines for the management of MI, with a class IIa recommendation and level of evidence B.

The best evidence for use of manual TA was provided by the randomized TAPAS trial[5] of 1071 patients, which demonstrated improved perfusion indices (myocardial blush score, degree of resolution of ST-segment elevation, and Q-wave count) and significantly reduced mortality and reinfarction after one year. However, the study has been criticized for lack of statistical power to prove reduced mortality, which was excessively high in the placebo group. A 2013 meta-analysis of randomized trials comparing aspiration and mechanical thrombectomy before primary angioplasty with conventional PCI demonstrated that only manual TA reduced major adverse events, including 6–12 month mortality.[6] However, other studies have reported negative clinical outcomes. This discrepancy may be explained by the fact that some studies were single- and others multicenter, with differences in patient selection, ischemic times, and occlusion of different arteries, among other factors.[7–9] In the most recent study, of one-year outcomes in 7244 patients in the registry-based TASTE trial,[10] no reduction was seen in all-cause mortality or in the composite endpoint of all-cause death, rehospitalization for MI or stent thrombosis, with TA compared to primary PCI alone. Results are awaited of the randomized TOTAL trial[11] of 10 700 patients in order to determine definitively the effect of manual TA.

For the moment, while use of TA has proved beneficial in improving myocardial perfusion and reducing distal embolization, there are still conflicting results in terms of clinical outcomes, including mortality.

The article by Luz et al.[12] published in this issue of the *Journal* assesses the impact of ineffective TA in a series of 417 consecutive patients at a single center where the technique was routinely used. The authors defined TA failure as persistence of TIMI flow 0 or 1, which was observed in 12.5% of the study population. Independent predictors of TA failure were total ischemic time and the SYNTAX score of complexity of coronary artery disease. The study also demonstrated that ineffective TA had no impact on medium-term mortality.

Few studies have addressed the problem of failed TA. In a study by Vink et al.[13] of 1399 patients, the aspiration catheter could not reach or cross the lesion in 10.3% of cases, independent predictors of failure being vessel tortuosity, calcified lesions and bifurcation. No thrombotic material could be retrieved in a further 27.3%, predictors for which were age and the circumflex being the infarct-related artery. In the TASTE registry,[8] thrombectomy was not possible in 16% and was ineffective in 11%; and in the INFUSE-AMI trial,[14] exclusively of patients with occlusion of the anterior descending artery, the failure rate was 1.7%. It is thus clear that aspiration thrombectomy may be impossible or ineffective in certain cases, important factors being the composition and size of the thrombus and coronary anatomy, and possibly operator experience.

It is not surprising that the anatomical features of lesions should affect the success of thrombectomy, especially since the technique is used in any artery with an occlusive thrombus; nor it is surprising that ischemic time should be a predictor of failure, since the degree of thrombus organization is likely to affect the procedure's efficacy, or that failure has no impact on mortality in the light of previous studies.

In the study by Luz et al.[12] mean ischemic time was over five hours in patients in whom TA was ineffective (332.5 min, interquartile range: 393 min) and significantly shorter in successful TA (210 min, p=0.002). By way of comparison, in the study by Vink et al.,[13] mean ischemic time was three hours for both effective and ineffective TA. With regard to clinical outcomes, Luz et al. reported no reflow in 35.3% of cases of ineffective TA (as opposed to 1.4% in effective TA, p<0.001), which may be related to Killip class III/IV (p=0.031) and use of intra-aortic balloon pump (p=0.002). There was also a tendency for higher in-hospital mortality (p=0.073), which might have been statistically significant had the study population been larger.

The greatest challenge now in the treatment of ST-elevation MI (STEMI) is not only to restore normal coronary flow but also to improve microvascular perfusion.

Recent years have seen considerable research into antithrombotic agents as adjunctive therapy in primary angioplasty. The acute phase of STEMI is a highly prothrombotic state and early, effective antiplatelet therapy is considered essential in achieving optimal myocardial reperfusion. P2Y12 receptor inhibitors (clopidogrel, prasugrel and ticagrelor) should be initiated as soon as possible before primary angioplasty, although their use in the pre-hospital phase is the subject of debate. A possible limitation is increased bleeding risk if taken together with glycoprotein (Gp) IIb/IIIa inhibitors and for this reason the latter are now being used less. The ideal antithrombotic therapy is far from consensual.

Intracoronary administration of Gp IIb/IIIa inhibitors was first described in 1999 as a way to dissolve thrombi and thus reduce adverse events in MI.[15] Local administration is more beneficial than intravenous infusion due to the higher drug concentration, and the benefits are even greater if the drug is delivered locally into the target artery by means of a dedicated perfusion catheter.[16]

The recent INFUSE-AMI randomized trial[14] compared manual aspiration thrombectomy and bolus intracoronary abciximab with conventional primary PCI in 452 patients with anterior MI. Only intracoronary abciximab was shown to reduce infarct size. Patients who underwent thrombectomy, with or without abciximab, showed a higher rate of TIMI flow 3 and those undergoing thrombectomy with abciximab had the greatest reduction in infarct size.[17] Comparing patients in terms of delay to reperfusion (<3 vs. >3 h), shorter ischemic time was an important predictor of reduced infarct size and mortality at one year.[18] Another recent study, albeit small, confirmed improved myocardial perfusion

with the combined use of intracoronary abciximab and TA.[19]

Similarly, intracoronary fibrinolysis with low-dose urokinase, tenecteplase or alteplase has also been described in cases of large thrombus burden and failed manual aspiration.[20,21]

It is surprising that in the study by Luz et al.,[12] while aspirin 300 mg and clopidogrel 600 mg were given to all patients before PCI, use of Gp IIb/IIIa inhibitors was low overall and similar in those with ineffective (38%) and effective TA (33.5%). In the Portuguese National Registry of Interventional Cardiology, of 3311 patients who underwent thrombectomy between January 2006 and December 2012 (performed in 46.1% of PCI procedures in 2012), use of Gp IIb/IIIa inhibitors was also low (36.9%) but significantly higher than in those undergoing primary angioplasty alone (18.9%, p=0.001).[22]

Bearing in mind that reperfusion remains suboptimal in 20–30% of patients, despite considerable advances in the techniques and equipment used in primary angioplasty, including manual TA, adjunctive drug therapy will continue to play a role. For the interventional cardiologist, the combination of TA and intracoronary or local delivery of Gp IIb/IIIa inhibitors is in theory an attractive option for maximizing microvascular perfusion. The challenge will be the judicious concomitant use of anticoagulants and potent antiplatelets that provides a positive risk-benefit ratio for the individual patient. In the meantime, the most important aspect of STEMI treatment remains reperfusion as early as possible.

Conflicts of interest

The author has no conflicts of interest to declare.

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