Thrombus aspiration in STEMI revisited: impact on coronary microcirculation?

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In this issue of Open Heart, Hoole et al present the IMPACT trial. The authors investigate the effect of thrombus aspiration (TA) on changes in microvascular function during primary percutaneous coronary intervention (PPCI) for ST elevation myocardial infarction (STEMI). However, no difference between the TA group and the control group receiving balloon angioplasty first line could be verified. This is a timely topic indeed, since the impact of TA on coronary microcirculation was an important rationale to suggest prognostic benefits in patients with STEMI in the past.

Early data from smaller and medium-sized randomised controlled trials (RCT) fuelled substantial enthusiasm about the concept of coronary thrombectomy with a view to reduce the thrombus burden, and avoid distal embolisation and consecutive ‘no reflow’ in PPCI. Of note, ‘no reflow’ following PPCI has been observed frequently in this patient cohort. This phenomenon has been closely associated with microvascular obstruction and increased myocardial infarct size, with worse adverse clinical outcome.

Similarly, dislodged debris from the culprit lesion, consisting of conglomerates of platelets and neutrophil granulocytes, may congest the microvasculature and deteriorate the ‘no reflow’. This is also a feature of the reperfusion injury (RI), which occurs after restoration of blood flow in the infarcted vessel. Notably, this RI has been estimated to account for up to 50% of the final infarct size, and efforts to mitigate the RI and ‘no reflow’ appear therefore as an appealing therapeutic approach.

Unfortunately, more recent larger RCTs investigating manual thrombectomy in the setting of PPCI yielded rather disappointing results. Earlier this year, the largest RCT in this field was published. More than 10 000 patients referred for PPCI were randomised to receive TA or balloon angioplasty followed by stenting. Neither the primary composite end point of cardiovascular death, cardiogenic shock, New York Heart Association (NYHA) class IV or recurrent myocardial infarction nor cardiovascular death after 6 months were improved by TA. Notably, 87% of patients had a significant thrombus burden. Some concern was raised over a slightly increased stroke rate in the TA group, however, very few events were observed in this patient cohort.

Thrombectomy was also tested on top of intracoronary abciximab (glycoprotein, GPIIb/IIIa inhibition) administration in the INFUSE-AMI trial. While abciximab reduced the infarct size as assessed by cardiac MRI, this was not confirmed for thrombectomy. Several other strategies to reduce distal embolisation and microvascular obstruction were investigated, mostly in smaller pilot trials. Sezer et al suggested applying low-dose streptokinase after PPCI to open the microvasculature and improve microvascular function. They repeated coronary angiography 2 days after the index event, and reassessed the coronary flow reserve and the index of microvascular resistance. Importantly, all outcome measures of microvascular function were significantly improved in the streptokinase group as compared to the control group. After 6 months, there was no difference in left ventricular function between the study groups. However, this was a pilot study with a limited sample size of 40 patients, so no definitive conclusions could be drawn.

The evaluation of the microvasculature by measuring the index of microvascular resistance and coronary flow are well established surrogate parameters to assess microvascular function, and are closely associated to outcome. Cuculi et al assessed microvascular resistance and coronary flow reserve as well as microvascular obstruction on cardiac MRI in patients undergoing primary PCI. The authors observed a severely dysfunctional microvasculature in those patients with
These patients did have improved left ventricular function, as assessed by OCT, associated with increased IMR after the first device was used. This group may represent the patient subset with modest thrombus burden and little distal embolisation per se, as these patients did have improved left ventricular function at follow-up. This finding might favour the idea of direct stenting or the use of mesh covered stents such as the MGuard device, rather than lesion preparation. In essence, patients with only modest thrombus burden might not benefit from TA at all, or TA might even be harmful in this subset of STEMI patients.

A limitation of the present study is its small sample size, which does not allow the detection of any differences in terms of clinical end points. There was a trend towards a superior left ventricular ejection fraction in the thrombectomy group, as well as an improved early and late microvascular obstruction (MVO), but again, the sample size was not sufficient to address such end points. Moreover, only patients with restored blood flow (≥thrombolysis in myocardial infarction (TIMI) 1) after wiring of the culprit vessel could be included. Patients with TIMI 0 flow and high thrombus burden after wiring were excluded. But these patients, in particular, might yield the greatest benefit from TA. Another limitation is the exclusive use of clopidogrel, while ticagrelor and prasugrel might also have had a favourable impact on spontaneous restoration of blood flow before PPCI and microvasculature.

Although the available data from most RCTs discourage the regular use of TA, it is important to keep a balanced perspective, given the fact that TA is only one intervention that is part of the complex PPCI approach. In general, only a handful of interventions that are commonly considered to be beneficial (eg, balloon angioplasty before stenting) translate into an improved clinical outcome. From our experience, patients with significant thrombus burden might still benefit.

In conclusion, the authors present an interesting study that failed to demonstrate any benefit on coronary microvascular function of TA over sole balloon angioplasty in PPCI. The results are in line with data from recent large RCTs. The growing data in this field do not support the routine use of TA in PPCI, which will rather be limited to certain indications with large thrombus burden.

### Table 1 Selected randomised trials to investigate thrombectomy versus first line balloon angioplasty in patients undergoing PPCI

| Study/year | Number of patients | Main conclusion |
|------------|--------------------|-----------------|
| TOTAL 2015 | 10 732             | No difference in cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or NYHA class IV heart failure within 180 days but increased risk of stroke at 30 days |
| TASTE 2014 | 249                | Similar flow and stent area, as assessed by OCT |
| TROFI 2013 | 141                | No differences at 30 days in the rate of major adverse cardiac and cerebral events |
| EXPORT 2008| 258                | No difference in no-reflow or slow flow phenomena |
| NONSTOP 2004| 196              | No difference in ST resolution 60 min after PPCI, no difference in mortality at 6 months |
| ITTI 2012  | 100                | No difference in 6-month MACE rate (death, reinfarction, target lesion revascularisation and stroke) |
| MUSTELA 2012| 208              | In patients with high thrombus load, TA yielded better postprocedural STR and reduced MVO at 3 months, but was not associated with a reduction in infarct size and transmurality |
| INFUSE-AMI 2012| 452             | In patients with large anterior STEMI undergoing PPCI with bivalirudin, infarct size at 30 days was significantly reduced by bolus intracoronary abciximab delivered to the infarct lesion site but not by manual aspiration thrombectomy |
| VAMPIRE 2008 | 355               | Reduced MACE rate after 8 months in the TA group |
| TAPAS 2008 | 1,071             | Improved ST-segment resolution and clinical outcome |

MACE, major adverse cardiac event; MI, myocardial infarction; MOV, microvascular obstruction; NYHA, New York Heart Association; OCT, optical coherence tomography; PPCI, primary percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; STR, ST-segment resolution; TA, thrombus aspiration.
REFERENCES
1. Hoole SP, Jaworski C, Brown AJ, et al. Serial assessment of the index of microcirculatory resistance during primary percutaneous coronary intervention comparing manual aspiration catheter thrombectomy with balloon angioplasty (IMPACT study): a randomised controlled pilot study. Open Heart 2015;2:e000238. doi:10.1136/openhrt-2015-000238
2. Ikari Y, Sakurada M, Kozuma K, et al. Upfront thrombus aspiration in primary coronary intervention for patients with ST-segment elevation acute myocardial infarction: report of the VAMPIRE (VAcuum asPiration thrombus REMoval) trial. JACC Cardiovasc Interv 2008;1:424–31.
3. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med 2008;358:557–67.
4. Rezkalla SH, Kloner RA. Coronary no-reflow phenomenon: from the experimental laboratory to the cardiac catheterization laboratory. Catheter Cardiovasc Interv 2008;72:950–7.
5. Jaffe R, Dick A, Strauss BH. Prevention and treatment of microvascular obstruction-related myocardial injury and coronary no-reflow following percutaneous coronary intervention: a systematic approach. JACC Cardiovasc Interv 2010;3:695–704.
6. Frohlich GM, Meier P, White SK, et al. Myocardial reperfusion injury: looking beyond primary PCI. Eur Heart J 2013;34:1714–22.
7. Jolly SS, Caimos JA, Yusuf S, et al. Randomized trial of primary PCI with or without routine manual thrombectomy. N Engl J Med 2015;372:1389–98.
8. Stone GW, Maehara A, Witzenbichler B, et al. Intracoronary abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction: the INFUSE-AMI randomized trial. JAMA 2012;307:1817–26.
9. Sezer M, Ozfaz H, Goren T, et al. Intracoronary streptokinase after primary percutaneous coronary intervention. N Engl J Med 2007;356:1823–34.
10. Cuculì F, De Maria GL, Meier P, et al. Impact of microvascular obstruction on the assessment of coronary flow reserve, index of microcirculatory resistance, and fractional flow reserve after ST-segment elevation myocardial infarction. J Am Coll Cardiol 2014;64:1894–904.
11. Solberg OG, Ragnarsson A, Kvarsnes A, et al. Reference interval for the index of coronary microvascular resistance. Eurointervention 2014;9:1069–75.
12. Stone GW, Abizaid A, Silber S, et al. Prospective, Randomized, Multicenter Evaluation of a Polyethylene Terephthalate Micronet Mesh-Covered Stent (MGuard) in ST-Segment Elevation Myocardial Infarction: the MASTER Trial. J Am Coll Cardiol 2012;60:1975–84.
13. Dziewierz A, Studzik Z, Rakowski T, et al. Impact of direct stenting on outcome of patients with ST-elevation myocardial infarction transferred for primary percutaneous coronary intervention (from the EUROTREAT registry). Catheter Cardiovasc Interv 2014;84:925–31.
14. Frobert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med 2013;369:1587–97.
15. Onuma Y, Thuesen L, van Geuns RJ, et al. Randomized study to assess the effect of thrombus aspiration on flow area in patients with ST-elevation myocardial infarction: an optical frequency domain imaging study–TROFI trial. Eur Heart J 2013;34:1050–60.
16. Chevalier B, Gilard M, Lang I, et al. Systematic primary aspiration in acute myocardial percutaneous intervention: a multicentre randomised controlled trial of the export aspiration catheter. Eurointervention 2008;4:222–8.
17. Kunhi H, Kijima M, Araki T, et al. Lack of efficacy of intracoronary thrombus aspiration before coronary stenting in patients with acute myocardial infarction: a multicenter randomized trial. J Am Coll Cardiol 2004;43:245A.
18. Dudek D, Mielecki W, Burzotta F, et al. Thrombus aspiration followed by direct stenting: a novel strategy of primary percutaneous coronary intervention in ST-segment elevation myocardial infarction. Results of the Polish-Italian Hungarian RAndomized Thrombectomy Trial (PIHRATE Trial). Am J Cardiol 2010;106:966–72.
19. Liu CP, Lin MS, Chiu YY, et al. Additive benefit of glycoprotein IIb/IIIa inhibition and adjunctive thrombus aspiration during primary coronary intervention: results of the Initial Thrombosuction and Tirofiban Infusion (ITTI) trial. Int J Cardiol 2012;156:174–9.
20. De Carlo M, Aquaro GD, Palmieri C, et al. A prospective randomized trial of thrombectomy versus no thrombectomy in patients with ST-segment elevation myocardial infarction and thrombus-rich lesions: MUSTELA (MUltidevice Thrombectomy in Acute ST-Segment ELevation Acute Myocardial Infarction) trial. JACC Cardiovasc Interv 2012;5:1223–30.