

REVIEW

Thrombus Aspiration, from "Heart to Soul"

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Microvascular obstruction (MVO) is one of the most frequent complications encountered during primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction. The embolization of thrombotic material seems to be the leading cause of MVO, and many clinical trials have demonstrated that thrombus aspiration (TA) may be a useful means of preventing this phenomenon. Continuous advancements in technology have contributed to the development of various devices for thrombus aspiration. However, a review of the literature indicates that there is disagreement regarding the role of TA in the prevention and treatment of MVO. TA is increasingly used in the treatment of acute stroke in patients who are admitted to the hospital within eight hours from the onset of symptoms. This review presents the current knowledge regarding the role of TA in the prevention of MVO.

Keywords: microvascular obstruction, thrombus aspiration, PCI**ARTICLE HISTORY**

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INTRODUCTION

Microvascular obstruction (MVO) during primary percutaneous coronary intervention (pPCI) for acute ST-segment elevation myocardial infarction (STEMI), occurs in approximately 40–50% of patients with successfully restored epicardial artery flow and has been proved to be associated with adverse ventricular remodeling and heart failure.^{1–3} So far, none of the available prophylactic and therapeutic strategies have been shown to be effective in the treatment of MVO.^{1–5} As a thrombus is considered to be the primary cause of the development of MVO, catheter retrieval of thrombotic material, known as manual thrombus aspiration (TA), is currently considered the most useful means of preventing an MVO during pPCI.

CLINICAL TRIALS ON THROMBUS ASPIRATION

Several clinical trials have investigated TA and have tried to identify the best therapeutic strategy which would avoid this complication associated with pPCI.

One of the leading clinical trials that examined the role of TA was the TAPAS trial (Cardiac death and reinfarction after one year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study) [NCT01013038], which aimed at determining if, in patients with STEMI, TA, before stent implantation, improves myocardial perfusion compared to conventional pPCI.⁶ The study demonstrated a significantly lower rate of cardiac death (3.6% vs. 6.7%, hazard ratio [HR] 1.93, 95% Confidence Interval [CI] 1.11–3.37, $p = 0.020$), or the composite endpoint of cardiac death or non-fatal re-

infarction (5.6% vs. 9.9%, HR 1.81, 95% CI 1.16–2.84, $p = 0.009$) at one year, in the thrombus aspiration group, compared to the conventional PCI group.

Following the TAPAS trial 6, which confirmed the clinical benefit of TA and a significant decrease in mortality of patients treated with TA, recent STEMI guidelines recommend the use of thrombectomy as a class IIa recommendation.^{7,8} However, the skepticism regarding the benefit of TA persisted, as two other large trials, TASTE, and TOTAL demonstrated a lack of benefit in all the related endpoints.^{9,10} The TASTE clinical trial (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) [NCT01093404], conducted in multiple Scandinavian centers on 7,244 patients with STEMI, who were randomized either to a TA followed by PCI group or to a conventional PCI group, found no significant differences regarding the endpoints such as mortality (2.8% in the thrombus aspiration group compared with 3.0% in the PCI-only group, HR 0.94, 95% CI 0.72–1.22, $p = 0.63$). Also, the rates of hospitalization for recurrent myocardial infarction at thirty days were not significantly different between the groups (0.5% vs. 0.9%, HR 0.61, 95% CI 0.34–1.07, $p = 0.09$), as well as the rates of stent thrombosis (0.2% vs. 0.5%, HR 0.47, 95% CI: 0.20–1.02, $p = 0.06$).⁶

On the other hand, the TOTAL trial (Trial of Routine Aspiration Thrombectomy with PCI versus PCI-alone in patients with STEMI) [NCT01149044] was a randomized, controlled, clinical trial involving 10,732 patients with STEMI, who underwent PCI and were randomized to upfront routine manual aspiration thrombectomy or percutaneous coronary intervention alone. Eight per cent of patients (395 of 5,035) died within one year in the thrombectomy group compared with 8% (394 of 5,029) in the PCI alone group (HR 1.00, 95% CI 0.87–1.15, $p = 0.99$).¹¹

As a consequence, the American College of Cardiology (ACC)/American Heart Association guideline update, published online in 2015, downgraded TA in STEMI from a IIa recommendation to a class III recommendation.¹²

THROMBUS ASPIRATION AND GLYCOPROTEIN IIb/IIIa INHIBITORS (GPIs)

GPIs are potent antiplatelet agents, having a strong anti-inflammatory effect and the capacity to disaggregate platelet aggregates already formed at the site of the thrombus.^{13,14} Despite the expected augmentation of their therapeutic effect, when associated with TA, this association between TA and intra-thrombotic administration of GP IIb/IIIa inhibitors failed to establish any results concerning the surrogate parameters of MVO.^{15,16}

For instance, the INFUSE-AMI trial (A 2 × 2 Factorial, Randomized, Multicenter, Single-Blind Evaluation of Intracoronary Abciximab Infusion and Aspiration Thrombectomy in Patients Undergoing Percutaneous Coronary Intervention for Anterior ST-Segment Elevation Myocardial Infarction) [NCT01059214] demonstrated that the association between TA and intracoronary infusion of Abciximab in STEMI patients leads to a decrease in one-year mortality from 10.4% to 4.5% ($p = 0.03$), a reduction in the incidence of severe heart failure from 10.3% to 4.2% ($p = 0.02$) and a lower rate of stent thrombosis, 3.8% versus 0.9% ($p = 0.046$).¹⁷

THROMBUS ASPIRATION IN LATE PRESENTERS

In STEMI patients presenting after the therapeutic window for interventional revascularization, it was shown that embolization of an older thrombus could be more detrimental because of its association with a higher risk of mechanical thrombus dislodgment and distal embolization, with subsequent microvascular injury and expansion of the infarct size.

In a recently published study, Desch *et al.* analyzed the results of TA in late presenters with STEMI, involving 152 patients randomly allocated to TA followed by pPCI, or conventional pPCI without TA.¹⁸ Disappointingly, the results were negative and similar to most of the previously published large trials. Neither MVO and infarct size, nor the myocardial recovery and left ventricular ejection fraction differed between the study groups.

Many questions have been raised in order to explain the role of TA in the treatment of STEMI, such as whether the thrombus can still be considered the primary cause of acute myocardial infarction, what are the particular aspects encountered when the time of embolism is not precisely known, or whether manual TA is not sufficiently efficient in removing the thrombotic material.

COMMERCIAL DEVICES FOR THROMBUS ASPIRATION

In order to clarify these controversies, consideration has been directed at physical or technical factors in addition to randomized clinical trials. Hara *et al.* compared the *in vitro* performances of six and seven French guide catheters from six manufacturers.¹⁹ They noted that the rigidity of the aspired material, its shape and deformability and its surface properties were linked to frictional resistance, as well as the form of the catheter lumen. Differences in the frictional resistance associated with

the catheter material appear to influence the efficiency of the TA.

Pioud *et al.* studied the influence of the coronary anatomy and the age of the thrombus on the performance of two types of catheters, the Export Advance™ aspiration catheter (Medtronic, Minneapolis, MN, USA) and the Proxis embolic protection catheter (St. Jude Medical, St. Paul, MN, USA).²⁰ The Export catheter has a proximal shaft braiding for support and a distal shaft braiding for flexibility with full wall variable braiding. The difference between the two devices consists in the presence of straight tubes with a single bend for the Export tubes and a double bend for the Proxis. Complete aspiration of the thrombus was obtained in only 55.3% of the tests, and no difference was observed between the two devices. Regarding the impact of the age of the thrombus, it was noted that total thrombectomy was achieved more frequently in cases where thrombus formation had occurred less than six hours, compared to cases where thrombus formation had occurred more than twelve hours.

In vitro results showed that the use of different commercial devices could produce varying degrees of thrombus removals, suggesting a primary dependence on the distal tip configuration of the catheter.

Pennati *et al.* used a computational methodology based on catheter tip modeling to investigate the factors affecting thrombus suction.²¹ Their analysis of the two-phase flow, fresh blood, and the clot was based on a crude representation of the clot rheology. The conclusion was that the addition of lateral holes in the catheter tip could be disadvantageous for thrombus removal when these are not in direct contact with the thrombotic mass. Based on the same modeling methodology, Li *et al.* confirmed Pioud's results regarding the impact of the thrombus' rheological properties, or age, on the efficiency of TA. Almost 50% of an older, more viscous thrombus remained trapped between the outer surface of the catheter tip and the interior surface of the vessel with consequential fragmentation.²²

The most comprehensive study on the effects of catheter tip design and rheological properties of a thrombus on the TA efficiency was conducted by Sajjad Soleimani-Amiri.²³ After thorough experimental investigations of the rheological properties of the clot, a CFD model based on several tip designs and clot rheological models was developed. The study indicated that a catheter with side holes performed better for fresh, lower viscosity clot, whereas older clots of higher viscosity were better treated with catheters without side holes. Regarding tip design, the simulations indicated that the catheter with a right-angle

tip performed better on clot aspiration, although most of the commercial catheters feature a beveled tip.

Based on these studies it may be concluded that, when it comes to absorbing older clots from a coronary artery, the efficiency of the TA devices is poor. Thrombus age appears to be critical because a fresh thrombus is considered the primary cause of distal microcirculation obstruction.

An OCT sub-study of the largest thrombectomy trial (TOTAL) has shown that in patients undergoing pPCI for STEMI, manual thrombectomy did not reduce the pre-stent thrombus burden when compared to PCI-alone. Moreover, both groups were associated with a low thrombus burden before the primary revascularization procedure.²⁴

DISTAL PROTECTION DEVICES IN THE PREVENTION OF MVO

The EMERALD and DEDICATION studies considered the role of distal protection devices in the prevention of MVO. The EMERALD trial (Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris) aimed to investigate if the protection of the distal microcirculation against the thromboembolic fragments during primary PCI can improve reperfusion and decrease the infarction area. Five-hundred one patients with ST-segment elevation MI were enrolled in the trial, who had presented at the emergency room within six hours from the onset of symptoms undergoing pPCI or rescue intervention, after failed thrombolysis. The study groups were patients who received PCI associated with distal microcirculatory protection system versus patients who underwent angioplasty without distal protection. There were no significant differences between the two groups regarding the ST-segment resolution (63.3% vs. 61.9%, $p = 0.78$) and left ventricular infarct size.²⁵ On the other hand, the DEDICATION study evaluated the use of distal protection during PCI for STEMI patients. The trial included 626 patients with STEMI referred within twelve hours of the onset of symptoms, who underwent PCI with or without distal protection.²⁶ The results of these trials were disappointing, as no differences were shown between the groups regarding the primary end-point which consisted of incomplete or >70% ST-segment resolution ($p = 0.29$), or secondary end-points such as infarct size or MVO surrogate parameters.^{26,27} It was concluded that intra-procedural embolism during PCI might be less relevant for MVO and the determination of infarct size. Several published data using Doppler guide wire detection suggested that only a small number of emboli occur during a PCI procedure, confirming the above-mentioned hypothesis.²⁸

TIMING FOR THROMBUS ASPIRATION

Considering these data, alternative approaches regarding the timing of embolism and the composition of embolic material require to be considered. In a study published by Kramer *et al.*, 40% of the patients had an old thrombus in materials extracted using TA.²⁹ Kramer suggested that an old thrombus requires a longer period of formation within the non-occlusive unstable coronary plaque. The presence of an older thrombus was associated with other conditions leading to higher mortality. Patients with older thrombi experience short, temporary, occlusive thrombosis before the onset of symptoms. Repeated episodes of recanalization resulting from partial, spontaneous lysis may be associated with more extensive embolism and MVO, resulting in less efficient reperfusion because of pre-procedural MVO. Statistically, significant differences were found in this study among patients with fresh compared to older thrombus regarding total ischemic time, which was significantly longer in the patients with older thrombus, as well as a higher incidence of mortality. Moreover, autopsy of sudden death patients showed intra-myocardial microemboli in approximately 50% of cases and confirmed this mechanism of MVO.³⁰

INDEX OF MICROCIRCULATORY RESISTANCE

De Maria *et al.* showed that 60% of patients presented with a pre-stenting index of microcirculatory resistance (IMR) higher than 40, suggesting the presence of pre-procedural MVO.³¹ In this group, the total ischemic time was longer, infarct size measured by the troponin test was larger, and more patients had a TIMI flow 0 at presentation. One-third of patients had evidence of impaired microvascular function after a revascularization procedure with an IMR of >40 after stent implantation. This suboptimal outcome reflected an incomplete normalization of an elevated IMR, and these patients were more commonly late clinical presenters, with longer ischemic times. However, in another subgroup of patients with a final IMR of <40, an increase in IMR was observed after stent implantation, which was associated with a larger thrombotic burden and/or higher implanted stent volume, suggesting an intra-procedural squeezing embolization. However, this study had some significant limitations. The authors used the IMR as a parameter of MVO, and the measurements were performed after pre-dilatation. Regarding the usefulness of the IMR for MVO evaluation, a recent paper showed that a pressure at zero flow (Pzf) measured at the time of pPCI was a better predictor of the extent of myocardial infarction than

IMR.³² Recently it was demonstrated that coronary wedge pressure (CWP), which is similar to Pzf, is a good means of estimating pre-procedural MVO.³³

TA has also been described as a valid option for the treatment of acute ischemic stroke. The data from the TOTAL trial demonstrated a high risk of stroke in the group of patients treated with TA, significantly greater than in the control group. With respect to the rates of stroke within one year, the TOTAL trial found significant differences between the two groups. 1.2% of patients from the thrombectomy group presented with stroke within one year compared to 0.7% of the patients from the PCI-only group, (HR 1.66, 95% CI 1.10–2.51, $p = 0.015$).¹¹ Thrombus dislodgment from coronary arteries into the cerebral circulation may have accounted for early ischemic strokes in patients undergoing TA. However, the more frequent occurrence of stroke, in the period between 90 and 180 days after PCI, remained difficult to explain. Probably small sized embolic materials could cause the development of local obstructions. The role of TA in acute embolic strokes is now recognized, following reports in studies. Jovin *et al.* included 206 patients with acute ischemic stroke randomized to TA with a Solitaire™ FR Revascularization retriever (Covidien, Irwin, CA, USA) versus standard medical care with alteplase.³⁴ The study used the Rankin scale to evaluate the severity of global disability at ninety days, ranging from 0 points to 6 points (no symptoms → to death). The study revealed that thrombectomy reduced the severity of the disability. In the TA group, 43.7% of patients scored between 0–2 on the modified Rankin scale at ninety days compared to 28.2% of the patients with only drug therapy ($p = 0.02$), proving that TA was associated with improved functional outcomes and higher rates of angiographic revascularization.³⁴

CONCLUSIONS

The leading cause of MVO is represented by the thrombus embolization occurring during coronary angioplasty procedures. TA is a technique that prevents the complications of MVO, decreasing the mortality in STEMI patients treated with pPCI. However, the efficacy of TA is largely based on the configuration of the absorption catheter. Nowadays, the indications of TA have been expanded to acute stroke, improving the outcomes obtained in the treatment of this devastating disease.

Finally, we agree with James C. Blankenship that "Oculo-thrombotic Reflex, Why We Will Never Stop Aspirating Coronary Thrombi", because of the emotional aspect of this issue.³⁵

CONFLICT OF INTEREST

Nothing to disclose.

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