Impact of Thrombus Aspiration on Myocardial Tissue Reperfusion and Left Ventricular Functional Recovery and Remodeling After Primary Angioplasty

Francesco Liistro, MD; Simone Grotti, MD; Paolo Angioli, MD; Giovanni Falsini, MD; Kenneth Ducci, MD; Silvia Baldassarre, MD; Alessandra Sabini, MD; Rossella Brandini, MD; Eugenia Capati, MD; Leonardo Bolognese, MD

Background—Failure to achieve myocardial reperfusion often occurs during percutaneous coronary intervention (PCI) in patients with myocardial infarction with ST-segment elevation. We hypothesized that manual thrombus aspiration during primary PCI would favorably influence tissue-level myocardial perfusion and left ventricular (LV) functional recovery and remodeling.

Methods and Results—We prospectively randomized 111 patients with ST-segment elevation myocardial infarction to either standard or thrombus-aspiration PCI. Primary end point of the study was postprocedural incidence of ST-segment resolution ≥70%. Secondary end points included Thrombolysis in Myocardial Infarction (TIMI) myocardial perfusion grade ≥2, the combination of TIMI myocardial perfusion grade ≥2 and ST-segment resolution ≥70%, post-PCI TIMI grade 3 flow, corrected TIMI frame count, myocardial contrast echocardiography score index, the absence of persistent ST-segment deviation, and time course of wall-motion score index, LV ejection fraction, and LV volume in the 2 groups. The incidence of ST-segment resolution ≥70% was 71% and 39% in the thrombus-aspiration and standard PCI groups, respectively (odds ratio, 3.7; 95% CI, 1.7 to 8.3; P=0.001). TIMI myocardial perfusion grade ≥2 was attained in 93% in the thrombus-aspiration group compared with 71% in the standard PCI group (P=0.006). The percentage of patients with ST-segment resolution ≥70% and TIMI myocardial perfusion grade ≥2 was significantly greater in the thrombus-aspiration group compared with the standard PCI group (69% versus 36%, P=0.0006). Myocardial contrast echocardiography score index was significantly higher in the thrombus-aspiration group compared with the standard PCI group (0.86±0.20 versus 0.65±0.31; P<0.0001). A significantly greater improvement in LV ejection fraction and in wall-motion score index from baseline to 6-month follow-up was observed in the thrombus-aspiration group compared with the standard PCI group (LV ejection fraction from 48±6% to 55±6% versus 48.7±7% to 49±8%, P<0.0001; wall-motion score index from 1.59±0.13 to 1.31±0.19 versus 1.64±0.20 to 1.51±0.26, P=0.008). Twelve patients (11%) developed LV remodeling at 6 months, 2 (4%) in the thrombus-aspiration group and 10 (18%) in the standard PCI group (P=0.02).

Conclusions—Manual thrombus aspiration in the setting of primary PCI improves myocardial tissue-level perfusion as well as LV functional recovery and remodeling. (Circ Cardiovasc Intervent. 2009;2:376-383.)

Key Words: thrombus aspiration ■ angioplasty ■ remodeling ■ myocardial infarction ■ reperfusion

Timely restoration of normal antegrade flow and tissue-level perfusion are key factors in the reduction of mortality in ST-segment elevation myocardial infarction. Despite restoration of epicardial blood flow with primary percutaneous coronary intervention (PCI), microvascular obstruction with diminished myocardial perfusion occurs in a large proportion of patients, contributing to increased infarct size and reduced survival.1–5 Mounting interest has emerged regarding the role of distal embolization as a major determinant of impaired myocardial perfusion after primary PCI.6,7 In this regard, the use of a mechanical device for thrombus removal is intuitively attractive for improving reperfusion and survival after primary PCI. Although many clinical trials testing these devices have been performed,8–20 they have yielded conflicting results, in part due to patient and device selection. In fact, these trials evaluated mechanical devices with different designs and operational mechanisms. Some mechanical devices may cause physical damage to the vessel endothelium, which may create new thrombi or distal embolization. A 6F or 7F compatible manual-aspiration catheter,

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From the Cardiovascular Department (F.L., S.G., P.A., G.F., K.D., S.B., A.S., R.B., E.C., L.B.), San Donato Hospital, Arezzo, Italy; and Department of Cardiology (E.C.), University of Siena, Italy.
Correspondence to Francesco Liistro, MD, Department of Cardiovascular Disease, San Donato Hospital, Arezzo, Italy. E-mail francescoliistro@hotmail.com
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PCI and Medications

Coronary angioplasty and stent implantation were performed according to institutional standards. For all patients, the first procedural step was the passing of a floppy, steerable guide wire through the target lesion; direct stenting was left to operator’s discretion and usually performed in patent vessel with no or mild calcification. In patients in the conventional PCI group, this step was followed by balloon dilation to establish antegrade flow. In patients in the thrombus-aspiration group, this step was followed by the advancing of the 6F Export Aspiration Catheter (Medtronic, Minneapolis, Minn; crossing profile, 0.068 in.) into the target coronary segment during continuous aspiration. Aspiration was started proximal to the occluded site, gently pushing the catheter through the occlusion and then pulling it in a proximal direction, keeping negative pressure even when the occlusion was crossed or when there was no longer back bleeding in the syringe. Withdrawal of the catheter from the artery and from the guiding catheter was performed with permanent negative pressure. When necessary for stent delivery, balloon dilation was performed before stenting. In all patients, after the restoration of antegrade flow, intracoronary nitrates were given to ensure maximal epicardial vasodilatation, to determine the size and length of the stent, and to facilitate stent placement. All placed stents were bare-metal stents.

Pharmacological treatment before PCI included the administration of aspirin (a loading dose of 500 mg), heparin (70 IU/kg), and clopidogrel (a loading dose of 600 mg). All patients also received the glycoprotein IIb/IIIa inhibitor abciximab with an intravenous bolus and a continuous intravenous infusion of 0.125 μg/kg/min for 12 hours and postprocedural infusion without heparin.

Data Analysis

Angiographic, echocardiographic, and clinical data were prospectively collected on dedicated case report forms. All coronary angiograms were evaluated by 2 readers without the knowledge of clinical status and treatment modality. Flow in the epicardial arteries was assessed for TIMI flow grade and corrected TIMI frame count by use of previously described methods. TMPG was used to assess myocardial tissue-level perfusion. A “closed” microvasculature was defined as either TMPG 0 or 1, with TMPG 2 or 3 representative of an “open” microvasculature. TMPG was assessed only in the area supplied by the culprit vessel.

Intracoronary MCE was performed on completion of coronary angioplasty. Two-dimensional contrast echocardiographic images were analyzed by 2 readers who had no knowledge of the clinical, treatment modality, and angiographic data. The left ventricle was divided according to a 16-segment model. The echocardiographic view that best delineated the vascular territory of the culprit vessel was chosen for contrast echocardiographic analysis. In this view, the contrast effect was determined in the postinjection cycles that showed the best delineation between contrast-enhanced and non-enhanced myocardium. A score of 1 within a segment of the area of interest after angioplasty was interpreted as adequate perfusion. A patient was considered to have adequate perfusion if ≥50% of the segments in the area of interest had a homogeneous contrast effect (score=1). In each patient, an MCE score index was derived by averaging the scores from each segment within the area of interest. Details pertaining to acquisition and analyses of echocardiographic data were reported elsewhere.

Regional wall motion was assessed by 2 readers who had no knowledge of the clinical, treatment modality, angiographic data, and MCE results, according to the same 16-segment model used for contrast echocardiography. For each segment, wall motion was scored as 1 (normal), 2 (hypokinetic), 3 (akinetik), or 4 (dyskinetic). In each patient, a wall-motion score index (WMSI) was derived by averaging the scores from each segment. LV volumes and ejection fraction (EF) were measured with the modified Simpson rule algorithm. The mean value of 3 measurements of the technically best cardiac cycles was taken from each examination. Intraobserver and interobserver variability values in the evaluation of end-diastolic volumes were ≤5%, which indicates the good reproducibility of the measurements. Temporal changes in LV volumes were calculated.
as the percentage changes at 6 months compared with baseline. The volume indexes were obtained by dividing the volume by the body surface area at each time point. LV remodeling was considered as an increase in LV end-diastolic volume > 20% at 6 months compared with baseline. EF was calculated from the formula: (end-diastolic volume - end-systolic volume)/end-diastolic volume.

The degree of resolution of ST-segment elevation (STR) was categorized as complete when ≥ 70% at 90 minutes. Persistent ST-segment deviation was defined as the sum of the ST-segment depression and the ST-segment elevation > 2 mm at 180 minutes. For the STR analysis, a consensus by 2 different readers blinded to treatment assignment, angiographic and echocardiographic data were required.

After the procedure, patients underwent repeated sampling (every 8 hours for 2 days, then every day) for creatine kinase-MB mass assessment.

**Study End Points**

The primary end point of the study was the comparison of STR ≥ 70% incidence between patients randomized to standard PCI and those randomized to manual thrombus aspiration.

The key secondary end points were the incidence of TMPG ≥ 2 and the combination of TMPG ≥ 2 and STR ≥ 70%. Other secondary end points included the TIMI 3 grade flow, corrected TIMI frame count, myocardial contrast echocardiography score index, the absence of persistent ST-segment deviation, time course of WMSI, LVEF, and LV volumes in the 2 groups.

**Power Calculation and Statistical Analysis**

The study sample size was powered to demonstrate a significant difference in the primary end point of incidence of STR ≥ 70%, which was ~50% in primary PCI studies, and from 58% to 90% in randomized trials, where thrombus aspiration/thrombectomy was systematically used. Starting from such figure and thus assuming a 50% event rate in the control arm with a 30% increase in the study arm, we estimated that 104 patients would provide ≥90% statistical power (1-β ≥ 0.90; α = 0.05) to detect such difference in a prospective 1:1 randomized study. The calculation of the sample size was based on a Z test. Odds ratios with 95% CIs were calculated to compare the incidence of the primary end point between the 2 study groups.

Continuous data are expressed as mean ± SD. Categorical variables (TIMI flow grade 3, TMPG ≥ 2, and the absence of persistent ST-segment deviation) were compared with the use of the χ² test or Fisher exact test. Repeated-measures ANOVA was used to analyze changes in LV volumes, LVEF, and WMSI. For the analysis of MCE data by segment, all the segments at risk for each patient were entered into the Generalized Estimating Equation method to take into account multiple segments per patient.

A backward stepwise multivariable logistic regression analysis, including the baseline clinical (age, gender, risk factors, door-to-balloon time, Killip class > 3) and angiographic variables (culprit vessel, multivessel disease, and prepercutaneous transluminal coronary angioplasty TIMI flow grade), was also used to further assess the independent predictive value of thrombus aspiration on the combination of STR ≥ 70% and TMPG ≥ 2.

To avoid the inflation of type I error due to multiple comparisons, Bonferroni’s correction was applied to secondary end points analyses by dividing nominal α error at 5% by the number of end points, setting final type I error for significance at P = 0.006. Statistical analyses were performed with SPSS 8.0 for Windows (SPSS Inc, Chicago, III). All analyses were based on an intention-to-treat approach.

**Results**

**Patient Population**

Between December 2006 and March 2008, 203 patients were referred to our institution for primary PCI. Of these, 32 patients (16%) were excluded for contraindications to platelet glycoprotein IIb/IIIa inhibitors use, 33 patients (16%) because of previous MI, and 27 patients (13%) for inadequate echocardiographic image quality. We randomized the remaining 111 patients to manual thrombus aspiration (n = 55) or standard PCI (n = 56). Baseline clinical and angiographic characteristics were well matched between the 2 groups (Table 1).

**Procedural Results and Angiographic Outcome**

There was no significant difference in the angiographic and procedural characteristics between the 2 study arms (Table 2).
In 2 patients, failure to advance the device across the culprit lesion without predilation was observed. There was a trend toward a decrease in the thrombus-aspiration group in the incidence of distal embolization (7% versus 25%; \(P=0.01\)) and no-reflow phenomenon (4% versus 18%; \(P=0.02\); Table 2).

In the multivariable analysis, the only independent predictors of the combination of STR \(\geq 70\%\) and TMPG \(\geq 2\) were randomization to thrombus aspiration (\(P=0.008\)); door-to-balloon time (\(P=0.02\)); and baseline TIMI 0 to 1 in the infarct-related artery (\(P=0.03\)).

**Perfusion by Myocardial Contrast Echocardiography**

Intracoronary MCE analysis was performed in all patients and included a total of 344 segments; of these, 246 (72%) showed homogeneous contrast effect (score=1). A higher number of perfused segments (score=1) was observed in the thrombus-aspiration group compared with standard PCI group (85% versus 64%; \(P<0.0001\), Generalized Estimating Equation adjusted). Similarly, myocardial contrast echocar-

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**Primary End Point of the Study**

The incidence of post-PCI STR \(\geq 70\%\) was 71% (39 of 55 patients) in the thrombus-aspiration group and 39% (22 of 56 patients) in the standard PCI group (odds ratio, 3.7; 95% CI, 1.7 to 8.3; \(P=0.001\); Figure 1).

**Key Secondary End Points**

Persistent ST-segment deviation, postprocedural TIMI 3 flow, corrected TIMI frame count and TMPG \(\geq 2\) in the 2 study groups are reported in Figure 2.

The incidence of TMPG \(\geq 2\) at the end of the PCI was 93% (51 of 55 patients) in the thrombus-aspiration group and 71% (40 of 56 patients) in the standard PCI group (\(P=0.006\)). The percentage of patients with STR \(\geq 70\%\) and TMPG \(\geq 2\) was significantly greater in the thrombus-aspiration group compared with the standard PCI group: 69% (38 of 55 patients) versus 36% (20 of 56 patients) (\(P=0.0006\); Figure 3).

In the multivariable analysis, the only independent predictors of the combination of STR \(\geq 70\%\) and TMPG \(\geq 2\) were randomization to thrombus aspiration (\(P=0.008\)); door-to-balloon time (\(P=0.02\)); and baseline TIMI 0 to 1 in the infarct-related artery (\(P=0.03\)).
diography score index was significantly higher in the thrombus-aspiration group than in the standard PCI group (0.86 ± 0.20 versus 0.65 ± 0.31; P < 0.0001). Analysis by patient showed that patients in the thrombus-aspiration group more frequently had a normal tissue-level perfusion by MCE than those in the standard PCI group (87% versus 61%; P = 0.002; Figure 4).

Time Course of Changes in Regional and Global Ventricular Function and LV Volumes

Echocardiographic follow-up was completed in all patients (Figure 5). At baseline, there were no significant difference in WMSI and LVEF between the thrombus-aspiration group and standard PCI group (panels A and B; LVEF: 48 ± 6 versus 48 ± 7%; P = 0.6; WMSI: 1.59 ± 0.13 versus 1.64 ± 0.20; P = 0.1, respectively). From baseline to 6-month follow-up, a greater improvement in LVEF (from 48 ± 6% to 55 ± 6% versus 48 ± 7% to 49 ± 8, P < 0.0001 by ANOVA) and WMSI (1.59 ± 0.13 to 1.30 ± 0.19 versus 1.64 ± 0.20 to 1.51 ± 0.26, P = 0.008 by ANOVA) was observed in the thrombus aspiration compared with the standard PCI group.

LV end-systolic volume index and end-diastolic volume index were similar in both groups at baseline. A significant increase in end-diastolic volume index (panel C) was observed only in the control group (P = 0.001 by ANOVA).

Panel D shows the time course of end-systolic volume index in the 2 groups. In the thrombus-aspiration group, end-systolic volume index significantly decreased between baseline and 6-month follow-up, whereas it remained substantially unchanged in the standard PCI group (P < 0.0001 by ANOVA).

Twelve patients (11%) developed LV remodeling at 6 months, 2 (4%) in the thrombus-aspiration group and 10 (18%) in the standard PCI group (P = 0.02).

Clinical Outcome at 6 Months

Six-month occurrence of death, reinfarction, LV failure, and new revascularization were similar in the 2 groups (Table 3).

Discussion

The results of the present randomized study show that manual thrombus aspiration in patients with ST-segment elevation myocardial infarction improves myocardial reperfusion, documented by a clear improvement in the myocardial blush grade, myocardial contrast enhancement by intracoronary MCE, and increased resolution of ST-segment elevation. In
addition, the observed improvement in tissue-level perfusion was associated with a significant improvement in regional and global contractile LV function and a decrease in the incidence of LV remodeling at 6 months.

**Thrombus Removal, Epicardial Flow, and Myocardial Reperfusion**

The clinical importance of embolization of atherothrombotic material from unstable plaques in patients with myocardial infarction with ST-segment elevation has been recognized, and the use of thrombectomy devices to reduce distal embolization preserving tissue-level perfusion has been tested in several studies with conflicting results. This variation in results may be in part related to the device used, because trials involving manual-aspiration devices have all shown favorable effects of aspiration on myocardial-perfusion variables. The recently published TAPAS trial and a large meta-analysis involving 9 studies dealing specifically with manual thrombectomy showed a significant reduction in 30-day and 1-year mortality, explained by the significant benefits in epicardial and myocardial perfusion, and less distal embolization. Randomized trials conducted so far on mechanical thrombectomy devices have failed to show benefits in terms on infarct size and myocardial perfusion. Whether the observed benefits in survival with manual thrombectomy but not other mechanical devices are strictly depending on device features and performance or the availability of larger number of trials, is still unknown. Nevertheless, our data convincingly show that manual thrombus aspiration in the setting of primary PCI is associated with a significant improvement both of the epicardial flow and myocardial perfusion, as assessed by the use STR, angiographic TMPG, and myocardial contrast enhancement by intracoronary MCE. The consistency and reproducibility of the results achieved by the use of different techniques to explore different aspects of microvascular integrity further enhance the strength of the tested hypothesis that distal embolization during primary PCI plays a significant role in the pathogenesis of microvascular obstruction because thrombus aspiration significantly reduces the severity and extent of the phenomenon.

**Prevention of Distal Embolization, LV Function Recovery, and LV Remodeling**

Survivors of AMI are at increased risk for subsequent fatal and nonfatal cardiovascular events. Early studies demon-
strated that total cardiac enzyme release, as an indicator of the extent of myocardial necrosis, is related with short- and long-term prognoses after myocardial infarction.33 Subsequent studies demonstrated that the degree of LV dysfunction and dilation correlates well with mortality and is useful in risk stratification of patients after AMI. LV remodeling after AMI is a precursor of the development of overt heart failure and is an important predictor of mortality.27,38 and the key role of microvascular dysfunction complicating mechanical reperfusion after AMI as a major predictor of early LV remodeling has already been demonstrated.27 Accordingly, LVEF and/or LV volumes have become the established predictors for mortality in patients with coronary artery disease and therapeutic interventions that improve LVEF and limit LV remodelling may have important clinical and prognostic implications.

Thus, it is conceivable to expect that a thrombus aspiration-related reduction in microvascular obstruction is associated with LV recovery and limited LV remodeling. This study shows that the improvement in tissue-level perfusion achieved by manual thrombus aspiration is mirrored by a significant recovery of LV regional and global function and a significant reduction in LV remodeling at 6 months. The effect of thrombus aspiration on LV remodeling has not fully investigated in randomized trials. The myocardial contrast echocardiography substudy of the REMEDIA trial enrolled 50 patients randomly assigned to thrombus aspiration or standard PCI. Thrombus aspiration was associated with a significant reduction in severity and extent of myocardial obstruction, but with only a slight, not significant reduction in LV remodeling at 6 months. However, the study was not powered to demonstrate prevention of LV remodeling. De Luca et al showed that, in 76 patients with anterior myocardial infarction, thrombus aspiration was associated with significantly lower end-diastolic and end-systolic LV volumes at 6 months than with conventional PCI. The results of this study confirm and expand these findings providing the pathophysiological missing link between thrombus removal, tissue-level perfusion, LV remodeling, and clinical outcome.

Study Limitations

The study reflects a single-center experience using surrogate end points and was not designed to test differences in a clinical outcome. Conversely, this study integrated different means of investigating the coronary circulation at the epicardial and tissue levels with a complete angiographic and echocardiographic analysis to obtain high-quality data.

It has been suggested that direct stenting without balloon predilatation in patients who have myocardial infarction with ST-segment elevation may result in improved distal flow and reduced embolization. Our study was not designed to evaluate the effect of dilation before stenting; however, the percentage of direct stenting was low and not significantly different in the 2 study group and should not have affected the results.

Conclusions

Manual thrombus aspiration in the setting of primary PCI improves myocardial reperfusion as assessed by myocardial blush, myocardial contrast enhancement by intracoronary MCE, and STR. The improvement in tissue-level perfusion is paralleled by a significant improvement in regional and global LV function and a significant reduction of LV remodeling at 6 months.

Disclosures

None.

References

Mounting interest has emerged regarding the role of mechanical devices for thrombus removal for improving reperfusion and survival after primary percutaneous coronary intervention. Whether observed improvements in myocardial reperfusion and clinical outcome with thrombus aspiration are directly connected to better follow-up left ventricular function and geometry has not yet been clarified. In this study, we evaluated the effect of manual thrombus aspiration on tissue-level perfusion as assessed using ST-segment resolution, Thrombolysis in Myocardial Infarction myocardial perfusion grade, and myocardial perfusion grade to mortality after administration of thrombolytic drugs. Circulation. 2000;101:125–130.


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