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ORIGINAL ARTICLES:
Preservation of Myocardial Microcirculation During Mechanical Reperfusion for Myocardial Ischemia with Either Abciximab or Eptifibatide

- **George Stoupakis, James Orlando, Harmit Kalia, Joan Skurnick, Muhamed Saric, Rohit Arora**

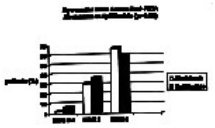
Myocardial Blush Grade (MBG) is an angiographic method of assessing myocardial microcirculation and provides independent risk stratification among patients with normal TIMI 3 flow. Although the beneficial effect of abciximab on microvascular perfusion is well established, the efficacy of eptifibatide in the prevention of platelet aggregation and distal microembolization is less proven. After a pharmacologic shift by our institution towards the use of eptifibatide in patients with unstable angina presenting for PCI, we sought to evaluate our experience by retrospectively comparing the effect on myocardial perfusion between abciximab and eptifibatide following PCI in stable angina or acute coronary syndrome. Microcirculatory perfusion was reviewed in 101 consecutive patients (23 stable angina, 61 unstable angina, 17 non-q MI) undergoing PTCA/stenting. This comparison was between the last group of 51 patients who routinely received standard bolus and infusion of abciximab and the first group of 50 patients who began receiving standard bolus and infusion of eptifibatide. Baseline characteristics between the two groups were balanced, except for more patients with previous CABG in the eptifibatide group. Angiograms were evaluated by 2 blinded independent reviewers for MBG as follows: 0, no blush; 1, minimal blush; 2, moderate blush; and 3, normal blush. TIMI 3 flow was seen in 98 patients. MBG scores were not significantly different in the abciximab group (67% MBG 3; 31% MBG 2; 2.0% MBG 0–1) than in the eptifibatide group (58% MBG 3; 36% MBG 2; 6.0% MBG 0–1); p = 0.34. Patients with prior PTCA/stenting had lower MBG scores (0–2) compared to patients without prior PTCA (58% vs 31%; p = 0.03). There were significantly lower MBG scores in all patients with prior PTCA or CABG compared to patients without (55% vs 30%; p = 0.03). MBG scores significantly and inversely correlated with peak troponin I levels (r = -0.18, one-tailed p = 0.04). The similarity in myocardial perfusion between abciximab and eptifibatide suggests that both compounds are equally effective in reducing platelet aggregation and microembolization during mechanical reperfusion. Lower MBG scores in patients with prior PTCA or revascularization may be explained by irreversible microvascular dysfunction resulting from distal microembolization during the previous procedure. Lower MBG scores in patients with higher troponin I levels may reflect more frequent microemboli and microinfarcts during an ischemic event. Larger prospective studies need to be performed to validate these findings.

Although rapid restoration of coronary flow in an infarct related artery is associated with improved survival, it is becoming increasingly evident that myocardial perfusion, and not just epicardial flow, is vital to myocardial salvage and viability. For example, patients with TIMI 2 flow are found to have a higher mortality than those with TIMI 3 flow, possibly as a result of impaired microcirculation.1 Myocardial blush grade (MBG) is an angiographic method of assessing myocardial microcirculation and provides independent risk stratification among patients with normal epicardial TIMI 3 flow. Higher blush grades are associated with better myocardial perfusion and clinical outcomes.2 More recently, the glycoprotein (GP) IIb/IIIa inhibitor, abciximab, has been shown to significantly improve myocardial microcirculation, as assessed by MBG, in patients undergoing primary coronary intervention (PCI) for acute ST elevation myocardial infarction (MI).3 This benefit was most prominent in diabetics and is presumed to result from reduced platelet aggregation and distal microembolization. In addition to electrocardiographic ST segment resolution,4 the beneficial effect of abciximab on microcirculatory perfusion has also been established using Doppler flow wire,5 myocardial contrast echocardiography,6 corrected TIMI frame count (CTFC)6 and TIMI myocardial perfusion grades.7 The ESPRIT trial demonstrated the benefit of eptifibatide in patients undergoing PCI.8 However, the effect of eptifibatide on microvascular perfusion is relatively unknown.

Figure 1

Based on data from the ESPRIT trial, our institution decided on a cost-effective shift towards the use of eptifibatide in all patients presenting with stable angina or acute coronary syndrome. However, there is no study comparing the efficacy of the monoclonal

antibody, abciximab, to the peptide, eptifibatide, on perfusion of myocardial microcirculation following PCI in either stable angina or acute coronary syndrome. Thus, to assess the efficacy of either GP IIb/IIIa receptor blocker, we performed a retrospective analysis comparing the effect on myocardial perfusion between the last 51 patients who routinely received abciximab for unstable or stable angina versus the first 50 patients who began to receive eptifibatide after the pharmacologic shift by our institution. The significance of prior revascularization on microcirculatory perfusion was also investigated. We hypothesized that there would be no difference in preservation of microcirculatory perfusion, as assessed by MBG, between both drugs.

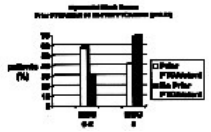


Bar graph demonstrating no significant difference in myocardial blush grade (MBG) between the abciximab group and the eptifibatide group.

Methods

Patients. One hundred and one consecutive patients who presented to our hospital with myocardial ischemia (23 stable angina, 61 unstable angina, 17 non-q MI) who underwent intracoronary revascularization between July 2001 and April 2002 were reviewed for microcirculatory perfusion. Fifty-one patients received standard bolus (0.25 mg/kg) and infusion (0.125 mg/kg/minute for 12 hours) of abciximab while fifty patients received standard bolus (two 180 ug/kg boluses given 10 minute apart) and infusion (2 mg/kg/minute for 18–24 hours) of eptifibatide. Saphenous venous graft lesions and patients with end-stage renal disease were excluded because of their increased risk of distal embolization. Successful percutaneous transluminal coronary angioplasty (PTCA) with stenting was performed in all patients. Troponin I (cTnI) levels were drawn on admission and every 6–8 hours up until cardiac catheterization and measured using the Abbott Axsym System in our central laboratory. By this method, the serum cTnI in a normal healthy population is < 5.0 ng/ml. Two-dimensional echocardiography was performed in the apical four-chamber, parasternal long-axis, and parasternal short-axis view with area-length method used to calculate ejection fraction.

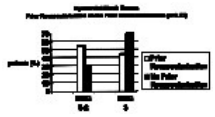
Figure 2



Bar graph demonstrating significantly lower myocardial blush grade (MBG) in patients with prior PTCA/stenting compared to patients without prior PTCA/stenting.

TIMI Flow Grades and Myocardial Blush Grades. Flow in the target vessel after the interventional procedure was graded using TIMI flow classification.9 Angiograms were evaluated for both TIMI flow and MBG by two experienced investigators who were blinded to all data apart from the coronary angiograms. Grading was assessed on cinefilm at 25 frames/second made in a General Electric digital coronary imaging catheterization laboratory. The best projection was selected in each patient to assess the myocardial region of the target vessel revascularized and to minimize superimposition of non-target-related territories. Blush was assessed distal to the stent of the culprit lesion. Left anterior oblique projections were chosen in 66%, right anterior oblique in 23%, anteroposterior in 9%, and a caudal view in 2%. Angiographic runs were long enough to allow for filling of the venous coronary system and backflow of contrast into the aorta had to be present to be certain of adequate contrast filling of the epicardial coronary arteries. Standard 6 French (Fr) guiding catheters were used in all angiograms. The duration of the cine filming was required to exceed 3 cardiac cycles in the washout phase to assess washout of the myocardial blush. Myocardial blush grades were defined as follows: 0, no blush or contrast density; 1, minimal blush or contrast density; 2, moderate blush or contrast density but less than that obtained during angiography of an ipsilateral or contralateral non-target-related coronary artery; and 3, normal blush or contrast density, comparable with angiography of an ipsilateral or contralateral non-target-related coronary artery.2 "Staining" of the myocardium by blush which persisted beyond the washout phase suggested leakage of the contrast medium into the extravascular space and was graded 0.10 The two observers agreed on MBG in 83% of the cases. In the remaining 17% of the cases, the difference was only one grade.

Figure 3



Bar graph demonstrating significantly lower myocardial blush grade (MBG) in patients with prior revascularization (PTCA or CABG) compared to patients without prior revascularization.

Figure 4

Demonstrates a trend toward lower myocardial blush grade (MBG) in smokers compared to nonsmokers. This trend was not statistically significant.

Statistical Analysis. Data are summarized as proportions or mean ± SEM. T-tests were used for group comparisons of age and left ventricular ejection fractions. Rank sum tests were used for group comparisons of myocardial blush grades and of peak cardiac enzyme levels. Fisher's Exact tests were used for comparisons of proportions. Spearman's rank correlation coefficient rS was used to assess the significance of associations among myocardial blush grades, cardiac

enzyme levels and ejection fractions. Unless stated otherwise, 2-tailed p values are reported; the criterion for statistical significance was $p < 0.05$. A sample size of 100 patients (50 per arm) would provide 80% power to detect differences of 25–30% in the proportion of MBG 3 between the two groups in a two-sided test at an alpha level of 0.05.

Results

Baseline characteristics. Although the patients were not randomized, there were no significant differences between patients receiving abciximab (n = 51) and patients receiving eptifibatide (n = 50) with respect to age, gender, left ventricular ejection fraction, peak cardiac enzyme levels, history of hypertension, diabetes mellitus, hypercholesterolemia, tobacco use, or diagnosis (Table 1).

Myocardial Blush Grades. In the abciximab group, 34/51 (67.0%) had MBG of 3, 16/51 (31.0%) had MBG of 2 and 1/51 (2.0%) had MBG of 0-1, compared to 29/50 (58.0%) who had MBG of 3, 18/50 (36.0%) who had MBG of 2 and 3/50 (6.0%) who had MBG of 0-1 in the eptifibatide group (Figure 1). There was no statistically significant difference in MBG between both groups ($p = 0.34$). However, overall patients with a previous history of PTCA/stenting had lower MBG scores (MBG 0-2) compared to patients without a history of previous PTCA [15/26 (58.0%) versus 23/75 (31.0%); $p = 0.03$] (Figure 2). MBG scores in all previously revascularized patients, by either PTCA or coronary artery bypass grafting, were statistically significantly lower compared to patients without a history of previous revascularization [17/31 (55.0%) versus 21/70 (30.0%); $p = 0.026$] (Figure 3). Prior stenting of the target vessel occurred in 30% of the patients with a history of prior PTCA/stenting. Prior revascularization of the target vessel occurred in 71% of the patients with a history of prior CABG. There was no statistically significant difference in MBG scores in patients with diabetes, hypertension or hypercholesterolemia. However, there was a trend toward lower MBG scores (0-2) in smokers compared to nonsmokers, which was not statistically significant [13/27 (48.0%) versus 25/74 (34.0%)] (Figure 4).

Relationship of MBG to contractile function. Cardiac troponin I (cTnI) levels were measured on admission and serially every 8 hours up until cardiac catheterization. Table 2 demonstrates that myocardial blush grade inversely correlated with peak cTnI ($r = -0.18$, one-tailed $p = 0.04$) which would be significant in a one tailed but not two tailed test. Myocardial blush grade did not correlate with left ventricular ejection fraction ($r = 0.09$; $p = 0.40$). Left ventricular ejection fraction did not correlated with peak cTnI (-0.20; $p = 0.09$).

Discussion

MBG has previously been described in the setting of acute ST elevation MI and has been well validated as an angiographic technique to assess myocardial perfusion in this clinical setting.11,12 Myocardial blush scores have been shown to stratify prognosis in patients achieving TIMI 3 flow after successful angioplasty in acute MI (AMI).13 In one study where TIMI 3 flow was achieved after successful angioplasty in AMI, the cumulative 1-year mortality was 6–8% for normal myocardial blush, 13.2% for reduced blush and 18% for absent blush.13 MBG 0-1 has also been established as an independent predictor for long term mortality after angioplasty in AMI.12 In a recent study by Poli et al., an integrated analysis of ST-segment elevation recovery and MBG after restoration of TIMI 3 grade flow by primary PTCA, was shown to allow for an early stratification of patients with different levels of microvascular perfusion and to predict the magnitude of LV functional recovery at 7 days and 6 months.14 Early (7 days) and late (6 months) functional recovery was found to be directly related to both MBG and ST-segment elevation recovery. However, when considered together, ST-segment elevation recovery was a better predictor of early recovery while MBG was a better predictor of late recovery.14 When compared to other invasive markers of reperfusion such as CTFC or coronary flow reserve, MBG was the best predictor of nonreperfusion as defined by intravenous myocardial contrast echocardiography.15

Assessment of myocardial perfusion by MBG has been largely understudied in the setting of acute coronary syndrome. However, the same mechanisms which are responsible for affecting microvascular integrity in acute ST elevation MI are likely to play a role in patients with non-ST elevation MI. Specifically, these are microvascular damage and necrosis due to prolonged ischemia, microvascular dysfunction resulting from embolization of platelet rich thrombi that release vasoconstrictive substances and "sludging" of atherosclerotic plaque material in the distal microvasculature during PCI. Likewise, no-reflow can also complicate PCI in acute coronary syndrome.16 Therefore, it is assumed appropriate to use this technique to assess myocardial perfusion in patients presenting with stable or unstable angina based on its validation in patients presenting with ST elevation AMI.

The era of GP IIb/IIIa receptor blockade began when the EPIC trial demonstrated that abciximab given as a bolus and 12-hour infusion protected patients with unstable angina and developing AMI undergoing

PTCA from ischemic complications.17 The EPILOG trial extended these benefits to low risk patients undergoing percutaneous coronary revascularization as well.18 Eptifibatide also reduces ischemic complications in patients undergoing PTCA.19 GP IIb/IIIa inhibition with abciximab has been shown to have important beneficial effects beyond the maintenance of epicardial patency.5 Specifically, Neumann et al. demonstrated greater improvement in peak flow velocity across the stented segment and regional wall motion in patients who presented with AMI and where treated with abciximab during PTCA as compared to those who were not.5 This greater peak flow velocity was attributed to greater myocardial perfusion in patients treated with abciximab.

Based on data from the ESPRIT trial, our institution decided on a cost-effective shift towards the use of eptifibatide in all patients presenting with stable or unstable angina. However, there is no randomized, prospectively controlled trial directly comparing the ability to preserve myocardial microcirculation between abciximab and eptifibatide during PCI in patients with stable angina or acute coronary syndrome. To assess our experience with eptifibatide, we performed a retrospective analysis comparing the effect on myocardial perfusion, by assessing MBG, between the last 51 patients who routinely received abciximab versus the first 50 patients who began to receive eptifibatide after the pharmacologic shift by our institution. Although the study had statistical power to detect only large differences in performance between the two GP inhibitors, the study was designed to present our experience to date with a new and less proven agent.

Our study demonstrated no significant difference in myocardial perfusion between the monoclonal antibody, abciximab, and the peptide, eptifibatide, suggesting that both compounds are equally effective in reducing platelet aggregation and microembolization downstream during mechanical reperfusion. However, there was reduced myocardial perfusion in patients with a history of previous PTCA or revascularization independent of the class of GP IIb/IIIa antagonist used. This may be explained by the possibilities that people requiring repeat revascularization may have more extensive cardiovascular disease or that coronary interventions may predispose to microvascular damage. Possible mechanisms by which previous PTCA/stenting can result in reduced myocardial perfusion are by irreversible microvascular dysfunction and microvascular plugging which resulted from distal microembolization during the previous revascularization procedure. Iatrogenic microembolization during coronary interventions is supported by the use of aspiration and filtration devices which capture particles of up to 700 microns.20 Microembolization during PTCA may result in elevations of troponin T and I as well as ST elevations on 12-lead EKG. It may occur as a single or as multiple repetitive events resulting in inflammatory responses characterized by leukocyte infiltration and secretion of TNF-a.21 Inflammation has been associated with an increased risk of developing cardiovascular events.22–24 In addition, an elevated white blood cell count is associated with an increased risk of AMI.25 The lower MBG seen in patients with a previous history of coronary artery bypass grafting (CABG) may be explained by distal embolization of friable vein graft material as well as irreversible microvascular dysfunction which occurred during surgery secondary to distal embolization or ischemia from a prolonged pump time. Microvascular plugging and dysfunction, in addition to a lack of good collateral flow, can also explain why few patients continue to suffer from chronic stable angina despite successful epicardial revascularization by PTCA/stenting or CABG. The lack of a correlation between MBG and ejection fraction can be explained by the moderately preserved left ventricular function in both groups.

The present study also demonstrated a significant and inverse correlation between myocardial blush grade and peak preprocedure cTnI levels (Table 2). This observation is consistent with data demonstrated by Wong et al who found that impaired tissue perfusion, assessed by TIMI myocardial perfusion grade, was associated with a nearly 2-fold increased risk of troponin elevation and a concomitant increased risk of death or MI at 6 months.26 The lower MBG scores in patients with elevated troponins may reflect more frequent microemboli and microinfarcts during an ischemic event. Elevated troponins in patients presenting with unstable angina or non-ST elevation MI represent a high-risk subgroup with more extensive disease. Strategies aimed at improving myocardial microcirculatory perfusion and reducing troponin elevation may improve long-term outcomes in patients presenting with acute coronary syndrome/non-ST elevation MI. Larger prospective randomized studies need to be performed to validate the findings in our study.

Limitations. There are several important limitations to the present study that deserve consideration. First, this was not a randomized prospective trial comparing abciximab to eptifibatide but rather a retrospective observational analysis from a single center of two groups of patients receiving a particular GP inhibitor based on the date of their presentation. Therefore, this analysis is prone to selection bias. Myocardial blush grades are also limited by the interobserver and intraobserver variabilities associated with subjective angiographic assessments and are comparable with variabilities in TIMI flow grades for epicardial coronary blood flow.2 MBG has also not been specifically validated in large groups of patients with previous revascularization by either PTCA or CABG, diminishing the applicability of our findings to these patients. A larger sample size would have allowed for smaller differences than the larger

differences of 60% versus 30%, observed in the present study. Furthermore, we did not evaluate and compare changes in regional wall motion associated with the distribution of the target-related coronary artery in both groups of patients, which may have contributed important information. Therefore, larger prospective studies need to be performed to validate these findings.

Conclusions

However, with these limitations, we observed that both the monoclonal antibody, abciximab, and the peptide, eptifibatide, are equally effective in reducing platelet aggregation and microembolization downstream during mechanical reperfusion. Reduced myocardial perfusion, as assessed by MBG, in patients with a history of previous PTCA may be explained by irreversible microvascular dysfunction resulting from distal microembolization during the previous procedure or may simply reflect more extensive cardiovascular disease in patients who require repeat revascularization.

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