Impact of Myocardial Blush on Left Ventricular Remodeling After First Anterior Myocardial Infarction Treated Successfully with Primary Coronary Intervention

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ABSTRACT: **Background:** Myocardial blush grade is a useful marker of microvascular reperfusion that may influence left ventricular dilation.

Objectives: To assess the impact of MB grade on LV remodeling in patients undergoing successful primary PCI for first anterior ST elevation myocardial infarction.

Methods: In 26 consecutive patients MB grade was evaluated immediately after primary PCI. Each patient underwent transthoracic echocardiography at 24 hours and 6 months after PCI for evaluation of LV volumes. LV remodeling was defined as an increase in end-diastolic volume by ≥ 20%.

Results: The presence of myocardial reperfusion (MB 2-3) after primary PCI was associated with a significantly lower rate of remodeling than the absence of myocardial reperfusion (MB 0-1) (17.6% vs. 66.6%, $P = 0.012$). Accordingly, at 6 months, patients with MB 2-3 had significantly smaller LV end-diastolic volume (94 ± 21.5 vs. 115.2 ± 26 ml) compared with patients with MB 0-1. In univariate analysis, only MB (0-1 versus 2-3) was associated with increased risk of LV remodeling (odds ratio 9.3, 95% confidence interval 1.45–60.21, $P = 0.019$).

Conclusions: Impaired microvascular reperfusion, as assessed by MB 0-1, may be associated with LV remodeling in patients with STEMI treated successfully with primary PCI.

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KEY WORDS: remodeling, blush, acute myocardial infarction, primary percutaneous coronary intervention, microvascular reperfusion

Left ventricular remodeling is a precursor of the development of overt heart failure and is an important predictor of worse prognosis after an ST elevation myocardial infarction [1]. The benefits of primary percutaneous coronary intervention in patients with STEMI have been ascribed to early restoration of thrombolysis in myocardial infarction grade 3 flow in the infarct-related artery that results in a limitation of infarct size and decreased mortality compared with thrombolytic treatment [2]. However, recent reports have shown quite a high prevalence of LV dilation that occurs in patients with STEMI even after successful primary PCI [3].

Restoration of epicardial blood flow in the infarct-related artery does not always correlate with the presence of adequate myocardial perfusion [4]. In fact, the success of STEMI treatment is not warranted solely by the reestablishment of patency of the infarct-related artery, but full reperfusion at the level of the myocardium is equally or even more important. Despite TIMI grade 3 flow, the infarct core may undergo limited reperfusion at the tissue level because of injury to the microvasculature and its subsequent obstruction by erythrocytes, neutrophils and debris, a phenomenon also known as the "no-reflow" phenomenon [5], which is a negative independent predictor of myocardial function recovery and long-term survival [6]. Several techniques can be used to assess reperfusion at the tissue level, such as myocardial contrast echocardiography [4], scintigraphy [7], positron emission tomography [8], and magnetic resonance imaging [9]. However, their application during the acute phase of STEMI is difficult and time consuming. By contrast, the angiographic myocardial blush score, based on the contrast dye density [10] and washout [11] in the infarcted myocardium, is a simple tool that correlates significantly with tissue-level perfusion shortly after recanalization of the infarct-related artery [12].

We hypothesized that after successful primary PCI (restoration of TIMI grade 3 flow) in patients with first anterior STEMI, analysis of MB grade may be used to predict LV remodeling. To test this hypothesis, we assessed myocardial reperfusion immediately after primary PCI using MB grade

LV = left ventricular
MB = myocardial blush
PCI = percutaneous coronary intervention
STEMI = ST elevation myocardial infarction

TIMI = thrombolysis in myocardial infarction and then evaluated baseline and 6 month LV volumes using echocardiography.

PATIENTS AND METHODS

The study population consisted of 29 consecutive patients with first anterior wall STEMI who were admitted to our institution between September 2004 and February 2006. The inclusion criteria were: a) confirmed anterior wall STEMI, defined as > 30 minutes of continuous typical chest pain and ST-segment elevation > 2 mm in two contiguous electrocardiography leads; b) primary PCI performed within 6 hours of symptom onset; and c) successful recanalization of the infarct-related artery, defined as TIMI grade 3 flow, and visually assessed residual stenosis < 20%. The exclusion criteria were: a) known coronary artery disease; b) valvular heart disease; and c) technically poor acoustic window for two-dimensional echocardiography. Of the 29 patients who were initially selected for the study, 1 (3%) was excluded for inadequate echocardiographic image quality and 2 (7%) did not perform the 6 month echocardiogram. Thus, 26 patients constituted the final study group. The study protocol was approved by the local ethics committee and all patients gave their written informed consent to participate in this trial.

ECHOCARDIOGRAPHY

Two-dimensional echocardiography was performed with the patient in the left lateral decubitus position, using a commercially available ultrasound unit (Sonos 5500, Phillips, USA). Echocardiography was performed in all patients within 24 hours of the STEMI and 6 months later. The following parameters of the left ventricle were determined from apical two- and four-chamber views: end-diastolic volume and end-systolic volume, and ejection fraction was calculated using Simpson's rule [13]. Two cardiologists who were blinded to the clinical and angiographic data performed the analysis of baseline and 6 month echocardiograms. LV remodeling was defined as an increase in EDV ≥ 20% six months after infarction.

PRIMARY ANGIOPLASTY TECHNIQUE

Primary PCI was performed with the conventional technique, and coronary stents were used without restriction. The infarct-related artery was the only target of the procedure. The use of glycoprotein IIb/IIIa inhibitors (eptifibaride) was left to the discretion of the operator. Both TIMI flow and MB were graded on the angiograms taken immediately after PCI in the best view showing the infarct-related artery. Ten seconds of cine filming was required to allow some filling of the venous system to evaluate the washout phase of contrast dye. Two cardiologists who were blinded to each other and to the clinical data carried out the analysis. TIMI flow grades were assessed as previously described [14]. Blush was graded according to the dye density score proposed by van't Hof et al. [10]: grade 0-1 was minimal to no MB or contrast density (relative to the dye density in uninvolved areas), grade 2 was moderate MB, and grade 3 was normal MB.

CLINICAL FOLLOW-UP

After hospital discharge, patients were referred to their private physician who regulated the therapy. All patients were asked to return to our outpatient clinic for evaluation by one of the investigators at 1 and 6 months after discharge and annually thereafter. The endpoint of interest was major adverse cardiovascular events, which were defined as cardiac death, non-fatal reinfarction, and revascularization. The diagnosis of reinfarction within 24 hours of primary PCI was based on re-elevation of CK-MB to more than three times the normal value, in association with ischemic symptoms. After 24 hours, reinfarction was defined as new pathological Q waves, or re-elevation of CK-MB to more than three times normal. The definition of revascularization was based on repeat PCI or coronary artery bypass graft performed within 24 hours of severe recurrent ischemic symptoms. Repeat angiography and revascularization were performed, in general, in response to clinical signs of recurrent ischemia. Only one event (the first that occurred) was tabulated for each patient.

STATISTICAL ANALYSIS

Statistical analysis was performed using STATISTICA software (StatSoft, Inc. Tulsa, OK, USA). Data were reported as means ± standard deviations for the continuous variables and as absolute and relative frequencies for categorical variables. All tests were two-tailed and a P value ≤ 0.05 was considered to indicate a statistically significant difference. The paired Student's t-test was used to assess statistical significance of continuous variables, and Fischer's exact test to compare categorical variables. Univariate regression analysis was used to analyze the effect of baseline characteristics, LV volumes, and MB on LV remodeling. Odds ratios and 95% confidence intervals were estimated from the model.

RESULTS

Twenty-six patients (58 ± 6 years, 24 males) with anterior wall STEMI underwent primary PCI 184.5 ± 97 minutes from the onset of symptoms. The study population was divided into two groups according to the presence (MB 2-3) or absence (MB 0-1) of myocardial reperfusion [Figure 1]. Immediately after primary PCI, MB grade 2-3 was found in 17 patients

EDV = end-diastolic volume

CK = creatine kinase

(65.4%) and MB 0-1 in 9 (34.6%). There were no significant differences between the groups in the prevalence of risk factors, comorbidities, or administration of medication. Peak CK did not differ between patients with the presence or absence of MB (1980 ± 1440 vs. 3100 ± 2800, $P = 0.2$), as well as the symptom-to-emergency room time (113 ± 85 vs. 110 ± 91, $P = 0.9$) and the symptom-to-balloon time (191 ± 88 vs. 178 ± 106, $P = 0.2$)

ECHOCARDIOGRAPHIC CHARACTERISTICS

The two groups did not differ in initial EDV, ESV, or EF. At 6 months, patients with MB 2-3 had significantly smaller LV end-diastolic (94 ± 21.5 ml vs. 115.2 ± 26 ml, $P = 0.04$) and end-systolic volume (38.6 ± 16.5 ml vs. 55.8 ± 17.5 ml, $P = 0.03$), and significantly higher LV ejection fraction (60.8 ± 9.9% vs. 50.3 ± 11.6%, $P = 0.03$) compared with patients with MB 0-1.

ANGIOGRAPHIC CHARACTERISTICS

Angiographic characteristics of both groups are presented in Table 1. There was no difference in the presence of multivessel disease among patients with compared to those without myocardial reperfusion. Stenting was performed in all patients of both groups. Baseline stenosis and final diameter stenosis were almost identical in patients with and those without myocardial reperfusion. More patients with MB 0-1 had transient "no reflow" phenomenon (45% vs. 6%, $P = 0.001$). The use of glycoprotein IIb/IIIa inhibitors was significantly lower in the patients with MB 0-1 (66.6% vs. 100%, $P = 0.004$). Both reference vessel diameter and stent diameter were borderline lower in patients without myocardial reperfusion as compared to those with myocardial reperfusion (3 ± 0.4 vs. 3.3 ± 0.5, and 3 ± 0.4 vs. 3.3 ± 0.6; $P = 0.1$ for both groups). No significant difference was found in lesion length or stent length between the two groups.

MB AND LV REMODELING

LV remodeling had occurred in 9 patients (34.6%) at 6 months. The LV remodeling rate was significantly lower in patients with MB 2-3 as compared to those with MB 0-1 (3 patients vs. 6 patients, 17.6% vs. 66.6%; $P = 0.012$). Only MB (odds ratio 9.3, 95% confidence interval 1.45–60.21, $P = 0.019$) was confirmed in univariate analysis to be a significant factor predisposing patients to the development of LV remodeling [Table 2].

MB AND CLINICAL OUTCOME

Clinical follow-up data were collected for all patients in the study. The mean length of clinical follow-up was 42 ± 10 months. In the group with MB 0-1, there were no deaths, one patient (11.1%) had a non-fatal myocardial infarction, and two patients (22.2%) underwent revascularization. In patients with MB 2-3 no endpoint was observed during the follow-up period. In the group with MB 0-1, the rate of major adverse cardiovascular events was borderline higher (22.2% vs. 0%, $P = 0.1$).

ESV = end-systolic volume
EF = ejection fraction

Figure 1. Coronary angiography showing a representative example of MB 0-1 (left) and MB 2-3 (right) of the left anterior descenaing coronary artery.

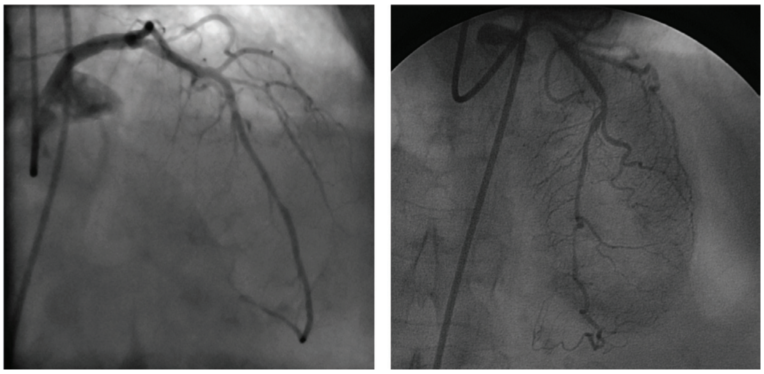

Table 1. Angiographic characteristics of study groups

	MB 0-1	MB 2-3	*P* value
Multivessel disease	5 (56)	5 (29)	0.2
Stenting	9 (100)	9 (100)	1
Baseline stenosis	97 ± 4	96 ± 5	0.5
Final diameter stenosis	2 ± 2	4 ± 2	0.6
Transient "no reflow"	4 (44)	1 (6)	0.001
IIb/IIIa inhibitor used	6 (67)	17 (100)	0.004
Reference vessel diameter (mm)	3 ± 0.4	3.3 ± 0.5	0.1
Stent diameter (mm)	3 ± 0.4	3.3 ± 0.6	0.1
Lesion length (mm)	16.6 ± 6	15.7 ± 5.6	0.7
Stent length (mm)	22.1 ± 6	19.5 ± 8	0.4

Data are presented as mean ± SD or number (%) of patients
IIb/IIIa inhibitor = glycoprotein IIb/IIIa-receptor inhibitors

Table 2. Factors predisposing patients to left ventricular remodeling

	Odds ratio	95% CI	*P* value
Myocardial blush	9.3	1.45–60.21	0.019
Age	0.9	0.89–1.05	0.44
Hypertension	1.8	0.95–3.9	0.65
Diabetes mellitus	1.8	0.95–3.9	0.65
Peak CK	1.0	1.0–1.0	0.78
Symptom-to-emergency room time	1.0	1.0–1.0	0.30
Symptom-to balloon time	1.0	1.0–1.0	0.99
Baseline EDV	1.0	0.97–1.09	0.32
Baseline ESV	1.0	0.95–1.1	0.4

CI = confidence interval

DISCUSSION

This study was undertaken to evaluate the impact of MB on LV remodeling in patients with first anterior STEMI treated successfully with primary PCI (restoration of TIMI grade 3 flow). The findings of our study were as follows: a) LV remodeling occurred in 34.6% of the entire study population despite restoration of TIMI flow grade 3 in the infarct-related artery; b) patients with poor myocardial reperfusion (MB 0-1) were at a higher risk for the development of LV remodeling at 6 months than patients with good myocardial reperfusion (MB 2-3); and c) poor myocardial reperfusion may be associated with increased major adverse cardiovascular events.

Early reperfusion of the occluded infarct-related artery results in myocardial salvage and subsequent increases in LV function and patient survival [15]. Since the introduction of primary PCI in acute settings of STEMI, its major advantages over intravenous thrombolysis have been more effective restoration of coronary patency, less recurrent myocardial ischemia, increased residual LV function, and better clinical outcome [2]. However, Bolognese and collaborators [3] found, as in the present study, that 6 months after successful treatment of STEMI with primary PCI, LV remodeling occurred in about 30% of patients, a rate close to the 34% observed in patients who underwent thrombolysis [16].

Table 3. Studies demonstrating the impact of myocardial blush (perfusion) on left ventricular remodelling in patients with STEMI

Reference	Year	No. of patients	Major findings
Bolognese et al. [18]	2004	124	In reperfused STEMI, microvascular dysfunction (inadequate myocardial reperfusion) is an important predictor of LV remodeling and unfavorable clinical long-term outcome. Microvascular dysfunction represented the only predictor of cardiac death.
Wu KC et al. [19]	1998	44	After STEMI, microvascular obstruction (inadequate myocardial reperfusion) as determined by MRI predicted post-infarction complications, LV remodelling and long-term prognosis after STEMI.
Araszkiewicz et al. [20]	2006	145	Impaired microvascular reperfusion was associated with LV remodelling and development of congestive heart failure in patients with anterior STEMI treated with primary PCI.
Stone et al. [22]	2002	173	Abnormal myocardial reperfusion is present in most patients following primary or rescue PCI in STEMI, despite restoration of brisk epicardial coronary flow. In high risk patients achieving TIMI-3 flow after intervention, the MB score may be used to stratify prognosis into excellent, intermediate, and poor.
De Luca et al. [23]	2004	1548	Patients with heart failure complicating STEMI have impaired myocardial perfusion, which accounts for the poor outcome observed in these patients.
Poli et al. [24]	2002	114	After successful primary PCI, integrated analysis of MB and ST segment recovery allows a real-time grading of microvascular reperfusion of the infarct area and predicts LV functional recovery.

Although mechanical reperfusion for STEMI significantly improves coronary epicardial flow, it does not necessarily restore microvascular flow and myocardial perfusion to normal. In fact, especially after primary PCI, serious physiologic changes – including neutrophil infiltration, endothelial and tissue edema, macro- and microembolization – lead to impairment of microcirculatory flow [4]. In 25–50% of cases in one animal study, despite rapid and sustained restoration of flow through a previously occluded epicardial coronary artery, lack of microvascular reperfusion was still observed [17]. The results of recent human studies investigating the effect of impaired myocardial reperfusion on LV remodeling are shown in Table 3. Bolognese et al. [18] strongly associated lack of myocardial reperfusion, as assessed by myocardial contrast echocardiography, with progressive LV dilation, whereas Wu and team [19] found that microvascular obstruction evaluated by magnetic resonance imaging 10 days after an infarct predicted LV remodeling and poor patient prognosis.

The present study evaluated the effectiveness of MB, which is a simple angiographic marker of microvascular reperfusion, in predicting LV remodeling after anterior wall STEMI treated successfully with primary PCI. Of several factors that were assessed, impaired myocardial reperfusion (MB 0-1) was the only factor confirmed in univariate analyses to play a crucial role in the development of LV remodeling. Echocardiographic measurements performed at 6 months follow-up showed that despite achievement of TIMI grade 3 flow in the infarct-related artery, overall significant LV dilation appeared in 34.6% of patients, a rate comparable to results of previous studies [3,16]. However, when MB assessment was taken into consideration, LV remodeling was significantly higher (66.6%) in patients with impaired myocardial reperfusion (MB 0-1) than in those with good myocardial reperfusion (MB 2-3) (17.6%). These rates of LV remodelling are higher than those reported by Araszkiewicz and colleagues [20], namely, 32% of patients with MB 0-1 and 14% of patients with MB 2-3. However, these researchers [20] found that LV dilation appeared in just 21% of the entire study group, a rate clearly lower than the results of our study (34.6%), as well as those of other studies using primary PCI (30%) or thrombolysis (34%) for treatment of STEMI [3,16].

Our study has certain limitations. First, the number of patients included in the study was relatively small, although the study group consisted only of patients with first STEMI of the anterior wall. Second, we used two-dimensional echocardiography for assessment of LV volumes and function, whereas in recent years MRI has been recognized as the standard of reference for assessing ventricular volumes and function [21]. However, MRI should be first performed after clinical stabilization, which takes much longer than 24 hours after the onset of STEMI; during this period changes in LV volumes cannot be excluded.

In conclusion, our study demonstrates that MB grade may predict LV remodeling 6 months after successful primary PCI (restoration of TIMI grade 3 flow) of an anterior STEMI. This finding supports the importance of achieving microvascular perfusion in STEMI patients treated by primary PCI.

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"Men rarely (if ever) managed to dream up a god superior to themselves. Most gods have the manners and morals of a spoiled child"

Robert A. Heinlein (1907-1988), U.S. science-fiction author

"Pedantry and mastery are opposite attitudes toward rules. To apply a rule to the letter, rigidly, unquestioningly, in cases where it fits and in cases where it does not fit, is pedantry... To apply a rule with natural ease, with judgment, noticing the cases where it fits, and without ever letting the words of the rule obscure the purpose of the action or the opportunities of the situation, is mastery."

George Polya (1887-1985), Hungarian born professor of mathematics