Integrated Analysis of Myocardial Blush and ST-Segment Elevation Recovery After Successful Primary Angioplasty

Real-Time Grading of Microvascular Reperfusion and Prediction of Early and Late Recovery of Left Ventricular Function

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Background—ST-segment elevation (ΣSTe) recovery and the angiographic myocardial blush (MB) grade are useful markers of microvascular reperfusion after recanalization of the infarct-related artery. We investigated the ability of a combined analysis of MB grade and ΣSTe changes to identify different patterns of myocardial reperfusion shortly after primary percutaneous coronary angioplasty (PTCA) and to predict 7-day and 6-month left ventricular (LV) functional recovery.

Methods and Results—MB grade and ΣSTe recovery were evaluated shortly after successful primary PTCA (restoration of TIMI grade 3 flow) in 114 consecutive patients with ΣSTe acute myocardial infarction. LV function was assessed by 2D echocardiograms before PTCA and at 7 days and 6 months thereafter. By combining MB and ΣSTe changes, 3 main groups of patients were identified. Group 1 patients (n=60) had both significant MB (grade 2 to 3) and ΣSTe recovery (>50% versus basal ΣSTe) and a high rate of 7-day (65%) and 6-month (95%) LV functional recovery. In group 2 patients (n=21), who showed MB but persistent ΣSTe, the prevalence of early LV functional recovery was low (24%) but increased up to 86% in the late phase. Group 3 patients (n=28), who had neither significant MB nor ΣSTe resolution, had poor early (18%) and late (32%) LV functional recovery.

Conclusions—After successful primary PTCA, integrated analysis of MB and ΣSTe recovery allows a real-time grading of microvascular reperfusion of the infarct area and predicts the time-course and magnitude of LV functional recovery. **(*Circulation*. 2002;106:313-318.)**

Key Words: myocardial infarction, acute ■ reperfusion ■ imaging

Several perfusion techniques have shown that microvascular dysfunction plays a crucial role in acute myocardial infarction (AMI) treated with thrombolysis or primary coronary angioplasty (PTCA).[1–4] In 25% to 50% of cases, despite a rapid and sustained restoration of flow through a previously occluded epicardial coronary artery, lack of microvascular reperfusion may still be observed. This occurrence, better known as no-reflow phenomenon,[5] is associated with unfavorable left ventricular (LV) remodeling and poor clinical prognosis.[1,4,6,7] Myocardial contrast echocardiography,[1,6,7] scintigraphy,[2] and positron emission tomography[3] are considered the most effective techniques for assessing microvascular integrity; however, their application during the acute phase of AMI is difficult and time consuming. On the other hand, the angiographic myocardial blush (MB) scores, based on the contrast dye density[8] and washout[9] in the infarcted myocardium, along with the resolution of ST-segment elevation on the 12-lead ECG,[10–13] are simple tools that correlate significantly with tissue-level perfusion shortly after recanalization of the infarct-related artery (IRA).

We hypothesized that after successful primary PTCA (restoration of TIMI grade 3 flow), analysis of MB grade, ST-segment elevation recovery, and their combination may be used early on to stratify patients with different levels of microvascular reperfusion and to predict the magnitude of 7-day and 6-month LV functional recovery.

Methods

Study Population

From September 1999 to May 2000, 136 consecutive patients, irrespective of age, presenting within 6 hours of symptom onset (typical chest pain lasting >30 minutes) with ST-elevation >0.2 mV in at least 2 contiguous leads, were treated with primary PTCA in our clinic. In one patient cardiogenic shock caused death, in 11 patients a suboptimal angiographic result (TIMI grade flow <3) was

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achieved, in 7 patients the quality of coronary angiograms did not allow adequate assessment of MB grade, and in 3 patients echocardiographic data were not available before PTCA. The remaining 114 patients represent the population of this study.

Primary Angioplasty

Primary PTCA was performed with the conventional technique, and coronary stents were used without restrictions. The IRA was the only target of the procedure. The judgment of the operator determined whether abciximab therapy was administered, and therapy usually started during the procedure. Intra-aortic counterpulsation was performed in case of hemodynamic instability. TIMI grade 3 coronary flow in the treated vessel with a residual stenosis <20% was considered successful PTCA.

Angiographic Analysis

The angiographic images were acquired with a Toshiba DFP-2000A single-plane system at a cine rate of 25 frames/s. Basal TIMI flow and collateral circulation to the culprit vessel were evaluated on the first angiogram. Both TIMI flow and MB were graded on the angiograms taken immediately after PTCA. Latero-lateral view for the left anterior descending coronary artery (LAD), right anterior oblique 45° view for the right coronary artery, and latero-lateral or right anterior oblique 45° views for the circumflex artery were used in most cases. Ten seconds of cine filming was required to allow some filling of the venous system to evaluate the washout phase of contrast dye. To facilitate the subjective grading of MB, angiograms were digitized and a logarithmic nonmagnified mask-mode background subtraction was applied to the image subset to eliminate noncontrast medium densities. The analysis was carried out by 2 cardiologists who were blinded to the patient's identity and ECG and echocardiographic findings. 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[8]: grade 0 to 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.

ECG Analysis

A 12-lead ECG was recorded just before and at the end of the procedure. Analysis was done by 1 observer unaware of the clinical and angiographic data. The sum of ST-segment elevation (ΣSTe) was measured manually 20 ms after the end of QRS complex from leads exploring the infarct area. Resolution of ΣSTe after PTCA was quantified as a percentage of the value obtained from the basal ECG. A >50% reduction of the initial value was considered significant ΣSTe recovery.[11]

Echocardiographic Analysis

A 2D echocardiogram was performed before primary PTCA and 7 days and 6 months thereafter, for the evaluation of LV wall motion and ejection fraction (EF). The analysis was carried out by 2 observers blinded to the clinical and angiographic data. A LV wall motion score index (WMSI) was calculated with the model proposed by the American Society of Echocardiography.[15] A segment was considered to have functional improvement when systolic wall thickening and endocardial motion appeared in a basally akinetic or dyskinetic segment or normal or near-normal wall motion and thickening became apparent in a severely hypokinetic segment. Significant functional recovery was considered to be present when the improvement involved at least 2 segments or 1 segment when only 2 were basally asynergic.

Clinical Follow-Up

In-hospital complications and one-year occurrence of death, heart failure, reinfarction, and angina requiring hospitalization were analyzed.

Statistical Analysis

Data were reported as mean and standard deviation for continuous variables and as absolute and relative frequencies for categorical variables. The association between MB and ΣSTe recovery was evaluated by means of a χ^2 test; the degree of agreement was evaluated by means of the kappa statistics. The primary end point (significant functional recovery) being defined as a binary variable (see above), the prognostic value of combined MB and ΣSTe recovery was assessed by means of a logistic model; odds ratios (ORs) together with their 95% CIs were computed to measure the strength of the association. Both the raw OR and the OR after controlling for a series of possible confounders (sex, age, left ventricular ejection fraction [LVEF], anterior MI, and time to reperfusion) were calculated by means of a univariate and a multivariate model, respectively. Predicted probabilities of LV functional recovery were computed and graphed for each category of the risk factor. Baseline characteristics were compared across groups by means of one-way ANOVA for continuous variables; post hoc comparisons were based on Scheffé test. In case of inhomogeneous variances, the Kruskall Wallis was used instead (and the Mann Whitney U test with Bonferroni correction for post hoc comparisons). The Fisher exact test was used to compare categorical variables. For post hoc comparisons, the Bonferroni correction was applied. Changes over time of EF and of WMSI were evaluated by means of a linear model for repeated measures, alone and according to MB and or ST recovery. A 2-sided probability value below 5% was considered statistically significance. Stata 7 (StataCorp) was used for computation.

Results

Myocardial Blush

Shortly after PTCA, MB grade 3 was found in 45 patients (39%), MB grade 2 in 36 patients (32%), and MB grade 0 to 1 in 33 patients (29%). There was a relation between MB grade, basal creatinine kinase (CK) value**,** peak CK value, site of AMI, and time to reperfusion (from chest pain onset to reperfusion); the higher the MB grade, the lower the basal CK (P=0.0015) and peak CK (P=0.0001) values and the prevalence of anterior AMI (P=0.009), and the shorter the ischemic time (P=0.096).

MB grade 3 and MB grade 2 patients showed better early (56% and 53%, respectively) and late (93% and 92%, respectively) functional recovery than MB grade 0 to 1 patients (18%, P=0.002 and 32%, P=0.000, respectively); however, no significant difference was found between MB grade 3 and MB grade 2 patients. Therefore, in the following statistical analysis, MB3 and MB2 grades were pooled in a single variable identified as "significant MB."

ST-Segment Changes

Sixty-three of 114 patients (55%) showed a >50% decrease of ΣSTe. Compared with patients who showed ΣSTe recovery, those without ΣSTe recovery more frequently had an anterior MI (P=0.005) with LAD coronary involvement (P=0.019) and higher peak CK value (P=0.00002)

ΣSTe recovery was associated with better early (62%) and late (94%) functional recovery than ΣSTe persistence (20%, P=0.000, and 55%, P=0.000, respectively).

Agreement Between Myocardial Blush and ST-Segment Changes

Coexisting presence of significant MB and ΣSTe recovery was found in 60 patients, whereas MB grade 0 to 1 and

TABLE 1. Clinical and Angiographic Variables in the 3 Groups of Patients Identified by Combination of MB and ΣSTe Changes

	Group 1 n=60	Group 2 n=21	Group 3 n=28	*P*
Mean age, y	59±10	64±11	59±11	0.1989
Male	48 (80)	16 (76)	19 (68)	0.447
Diabetes	6 (10)	3 (14)	5 (18)	0.590
Previous AMI	4 (7)	1 (5)	3 (11)	0.784
Time to reperfusion, min	156±80	176±108	208±130	0.2867
Anterior AMI	20 (33)	13 (62)	18 (64)	0.008
Basal CK, u/L	173±150	266±246	397±626	0.0088
Peak CK, u/L	1580±1143	2696±1898	3715±2105	0.0001
MB grade 3	41 (68)	4 (19)	0 (0)	0.000
Basal TIMI flow >1	12 (20)	9 (43)	4 (14)	0.058
Multivessel disease	20 (33)	6 (29)	10 (36)	0.891
Collateral circulation	17 (28)	5 (24)	2 (7)	0.064
Stent	58 (97)	20 (95)	29 (97)	0.991
Abcximab	33 (55)	11 (52)	14 (50)	0.934
Killip class >1	11 (18)	6 (29)	20 (71)	0.000
IABP	1 (1.7)	1 (5)	5 (18)	0.010
ACE inhibitors	26 (43)	15 (71)	26 (93)	0.000
Diuretics	14 (23)	12 (57)	21 (75)	0.000
β-Blockers	28 (47)	8 (38)	10 (36)	0.609

Values are presented as mean±SD or n (%).
ACE indicates angiotensin-converting enzyme.

persistence of ΣSTe occurred in 28 patients. ΣSTe recovery and significant MB were slightly associated (κ 0.55). By combining MB grade and ΣSTe changes, 3 main groups of patients were identified early after primary PTCA. Group 1 was composed of 60 patients who showed both significant MB and ΣSTe recovery. Group 2 included 21 patients who showed significant MB but persistent ΣSTe. Group 3 was composed of 28 patients with neither significant MB nor ΣSTe resolution. Two patients were excluded from the analysis because they died before the 7th day echocardiographic control. Compared with group 1, group 2 patients had a lower prevalence of MB grade 3 ($P=0.000$), lower basal LVEF ($P=0.046$), a higher rate of anterior MI ($P=0.038$), and higher peak CK value ($P=0.0132$). They differed from group 3 patients with respect to lower peak CK value ($P=0.0631$; Table 1).

Only 3 patients without significant MB showed early ΣSTe recovery and were not considered as a group; when included in group 2 or 3 patients, they did not change the prognostic value of combination of MB and ΣSTe recovery and consequently were dropped from the analysis.

Early Functional Recovery

A significant 7-day LV functional recovery was found in 44% of 112 patients surviving the acute phase of MI.

At univariate analysis, both significant MB (OR 6.18, 95% CI 2.16–17.7, $P=0.0001$) and ΣSTe recovery (OR 6.33, 95% CI 2.67 to 14.99, $P=0.000$) were predictive of early functional recovery. After accounting for ΣSTe recovery (OR 4, 95% CI 1.52 to 11, $P=0.005$), however, MB had no independent short-term prognostic relevance (OR 2.6, 95% CI 0.77 to 8.98, $P=0.121$). Group 1 patients had a significantly better functional recovery (65% of cases; OR 8.54, 95% CI 2.83 to 25.74, $P=0.000$) than group 2 patients (24%; OR 1.44, 95% CI 0.35 to 5.79, $P=0.610$) and group 3 patients (18%); however, no difference was observed between group 2 and group 3 patients (Figure 1A). In the multivariate model, MB had no additional prognostic relevance after accounting for ΣSTe recovery. The combination of MB and ΣSTe recovery maintained its prognostic value after accounting for possible confounders (sex, age, LVEF, anterior MI, and ischemic time; Figure 1B).

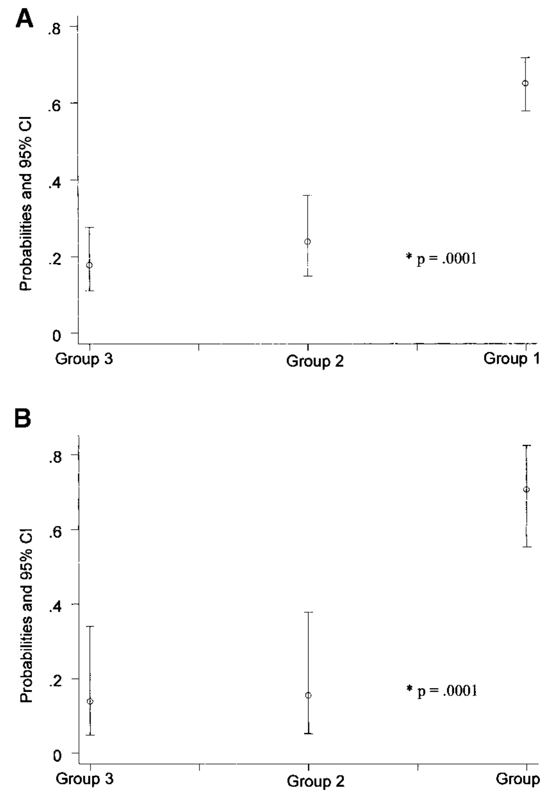

Figure 1. A, Unadjusted probabilities and 95% CI of 7-day LV functional recovery according to group as computed by univariate analysis. B, Probabilities and 95% CI of 7-day LV functional recovery adjusted for confounders according to group as computed at multivariate analysis. *Likelihood ratio test for difference of 3 probabilities.

Late Functional Recovery

An echocardiographic control was available in all patients 6±1 months after the acute event. Significant LV functional recovery was detected in 84 patients (77%).

At the univariate analysis, both MB (OR 22.73, 95% CI 7.49 to 68.98, $P=0.0000$) and ΣSTe recovery (OR 12, 95% CI 3.77 to 38.28, $P=0.0000$) were predictive of late functional recovery. After accounting for MB (OR 11.85, 95% CI 3.36 to 41.84, $P=0.000$), however, ΣSTe recovery was no longer an independent prognostic factor for functional recovery at 6 months (OR 3.46, 95% CI 0.86 to 13.95, $P=0.080$). Both groups of patients with significant MB had a significantly better functional recovery at 6 months (group 1: 95%

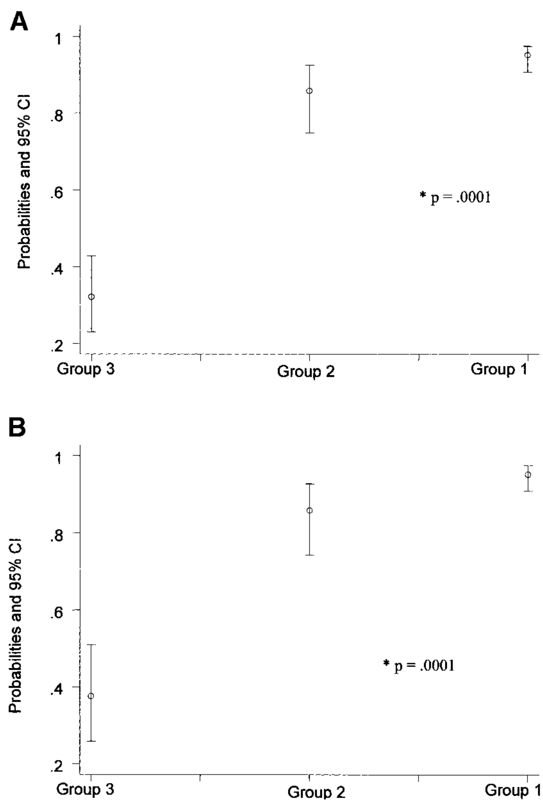

Figure 2. A, Unadjusted probabilities and 95% CI of 6-month LV functional recovery according to group as computed by univariate analysis. B, Probabilities and 95% CI of 6-month LV functional recovery adjusted for confounders according to group as computed at multivariate analysis. *Likelihood ratio test for difference of 3 probabilities.

of cases; OR 40.11, 95% CI 9.83 to 163.63, P=0.000; and group 2: 86% of cases; OR 12.66, 95% CI 2.95 to 54.38, P=0.001) than group 3 patients (32% of cases; however, no difference was observed between group 1 and group 2 patients (OR 3.16, 95% CI 0.58 to 17.08, P=0.180; Figure 2A). Thus, no additional information came from ΣSTe recovery once MB was accounted for. The combination of MB and ΣSTe recovery maintained its prognostic value after accounting for possible confounders (Figure 2B).

Left Ventricular WMSI and EF

EF did significantly increase over time, but with a different rate for each group (interaction present). Similarly, LV WMSI significantly decreased over time, again with a different rate for each group (interaction present). The lowest decrease was observed in group 3 patients (P=0.23). Changes in LVEF and WMSI in the 3 groups are shown in Figures 3 and 4.

Clinical Outcome

Two patients (1.7%) died during hospitalization, 1 because of cardiogenic shock (day 2) and 1 because of cardiac rupture (day 4). In-hospital occurrence of Killip class >I and need for intra-aortic counterpulsation, diuretics, and angiotensin-converting enzyme inhibitor therapy increased significantly from group 1 to group 3 patients (Table 1). Likewise, 1-year

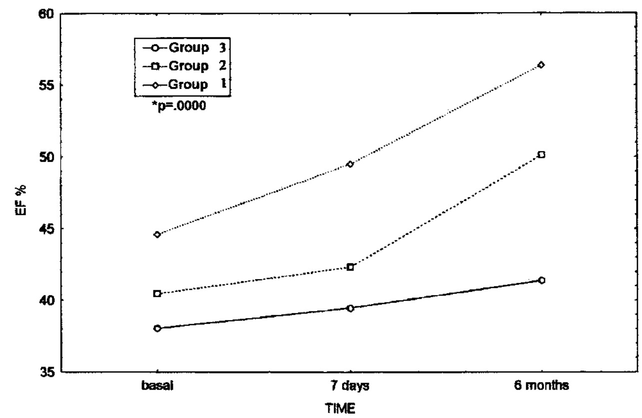

Figure 3. Changes in EF over time according to groups identified by combination of MB and ΣSTe changes. Standard deviation for group 1=8.8; for group 2=6.52; and for group 3=6.19.

clinical outcome was significantly influenced by different combinations of MB and ΣSTe recovery (Table 2).

Discussion

Several data indicate that the main determinant of the recovery of LV function[1,3] and ultimately of the prognosis[6,7] in patients with AMI is the microvascular reperfusion of the infarct zone. The angiographic MB scores and the resolution of ΣSTe are simple markers of myocardial reperfusion that correlate with LV functional recovery and mortality independently from TIMI grade flow.[8–12,16] Few data exist, however, about their correlation and clinical significance. Van't Hoff et al[8] showed a distinct relation between TIMI flow, ΣSTe resolution, and MB grades, as well as between MB grades, infarct size, and LVEF in patients treated with PTCA.

This is the first study demonstrating that, after restoration of TIMI 3 grade flow by primary PTCA, integrated analysis of MB and ΣSTe changes in the single patient allows better characterization of microvascular reperfusion of the infarct area and predicts the time course and magnitude of LV function recovery.

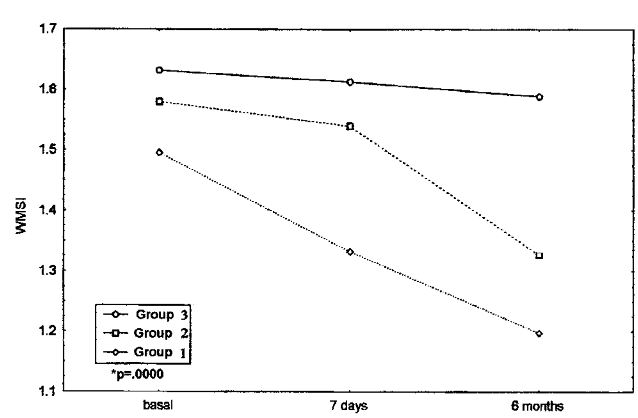

Figure 4. Changes in WMSI over time, according to groups identified by combination of MB and ΣSTe changes. Standard deviation for group 1=0.29; for group 2=0.19; and for group 3=0.24.

TABLE 2. One-Year Outcome

	Group 1 (n=60)	Group 2 (n=21)	Group 3 (n=30)	*P*
Death	0	0	2 (7)	0.064
Unstable angina/re-AMI	3 (5)	1 (5)	3 (10)	0.622
Hospitalization for CHF	0	0	3 (10)	0.016
NYHA class >I	2 (3)	3 (14)	11 (37)	0.000

Values are n or n (%).

CHF indicates congestive heart failure; NYHA, New York Heart Association.

Grading of Myocardial Reperfusion

The relationship we found between MB and ΣSTe changes is similar to that observed by Santoro et al[17] who used myocardial contrast echocardiography as a marker of tissue perfusion. Although early resolution of ΣSTe is specific (90%) for myocardial perfusion (MB), sensitivity is quite low (74%). Indeed, ΣSTe recovery is present in the majority of patients with myocardial reflow (as detected by MB). Nonetheless, lack of ΣSTe recovery is not always a marker of failed microvascular reperfusion because these patients consistently show the presence of significant MB.

Three different scenarios are possible early after recanalization of IRA. The first is the coexisting presence of significant MB and resolution of ΣSTe (group 1 patients). This combination identifies successful microvascular reperfusion (higher prevalence of MB grade 3 than MB grade 2) of the infarcted area. In such patients, ischemia-induced damage was less severe than in the other 2 groups, as shown by the lowest basal and peak CK values and time to reperfusion. A high proportion of these patients (65%) showed early significant LV functional recovery. Further functional recovery was detectable in 95% of patients after 6 months. It is likely that such patients maintain a functional integrity of microvascular network leading to an early contractile recovery of a predominantly stunned region.

The second scenario is the presence of significant MB without early ΣSTe resolution (group 2 patients). This situation identifies patients in whom microvascular function, even if preserved, is not yet normalized (higher prevalence of MB grade 2 than MB grade 3) into a myocardial area where ischemic injury has been more sustained, as shown by higher basal and peak CK values than in group 1 patients. These patients show poor early LV functional recovery (23% of cases), but late functional recovery occurs in a percentage of patients (86%) comparable to that observed in group 1. As previously suggested,[18] it is likely that in such patients a deeper but still reversible injury of microvasculature (microvascular stunning) occurs, resulting in prolonged myocardial stunning.

The third scenario is the absence of significant MB and ΣSTe resolution (group 3 patients). Such patients have no microvascular reperfusion in a severely damaged myocardial region. They had the highest basal and peak CK values and the longest time to reperfusion among the 3 groups. This condition is associated with poor early and late LV functional recovery (18% and 31% of cases, respectively).

Prediction of LV Functional Recovery

After normalization of epicardial flow by primary PTCA, integrated analysis of MB and ΣSTe recovery provides complementary information about the likelihood of LV functional recovery over time. Both significant MB and ΣSTe recovery are predictive of early and late functional recovery. When considered together, ΣSTe recovery is a stronger predictor of early functional recovery than MB. Thus, among patients with significant MB, ΣSTe recovery identifies those with 7-day functional recovery. Otherwise, MB shows a higher predictive value for 6-month functional recovery than ΣSTe recovery. Therefore, the evaluation of MB among patients without ΣSTe resolution may identify those with late LV functional recovery. This observation has a particular prognostic relevance in anterior AMI because, as previously reported,[10,13] we confirmed that anterior AMI is associated with less ΣSTe recovery than is inferior AMI.

Finally, by assessing LV function before primary PTCA, we detected a significant functional recovery in 44% of patients within 7 days. Such patients have a large amount of myocardium showing early resolution of functional stunning, which can be well predicted by the association of significant MB and ΣSTe recovery. This phenomenon may have been overlooked by previous investigators who measured basal LV function a few days after PTCA and thus underestimated the true benefit of the procedure[19] as well as the practical value of MB[8] or ΣSTe resolution[12] in predicting LV functional recovery.

Limitations

Subjective angiographic assessment of MB represents a major limitation in the attempt to standardize and reproduce the clinical information provided by this variable in different centers. Quantification of contrast dye density in the myocardial area of interest has been proposed; however, the complexity of the method limits its applicability in the acute phase of AMI.[20]

The small sample size should be noted as a caution in interpreting our data because, in a larger data set, both MB and ΣSTe recovery might be similarly predictive of both early and late LV functional recovery.

Clinical Implications

Patients with both MB and ΣSTe resolution after recanalization of the IRA show the highest prevalence of early recovery of LV function, have a low in-hospital complication rate, and are candidates for early discharge from the hospital. Moreover, they have a good 1-year clinical outcome. Patients without resolution of ΣSTe despite the presence of significant MB need a closer scrutiny during hospitalization because they have clinical signs of LV dysfunction as a consequence of a more profound and persistent stunning of the infarcted area more frequently than group 1 patients. Finally, patients with absence of MB and ST-segment resolution after primary PTCA are those who need the greatest efforts to improve their short and long-term outcome.

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