Tissue Inflammation Impairs Tissue-Level Perfusion and Promotes Left Ventricular Remodeling in Patients With Acute Myocardial Infarction

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Abstract

Background. C-reactive protein (CRP) level and monocytosis are associated with left ventricular (LV) remodeling in patients with AMI.

Methods. One hundred twenty-nine consecutive patients with the first acute myocardial infarction (AMI) underwent myocardial contrast echocardiography (MCE) 2 weeks after successful reperfusion.

Results. LV end-diastolic volume index (LVEDVI) at pre-discharge was significantly higher in the no-reflow group than the reflow group (64 ± 17 vs. 58 ± 11 mL/m², $p < 0.01$). The no-reflow group had a higher CRP level and peak monocyte counts than the reflow group (9.5 ± 5.2 vs. 5.8 ± 3.5 mg/dl, $p < 0.0001$; and 1026 ± 400 vs. $824 \pm 278/\mu\text{l}$, $p < 0.001$, respectively). Peak CRP (relative risk [RR] 1.21, 95% confidence interval [CI] 1.01-1.45, $p < 0.05$) and peak monocyte counts (RR 1.003, 95% CI 1.001-1.006, $p < 0.01$) were independent determinants of the no-reflow phenomenon.

Conclusion. Microvascular dysfunction following tissue inflammation may play an important role in the LV remodeling after AMI. (J Echocardiogr 2005; 3: 83-90)

Key words: No-reflow, Inflammation, Monocyte, Myocardial infarction, Microcirculation

Introduction

Increasing evidences implicate the inflammation response after acute myocardial infarction (AMI) to be a factor related to patient mortality. C-reactive protein (CRP) dramatically increases after AMI [1], and its peak value is correlated to the mortality after AMI [2-3]. Elevated CRP level after AMI is also related to left ventricular aneurysm [4-5] and cardiac rupture [4]. Cytokine such as interleukin-6 also increased after AMI [6], and their level is correlated with mortality.

Another sign of tissue inflammation in AMI is an increase in the number of peripheral leukocytes. The higher white blood cell count is associated with an increase in the rate of mortality [7] and re-infarction [8] after AMI. A recent clinical study documented the observation that the peripheral monocyte count is correlated to left ventricular remodeling and cardiac events after AMI [9]. However, the mechanism by which the inflammatory response affects the ventricular remodeling after AMI is still not fully understood as yet.

The no-reflow phenomenon is another factor that is associated with poor functional and clinical outcomes after AMI [10-13]. Myocardial contrast echocardiography (MCE) demonstrated that the no-reflow phenomenon is observed in 25% to 30% of patients with AMI despite successful coronary recanalization [10, 14]. The no-reflow phenomenon may persist in subacute phase, and correlate with progression of microvascular dysfunction. Several mechanisms are postulated to

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explain the development of the no-reflow phenomenon [15-16], however, the contribution of tissue inflammation remains unknown. Ott *et al.* reported that monocyte Mac-1 expression and monocyte procoagulant activity increased after angioplasty along with the levels of interleukin-6 and CRP in patients with AMI [17]. To clarify whether this procoagulant inflammatory response of monocytes is related to the no-reflow phenomenon after AMI, we examined the parameters that reflect inflammatory responses in relation to the no-reflow phenomenon in patients with AMI.

Methods

Study population.

One hundred eighty-six consecutive patients with the first AMI who were admitted to Sakurabashi Watanabe Hospital were enrolled in this study between June 2001 and August 2003. All patients underwent primary percutaneous coronary intervention (PCI, angioplasty and/or stent) for arteries exhibiting Thrombolysis in Myocardial Infarction (TIMI) flow grade 0 or 1 within 24 hours after symptom onset; subsequently, they underwent MCE examination. The AMI diagnosis was based on prolonged chest pain $\geq$ 30 minutes, ST segment elevation of $\geq$ 2 mm in at least two contiguous electrocardiography (ECG) leads, and greater than a three-fold increase in serum creatine kinase levels. Fifty-seven patients were excluded; 32 patients suffered cardiogenic shock; in 16 patients association of collagen disease was observed; and 9 patients showed malignancy or infectious disease. Therefore, the final study population consisted of 129 patients. The study protocol was approved by the hospital's Ethics Committee, and patients gave their written informed consent.

Study protocol

Immediately after admission, a 12-leads ECG was recorded and the blood glucose level was measured in each patient. All patients underwent two-dimensional echocardiography with a SONOS 5500 system (Philips Medical Systems). We performed coronary angioplasty using the appropriate balloon catheters. We repeated angioplasty or implanted a stent to reduce residual diameter stenosis to $< 50\%$. On admission to the hospital, venous blood samples were obtained every 24 hours for at least 5 days. Total and differential leukocyte counts were measured by an automated hematology analyzer (MAXM-Retic, BECKMAN COULTER, Tokyo, Japan). Serum creatine kinase (CK) activity

and CRP levels were measured by latex photometric immunoassay (SYNCHRON LX20, BECKMAN COULTER, Tokyo, Japan) with the use of an autoanalyzer (RadiSys, RadiSys Corporation) to obtain the peak CK and CRP levels.

We performed MCE 2 weeks after the onset of AMI using SONOS5500 (Philips Medical Systems) with the S3 probe. We depicted apical 4- and 2-chamber views with harmonic power Doppler (HPD) mode [18-20], and ultrasound was transmitted at 1.8 MHz and received at 3.6 MHz. The focus was placed at the mitral level, and the mechanical index and dynamic range were set to the maximum, 1.6 and 40 dB, respectively. Overall gain was adjusted to minimize artifacts in the baseline study. A solution of LevovistTM (concentration of 300 mg/mL, Schering AG) [19-21] was administered as bolus (3 mL) at a rate of 0.5 mL/s with a volumetric pump (PULSAR, Medrad). MCE images were recorded for at least 180 seconds after the contrast injection. End-systolic images were obtained every 4 heart beats, and they were stored on a magneto-optical disk. Imaging was performed with 2 triggers (multi-frame triggering mode) [22]. The first pulse was used for myocardial opacification; the second pulse was used only for bubble destruction to assess the quality of images, and we reduced the motion artifact as much as possible by adjusting the triggering time.

Analysis of MCE data

Left ventricular myocardium was divided into 6 segments using both apical 4- and 2-chamber views according to the segmentation of the American Society of Echocardiography. We analyzed MCE images 100 seconds after injection to evaluate the perfusion defect. At each myocardial segment, we judged the presence of the perfusion defect. The perfusion defect was defined as the lack of staining of myocardial tissue at the end systole (Figure 1). If there were at least one segment that showed the perfusion defect, we defined it as the no-reflow group, and if no perfusion defect was detected, we evaluated as reflow group. The evaluation was not performed if any of the following features was present: absolutely no contrast enhancement, termed drop-out, and apparent motion artifacts. This judgment was taken by at least two well-trained sonographers.

Statistical analysis

Continuous data are expressed as the mean value $\pm$ SD. Comparison between two groups was performed

Fig. 1. Myocardial contrast echocardiographic (MCE) images in the patients with reperfused AMI.

In the image on the left, myocardial perfusion was well preserved in all myocardial segments. On the other hand, the image on the right shows perfusion defect within apical lesions, which is indicated between the arrows.

Table 1. Patient characteristics between two groups

	Reflow (n=81)	No-reflow (n=48)	P value
Age	60 ± 10	62 ± 11	0.33
Male gender	73 (90)	40 (83)	0.26
Hypertension	40 (49)	21 (44)	0.54
Current smoking	62 (77)	35 (73)	0.64
Hyperlipidemia	41 (51)	15 (31)	0.03
Diabetes mellitus	26 (32)	15 (31)	0.92
Anterior MI	20 (25)	37 (77)	<0.0001
Preinfarction angina	42 (52)	26 (54)	0.8
ACE inhibitors	15 (19)	12 (25)	0.38
Elapsed time	5.1 ± 4.3	6.4 ± 5.4	0.14
Stent use	70 (86)	42 (88)	0.86

Values are expressed as number(%) or mean ± SD unless otherwise noted.

ACE = angiotensin-converting enzyme

Fig. 2. The left ventricular end diastolic volume index (LVEDVI) and ejection fraction (EF) at the follow up study.

LVEDVI and EF were measured in the left ventriculogram performed after an average gap of 5 months after AMI onset. The group showing no-reflow on MCE had significantly higher LVEDVI (left) and lower EF (right) than those with good reflow. The bars demonstrate the mean $\pm$ SD values.

Fig. 3. Peak CRP levels and peak monocyte counts at the early stage of AMI.

The no-reflow group had significantly higher peak CRP levels (left) and peak monocyte counts (right) than the good reflow group.

by using the unpaired *t*-test for continuous variables and by using the chi-square test for categorical variables. Multiple logistic regression analysis was used to assess the effect of various factors on the no-reflow phenomenon. Variables, including those with $p < 0.10$ obtained by univariate analysis, were further investigated by a multiple logistic regression test. P value < 0.05 was considered statistically significant. All statistical analyses were performed using Statview 5.0 software (SAS Institute Inc., Cary, North Carolina).

Results

Patient characteristics

Of the total number of patients who entered this study, 113 were men and 16 were women, with a mean age of 61 ± 11 (range 38 to 89). The average interval from the symptom onset to the arrival at hospital was 4.4 hours, and the interval to reperfusion was 5.8 hours. The patients were divided into two groups based on the MCE findings, the no-reflow group ($n = 48$, 37%) and the reflow group ($n = 81$, 63%). There

were no significant differences in age, gender, symptom onset-reperfusion time, and use of stents between these two groups. Hyperlipidemia and anterior wall infarction were more frequently seen in the no-reflow group than in the reflow group (Table 1). Three weeks after the symptom onset the left ventricular end-diastolic volume index was higher in the no-reflow group than in the reflow group (64 ± 17 vs. 58 ± 11 mL/m², $p < 0.01$). In contrast, the left ventricular ejection fraction was lower in the no-reflow group than in the

reflow group (45 ± 9 % vs. 55 ± 8 %, $p < 0.001$) (Figure 2).

Factors related to the no-reflow phenomenon

There was no difference in the interval from symptom onset to peak CRP between the two groups, and this interval was approximately 3 days from reperfusion. Peak CRP was higher in the no-reflow group than in the reflow group (9.5 ± 5.2 vs. 5.8 ± 3.5 mg/dl, $p < 0.0001$) (Figure 3). Although the peak number of leukocytes was comparable between the two groups

Table 2. Univariate analysis for no-reflow phenomenon

	Reflow (n=81)	No-reflow (n=48)	P value
Peak CK	2278 $\pm$ 1450	5255 $\pm$ 2869	<0.0001
Peak WBC	11436 $\pm$ 2849	12238 $\pm$ 3229	0.14
BG on admission	140 $\pm$ 31	157 $\pm$ 41	0.013
Peak monocyte counts	824 $\pm$ 278	1026 $\pm$ 400	0.001
Peak CRP	5.8 $\pm$ 3.5	9.5 $\pm$ 5.2	<0.0001
ST re-elevation	23 (28)	31 (65)	<0.0001
WMS on admission	11.5 $\pm$ 4.6	17.6 $\pm$ 6.7	<0.0001
Killip>2	5 (6)	14 (29)	0.0004

Values are expressed as number(%) or mean $\pm$ SD unless otherwise noted.

BG = blood glucose WMS = wall motion score

Table 3. Multivariate analysis for no-reflow phenomenon

	χ^2	Relative risk	95% CI	P value
Age	12.1	1.08	1.01 – 1.16	0.026
Male gender	1.02	0.41	0.07 – 2.31	0.31
Peak CK	12.2	1.001	1.000 – 1.001	0.0005
Peak monocyte	6.92	1.003	1.001 – 1.006	0.009
Reperfusion injury	4.60	4.26	1.13 – 16.0	0.032
Peak CRP	4.21	1.21	1.01 – 1.46	0.040
Anterior MI	4.16	3.65	1.05 – 12.7	0.042
WMS on admission	1.96	1.11	0.96 – 1.27	0.16
BG on admission	0.38	1.005	0.99 – 1.02	0.54
Hyperlipidemia	0.22	0.76	0.24 – 2.38	0.64
Killip>2	0.05	1.25	0.18 – 8.65	0.82

CI = confidence interval; CK = creatine kinase

(12238 ± 3229 vs. $11436 \pm 2849/\mu\text{l}$, $p = 0.14$), peak monocyte counts were higher in the no-reflow group than in the reflow group (1026 ± 400 vs. $825 \pm 278/\mu\text{l}$, $p = 0.001$) (Figure 3). This interval was approximately 2 days from reperfusion. The ST re-elevation was more frequently observed immediately after coronary recanalization in the no-reflow group than in the reflow group (31/48, 65% vs. 23/81, 28%, $p < 0.0001$) (Table 2). However, presence or absence of ST re-elevation was not correlated with peak CRP levels ($p = 0.21$). In all cases, there were no subacute occlusion of culprit lesion in coronary angiography 3 weeks after AMI.

The predictive factors of the no-reflow phenomenon

In the univariate analysis, the factors related to the no-reflow phenomenon were as follows: anterior MI, peak CK, peak monocytes counts, peak CRP, Killip >2 on admission, blood glucose on admission, ST re-elevation, hyperlipidemia, and the wall motion score (WMS) on admission (Table 2). Multiple logistic regression analysis showed that anterior MI (relative risk [RR] 3.65, 95% confidence interval [CI] 1.05 to 12.7, $p = 0.042$), peak CK (RR 1.001, 95% CI 1.000 to 1.001, $p = 0.0005$), peak CRP (RR 1.21, 95% CI 1.01 to 1.46, $p = 0.040$), the presence of ST re-elevation (RR 4.26, 95% CI 1.13 to 16.0, $p = 0.032$), and peak monocyte counts (RR 1.003 95% CI 1.001 to 1.006, $p = 0.009$) were independent predictive factors of the no-reflow phenomenon (Table 3).

Discussion

In the present study, we investigated the relationship between the inflammatory response and the no-reflow phenomenon in patients with first reperfused AMI. Left ventricular end diastolic volume index was greater and the left ventricular ejection fraction was lower in the no-reflow group than in the reflow group 3 weeks after AMI. The no-reflow group demonstrated two weeks after AMI showed higher monocyte counts and CRP levels than the reflow group. Multivariate analysis revealed that peak monocyte count and peak CRP level were independent factors that are associated with the no-reflow phenomenon. Our results suggest that a possible role of tissue inflammation on the coronary microcirculation and incomplete tissue perfusion is associated with the deterioration of functional outcomes and left ventricular remodeling 3 weeks after AMI.

Tissue inflammation and the no-reflow phenomenon

Leukocytes increase in the early stage of AMI, and

this is used as a parameter to diagnose AMI. Neutrophil plugging in post-ischemic capillary networks is a cause of the no-reflow phenomenon, and this process is accelerated by coronary reperfusion. Our result, however, demonstrated that leukocyte count in itself is not indicative of the no-reflow phenomenon. Recently, Maekawa *et al.* reported that peripheral monocytes increase in the patients with AMI. The higher peak monocyte count was associated with the worst short and long-term outcomes as well as with the left ventricular remodeling after AMI [9]. In the region of severe ischemic damage, monocytes adhere to the endothelial wall, migrate through it into the infarcted tissue, and finally transform themselves to macrophages. Previous experimental study demonstrated that an increase in peripheral monocytes precedes an increase in macrophages in the infarcted tissue [23]. The macrophages initiate a potent inflammation process in tissue. They release several cytokines, including IL-6, IL-1, and TNF- α , to accelerate tissue inflammation and edema and, thus, injure capillary networks. These cytokines also activate neutrophils and endothelial cells, promote the adherence of neutrophils to the endothelial cells resulting in their transendothelial migration and tissue injury, and finally, further worsen tissue perfusion [24].

Post-inflammatory cytokines and acute phase reactants, such as CRP, also increase in the acute stage of AMI. These cytokines induce liver cells to produce CRP. Ikeda *et al.* reported a close correlation between the serum IL-6 levels and CRP levels in AMI patients [6]. As a consequence of AMI, severe tissue inflammation occurs with more monocytes infiltrating into the infarcted tissue to produce the extensive capillary obstruction and myocardial necrosis. This process might be detected with the higher CRP level in this study.

In previous studies, we have reported the independent predictors related to the no-reflow phenomenon that was documented immediately after coronary reperfusion. They include the initial WMS as the size of risk area, the development of Q wave on admission, patent infarct-related artery, preconditioning angina, and acute-stage hyperglycemia [25]. In this study, we evaluated tissue perfusion in the convalescence stage in order to reduce the impact of microemboli on microcirculation as much as possible and to evaluate total capillary damage that is caused by ischemia as well as by reperfusion injury. The determinant factors that are

associated with the no-reflow phenomenon are different from those of the acute phase. For example, high blood glucose levels positively correlated with the no-reflow phenomenon; however, it was no longer an independent factor of the no-reflow phenomenon in this study.

Poor myocardial perfusion and LV remodeling

Progressive LV remodeling is occasionally observed in patients surviving AMI, and it delays their prognosis [26-29]. Several factors related to LV remodeling are postulated, such as infarct size, anterior location, transmural extent of infarction, loading condition, and patency of the infarct-related artery [26-28]. Recently, the importance of microvascular obstruction has been stressed. Wu and colleagues have reported that microvascular obstruction assessed by MRI 10 days after the onset of AMI predicts LV remodeling and poor prognosis [30]. In the ischemia/reperfusion rat model, the no-reflow phenomenon persists for one month after reperfusion, and it predicts worse scar thinning and infarct expansion [31]. We studied coronary microvascular function from the coronary blood flow velocity pattern, recorded by transthoracic Doppler, in the patients with reperfused anterior MI. Prolonged microvascular dysfunction, as assessed from short diastolic deceleration time, is associated with LV remodeling.

Besides salvaging the jeopardized myocardium in the epicardial layer, better myocardial perfusion accelerates the healing process of infarct tissue. Tissue perfusion accelerates the washout of infarct debris, the migration of leukocytes, and augments the healing process of the infarct tissue that is resistant to mechanical stress. In contrast, impairment of tissue perfusion for a long period due to capillary obstruction delays the healing process of the infarct tissue, resulting in infarct expansion and subsequent LV remodeling.

Study limitations

This is a retrospective study and selection bias might be included. However, we enrolled consecutive AMI patients who survived at least 2 weeks after the symptom onset and underwent MCE. Second, the serum level of monocyte-related cytokines, such as IL-6, M-CSF, and MCP-1, might be required to study the function of monocytes. In the clinical study, there was no evidence to demonstrate that an increase in peripheral monocytes is associated with tissue macrophage in the infarct region, although experimental studies have documented it.

Conclusions

Tissue inflammation is an important factor that impairs tissue-level perfusion. Microvascular dysfunction may play an important role in the development of LV remodeling after reperfused AMI.

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