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Microvascular Integrity as a Predictor of Left Ventricular Remodeling after Acute Anterior Wall Myocardial Infarction

The purpose of this study was to investigate the relation of microvascular integrity and ventricular remodeling after acute myocardial infarction. Twenty-six patients with first acute anterior myocardial infarction were studied before discharge with myocardial contrast echocardiography (MCE). Opacification index (OI) and wall motion index were calculated in the left anterior descending artery territory and left ventricular diastolic volume was measured at baseline and during a 9-month follow-up. In total 26 patients, the regional wall motion improved but the left ventricular volume and global function was not changed significantly at follow-up. When the patients were divided into 3 groups according to opacification index ($\geq$0.75, 0.5~0.75, $\leq$0.5) at baseline, functional recovery was not observed and significant left ventricular dilatation was developed in patients with $\leq$0.5 OI. Among the baseline echo-parameters such as ejection fraction, wall motion score, left ventricular volume and opacification index, the best predictor for long term left ventricular dilatation was the opacification index by multivariate analysis. In patients with acute anterior wall infarction the assessment of microvascular integrity by MCE at acute stage provides useful information regarding recovery of dysfunctional regional wall motion and ventricular remodeling.

Key Words : *Myocardial diseases; Echocardiography; Myocardial infarction; Ventricular remodeling*

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INTRODUCTION

Left ventricular dilatation after acute myocardial infarction was reported to be associated with increased morbidity and mortality (1-5). This remodeling process is characterized by regional thinning of infarcted myocardial segments in early phase and lengthening and hypertrophy of noninfarcted myocardium in late phase that takes place several months to years (6-9). The factors that determine cardiac dilatation after myocardial infarction are the size and location of infarct and patency of infarct related artery (10). But in patients with acute myocardial infarction, it has been known that the patency status of infarct related artery does not reflect myocardial perfusion status (11, 12). Because variable amounts of microvasulature was destroyed within the risk area of myocardium by prolonged ischemia, the flow to the infarct myocardium may be reduced after infarct related artery opened and the remodeling process may be variable according to microvascular flow status.

Recent studies have demonstrated that myocardial contrast echocardiography (MCE) is one of the most useful method for evaluation of myocardial perfusion using microvasculature tracer (13, 14). After coronary artery occlusion, the microvascular flow abnormality due to damaged microvascular integrity occurs (11, 15) exclusively within the confines of the infarct area. Thus, the nonopacified myocardium after reflow by MCE was considered nonviable by several investigators (12, 16). But the impact of microvascular damage on the remodeling of left ventricule after myocardial infarction was not studied extensively. To date one study (17) was done about the relation of myocardial perfusion by MCE and change of left ventricular size at twenty-five days after acute myocardial infarction. But several studies (6, 7) indicate that the ventricular remodeling after myocardial infarction may continue for many months and the changing pattern is variable between patients.

In this study, the long term change of left ventricular function and size was investigated according to the per-

fusion status by MCE in twenty-six reperfused acute first anterior myocardial infarction.

METHODS

Study population

Twenty-six consecutive patients from November 1995 to December 1996 with acute anterior wall myocardial infarction hospitalized in our institution entered the study. The diagnosis of acute myocardial infarction was made on the basis of chest pain lasting more than 30 minutes, more than 2 mm ST elevation in two contiguous electrocardiographic leads and more than threefold increase of serum creatinine kinase. Patients with prior myocardial infarction, prior coronary revascularization procedure, significant valvular heart disease or ischemic events during follow-up period were excluded from the study.

The mean age was 60±10 years and 20 patients were men and all patients had a Q-wave infarction. All patients gave written informed consent for both the cardiac catheterization and MCE.

Coronary angiography

In 24 patients, intravenous thrombolysis was performed with urokinase within 6 hours of chest pain onset. Coronary angiography was done 90 minutes after reperfusion therapy in this patients. In 3 patients with failed thrombolysis, rescue angioplasty was done. Two patients underwent direct angioplasty because thrombolysis was contraindicated.

After reperfusion therapy, TIMI grade III flow was obtained in 23 patients and grade II in 3 patients. Seven to ten days later, second coronary angiography was done and angioplasty was performed in 14 patients. Thus, there was no critical stenosis in infarct-related artery in every patient discharged from the hospital.

Myocardial contrast echocardiography

Two dimensional echocardiographic images were obtained by using commercially available phased array system (Hewlett Packard 1500). Sonicated Hexabrix (meglubine ioxaglic acid sodium, Taejoon Corp., Korea) was injected into left main (3 ml) and right coronary (2 ml) arteries during simutaneously performed two-dimensional echocardiography in apical four and two chamber view after reperfusion therapy. The percent stenosis of coronary artery by qualitative analysis at the time of MCE was 71±27%. The timing of MCE was 90 minutes after thrombolysis in 23 patients and 7-10 days after myocardial infarction onset in 3 patients.

During MCE the gain setting was held constant throughout the study by adjusting optimal identification of the endocardium and epicardium. A 16-segment model of left ventricle was used for the analysis of degree of myocardial opacification after contrast injection. Each segment was assigned as 0 (no opacification), 0.5 (partial opacification) or 1 (homogeneous opacification) as previously reported (17). The opacification index was calculated by dividing the sum of opacification score by the number of segments within left anterior descending coronary artery territory.

Two-dimensional echocardiography

Baseline two-dimensional echocardiography was done at the time of MCE and 9 months (range 3-15 months) after acute myocardial infarction. At each segment of left ventricle, wall motion was scored as follows; 0, normal; 1, mild hypokinesia; 2, severe hypokinesia; 3, akinesia; 4, dyskinesia. Wall motion score index was calculated in left anterior artery territory. These wall motion analysis was done by two observers independently who were not given the MCE data.

Baseline and follow-up left ventricular volume was determined. In brief, end-diastolic and end-systolic frames were outlined from apical four chamber view using the cardiac analysis system (Imagevue, Nova Microsonics) and left ventricular volume was calculated using the modified Simpson's rule. An increase of >15% in left ventricular volume from baseline to follow up was defined as left ventricular dilatation. Tracing of endocardial borders was performed by one observer and at least three measurements were taken and averaged for each examination. Ejection fraction was calculated as (End-Diastolic Volume-End Systolic Volume) / End-Diastolic Volume.

Statistical analysis

All data is expressed as mean±SD. The unpaired student t test or one way analysis of variance was performed for comparison of variables between groups. Data within the same patients was compared using paired t test. Correlation between opacification index, baseline and follow up left ventricular volume and wall motion index was performed by linear regression analysis. Multiple regression analysis was performed to determine the best predictor of long term change of left ventricular volume. A value of $p<0.05$ was required for statistical significance.

RESULT

Patient characteristics

All 26 selected patients had a first anterior myocardial infarction with Q waves in precordial leads.

Four patients had hypertension and 3 patients had diabetes mellitus. Eighteen patients were smokers. Five out of 26 patients had a multivessel disease. ACE inhibitor was prescribed in all patients if there is no contraindication during follow up period.

Change of left ventricular volume and function

Left ventricular dilatation, defined as an increase of >15% in end-diastolic left ventricular volume was observed in 9 of the 26 patients and assigned as group I. Seventeen patients without left ventricular dilatation were assigned as group II. There was no difference in infarct related coronary artery stenosis between group I and group II (72±27% vs 71±28% p>0.05) when MCE was performed.

In all cases mean left ventricular systolic and diastolic volume (baseline to follow-up, 47±20 ml to 50±24 ml p<0.05, 96±20 ml to 106±29 ml p>0.05 respectively) and ejection fraction (baseline to follow-up, 52±10% to 54±10% p>0.05), were not changed significantly at follow-up. But the wall motion index of left anterior descending artery territory improved from 1.88±0.74 to 1.36±0.94 during the period of observation (p=0.0002) (Table 1). But this improvement of regional wall motion by follow up was shown in group II only: wall motion index decreased from 1.62±0.75 to 0.80±0.56 (p<0.0001). In contrast, wall motion index was not changed in group I.

Table 1. Opacification index, at left ventricular volume and function

	Baseline	Follow up	p value
OI			
Group I	0.39±0.20*		
Group II	0.80±0.15*		
LVVD (ml)			
Total	96±20	106±29	NS
Group I	99±28	136±27*	0.0001
Group II	95±15	90±14*	NS
LVSV (ml)			
Total	47±20	50±24	NS
Group I	56±27	76±23*	0.01
Group II	43±14	37±8*	NS
LV EF (%)			
Total	52±12	54±10	NS
Group I	46±12†	45±8.2*	NS
Group II	55±11†	59±6.1*	NS
WMI			
Total	1.88±0.74	1.360±0.94	0.0002
Group I	2.38±0.43*	2.42±0.44*	NS
Group II	1.62±0.75*	0.799±0.563*	<0.0001

OI, opacification index; LVVD, diastolic left ventricular volume; LVSV, systolic left ventricular volume; LV EF, left ventricular ejection fraction; WMI, Wall motion index.
*: p<0.05, †: p=0.052.

There was no significant difference in baseline left ventricular volume and ejection fraction between group I and II (46±12% vs 55±11% p>0.05) but wall motion index was higher (2.38±0.43 vs 1.62±0.7 p<0.05) and opacification index was lower (0.39±0.2 vs 0.80±0.15 p<0.05) in group I than group II. At follow up,

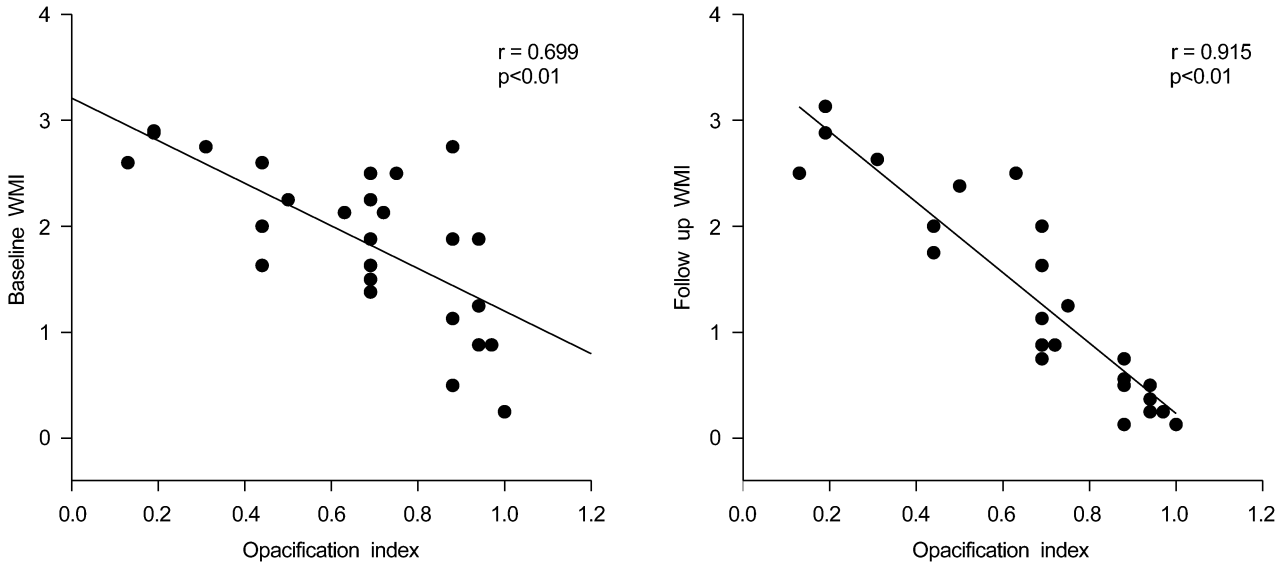

Fig. 1. Correlation between opacification index and wall motion index (WMI) at baseline and follow up.

group II had lower wall motion index and higher ejection fraction than group I.

Influence of opacification index on functional improvement

The correlation of opacification index and wall motion index within the left anterior descending coronary territory at baseline was −0.699 ($p<0.0001$) and increased to −0.915 ($p<0.0001$) at follow up (Fig. 1). The patients were divided into three groups based on their opacification index: ≥0.75 (n=9), >0.50 to <0.75 (n=9), ≤0.5 (n=8). The baseline wall motion index in each group was 1.27±0.78, 1.99±0.42, 2.4±0.45, respectively. The follow-up wall motion index improved to 0.38±0.21 in ≥0.75 group and 1.41±0.59 in >0.5 to <0.75 group ($p=0.003$, 0.01, respectively). But in the group with ≤ 0.5 opacification index, no functional improvement at follow up was observed (Fig. 2).

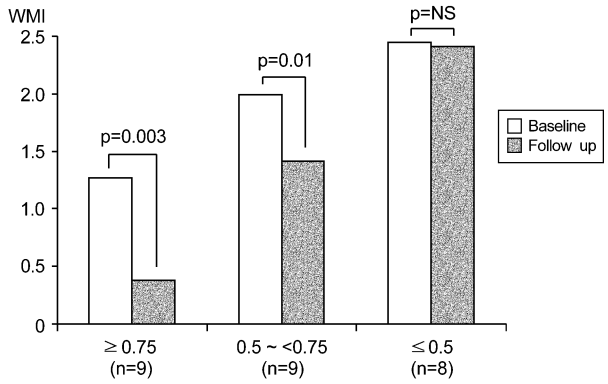

Fig. 2. Changes of WMI from baseline to follow up according to opacification index.

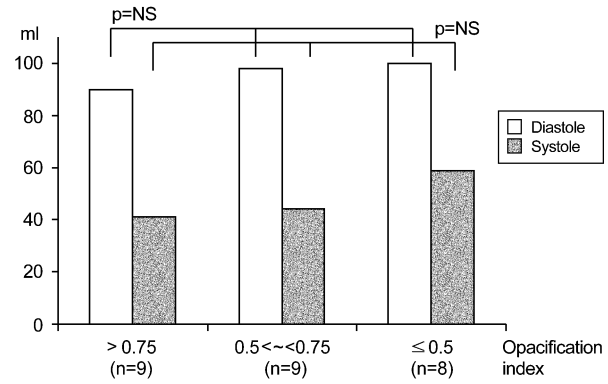

Fig. 3. Baseline left ventricular volume as analysed by opacification index.

Influence of opacification index on left ventricular dilatation

The baseline diastolic and systolic volume did not differ between groups according to their opacification index as depicted in Fig. 3. But percent changes of left ventricular volume from baseline to follow up was higher in patients with low opacification index. Fig. 4 shows the mean percent change of ventricular volume at follow up according to their opacification index. In the group of patients with ≤0.5 opacification index, the baseline left ventricular diastolic and systolic volume increased by 33 % and 49% at follow up. Compared to the group of patients with more than 0.5 opacification index, the changes of left ventricular volume is significantly larger in patients with less than 0.5 opacification index ($p<0.05$).

Predictors of left ventricular volume

Among the echocardiographic parameters on admission the best predictors of left ventricular dilatation after myocardial infarction were analyzed by stepwise multiple-regression method (Table 2). The opacification index was the most influential variable that predict left ventricular

Table 2. Multiple regression analysis for predictors of left ventricular dilatation

	% change of LVVD		% change of LVVS	
Variables	Uni	Multi	Uni	Multi
OI	0.0001	0.00001	0.001	0.00001
LVVD	0.373	0.0068	0.097	0.6035
LVSD	0.924	0.7925	0.148	0.00001
WMI	0.123	0.1710	0.418	0.5933
LVEF	0.376	0.8473	0.339	0.5832

LVVD, diastolic left ventricular volume; LVVS, systolic left ventricular volume; OI, opacification index; WMI, wall motion index; Uni, univariate p value; Multi, multivariate p value.

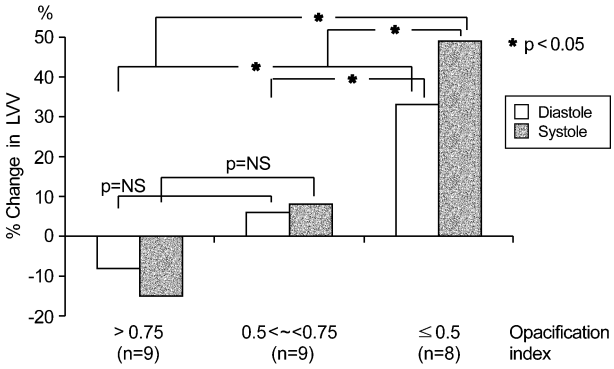

Fig. 4. Percent changes in left ventricular volume from baseline to follow up according to opacification index.

dilation after myocardial infarction. Other variables that was related to left ventricular dilatation were initial left ventricular diastolic volume and systolic volume.

DISCUSSION

This study showed that the extent of myocardial no-reflow after reperfusion in patients of acute myocardial infarction predicts long-term left ventricular dilatation as well as functional recovery.

After acute myocardial infarction, the ventricular remodeling is a progressive process beginning in the early phase and continuing for months and years (6, 7, 10). Dilatation of left ventricle, resulting from left ventricular remodeling, represents the most influential long-term prognostic indicator for clinical events (1-3). The patients with larger ventricle, in particular end-systolic volume, are at higher risk of congestive heart failure and death. One of the most important factors that determines left ventricular dilatation after infarction is occluded infarct-related artery (10). The early restoration of myocardial perfusion in acute myocardial infarction is crucial in limiting infarct size. In addition, several investigators demonstrated (18-22). that the patency status of infarct related artery have an additive and complementary impact in reducing ventricular dilation after myocardial infarction even compared in same size of myocardial infarction. But patent epicardial coronary artery does not guarantee myocardial perfusion in patients with acute myocardial infarction (11), because substantial amount of myocardium has been destroyed already by abolition of blood flow before restoration of coronary flow. Recent studies (12, 13, 17) have demonstrated that MCE plays an important role in assessing microvascular integrity because it uses small microbubbles that traverse the myocardium through microvasculature. As myocellular necrosis has been associated with loss of microvascular integrity, the assessment of microvascular perfusion can be used as a method for identifying myocardium at risk of necrosis. Thus, patients with large nonopacified myocardium by MCE can be regarded as a risk group for ventricular remodeling after infarct, because the amount of myocardial necrosis is the most influential factor for left ventricular dilatation.

Data, concerning the relation of myocardial no reflow after reperfusion with ventricular remodeling, is scarce. Ito et al. (15) demonstrated that the patients with substantial size of the MCE no-reflow after reperfusion developed left ventricular dilatation during the 25 days of follow-up period. But the patterns and time course of left ventricular dilatation after infarction is reported to be heterogenous in individual patient (6, 7). It may appear early or occur remote from infarction or shows a progressive pattern or stabilize after initial dilatation in some patients. Thus, for the observation of left ventrivular remodeling, extended period may be necessary. In our study, the mean follow-up period was 9 months. Therefore, current study support the previous findings of relation of MCE reflow and left ventricular dilatation and extends them in a longterm period.

In addition to patency status of the infarct-related artery, previous clinical studies have evaluated variables that predict an increase in left ventricular volume. Those are the extent of ventricular dysfunction and infarct location (7, 10, 23), baseline ejection fraction (10), left ventricular volume (23), left ventricular end-diastolic pressure (24), and transmurality (25). To control these contributing factors, only the patients with reperfused first anterior myocardial infarction with Q waves were included for the study. In our data, the on admission echocardiographic variables that predict long term left ventricular dilatation were opacification index and left ventricular volume. Though the degree of global and regional left ventricular function was lower in group I than in group II patients, it did not predict left ventricular dilation by multivariate analysis. As considerable amount of dysfunctional myocardium immediately after reperfusion is due to myocardial stunning, functional recovery is expected when the irreversible myocardial damage did not occur. Because of this wall motion index immediately after reperfusion is not a predictor for long-term ventricular dilatation. In previous studies using MCE, the recovery of nonopacified dysfunctional myocardium was poor (12, 17). Our data is consistent with these previous findings. As shown in Fig. 2, functional recovery was seen only in patients with more than 0.5 opacification index. The correlation of opacification index and wall motion index was better at follow up than baseline as expected. Therefore, by doing a MCE in early stage of acute myocardial infarction, we may discover patients who are not expected to show functional recovery and eventually develop left ventricular dilatation.

In interpreting the present study, several limitations must be considered. First, the number of patients enrolled for the study is small. Some echocardiographic variables may have predictability if the patient's numbers was large enough to be statistical. Second, as the first anterior myocardial infarction was enrolled for the study, the results of our study cannot be applied to patients with inferior or posterior wall myocardial infarction. Thirdly, myocardial opacification is influenced by physical property of microbulbbles and the analysis of MCE was done qualitatively. Similary, echocardiographic measurements of ventricular volume was based on geometric assumption that is not perfectly met in patients with

disfigured shape due to myocardial infarction. But over the past years, echocardiography has become a established useful tool in measuring serial changes of left ventricular volume when performed in experienced laboratory (26). Another limitation of our study is that the patency of coronary artery was not confirmed at follow up. As the reocclusion of the reperfused infarct-related artery was reported (27) to be one predictor of left ventricular dilatation, it may influence our result to some extent.

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