Dyslipidemia, Low Left Ventricular Ejection Fraction and High Wall Motion Score Index Are Predictors of Progressive Left Ventricular Dilatation After Acute Myocardial Infarction

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ABSTRACT

Background and Objectives: Left ventricular (LV) remodeling is a heterogeneous process, involving both infarcted and non-infarcted zones, which affects wall thickness and chamber size, shape and function. Subjects and Methods: A total of 758 consecutive patients (62.8 ± 12.0 years, 539 males) with acute myocardial infarction (AMI), who were examined by echo-cardiography at admission and after 6 months. An increase in LV end-diastolic volume index >10% was defined as a progressive LV dilation. They were divided into two groups according to the extent of progressive LV dilatation during 6 months. Group I with progressive LV dilatation (n=154, 61.4±11.0 years, 110 males) vs. group II without LV dilatation (n=604, 64.1±12.0 years, 429 males). Results: The age and gender were no significant differences between two groups. The levels of glucose, creatinine, maximal creatine kinase (CK), CK-MB, troponin T and I were significantly increased in group I than in group II (p<0.05). Low ejection fraction (EF) and high wall motion score index (WMSI) were more common in group I than in group II (p<0.05). The presence of dyslipidemia (odds ratio (OR); 1.559, confidence interval (CI); 1.035-2.347, p=0.03), low EF less than 45% (OR; 3.328, CI 2.099-5.276, p<0.01) and high WMSI above 1.5 (OR; 3.328, CI 2.099-5.276, p<0.01) were significant independent predictors of progressive LV dilatation by multivariate analysis. Conclusion: Dyslipidemia, decreased systolic function and high WMSI were independent predictors of LV remodeling process in patients with AMI. (Korean Circ J 2011;41:124-129)

KEY WORDS: Myocardial infarction; Heart failure; Prognosis.
acute MI stimulates the interaction of a number of factors, such as loss of contractile elements, activation of circulating neurohormones and patency of the infarct-related artery (IRA), initial infarction size and LV size to normalize wall stress. It can begin very soon after AMI and, if not attenuated or reversed by intervention, has a poor prognosis.

The purpose of this study was to assess the associated factors with LV remodeling in the first 6 months following MI, and to define the clinical, biochemical, echocardiographic and angiographic predictors of LV dilatation after AMI.

Subjects and Methods

Study population

A total of 758 consecutive patients (62.8 ±12.0 years, 539 males) with AMI were examined by echocardiography at admission and after 6 months. An increase in left ventricular end-diastolic volume index (LVEDVI) more than 10% was defined as progressive LV dilatation. They were classified into two groups according to the extent of progressive LV dilatation in 6 months. Group I with progressive LV dilatation (n=154, 61.4 ±11.0 years, 110 males 44 females) vs. group II without LV dilatation (n=604, 63.1 ±1.02 years, 429 males 175 females).

Definition of hypertension, diabetes, dyslipidemia and myocardial infarction

Subjects were considered to be hypertensive if their blood pressure was more than 140≥90 mmHg as Joint National Committee VII or if they were on treatment for hypertension. The American Diabetes Association criteria were used to define diabetes (DM). We considered a subject to have DM when the fasting plasma glucose levels were more than 126 mg/dL in 2 consecutive assessments, or if they were on treatment for DM. Dyslipidemia was diagnosed according to the 2004 update of the National Cholesterol Education Program guidelines. According to these guidelines, high level of low density lipoprotein-cholesterol (LDL-C) more than 160 mg/dL, low high density lipoprotein-cholesterol (HDL-C) less than 40 mg/dL and high triglycerides more than 150 mg/dL were included.

The presence of ST-segment elevation MI was determined by more than 30 minutes of continuous chest pain, a new ST-segment elevation more than 2 mm on at least two contiguous electrocardiographic leads, creatine kinase (CK)-MB or troponin more than 3 times normal. The presence of non-ST-segment elevation MI was diagnosed by chest pain and a positive cardiac biomarker without new ST-segment elevation. Infarct-related arteries were identified using a combination of electrocardiographic findings, LV wall motion abnormalities on two-dimensional echocardiography and coronary angiography. Family history means early cardiovascular disease in direct relatives. Hospital records of patients were reviewed to obtain information on clinical demographics.

Measurement of serum biomarkers

Serum N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) was measured using the electrochemiluminescence sandwich immunoassay method for NT-pro-BNP with an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany). This method has high sensitivity and specificity, and large detection range. The analytic range of the NT-pro-BNP assay extends from 5 to 35,000 pg/mL. High sensitivity C-reactive protein (hs-CRP) was measured by immunoturbidimetric CRP-Latex (II) high-sensitivity assay using an Olympus 5431 autoanalyzer.

Measurement of progressive left ventricular dilatation

Two-dimensional, M-mode echocardiography and Doppler ultrasound examination were performed with GE Vivid 7 Ultrasound (General Electronic Healthcare, Vingmed, Horten Norway) with a 2.5 MHz probe. Image-Point at the time of initial admission and at 6 months after MI. LV volume and ejection fraction (EF) were measured using the Simpson’s formula. LV volume indices were obtained by dividing the volume by the body surface area. The mean values of three measurements of the technically best cardiac cycles were taken from each examination performed by two independent inter-observers. Intra-observer and inter-observer variabilities of the Simpson’s method were 4±5% and 5±4% (absolute difference divided by mean value of measurement). In each patient the wall motion score index (WMSI) was derived. The LV was divided according to a 17-segment model. In each segment wall motion was scored from 1 (normal) to 4 (dyskinetic). An increase in LVEDVI >10% between initial and 6 month follow up was considered as a progressive LV dilatation pattern.

Statistical analysis

The Statistical Package for Social Sciences for Windows, version 15.0 (Chicago, IL, USA) was used for all analysis. For each parameter mean, median and standard deviation were calculated. Statistical significance between means for different groups was calculated by the non-parametrical Wilcoxon signed rank test. Statistical significance between frequencies was calculated by the chi square test with Yates correction or, if the expected value was less than 5, by Fisher's exact test. Relative risk and confidence interval (CI) were also calculated. A p of less than 0.05 was required to reject the null hypothesis. The variables that were significant in univariate analysis were entered into the multivariate models.

Results

Baseline clinical characteristics

The baseline characteristics are summarized in Table 1. Age and gender exhibited no significant differences between...
two groups. The prevalence of dyslipidemia was higher in group I than group II (p<0.05). The proportion of ST-segment elevation MI was more frequent in group I than in group II (p<0.05). There was no difference between the groups with respect to the initial vital sign or Killip class.

### Biochemical, echocardiographic and coronary angiographic parameter associated with progressive left ventricular dilatation

The levels of glucose, maximal CK, CK-MB, troponin-T and troponin-I were significantly increased in group I compared to group II (p<0.05) (Table 2). LV end-diastolic and systolic dimension, interventricular septal thickness, posterior wall thickness were increased in group II compared to group I at admission. However, 6-month follow up echocardiography showed reversal of LV size mentioned above. LV dimension and volume were more increased in group I compared to group II at 6 months (p<0.05). Although the mean value of EF and total wall motion score (TWMS) at admission were not significantly different between the groups, the percentage of low EF (<45%) and high WMSI (≥1.5) were higher in group I than in group II (p<0.05). Six-month EF and wall motion score were deteriorated compared to the initial score (p<0.05) (Table 3). Changes in LV volume at admission and at 6 months were significantly increased in group I, but not in group II (Fig. 1A). Fig. 1B showed decreased EF in group I and no significant change in group II during the 6-month period. Serial changes of TWMS at admission and at 6 months are illustrated in Fig. 1C. It was decreased TWMS in group II and no significant

### Table 2. Biochemical parameters of left ventricular dilatation in patients with acute myocardial infarction

|                  | Group I (n=154) | Group II (n=604) | p     |
|------------------|----------------|------------------|-------|
| Glucose (mg/dL)  | 182.94±85.0    | 168.27±74.3      | 0.031 |
| Creatinine (mg/dL) | 1.07±0.69    | 1.15±1.09        | 0.412 |
| Creatinine kinase (IU/L) | 2145±2312   | 1342±1668        | <0.001|
| Creatinine kinase MB (IU/L) | 126.8±132  | 82±100           | <0.001|
| Troponine T (µg/L) | 68.1±71.94  | 49.2±114.76      | 0.004 |
| Troponine T (µg/L) | 7.15±7.23    | 5.02±6.38        | <0.001|
| Total cholesterol (mg/dL) | 183.9±45.27 | 179.5±40.36      | 0.246 |
| Triglyceride (mg/dL) | 117.2±53.17  | 116.4±67.19      | 0.825 |
| HDL-C (mg/dL)    | 50.3±43.74    | 46.5±24.39       | 0.064 |
| LDL-C (mg/dL)    | 121.11±39.72 | 117.07±35.81     | 0.195 |
| hs-CRP (mg/L)    | 2.43±2.74     | 2.12±3.95        | 0.366 |
| NT-proBNP (pg/mL)| 2947.8±6708   | 2311.5±5134      | 0.230 |

HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, hs-CRP: high sensitivity C-reactive protein, NT-pro-BNP: N-terminal pro B natriuretic peptide

### Table 3. Echocardiographic parameters of left ventricular dilatation in the patients with acute myocardial infarction

|                  | Group I (n=154) | Group II (n=604) | p     |
|------------------|----------------|------------------|-------|
| LV end-diastolic dimension (mm) | 47.9±5.0     | 51.9±18.8        | 0.009 |
| LV end-systolic dimension (mm) | 32.8±5.9     | 51.5±6.7         | <0.001|
| LVEDV (mm³)      | 155.6±42.2    | 177.3±37.8       | 0.002 |
| LVESV (mm³)      | 73.5±39.1     | 83.5±34.0        | 0.037 |
| Interventricular septum (mm) | 10.3±2.2     | 9.6±1.8          | 0.002 |
| Posterior wall thickness (mm) | 10.1±2.5     | 9.6±2.0          | 0.037 |
| EF (%)           | 57.6±11.7     | 58.6±11.9        | 0.339 |
| EF <45% (%)      | 43 (31.8)     | 130 (21.5)       | 0.034 |
| Ascending aorta diameter (mm) | 30.8±3.9     | 31.7±4.3         | 0.333 |
| LA dimension (mm) | 37.8±6.8     | 38.3±13.9        | 0.735 |
| E (m/sec)        | 0.64±0.21     | 0.90±0.53        | 0.627 |
| A (m/sec)        | 1.03±0.19     | 0.86±1.65        | 0.606 |
| E/A              | 0.86±0.37     | 0.94±0.47        | 0.122 |
| Deceleration time (sec) | 183±54.6   | 187±61.1         | 0.598 |
| E' (cm/sec)      | 0.059±0.01    | 0.064±0.04       | 0.266 |
| A' (cm/sec)      | 0.093±0.02    | 0.18±1.73        | 0.658 |
| S' (cm/sec)      | 0.32±0.8      | 0.08±0.1         | 0.585 |
| E/E'             | 11.2±5.3      | 11.5±7.9         | 0.643 |
| Wall motion score | 22.7±5.2     | 22.0±5.6         | 0.213 |
| Wall motion score index ≥1.5 (%) | 49 (31.8) | 146 (24.1) | 0.032 |
| 6 month LVEDV (mm³) | 197.7±48.1   | 101.1±85.2       | <0.001|
| 6 month LVESV (mm³) | 101.2±48.2  | 46.1±44.0        | <0.001|
| 6 month EF (%)   | 47.9±10.4    | 52.7±9.3         | 0.006 |
| 6 month E/E'     | 11.5±5.6     | 10.5±5.9         | 0.108 |
| 6 month wall motion score | 21.8±5.5 | 19.7±4.4        | <0.001|

LV: left ventricle, EF: ejection fraction, LA: left atrium; LVEDV: LV end diastolic volume, LVESV: LV end systolic volume
change in group I. A total of 71 patients were treated with thrombolytic therapy in this patient group. Thrombolytic therapy did not affect progressive LV dilatation. There were no significant differences between groups in the stenting rate, involved vessel number, IRA, post-PCI thrombolysis in myocardial infarction (TIMI) flow and the percentage of restenosis on follow-up coronary angiography. The percentage of low TIMI flow (≤2) was higher in group I than in group II (p<0.05). Medication history of angiotensin converting enzyme inhibitor, angiotensin receptor blocker, statin, and beta blocker did not affect progressive LV dilatation (Table 4).

Independent predictors of progressive left ventricular dilatation
The presence of dyslipidemia (odd ratio (OR); 1.559, CI; 1.035-2.347, p=0.03), low LVEF less than 45% (OR; 3.328, CI 2.099-5.276, p<0.01) and high WMSI above 1.5 (OR; 3.328, CI 2.099-5.276, p<0.01) were significant independent predictors of progressive LV dilatation by multivariate analysis (Table 5).

Discussion
The acute loss of myocardium in AMI results in an abrupt increase in loading conditions that induces a unique pattern of remodeling, involving the infarct border zone and remote non-infarcted myocardium.19 Myocyte necrosis and the resultant increase in load trigger a cascade of biochemical intracellular signaling processes that indicate and subsequently modulates reparative changes, including dilatation, hypertrophy, and the formation of a discrete collagen scar. Ventricular remodeling may continue for weeks or months until the distending forces are counterbalanced by the tensile strength of the collagen scar. Failure to normalize increased wall stresses results in progressive dilatation, recruitment of border zone myocardium into the scar, and deterioration in contractile function. This balance is determined by the size, location, and transmurality of the infarct, the extent of myocardial stunning, the patency of the IRA, and local tropic factors.20 Therefore, it may be important to identify patients at risk of LV remodeling to prevent LV dilation after AMI.

Dyslipidemia is a well-established risk factor for coronary artery disease, but few information is available on its effects on microvascular perfusion. Experimental studies showed that independent of coronary artery stenosis severity, dyslipidemia may reduce myocardial flow reserve and capillary
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density, and may increase capillary endothelial cell apoptosis following ischemia and reperfusion, thus contributing to reduced LV function after AMI.\(^{12,23}\) Among the clinical risk factor criteria, only the incidence of dyslipidemia was significantly higher in the LV dilatation group (p<0.05), whereas there were no statistical differences between groups in the other risk factors. Our data showed that dyslipidemia affected independent progressive LV dilatation after 6 months in AMI patients. Treatment of dyslipidemia may reduce microvascular perfusion and myocardial salvage after AMI, and improve LV remodeling.

Studies have shown that inflammatory cytokines were involved in the process of LV remodeling after AMI, anti-inflammatory treatment ameliorated LV remodeling and improved cardiac performance. Hydroxymethylglutary coenzyme A reductase inhibition (statins) could affect the expression of inflammatory cytokines.\(^{23,24}\) Therefore, treatment of dyslipidemia with statins may help to reduce progressive LV dilatation. If we recorded lipid levels one or two months after discharge, it would be more helpful to understand LV progression pattern. Unfortunately, we do not have sufficient data of the follow up lipid levels one or two months after AMI.

According to early reports, a major determinant of ventricular remodeling following AMI could be infarct size.\(^{25}\) Myocyte injury markers such as cardiac troponin I and T, CK and CK-MB appear to be useful in predicting late ventricular dilation. Anterior myocardial infarction, perfusion status of the culprit lesion, and CHF on admission are major predictors of LV dilatation.\(^{26,27}\) Several studies showed an association between elevated blood glucose at admission and subsequent adverse events, such as CHF, cardiogenic shock, and death.\(^{28}\) Recently, hs-CRP, BNP and cardiac troponin I have been examined as potential predicting biomarkers of LV remodeling.\(^{29}\) High WMSI and markedly increased cardiac enzymes suggest large infarction. As mentioned above, our study showed high wall motion score and low EF affected progressive LV dilatation. The mean values of hs-CRP and BNP were increased in the LV dilatation group, consistent with the outcomes of previous studies. However, there was no statistical significance demonstrated.

Early reperfusion treatment improves survival by limiting infarct size and consequently preserving LV function. Early reperfusion therapy and patency of the IRA is crucial for reducing infarct expansion and LV enlargement. Some investigators have tested the hypothesis that LV remodeling occurs after percutaneous coronary intervention (PCI), despite persistent patency of the IRA, and may influence the prognosis.\(^{30}\)

Some reports showed Post-PCI TIMI grade was significantly related to the change in LVEDVI and left ventricular end-systolic volume index after 9 month.\(^{30}\) But our data had no significance of post TIMI flow.

The limitation of our study was a lack of knowledge of long term patency of the IRA because we did not perform routine follow-up coronary angiography. We only performed follow-up coronary angiography on 365 patients (48.1%). AMI patients with dyslipidemia, low EF and high wall motion score at admission should be carefully monitored by clinical and serial echocardiographic examinations, which should serve helpful guidance to prevent or reverse LV remodeling.

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REFERENCES

1) Pfifer MA, Braunwald E. Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. Circulation 1990;81:1161-72.
2) Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling: concepts and clinical implications: a consensus paper from an international forum on cardiac remodelling. J Am Coll Cardiol 2000;35:569-82.
3) Ko JS, Jeong MH, Lee MG, et al. Left ventricular dysynchrony after acute myocardial infarction is a powerful indicator of left ventricular remodeling. Korean Circ J 2009;39:236-42.
4) Erlebacher JA, Weiss JL, Weisfeldt ML, Bulkley BH. Early dilation of the infarcted segment in acute transmural myocardial infarction: role of infarct expansion in acute left ventricular enlargement. J Am Coll Cardiol 1984;4:201-7.
5) Bolognese L, Neskovsk AN, Parodi G, et al. Left ventricular remodeling after primary coronary angioplasty: patterns of left ventricular dilation and long-term prognostic implications. Circulation 2002;106:2351-7.
6) Gaudron P, Kugler I, Hu K, Bauer W, Eiles C, Ertl G. Time course of cardiac structural, functional and electrical changes in asymptomatic patients after myocardial infarction: their inter-relation and prognostic impact. J Am Coll Cardiol 2001;38:33-40.
7) White HD, Norris RM, Brown MA, Brand PW, Whitlock RM, Wild CJ. Left ventricular end systolic volume as the major determinant of survival after recovery from myocardial infarction. Circulation 1987;76:44-51.
8) Gaudron P, Eiles C, Kugler I, Ertl G. Progressive left ventricular dysfunction and remodeling after myocardial infarction: potential mechanisms and early predictors. Circulation 1993;87:755-63.
9) Giannuzzi P, Temporelli PL, Bosimini E, et al. Heterogeneity of left ventricular remodeling after myocardial infarction: results of the Gruppo Italiano per lo Studio della Sopravvenienza nell’Infarto Miocardico-3 Echo Substudy. Am Heart J 2001;141:131-8.
10) Sim DS, Kim JH, Jeong MH. Differences in clinical outcomes between patients with ST-elevation versus non-ST-elevation acute myocardial infarction in Korea. Korean Circ J 2009;39:297-303.
11) Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. JAMA 2003;289:2560-72.
12) Expert Committee on the Diagnosis and the Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and the classification of diabetes mellitus. Diabetes Care 1997;20:1183-97.
13) Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227-39.
14) Hatzitolios AI, Athyros VG, Karagiannis A, et al. Implementation of strategy for the management of overt dyslipidemia. The IMPROVE-
dyslipidemia study. Int J Cardiol 2009;134:322-9.
15) Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. Circulation 2004;110:e82-293.
16) Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2002;40:1366-74; Circulation 2002;106:1893-900.
17) Simonson JS, Schiller NB. Descent of the base of the left ventricle: an echocardiographic index of the left ventricle. J Am Soc Echocardiogr 1989;2:25-35.
18) Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the cardiac imaging committee of the council on clinical cardiology of American Heart Association. Circulation 2002;105:539-42.
19) Rouleau JL, de Champlain J, Klein M, et al. Activation of neurohumoral systems in postinfarction left ventricular dysfunction. J Am Coll Cardiol 1993;22:390-8.
20) Warren SE, Royal HD, Markis JE, Grossman W, McKay RG. Time course of left ventricular dilation after myocardial infarction: influence of infarct-related artery and success of coronary thrombolysis. J Am Coll Cardiol 1988;11:12-9.
21) Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation 2000;101:2981-8.
22) Zeiher AM, Drexler H, Wollschlager H, Just H. Endothelial dysfunction of the coronary microvasculature is associated with coronary blood flow regulation in patients with early athelosclerosis. Circulation 1991;84:1984-92.
23) Eefting FD, Cramer MJ, Stella PR, Rensing BJ, Doevendans PA. A randomised trial with serial cardiac MRI follow-up testing the ability of atorvastatin to reduce reperfusion damage after primary PCI for acute MI. Neth Heart J 2006;14:95-9.
24) Hong YJ, Jeong MH, Hyun DW, et al. Prognostic significance of simvastatin therapy in patients with ischemic heart failure who underwent percutaneous coronary intervention for acute myocardial infarction. Am J Cardiol 2005;95:619-22.
25) Hochman JS, Choo H. Limitation of myocardial infarct expansion by reperfusion independent of myocardial salvage. Circulation 1987;75:299-306.
26) Yellon DM, Baxter GF. Protecting the ischaemic and reperfused myocardium in acute myocardial infarction: distant dream or near reality. Heart 2000;83:381-7.
27) Lim SC, Bhee JA, Jeong MH, et al. Predictive factors for the recovery of left ventricular function in patients with acute myocardial infarction. Korean Circ J 2007;37:113-8.
28) Bolk J, van der Ploeg TJ, Cornel JH, Arnold AE, Sepers J, Umans VA. Impaired glucose metabolism predicts mortality after a myocardial infarction. Int J Cardiol 2001;79:207-14.
29) Bolognese L, Neskovic AN, Parodi G, et al. Left ventricular remodeling after primary coronary angiography: patterns of left ventricular dilatation and long term prognostic implications. Circulation 2002;106:2351-7.
30) Cerisano G, Bolognese L, Buonamici P, et al. Prognostic implications of restrictive left ventricular filling in reperfused anterior acute myocardial infarction. J Am Coll Cardiol 2001;37:793-9.
31) Choi SY, Tahk SJ, Yoon MH, et al. Comparison of TIMI myocardial perfusion grade with coronary flow reserve for prediction of recovery of LV function and LV remodeling in acute myocardial infarction. Korean Circ J 2004;34:247-57.