Circ J 2007; **71:** 1219–1224

Relationship Between Peripheral Monocytosis and Nonrecovery of Left Ventricular Function in Patients With Left Ventricular Dysfunction Complicated With Acute Myocardial Infarction

Young Joon Hong, MD; Myung Ho Jeong, MD; Youngkeun Ahn, MD; Nam Sik Yoon, MD; Sang Rok Lee, MD; Seo Na Hong, MD; Jae Youn Moon, MD; Kye Hun Kim, MD; Hyung Wook Park, MD; Ju Han Kim, MD; Jeong Gwan Cho, MD; Jong Chun Park, MD; Jung Chaee Kang, MD

Background Although ischemic heart failure is a major cause of mortality after acute myocardial infarction (AMI), the factors that may influence the nonrecovery of left ventricular function (LVF) after an AMI are still unclear. The aim of this study was to identify predictors of nonrecovery of LVF in patients with left ventricular (LV) dysfunction (defined as an echocardiographic ejection fraction (EF) <40%) complicated with AMI who undergo successful primary percutaneous coronary intervention (PCI).

Methods and Results LVF recovery was defined as improvement of LVEF more than 10% compared with baseline LVEF at follow-up. One hundred and eight patients with LV dysfunction after AMI were divided into 2 groups according to the LVF recovery at follow-up: patients with LVF recovery (n=64) vs patients without LVF recovery (n=44). The follow-up LVEF was measured at 8±4 months after PCI. Patients without LVF recovery were older (76±13 years vs 59±14 years, p=0.023) and the baseline peak monocyte count, creatine kinase, and troponin I levels were significantly higher in patients without LVF recovery than in patients with LVF recovery. Delta LVEF (follow-up LVEF−baseline LVEF) correlated with baseline peak monocyte count (r=–0.417, p<0.001), baseline peak creatine kinase (r=–0.269, p=0.005), and baseline peak troponin I levels (r=–0.256, p=0.007). Multivariate analyses showed that baseline peak monocyte count and old age were the independent predictors of nonrecovery of LVF (hazard ratio; 3.38, 95% confidence interval (CI): 1.16–5.43, p=0.012, and hazard ratio; 2.38, 95% CI: 1.09–4.87, p=0.025, respectively).

Conclusion Peripheral monocytosis is associated with nonrecovery of LVF in patients with LV dysfunction complicating an AMI who underwent successful primary PCI. These results suggest an important role of monocytes in the expansion of the infarct and the development of chronic ischemic heart failure after reperfusion therapy. (*Circ J* 2007; **71:** 1219–1224)

Key Words: Angioplasty; Heart failure; Inflammation; Myocardial infarction

Acute myocardial infarction (AMI) is associated with increased short- and long-term mortality[1] The development of left ventricular (LV) dysfunction complicating an AMI is particularly serious because these patients have a several-fold increase in the risk of mortality compared with AMI survivors without LV dysfunction[1,2] or compared with nonischemic heart failure (HF)[3] The risk of LV dysfunction is greatest in the first few days after AMI. Studies have demonstrated that patients undergoing treatment for an initial AMI have a 22% incidence of acute HF during hospitalization, and the incidence in patients with recurrent myocardial infarction (MI) is 33%[4,5] Because of the high incidence of acute HF early after acute MI, the emphasis of previous studies has been on the predictors and outcomes of HF immediately following MI.

So far, several studies have demonstrated the factors affecting recovery of LV function (LVF) in patients with AMI[6–11] but little is known about the predictors of nonrecovery of LVF in patients with LV dysfunction complicating an AMI who have undergone successful percutaneous coronary intervention (PCI). It is very important to identify the factors that are important for nonrecovery of LVF in AMI survivors without a history of HF before the index MI because a better understanding of these factors will better identify high-risk patients more likely to benefit from more intensive medical therapy. Therefore, the aim of this study was to identify the factors predicting the nonrecovery of LVF in patients with LV dysfunction complicated with AMI who underwent successful primary PCI.

Methods

Study Population

We examined 108 patients ≥18 years of age with first ST segment elevation MI, symptom onset within 12 h of under-

(Received March 15, 2007; revised manuscript received April 11, 2007; accepted May 2, 2007)

The Heart Center of Chonnam National University Hospital, Chonnam National University Research Institute of Medical Sciences, Gwangju, Korea

Mailing address: Myung Ho Jeong, MD, PhD, FACC, FAHA, FESC, FSCAI Professor, Director of Cardiac Research Laboratory, The Heart Center of Chonnam National University Hospital, 8 Hak-dong, Dong-gu, Gwangju 501-757, Korea. E-mail: myungho@chollian.net

Table 1 Baseline Clinical Characteristics

	LVF recovery (n=64)	LVF nonrecovery (n=44)	p value
Age (years)	*59±14*	*76±13*	*0.023*
Female	*13 (20%)*	*10 (23%)*	*NS*
Anterior wall myocardial infarction	*34 (53%)*	*32 (73%)*	*0.040*
Hypertension	*43 (67%)*	*30 (68%)*	*NS*
Diabetes mellitus	*17 (27%)*	*14 (32%)*	*NS*
Smoking	*22 (34%)*	*20 (45%)*	*NS*
Time from onset of symptoms to vessel opening (h)	*283±127*	*307±189*	*NS*
Prior PCI	*5 (8%)*	*7 (16%)*	*NS*
Cardiogenic shock	*4 (6%)*	*9 (21%)*	*0.026*
ACE inhibitor use	*48 (75%)*	*28 (64%)*	*NS*
β-blocker use	*57 (89%)*	*32 (73%)*	*0.028*
Statin use	*48 (75%)*	*23 (52%)*	*0.014*
Baseline ejection fraction (%)	*36±8*	*34±6*	*NS*
Follow-up ejection fraction (%)	*58±7*	*38±7*	*<0.001*

LVF, left ventricular function; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme.

going primary PCI and LV ejection fraction (LVEF) <40%. All patients were admitted to Chonnam National University Hospital, Gwangju, Korea, between July 2001 and June 2002 and underwent successful reperfusion (final Thrombolysis in Myocardial Infarction flow grade 3 in the infarct-related coronary artery without any residual stenosis). Baseline and follow-up echocardiography were performed to determine LVEF.

We excluded patients with baseline LVEF >40%, prior MI, prior LV systolic dysfunction, subacute or late stent thrombosis, restenosis after stenting, use of thrombolytic therapy prior to the present admission, coronary artery bypass graft failure, chronic renal failure, advanced liver disease, malignancies, and concomitant infectious diseases. The diagnosis of AMI was according to a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction[12] Infarct-related arteries were identified using a combination of ECG findings, LV wall motion abnormalities on echocardiography and coronary angiography findings.

Laboratory Analysis

Blood sampling was performed carefully and gently to avoid hemolysis. Total white blood cells and each fraction were measured with an automated hematology analyzer (Coulter Gen S, Beckman Coulter, USA) on admission and every 24 h for at least 3 days. Serum samples were stored at –70°C and were later analyzed to determine creatine kinase (CK), troponin I, and high-sensitivity C-reactive protein (hs-CRP) levels. Plasma CK and troponin I levels were measured on admission, and at 1, 6, 12, 24, and 48 h after PCI; hs-CRP was assessed by the immunoturbidimetric C-reactive protein-Latex (II) hs assay using an Olympus 5431 autoanalyzer, following the manufacturer's protocol, which has been validated against the Dade-Behring method[13] In all patients, serum was collected the day after primary PCI for measuring lipid profiles. The serum levels of total cholesterol, triglycerides, low-density lipoprotein (LDL)-cholesterol, and high-density lipoprotein-cholesterol were measured by standard enzymatic methods. Serum levels of all these parameters were measured at baseline and at follow-up.

LVF Recovery

Echocardiography was performed before or shortly after primary PCI and at follow-up (8±4 months after PCI). LVEF was measured by Simpson's method and LVF recovery was defined as an improvement in the LVEF at follow-up of more than 10% when compared with baseline LVEF[14]

PCI and Medications

Coronary angiography was performed through the femoral artery. All 108 infarct lesions were treated with bare-metal stent implantation. Dalteparin was administered 120 units/kg body weight intravenously every 12 h, or unfractionated heparin as an intravenous bolus (usually 5,000 units) followed by a continuous infusion at a dose adjusted according to the aPTT. After PCI, all patients received aspirin (100 mg daily, indefinitely) and ticlopidine (250 mg daily continued for at least 6 months) or clopidogrel (75 mg daily continued for at least 6 months). 76 patients were treated with angiotensin-converting enzyme inhibitors, 89 were treated with β-blockers, and 71 were treated with statins after PCI. Medications were assessed at baseline and every 4 weeks during clinic examinations. Medications, exact dates of initiation and cessation, and doses were recorded.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) for Windows, version 11.0 (Chicago, IL, USA) was used for all analyses. Continuous variables are presented as the mean value ± SD; comparisons were conducted by Student's t-test or nonparametric Wilcoxon test if normality assumption was violated. Discrete variables are presented as percentages and relative frequencies; comparisons were conducted using the chi-square test or Fisher's exact test as appropriate. Pearson's correlation coefficient was used to evaluate the correlations between ΔLVEF (follow-up LVEF – baseline LVEF) and baseline peak monocyte count, peak CK, peak troponin I, hs-CRP, and lipid profiles. Logistic regression analysis was used to identify the independent predictors of LVF nonrecovery. A p-value <0.05 was considered statistically significant.

Results

Baseline Clinical Characteristics and Angiographic Findings

Follow-up ejection fraction (EF) was 58±7% in patients

Table 2 Coronary Angiography Findings

	LVF recovery (n=64)	LVF nonrecovery (n=44)	p value
No. of diseased vessels			*NS*
1	*34 (53%)*	*26 (59%)*	
2	*21 (33%)*	*9 (21%)*	
3	*9 (14%)*	*9 (21%)*	
Infarct-related artery			*0.048*
Left anterior descending	*34 (53%)*	*32 (73%)*	
Left circumflex	*13 (20%)*	*5 (11%)*	
Right	*17 (27%)*	*7 (16%)*	
ACC/AHA type			*NS*
B1	*37 (58%)*	*28 (64%)*	
B2	*11 (17%)*	*9 (21%)*	
C	*16 (25%)*	*7 (16%)*	
Baseline TIMI flow grade			*NS*
0	*24 (38%)*	*22 (50%)*	
1	*19 (30%)*	*14 (32%)*	
2	*12 (19%)*	*4 (9%)*	
3	*9 (14%)*	*4 (9%)*	
Final TIMI 3 flow grade	*64 (100%)*	*44 (100%)*	*NS*

ACC/AHA, American College of Cardiology/American Heart Association; TIMI, Thrombolysis In Myocardial Infarction Flow. Other abbreviation see in Table 1.

Table 3 Baseline and Follow-up Laboratory Findings

	LVF recovery (n=64)	LVF nonrecovery (n=44)	p value
Baseline			
Peak white blood cell (/mm^3)	*9,518±2,891*	*9,755±2,613*	*NS*
Peak monocyte (/mm^3)	*642±326*	*1,013±962*	*0.005*
Peak creatine kinase (IU/L)	*976±491*	*1,245±790*	*0.018*
Peak troponin I (ng/ml)	*23.5±21.0*	*35.3±25.5*	*0.038*
C-reactive protein (mg/dl)	*2.1±1.9*	*3.5±3.1*	*0.043*
Total cholesterol (mg/dl)	*189±21*	*199±37*	*NS*
Triglyceride (mg/dl)	*126±59*	*152±74*	*NS*
LDL-cholesterol (mg/dl)	*129±19*	*138±28*	*NS*
HDL-cholesterol (mg/dl)	*43±9*	*41±8*	*NS*
Lipoprotein (a) (mg/dl)	*26±21*	*32±25*	*NS*
Follow-up			
White blood cell (/mm^3)	*7,556±1,799*	*7,649±2,982*	*NS*
Monocyte (/mm^3)	*563±236*	*780±273*	*0.032*
C-reactive protein (mg/dl)	*0.9±1.2*	*1.6±1.2*	*0.040*
Total cholesterol (mg/dl)	*171±33*	*189±50*	*NS*
Triglyceride (mg/dl)	*109±99*	*112±50*	*NS*
LDL-cholesterol (mg/dl)	*102±38*	*127±68*	*0.029*
HDL-cholesterol (mg/dl)	*46±7*	*40±8*	*NS*
Lipoprotein (a) (mg/dl)	*25±17*	*34±25*	*NS*

LDL, low-density lipoprotein; HDL, high-density lipoprotein. Other abbreviation see in Table 1.

with LVF recovery and 38±7% in patients without LVF recovery. Patients without LVF recovery were older and more had an anterior wall MI compared with patients with LVF recovery. Cardiogenic shock occurred more frequently in patients without LVF recovery compared with patients with LVF recovery. Beta-blockers and statins were less frequently used in patients without LVF recovery compared with patients with LVF recovery (Table 1). The left anterior descending artery was involved more frequently in patients without LVF recovery compared with patients with LVF recovery (Table 2).

Laboratory Findings

The baseline peak monocyte count and the peak CK, peak troponin I and hs-CRP levels were significantly higher in patients without LVF recovery compared with patients with LVF recovery. At follow-up, the monocyte count and the hs-CRP, and LDL-cholesterol levels were decreased in both groups. At follow-up, the monocyte count and the hs-CRP, and LDL-cholesterol levels were significantly higher in patients without LVF recovery compared with patients with LVF recovery (Table 3).

Parameters Correlating With ΔLVEF

Delta LVEF correlated with baseline peak monocyte count (r=–0.417, p<0.001) and baseline peak CK (r=–0.269, p=0.005), and baseline peak troponin I (r=–0.256, p=0.007) levels, but not with baseline hs-CRP and baseline LDL-cholesterol levels (Fig 1).

Predictors of Nonrecovery of LVF

Univariate predictors of the nonrecovery of LVF at follow-up were baseline peak monocyte count, age >70 years, not taking statins or β-blockers, and the baseline CK level

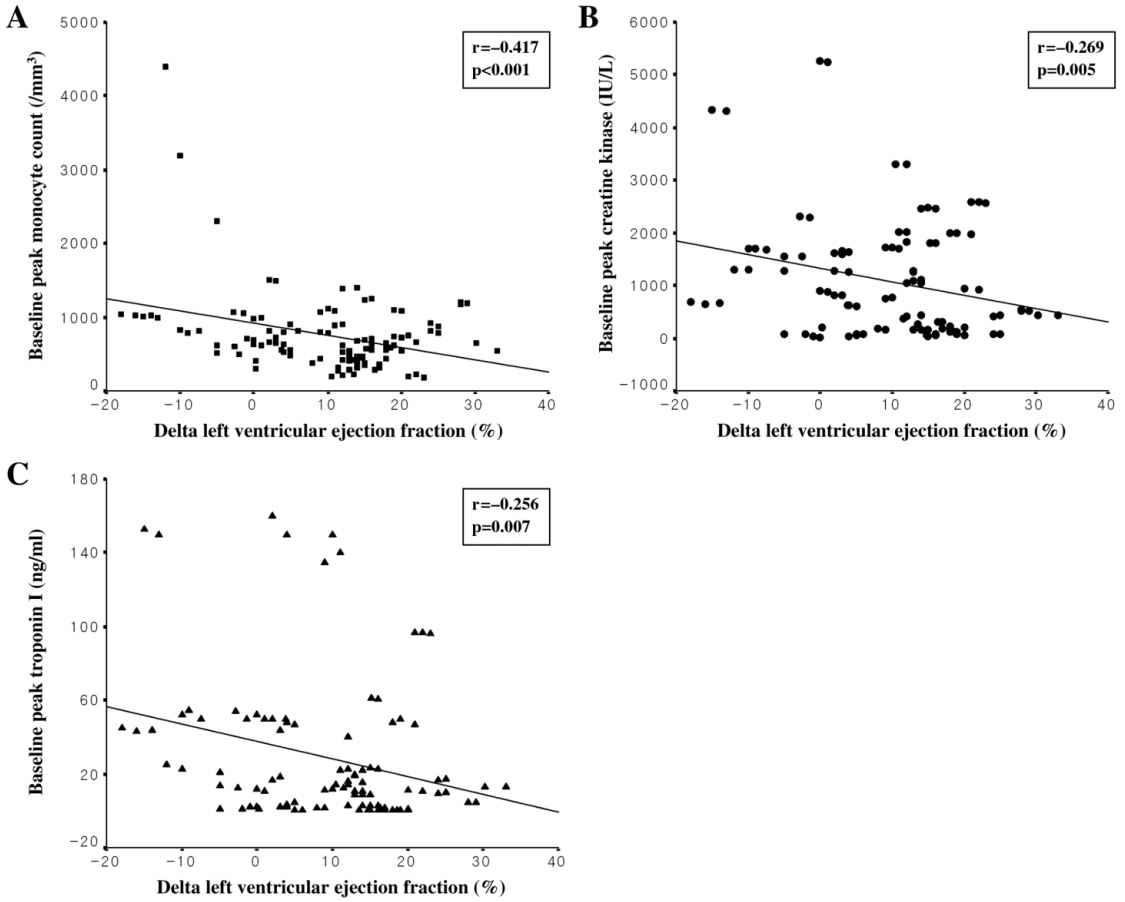

Fig 1. Correlations between Δleft ventricular ejection fraction and (A) baseline peak monocyte count, (B) baseline creatine kinase, and (C) baseline troponin I.

Table 4 Univariate Predictive Factors of Nonrecovery of LVF

	Hazard ratio	*95% CI*	*p value*
Baseline peak monocyte count (/mm³)	*3.47*	*1.30–6.19*	*0.014*
Age >70 years	*2.75*	*1.11–5.98*	*0.020*
Statin use	*0.33*	*0.22–0.92*	*0.023*
β-blocker use	*0.36*	*0.16–0.88*	*0.027*
Baseline peak creatine kinase (IU/L)	*2.07*	*1.10–4.45*	*0.045*

CI, confidence interval. Other abbreviation see in Table 1.

(Table 4). In the multivariate logistic regression analysis, baseline peak monocyte count and old age were the independent predictors of the nonrecovery of LVF (hazard ratio; 3.38, 95% confidence interval (CI): 1.16–5.43, p=0.012, and hazard ratio; 2.38, 95% CI: 1.09–4.87, p=0.025, respectively).

Discussion

This study identified factors that are important for nonrecovery of LVF in patients with LV dysfunction complicating an AMI after undergoing successful primary PCI. The baseline peak monocyte count was significantly higher in patients without LVF recovery compared with patients with LVF recovery and the change in LVEF correlated with baseline peak monocyte count. Independent predictors of nonrecovery of LVF included baseline peak monocyte count and old age.

Patients who develop HF after surviving AMI have a markedly increased risk of death compared with patients who do not develop HF[1,2] or compared with patients with nonischemic HF[3] The Cholesterol And Recurrent Events (CARE) trial[15] reported several factors that are important independent predictors of HF development in long-term MI survivors, including 4 historical variables (age, history of hypertension, history of MI, and diabetes mellitus), 1 physical examination variable (heart rate), 1 hemodynamic variable (EF), and 1 behavioral characteristic (exercise level). In that study, the impact of developing HF on the risk of death in patients surviving a minimum of 3 months after MI was more than 10-fold higher than in patients not developing HF.

Halkin et al reported that the predictors of LVF recovery at 7-month follow-up in patients with AMI treated with primary PCI were: no history of previous MI, depressed LVEF during the index PCI, spontaneous reperfusion

before PCI, and the degree of restenosis of the infarcted artery.[16] In the present study, there was no significant difference in the restenosis rate between patients with and without LVF recovery at follow-up (31.3% vs 34.1%), and restenosis of the infarct-related artery was not an independent predictor of the nonrecovery of LVF. Although primary PCI is the most effective treatment strategy of reperfusion for AMI and stent implantation is beneficial in regard to restenosis, PCI per se does not enhance recovery of LVF.

Several studies have demonstrated a relationship between peripheral monocytosis and LVF recovery. Maekawa et al[10] studied 149 patients with first Q-wave AMI to determine the significance of peripheral monocytosis in clinical outcome after reperfused AMI. Their patients with HF had higher peak monocyte counts than those without HF, and the peak monocyte count positively correlated with LV end-diastolic volume and negatively correlated with EF; a peak monocyte count >900/mm^3 was an independent determinant of HF and cardiac events. Mariani et al[11] reported that peripheral monocytosis was independently associated with contractile recovery of the infarcted area at 6-month follow-up of 238 AMI patients treated with successful primary PCI. These 2 previous studies both included AMI patients with and without LV dysfunction after successful reperfusion therapy and both suggested a possible role of monocytes in LV remodeling after reperfused AMI. The results of the present study concur with those studies, but unlike them, we included not all AMI patients but only those with LV dysfunction (EF <40%) complicating an AMI after successful reperfusion by primary PCI. In fact, we focused on the contractile recovery in patients with LV dysfunction. In the present study, baseline and follow-up peak monocyte counts were significantly higher in patients without LVF recovery compared with patients with LVF recovery, and the change in LVEF correlated with baseline peak monocyte count, which was an independent predictor of the nonrecovery of LVF. Our results suggest an important role of monocytes in expansion of the infarct and the development of chronic ischemic HF after successful reperfusion in patients with LV dysfunction complicating an AMI. However, it is unclear if monocytosis is a cause or an effect of a larger infarct or infarct expansion that leads to LV remodeling. Actually, in the present study more patients had an anterior wall AMI and cardiogenic shock was observed more frequently in patients without LVF recovery compared with patients with LVF recovery. So, a large infarct may enhance cytokines or chemokines to induce monocyte migration into the infarcted region and may also enhance peripheral monocytosis; that is, the increment in the number of monocytes might be a result of a large infarct. However, it must be noted that the multiple regression analysis showed that the baseline peak monocyte count was an independent predictor of the nonrecovery of LVF, suggesting that monocytosis may have a negative action on contractile recovery of the infarcted area. After AMI, the resident macrophages in infarcts are activated and marginating monocytes localized close to the endothelium migrate into the necrotic myocardium through interaction with adhesion molecules. The macrophages and monocytes synthesize and secrete cytokines that induce peripheral monocytosis and infiltration of monocytes into the necrotic myocardium.[17–19] It is possible that monocyte-secreted cytokines would have a direct toxic effect on infarcted myocardium, inhibiting LVF recovery, and that persistent and excessive monocytosis could be deleterious for LV remodeling.

Study Limitations

The present study was retrospective, so is subject to the limitations inherent in this type of clinical investigation. Therefore, further prospective studies are needed. Second, the group sizes are relatively small for correct analyses. Third, we did not perform functional analysis of peripheral monocytes. Measurements of monocyte-related cytokines are needed to assess monocyte activation following AMI. Fourth, we did not demonstrate that increased numbers of peripheral monocytes infiltrate into the necrotic myocardium and contribute to the healing process of the infarct. Fifth, we could not precisely evaluate the effect of ACE inhibitors, β-blockers or statins on peripheral monocytosis, because the dose and time from onset to initial administration of these drugs varied among the patients.

Conclusions

Peripheral monocytosis is associated with nonrecovery of LVF in patients with LV dysfunction complicating an AMI after successful reperfusion by primary PCI. Our results suggest an important role of monocytes in infarct expansion and the development of chronic ischemic HF after reperfused AMI.

Acknowledgments

This study was supported by grants of the Korea Health 21 R&D Project Ministry of Health & Welfare, Republic of Korea (A050174), and Cardiovascular Research Foundation Asia.

References

1. Kannel WB, Sorlie P, McNamara PM. Prognosis after initial myocardial infarction: The Framingham study. *Am J Cardiol* 1979; **44:** 53–59.
2. Herlitz J, Waagstein F, Lindqvist J, Swedberg K, Hjalmarson A. Effect of metoprolol on the prognosis for patients with suspected acute myocardial infarction and indirect signs of congestive heart failure (a subgroup analysis of the Goteborg Metoprolol trial). *Am J Cardiol* 1997; **80:** 40J–44J.
3. Shiba N, Watanabe J, Shinozaki T, Koseki Y, Sakuma M, Kagaya Y, et al. Poor prognosis of Japanese patients with chronic heart failure following myocardial infarction: Comparison with nonischemic cardiomyopathy. *Circ J* 2005; **69:** 143–149.
4. Moss AJ, Benhorin J. Prognosis and management after a first myocardial infarction. *N Engl J Med* 1990; **322:** 743–753.
5. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: The Framingham Study. *J Am Coll Cardiol* 1993; **22:** 6A–13A.
6. Tani S, Nagao K, Watanabe I, Kikushima K, Watanabe K, Anazawa T, et al. Increasingly well-preserved left ventricular function in hospital survivors with acute myocardial infarction: Effect of early and complete reperfusion strategy on left ventricular remodeling. *Circ J* 2007; **71:** 180–185.
7. Savoye C, Equine O, Tricot O, Nugue O, Segrestin B, Sautiere K, et al. Left ventricular remodeling after anterior wall acute myocardial infarction in modern clinical practice (from the REmodelage VEntriculaire [REVE] study group). *Am J Cardiol* 2006; **98:** 1144–1149.
8. Nagashima M, Itoh A, Otsuka M, Kasanuki H, Haze K. Reperfusion phenomenon is a strong predictor of left ventricular remodeling after acute myocardial infarction. *Circ J* 2005; **69:** 884–889.
9. Wada H, Yasu T, Kotsuka H, Hayakawa Y, Tsukamoto Y, Kobayashi N, et al. Evaluation of transmural myocardial perfusion by ultra-harmonic myocardial contrast echocardiography in reperfused acute myocardial infarction. *Circ J* 2005; **69:** 1041–1046.
10. Maekawa Y, Anzai T, Yoshikawa T, Asakura Y, Takahashi T, Ishikawa S, et al. Prognostic significance of peripheral monocytosis after reperfused acute myocardial infarction: A possible role for left ventricular remodeling. *J Am Coll Cardiol* 2002; **39:** 241–246.
11. Mariani M, Fetiveau R, Rossetti E, Poli A, Poletti F, Vandoni P, et al. Significance of total and differential leucocyte count in patients with acute myocardial infarction treated with primary coronary angioplasty. *Eur Heart J* 2006; **27:** 2511–2515.

12. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined-a consensus document of the Joint. *J Am Coll Cardiol* 2000; **36:** 959–969.
13. Roberts WL, Moulton L, Law TC, Farrow G, Cooper-Anderson M, Savory J, et al. Evaluation of nine automated high-sensitivity C-reactive protein methods: Implications for clinical and epidemiological applications: Part 2. *Clin Chem* 2001; **47:** 418–425.
14. Hong YJ, Jeong MH, Hyun DW, Hur SH, Kim KB, Kim W, 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:** 619–622.
15. Lewis EF, Moye LA, Rouleau JL, Sacks FM, Arnold JM, Warnica JW, et al. Predictors of late development of heart failure in stable survivors of myocardial infarction: The CARE study. *J Am Coll Cardiol* 2003; **42:** 1446–1453.
16. Halkin A, Stone GW, Dixon SR, Grines CL, Tcheng JE, Cox DA, et al. Impact and determinants of left ventricular function in patients undergoing primary percutaneous coronary intervention in acute myocardial infarction. *Am J Cardiol* 2005; **96:** 325–331.
17. Annema A, Sluiter W, van Furth R. Effect of interleukin 1, macrophage colony-stimulating factor, and factor increasing monocytopoiesis on the production of leukocytes in mice. *Exp Hematol* 1992; **20:** 69–74.
18. Arai K, Lee F, Miyajima A, Miyatake S, Arai N, Yokota T. Cytokines: Coordinators of immune and inflammatory responses. *Ann Rev Biochem* 1990; **59:** 783–836.
19. Tashiro H, Shimokawa H, Yamamoto K, Nagano M, Momohara M, Muramatu K, et al. Monocyte-related cytokines in acute myocardial infarction. *Am Heart J* 1995; **130:** 446–452.