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Impact of Chronotropic Effect of Cilostazol After Acute Myocardial Infarction

—— Insights From Change in Left Ventricular Volume and Function ——

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Backgound Cilostazol, a phosphodiesterase inhibitor, is an antiplatelet agent with positive chronotropic effect, the impact of which on left ventricular (LV) volume and function in acute myocardial infarction (AMI) was evaluated in the present study.

Methods and Results In 56 patients with AMI treated with primary coronary stenting, serial echocardiographic studies within 24 h and at 6 months were performed. Patients received a conventional antiplatelet regimen either without cilostazol (group 1, n=29) or with cilostazol (group 2, n=27). At 6 months, the difference in the change in heart rate between group 1 and group 2 was statistically significant (9.9 beats/min; p=0.04). However, changes in LV end-systolic volume (LVESV) (7.1±8.2 vs 10.0±21.7 ml, p=0.60), LV ejection fraction (EF) (8.2±9.9 vs 9.0±12.6%, p=0.85) and the ratio of early mitral inflow velocity to the mitral annular velocity (E/E') (0.6±3.7 vs –1.7±3.2) were not different between the 2 groups. Cardiac event rate was similar between the 2 groups. On multivariate regression analyses, cilostazol therapy had no significant influence on the changes in LVESV, LVEF or E/E'.

Conclusions In this study, the addition of cilostazol on conventional drug therapy had no adverse influence on LV remodeling or LV function after AMI. (*Circ J* 2007; **71:** 106–111)

Key Words: Cilostazol; Heart rate; Myocardial infarction; Ventricular remodeling

Left ventricular (LV) dysfunction and remodeling after acute myocardial infarction (AMI) are precursors of the development of heart failure and predictors of prognosis[1] Cardiac remodeling is influenced by hemodynamic load, neurohormonal activation and other factors still under investigation[2] Among them, heart rate (HR) has been identified as one of the predictors of the development of heart failure[3] and the change in LV volume and its function[4]

Cilostazol, a type III phosphodiesterase inhibitor, is an antiplatelet agent with vasodilating properties. It has been used for the reduction of intermittent claudication and as an antiplatelet agent in patients undergoing coronary stenting. A frequent observation in cilostazol studies is a positive chronotropic effect[5–7] However, because of the action mechanism of a phosphodiesterase inhibitor, there have been concerns about the cardiovascular safety of cilostazol in patients with LV dysfunction[8,9] Furthermore, little is known about the clinical experience with cilostazol in AMI patients[1,10] In addition, data about the impact of its chronotropic effect on LV remodeling and function have not yet been reported in this population.

Therefore, we evaluated the effect of cilostazol on LV volume and function in patients with AMI.

Methods

Study Population

The study was performed with institutional review board approval and informed consent from each subject. We retrospectively evaluated 56 AMI patients who underwent primary coronary stenting and were discharged alive. Eighty-three AMI patients from October 2003 to September 2004 were firstly drawn from the institutional patient database. Inclusion criteria were confirmed AMI, successful primary coronary stenting with grade 3 flow by the Thrombolysis in Myocardial Infarction trial classification within 6 h of the onset of symptoms or between 6 and 12 h if there was evidence of continuing ischemia. AMI was identified by clinical symptoms, initial ECG showing a new ST segment, T wave changes or left bundle branch block, and an increase in the serum creatine kinase myocardial isoform (CK-MB) value above twice the upper reference limit of 3.5 ng/ml. Serial measurement of CK-MB was performed at baseline, and at 6, 12 and 24 h. Patients were excluded if they were in Killip class IV heart failure or cardiogenic shock, were pregnant, had severe valvular disease or if they had known malig-

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nancy. Other exclusion criteria included a platelet count <150,000/ml, a known bleeding diathesis, intolerance to cilostazol or aspirin, severe hepatic or renal dysfunction (serum creatinine level >2.0 mg/dl), or untreated endocrine disorders. Twenty-seven patients who did not meet the inclusion criteria or met the exclusion criteria were finally excluded from the study population. All eligible patients who underwent successful coronary stenting were analyzed after they were retrospectively divided into 2 groups: no-cilostazol (aspirin plus clopidogrel, group I, [n=29]), and cilostazol (aspirin plus clopidogrel plus cilostazol, group 2, [n=27]). A loading dose of each agent was administered before or immediately after stenting. The loading/maintenance dose for each agent was 300 mg/100 mg q.d. for aspirin, 300 mg/75 mg q.d. for clopidogrel, 200 mg/100 mg b.i.d. for cilostazol. Unless contraindicated or not tolerated, patients were required to have received treatment with angiotensin-converting enzyme inhibitors (ACEI) and β-blockers at least 48 h after AMI. HR (beats/min), systolic and diastolic blood pressure (BP) were measured before the index procedure and at 6 months. They were measured by experienced nurses during the morning. After patients had rested supine for ≥5 min, 2 exact readings of HR and BP were obtained and the lowest readings were chosen for the data.

Echocardiography

Comprehensive transthoracic echocardiography was performed within 24 h and at 6 months after AMI. Standard M-mode, 2-dimensional (D) and color Doppler imaging were performed in the parasternal and apical views using commercially available equipment (Vivid 7, GE Vingmed ultrasound, Horten, Norway). End-diastole was defined as the frame with the largest cavity immediately before the onset of the QRS and end-systole as the frame with the smallest cavity area. Two-D LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LV ejection fraction (LVEF) were calculated from 2-D recordings using the modified biplane Simpson's method[11] Left atrial (LA) volume was assessed by the modified biplane area–length method[12] and was indexed to body surface area. Early mitral inflow velocity (E) was measured using the pulsed wave Doppler method, by placing the sample volume at the level of the mitral valve leaflet tips. The tissue Doppler-derived diastolic mitral annular velocity (E') was measured from the septal corner of the mitral annulus in the apical 4-chamber view. Measurements were averaged for 3 cardiac cycles in subjects with sinus rhythm and for 5 cardiac cycles in patients with atrial fibrillation.

Follow-up Protocol

The primary end-point was change (value at 6 months – value at the baseline) in LVESV at 6 months. Secondary end-points were change in LVEF at 6 months, and change in the ratios of E to E' (E/E'), and in the LA volume index at 6 months. Follow-up protocol included medical visits to the outpatient clinic at 30 days and 3 months after the procedure, and once every 3 months thereafter. The clinical outcomes in each group were compared in terms of the number of adverse cardiovascular events.

Statistical Analysis

Group differences in categorical variables were assessed by Fisher's exact test and in continuous variables by Student's t-test. A relation was sought between cilostazol therapy and changes in LV volumes and LV functional parameters (LVESV, LVEF, E/E'). Assessment of the relation between the clinical and echocardiographic variables, and changes in LV volume and LV functional parameters were examined by univariate and multivariate regression analyses. Independent variables included age, sex, diabetes mellitus, history of hypertension, prior myocardial infarction (MI), log CK-MB, location of MI, extent of coronary artery disease, time from the onset of chest pain to reperfusion, baseline LVESV, baseline LVEF, baseline E/E', follow-up HR and BP, and treatment with ACEI, β-blockers and cilostazol. All identified univariate predictors were entered in a forward stepwise manner into the multivariate model. Two-sided p-values <0.05 were considered to be statistically significant. SPSS 12.0 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses.

Table 1 Baseline Characteristics of the Patients

	No cilostazol (n=29)	*Cilostazol (n=27)*	*p value*
Age (years)	*53±12*	*60±10*	*0.15*
Men	*24 (83)*	*24 (89)*	*0.74*
Medical history			
Prior MI	*1 (3)*	*3 (11)*	*0.54*
Hypertension	*7 (24)*	*11 (41)*	*0.47*
Diabetes mellitus	*10 (34)*	*6 (22)*	*0.61*
Smoking	*19 (66)*	*16 (59)*	*0.92*
Dyslipidemia	*6 (21)*	*11 (41)*	*0.20*
Renal failure	*1 (3)*	*0 (0)*	*0.47*
Heart rate (beats/min)	*68±11*	*71±11*	*0.45*
Systolic BP (mmHg)	*106±6*	*110±11*	*0.30*
Diastolic BP (mmHg)	*69±6*	*69±8*	*0.98*
Infarct characteristics			
ST elevation MI	*23 (79)*	*21 (78)*	*0.73*
Symptomatic heart failure	*9 (31)*	*8 (30)*	*0.90*
Site of infarction			
Anterior	*11 (38)*	*16 (59)*	
Inferior	*17 (59)*	*11 (41)*	*0.48*
Other	*1 (3)*	*0 (0)*	
Peak CK-MB (ng/ml)	*174±190*	*135±154*	*0.60*
Early reperfusion (<6 h)	*16 (55)*	*15 (56)*	*0.68*
Multivessel disease	*15 (52)*	*11 (41)*	*0.56*
DES implantation	*16 (55)*	*9 (33)*	*0.34*
Echocardiographic indices			
LV end-diastolic volume (ml)	*97±18*	*90±16*	*0.38*
LV end-systolic volume (ml)	*45±16*	*41±21*	*0.57*
LV ejection fraction (%)	*53±14*	*55±15*	*0.66*
LV ejection fraction <50%	*13 (45)*	*6 (22)*	*0.20*
LA volume index (ml/m²)	*21.0±5.5*	*19.3±5.7*	*0.45*
E/E'	*12.6±5.0*	*12.5±4.2*	*0.98*
Medications			
ACE inhibitors	*29 (100)*	*24 (89)*	*0.14*
β-blockers	*28 (97)*	*24 (89)*	*0.60*
Diuretics	*4 (14)*	*6 (22)*	*0.48*
Statins	*28 (97)*	*27 (100)*	*0.48*

Data are number (percentage of group), means ± SD.
MI, myocardial infarction; dyslipidemia, low-density lipoprotein-cholesterol ≥130 mg/dl; renal failure, s-creatinine ≥1.5 mg/dl; BP, blood pressure; CK-MB, creatine kinase myocardial isoform; DES, drug-eluting stent; LV, left ventricular; LA, left atrial; E/E', early mitral inflow velocity to diastolic mitral annular velocity; ACE, angiotensin converting enzyme.

Results

Baseline Characteristics

The baseline clinical characteristics are listed in Table 1. Clinical features and echocardiographic variables were well matched between treatment groups. Mean age was 55±11 years, 48 (86%) were male, 44 (79%) had ST elevation MI,

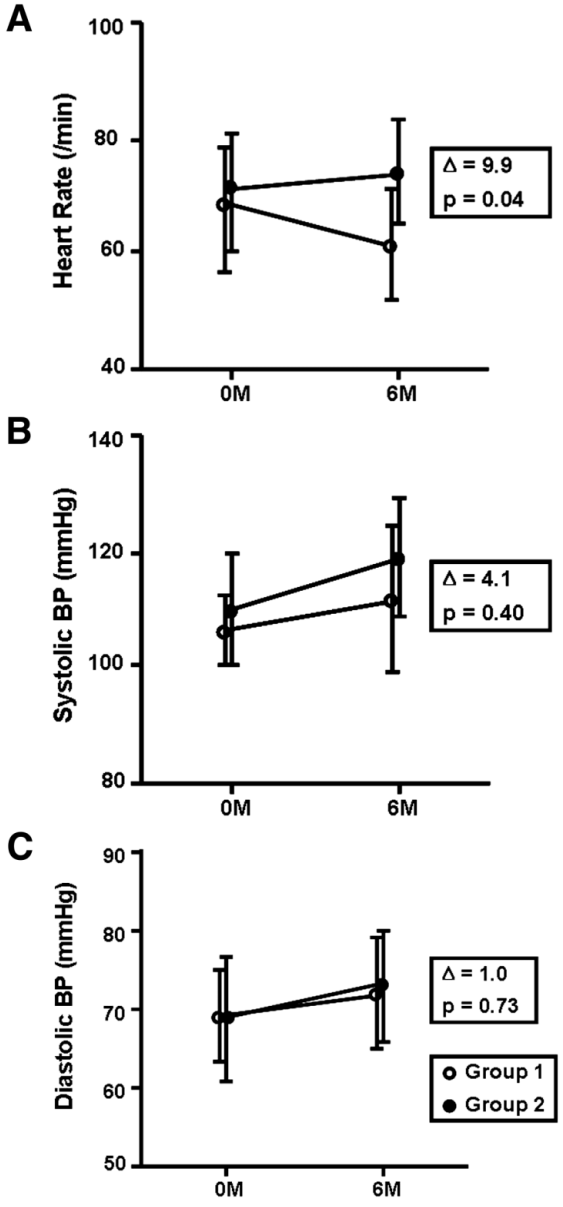

Fig 1. Changes in heart rate (A) and blood pressure (BP: B,C) from baseline to 6 months.

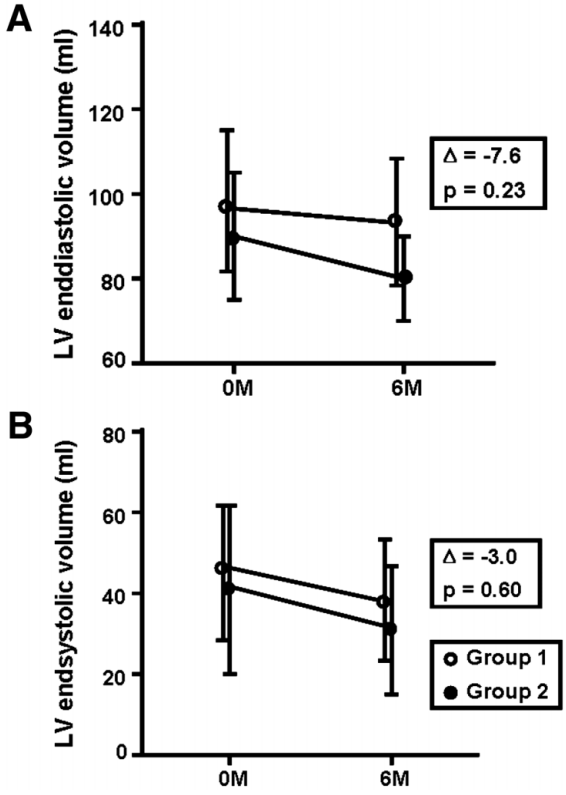

Fig 2. Changes in left ventricular (LV) end-diastolic volume (A), and LV end-systolic volume (B) from baseline to 6 months.

27 (48%) had an anterior MI, 19 (34%) showed low LVEF (<50%), and 17 (30%) showed symptomatic heart failure. There was no significant difference between the 2 groups particularly regarding frequency of heart failure, site of infarction or infarct size, based on peak CK-MB level. Time from the index infarction to primary coronary stenting was <6 h in 31 (55%) patients. Ninety-five percent received ACEI and 93% received β-blockers at AMI. Seventeen patients (60 mg/day for 9 patients, 120 mg/day for 8 patients) in group 1 and 18 (60 mg/day for 13 patients, 120 mg/day for 5 patients) in group 2 were given propranolol. Eleven (12.5 mg/day for 1 patient, 25 mg/day for 10 patients) in group 1 and 6 (25 mg/day for 6 patients) in group 2 received carvedilol. The frequency and dose of each β-blocker were not different between the 2 groups. No patient in either group received verapamil or diltiazem, whereas 2 patients in group 1 were prescribed amlodipine. There was no difference between the groups with regard to concomitant medications. The patients exhibited mean LVEDV of 95±18 ml and LVESV of 44±17 ml and mean LVEF of 54±14%.

HR and BP

HR decreased by 6.9±10.4 beats/min in group 1 at 6 months; in contrast, in group 2, it increased by 3.0±12.7 beats/min. In group 1, systolic and diastolic BP increased by 4.7±12.0 mmHg and 3.4±6.8 mmHg, respectively, at 6 months, whereas in group 2, they increased by 8.8±8.3 mmHg and 4.4±5.0 mmHg, respectively. The difference in the change in HR between group 1 and group 2 was statistically significant (9.9 beats/min; p=0.04). After eliminating patients who did not receive β-blockers, the changes in HR at 6 months were –6.6±10.6 beats/min in group 1 and 4.5±12.7 beats/min in group 2. The difference in the HR change between the 2 groups also remained significant (p=0.03). Moreover, the correlation between cilostazol therapy and the change in HR was not altered after controlling the baseline HR (β=0.48; p=0.003). However, changes in systolic and diastolic BP were higher only by 4.1 mmHg (p=0.40) and 1.0 mmHg (p=0.73) in group 2 compared with group 1, respectively (Fig 1).

Effects of Cilostazol on LV Volume and Function

In group 1, LVESV decreased by 7.1±8.2 ml at 6 months, whereas in group 2, it decreased by 10.0±21.7 ml. There was no statistically significant difference in the change in LVESV between the 2 groups (–3.0 ml; p=0.60). In group 1, LVEDV decreased by 2.7±13.8 ml, and by 10.3±18.1 ml in group 2, at 6 months. The difference in the change in LVEDV between the groups was not significant (–7.6 ml; p=0.23) (Fig 2).

In group 1, LVEF increased by 8.2±9.9% at 6 months, whereas in group 2, it increased by 9.0±12.6%. There was no statistically significant difference in the change of LVEF between the 2 groups (0.8%; p=0.85). The difference in change in E/E' between the groups was not statistically significant (–2.3; p=0.17). In the subgroup of inferior MI, there was a non-significant trend to a greater reduction in E/E' in group 2 and the difference in the change of E/E' between the groups was –3.7 (p=0.07). The difference was –0.3 (p=0.93) in the subgroup of anterior MI. In group 1, LA volume index increased by 1.8±4.1 ml/m^2 at 6 months, but decreased by 1.9±5.9 ml/m^2 in group 2. However, the difference in the changes in LA volume index between the groups was marginal (–3.7 ml/m^2; p=0.07) (Fig 3).

Univariate and multivariate regression analyses showed that log CK-MB (β=0.52; p<0.001), baseline LVESV (β= –0.64; p<0.001) and follow-up HR (β=–0.37; p=0.006) were independent predictors of change in LVESV. Baseline LVEF was independently predictive of change in LVEF (β=–0.59; p<0.001), whereas baseline E/E' was a single independent determinant of change in E/E' (β= –0.62; p=0.002). However, cilostazol therapy had no significant influence on the changes in LVESV, LVEF or E/E'.

Clinical Outcomes

Clinical follow-up was completed in 53 patients (95%): 4 patients and 3 subjects from group 2 from group 1 underwent target lesion revascularization at 6 months. There were no statistically significant differences in the cardiac event rate between the 2 groups (15% vs 12%; p=0.73).

Discussion

The results of our study show an increase in HR in the cilostazol group compared with the no-cilostazol group in patients with AMI treated with primary coronary stenting. However, the addition of cilostazol to conventional drug therapy did not cause adverse effects on LV remodeling and function in this population.

Use of Cilostazol in Patients With AMI

Cilostazol, a type Ⅲ phosphodiesterase inhibitor, is used for the reduction of the symptoms of intermittent claudication and as an antiplatelet agent in patients undergoing coronary stenting[13–16] Cilostazol selectively inhibits cyclic adenosine monophosphate-selective phosphodiesterase, increasing the intracellular level of cyclic adenosine monophosphate. As would be expected, it may increase HR, myocardial contractility, and ventricular automaticity. Because of the action mechanism of phosphodiesterase inhibitors, there has been concern about the cardiovascular safety of cilostazol, not based on evidence of cilostazol toxicity but rather the unfavorable results from previous reports on compounds having similar effects[8]

LV Remodeling After AMI

After AMI, cardiac remodeling may develop as a physiologic and pathologic condition[2] With progressive postinfarction dilation, the ventricular volume increases and the EF declines, and these are predictive of mortality[17,18] Infarct size[17,19] infarct location[17,20] perfusional status of the infarct-related artery[19] and baseline LV systolic function[17,18] have been identified as predictors of LV dilation after AMI.

Our data show that mean LVESV and LVEDV were smaller, though not significantly, at 6 months compared with baseline in both groups. This result is in contrast with the report by Bolognese et al[18] in which LV enlargement occurred after AMI despite successful primary coronary angioplasty. EF is a significant predictor of ventricular remodeling and LV dilation can be limited in patients with preserved LV systolic function[17,18] On the other hand, ACEI and β-blockers have a favorable influence on LV remodeling[1,22] Sixty-six percent of our study subjects had preserved LV systolic function at baseline and most patients received both ACEI and β-blockers. These factors may explain the lack of LV dilation in the majority of our study population.

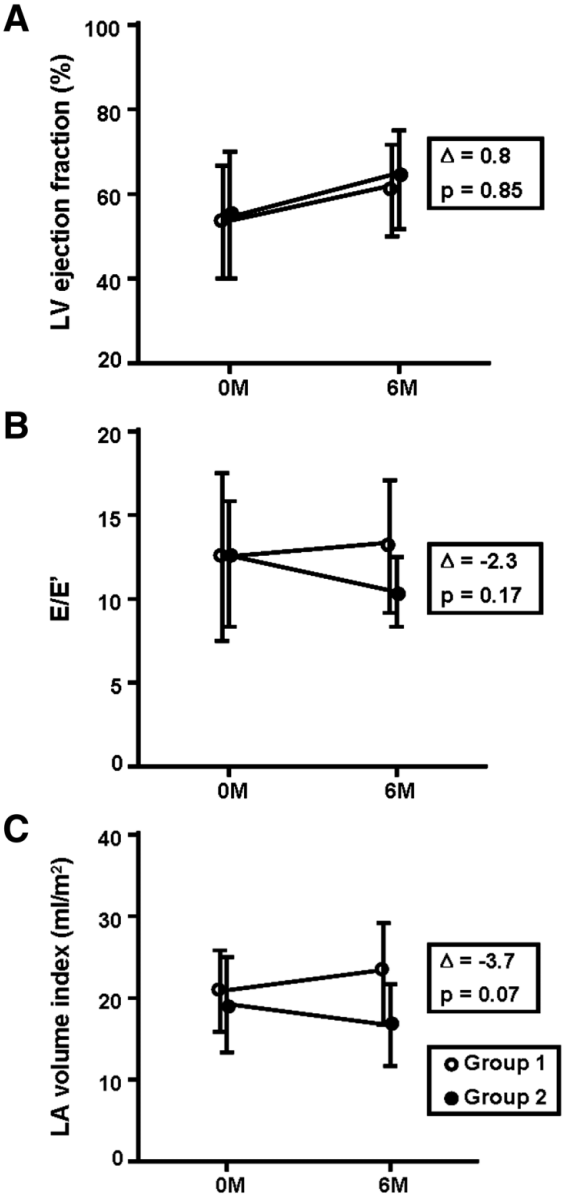

Fig 3. Changes in left ventricular (LV) ejection fraction (A), early mitral inflow velocity to diastolic mitral annular velocity (E/E') (B), and left atrial (LA) volume index (C) from baseline to 6 months.

Chronotropic Effect of Cilostazol and Its Impact on LV Volume and Function

Recent studies[22,23] demonstrate that treatment with a β-

blocker, carvedilol, results in attenuation of LV remodeling after AMI. In those studies, significant reduction in HR occurred in patients receiving carvedilol compared with placebo. In contrast, higher HR is a risk factor for the late development of heart failure in survivors of MI.[3] Increase in HR reduces LVEF in patients with coronary artery disease.[4] In addition, HR is known to influence Doppler parameters of LV diastolic function.[24] Treatment with cilostazol has exhibited a significant positive chronotropic effect in healthy subjects,[6] as well as in patients with bradyarrhythmia.[5,7] Because of the beneficial effect of lower HR and the adverse effect of higher HR on LV function, the impact of the chronotropic effect of cilostazol on LV function and remodeling can be unfavorable.

In our data, the increase in HR in patients receiving cilostazol did not show a negative influence on LV function and volume. This result was not altered when possible confounding variables were taken into account in the multivariate analyses. On the other hand, our results showed that the follow-up HR had a negative correlation with the change in LVESV. However, this correlation was not strong and may not be generalized to a wide range of HR. Cilostazol did not influence changes in the E/E' or the LA volume index. Both echocardiographic parameters are reported to be significantly correlated with LV diastolic function, reflecting LV filling pressure[25] and the status of LA pressure,[26] respectively. Although the change in HR was significantly higher in the present cilostazol group, most subjects were prescribed β-blockers and follow-up HR were within normal range in both groups. The lack of influence of cilostazol on LV volume, LVEF and E/E' is possibly related to that point, particularly in patients who received β-blockers and ACEI simultaneously.

Study Limitations

First, our study was not randomized and there were differences, although not statistically significant, in several variables such as the site of infarction. However, baseline characteristics at the time of AMI, such as the presence of symptomatic heart failure, time to reperfusion, and the infarct size based on CK-MB, were similar between the 2 groups. Second, our study population included non-ST elevation MI, and the pattern of change in LV volume and function might be quite different from that of ST elevation MI. Moreover, many subjects were without symptomatic heart failure, and our results on the safety of cilostazol do not bear direct generalization to AMI with overt heart failure. Third, E' was measured only at the septal corner and the site of infarction may have influenced the measurements. The ratio of anterior to inferior MI was higher in group 2 and there was a greater reduction in E/E' at 6 months in group 2. Although the difference in the change of E/E' between the groups was not significant in subgroup analyses according to the infarction site, it may have contributed to a type II statistical error.

Conclusion

In summary, our study shows no adverse influence of the positive chronotropic effect of cilostazol on LV volume and function, at least while conventional drugs such as β-blockers and ACEI are prescribed simultaneously.

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