Predictive Utility of the Changes in Matrix Metalloproteinase-2 in the Early Phase for Left Ventricular Reverse Remodeling After an Acute Myocardial Infarction

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Background—The relationship between the serum levels of matrix metalloproteinase (MMP) and tissue inhibitors of MMP (TIMP) and left ventricular (LV) reverse remodeling (LV-RR) after an acute myocardial infarction (AMI) has not been sufficiently examined.

Methods and Results—In 25 patients with successful reperfusion after an AMI and 15 normal control subjects, the serum MMP-2 and TIMP-2 levels were measured on days 1, 2, 3, and 7 and at 1 and 6 months after the AMI onset. LV-RR was defined as a >15% decrease in the LV end-systolic volume index at 6 months after the AMI. The MMP-2 level on day 1 and TIMP-2 levels throughout the study period were comparable between the patients with and without LV-RR. The MMP-2 on day 7 ($P<0.05$) and the changes in the MMP-2 from day 1 to day 7 (ΔMMP-2; $P<0.01$) were lower in patients with than in those without LV-RR. The ΔMMP-2 was strongly correlated with the changes in the LV volume and ejection fraction from 1 month to 6 months after the AMI. The ΔMMP-2 value of <-158.5 ng/mL predicted LV-RR with a high accuracy (91.7% sensitivity and 76.9% specificity; area under the curve=0.82).

Conclusions—Changes in MMP-2 are associated with LV-RR after an AMI. The ΔMMP-2 might be a useful predictor of subsequent LV-RR. (*J Am Heart Assoc*. 2015;4:e001359 doi: 10.1161/JAHA.114.001359)

Key Words: acute myocardial infarction • metalloproteinase • remodeling

Left ventricular remodeling after an acute myocardial infarction (AMI) contributes significantly to the left ventricular (LV) dilatation and dysfunction in the chronic phase, which leads to a disabling state and mortality.[1] Remodeling of the extracellular collagen matrix plays a pivotal role in LV remodeling.[2] The LV remodeling process is dynamic and time dependent and progresses in parallel with healing over months.[3] LV reverse remodeling (LV-RR) is a reduction in LV volume and an improvement in ejection fraction.[4] LV-RR after AMI is also reported,[5] and patients with LV-RR have a significantly lower cardiac event than do patients without LV-RR.[4] Thus, obtaining LV-RR after AMI is a key to maintaining ventricular function. Matrix metalloproteinases (MMPs) affect the collagen turnover, and an imbalance in the MMP and tissue inhibitors of MMP (TIMPs) can result in adverse remodeling.[2,6] A recent study reported that increased serum levels of MMP lead to adverse negative remodeling, ventricular dilatation, and wall thinning.[7] Another study showed that pravastatin suppresses the increase in the MMP-2 activity and attenuates the LV dilatation.[8] MMP concentrations after AMI and associations with LV volume in early phase are also reported.[9] However, the relationship between the MMP activity and LV-RR after an AMI has not been clarified sufficiently or extensively. Accordingly, we performed serial measurements of the serum MMP-2 and TIMP-2 levels after an AMI, and we examined the correlation between those and LV-RR after the AMI.

Methods

Study Subjects and Design

This study included 25 consecutive patients with an AMI (mean age, 68.8±11.7 years; 7 women) in whom successful reperfusion was achieved with a primary percutaneous coronary intervention, and serial measurements of the serum MMP-2 and TIMP-2 levels were measured at the University of Fukui

Hospital. The diagnosis of an AMI and a reperfusion procedure were performed as previously described.[8] All patients with AMI were treated with a bare-metal stent. In this study, as sex- and age-matched controls (within a 5-year gap), serum MMP-2 and TIMP-2 levels were measured in 15 control subjects who had no history of cardiovascular disease (mean age, 61.4±10.9 years; 6 women). The present study did not include patients with a history of neoplastic, hepatic, infectious, autonomic, or peripheral atherosclerotic diseases or who had undergone any surgical procedure in the preceding 6 months, and none had inflammatory signs at the time of the evaluation. In Japan, follow-up angiography is performed in nearly all percutaneous coronary intervention patients 3 to 12 months after percutaneous coronary intervention, regardless of whether ischemic signs and/or symptoms are present. Follow-up angiography was performed at 6 months after AMI. No major adverse cardiovascular event, defined as revascularization, lethal arrhythmia, stent thrombosis, restenosis, hospitalization for any reason, and all-cause death, was observed during 6-month follow-up period. The study was approved by the institutional review committee, and all patients gave their written informed consent before participation.

Measurement of Serum MMP-2 and TIMP-2 and B-Type Natriuretic Peptide Plasma Levels

Whole blood was withdrawn from the forearm or femoral vein and kept on ice, and the serum samples were separated via centrifugation within 30 minutes. After centrifugation, the serum samples were frozen and stored at −80°C until use. A sandwich enzyme immunoassay was performed to measure the concentrations of serum MMP-2 and TIMP-2 with monoclonal antibodies against each substance (Fuji Chemical Industries Ltd).[8,10]

In all patients with an AMI, the plasma levels of the B-type natriuretic peptide (BNP) during hospitalization were measured and determined by using a chemiluminescent enzyme immunoassay (MI02 Shionogi BNP; Shionogi Inc).[11]

Left Ventriculography

Left ventriculography was performed at 4 weeks and 6 months after AMI onset. The left ventriculogram was analyzed by using a digitizer and a computer (Kontron Elektronik Cardio 98). The end-diastolic frame was determined as the frame nearest to the peak of the R wave. The frame with the smallest ventricular volume was taken to show the end-systolic volume (ESV), and the ventricular volume was calculated with a modification of the Dodge's formula.[12] We measured the LV end-systolic volume index (LVESVI), LV end-diastolic volume index (LVEDVI), and LV ejection fraction (LVEF) and assessed the changes in the LVESVI (ΔLVEDVI),

LVEDVI (ΔLVEDVI), and LVEF (ΔLVEF) from 4 weeks and 6 months after the AMI onset in all patients.

Definition of Reverse Remodeling

The LV-RR was defined as a decrease in the LVESV of ≥15% at 6-month follow-up,[13] compared with the baseline value 4 weeks after the AMI. The patients were classified into 2 groups: patients who had LV-RR (group 1) and those who did not (group 2).

Statistical Analysis

Continuous variables are expressed as the mean±SD. A Student t test or the Mann–Whitney U test for non-normally distributed data was used to analyze the differences between the groups, as appropriate. Categorical variables were compared by using a χ^2 analysis. The Friedman's test and Wilcoxon signed rank tests were used to evaluate the difference in the time-dependent MMP-2 and TIMP-2 changes with the P value adjusted according to Bonferroni's multiple pairwise method. Univariate and multivariate logistic regression analyses were used to identify predictors of LV-RR. The logistic regression analyses is biased due to the small sample size and result in odds ratio estimates that are biased away from the null.[14] Thus, these data are not shown in this study. A receiver operating characteristic curve analysis was used to determine the ability of the measurement variable to predict LV-RR. The optimal cutoff points were calculated to provide the greatest sum of the sensitivity and specificity. Correlations between 2 variables were assessed by using a Spearman rank test (rs). A value of $P<0.05$ was considered significant. All statistical analyses were performed by using SPSS version 20 (SPSS Inc).

Results

Patient Characteristics for Those With and Without Reverse Remodeling

At 6 months after the AMI onset, 13 (52%) patients, who exhibited a ≥15% reduction in the LVESVI, were classified into group 1, and the remaining 12 (48%) were classified into group 2. There was no significant difference between the 2 groups in the baseline demographic and clinical parameters, measurement variables, or severity or distribution of coronary arterial stenosis (Table 1).

Serum MMP-2 and TIMP-2 Levels After the AMI and Their Derivatives

Serial changes in the serum MMP-2 and TIMP-2 levels in the patients with an AMI and control subjects are shown in Figure 1.

Table 1. Baseline Patient Characteristics

Measurement Variable	Group 1 (Reverse Remodeling [+]) (n=13)	Group 2 (Reverse Remodeling [−]) (n=12)	P Value
Age, y	67.6±7.8	70.2±15.1	0.53
Men, n (%)	9 (69.2)	9 (75.0)	>0.99
Hypertension, n (%)	5 (38.4)	5 (41.6)	>0.99
Diabetes mellitus, n (%)	4 (30.7)	4 (33.3)	>0.99
Hyperlipidemia, n (%)	3 (23.0)	2 (16.6)	>0.99
Smoking, n (%)	6 (46.1)	8 (66.6)	0.51
Obesity, n (%)	6 (46.1)	5 (41.6)	>0.99
β-Blocker, n (%)	1 (0.0)	0 (0.0)	>0.99
ARB/ACEI, n (%)	11 (84.6)	9 (75.0)	0.90
Statin, n (%)	5 (38.4)	2 (16.6)	0.43
Nicorandil, n (%)	10 (76.9)	12 (100.0)	0.20
Culprit lesion, n (%) (LAD/non-LAD)	9 (69)/4 (31)	3 (25)/9 (75)	0.06
1-vessel disease, n (%)	13 (100)	9 (75)	0.18
Peak CPK, IU/L	2433±1296	3684±3069	0.73
Time to reperfusion, h	1.09±0.84	1.83±0.87	0.31
Left ventriculography 4 weeks after the AMI onset			
End-diastolic volume index, mL/m^2	118.8±26.6	113.4±34.4	0.62
End-systolic volume index, mL/m^2	57.8±19.5	53.2±32.0	0.24
Ejection fraction, %	51.5±9.9	54.6±13.3	0.49
Plasma BNP concentration, pg/mL	132.4±139.9	253.8±294.5	0.27

The values are reported as the mean±SD or number of patients (%). ARB indicates angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; LAD, left anterior descending coronary artery; CPK, creatine phosphokinase; AMI, acute myocardial infarction; BNP, B-type natriuretic peptide.
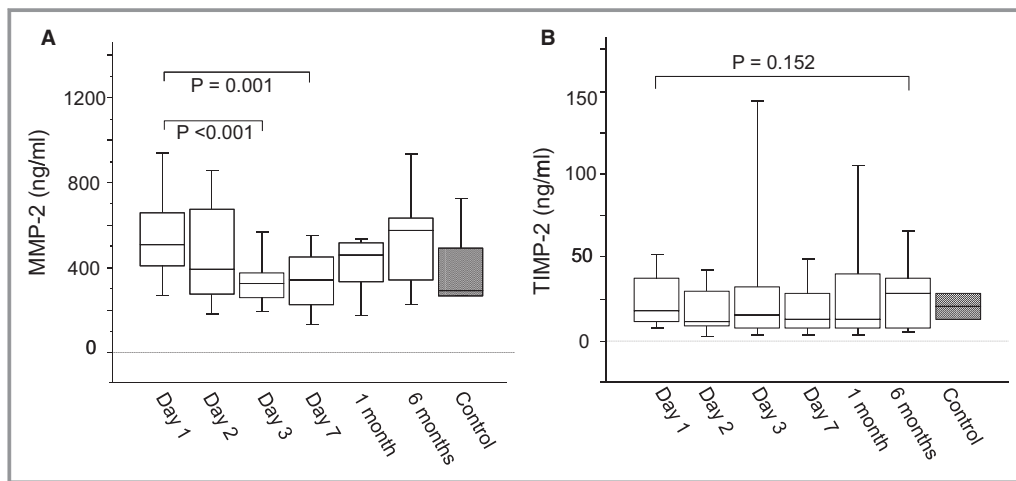
Figure 1. Box plot graphs illustrating the time-dependent change in the serum matrix metalloprotease–2 (MMP-2; A) and tissue inhibitor of MMP-2 (TIMP-2; B) levels in 25 patients with an AMI and 15 control subjects. The plot's horizontal line represents the median; the box encompasses the 25th to 75th percentiles; and the error bars encompass the 10th to 90th percentiles. The P values were derived using an analysis with a Wilcoxon signed-rank test and Bonferroni correction and were comparisons of day 1 vs day 3 and day 7, all other pairwise comparisons were not significant in (A). P value was based on the Friedman's test in (B). All pairwise comparisons of TIMP-2 levels during follow-up period were not significant in (B). AMI indicates acute myocardial infarction.

The serum MMP-2 levels that were serially measured after the AMI were greater than those in the control subjects (P=0.001) (Figure 1A).

In a total of 25 patients with an AMI, the MMP-2 levels on day 1 after the AMI were higher than those in the control subjects (Figure 1A). Further, they gradually decreased, and 11 patients (44%) had the lowest value on days 3 and 9 patients (36%) had the lowest value on day 7. After the lowest level of the MMP on day 3 or 7 after the AMI, the level increased until 6 months after the AMI (Figure 1A). Fourteen patients (56%) had the highest value of MMP-2 on day 1 and 17 patients (68%) had the highest value within 1 week after AMI. In contrast, the serum TIMP-2 level in the patients with an AMI was compatible throughout the 6-month follow-up period after the AMI, and each serum TIMP-2 level was comparable with that of the control subjects (Figure 1B).

MMP-2 and TIMP-2 Serum Concentrations and Their Derived Measurement Variables in Patients With and Without LV-RR

In the LV-RR group patients, the serum MMP-2 and TIMP-2 levels at 1 week after the AMI were significantly smaller than those in the No-LV-RR group (both P<0.05; Figure 2). Among the measurement variables derived from the serum MMP-2 and TIMP-2 levels, the change in the serum MMP-2 level from day 1 to

1 week after the AMI onset (ΔMMP-2 [1 week−day 1]) was much smaller in the LV-RR group than in the No-LV-RR group (P=0.007; Figure 3B).

The Relationship Between the Serum MMP-2 and TIMP-2 Levels 1 Week After the AMI and the ΔMMP-2 (1 Week−Day 1), and the ΔLVEDVI, ΔLVESVI, and ΔLVEF

The serum MMP-2 and TIMP-2 levels at 1 week after the AMI were positively correlated with the ΔLVEDVI and ΔLVESVI (all P<0.05; Table 2). Further, the serum TIMP-2 level at 1 week after the AMI was negatively correlated with the ΔLVEF (P<0.05; Table 2).

The ΔMMP-2 (1 week−day 1) was positively correlated with the ΔLVEDVI and ΔLVESVI (both P<0.001; Figure 4A and 4B). Conversely, there was a negative correlation between the ΔMMP-2 (1 week−day 1) and ΔLVEF (P=0.019; Figure 4C).

Predictors of LV-RR

A logistic regression analysis revealed that the ΔMMP-2 (1 week−day 1) was the only independent predictor of LV-RR after the AMI (data not shown). By receiver operating characteristic curve analysis, ΔMMP-2 (1 week−day 1) of −158.5 ng/mL as the cut-off point for predicting LV-RR had 91.7% sensitivity and 76.9% specificity (area under the curve=0.82).
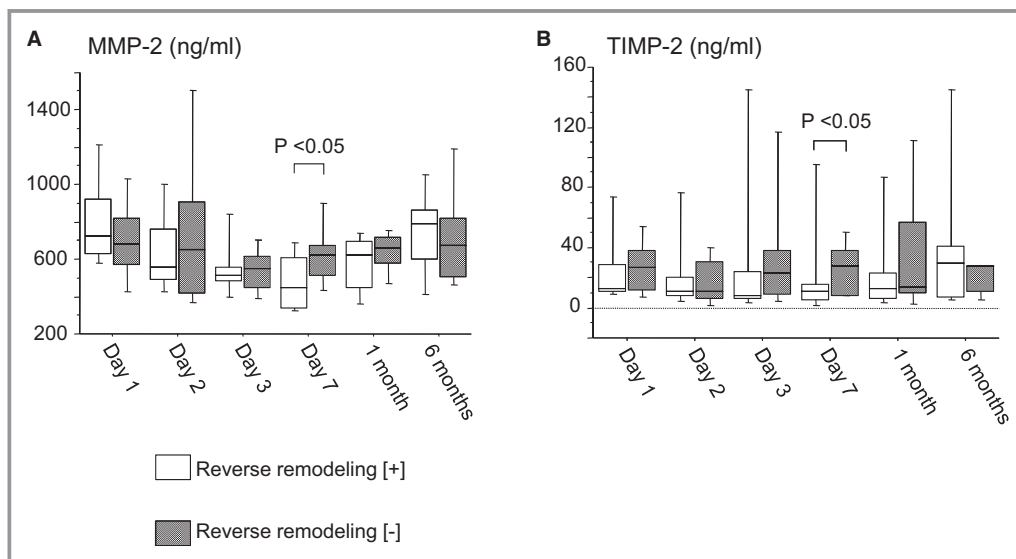
Figure 2. Box plot graphs illustrating serum concentrations of the matrix metalloprotease -2 (MMP-2; A) and tissue inhibitor of MMP-2 (TIMP-2; B) levels with or without reverse remodeling during follow up period in 25 patients with an AMI. The plot's horizontal line represents the median; the box encompasses the 25th to 75th percentiles; and the error bars encompass the 10th to 90th percentiles. The P values were comparisons of value with or without reverse remodeling in each time points. All other pairwise comparisons were not significant. AMI indicates acute myocardial infarction.
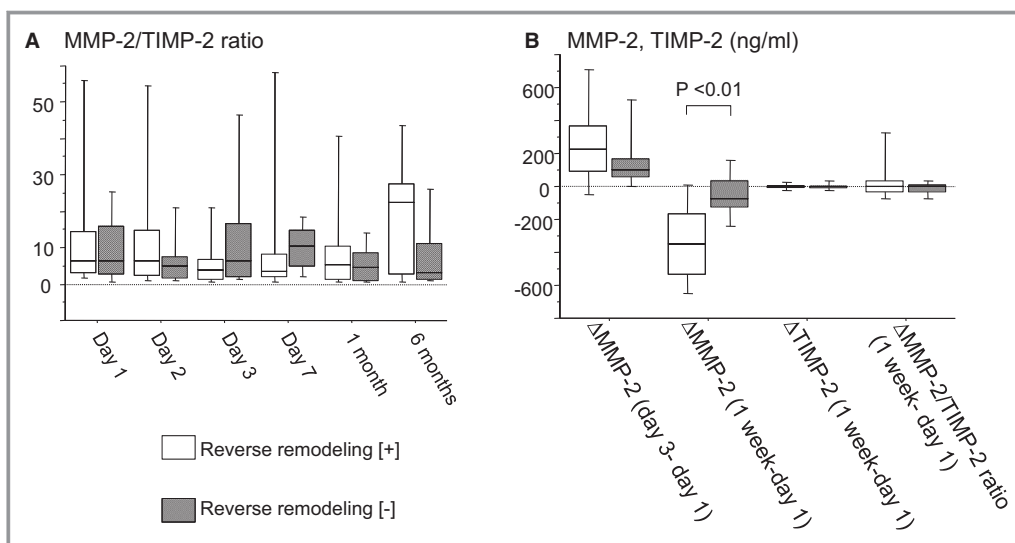
Figure 3. Box plot graphs illustrating serum concentrations of the matrix metalloprotease (MMP)-2 and tissue inhibitor of MMP (TIMP)-2 and their derived measurement variables levels in 25 patients with an AMI (MMP-2/TIMP-2 ratio; A: MMP-2 and TIMP-2 derived variables; B). The plot's horizontal line represents the median; the box encompasses the 25th to 75th percentiles; and the error bars encompass the 10th to 90th percentiles. The *P* values were comparisons of value with or without reverse remodeling in each time points. All other pairwise comparisons were not significant. AMI indicates acute myocardial infarction.

Table 2. Correlation of the Serum MMP-2 and TIMP-2 Levels to the Change in the LV Functional Parameters From 4 Weeks to 6 Months After the Acute Myocardial Infarction

	MMP-2 (1 Week)		TIMP-2 (1 Week)	
	rs	*P* Value	rs	*P* Value
ΔLVEDVI	0.483	0.015	0.488	0.025
ΔLVESVI	0.446	0.025	0.645	0.002
ΔLVEF	−0.156	0.45	−0.535	0.012

ΔMMP-2 indicates the change in the serum MMP-2 level during the period in parentheses; LVEDVI, left ventricular (LV) end-diastolic volume index; LVEF, LV ejection fraction; LVESVI, LV end-systolic volume index; MMP, matrix metalloprotease; rs, Spearman's rank correlation coefficient; TIMP, tissue inhibitor of MMP.

Characteristics of the Patients With a ΔMMP-2 (1 Week−Day) of <−158.5 ng/mL and Those With ≥−158.5 ng/mL

The demographics and clinical characteristics were compared between the patients who had a ΔMMP-2 (1 week−day) of <−158.5 ng/mL and those who did not. There was no significant difference for each of those parameters between the 2 groups (Table 3).

Discussion

Major Findings

The results of this study demonstrated the following findings: (1) in patients with an AMI, the serum MMP-2 level on day 1 was higher than that of the control subjects, and it changed dynamically and exhibited a U-shaped curve at its bottom by 3 days or 1 week after the AMI during the 6-month period after the AMI onset; (2) no dramatic change was found in the TIMP-2 level during this period of the AMI, and its value was comparable with that of the control subjects during the 6 months after the AMI; (3) the ΔMMP-2 (1 week−day 1) was strongly correlated with the ΔLVEDVI, ΔLVESVI, and ΔLVEF; (4) a ΔMMP-2 (1 week−day 1) of <−158.5 ng/mL predicted LV-RR with a high accuracy.

These findings indicate that (1) MMP-2 might play a more important role in the development of LV-RR after an AMI than TIMP-2 and (2) the ΔMMP-2 (1 week−day 1) covering the fluctuation band of the serum MMP-2 levels during the acute phase of an AMI might be a useful marker for predicting the magnitude of the subsequent LV-RR.

Significance of the Serum MMP-2 and TIMP-2 Measurements in AMIs

In this study, the serum MMP-2 levels changed dynamically and promptly during the 6-month period after the AMI. The early rise in the MMP-2 level decreased to a minimum value within 1 week after the AMI, and, then, it increased until 6 months after the AMI. The difference in the sources of the MMP-2 might be responsible for this U-shaped appearance (the early rise and later upregulation pattern) after the AMI: the former from inflammatory cells and plaque rupture[15] and the latter from myocardial matrix degradation and a prolonged
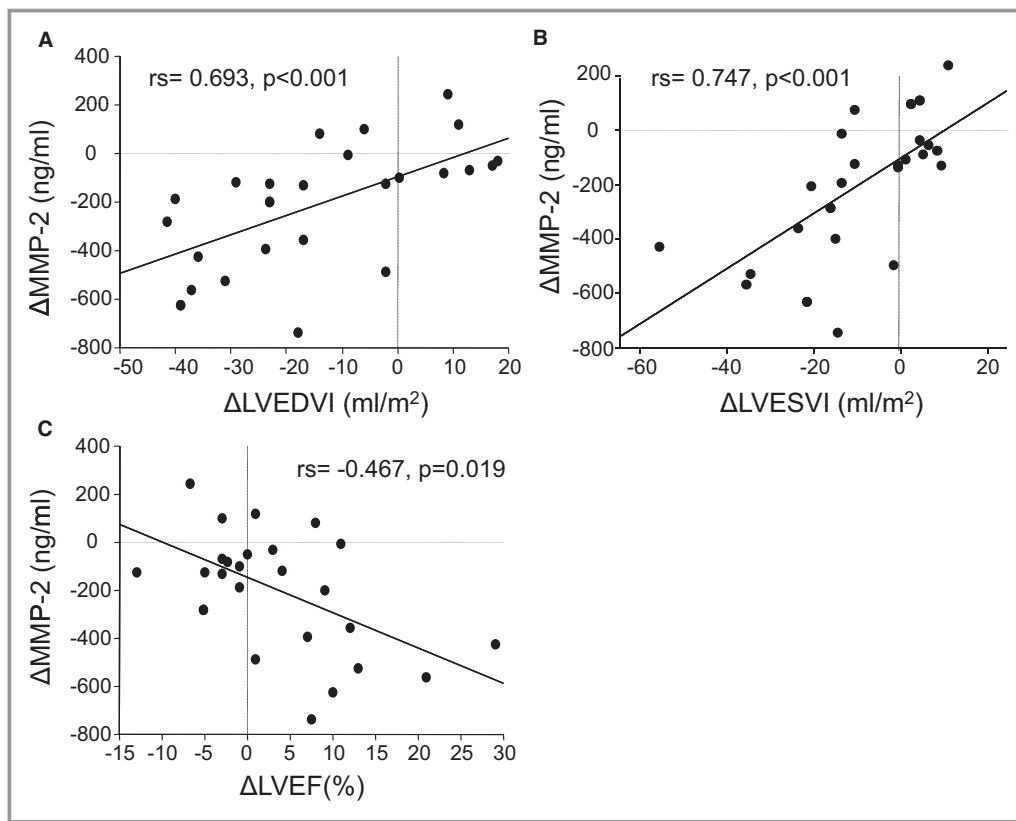
Figure 4. The correlation between the ΔMMP-2 and the ΔLVEDVI (A), ΔLVESVI (B) and ΔLVEF (C). The ΔLVED(S)VI indicates the change in the left ventricular end-diastolic (end-systolic) volume index from 1 month to 6 months; ΔLVEF, the changes in left ventricular ejection fraction from 1 month to 6 months; ΔMMP-2 the changes in serum MMP-2 level from day 1 to day 7; rs, Spearman's rank correlation coefficient.

inflammatory process of the myocardium.[16] Increased MMP-2 levels on admission for an AMI are reported to be associated with the progression and destabilization of atherosclerotic plaque[17,18] and could be a scavenger of the myocardial infarction site to elucidate the angiogenesis and healing of the myocardium.[19] On the other hand, chronic and persistent upregulation of MMP-2 has an adverse effect on LV-RR after an AMI, implicating the role of extracellular matrix turnover in loosening the myocyte interaction and dilating the LV dimension.[2,8,16,20]

In this study, the ΔMMP-2 (1 week−day 1) that covered the fluctuation band of the serum MMP-2 levels during the acute phase of the AMI correlated with the changes in the LVEDVI, LVESVI, and LVEF during the 6 months after the AMI. The serum MMP-2 (day 1) level did not differ between the LV-RR and No–LV-RR groups, but the serum MMP-2 (1 week) level was significantly lower in the LV-RR group than in the No–LV-RR group. The delayed elimination of the MMP-2 from the myocardium after the reperfusion therapy and a sustained presence of MMP-2 in the ventricular myocardium might result in impairment of LV-RR. In this study, we could not clarify what was the determinant of the serum ΔMMP-2

(1 week) level. However, the presence and magnitude of the ischemia–reperfusion injury of the myocardium after the AMI might be responsible for the elevated level of the serum MMP-2 (1 week).[21] We compared the patient's clinical characteristics to elucidate the factors affecting ΔMMP-2. However, in this study, we could not find the significant difference in parameters as reported in Tables 1 and 3. Conversely, we presume that ΔMMP-2 might be independently associated with reverse remodeling, regardless of the parameters investigated in Tables 1 and 3. We infer that measuring MMP-2 has a clinical benefit as an early diagnostic marker for reverse remodeling.

In this study, no significant changes were observed in the TIMP-2 levels throughout the postinfarction period. TIMPs have been proposed as potential biomarkers for heart failure development and predictors of the mortality in heart failure patients.[22] However, in our study, the TIMP-2 levels did not vary in the acute to subacute phases during the post-AMI period. These observations imply that MMP is the dominant regulator of the extracellular matrix degradation. Measuring the MMP-2 might be sufficient to assess the extracellular matrix degradation.

Table 3. Baseline Patient Characteristics

Measurement Variable	ΔMMP-2 (1 Week−Day 1)		P Value
	<−158.5 ng/mL (n=14)	≥−158.5 ng/mL (n=11)	
Age, y	70.1±14.2	67.2±7.7	0.41
Men, n (%)	10 (71.4)	8 (72.7)	0.94
Hypertension, n (%)	5 (35.7)	5 (45.4)	0.62
Diabetes mellitus, n (%)	3 (21.4)	5 (45.4)	0.20
Hyperlipidemia, n (%)	2 (14.2)	3 (27.2)	0.42
Smoking, n (%)	2 (14.2)	5 (45.4)	0.21
Obesity, n (%)	6 (42.8)	7 (63.6)	0.45
β-Blocker, n (%)	0 (0.0)	1 (9.0)	0.25
ARB/ACEI, n (%)	11 (78.5)	9 (81.8)	>0.99
Statin, n (%)	3 (21.4)	4 (36.3)	0.69
Nicorandil, n (%)	13 (92.8)	9 (81.8)	0.50
Culprit lesion, n (%) (LAD/non-LAD)	4 (29)/10 (71)	8 (73)/3 (27)	0.07
Multivessel disease (1/2/3-vessel disease), n (%)	11 (79)/3 (21)/(0)	11 (100)/0 (0)/0(0)	0.29
Peak creatine phosphokinase, IU/L	3117±2109	2842±2536	0.74
Time to reperfusion, h	1.66±0.95	1.08±0.81	0.32
Left ventriculography 4 weeks after the AMI onset			
End-diastolic volume index, mL/m^2	111.3±33.5	122.5±25.3	0.35
End-systolic volume index, mL/m^2	51.3±29.9	61.1±19.4	0.06
Ejection fraction, %	55.0±12.6	50.4±9.9	0.31
Plasma BNP concentration, pg/mL	253.8±294.5	132.4±139.9	0.27

The values are reported as the mean±SD or number of patients (%).ΔMMP-2 indicates the change in the serum MMP-2 level during the period in parentheses; ARB, angiotensin II receptor blocker; ACEI indicates angiotensin-converting enzyme inhibitor; LAD, left anterior descending coronary artery; AMI, acute myocardial infarction; BNP, B-type natriuretic peptide.

Clinical Implications

Our study showed the importance of the ΔMMP-2 (1 week−day 1) measurement for predicting LV-RR during the chronic phase. In patients who had a ΔMMP-2 (1 week−day) of <−158.5 ng/mL, a satisfactory recovery of the LV volume and function might be expected during the chronic phase. Conversely, in patients with a ΔMMP-2 (1 week−day) of ≥−158.5 ng/mL, there is little probability of LV-RR. In those patients, attention should be paid to the development of heart failure due to the LV dysfunction during the chronic phase of an AMI, and additional interventions to further downregulate the MMP activity via uptitration of cardioprotective drugs might be needed. Previous studies demonstrate that the serum MMP-2 activity can be attenuated with several drugs and interventions, such as angiotensin-converting enzyme inhibitors,[23] statins,[8] eplerenone,[24] spironolactone, and LV assist devices.[25] In the present study, a considerable number of patients received those drugs during the baseline, and sustained activation of the MMP-2 was observed. Therefore, our study may provide opportunities for additional interventions to further downregulate the MMP activity through uptitration of cardioprotective drugs. In patients with a ΔMMP-2 (1 week−day) of ≥−158.5 ng/mL, the addition or uptitration of those drugs to obtain an adequate suppression of the MMP-2 levels has the potential to yield additional benefits for LV-RR.

Limitations

First, this study consisted of observational research only in patients with successful revascularization and, hence, might not have fully established a cause−effect relationship of drug interventional therapy for LV-RR, and we did not examine subjects without ischemic cardiomyopathy. Second, although the serum MMP-2 and TIMP-2 levels were measured, the MMP expression within the myocardium was not assessed. Finally, we assessed the MMP-2 and TIMP-2 levels within 1 month after the AMI. The subsequent changes in the MMP-2 and TIMP-2 levels or other matrix proteases (ie, MMP-9[4]) might also have influenced the LV-RR 6 months after the AMI. We focused on MMP-2 and TIMP-2 as candidate markers for

reverse remodeling in this study. We previously reported that MMP-2 levels were related with BNP in chronic heart failure patients,[11] and MMP-2 levels varied after AMI and correlated with late changes in LVEDVI.[8] Other MMPs, such as MMP-9, also influence extracellular matrix with gelatinase activity. MMP-9 activation was mainly triggered by inflammatory stimulation. On the contrary, MMP-2 is synthesized mainly by fibroblasts and endothelial cells. MMP-2 is more continually produced in failing hearts.[26] We consider MMP-2 to be more relevant to reverse remodeling than is MMP-9. Further, we could not clarify what kinds of factors influenced the ΔMMP-2 (1 week–day 1). Therefore, further prospective studies with a larger sample size, long-term follow-up, and serial measurements of a variety of MMPs for a longer period may be needed to resolve these limitations and to confirm and enhance our results.

Conclusions

During the development of LV-RR after an AMI, MMP-2 might play a more important role than TIMP-2. The ΔMMP-2 (1 week–day 1) covering the fluctuation band of the serum MMP-2 levels during the acute phase of an AMI might be a useful marker for predicting the magnitude of the subsequent LV-RR.

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Disclosures

None.

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