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Serum Tenascin-C Might Be a Novel Predictor of Left Ventricular Remodeling and Prognosis After Acute Myocardial Infarction

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OBJECTIVES We investigated clinical implications of serum tenascin-C (TN-C) levels in patients with acute myocardial infarction (AMI).

BACKGROUND Tenascin-C, an extracellular matrix glycoprotein, is not normally expressed in the adult heart, but transiently appears during pathological conditions and plays important roles in tissue remodeling.

METHODS Serum TN-C levels were measured by ELISA in 105 AMI patients at various time points, in 10 old myocardial infarction (OMI) patients, and 20 normal controls.

RESULTS The mean serum TN-C level of AMI patients on admission (63.3 ± 30.1 ng/ml) was significantly higher than that of controls and OMI (30.9 ± 8.8 ng/ml and 27.4 ± 11.7 ng/ml, respectively, $p < 0.01$), and peaked at 5 days (83.2 ± 43.0 ng/ml). Follow-up examination (mean: 43.9 ± 19.6 months) revealed that 25 of 105 AMI (23.8%) patients showed left ventricular (LV) remodeling (≥20% end-diastolic volume increase), and in 15 (14.3%), major adverse cardiac events (MACE) were detected. The peak TN-C level was significantly higher in the remodeling group than the nonremodeling group (112 ± 37 ng/ml vs. 66 ± 29 ng/ml; $p < 0.0001$). By receiver-operating characteristic (ROC) analysis, TN-C levels clearly discriminated prediction of LV remodeling and MACE compared with other variables including plasma B-type natriuretic peptide, creatine kinase-MB, and LV function. Best predictive values of TN-C for remodeling and MACE were 84.8 and 92.8 ng/ml, respectively. Cox proportional hazards model analysis showed that TN-C was an important independent predictor of MACE.

CONCLUSIONS The findings suggest that serum TN-C levels might be useful in predicting LV remodeling and prognosis after AMI. (J Am Coll Cardiol 2006;47:2319–25) © 2006 by the American College of Cardiology Foundation

Left ventricular (LV) remodeling following acute myocardial infarction (AMI) is a major predictor of morbidity and mortality for overt congestive heart failure (CHF) and life-threatening arrhythmias (1). It occurs in an appreciable proportion of patients with AMI successfully treated with primary percutaneous transluminal coronary angioplasty despite sustained patency of the infarct-related artery and preservation of regional and global LV functions (2). Therefore, it may be important to identify patients at risk of LV remodeling to prevent LV dilation after AMI. It has been reported that infarct size, anterior infarct location, perfusion status of the culprit lesion, and CHF on admission are major predictors of LV dilation. Recently, several factors, including B-type natriuretic peptide (BNP), cardiac troponin I, and high-sensitivity C-reactive protein, have been examined as potential predicting biomarkers of LV remodeling (2).

Tenascin-C (TN-C) is an extracellular matrix protein specifically expressed at high levels during embryonic development, wound healing, and cancer invasion and involved in regulation of cell behavior during tissue remodeling in various tissues (3–6). In the heart, TN-C is normally expressed in early-stage embryos, playing important roles in development of the myocardium, valves, and coronary vessels; but is not detected in adults (7). However, it is re-expressed under pathologic conditions such as AMI (8,9), hibernation (10), and myocarditis (11–13) and is closely associated with tissue injury and inflammation. Based on these specific expression patterns, we recently revealed that immunostaining of myocardial tissues (11,13) and immunoscintigraphic imaging (12) for TN-C could be useful in diagnosis of active myocarditis. Furthermore, using an experimental model of myocardial infarction, we found that TN-C transiently appeared during acute stages, with several significant roles in myocardial tissue remodeling (8,14). Therefore, we hypothesized that TN-C expression levels might be useful for the diagnosis and determination of LV remodeling following AMI. In the present study, to

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Abbreviations and Acronyms

AMI = acute myocardial infarction
CHF = congestive heart failure
LV = left ventricle
LVEDV = left ventricular end-diastolic volume
LVESV = left ventricular end-systolic volume
MACE = major cardiac adverse events
MMP = matrix metalloproteinase
OMI = old myocardial infarction
ROC = receiver-operating characteristic
SPECT = single photon emission computerized tomography
TDS = total defect score
TN-C = tenascin-C

clarify clinical implications of TN-C levels in patients with AMI, we assessed serum TN-C concentrations with reference to cardiac function and patient outcomes.

METHODS

Study population. We prospectively studied 105 patients with AMI (73 men and 32 women, mean age 66 ± 12 years) admitted to Yokosuka Kyosai Hospital between January 2000 and March 2003, 10 patients with old myocardial infarction (OMI) (8 men and 2 women, mean age 66 ± 9 years), and 20 normal volunteers (14 men and 6 women, mean age 49 ± 15 years). Inclusion criteria for this study for AMI patients were as follows: 1) chest pain >30 min in duration and present within 12 h after onset of symptoms; 2) ST-segment elevation >0.1 mV with two contiguous electocardiographic leads; 3) total occlusion of the infarct-related artery; 4) elevated creatine kinase (CK)-MB isoenzymes within 12 h of chest pain; and 5) successful primary coronary angioplasty (defined as Thrombolysis In Myocardial Infarction flow grade 3 [15] and residual diameter stenosis <30%). Clinical characteristics of the AMI patients on hospital admission are described in Table 1. The drugs listed in Table 2 were administered at the time of admission according to the discretion of the treating physicians. Written informed consent was obtained from all patients and volunteers, and the study protocol was approved by our institutional review board.

Table 1. Clinical Characteristics of 105 Patients With Acute Myocardial Infarction Undergoing Successful Primary Percutaneous Coronary Intervention

Age (yrs)	66 ± 12
Male (%)	70
Risk factors	
Current smoker (%)	53
Diabetes (%)	15
Hypertension (%)	39
Hyperlipidemia (%)	48
Infarct location	
Anterior (%)	54
Inferior (%)	26
Lateral (%)	20
Reperfusion times (h)	6.4 ± 4.7

Table 2. Clinical Characteristics of Patients in the Remodeling and Non-Remodeling Groups

	Non-Remodeling (n = 80)	Remodeling (n = 25)	p Value
Age (yrs)	66.0 ± 12.3	64.6 ± 11.1	0.401
Anterior MI (%)	48	62	0.361
Reperfusion times (h)	6.4 ± 5.1	6.6 ± 4.0	0.476
SBP (mm Hg)	122 ± 15	117 ± 15	0.436
Peak TN-C (ng/ml)	66 ± 29	112 ± 37	<0.0001
Peak CK-MB (IU/l)	250 ± 149	419 ± 227	0.0011
BNP on day 5 (pg/ml)	104 ± 73	190 ± 91	<0.0001
BNP on day 28 (pg/ml)	97 ± 66	233 ± 198	0.0003
Left ventricular			
EDV on admission (ml)	93 ± 25	109 ± 33	0.051
ESV on admission (ml)	45 ± 17	60 ± 22	0.013
EF on admission (%)	52 ± 11	46 ± 7	0.033
TDS on admission	13.2 ± 6.8	19.1 ± 4.5	0.0001
Drugs			
ACE inhibitors	57%	73%	0.172
ARB	23%	12%	0.24
Calcium antagonists	21%	19%	0.899
Diuretics	21%	34%	0.205
Beta-blockers	31%	27%	0.738

Values are means ± SD.
ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BNP = B-type natriuretic peptide; CK-MB = creatine kinase-MB; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; MI = myocardial infarction; SBP = systolic blood pressure; TDS = total defect score. TN-C = tenascin-C.

Assay of serum TN-C levels by ELISA. Blood samples were centrifuged at 15,000 *g* for 15 min, and resulting supernatants were stored at −80°C until analysis. Serum levels of TN-C with the large subunit containing the C domain of FNIII repeats were determined using an ELISA kit with two monoclonal antibodies, 4F10TT and 19C4MS (IBL, Gunma, Japan), as previously described (16).

Biochemical analyses. Serum CK-MB levels were analyzed by enzymatic means and plasma BNP concentrations were measured using a specific immunoradiometric commercial assay kit (Shionogi, Japan).

Radionuclide imaging. Electrocardiogram-gated myocardial single-photon emission computerized tomography (SPECT) with ^{99m}Tc-tetrofosmin was performed on admission and 6 months later. Imaging was performed at rest in the supine position 1 h after intravenous injection of 740 MBq ^{99m}Tc-tetrofosmin as the radiotracer at both time points using a double-detector SPECT system (Picker Prism 2000 XP, Shimadzu Corp., Kyoto, Japan) equipped with a low-energy high-resolution collimator. Seventy-two projection data were obtained with a 64 × 64 matrix over 360°. Data were acquired for 40 s for each projection. The total acquisition time was approximately 24 min. Images were gated at 16 frames per cardiac cycle with an R-wave trigger and standard parameters similar to the left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV), which are commercially available with Germano software (17). The

SPECT images of the LV were divided into 17 segments according to the American Heart Association/American College of Cardiology recommendations (18). Short-axis slices were separated into eight segments at the basal and midventricular levels, and the apical portion of one segment was evaluated using vertical long-axis slices. Each segment was visually scored according to four grades (0 = normal uptake; 1 = mildly decreased uptake; 2 = moderately decreased uptake; 3 = severely decreased uptake), and total defect scores (TDS) were calculated by summation.

Definition of LV remodeling and monitoring of clinical events. The LV remodeling was defined as an increase in end-diastolic volume at six months after infarction of ≥20% in comparison with that based on measurements in individual patients, according to Bolognese et al. (19). Major adverse cardiac events (MACE), defined as cardiac death, nonfatal AMI, and hospitalization for CHF, were the primary outcomes for the present analysis. After hospital discharge, all patients on medication were monitored at our outpatient clinic for up to 5.5 years.

Immunohistochemistry of TN-C. Immunostainings of heart tissues obtained from three AMI, three OMI, and three noncardiac disease autopsy cases were performed as previously described (20) using two anti–TN-C mouse monoclonal antibodies. In brief, after treatment with pepsin for 10 min or heating in an autoclave for antigen retrieval, sections were incubated with antibody clone 4F10TT (1 μg/ml) or 6C6MS (10 μg/ml), and then processed using an LSAB kit (Dako Japan, Kyoto, Japan). The 6C6MS antibody recognizes the same FNIII repeat of TN-C as 19C4MS antibody but gives more intense immunostaining than 19C4MS in paraffin-embedded tissues.

Statistical analysis. The multivariate analysis included all risk factors with probability values of <0.05 in a backward stepwise regression model. Receiver-operating characteristic (ROC) analysis was used to determine optimal cut-off values of clinical variables for predictions of LV remodeling and MACE. The ROC curve represents relationships between sensitivity and specificity by plotting true-positive rates against false-positive rates as the cut-off level of the model varies. The area under the ROC curve (AUC) provides a measure of overall accuracy that is independent of decision criterion. The best cut-off value was defined as the point with the highest sum of sensitivity and specificity. Evaluation of statistical differences between groups was determined using Kruskal-Wallis analysis, the Mann-Whitney *U* test and one-way analysis of variance. Correlations were estimated using the Spearman rank correlation test. Event-free survival curves for MACE were constructed using the Kaplan-Meier method, and statistical differences between curves were assessed using the log rank test. Values of $p < 0.05$ were considered significant.

RESULTS

Expression of TN-C in human myocardium following myocardial infarction. Positive immunostainings with the two monoclonal antibodies, 6C6MS and 4F10TT, were observed in infarct lesions of myocardia in AMI patients. In contrast, scar tissue in OMI patients and normal myocardia were negative with both antibodies (Fig. 1).

Sequential changes in serum TN-C concentrations following AMI. The peak TN-C levels in AMI patients (85.9 ± 41.7 ng/ml) were significantly higher than in OMI (27.4 ± 11.7 ng/ml) ($p < 0.01$) and control patients (30.9 ± 8.8 ng/ml) ($p < 0.01$) (Fig. 2). The TN-C levels were not statistically distinguishable between control and OMI patients. Whereas CK-MB levels peaked within 12 h and rapidly decreased within 5 days following infarction, serum TN-C levels were elevated on admission (63.3 ± 30.1 ng/ml), peaked at day 5 (83.2 ± 43.0 ng/ml), and then gradually decreased, although they remained elevated at day 28 (51.8 ± 17.8 ng/ml) (Fig. 3).

Comparison of clinical characteristics and LV parameters between remodeling and nonremodeling groups. Out of 105 patients, 25 (23.8%) showed LV remodeling at 6 months. During the follow-up period (mean 43.9 ± 19.6 months), 15 MACE (14.3%) including 8 deaths and 7 hospitalizations for worsening heart failure were observed. Incidence of MACE in the LV remodeling group was higher (12 of 25) than in the nonremodeling group (3 of 80) ($p < 0.01$).

Clinical characteristics and LV parameters of the study patients are shown in Table 2. There were no significant differences in age, perfusion time, infarct location, systolic blood pressure, and use of cardiovascular medications between the two groups. Peak TN-C levels were significantly higher in the remodeling group than in the nonremodeling group (112 ± 37 vs. 66 ± 29; $p < 0.0001$). Peak CK-MB, LVESV and total defect scores on admission, and BNP levels on days 5 and 28 after onset of AMI were also significantly higher in the remodeling group than in the nonremodeling group, whereas LVEF on admission was significantly lower in the remodeling group. No siginificant relationship was found between peak TN-C and peak CK-MB or total defect score.

ROC analysis of clinical variables for predicting LV remodeling and MACE. We performed ROC analysis of the following clinical variables: peak serum TN-C levels and plasma BNP levels on days 5 and 28 after AMI and peak CK-MB, LVEDV, LVESV, and LVEF on admission for prediction of LV remodeling and MACE (Table 3). For prediction of LV remodeling, the AUC of the peak serum TN-C level was 0.849, and highest among the analyzed variables. The best cut-off value of serum TN-C for prediction of LV remodeling was 84.8 ng/ml, with a sensitivity of 84% and specificity of 77%.

For prediction of MACE, the AUC of the peak serum TN-C level was 0.788, which was also higher than any other

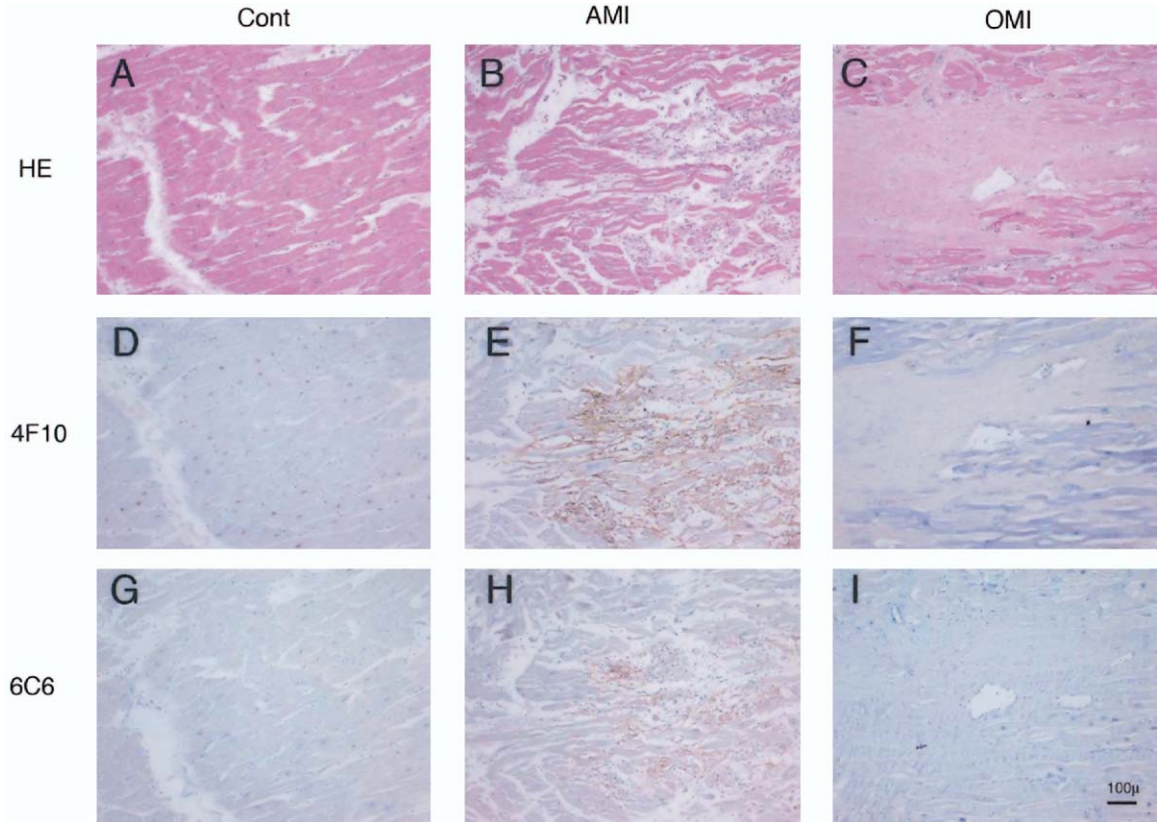

Figure 1. Representative microscopic images of tenascin-C expression in autopsied human myocardia from a normal case **(A, D, G)**, an acute myocardial infarction (AMI) patient 36 h after myocardial infarction **(B, E, H)**, and an old myocardial infarction (OMI) patient **(C, F, I)**. **(A, B, C)** H & E staining; **(D, E, F)** immunolabeling with antibody clones 4F10TT and **(G, H, I)** 6C6MS. Positive immunostainings with the two monoclonal antibodies were observed in the infarcted myocardial lesion of the AMI patients. **Bar** = 100 μm.

variables. The best cut-off value for prediction of MACE was 92.8 ng/ml, with a sensitivity of 73% and specificity of 80%. The AUC of plasma BNP on day 28 was also high for prediction of MACE (0.783). The best cut-off value of BNP level was 163 pg/ml with a sensitivity of 80% and specificity of 59%.

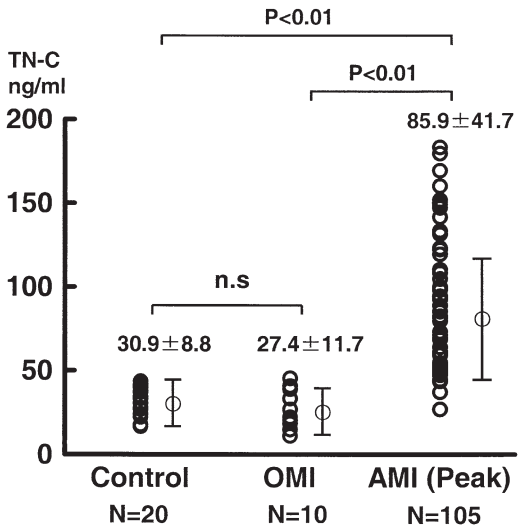

Figure 2. Comparisons of serum tenascin-C (TN-C) levels between acute myocardial infarction (AMI), old myocardial infarction (OMI), and control cases. n.s. = not significant.

Univariate and multivariate predictors of MACE. Table 4 shows the results of univariate and multivariate Cox proportional hazards model analyses between 10 variables related to MACE. In the univariate analysis, the peak TN-C level, plasma BNP level on days 5 and 28, LVESV, LVEF, and total defect scores on admission were predictive factors. According to multivariate analysis, peak TN-C level was the most important independent predictor of MACE during a follow-up period of up to 5.5 years after infarction. Plasma BNP level on day 28 was also a significant predictor of MACE.

Kaplan-Meier analysis. During the follow-up period (mean 43.9 ± 19.6 months), there were five deaths and five hospitalizations for worsening heart failure in patients with TN-C ≥92.8 ng/ml, and three deaths and two hospitalizations for worsening heart failure in patients with TN-C <92.8 ng/ml. Kaplan-Meier MACE demonstrated the higher risks of death and hospitalization of patients with TN-C ≥92.8 ng/ml than of those with TN-C <92.8 ng/ml ($p < 0.0001$).

DISCUSSION

Major novel findings in the present study were as follows: 1) Serum TN-C levels were significantly elevated during acute stages after AMI; 2) TN-C levels were significantly higher

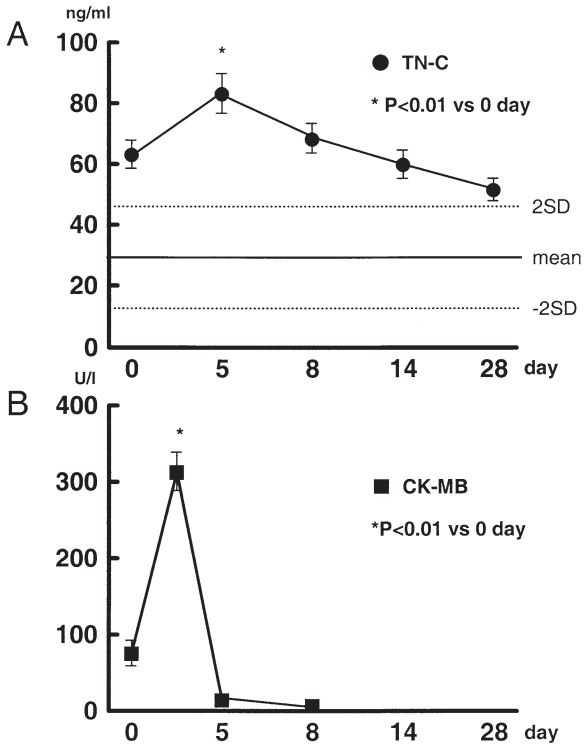

Figure 3. Serial changes in serum tenascin-C (TN-C) and creatine kinase (CK)-MB levels in patients with acute myocardial infarction (AMI). Values represent the mean and standard error. Serum TN-C levels were elevated on admission, peaked at day 5, and then gradually decreased **(A)**. In contrast, CK-MB levels peaked within 12 h and then rapidly decreased **(B)**.

in the LV remodeling group than in the nonremodeling group; and 3) AMI patients with high TN-C levels were at much higher risk of MACE for up to 5.5 years. Thus, serum TN-C levels in acute stages following AMI might be a predictive biomarker of LV remodeling during the recovery phase and prognosis.

Elevated serum TN-C levels in AMI patients. Using rat and mouse myocardial infarction models, we previously reported that TN-C was synthesized during acute stages by interstitial fibroblasts in the border zone myocardium surrounding infarcted lesions (8) and could play several important roles in myocardial repair (8,14,21). In the present paper, we demonstrated that serum TN-C levels in AMI patients were significantly higher than those in OMI patients and controls. Immunostaining of autopsied specimens confirmed expression of TN-C in human myocardium in acute stages following infarction, whereas no expression was detected in normal myocardium or in scar tissues of OMI patients. Therefore, TN-C synthesized in infarcted myocardium could enter the bloodstream and cause elevation of serum TN-C levels in AMI patients. In various tissue injuries, TN-C molecules are synthesized by interstitial cells residing in injured sites. While molecules are deposited in extracellular spaces and regulate cell behavior in the local environment, soluble forms might also be released into body fluids. For example, TN-C levels in synovial fluid from patients with osteoarthritis (16) and aseptic loosening after arthroplasty (22) and in serum of patients with hepatic fibrosis (23) are reported to increase in correlation with disease activity.

In our AMI patients, significantly elevated TN-C levels were noted within 24 h after onset. Levels peaked at day 5 and then gradually decreased. This time course of serum TN-C levels was previously shown to correspond to local expression of TN-C in infarcted myocardia of humans (9) and rats (8), as detected by immunohistochemistry. It is noteworthy that the peak of serum TN-C occurred later than that for CK-MB, and persisted much longer. Furthermore, peaks of TN-C did not significantly correlate with total defect scores on myocardial SPECT with ^{99m}Tc-tetrofosmin or with peaks of CK-MB. These results indi-

Table 3. Prognostic Value of Each Clinical Variable in Predicting LV Remodeling and Cardiac Events According to Receiver-Operating Characteristic Analysis

	AUC	Cut-Off Value	Sensitivity (%)	Specificity (%)
LV remodeling				
Peak TN-C (ng/ml)	0.849	84.8	84	77
BNP on day 5 (pg/ml)	0.817	138	92	71
BNP on day 28 (pg/ml)	0.769	143	76	67
Peak CK-MB (IU/l)	0.743	322	76	71
LVEDV (ml)	0.646	101	64	70
LVESV (ml)	0.684	53	72	57
LVEF (%)	0.706	48	76	57
Cardiac events				
Peak TN-C (ng/ml)	0.788	92.8	73	80
BNP on day 5 (pg/ml)	0.760	148	80	59
BNP on day 28 (pg/ml)	0.783	163	80	65
Peak CK-MB (IU/l)	0.669	335	73	67
LVEDV (ml)	0.640	102	60	62
LVESV (ml)	0.686	55	73	54
LVEF (%)	0.689	47	67	60

AUC = area under the receiver-operating characteristic curve; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; EF = ejection fraction; other abbreviations as in Table 2.

Table 4. Univariate and Multivariate Analyses of the Value of Each Variable in Predicting Cardiac Events

Predictive Factors During the Acute Phase	Univariate		Multivariate	
	Chi-Square	p Value	Chi-Square	p Value
Age	3.13	0.076		
Reperfusion time	1.38	0.238		
Peak CK-MB	3.01	0.082		
Peak TN-C	14.8	0.0001	10.82	0.001
BNP on day 5	4.32	0.037		
BNP on day 28	7.94	0.004	4.23	0.039
LVEDV	3.61	0.057		
LVESV	8.76	0.003	0.36	0.543
LVEF	6.96	0.008	0.76	0.381
Total defect scores	6.51	0.011	0.03	0.852

Abbreviations as in Tables 2 and 3.

cate that elevation of TN-C levels might not directly reflect cardiomyocyte death. Synthesis of TN-C by cardiac fibroblasts is stimulated by various cytokines, growth factors, hypoxia, acidosis, mechanical stress, and angiotensin II (21), which could be closely related to myocardial injury and inflammation during the wound healing process. Although the infarct size could be one of major determinants of TN-C expression levels, which might reflect interstitial response secondary to myocardial injury, some other factors of individual patients might also influence TN-C expression.

TN-C as a marker for LV remodeling and long-term clinical outcomes. Most importantly, patients with LV remodeling showed higher peak TN-C levels than patients without LV remodeling, and patients with higher peak TN-C levels had a greater incidence of MACE and worse long-term prognosis. A previous report revealed that patients with significant LV remodeling six months after infarction had worse long-term clinical outcomes (2). Because TN-C levels peaked within one week after infarction, our results suggest that TN-C could be an early predictive marker for future ventricular remodeling.

One of the major determinants of ventricular remodeling following AMI could be infarct size (2,24). Therefore, myocyte injury markers such as cardiac troponin I and T, CK, and CK isoforms appear to be useful in predicting late ventricular dilation (2). It was also suggested that the systemic inflammatory marker C-reactive protein (25,26) and neurohormones secreted by cardiomyocytes, including atrial natriuretic peptide (27) and BNP (28), are further biomarkers of ventricular remodeling. A recent report suggested that plasma BNP levels at three to four weeks after AMI could be independent predictors of cardiac death (29). In the present study, our analysis of the prognostic value of various clinical variables also supported the possibility that large infarction and high plasma BNP levels might predict MACE.

Left ventricular remodeling involves multi-step reactions which orchestrate structural alteration and rearrangement of cells and connective tissues. During these processes, disproportionate activation of matrix metalloproteinases (MMPs) has recently received increasing attention in progression of unfavorable tissue remodeling (30–33). Several reports have suggested that deletions of MMP2 and MMP9 attenuate ventricular remodeling (34–36) and that MMPs could act as biomarkers of ventricular remodeling (37–39).

Tenascin-C has many biologic effects, including regulation of cell activity during early stages of tissue repair (4,8,11,14,40). It up-regulates MMP expression in a number of cell types (41,42) and inhibits strong linkages between cardiomyocytes and connective tissues (8,21). Therefore, excessive amounts of TN-C might cause disproportionate MMP activation, which would lead to progressive degradation of connective tissues and slippage of myocytes within the LV wall, finally resulting in LV wall thinning and dilation. On the other hand, TN-C also has the potential to promote myocardial repair and prevent ventricular dilation by recruitment of myofibroblasts and enhancement of collagen fiber contraction (14,43). Thus, the effects of TN-C on ventricular remodeling are not simple but rather are bidirectional. In the present study, we found that high levels of serum TN-C could be related to a greater incidence of ventricular remodeling and poor prognosis, suggesting that excessive and sustained increments of TN-C could cause inappropriate reconstruction of infarcted ventricular walls.

Clinical implications and limitations. This preliminary study suggests that serum TN-C might be a novel marker reflecting active structural remodeling in the myocardium following infarction, with high TN-C levels at acute stages possibly predicting progression of LV remodeling.

However, despite the findings, the current study has some limitations. First, the sample size was relative small. Second, prognosis of our AMI patients receiving primary coronary angioplasty was good, and there were only eight deaths and seven hospitalizations due to heart failure out of 105 patients during the follow-up period of 3 to 5.5 years. Further large-scale prospective investigations and careful comparisons with other clinical parameters are therefore required to confirm the predictive ability of TN-C in LV remodeling and MACE.

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