Time-dependent changes of serum carboxy-terminal peptide of type I procollagen and carboxy-terminal telopeptide of type I collagen concentrations in patients with acute myocardial infarction after successful reperfusion: correlation with left ventricular volume indices


To test the hypothesis that in patients with acute myocardial infarction (AMI), changes in the concentrations of the serum carboxy-terminal peptide of type I procollagen (PICP) and the carboxy-terminal telopeptide of type I collagen (ICTP) reflect extracellular matrix reformation and degradation, respectively, in the infarct healing processes, we measured these serum concentrations by RIA and compared their values with left ventricular (LV) indices obtained by left ventriculography. We studied 13 consecutive patients with their first AMI who underwent successful reperfusion. Blood samples were taken the day of admission and on days 2, 3, 4, 5, 7, and 14. LV volume indices were determined at 1 month after AMI, when LV remodeling was almost completed. The serum concentrations of both PICP and ICTP changed in a time-dependent manner. The average serum PICP concentration was lower than 1 SD below the mean control values on days 2 and 3 and increased thereafter, returning to the lower end of the control range at day 14. The area under the curve (AUC) for PICP was significantly correlated with the LV end systolic (ES) and end diastolic (ED) volume indices and LV ejection fraction for the first 14 days after AMI. The serum PICP on days 5–14 was inversely correlated or tended to be correlated with the LVES and LVED volume indices. The average serum ICTP concentrations on admission were within the control range, began to increase on day 2, and reached maximal concentrations on day 5, remaining at a plateau concentration until day 14. Although the AUC of ICTP for 14 days, the ICTP concentrations on days 1 and 14, and the minimal and maximal concentrations were significantly correlated with creatine kinase (CK) release and the period from AMI onset to the peak CK time, the concentrations were not significantly correlated with any LV indices except for the concentration on day 4, which was weakly correlated with the LVES volume index. The serum concentrations of PICP showed a significant time-dependent change that correlated with LV indices, indicating that PICP may provide additional information for evaluating the healing process because it affects LV remodeling after AMI. Although the serum concentration of ICTP changed in association with CK release, the ICTP concentration was found to be a poor indicator for LV indices.

Ventricular remodeling, which occurs after acute myocardial infarction (AMI), 1 is one of the major determinants for the long-term prognosis of AMI patients (1, 2). The evaluation of ventricular remodeling is thus essential with

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1 Nonstandard abbreviations: AMI, acute myocardial infarction; ECM, extracellular matrix; PICP, carboxy-terminal peptide of type I procollagen; ICTP, carboxy-terminal telopeptide of type I collagen; LV, left ventricular; CK, creatine kinase; AUC, area under the curve; ED, end diastolic; ES, end systolic; and EF, ejection fraction.

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respect to the prognosis of AMI patients. Three independent factors influence ventricular remodeling (1, 2): infarct size, ventricular wall stress, and infarct healing. Extracellular matrix (ECM) reformation is an essential process in the healing process following AMI. The major constituents of ECM are collagens, proteoglycans, and glycoproteins.

Type I collagen, one of the most abundant components of ECM, shows the greatest tensile strength and plays a major role in collagen matrix formation. Although collagen does not appear within the first few hours after AMI, it appears after the fibronectin scaffold (3) and thus plays a key role in preventing ventricular enlargement during this period of the healing process (2, 4, 5). It has been reported that the synthesis and breakdown of fibrillar collagen can be altered during physiological and pathological events, including ischemic and reperfusion injury (5, 6).

Type I collagen is synthesized in the form of a larger protein, type I procollagen, which contains an additional sequence at both the N and C termini; these additional sequences are removed by specific proteinases before the collagen molecules are assembled into fibers (7–9). The peptide removed from the C terminus, i.e., the carboxy-terminal peptide of type I procollagen (PICP), appears in the blood stream during type I collagen synthesis. Serum PICP theoretically increases when type I collagen synthesis is exaggerated, and the ratio between the number of type I collagen molecules produced and that of PICP released is theoretically 1:1 (9).

The carboxy-terminal telopeptide of type I collagen (ICTP) cross-links with the COL domain of type I collagen in collagen matrix formation (10). Contrary to PICP, ICTP is removed from cross-links between the COL domains when type I collagen is degraded. It has been speculated that serum ICTP increases when type I collagen degradation increases in the setting of AMI, both collagen matrix breakdown and synthesis occur. We hypothesized that serum PICP and ICTP change in relation to left ventricular (LV) remodeling after AMI. To our knowledge, no prior studies have examined the serum concentrations of these peptides after AMI. Accordingly, we measured the serum PICP and ICTP by RIA and examined the relationship between the serum concentrations and the LV volume of patients.

**Patients and Methods**

To determine the serial changes in the serum concentrations of PICP and ICTP from the day of infarct onset, we studied 13 consecutive patients with their first AMI who were admitted within 12 h from AMI onset and who underwent reperfusion therapy by means of coronary angioplasty. The procedure complied with the rules of the Helsinki Declaration, informed consent was given by all patients, and the study was approved by the institutional ethics committee for human research (11). The patients included 8 men and 5 women, ages 42–76 years (mean ± SD, 64 ± 8 years). Reperfusion without flow delay was successfully established in all 13 patients. Consequently, this study did not include patients without reperfusion. The lesion was located at segment 6 according to the American Heart Association classification (12) in nine patients, at segment 5 in one patient, and at segment 7 in three patients. Patients in whom the responsible lesion was located in the left circumflex coronary artery were excluded from the study because LV indices were evaluated on left ventriculograms obtained in the right anterior oblique view. The interval from onset to admission ranged from 0.5 to 12 h (mean, 4.5 h).

Electrocardiographic or enzymatic evidence of reocclusion (13, 14) was not observed in any patient studied. The patency of the infarct-related artery was confirmed by follow-up coronary angiography performed 4 weeks after the AMI. Patients with associated bone and joint diseases, diabetes mellitus, depressed renal function, liver disease, or a malignant disorder were also excluded from the study. AMI was diagnosed on the basis of typical chest pain, ST segment elevation of >0.1 mV in more than two leads in 12-lead electrocardiography, and the increase of both creatine kinase (CK) and its MB isoenzyme to more than twice the upper limit of the health-related reference range. Emergency coronary angiography was performed, and reperfusion therapy with coronary angioplasty was attempted. There were no complications with cardiogenic shock that disturbed liver circulation and thus caused liver damage.

**Serum PICP and ICTP**

Blood samples were drawn immediately after admission and on days 2, 3, 4, 5, 7, and 14. The serum PICP concentration was measured by an established method (9). An RIA with polyclonal antibodies against the PICP purified from human skin fibroblasts was used (Orion Diagnostica) (9). The antibody used does not react with other fragments of collagens. The detection limit of this PICP assay system is 1.2 µg/L, and the assay is linear from 6.25 to 500 µg/L. The intra- and interassay imprecision (CV) was 1.67–6.65% and 1.27–5.09%, respectively.

The serum ICTP was measured according to the established method (10). An RIA with a polyclonal antibody purified from human femoral bone was used (Orion Diagnostica) (10). The detection limit of this ICTP assay system is 0.25 µg/L, and the assay is linear from 0.25 to 50 µg/L. The intra- and interassay CVs were 4.75–6.85% and 3.87–7.71%, respectively.

The control ranges for PICP and ICTP were obtained from 20 age- and gender-matched healthy volunteers (12 men and 8 women; 62 ± 8 years). The ranges within 1 SD of the mean (mean ± SD) of the controls for PICP and ICTP were 72–141 µg/L (99.4 ± 20.7 µg/L) and 1.7–3.7 µg/L (2.37 ± 0.45 µg/L), respectively.

In addition to the serum concentrations on each day, the area under the curve (AUC) of the patients' serum
concentrations for the first 14 days after the AMI was analyzed to determine its relationship with LV volume indices.

**LEFT VENTRICULOGRAPHY**

Although most of the LV remodeling occurs in the first month, it continues for at least 6 months after AMI, and the changes of LV volume at 6 months are correlated closely with those at 1 month (15, 16). The LV indices determined by the left ventriculography performed ~1 month after the onset of AMI were applied to examine the relationship between the serum PICP and ICTP concentrations and LV remodeling. The left ventriculogram was analyzed using a digitizer and a computer (SONY Graphic Digitizer KD4030B). The LV end diastolic (ED) frame was determined, using the electrocardiogram recorded simultaneously on cine film, as the frame nearest the peak of the R wave. The frame with the smallest ventricular volume was taken to show the LV end systolic (ES) volume, and the LV volume was calculated by a modifi-

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**Fig. 1.** Serial changes in serum PICP (top panel) and ICTP (bottom panel) concentrations in 13 patients with AMI. 

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**Fig. 2.** Relationship between the AUC of the serum PICP concentrations of the 13 AMI patients for the first 14 days after AMI and their LV indices 4 weeks after the onset of AMI. Relationship between the PICP AUC and LVEF (A), LVED volume indices (LVEDVI; B), and LVES volume indices (LVESVI; C). The solid lines are the regression lines; the dashed lines are the 95% confidence concentrations.
cation of the Dodge formula (17). In addition, regional ventricular function was determined by the centerline method (18).

CK RELEASE
Blood samples for a CK assay were obtained immediately after admission and every 4 h thereafter for 48 h, and then were collected once every day. The CK activity was measured by the modified Rosalki method (19). The total CK release was calculated according to modified method reported by Norris et al. (20) and Shell et al. (21) and compared with the serum PICP and ICTP concentrations. Although total CK release has been indicated to overestimate the infarct size in patients with successful reperfusion, total CK release has been demonstrated to be correlated with the infarct size of both reperfused and nonreperfused hearts determined pathologically (22). The present study examined only patients with successful reperfusion, i.e., the present study did not include patients without reperfusion. Thus, total CK release could be used to examine the relative relationship between serum ICTP and PICP concentrations and infarct size. The duration from the onset to peak CK time was reported recently to be correlated with infarct size in patients with successful reperfusion (23). The duration from the onset to peak CK time in addition to total CK release were thus also determined.

STATISTICAL ANALYSIS
We used ANOVA to assess the time-dependent changes in both PICP and ICTP concentrations. The Pearson correlation analysis was used to determine the relationship between PICP and ICTP concentrations and the LV volume indices. To compare the sequential changes between serum PICP and ICTP concentrations, sequential changes in their serum mean concentrations were fitted to exponential curves by the least-squares method. A P value <0.05 was considered significant.

Results
PICP
Time course. The top panel of Fig. 1 shows the time-dependent changes in serum PICP concentrations after AMI in the 13 patients examined. Serum PICP concentrations decreased after the admission value and reached a minimum on day 2 or day 3. The concentrations then returned gradually to the health-related reference range by days 7 to 14. The ANOVA revealed that this change was significant (P <0.01).

Relationship with LV indices. The AUC of the serum PICP concentration for 14 days was negatively correlated with the LVED and LVES volume indices and positively correlated with LV ejection fraction (LVEF), with correlation coefficients of 0.60 to 0.74 (Fig. 2). The serum PICP concentrations at days 5 and 7 and the individual patients’ minimum concentrations were inversely correlated with
the LVED volume index, with correlation coefficients of −0.55 to −0.77 (Fig. 3), and the concentrations on days 14 tended to be correlated (0.10 > P > 0.05) with the LVED volume index. Similarly, the serum PICP concentrations on days 4, 5, 7, and 14 and the minimum concentration were inversely correlated with the LVES volume index, with correlation coefficients of −0.60 to −0.71 (Fig. 4). The serum PICP at days 7 and 14 were positively correlated with the LVEF (Fig. 5).

Relationship with CK. On all days on which the serum PICP concentration was measured, there was no significant correlation with CK release or the duration from the onset to the peak CK time.

**ICTP**

**Time course.** The bottom panel of Fig. 1 shows the time-dependent changes in the serum ICTP concentration after AMI in the 13 patients examined. The serum ICTP concentrations were in the lower half of the health-related reference range at admission, and the concentrations then increased, reaching the maximum (plateau) concentration on day 3. The maximum concentration was 4.7-fold the mean control value. An ANOVA revealed that this change was significant (P <0.01).

**Relationship with LV indices.** The AUC of the serum ICTP concentrations for 14 days and the serum ICTP concentrations on any day were not significantly correlated with...
LV indices except for the concentration at day 4, which was weakly correlated with the LVES volume index ($r = 0.56; P < 0.05$); the concentration at day 14 was negatively correlated with the LVEF ($r = -0.58; P < 0.05$).

**Relation to CK.** The AUC of the serum ICTP concentration was significantly correlated with the period from the AMI onset to the peak CK time, with correlation coefficients of 0.58 to 0.80 (Fig. 6). The ICTP concentration on days 1 and 14 and the individual patients' minimum and maximum concentrations were significantly but weakly correlated with the CK release ($r = 0.57–0.63$).

**Correlation Between Serum PICP and ICTP Concentrations**
Significant correlation between the AUC of the serum PICP and ICTP concentrations was not obtained. On all days on which the serum PICP concentration was measured, there was no significant correlation with the serum ICTP concentrations. The ratio of serum PICP to serum ICTP on each day was not significantly correlated with any of LV indices.

Because the minimal concentrations of PICP on day 2 were speculated to be basal resting PICP concentrations, as discussed below, the mean values for serum PICP on days 2–14 were used for the exponential curve fitting. The mean serum PICP concentrations were significantly fitted to the exponential curve (Fig. 1, top panel). The mean ICTP concentrations were also significantly fitted to the exponential curve (Fig. 1, bottom panel). The PICP curve was located to the right compared with the ICTP curve.

**Outcome of Patients Examined**
During the follow-up period (mean ± SD, 37 ± 4 months) for the 13 patients examined, 1 patient died of heart failure 13 months after AMI. The AUC of his serum ICTP concentration was high (92.8 μg·day/L) compared to his serum PICP AUC (906 μg·day/L).

**Discussion**
This study demonstrated the time-dependent changes in the serum concentrations of PICP, which correlate with the LV indices, indicating that the PICP concentration may provide additional information for evaluating the healing process as it affects LV remodeling after AMI. Although the changes in serum ICTP were correlated with CK release and onset of AMI to peak CK time, the ICTP concentrations did not show any meaningful correlation with the LV indices.

The present methods for determining serum PICP and ICTP concentrations are well established (9, 10), and the intra- and interassay CVs are sufficiently small. Left ventriculography was performed in a single projection (the right anterior oblique view). Greene et al. (17) reported a good correlation between the LV volumes measured using single plane and biplane methods. Moreover, we carefully selected only patients with a lesion located in the left anterior descending coronary artery. Taken together, these factors indicate that the present assay methods were appropriate.

The serum concentrations of PICP on days 2 and 3 were lower than 1 SD below the mean control value. An initial decrease of serum PICP concentrations has been reported (24). PICP is tightly controlled by a variety of
mechanisms and has important roles in ECM degradation and remodeling. Although the present results did not provide any evidence indicative of the mechanism by which the serum PICP concentration is affected in AMI, the low serum PICP concentrations might be explained by one or more of three mechanisms: reduced synthesis, increased degradation or turnover of serum PICP, and changes in equilibrium between serum and tissue concen-

Fig. 6. Relationship between the time from AMI onset to peak CK time and the serum ICTP concentrations of the 13 AMI patients.

Relationship between the time from AMI onset to peak CK and the AUC for ICTP (A); the dynamic range (B) of serum ICTP concentrations; individual patients’ maximal (C) and minimal (D) serum ICTP concentrations; and serum ICTP on day 1 (E), day 5 (F), day 7 (G), and day 14 (H). The solid lines are the regression lines; the dashed lines are the 95% confidence concentrations.
trations, i.e., reduced release from tissue and/or mobilization from serum to tissue. A recent biological study disclosed that PICP in serum originates mainly from bone matrix turnover (25). The serum PICP concentration has been reported to be associated with physical activity (26, 27). Pedersen et al. (26) observed that bed rest decreased serum PICP concentrations. Glucocorticoids have also been shown to decrease serum concentrations of PICP by attenuating type I collagen synthesis (28, 29). Serum concentrations of glucocorticoids are increased after AMI. Type I collagen mRNA appears in infarct tissue a few days after the onset of AMI (30). These lines of evidence led us to speculate that the basal serum PICP concentrations may be shifted in patients with AMI because of a decrease of type I collagen synthesis throughout the body, including in bone. Serum PICP increased after serum ICTP concentrations increased. The manner of increase in PICP was the same as that of serum ICTP, i.e., exponentially. This result would be expected if serum PICP concentrations reflect collagen matrix reformation and the serum ICTP concentrations reflect collagen degradation in AMI.

In the present study, the serum concentrations of PICP increased from minimum concentrations on day 2 or 3, and the concentrations on days 5 and 7 and the AUC were correlated with the LVES and LVED volume indices. The significant inverse correlation suggests that serum PICP reflects infarct healing processes. Higher serum PICP concentrations would reflect greater collagen synthesis and thus increased healing; conversely, lower PICP concentrations may indicate decreased healing. Although a significant correlation of serum PICP with LV indices was obtained, the correlation was somewhat low. Many factors affect infarct healing processes, including infarct size (1), growth factors (31), and proteases (32, 33), and these factors may vary in individual patients, leading to a relatively low correlation of serum PICP concentrations with LV indices.

Serum ICTP increased and reached a maximum and plateau concentration by day 5. When type I collagen is degraded, ICTP is removed from cross-links between the COL domains, increasing serum ICTP concentrations. In fact, increased serum ICTP concentrations have been reported in patients with liver fibrosis (34), bone destruction (35, 36), and skin diseases (37). In AMI, type I collagen degradation begins as early as several hours after onset and continues for several weeks. Our observations of serial increases in serum ICTP are coincident with type I collagen degradation. The serum ICTP concentrations on days 1 and 14 and the minimum and maximum concentrations showed significant correlations with the time to peak CK and CK release, which are reported to reflect infarct size. The time to peak CK and CK release indicate the loss of myocytes, whereas that ICTP responds to ECM damage of the infarct is theoretically reasonable. It can also be surmised that the ECM structure differs from patient to patient, relative to the number of myocytes.

This would at least partly account for the weak correlation between integral CK release and the serial changes of ICTP.

Serum ICTP concentrations were not significantly correlated with LV indices in the patients in this study. LV remodeling is affected by infarct size, infarct healing, and ventricular wall tension. As stated above, the serum ICTP concentration was correlated with CK release and/or time to peak CK, indicating that the serum ICTP concentration reflects infarct size, although other factors such as infarct healing speed and/or ventricular wall tension may mask the relationship between the ICTP concentrations and LV volume indices.

Several biological substances have been studied in relation to LV indices; however, no ideal serum measurement faithfully reflecting the LVEF has been found. For example, in patients with successful reperfusion, a correlation coefficient of determination of ~0.50 has been reported for the relationship between the cumulative release of CK or cardiac myosin light chain and the LVEF (38). Thus, the serum concentrations of type IV collagen might be informative in some patients.

In the present study, one patient with approximately mid-range serum PICP AUC and high serum ICTP AUC died during the follow-up period. The relatively low serum PICP AUC compared with high ICTP AUC suggested that collagen synthesis would be low in relation to collagen breakdown, causing insufficient collagen matrix reformation in the infarct zone, i.e., poor LV remodeling. Because only one patient died in this series, further discussion regarding the relationship between serum PICP and ICTP concentrations and patient outcome is inappropriate. Further studies of outcomes (including death and reinfections) are needed.

One of the limitations of this study was that because we carefully selected patients, a relatively small number of patients was examined.

In conclusion, we used RIAs to determine the serial changes in the serum PICP and ICTP concentrations of patients after AMI and found that the measurement of these peptides may provide useful information regarding LV remodeling.

References


