

SCIENTIFIC LETTER

Time course of plasma markers of collagen turnover in patients with acute myocardial infarction

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Ventricular remodelling following acute myocardial infarction (AMI) is a powerful adverse prognostic indicator, characterised by alterations to left ventricular (LV) size, shape, and function.¹ Until recently, a clear distinction was made between the early changes of infarct expansion and LV dilatation and the later changes of fibrosis, scar formation, and continued alteration to LV geometry and function. However, it is increasingly recognised that remodelling is a continuum,² starting during the acute event and progressing thereafter. The remodelling continuum is dependent on the balance between extracellular collagen degradation and synthesis,³ the extent of which can be examined biochemically.⁴ Procollagen type I carboxy-terminal propeptide (PICP) is cleaved from procollagen during the formation of type I collagen and is therefore a marker of collagen synthesis. Similarly, C-telopeptide for type I collagen (CITP) is released by endopeptidase cleavage by matrix metalloproteinases (MMP) during collagen degradation and is a marker of breakdown. Clearly, MMP activity must be tightly regulated and they are specifically inhibited by the tissue inhibitors of metalloproteinases (TIMPs). We examined plasma concentrations of PICP, CITP, and TIMP-1 as serological markers of collagen turnover in patients presenting with AMI.

METHODS

We recruited 64 patients presenting with their first AMI, with electrocardiographic criteria for thrombolysis. Serial blood sampling was performed on admission, at 12 hours, 24 hours, 2 days, 3 days, 4 days, and 30 days for estimation of plasma PICP and CITP concentrations by radioimmunoassay (Orion Diagnostica, Finland), TIMP-1 concentration by enzyme linked immunosorbent assay (ELISA) (Amersham Pharmaceuticals, UK), and creatine kinase (CK) concentration. Mean plasma concentrations in our local normal population are: PICP 129 (32) ng/ml, CITP 2.6 (0.3) ng/ml, and TIMP-1 202 (22) ng/ml. The TIMP-1 assay was unexpectedly discontinued, and so only 30 patients underwent analysis of TIMP-1. Heart failure was defined as development of crepitations in > 1/3 of lung fields or signs of pulmonary oedema on chest radiography during admission. Exclusion criteria were: concurrent fibrotic disease, creatinine concentrations of > 130 μ mol/l, alanine aminotransferase concentrations more than twice the upper limit of normal, and angiotensin converting enzyme inhibitor/angiotensin II receptor blocker/spironolactone use.

Biochemical variables were log transformed to allow parametric testing. All data are presented in non-logarithmic format. Continuous variables are expressed as mean (SEM) and changes over time were tested by repeated measurement of analysis of variance. Student's *t* test was employed for comparison of means and Pearson's correlation coefficient tested correlation between variables. Statistical analyses were performed using Minitab statistical software (Minitab Inc,

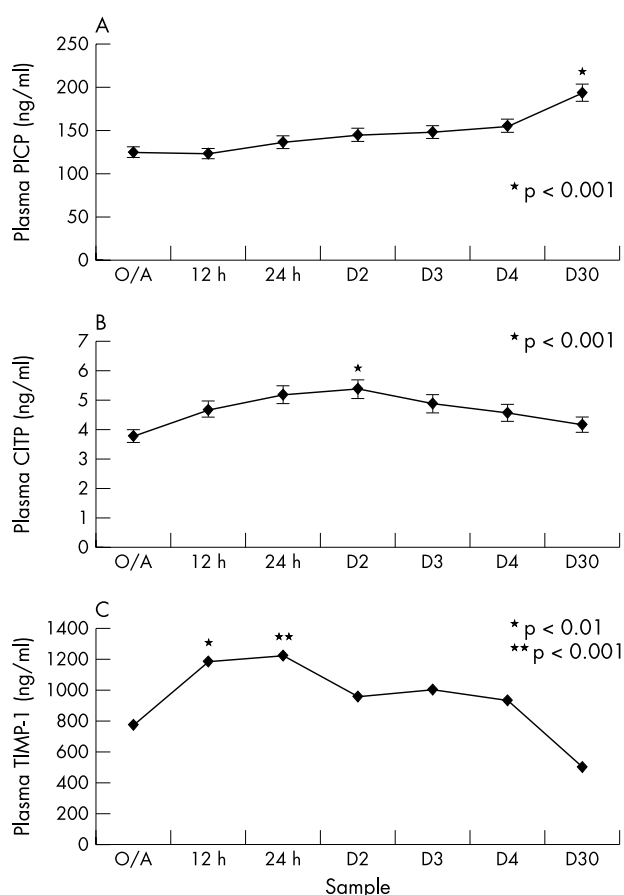


Figure 1 Time course of (A) plasma PICP, (B) plasma CITP, and (C) plasma TIMP-1 following AMI.

USA). A probability value of $p < 0.05$ was considered significant.

RESULTS

The majority of patients were male (72%) and the mean age was 62 years. All patients presented within six hours of the onset of pain and the infarct was sited 62% inferior, 30% anterior, 8% unknown (left bundle branch block). Fifty eight of the 64 patients received intravenous thrombolysis. Seventeen patients developed LV failure during admission. Four patients died by day 30, with a further five deaths at six months.

Abbreviations: AMI, acute myocardial infarction; CK, creatine kinase; CITP, C-telopeptide for type-I collagen; LV, left ventricular; MMP, matrix metalloproteinase; PICP, procollagen type-I carboxy-terminal propeptide; PIIINP, procollagen type-III amino-terminal propeptide; TIMP, tissue inhibitor of metalloproteinase

All three plasma markers increased over the study time period ($p < 0.001$) (fig 1). Mean admission concentration of PICP was within the normal range at 124 (4.4) ng/ml, peaking at 194 (9) ng/ml on day 30 ($p < 0.01$). In contrast, admission CITP was elevated at 3.8 (0.25) ng/ml, more than two standard deviations higher than the normal population mean of 2.6 ng/ml, peaking at 5.2 (0.27) ng/ml on day 2 ($p < 0.01$), before falling towards admission concentrations by day 30. Mean plasma TIMP-1 was notably elevated on admission compared to normal population concentrations, 775 (101) ng/ml v 202 (22) ng/ml. Concentrations increased further within 12 hours, peaking at 24 hours ($p < 0.001$), before falling to 499 (45) ng/ml by day 30. There was no correlation between admission or peak concentrations for any of the three markers, peak CK, infarct size, thrombolytic use, reperfusion or early or late death. However, in those who developed LV failure, admission CITP was significantly higher than those who remained failure free (5.0 ng/ml v 3.3 ng/ml, $p = 0.04$), a feature not seen with PICP or TIMP-1.

DISCUSSION

We have demonstrated time dependent changes in plasma PICP, CITP, and TIMP-1 concentrations following AMI. There is little change in plasma PICP over the first few days, remaining within normal range before peaking at day 30. In contrast, changes in plasma concentrations of CITP occur earlier and are more pronounced. Mean CITP was elevated on admission, increasing further within the first few days before returning towards normal by day 30. These patterns of change are consistent with the pathophysiology of ventricular remodelling.

Early and late phases of the remodelling process are characterised by different changes within the extracellular matrix. Breakdown of collagen by MMPs is the key in early remodelling, allowing infarct expansion and LV dilatation. Given that CITP is liberated from collagen during breakdown, the demonstrated early elevation of CITP is in keeping with this observation. Conversely, late remodelling is characterised by collagen synthesis and tissue fibrosis with further changes to LV geometry and function. Again, the pattern of change of plasma concentrations of PICP, a marker of collagen synthesis, is consistent with concentrations within the normal range in the early phase, peaking at day 30. This appears at odds with previous studies showing early elevation of procollagen type-III amino-terminal propeptide (PIIINP) following AMI.^{5,6} However, one should remember that unlike PICP, PIIINP is incompletely cleaved during the production of type-III collagen and is consequently released when collagen is degraded. Concentrations of PIIINP are therefore also influenced by collagen breakdown which may explain the increased concentrations observed in these studies.

There is also a time dependent change in plasma TIMP-1 following AMI; concentrations are notably elevated on admission and continue to rise before falling by 30 days. If collagen breakdown is the principal finding during the early phase of remodelling, one may expect concentrations of TIMP-1 to be reduced, given that TIMP-1 is a marker of inhibition of degradation. However, the assay for TIMP-1 does not differentiate between free TIMP-1 and TIMP-1 bound to MMP. This, coupled with experimental evidence from this study of increased collagen breakdown, as manifested by raised CITP, suggests that the TIMP-MMP balance shifts towards increased MMP activity following AMI. It is therefore likely that the rise in plasma concentrations of TIMP-1 is driven by increased collagen degradation, and we hypothesise that these increased concentrations reflect TIMP-1 bound to MMP or may be a consequence of attempted negative feedback.

In summary, the pattern of change of collagen markers demonstrated by this study mirrors the pathophysiology of remodelling. This, coupled with serological evidence of increased collagen degradation in those who developed early heart failure, provides further evidence to support plasma concentrations of these markers as evidence of changes in collagen flux at a tissue level; it also raises the possibility of using these markers to monitor the early phase of the remodelling process. Further studies examining the relation of these markers with functional changes within the heart and with prognoses will provide additional information in this regard.

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