Relationship Between Serum Amino-Terminal Propeptide of Type III Procollagen and Changes of Left Ventricular Function After Acute Myocardial Infarction

Steen H. Poulsen, MD, PhD; Nis B. Høst, MD, PhD; Svend E. Jensen, MD; Kenneth Egstrup, MD, DMSci, FESC

Background—The amino-terminal propeptide of type III procollagen (PIIINP) is a marker of type III collagen synthesis, which has previously been shown to correlate with infarct size in nonthrombolyzed myocardial infarction (MI) and to provide prognostic information after MI.

Methods and Results—The relationship between PIIINP and changes of left ventricular (LV) function was studied in 47 consecutive patients with first acute MI and 16 control subjects. Serum PIIINP analysis was measured daily during hospitalization and on days 90, 180, and 360. LV function was assessed by echocardiography on days 1, 5, 90, and 360. Patients with MI were stratified according to their serum PIIINP value at day 4 (group A, ≤5.0 μg/L; group B, >5.0 μg/L). On arrival, LV function and size were comparable between groups A (n=31) and B (n=16). LV ejection fraction, initially depressed (day 1: group A, 47±7% versus group B, 47±8%; P=NS), increased significantly in group A (day 360: 54±8%, P<0.001) but was unchanged in group B (day 360: 43±8%, P=NS). LV volumes increased significantly in group B (P<0.05) but not in group A. Furthermore, patients in group B developed signs of restrictive LV diastolic filling. Multivariate regression analysis identified PIIINP >5.0 μg/L and deceleration ≥140 ms as independent predictors of cardiac death or complicating heart failure during follow-up.

Conclusions—PIIINP assessed in the subacute phase of MI relates to long-term changes of LV function and provides clinical prognostic information.

Key Words: myocardial infarction • remodeling • collagen • systole • diastole

Left ventricular (LV) myocardial contractility, relaxation, and stiffness are affected in acute myocardial infarction (MI).1–4 Infarct expansion with regional dilatation and thinning of the infarct zone occurs early after MI, which can be followed by dilatation of the entire LV involving the infarct area as well as the noninfarcted areas.5–8 The changes of LV shape and size referred to as geometric remodeling affect LV systolic and diastolic myocardial performance, which are known to be important predictors of morbidity and mortality after acute MI.9–12 However, LV geometric remodeling varies considerably depending on several factors, such as size and location of the MI as well as therapeutic interventions.13–16 Furthermore, the extent and quality of the repair processes involving collagen deposition are also believed to influence the remodeling process after MI.17–21

Collagen type III is a major fibrillar constituent of developing granulation tissue.19–22 The amino-terminal propeptide of type III procollagen (PIIINP) is an extension peptide of the procollagen type III, which is cleaved off stoichiometrically during conversion from type III procollagen to type III collagen and liberated to serum.23 Elevated serum PIIINP is believed to reflect enhanced collagen turnover, including synthesis and deposition as well as alteration in degradation and elimination.22–24 In the rat heart after induction of MI, degradation of existing collagen occurs at the infarct site at day 1 to 2 and is associated with increased collagenase activity.25 Collagenolysis at the infarct site peaks at day 7 and declines over the next 14 days.26 Type III procollagen mRNA is increased 2 days after infarction, and accumulation of fibrillar collagen is seen a few days later. The synthesis of type III procollagen peaks after 3 weeks and seems to normalize only after months.26 In the rat heart, the increased collagen turnover reflected by increased serum PIIINP in the subacute phase of MI seems to represent increased collagenolysis with an overlapping but more delayed increased collagen synthesis. In patients with thrombolysed MI, serum PIIINP displays a characteristic sequential pattern with increased serum levels during the first 1 to 4 hours and a second increase at day 3 to 5.27 The initial increase of PIIINP is related to a non–organ-specific collagen degradation due to activation of latent collagenases and to collagen breakdown at the site of infarcted ventricular tissue, whereas the second rise
relates predominantly to the process of healing after MI. Furthermore, PIIINP is associated with poor prognosis in patients after acute MI.

To evaluate whether increased serum levels of PIIINP are associated with development of LV dysfunction and geometric remodeling, serial 2D and Doppler echocardiography were used to examine LV function after first acute MI.

**Methods**

**Patients and Protocol**

We prospectively studied 47 consecutive patients admitted to the coronary care unit with first acute MI, defined as (1) creatine kinase (CK) >210 IU/L and CK fraction B >20 IU/L (normal upper limit 56 U/L), (2) typical chest pain, and (3) ECG evidence of MI. Sixteen patients admitted with suspected acute MI that was disproved by lack of enzyme release and ECG changes served as controls. These patients had no prior history of MI but were considered to have angina pectoris because they had ≥1 of the following characteristics besides typical chest pain: (1) positive exercise test, (2) coronary angiogram with ≥1 stenotic lesion exceeding 75%, or (3) previous treatment with percutaneous transluminal angioplasty. Eligible for the study were patients in sinus rhythm, 40 to 75 years old, and without valvulopathy. Congestive heart failure was defined as Killip class ≥2, n (%) 0 (0) 4 (13) 7 (44) NS.

**Laboratory Analyses**

The concentration of PIIINP antigens in serum was determined by an equilibrium-type radioimmunoassay (PIIINP-RIA Kit, Orion Diagnostica) with normal serum range 3.1 ± 0.6 mg/L. Interassay and intra-assay variations for the PIIINP analyses ranged between 6% and 8%. Serum samples for PIIINP measurements were obtained on admission and once a day during the following 3 days or until discharge if this preceded day 4, and in patients with MI, PIIINP was also measured after 90, 180, and 360 days. On the basis of blood samples taken on day 4 after admission, the patients with MI were stratified into 2 groups according to their serum PIIINP level (group A, serum PIIINP ≤5.0 μg/L and group B, serum PIIINP >5.0 μg/L). The level of cutoff was chosen as the peak value for serum PIIINP in the control group plus 2 SD (3.4 ± 0.8 μg/L). Day 4 was selected to avoid the initial release of PIIINP from non–organ-specific sources due to use of thrombolysis, and PIIINP relates not only to degradation but also to the process of healing.

**Echocardiography**

2D and pulsed Doppler echocardiographic examinations were performed within 1 hour after admission on days 5, 90, and 360 by 2...
TABLE 2. Echocardiographic Variables in Control Subjects and Patients From Groups A and B

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 5</th>
<th>Day 90</th>
<th>Day 360</th>
<th>( P )</th>
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<tr>
<td></td>
<td>Day 1 vs 360</td>
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<tr>
<td>LA, mm</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Group A</td>
<td>36±5</td>
<td>38±5</td>
<td>38±4</td>
<td>38±4</td>
<td>NS</td>
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<tr>
<td>Group B</td>
<td>37±4</td>
<td>41±5</td>
<td>41±5</td>
<td>42±4*</td>
<td>0.01</td>
</tr>
<tr>
<td>Control</td>
<td>34±5</td>
<td>34±5</td>
<td>34±6</td>
<td>34±6</td>
<td>NS</td>
</tr>
<tr>
<td>E/A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>0.91±0.21</td>
<td>0.89±0.22</td>
<td>0.89±0.30</td>
<td>0.83±0.21</td>
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<tr>
<td>Group B</td>
<td>0.88±0.23</td>
<td>1.17±0.27*</td>
<td>1.13±0.23*</td>
<td>0.92±0.30</td>
<td>NS</td>
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<tr>
<td>Control</td>
<td>0.84±0.20</td>
<td>0.86±0.25</td>
<td>0.91±0.87</td>
<td>0.87±0.27</td>
<td>NS</td>
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<tr>
<td>IRT, ms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Group A</td>
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<td>90±18</td>
<td>100±26</td>
<td>105±15</td>
<td>0.05</td>
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<tr>
<td>Group B</td>
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<td>80±20</td>
<td>79±20*</td>
<td>106±17</td>
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<tr>
<td>Control</td>
<td>94±19</td>
<td>88±18</td>
<td>87±15</td>
<td>91±21</td>
<td>NS</td>
</tr>
<tr>
<td>DT, ms</td>
<td></td>
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<tr>
<td>Group A</td>
<td>175±26</td>
<td>191±31</td>
<td>218±30</td>
<td>223±25</td>
<td>0.01</td>
</tr>
<tr>
<td>Group B</td>
<td>174±29</td>
<td>160±23†</td>
<td>172±28†</td>
<td>215±28</td>
<td>0.01</td>
</tr>
<tr>
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<td>202±30</td>
<td>205±34</td>
<td>201±29</td>
<td>199±32</td>
<td>NS</td>
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<tr>
<td>S/D</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Group A</td>
<td>1.18±0.21</td>
<td>1.13±0.22</td>
<td>1.22±0.20</td>
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<td>NS</td>
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<tr>
<td>Group B</td>
<td>1.03±0.23</td>
<td>0.75±0.20†</td>
<td>0.96±0.17*</td>
<td>1.27±0.18</td>
<td>0.05</td>
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<tr>
<td>Control</td>
<td>1.40±0.28</td>
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<td>1.21±0.30</td>
<td>1.28±0.31</td>
<td>NS</td>
</tr>
<tr>
<td>R, cm/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A</td>
<td>24±4</td>
<td>24±3</td>
<td>23±3</td>
<td>24±4</td>
<td>NS</td>
</tr>
<tr>
<td>Group B</td>
<td>29±3*</td>
<td>29±3*</td>
<td>27±3</td>
<td>24±3</td>
<td>0.01</td>
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<tr>
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<tr>
<td>EDVI, ml/m²</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Group A</td>
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<td>71±14</td>
<td>71±15</td>
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</tr>
<tr>
<td>Group B</td>
<td>64±16</td>
<td>73±16</td>
<td>73±16</td>
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</tr>
<tr>
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<td>57±16</td>
<td>54±16</td>
<td>55±14</td>
<td>NS</td>
</tr>
<tr>
<td>ESVI, ml/m²</td>
<td></td>
<td></td>
<td></td>
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<td>34±9</td>
<td>35±10</td>
<td>34±10</td>
<td>NS</td>
</tr>
<tr>
<td>Group B</td>
<td>34±13</td>
<td>42±11†</td>
<td>41±11†</td>
<td>43±12†</td>
<td>0.01</td>
</tr>
<tr>
<td>Control</td>
<td>21±9</td>
<td>21±9</td>
<td>21±8</td>
<td>21±8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. LA indicates left atrium; E/A, ratio between peak mitral flow velocities of early and late diastole; IRT, isovolumetric relaxation time; DT, mitral E deceleration time; S/D, ratio between systolic and diastolic pulmonary venous peak flow velocities; R, peak pulmonary venous flow velocity at atrial contraction; EDVI, end-diastolic volume index; and ESVI, end-systolic volume index.

*P<0.05 A vs B; †P<0.01 A vs B.

examiners (S.H.P and S.E.J.) using an ATL Ultramark 7 cardiac ultrasound unit with a 2.5-MHz transducer. LV volume and ejection fraction were measured from the apical views by Simpson's biplane method. The mean of 3 measurements was used. Pulsed Doppler recordings of the mitral and pulmonary venous flow patterns were used to assess diastolic function. Doppler measurements were calculated from an average of 5 consecutive cardiac cycles. Interobserver and intraobserver variability analyses were for all Doppler parameters <5% in 15 randomly chosen patients. All echocardiographic measurements were analyzed without knowledge of the clinical data.

Statistical Analysis
All results were expressed as mean±1 SD. Unpaired t test was used for continuous variables between groups, and paired t test was used for within-group comparison. A \( \chi^2 \) test was used for dichotomous data. Changes over time were assessed by repeated measurements of variance within and between groups. Multivariate stepwise logistic regression analyses were performed to identify independent correlates for cardiac death or presence of congestive heart failure during hospitalization or New York Heart Association functional class score ≥II during 12 months of follow-up. Correlations were calculated by use of the Spearman rank correlation coefficient. Values of \( P<0.05 \) were considered statistically significant.

Results

Serum PIIINP
Peak PIIINP measured on day 4 was significantly higher among patients with MI than in control subjects (5.2±1.6 versus 3.4±0.8 µg/L, \( P<0.001 \)). No change of PIIINP was
noted in group A, whereas a significant decrease from an elevated level was observed in group B during follow-up (Figure 1). PIIINP was significantly higher in group B than group A during the first 90 days of follow-up (Figure 1). Patients in groups A and B had significantly higher PIIINP values than control subjects during the hospital stay ($P < 0.05$ and $P < 0.0001$, respectively). The maximal CK-B values and the difference between PIIINP on day 1 and day 4 were correlated in the total MI study population ($r = 0.47$, $P < 0.05$) and in MI patients treated or untreated with thrombolysis, respectively ($r = 0.31$, $P < 0.10$; $r = 0.56$, $P < 0.01$).

**Serial Changes of LV Systolic and Diastolic Function**

LV volumes at baseline and during follow-up are listed in Table 2. Changes of end-systolic volume index during follow-up and PIIINP were significantly correlated (Figure 2). LV ejection fraction increased significantly in group A but remained depressed and unchanged in group B during follow-up (Figure 3). At day 1, ejection fraction was similar in groups A and B, but it was significantly lower in group B during the out-of-hospital phase (Figure 3). Changes of LV ejection fraction from days 1 to 360 and PIIINP at day 4 were significantly correlated (Figure 4). Ejection fraction was significantly higher and LV volumes were lower in the control group than in patients in group A or B ($P < 0.001$). The mitral and pulmonary venous flow velocities are shown in Table 2. A more restrictive LV filling pattern developed in group B than in group A during the first 3 months.

**Clinical Outcome**

Four cardiac deaths were observed, with 1 patient from group B (heart failure) and 3 patients from group A (2 sudden deaths and 1 from complications due to coronary bypass surgery). One patient from group A was readmitted with reinfarction. Revascularizing procedures were performed in 2 patients, 1 from each group, during follow-up. In-hospital congestive heart failure was noted in 3 from group A and in 9 from group B. Patients in group B had significantly higher NYHA class scores (NYHA class II, 7 patients; class III, 2 patients) compared with group A during follow-up (NYHA class II, 3 patients; class III, 1 patient) ($P < 0.05$). Three patients in group B and 1 in group A were readmitted because of heart failure.

Univariate regression analysis identified LV ejection fraction ($\chi^2 = 3.4$, $P < 0.01$), LV end-systolic volume index ($\chi^2 = 3.2$, $P < 0.05$), mitral E deceleration time $\leq 140$ ms ($\chi^2 = 7.9$, $P < 0.001$), PIIINP measured day 4 $> 5.0$ mg/L ($\chi^2 = 7.6$, $P < 0.001$), and anterior MI ($\chi^2 = 3.0$, $P < 0.05$) as significant correlates to the cardiac death or development of congestive heart failure during hospitalization or NYHA class score $\geq II$ during follow-up. However, multivariate stepwise regression analysis identified only mitral E deceleration time $\leq 140$ ms ($\chi^2 = 4.0$, $P < 0.01$) and PIIINP $> 5.0$ ($\chi^2 = 3.3$, $P < 0.05$) as independent predictors of development of in-hospital congestive heart failure or cardiac death.
Discussion

In the present study, patients with acute MI and elevated PIIINP (group B) demonstrated significant LV dilatation and persistently depressed LV ejection fraction compared with patients with lower PIIINP level (group A) during 1 year of follow-up. Furthermore, Doppler analyses of transmural and pulmonary venous flow indicated a more restrictive LV diastolic filling in patients from group B than group A during the first 3 months. These changes of LV function could not be explained by differences in baseline characteristics, peak enzyme values, use of thrombolytic therapy, or LV function at baseline. From previous studies in rat heart, it is known that collagen degradation occurs at day 1 to 2 due to increased collagenolytic activity. Both LV dilatation and increased PIIINP were present at day 1, which indicates a relationship between collagen degradation and early LV dilatation, known as infarct expansion, in patients with acute MI. Previous studies have indicated that increased PIIINP at day 3 to 5 is associated with the onset of collagen synthesis overlapping the ongoing collagen degradation. This is followed within weeks by a period with predominantly collagen synthesis and deposition. Notably, patients from group B demonstrated persistently increased PIIINP levels during the first 3 months. The elevation of PIIINP in group B at day 1 to 2 could be a consequence of unsuccessful reperfusion of the infarct-related vessel leading to more pronounced damage on the interstitial matrix. After a period with increased collagen degradation, it would be expected that collagen synthesis and deposition would increase as an adequate response of healing, which could explain the persistent elevation of PIIINP. However, the persistent elevation of PIIINP indicates a constant drive on collagen synthesis during the first 3 months, which might represent an insufficient modulation of collagen synthesis, as seen in patients in the formation of ventricular aneurysms after MI. The observed association between persistent increased collagen turnover and LV dilatation and depressed ejection fraction might be related to impaired quality of healing due to impaired patency of the infarcted vessel. It was demonstrated previously that impaired vessel patency of the infarct-related vessel is related to persistently depressed ejection fraction, dilatation, and myocardial ischemia leading to geometric LV remodeling. Because patients in group B demonstrated persistently depressed LV ejection fraction and dilatation during follow-up, this group of patients might represent a subgroup of patients with decreased patency of the infarct-related vessel. The suggested relation between changes of LV size and function, vessel patency, and collagen repair is supported by a recent study demonstrating that PIIINP levels during the first 10 days after MI is correlated with coronary artery patency. Notably, patients in group A displayed a significant improvement of LV ejection fraction without dilatation during follow-up. The initial depression and subsequent recovery of LV ejection fraction in group A is probably related to myocardial stunning, and these patients might represent patients with patency of the infarct-related vessel due to spontaneous reperfusion or successful thrombolytic therapy. A more restrictive LV filling pattern was noted among patients in group B during the first 3 months. Restrictive LV filling is associated with increased LV end-diastolic pressure, which can be due to increased myocardial stiffness and/or increased LV volumes. The development of a restrictive LV filling in group B is likely to be due to increased LV volumes. However, increased collagen deposition might also contribute to the development of this filling pattern. It was demonstrated previously that increased collagen deposition may occur not only at the infarct zone but also at remote sites in the ventricle, which might increase myocardial stiffness.

Multivariate regression analysis identified PIIINP >5.0 μg/L and deceleration time = 140 ms as predictors of adverse clinical outcome. Restrictive LV filling was shown previously to be related to poor prognosis after MI, which is confirmed by the present study. Traditionally, infarct size is expressed by peak myocardial enzyme values, which reflect the extent of damage of the myocytes. We demonstrated that peak CK-B was significantly correlated to PIIINP but was not related to clinical outcome. The persistent increase of PIIINP seems to reflect the reparative process after the damage to the myocytes but also to the interstitial tissue. Because PIIINP was related to the changes of LV function and clinical outcome, the assessment of the reparative process seems to be important compared with measurements of myocardial enzymes in this regard. The clinical value of PIIINP has also been demonstrated previously in MI, which supports our data.

Study Limitations

Angiography and invasive revascularization procedures were not performed routinely in this study, so vessel patency remained unknown.

Conclusions

Increased serum PIIINP measured in the subacute phase of MI was associated with persistently depressed LV ejection fraction, dilatation, and restrictive diastolic filling and provides clinical prognostic information after MI.

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References


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