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# PTX3, A Prototypical Long Pentraxin, Is an Early Indicator of Acute Myocardial Infarction in Humans

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**Background**—Inflammation is an important component of ischemic heart disease. PTX3 is a long pentraxin whose expression is induced by cytokines in endothelial cells, mononuclear phagocytes, and myocardium. The possibility that PTX3 is altered in patients with acute myocardial infarction (AMI) has not yet been tested.

**Methods and Results**—Blood samples were collected from 37 patients admitted to the coronary care unit (CCU) with symptoms of AMI. PTX3 plasma concentrations, as measured by ELISA, higher than the mean +2 SD of age-matched controls (2.01 ng/mL) were found in 27 patients within the first 24 hours of CCU admission. PTX3 peaked at 7.5 hours after CCU admission, and mean peak concentration was  $6.94 \pm 11.26$  ng/mL. Plasma concentrations of PTX3 returned to normal in all but 3 patients at hospital discharge and were unrelated to AMI site or extent, Killip class at entry, hours from symptom onset, and thrombolysis. C-reactive protein peaked in plasma at 24 hours after CCU admission, much later than PTX3 ( $P < 0.001$ ). Patients  $>64$  years old and women had significantly higher PTX3 concentrations at 24 hours ( $P < 0.05$ ). PTX3 was detected by immunohistochemistry in normal but not in necrotic myocytes.

**Conclusions**—PTX3 is present in the intact myocardium, increases in the blood of patients with AMI, and disappears from damaged myocytes. We suggest that PTX3 is an early indicator of myocyte irreversible injury in ischemic cardiomyopathy. (*Circulation*. 2000;102:636-641.)

**Key Words:** myocardial infarction ■ pentraxins ■ myocytes ■ proteins

Several markers have been used to detect indexes of inflammation in unstable angina, during the acute phase of myocardial infarction (AMI), and in severe heart failure.<sup>1-5</sup> In these circumstances, proteins of the acute phase of inflammation,<sup>6</sup> such as C-reactive protein (CRP), are increased in the blood. In particular, increased CRP production in AMI has been considered a nonspecific response to myocardial injury.<sup>5</sup> More recently, evidence has been provided that CRP concentrations that are high but within the normal range predict subsequent coronary events years later in patients with angina<sup>3</sup> and in apparently healthy men.<sup>7</sup> These latest findings support the hypothesis that a low-grade subclinical local inflammatory response may be associated with cardiac ischemic events.<sup>1,7-9</sup>

CRP belongs to the pentraxin family of proteins (CRP and serum amyloid P component, SAP) conserved during evolution from *Limulus polyphemus* to humans.<sup>10-13</sup> CRP and SAP are made in the liver in response to inflammatory mediators, most prominently interleukin (IL)-6.<sup>14,15</sup> Pentraxins play a

major role in innate resistance against microbes, tools to scavenge cellular debris, and components of the extracellular matrix, as illustrated by amyloid deposits.<sup>6,12</sup>

PTX3 is structurally related but distinct from classic pentraxins. PTX3 was cloned as an IL-1-inducible gene in endothelial cells<sup>16</sup> and as a tumor necrosis factor (TNF)-inducible gene in fibroblasts.<sup>17</sup> Inflammatory cytokines induce PTX3 expression in a variety of cell types, most prominently endothelial cells and mononuclear phagocytes.<sup>16,18,19</sup> The COOH half-domain of PTX3 aligns with the full-length sequence of CRP and SAP, whereas the NH<sub>2</sub>-terminal part of the protein does not show any significant homology with other known proteins, thus rendering PTX3 the prototype member of the "long-pentaxin" family. After PTX3 cloning, other long pentraxins were identified.<sup>20</sup> Recent evidence suggests that PTX3 may serve as a mechanism of amplification of inflammation and innate immunity.<sup>21</sup>

The cloning of mouse PTX3 allowed the analysis of the in vivo expression of this molecule in mice.<sup>19,22</sup> After adminis-

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### Characteristics of Myocardial Samples Used for Morphological Study

	n	Age, y	F	Heart Weight, g
Infarcted hearts	12	74±8	4	566±113
Controls				
Normal hearts	4	64±14	2	370±72
Hypertrophied hearts	5	58±31	4	623±99
Left ventricular biopsies during surgery in perfused myocardium	6	66±3	1	...
Right auricles	9	64±11	1	...

n indicates number of cases; F, female. Data are mean±SD.

tration of bacterial lipopolysaccharides, PTX3 was expressed at high levels in the heart.<sup>22</sup> These observations raised the question whether PTX3 could be expressed in cardiomyocytes and released during cardiac ischemia, serving as a novel, independent indicator of myocyte damage.

## Methods

### Patients for the Clinical Study

Thirty-seven patients with chest pain suggestive of AMI who were admitted to the coronary care units (CCUs) of 5 hospitals were studied. In addition to typical symptoms, AMI was diagnosed by the occurrence of new Q waves at the surface ECG and serum creatine kinase (CK) >2-fold above upper reference values. All qualifying ECG tracings were centrally reviewed by one of the authors (A.P.M.) to confirm the presence of pathological Q waves and define the site. The ratio between the maximal CK serum concentration and the upper limit of the normal range for each laboratory was used as an enzymatic index of infarct extent. CK-MB peak serum concentration was also measured and its maximal value reported; troponin I was assayed at 10 different times after MI in a subgroup of 11 patients in whom PTX3 and CRP had been assayed at the corresponding times. In each case, 5 mL of blood was drawn in K-EDTA vacuum containers for PTX3 measurement and 2 mL into tubes without additives for CRP determination at entry (time 0), after 24 hours, and at hospital discharge. In a subset of 16 patients, blood was sampled at 0, 3, 6, 9, 12, 18, 24, 48, and 72 hours after admission and at hospital discharge to describe the time course of PTX3 and CRP after AMI. Serum or plasma was frozen at -20°C until analysis. One patient was excluded from the analysis because PTX3 plasma concentration was much higher (604 ng/mL) than the rest of the population. Patients with a history of acute or chronic inflammatory diseases were excluded. All patients signed informed acceptance of the study when their clinical conditions allowed a free and unbiased consent. Twenty patients from the same cardiology divisions matched for age without ischemic heart disease acted as control subjects. The investigation conforms to the principles outlined in the Declaration of Helsinki.

### Patients for Morphological Analysis

Myocardial samples from patients who died after AMI and were submitted to diagnostic autopsy (June 1998 to February 1999, Department of Pathology, University of Parma) were fixed in 10% buffered formalin for 24 to 48 hours and embedded in paraffin, and sections 5 μm thick were prepared and stained with hematoxylin and eosin (H&E). From this primary sampling, 12 cases (8 from men and 4 from women) in which areas of necrotic myocytes were easily recognizable were selected (Table). The interval between death and autopsy varied from 7 to 24 hours; that between symptom onset and death was <16 hours in 7 patients. Ventricular and atrial myocardium from 4 patients who died of noncardiac causes (a multiorgan donor with cerebral hemorrhage, 2 with rupture of cerebral aneurysms, and 1 patient 81 years old without particular diseases) were used as normal controls according to published criteria.<sup>23</sup> Five

additional patients with cardiac hypertrophy of different origin were also examined because infarcted hearts were hypertrophied. To check for possible artifacts in autopsy samples, heart specimens from 15 patients undergoing cardiac surgery were collected: 9 from right auricles and 6 from nonischemic left ventricular myocardium, during myocardial revascularization in 4 patients and during aortic valvular repair in 2. Patients with evidence of concomitant infections were excluded.

### Assays

PTX3 was measured with a sandwich ELISA based on a monoclonal antibody (mAb) MNB4 (ascites diluted 1:5000 in coating buffer) and rabbit antiserum.<sup>24</sup>

When plasma PTX3 levels were measured with affinity-purified rabbit antibodies, results were identical to those with whole rabbit serum. Moreover, recombinant PTX3 completely competed for binding of immunoreactive material present in plasma from AMI patients. The ELISA assay did not cross-react with the short pentraxins CRP and SAP.

Serum concentrations of CRP were measured by enzyme immunoassay with polyclonal antibody sandwich kits (Hemagen Diagnostics Inc).

Troponin I was measured in plasma of selected patients by a microparticle enzyme immunoassay (AxSYM, Abbott Diagnostics).

### Immunohistochemistry

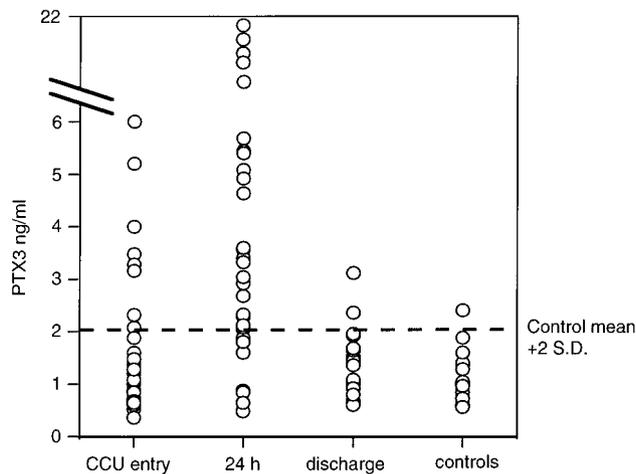
Myocardial sections 5 μm thick were deparaffinized and after 5 minutes of microwave treatment (3 cycles at 650 W) in citrate buffer were incubated for 12 hours at room temperature with anti-PTX3 (MNB6) mAb diluted 1:50 in PBS. After they had been washed with PBS, sections were incubated with mouse anti-rat IgG conjugated with peroxidase that was revealed by DAB. All the sections were counterstained with hematoxylin. Negative control procedures involved the omission of the primary antibody and the absorption of the mAb with the specific recombinant antigen. In addition, sections of liver, kidney, lung, and brain without apparent lesions from specimens sent to the Department of Pathology for diagnostic evaluation were stained with the same monoclonal antibody as for the heart.

### Statistical Analysis

Data are expressed as mean±SD or median when appropriate. Statistical comparisons between groups were made with Student's *t* test for independent samples. The existence of a relationship between plasma concentrations of PTX3 and CRP in each patient at entry, at 24 hours, and at discharge was verified by linear regression analysis.

## Results

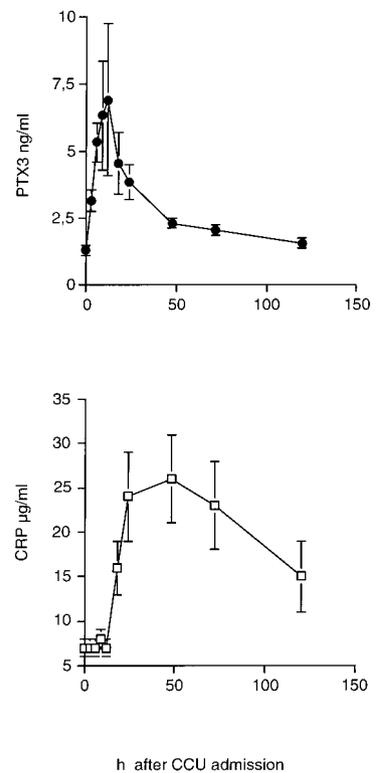
The mean age of the 37 AMI patients, 6 women, was 62±11 years, and they were admitted to CCU within 3.2±3.2 hours after onset of symptoms. The presence of new Q waves was confirmed in all cases by central reading, and AMI site was defined as anterior in 15 patients and inferior or other in 22. The mean ratio of peak CK/upper limit of normal range was 10.2±7.6. CK-MB peak serum concentration ranged from 20 to 452 ng/mL (mean 170 ng/mL). All patients had an elevation of ≥2 times the upper reference value. Troponin I peaked at a median time of 9 hours. Troponin I peak concentrations ranged from 52.3 to 1030 ng/mL (mean, 294 ng/mL). Thirty patients entered in Killip class 1 and 7 in Killip classes 2 and 3. A thrombolytic agent and aspirin were given to 31 patients (84%) and 25 patients (68%), respectively. All patients were discharged from hospital after 12±4 days except 1 who died within the first 24 hours after onset of symptoms.



**Figure 1.** PTX3 plasma levels in human AMI. PTX3 plasma levels in AMI patients were measured at entry to CCU, at 24 hours, and at discharge from hospital. Controls were age-matched patients from same cardiology divisions without ischemic heart disease. Dashed line represents cutoff value (control mean+2 S.D.).

PTX3 plasma concentrations in 20 control patients without a history or evidence of ischemic heart disease averaged  $0.99 \pm 0.51$  ng/mL. On the basis of this value, the cutoff for normal PTX3 concentration was set at  $2.01$  ng/mL, ie, mean value +2 SD. Accordingly, a concentration of  $2.56$   $\mu$ g/mL was defined as normal for CRP. Average PTX3 concentration at entry was  $1.74 \pm 1.49$  ng/mL, but 9 patients had values higher than normal (Figure 1). Twenty-four hours after admission, in 26 of 34 patients (76%; 2 samples missing and 1 patient excluded from analysis), PTX3 plasma levels were elevated, and only in 3 were they still high at hospital discharge. The numbers of patients with concentrations of CRP higher than normal were 16 of 34 (47%) at entry, increased to 31 of 34 (91%) at 24 hours, and decreased to 24 of 33 (73%) at discharge.

Figure 2 shows the complete time course of PTX3 and CRP in plasma of 15 patients whose blood was sampled more frequently. The kinetics of the 2 pentraxins are different: PTX3 peaks much earlier (7.5 hours median) than CRP (24 hours) after AMI ( $P < 0.001$ ). No correlation was found between plasma concentrations of PTX3 and CRP at entry, after 24 hours, or at discharge in all 36 patients (Figure 3). Neither time from symptom onset nor clinical variables such as Killip class at entry, AMI site, CK peak, or previous AMI could explain the interindividual variability of PTX3 concentrations at entry, at 24 hours, and at discharge. Thrombolysis or aspirin did not affect PTX3 concentrations. The only significant difference was found with age: patients  $> 64$  years old (median value for the population) had higher PTX3 concentrations at 24 hours than younger ones ( $5.93 \pm 5.57$  versus  $2.87 \pm 1.31$  ng/mL;  $P = 0.035$ ). The higher concentration of PTX3 found in women versus men may be explained by the higher age of women (72 years versus 60 years for men). When patients were divided into 2 groups based on PTX3 concentration at 24 hours (ie,  $\leq 2.01$  ng/mL, 8 patients, versus  $> 2.01$  ng/mL, 26 patients), no significant difference was found in terms of age, hours from symptom onset, site of AMI, peak CK, Killip class at entry, and thrombolysis. The



**Figure 2.** Time course of circulating PTX3 and CRP in 15 AMI patients. CRP and PTX3 were measured by ELISA.

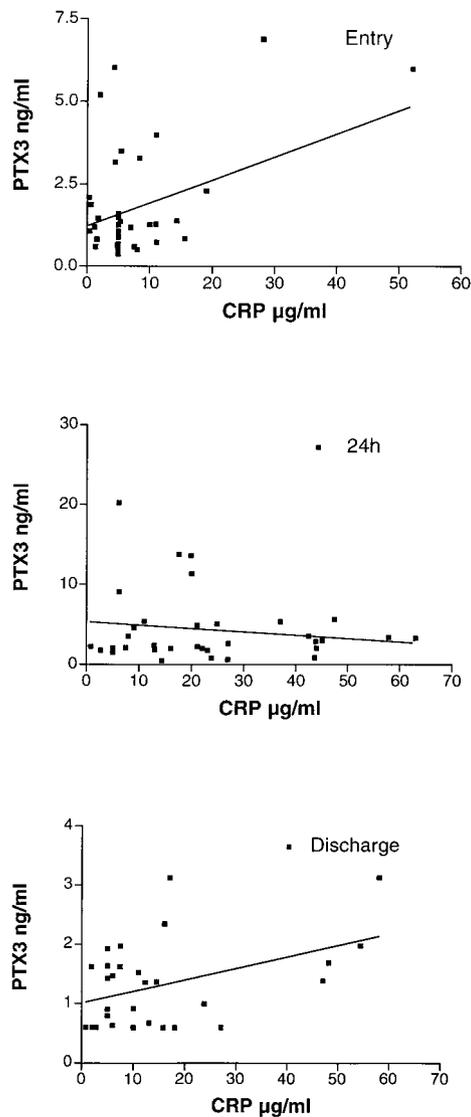
only possible difference was in sex, women being absent from the group with normal 24-hour PTX3 concentration. Higher plasma concentrations of CRP were associated with the presence of heart failure at entry (Killip class 2 to 3,  $37.1 \pm 10.1$   $\mu$ g/mL versus Killip class 1,  $20.7 \pm 2.5$   $\mu$ g/mL;  $P = 0.029$ ). Patients on maintenance aspirin had significantly lower CRP concentrations than untreated patients ( $17.98 \pm 4.7$  versus  $29.79 \pm 2.84$   $\mu$ g/mL;  $P = 0.032$ ).

### Morphological Analysis

The average age, sex, and heart weight of the infarcted, hypertrophied, and control patients are listed in the Table. In control and hypertrophied hearts, a dense staining of all myocyte sarcoplasm with anti-PTX3 mAb was always found (Figure 4, top). Similar findings were seen in left ventricular biopsies and in specimens collected from the auricles. The same labeling was detectable in myocytes of left and right ventricles, septum, and atria. Interstitial and endothelial cells were not stained. The absorption of monoclonal antibody with the antigen (Figure 4, bottom) and the omission of the primary antibody completely abolished myocyte labeling.

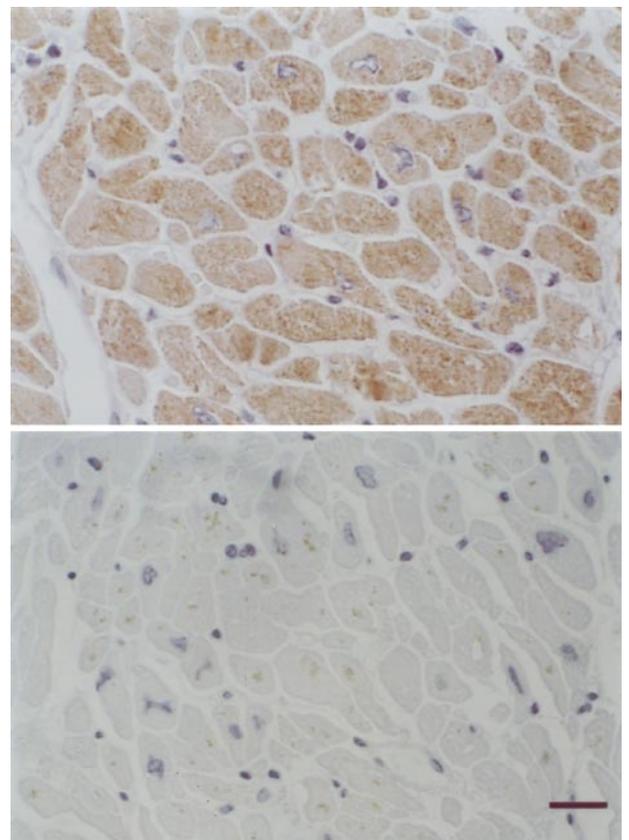
Other tissues were negative after staining with anti-PTX3 antibody. Only some segments of kidney tissue were weakly positive, in agreement with what was found by in situ hybridization in the mouse.<sup>22</sup>

All specimens from infarcted myocardium were examined by H&E to confirm the presence of necrotic myocytes in the infarcted myocardium. Three different areas of damaged myocardium were found in all these 12 hearts. In the first, myocytes were necrotic, without recognizable striations or nuclei. In the second, myocytes were weakly stained or not



**Figure 3.** Correlation between plasma or serum concentrations of PTX3 and CRP at entry to CCU, after 24 hours, and at hospital discharge. No significant correlation was present between PTX3 and CRP.

stained in comparison with the surrounding tissue but had a well-preserved cytoplasm and nuclear morphology. In the third, only occasional residual myocytes were visible in the reparative tissue. The staining of the myocardium with anti-PTX3 mAb revealed in all 12 cases that infarcted areas detectable with H&E staining (Figure 5, top) did not contain PTX3-positive myocytes (Figure 5, bottom). In contrast, a consistent and intense labeling of myocytes bordering the infarcted zone similar to that seen in the normal or hypertrophied myocardium was evident (Figure 5, bottom). At times, a few labeled myocytes were apparent within the reparative tissue together with inflammatory cells (Figure 6, top). Finally, some myocytes in which the striation was still evident, surrounded by positive cells, were not labeled by anti-PTX3 mAb (Figure 6, bottom). The latter findings were present in all patients but were more apparent in hearts of patients who died shortly after cardiac symptoms.

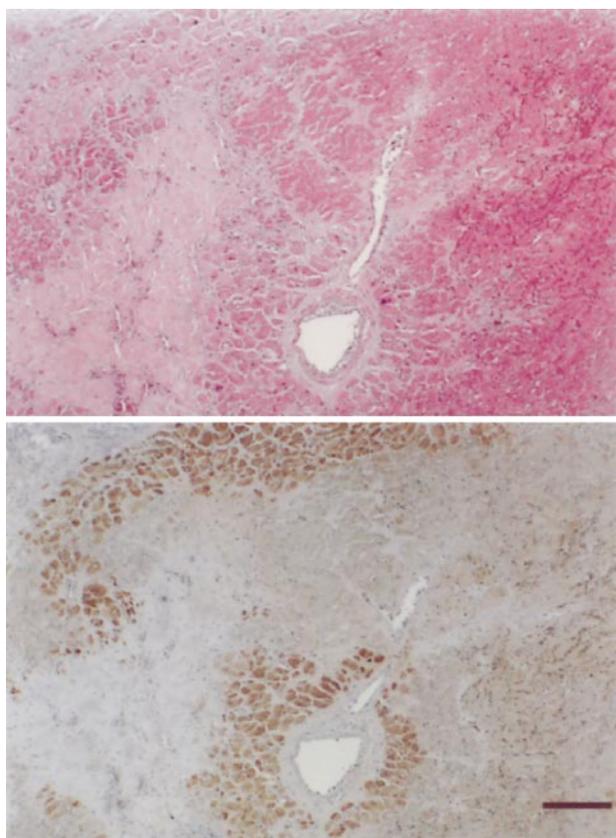


**Figure 4.** Photomicrographs showing (top) myocytes from control heart labeled by mAb to PTX3 as revealed by brown color of DAB reaction. Bottom, Adjacent section was exposed to mAb and excess of antigen before DAB reaction. Note complete absence of labeling in myocytes. Both sections were slightly counterstained with hematoxylin. Bar=15  $\mu$ m.

## Discussion

The present results demonstrate that the long pentraxin PTX3 is present in normal and hypertrophied human cardiomyocytes, is increased in the blood of patients with AMI, and disappears from necrotic myocytes. On average, PTX3 peaked rapidly after admission to the hospital and preceded the increase of the short pentraxin CRP. Taken together, these results seem to suggest that PTX3 increases in the blood of patients with AMI because it is released from dying or necrotic cells.

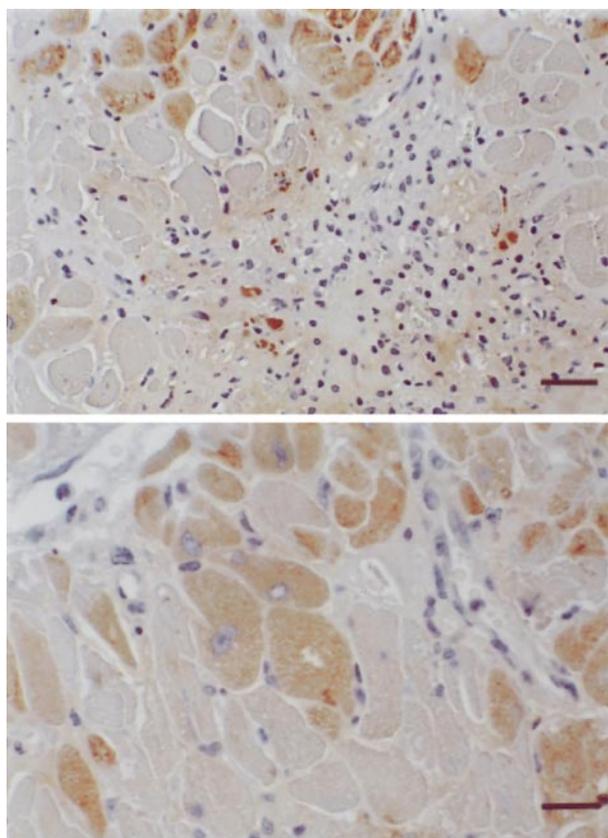
The long pentraxin PTX3 was originally identified as an IL-1/TNF-inducible gene.<sup>16,17</sup> *In vivo*, the PTX3 gene was most prominently induced in mouse heart and skeletal muscle.<sup>18</sup> The presence of PTX3 in the human heart described here suggests that cardiac myocytes are a major site of production of this molecule. This constitutive expression of the molecule in the human heart is clearly different from previous observations in rodents, in which induction was required for high expression.<sup>22</sup> In agreement with the results obtained here, we have found that PTX3 transcripts were readily detectable in commercially available normal heart RNA (Clontech). The constitutive presence of PTX3 in human myocardium versus the inducible mRNA expression in rodent hearts may be dependent on a species difference in expression regulation, although promoter region analysis in



**Figure 5.** Photomicrographs showing adjacent sections of same field from infarcted heart stained with H&E (top) and with mAb to PTX3 (bottom). Correspondence between damaged myocytes not stained with mAb and weakly (left) or heavily (right) stained with H&E is apparent. Myocytes stained with mAb in border zone do not show necrotic lesions by H&E. Bar=100  $\mu$ m.

humans and mice has not highlighted substantial differences.<sup>17,25</sup> Physical stress was able to induce PTX3 gene expression in the rat heart (unpublished data). Therefore, one cannot completely exclude the possibility that the constitutive expression of PTX3 may be a reflection of stress or other unrecognizable causes associated with death or surgical procedure. PTX3 was localized in intact cardiomyocytes, whereas damaged cells showed little or no staining. These findings suggest that dying or necrotic cells may release PTX3, because myocyte permeability is altered as a result of the necrotic process.<sup>26</sup> The cellular distribution of PTX3 in the myocardium of infarcted patients is clearly distinct from that of CRP. The short pentraxin CRP is localized in necrotic areas together with C3 and C4 components, but not in the functioning myocardium.<sup>27</sup> This differential distribution may reflect the different sources of the 2 molecules: the liver and the blood for CRP versus the heart for PTX3.

Two major differences are apparent between CRP and PTX3 plasma concentration time courses after AMI: time to peak of PTX3 is much earlier than that of CRP, and at discharge most of the patients have normal levels of PTX3, whereas  $\approx 75\%$  of them have abnormal concentrations of CRP. In addition, CRP correlates with AMI severity, expressed as Killip class at entry, whereas PTX3 was highest in elderly patients. Surprisingly, neither severity, extent, nor site



**Figure 6.** Photomicrographs of section of left ventricular myocardium from infarcted heart stained with mAb to PTX3. Top, Area of reparative tissue with inflammatory cells and labeled and unlabeled myocytes. Note a few fragments labeled with mAb within reparative tissue. Bar=18  $\mu$ m. Bottom, Although all myocytes have normal morphology, only some are labeled by mAb to PTX3. Bar=10  $\mu$ m.

of AMI had any relation to PTX3 concentrations. In the attempt to understand the determinants of increased circulating PTX3 in AMI, PTX3 was assayed in plasma of patients with unstable angina or with heart failure of nonischemic etiology. Twenty-six patients with unstable angina admitted to the CCU showed circulating PTX3 concentrations of  $2.38 \pm 2.35$  ng/mL (12 of the 26 higher than the cutoff value of 2.01 ng/mL) within 12 hours of the last episode of typical pain, whereas in 29 patients with moderate to severe nonischemic heart failure, PTX3 averaged  $1.78 \pm 0.93$  ng/mL (12 of the 29 higher than cutoff; our unpublished results). The concentrations of PTX3 in these 2 groups of patients are intermediate between normal subjects and AMI patients.

Distinct differences exist in the aging process of the heart,<sup>28</sup> and aging per se is a negative prognostic indicator in patients with AMI.<sup>29</sup> It is tempting to speculate that ongoing myocyte cell loss found in old and senescent human hearts<sup>23</sup> is the mechanism for PTX3 elevation in the blood with aging.

SAP and CRP are acute-phase proteins that are elevated in ischemic heart disease.<sup>1,3,4,9</sup> Although others have shown that in unstable angina, CRP did not increase during episodes of myocardial ischemia,<sup>9</sup> our findings in AMI show a clear response to the ischemic event, as already demonstrated by others.<sup>5</sup> These reactants are made in the liver, where they are

induced by primary inflammatory cytokines, primarily IL-6, which are elevated in AMI, angina, and chronic heart failure.<sup>2,4</sup> In contrast to these acute-phase proteins, the long pentraxin PTX3 is made only in small amounts in the liver,<sup>19,22</sup> but more in muscular tissue, including the heart.<sup>22</sup> PTX3 is induced directly by bacterial products TNF and IL-1 and is made by different cell types, including cardiomyocytes, as shown here in humans. In this perspective, it is of interest that PTX3 levels are not significantly correlated with those of CRP and SAP. Thus, PTX3 may represent an independent indicator of inflammatory components in ischemic cardiomyopathies being produced and released locally. PTX3 binds the first component, C1q, of the classic pathway of complement activation as CRP and SAP.<sup>21</sup> Complement is activated locally in AMI via the classic pathway,<sup>30</sup> and it represents a mechanism of amplification of tissue damage.<sup>31</sup> The myocardial molecule(s) responsible for binding of C1q and initiation of the classic complement cascade has not been defined. The present study strongly suggests that local production of the long pentraxin PTX3 may be part of this loop of amplification of tissue damage.

The construction of gene-targeted mice currently under way may help define the role of PTX3 in the heart and in AMI.

In conclusion, although the significance of PTX3 in intact myocytes remains to be determined, its increase in plasma early after symptoms of AMI might help in identifying myocyte cell damage.

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