Serum amyloid A protein, apolipoprotein A-I, and apolipoprotein B during the course of acute myocardial infarction

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SUMMARY Serum amyloid A protein (SAA), apolipoprotein A-I (apoA-I), apolipoprotein B (apoB) concentrations, and creatine kinase (CK)-MB isoenzyme activity were serially measured in 10 patients during the course of acute myocardial infarction. Pronounced increases in SAA concentrations were observed in all patients during infarction. The highest SAA values were observed, on average, 67 hours after the onset of chest pain. After infarction both apoA-I and apoB concentrations decreased. The reduction in apoA-I concentration 67 to 72 hours after the onset of chest pain was (31%) ($p < 0.01$) and the reduction in apoB concentration 55 to 60 hours after the onset of pain was (34%) ($p < 0.01$). Negative correlations were found between the concentrations of SAA and apoproteins A-I and B; this inverse relation was stronger between SAA and apoB than between SAA and apo-AI.

Serum amyloid A (SAA) is a low molecular weight protein ($M_r \sim 12000$) which is associated with high density lipoproteins in the circulation.¹⁻³ In plasma from normal subjects SAA is present only in trace amounts but in disease states characterised by tissue injury and inflammation the plasma concentration of this acute phase reactant is much increased.⁴⁻⁶ Macrophage/monocyte-derived interleukin 1^{7,8} has been shown to be a potent inducer of SAA synthesis in hepatocytes. The mechanism by which interleukin 1 stimulates the synthesis seems to be a direct modulation of the expression of the genes coding for SAA.⁹ A recent study suggests that tumour necrosis factor- α may also induce acute phase protein synthesis.¹⁰

During the acute phase state SAA comprises a substantial part of the protein component of high density lipoprotein.¹¹⁻¹³ It is assumed that SAA associates with existing high density lipoprotein particles and causes remodelling.¹⁴ In a recent study Clifton *et al* showed that the presence of high concentrations of SAA was associated with phospholipid-depleted and triglyceride-enriched lipoprotein particles with a density comparable with that of normal high density lipoprotein,¹³ but a size larger than normal high

density lipoprotein. How the association between SAA with high density lipoprotein changes lipoprotein metabolism is still unclear. Data from studies on animals are conflicting: some suggest that high density lipoprotein particles enriched with SAA are catabolised more rapidly than normal particles^{15,16}; in another study this was not the case.³

Myocardial infarction is associated with an acute phase response.¹⁷⁻²¹ No detailed studies on the kinetics of the SAA response or on the quantitative relation between SAA and apolipoproteins have, however, been reported in man. To address these questions we prospectively examined the SAA, apoA-I, and apoB responses to myocardial infarction and evaluated whether the changes in SAA concentrations could be correlated with the severity of myocardial injury.

Patients and methods

Ten consecutive patients admitted to the coronary care unit with acute myocardial infarction were studied (table 1). The diagnosis was confirmed by an electrocardiogram and increased creatine kinase (CK)-MB concentration in all cases. Venous blood samples were obtained from the patients on admission and then at six hourly intervals for the first 72 hours,

Table Clinical data of 10 patients

Case No	Age/sex	ECG result	Peak CK-MB activity (U/l)	Comments
1	73/F	Anteroseptal transmural injury	240	Uncomplicated recovery
2	77/F	Left ventricular hemiblock, anterolateral injury	206	At presentation pulmonary oedema
3	84/M	Anterolateral injury, atrial fibrillation	183	3 months later fatal reinfarction
4	66/M	Large inferoapical transmural injury	370	At presentation in cardiogenic shock; died on day 7; postmortem examination showed rupture of the posterior left ventricular wall
5	75/M	Large anterolateral transmural injury	600	At presentation resuscitated; died on day 4; at postmortem examination large anterior myocardial infarction
6	80/F	Large infero-postero-apical transmural injury	263	Developed left ventricular failure on day 3
7	50/M	Anteroseptal injury	144	Uneventful recovery
8	56/M	Posterior injury	128	Uneventful recovery
9	72/F	Large anteroseptal injury	254	In 1974 renal transplantation because of polycystic kidneys; in the postinfarction period left ventricular failure, immunosuppressive treatment
10	78/M	Left bundle branch block	100	Four myocardial infarctions previously; died on day 2, postmortem examination showed fresh infarction in the anterior and lateral walls

and subsequently daily during the patients' stay in the unit.

SAA was measured by radial immunodiffusion as described previously.²² The SAA concentration in 50

healthy blood donors ranged from <1 mg/l to 15 mg/l.²³

The apoA-I and apoB concentrations were measured in a Kone C clinical analyser (Kone, Fin-

Fig 1 Individual SAA curves in 10 patients with acute myocardial infarction. Numbers refer to patients and are the same as in table 1.

Fig 2 Summary of sequential changes in apoA-I, apoB, SAA and CK-MB concentrations in 10 infarct patients. Values are mean (SEM).

land) with a turbidometric method using the apoA-I (normal reference range 0.86–1.46 g/l) and apoB (normal reference range 0.92–1.33 g/l) kits (Orion Diagnostica, Espoo, Finland).

CK-MB activity was measured by immunoassay using a kit from Boehringer-Mannheim (Mannheim, Federal Republic of Germany).

Paired Student's *t*-test (two-tailed) and linear regression analysis (after transformation of the data to the natural logarithms) were used.

Results

Significant increases in the plasma SAA concentration occurred in all 10 patients with acute myocardial infarction (fig 1). The mean peak value of SAA concentration during infarction was 362 (SE 83) mg/l (median 435 mg/l, range 31 to 645 mg/l). The highest SAA value was attained, on average, 67 hours (range 51 to 74 hours) after the onset of chest pain but increased concentrations were observed earlier (fig 2). The temporal relation between the kinetics of the changes in SAA concentrations and in CK-MB isoen-

zyme activities in the 10 patients is summarised in fig 2. The highest CK-MB activity could be measured about 13 to 16 hours after the onset of chest pain and thus preceded the maximal increase in SAA concentrations by about two days. A weak positive correlation ($r = 0.58$, $n = 10$, NS) was found between the peak concentrations of SAA and the peak activity of CK-MB during myocardial infarction; the correlation was stronger between SAA concentrations and total CK-activity ($r = 0.70$; $n = 10$, $p < 0.05$).

The concentrations of apoA-I fluctuated during the period immediately after infarction (fig 3). A decrease in the concentrations was, however, evident (figs 2 and 3). The mean concentrations were lowest at 67 to 72 hours (31% reduction, $1 p < 0.01$; 95% confidence interval 0.84–1.30 g/l) after the onset of infarct pain.

The concentration of apoB showed pronounced variation during the immediate period after infarction (fig 4). A decrease in the concentrations was, however, observed (figs 2 and 4). The mean concentration was lowest at 55 to 60 hours (34% reduction, $1 p < 0.01$; 95% confidence interval 0.60–0.85 g/l) after the onset of infarct pain.

Fig 3 Individual apoA-I protein curves in 10 patients with myocardial infarction. Numbers refer to patients and are the same as in table 1.

Fig 4 Individual apoB protein curves in 10 patients with myocardial infarction. Numbers refer to patients and are the same as in table 1.

Analysis of the combined data showed an inverse correlation between the concentrations of SAA and the apolipoproteins A-I and B (fig 2). This correlation was stronger between SAA and apoB (pooled data, $n = 143$, $r = -0.41$, $p < 0.001$) than between SAA and apoA-I (pooled data, $n = 143$, $r = -0.27$, $p < 0.01$). ApoA-I and apoB correlated positively with each other (pooled data, $n = 143$, $r = 0.33$, $p < 0.001$). There were, however, pronounced individual variations in the relation between SAA and apoproteins A-I and B during the course of myocardial infarction.

Discussion

These results show that acute myocardial infarction is associated with noticeable changes in the SAA, apoA-I, and apoB protein concentrations associated with high density lipoprotein. During the early phase of acute myocardial infarction an inverse relation was found between SAA and apoB concentrations and also, though weaker, between SAA and apoA-I concentrations. With respect to SAA, our results agree with those of two recent reports.^{20 21}

The peak SAA concentration correlated with peak total CK activity, and, to a lesser degree, with CK-MB activity, which is a fairly good index of infarct size.²⁴ The mechanism of increase in SAA is therefore probably related to the injured myocardial tissue; cell damage and necrosis lead to the activation of monocytes/macrophages, which release soluble mediators, inducing the acute phase synthesis of SAA by the hepatocytes. Interleukin 1 has been identified as a mediator of SAA synthesis^{7 8} but other factors may also have a role.^{10 25 26}

In an experimental model Morrow and associates showed 500- to 2000-fold increases in mRNA for SAA during the acute phase state,^{27 28} and a recent study suggests that interleukin 1 directly modulates acute phase gene expression.⁹ Although the liver is the main site of the acute phase SAA synthesis,^{7 8 27 28} the possibility of extrahepatic synthesis should also be considered.²⁹⁻³¹

In the circulation the bulk of SAA is associated with high density lipoprotein; more than 75% being associated with HDL₃. During the acute phase, SAA becomes an important apolipoprotein of high density lipoprotein. When calculated as protein mass per particle, SAA may sometimes even become the major apoprotein of high density lipoprotein, which under normal conditions is apo A-I.^{13 32 33} The acquisition of apoSAA results in the displacement of apoA-I and apoA-II from the high density lipoprotein particles.³² There is some evidence that high density lipoprotein particles enriched with SAA are more rapidly catabolised than normal particles.^{15 16} Our results showing an inverse relation between the circulating concentra-

tions of SAA and apoA-I are of interest in this regard and are in agreement with the findings of Avogaro *et al*, who showed reduced apoA-I concentrations during the early period after infarction.³⁴ The decrease in apoA-I concentrations after infarction is probably due to reduced synthesis, but enhanced uptake from the circulation may also contribute.

Apolipoprotein B is found in low density lipoprotein, very low density lipoprotein, and chylomicrons. Most of the plasma apoB resides in low density lipoprotein and apoB is virtually the only low density lipoprotein apoprotein. Our results, showing a significant fall in circulating apoB concentration in the period immediately after infarct agree with the results of Avogaro *et al*³⁴ and Ryder *et al*.³⁵

In conclusion, our results show that myocardial infarction induces pronounced changes in the plasma concentrations of SAA, apoA-I, and apoB. Further studies are therefore needed to assess the clinical relevance of these findings and to evaluate whether measurements of SAA would be of help in the assessment of prognosis and in the recognition of complications in patients with acute myocardial infarction.

We thank A-M Teppo for performing the SAA assays. This study was supported by the Sigrid Jusélius Foundation, Finland.

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