

## Alpha<sub>1</sub>-antitrypsin in acute myocardial infarction

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**SUMMARY** Alpha<sub>1</sub>-antitrypsin serum levels were measured in 48 patients with acute myocardial infarction and in 19 control patients either with coronary heart disease without necrosis, or with neither coronary disease nor inflammation. Alpha<sub>1</sub>-antitrypsin was significantly raised in the group of patients with acute myocardial infarction. As some patients individually showed no change in alpha<sub>1</sub>-antitrypsin levels, however, they were divided into two groups according to the maximum serum levels attained. Patients with non-increasing levels of alpha<sub>1</sub>-antitrypsin showed increased mortality and a higher incidence of cardiogenic shock, whereas reinfarction occurred more frequently in the group with high alpha<sub>1</sub>-antitrypsin levels. Our findings may suggest that the course of a myocardial infarction is determined not only by the severity of the ischaemic event, but also by the response of the "acute phase reaction" mechanism. We conclude that a failure of alpha<sub>1</sub>-antitrypsin levels to increase after myocardial infarction may be associated with a worse clinical course.

At normal serum concentrations, alpha<sub>1</sub>-antitrypsin is a powerful inhibitor of proteolytic enzymes.<sup>1,2</sup> Since a rise in the plasma levels occurs during tissue injury,<sup>3,4</sup> it is considered to be one of the "acute phase reactant" proteins. The mean plasma levels of alpha<sub>1</sub>-antitrypsin have been shown to increase after myocardial necrosis.<sup>5,6</sup> The correlation between the alpha<sub>1</sub>-antitrypsin levels and the clinical course of the infarction has not been previously discussed. Recent evidence has linked some mildly deficient phenotypes of alpha<sub>1</sub>-antitrypsin with a variety of immunological and inflammatory disorders. The disease susceptibility in phenotypes associated with reduced serum levels may be the result of alterations in lymphocyte responses, complement activation and leucocyte migration. Alpha<sub>1</sub>-antitrypsin can also influence the autolytic effects of leucocytic enzymes on tissues and may inhibit some aspects of coagulation and fibrinolysis.<sup>2</sup>

In theory, failure of alpha<sub>1</sub>-antitrypsin levels to rise would enhance damage to the myocardial wall by the proteolytic enzymes associated with the inflammatory process. A study was therefore carried out in which alpha<sub>1</sub>-antitrypsin levels in patients with acute myocardial infarction were correlated with the clinical course of the disease.

### Patients and methods

Studies were carried out using sera from 48 patients who were admitted to the intensive cardiac care unit with acute myocardial infarction. The diagnosis of acute myocardial infarction was made when at least two of the following three criteria were present: (a) typical symptoms, (b) new Q waves developed on the electrocardiograph, and (c) increased levels of the serum enzymes, creatine kinase (CK) and aspartate aminotransferase. Patients were received in the intensive cardiac care unit about four hours after the onset of symptoms, and the duration of stay in the unit ranged from two to eight days. The coronary prognostic index of Norris *et al.*<sup>7</sup> was constructed to every patient on admission. Attention was paid to the incidence of the complications of heart failure, hypotension, pericarditis, and cardiogenic shock, according to criteria previously reported.<sup>8</sup> Reinfarction was diagnosed by the development of new and severe retrosternal pain, followed by a rise in serum enzymes and dynamic electrocardiographic abnormalities. Patients who died during the first 48 hours were excluded from the study.

Two control patient groups were studied. Group A consisted of 11 patients who suffered from typical ischaemic chest pain, with ST changes on the electrocardiogram, but without evidence of myocardial infarction. (No new Q waves and normal enzymes.)

Group B included eight patients without chronic ischaemic heart disease or an acute inflammatory process. The control groups were similar in age and sex distribution to the infarction group.

#### LABORATORY STUDIES AND STATISTICS

Peripheral venous blood samples were obtained within 24 hours of admission to the intensive cardiac care unit, and were followed by morning fasting samples every 24 hours. Patients from whom fewer than two samples were obtained during the first four days were excluded from the study. Eighty per cent of the patients had four or more consecutive examinations. The clotted blood was centrifuged and the sera frozen at  $-16^{\circ}\text{C}$  until required for analysis.

Alpha<sub>1</sub>-antitrypsin levels were measured by radio-immunodiffusion by the method of Mancini, using Highland test plates. CK levels were measured by fluorometry.<sup>9</sup>

Statistical analyses were carried out using the  $\chi^2$ , Student's *t*, and multifactorial tests.

#### Results

The average serum level of alpha<sub>1</sub>-antitrypsin rose in patients with myocardial infarction, as compared with both control groups (Fig. 1). The plasma alpha<sub>1</sub>-antitrypsin level rose significantly on the fourth day ( $p < 0.01$ ) and fifth day after infarction ( $p < 0.001$ ). Among the patients with acute myocardial infarction the CK curve and the alpha<sub>1</sub>-antitrypsin curve moved

in opposite directions. The CK curve moved towards normal values when the alpha<sub>1</sub>-antitrypsin curve started to rise (Fig. 2).

In order to assess the possible association between alpha<sub>1</sub>-antitrypsin levels and clinical complications, the patients with myocardial infarction were divided into two groups, according to the highest alpha<sub>1</sub>-antitrypsin levels attained during any of the four days after the acute event. Each of the 23 patients in group 1 had at least one value greater than 350 mg/100 ml. Group 2 (25 patients) did not show any values greater than 350 mg/100 ml. This was chosen as a rough upper limit of healthy adults in our laboratory.

As shown in Fig. 3, all values in group 1 were, on the average, significantly higher than those of group 2 ( $p < 0.001$ ). Group 2 began with lower values of alpha<sub>1</sub>-antitrypsin and showed little if any rise during the subsequent five days. Group 2 levels, however, were the same as those in the control group (Fig. 1 and 2).

Complications after myocardial infarction in the two groups are shown in the Table. Cardiogenic shock and a late (after 48 hours) fatal outcome of myocardial infarction were significantly more likely to occur in group 2, which was characterised by failure to raise the alpha<sub>1</sub>-antitrypsin level. On the other hand, reinfarction was more likely to occur in group 1.

It is of interest that six out of seven patients with reinfarction showed a significant fall ( $p < 0.01$ ) in alpha<sub>1</sub>-antitrypsin levels during the first 24 hours after

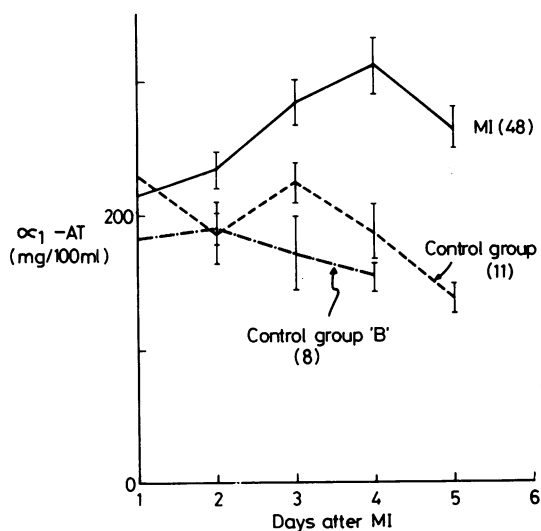


Fig. 1 Daily levels of alpha<sub>1</sub>-antitrypsin after myocardial infarction and in control subjects. Vertical lines in this and other graphs represent standard error of the mean.

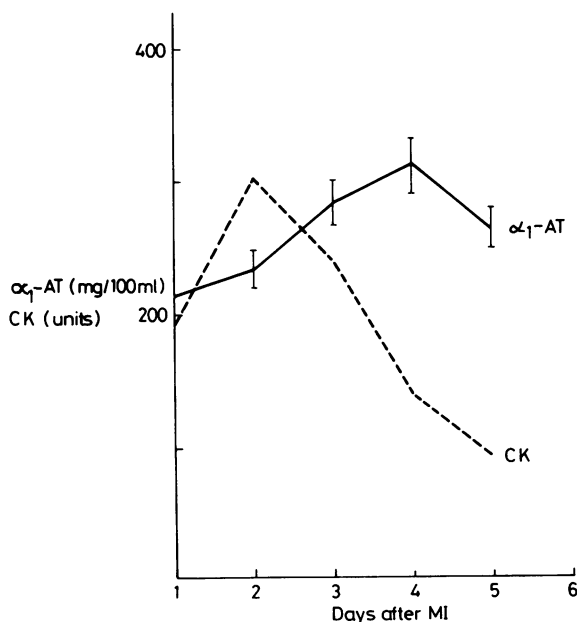


Fig. 2 Daily levels of alpha<sub>1</sub>-antitrypsin and CK after myocardial infarction.

Table Complications after acute myocardial infarction in patient groups with higher or lower than 350 mg/100 ml  $\alpha_1$ -antitrypsin serum levels

Patient group	No.	Pericarditis	Congestive heart failure	Reinfarction	Cardiogenic shock	Death
Alpha <sub>1</sub> -antitrypsin >350 mg/100 ml	(23)	(9)	(13)	(6)	(0)	(0)
Alpha <sub>1</sub> -antitrypsin <350 mg/100 ml	(25)	(5)	(14)	(1)	(4)	(5)
Statistical significance		*NS	*NS	p<0.05	p<0.05	p<0.01

\*Not significant.

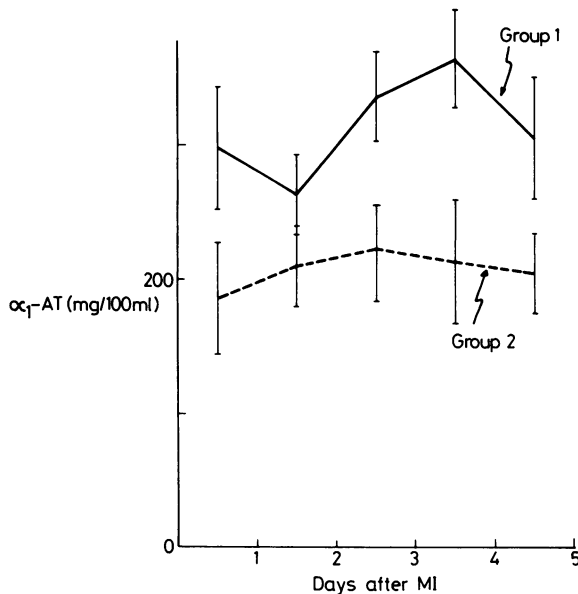


Fig. 3 Alpha<sub>1</sub>-antitrypsin in high level group 1 (heavy line) and low level group (dotted line). See text for definition of the two patient subgroups.

the new ischaemic event, followed by a quick rise to previous levels (Fig. 4).

## Discussion

Our study supports previous observations<sup>5,6</sup> showing that myocardial necrosis may be followed by a rise in the blood levels of alpha<sub>1</sub>-antitrypsin. When our patients with myocardial infarction were grouped according to the maximum level of alpha<sub>1</sub>-antitrypsin reached during the acute phase, some interesting features became evident. About half of the patients (25 out of 48) showed a relatively small rise above the normal range, and of these, 11 patients did not show any rise at all.

Observations of the clinical course of patients with

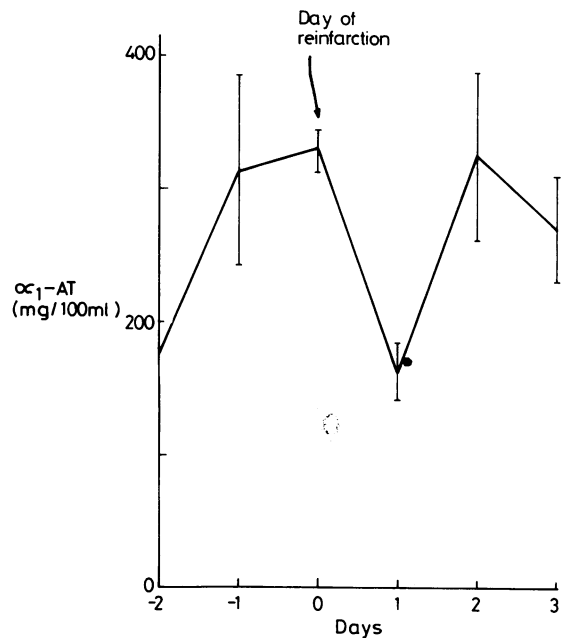


Fig. 4 Alpha<sub>1</sub>-antitrypsin levels after reinfarction. Results are the SE mean for seven patients with reinfarction.

myocardial infarction in the present study indicate that cardiogenic shock and mortality are more likely to occur in those patients who failed to raise their alpha<sub>1</sub>-antitrypsin levels.

Congenital deficiency of alpha<sub>1</sub>-antitrypsin is known to be associated with hepatic or lung damage.<sup>10-12</sup> The heart can, however, be damaged if alpha<sub>1</sub>-antitrypsin is deficient as shown by the development of congestive cardiomyopathy in turkeys suffering from congenital deficiency of alpha<sub>1</sub>-antitrypsin ("round heart disease").<sup>13</sup>

One case of possible association between this deficiency and congestive cardiomyopathy in man has been described.<sup>14</sup>

Under what circumstances might an acute myo-

cardial infarction be associated with a failure to raise the blood levels of alpha<sub>1</sub>-antitrypsin? Three possibilities may be suggested: (1) a small infarct may be unable to trigger the acute phase response; (2) a very large infarct may consume significant quantities of circulating alpha<sub>1</sub>-antitrypsin; and (3) the anti-inflammatory system may fail to respond to the stimulus of the infarct.

The first possibility can be easily ruled out, if we take into consideration the high CK levels and the worse clinical course among patients in the group with low alpha<sub>1</sub>-antitrypsin values. Our data do not indicate which of the remaining two possibilities is correct or whether both are. On the one hand, the fall and subsequent rapid rise in the blood levels of alpha<sub>1</sub>-antitrypsin observed in six out of the seven patients in whom a reinfarction developed, strongly suggest that consumption of the circulating inhibitor occurs and support the possibility that large necrotic areas may consume more alpha<sub>1</sub>-antitrypsin and in this way contribute to lowering of the blood level.

On the other hand, the possibility that large necrotic areas are not the cause, but are the result of a defective activation of the anti-inflammatory system is suggested by the finding of similar CK levels among the two groups and the distribution of patients in groups of similar coronary prognostic index scores on admission. This second possibility is further supported by pathological<sup>15</sup> and clinical<sup>16</sup> observations suggesting that the most common cause of mortality or poor clinical course in patients with acute myocardial infarction is the "expansion" of the necrotic area.

Hutchins and Bulkley<sup>15</sup> defined "expansion" as a dilatation and thinning of the area of infarction not accompanied by new necrotic areas, and explained the dilatation and thinning as the result of stretching and disruption of necrotic muscle cells at sites where acute inflammatory cells are disintegrating and reparative responses are minimal. The concept of "expansion" of the necrotic area suggests that the course of a myocardial infarction is determined not only by the severity of the ischaemic event but also by the "acute phase reaction" mechanism. Alpha<sub>1</sub>-antitrypsin appears to be an important regulatory protein involved in the suppression of immunological and inflammatory reactions. Patients with deficient response or deficient phenotypes or both, are likely to have abnormal regulation of the reparative process with a propensity to defective response of the anti-inflammatory mechanism.<sup>2</sup> A defective response of the anti-inflammatory mechanism, manifested in our patients by a failure to increase the alpha<sub>1</sub>-antitrypsin levels, may predispose expansion of the necrotic area, and in this way, be a more hazardous clinical course.

We suggest that a failure of alpha<sub>1</sub>-antitrypsin serum levels to rise during the acute phase of myocardial

infarction predicts a worse clinical course of the ischaemic event. This may be the result of initially large necrotic areas or of a defective response of the "acute phase reaction" mechanism. Further studies are necessary to clarify the role played by the anti-inflammatory system in the prognosis of a patient with an acute myocardial infarction.

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