Changes in protease inhibitors after acute myocardial infarction

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SYNOPSIS  Plasma levels of fibrinogen, α1-antitrypsin, α2-macroglobulin, antithrombin III, and Cl inactivator were measured serially for 10 days in 11 patients after acute myocardial infarction. Both fibrinogen and α1-antitrypsin rose markedly to reach peak levels 5-7 days after infarction while Cl inactivator levels rose slowly with the highest observed mean level on the 10th postinfarction day. Neither antithrombin III nor α2-macroglobulin changed significantly after myocardial infarction. No relationship between Cl inactivator levels and either fibrinogen or α1-antitrypsin was found in a study of 30 patients with a variety of disorders while fibrinogen and α1-antitrypsin levels were significantly correlated.

Myocardial infarction is followed by changes in a number of serum proteins including components of the haemostatic mechanism: an increase in the level of antiplasmin activity in the immediate postinfarction period has been described by a number of investigators (Bennett et al, 1967; Tsitouris et al, 1967). Four protease inhibitors have been established as having antiplasmin activity—α2-macroglobulin (Ganrot, 1967), α1-antitrypsin (Rimon et al, 1966), antithrombin III (Highsmith and Rosenberg, 1974), and Cl inactivator (Ratnoff et al, 1969). We report a study of the changes in these protease inhibitors and fibrinogen over the days following acute myocardial infarction.

Methods

α2-Macroglobulin, α1-antitrypsin, antithrombin III, and Cl inactivator levels were measured by single radial immunodiffusion (Mancini et al, 1965) using reagents obtained from Hoechst Pharmaceuticals, Hounslow, Middlesex. Standard Human Serum, Stabilized and Protein Standard Plasma, both obtained from Hoechst Pharmaceuticals, were used for standardization of α2-macroglobulin and of α1-antitrypsin and antithrombin III immunoplates respectively. For the standardization of Cl inactivator a plasma pool from 20 healthy young men was taken as 100%.

Fibrinogen was assayed in plasma by the method of Ratnoff and Menzie (1951) as modified by Ogston and Ogston (1966).

Patients

Eleven men aged 36 to 63 (mean 50) years who had sustained a myocardial infarction and did not subsequently develop a deep-vein thrombosis were studied. The diagnosis was established by unequivocal electrocardiographic appearances together with serial changes in the serum aspartate aminotransferase level. The initial venous blood sample was obtained within 24 hours of the onset of symptoms of infarction (day 1), and further samples were withdrawn on days 2, 3, 5, 6 to 8, and 10. All patients received 100 μCi 125I-fibrinogen intravenously 5 to 12 hours after admission for the detection of deep venous thrombosis using the criteria of Kakkar et al (1970). Those patients who developed a deep-vein thrombosis were excluded from the study.

A further 30 patients were selected for measurement of their plasma level of fibrinogen, α1-antitrypsin, and Cl inactivator. A few had no detectable abnormality, and the remainder were suffering from a variety of infective, neoplastic, and degenerative diseases.

Results

After myocardial infarction the mean plasma fibrinogen concentration rose to approximately twice the initial level, reaching a peak on day 7. In some patients the peak level was reached by day 5, in others as late as day 10. α1-Antitrypsin levels showed almost parallel changes (figure) with the highest mean level on day 5 after infarction. In con-
contrast, the Cl inactivator level fell until day 3, this fall being followed by a progressive increase, the highest mean level being found on the 10th post-myocardial infarction day. Further assays beyond that time were not made. The $\alpha_2$-macroglobulin level did not alter significantly and showed no trend in the postinfarction period. While the mean antithrombin III concentration showed a small fall from the initial reading on day 1, none of the differences from that level reached statistical significance.

Thirty patients with a variety of disorders had a single assay of their plasma fibrinogen, $\alpha_1$-antitrypsin, and Cl inactivator. The correlation between fibrinogen and $\alpha_1$-antitrypsin levels ($r = + 0.7099$) was highly significant ($p < 0.001$), while neither that between Cl inactivator and fibrinogen ($r = + 0.2141$) nor that between Cl inactivator and $\alpha_1$-antitrypsin ($r = + 0.2912$) reached statistical significance ($p > 0.1$).

Discussion

During the course of a variety of disease processes and after injury alterations occur in a number of serum proteins; these have been termed acute phase reactants (Kelley, 1952) and include fibrinogen, $\alpha_1$-antitrypsin, and ceruloplasmin. An acute phase reaction occurs after myocardial infarction; the changes in fibrinogen are well documented (Meyers, 1948; Losner et al, 1954; Bennett et al, 1967), and a rise in $\alpha_1$-antitrypsin has also been observed (Bachmann et al, 1968).

In the present study we have confirmed the marked rise in both fibrinogen and $\alpha_1$-antitrypsin in the days following a myocardial infarction and have examined the changes in other plasma protease inhibitors. In contrast to the finding of McBean et al (1974), we found no increase in the level of $\alpha_2$-macroglobulin in the immediate postinfarction period. It has been claimed that antithrombin III levels are reduced after thrombotic episodes, including myocardial infarction (von Kaula and von Kaula, 1967), as a result of consumption. Our results show a decline after infarction although none of the differences from the initial postinfarction reading was significant. Cl inactivator, an $\alpha_2$-neuraminoglycoprotein, has inhibitory activity on
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Cl esterase and a number of components of the coagulation and fibrinolytic systems including plasmin, activated factor XII, and activated factor XI. Levels of Cl inactivator in disease states other than hereditary angioedema have received little attention. However, Donaldson (1966) observed a rise in the inhibitor level in acute rheumatic fever, a disorder associated with a rise in acute phase reactants. We have noted a rise in Cl inactivator levels after myocardial infarction, but the time scale of the changes differs from those in α₁-antitrypsin and fibrinogen levels (figure). Further, in a study of patients with a variety of diseases a high positive correlation between fibrinogen and α₁-antitrypsin was detected but no correlation was found between Cl inactivator and either fibrinogen or α₁-antitrypsin levels. We concluded that although Cl inactivator levels rise markedly after acute myocardial infarction, the behaviour of this protein does not follow the pattern of changes observed in acute phase reactant proteins.

The significance of changes in protease inhibitors after myocardial infarction is not clear. The changes in α₁-antitrypsin closely parallel those of total antiplasmin activity after an infarction, suggesting that this inhibitor is principally responsible for the rise in antiplasmin activity in this situation. It is possible that the rises in α₁-antitrypsin and fibrinogen might contribute to the increased liability to venous thrombosis after a myocardial infarction.

References


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