Plasma Fibrinogen Levels as an Indicator of Myocardial Necrosis

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The diagnosis of acute myocardial necrosis has important therapeutic and prognostic implications, but classical electrocardiographic and enzymatic criteria for its diagnosis are relatively insensitive[1,2]. Isotopic techniques, particularly the heart scan with technetium 99m pyrophosphate (Tc 99m PYP), have proved to be sensitive and specific methods of detecting the presence and the localisation of myocardial necrosis[3-7]. Practical limitations of heart scanning are that the equipment required is sophisticated and expensive and cannot always be brought to the patient's bedside.

The plasma fibrinogen level is known to be a sensitive indicator of tissue necrosis in general[8] and myocardial necrosis in particular[9-11]. Since this parameter can be easily measured, we decided to investigate whether monitoring of the plasma fibrinogen level could predict the results of the heart scan and thus be used to discriminate between myocardial ischaemia and necrosis.

Methods

Patients were included in the study if they fulfilled the following criteria:

1. Admission to the coronary care unit with a typical history of ischaemic retrosternal pain lasting for more than half an hour, occurring within the previous 24 hours.
2. Dynamic ST-T changes developed in subsequent electrocardiograms.
3. Failure to develop pathological Q waves in the ECG or to have a significant rise in the serum level of cardiac enzymes (SGOT, CPK and LDH) on at least three consecutive days following admission.

Patients with a history of myocardial infarction, surgery or infection within the preceding three months were excluded from the study.

In patients admitted to the study, the plasma fibrinogen level was measured within 24 hours of the onset of symptoms, and repeated on the second and third days following admission, between the fifth to seventh day, and after 14 days. Plasma fibrinogen level was determined by the nephelometric method[12]. The upper limit of normality for our laboratory (400 mg/100 ml) is similar to previously reported values[11,13].

According to the plasma fibrinogen levels found, curves were constructed for each patient. Three different types of curves were identified:

Type A—All measurements of fibrinogen below 500 mg/100 ml.

Type B—An increase of more than 100 mg/100 ml between any two measurements and a peak of over 500 mg/100 ml.

Type C—A flat curve but fibrinogen values higher than 500 mg/100 ml.

Type A was considered the normal fibrinogen profile. Types B and C were considered pathological curves.

Cardiac scan was performed between two and four days after admission in all the patients, and repeated where technical quality of the scan or doubt about interpretation were present. Tc 99m PYP (15-20 cc) was administered intravenously and heart scan was performed 90-120 minutes after the injection. Imaging was obtained in the anterior, 45° left anterior oblique, and left lateral views, using a CEI gamma camera with a computerised Dycomette (Elscint). Visual assessment of the presence, localisation, and intensity of abnormal cardiac uptake was made by two independent observers, and the findings were scored according to the following criteria:

0 no uptake or uptake less than the ribs or due to blood pooling.
1 diffuse uptake—myocardial uptake exceeding uptake over the right hemithorax and less intense than the sternum.
2 focal uptake—focal abnormality less, equal to or more intense than the sternum.

This is a simplified version of the groupings described by other classifications. We have considered an uptake of intensity of 2+ or greater (of other classifications), whether diffuse or fixed, to be pathological.

Since an abnormal diffuse scan has been most often associated with apparent false positive results, its inclusion as abnormal was expected to increase the false

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positives in this study. This would more stringently test any correlation between heart scan and fibrinogen data. Patients showing a diffuse uptake were also considered separately.

The clinical course of the disease reported in this study is from a six-month follow-up of all patients.

Results

During a six month period (from January to July 1979) 42 patients who entered the coronary care unit fulfilled the criteria for inclusion in the study, 32 being men and 10 women, with a mean age of 59 years (range 21-85 years). The mean arrival time in the coronary care unit was $4\frac{1}{2}$ hours from the onset of chest pain. In 37 of the patients this chest pain was the only presenting symptom. In the other 5 patients, 3 also had symptoms of pulmonary oedema, and 2 had syncope.

The fibrinogen plasma levels were plotted as curves for individual patients (Fig. 1). Twenty-one patients showed

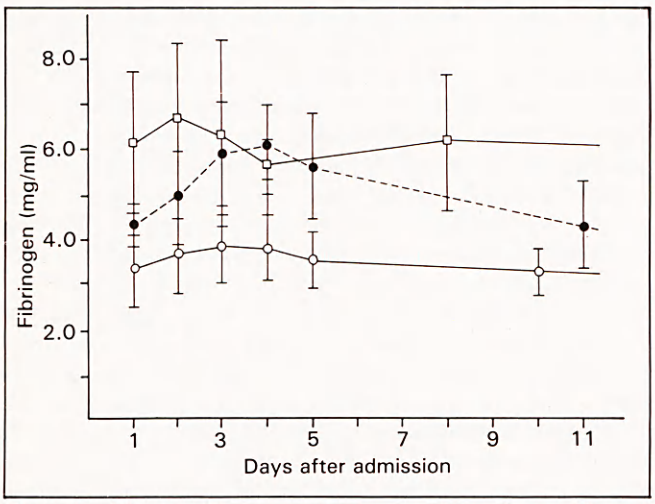

Fig. 1. *Plasma fibrinogen levels in 42 patients. Normal fibrinogen curve Type A (21 patients)* o——o. *Abnormal fibrinogen curve Type B (15 patients)* •-----•, *Type C (6 patients)* □------□.

normal values and a flat curve (Type A), the mean value on the first day being 337 mg/100 ml ± 81 mg/100 ml. Fifteen patients showed a Type B curve with a mean on the first day of 477 mg/100 ml ± 81 mg/100 ml. The average peak was 620 mg/100 ml ± 80 mg/100 ml. The remaining 6 patients showed a Type C curve with an average on the first day of 618 mg/100 ml ± 151 mg/100 ml.

The Tc 99m PYP heart scan was normal in 24 patients (57 per cent). In 18 (43 per cent), pathological findings were seen: diffuse 5, focal 12 and false positive 1, the last being so because of concentration of the abnormal uptake in the thoracic wall following electrical cardioversion.

The mean age, sex distribution, and presence of ischaemic and associated diseases were compared in the different sub-sets. These were similar when divided according to fibrinogen data or heart scan.

The correlation between the heart scan and the fibrinogen curve is shown in Table 1. The reliability of the fibrinogen data to predict a normal heart scan was 95 per cent (20 of 21), and for an abnormal heart scan was 81 per cent (17 of 21).

Table 1. Correlation between fibrinogen curve and Tc 99m PYP heart scan in 42 patients.

Fibrinogen curve (as defined in text)	Tc 99m Heart Scan			
	Normal	Abnormal		
		Diffuse	Focal	False positive
Type A 21 patients	20	1	-	-
Type B 15 patients	3	3	8	1
Type C 6 patients	1	1	4	-

The findings on six-month follow-up of the 42 patients are shown in Table 2. All 42 patients were discharged from hospital, 21 with a normal fibrinogen Type A curve, of whom two (9.5 per cent) later showed complications. One underwent coronary surgery because of unstable angina and one died after four months from an acute myocardial infarction. Of 15 patients with an abnormal fibrinogen Type B curve 5 (33.3 per cent) developed complications. One had recurrent pulmonary oedema, one underwent coronary surgery for unstable angina, two developed an acute myocardial infarction (of whom one died) and a further patient died suddenly outside hospital. Of six patients with an abnormal fibrinogen Type C curve five (83.3 per cent) developed complications; two had coronary surgery for unstable angina, and three had a recurrent myocardial infarction from which two died.

Table 2. Clinical course—6 months' post AMI.

Fibrinogen curve	No. of Patients	Heart Scan		Complications* No. of Patients	Unstable Angina	Myocardial Infarction	Pulmonary Oedema	Death
Type A	21	Normal	20	2	1	1	-	1
		Abnormal	1	-	-	-	-	-
Type B	15	Normal	3	1	-	-	1	-
		Abnormal	12	4	1	2	-	2
Type C	6	Normal	1	1	1	-	-	-
		Abnormal	5	4	1	3	-	2

*An individual may have more than 1 complication

Discussion

Patients presenting with typical ischaemic pain and in whom the ECG showed only ST-T changes and a normal profile of cardiac enzymes, represent an ill-defined group within the clinical spectrum of acute coronary heart disease. This group has been identified as possible myocardial infarction, acute coronary insufficiency, unstable angina, intermediate syndrome or prolonged myocardial ischaemia[14-17]. This confused nomenclature illustrates the difficulty in accurately differentiating between transient ischaemia and myocardial necrosis.

Studies with Tc 99m PYP have shown in this group an incidence of positive heart scanning ranging from 8-42 per cent[18-21], a range so wide that it has prompted much discussion as to whether the scan gives false positive results or really demonstrates the presence of myocardial necrosis under-diagnosed by conventional methods. Clinical, pathological and experimental studies[7,21] strongly support the thesis that the Tc 99m PYP is a very sensitive detector of myocardial necrosis and, if well-recognised causes of false positive results are clinically excluded, the incidence of a false positive heart scan is very low[21].

Elevation of plasma levels of fibrinogen is seen in response to a variety of stimuli, including tissue damage. Among 242 reported cases of myocardial infarction in whom the fibrinogen level was monitored, only 2 cases failed to show a two- to threefold rise in the three to six days following the acute event[10-13].

In the present study, the plasma fibrinogen level has been correlated with the results of the heart scan. Of the 21 patients who had a normal fibrinogen curve after ischaemic pain, 20 also had a normal heart scan. In the remaining patient a diffuse type of Tc 99m PYP uptake was seen.

Of the 21 patients with an abnormal fibrinogen curve, 16 showed abnormalities on heart scan, 12 of the focal type and 4 of the diffuse type. In the other 5 patients, the abnormal fibrinogen curve did not correlate with the heart scan, as the Technetium uptake did not suggest myocardial necrosis. But in 4 of these 5 patients there was a possible explanation for the abnormal fibrinogen curve; two had undergone electrical cardioversion immediately before admission (in one the scan showed a false positive due to abnormal isotope uptake over the chest wall); one was admitted with pulmonary oedema, and one had recurrent prolonged episodes of chest pain in the month before admission.

Clinical follow-up showed a more benign medium-term prognosis among patients with a normal fibrinogen curve (Type A). Four of the five patients whose scan was of the diffuse type had abnormal fibrinogen curves.

These findings support previous observations[7,21] and reinforce the view that the diffuse pattern of Tc 99m PYP uptake does represent a pathological finding in the majority of such patients.

The sub-group of six patients with persistently elevated plasma fibrinogen was particularly interesting; five had an abnormal heart scan and five had a stormy clinical course (Tables 1 and 2). High plasma fibrinogen levels were found in four patients during subsequent repeat hospitalisations because of acute complications. The diagnostic and prognostic implications of a persistently elevated plasma fibrinogen level are not clear.

In the present study, 16 of 42 patients (38 per cent) admitted to the coronary care unit with prolonged ischaemic pain had myocardial necrosis, as shown by the heart scan. This is within the expected proportion for this group of patients[20,21]. Our results showed that, in the majority of patients presenting with typical ischaemic pain, the presence of myocardial necrosis can be identified by nephelometric monitoring of plasma fibrinogen levels. The plasma fibrinogen level is a sensitive, but non-specific, indicator of the presence of myocardial necrosis. It correlates with isotopic heart scan and has the merits of being cheap and easily available.

References

1. Rosenberg, B. A., and Malach, M. (1960) *American Journal of Cardiology,* **6,** 272.
2. Melichor, F., Jedlicka, V. and Houlik, L. (1963) *Acta Medica Scandinavica,* **174,** 761.
3. Bonte, F. L., Parkey, R. W., Graham, K. D., Moore, J. and Stokely, E. M. (1974) *Radiology,* **110,** 473.
4. Bruno, F. P., Cobb, F. R., Rives, F. and Goodrich, J. K. (1976) *Circulation,* **54,** 74.
5. Okada, R., Woolfendin, J. M., Roessler, K. L., Groves, B. M. and Markus, F. I. (1977) *Cardiology,* **62,** 305.
6. Holman, B. L., Chisholm, R. L. and Brouwald, E. (1978) *Circulation,* **57,** 320.
7. Poliner, L. R., Buje, M. L., Parkey, R. W., Bonte, F. J. and Willerson, S. T. (1979) ibid., **59,** 257.
8. Innes, D. and Sewitt, S. (1964) *Journal of Clinical Pathology,* **17,** 13.
9. Losner, S., Volk, B. W. and Wilensky, N. D. (1954) *Archives of Internal Medicine,* **93,** 231.
10. Myers, L. (1948) ibid., **82,** 419.
11. Fulton, R. M. and Duckett, K. (1976) *Lancet,* **2,** 1161.
12. Rice, E. W. and Muesse, D. E. R. (1972) *Clinical Chemistry,* **18,** No. 1, 73.
13. Cotton, R. C., Bloor, K. and Archibald, G. (1972) *Atherosclerosis,* **16,** 332.
14. Nomenclature and criteria for diagnosis of ischaemic heart disease. Special Report (1979) *Circulation,* **53,** 607.
15. Krauss, K. R., Hutter, A. M. and De Sanitis, R. W. (1972) *Archives of Internal Medicine,* **129,** 808.
16. Scheidt, S., Wolk, M. and Killip, Th. (1976) *American Journal of Medicine,* **60,** 409.
17. Bertolosi, C. A., Tronge, S. E., Ricitelli, M. A., Vileomagis, R. M. and Zuffardi, E. (1976) *Chest,* **70,** 596.
18. Abdulla, A. M., Coneda, M. I., Cortez, B. C., McGinnis, K. D. and Wilhelm, S. K. (1976) ibid., **69,** 168.
19. Welsh, W. F., Keruneretane, H. B., Resneko, L., Fill, H. R. and Harper, P. V. (1977) *British Heart Journal,* **39,** 974.
20. Lessem, J., Johansson, B. W., Nosslin, B. and Thorell, S. (1978) *Acta Medica Scandinavica,* **203,** 491.
21. Jaffe, A. S., Klein, M. S., Patel, B. R., Siegel, B. A. and Roberts, R. (1979) *American Journal of Cardiology,* **44,** 61, 1035.