Plasma ^{125}I -labelled fibrinogen clearance in diagnosis of deep venous thrombosis after myocardial infarction

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Plasma ^{125}I -labelled fibrinogen clearance has been determined in 72 patients with myocardial infarction. No significant variation in clearance rates was observed whether or not deep venous thrombosis of the legs occurred. It is suggested that ^{125}I -labelled fibrinogen clearance from the plasma is influenced by the degree of fibrinogen accumulation in the heart and by the degree of stability of the ^{125}I binding to the fibrinogen, rather than by the presence of deep venous thrombosis of the legs.

The use of ^{125}I -labelled fibrinogen in the detection of deep venous thrombosis of the legs has now been established (Negus *et al.*, 1968).

The method involves the detection of increased radioactivity at the site of the thrombus demonstrated by counting apparatus which successively records the radioactivity at several points on both legs. It is assumed that ^{125}I -labelled fibrinogen injected intravenously at the start of a study joins the vascular fibrinogen pool and, thereafter, behaves similarly to endogenous fibrinogen (McFarlane, 1957). Using this method, deep vein thrombosis has been found to occur in approximately 30 per cent of postoperative patients (Negus *et al.*, 1968) and in a similar percentage of patients after myocardial infarction (Nicolaidis *et al.*, 1971; Murray *et al.*, 1970).

The standard technique is time consuming, and in an attempt to simplify the technique Jeyasingh *et al.* (1970) measured the decline in radioactivity in the blood over a number of days in 14 patients after operation or myocardial infarction. They concluded that an increased rate of decline, or increased plasma clearance, occurred in patients who developed deep vein thrombosis, and that this was observable before any increase in leg counts occurred. Thus, it seemed likely that study of ^{125}I -labelled fibrinogen clearance curves in

the blood or plasma would detect deep vein thrombosis, both more simply and earlier, enabling the method to be more generally applied to screen patients in circumstances known to be associated with a high incidence of deep vein thrombosis.

An objection to the above conclusion lies in the possibility that any increased rate of fall in blood radioactivity may be associated also with consumption of fibrinogen at the site of operation or in the heart after myocardial infarction. If such consumption occurs to any extent the rate of fall in blood radioactivity so caused may overshadow any changes due to deep vein thrombosis. This possibility has been studied in patients with myocardial infarction. The plasma ^{125}I -labelled fibrinogen clearance rates have been compared with leg counting measurements and the degree of accumulation of fibrinogen in the heart estimated. Urinary excretion of ^{125}I has also been measured.

Materials, patients, and methods

Seventy-seven patients were selected for study. All were admitted to the coronary care ward at Bradford Royal Infirmary. Admission procedures and patient management details have been described previously (Reynell, 1969). Selection for study depended on two factors; the availability of ^{125}I -labelled fibrinogen and the high probability that myocardial infarction had occurred. The admitting officers assessed the clinical features and the admission electrocardiogram of the patient. If a diagnosis of myocardial infarction was certain or probable, potassium iodide 100 mg was given orally and 50 mg was subsequently

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given twice daily for 28 days in order to block the thyroid uptake of ^{125}I . Marks at 9 cm intervals were made on each leg along a line from the medial malleolus to the intersection of the femoral vein and inguinal ligament.

Next morning, after explanation and with the patient's permission, an intravenous injection of approximately 100 μCi ^{125}I -labelled fibrinogen was given. Thirty to sixty minutes after injection 10 ml blood was taken into citrate from a vein other than that injected with ^{125}I -labelled fibrinogen. At about the same time counts were taken at the mark points on the legs with a collimated NaI(Tl) crystal 1 mm thick by 3.8 cm diameter with photomultiplier tube and associated electronics including a pulse height analyser. These counts were compared with the average of three or four praecordial counts. Blood samples were collected and leg and praecordial measurements made daily for 10 days with the exception of Sundays when only blood samples were taken. Counting times were either 20, 40, or 80 seconds depending on the count rate.

The counts over each leg mark were expressed as a percentage of the mean praecordial count for that day, this being referred to as percentage uptake. A difference of more than 15 per cent lasting more than 24 hours between adjacent points on a leg or between identical points on each leg was taken to indicate the development of venous thrombosis (Jeyasingh *et al.*, 1970).

Blood samples were centrifuged and the radioactivity of 2 ml aliquots of plasma measured in a well scintillation counter. The radioactivity was corrected for decay and expressed as a percentage of the initial blood sample. Plasma radioactivity clearance curves were drawn for each patient. Daily praecordial counts were treated in a similar fashion; the first post-injection praecordial count being taken as 100 per cent. These daily values are hereafter referred to as 'plasma percentages' or 'praecordial percentages'.

Urine collections were made for 24 hours in 40 patients and for 10 days in 24 of these, the usual difficulties of continued collection being experienced. Aliquots of 3 ml were measured in a well scintillation counter, the volume excreted was measured, and the total activity in μCi calculated. In 14 patients a 10 per cent standard of the administered dose was retained and for these the activity excreted was calculated as a percentage of this administered dose.

Patients were assessed later to confirm or refute the diagnosis of myocardial infarction. The diagnosis was not made unless characteristic electrocardiographic abnormalities and a rise in serum enzymes occurred. Of the 77 patients initially included in the study, 5 were rejected as not fulfilling the above diagnostic criteria. Data obtained from these 5 patients do not appear in the results.

Anticoagulants were not used routinely in patients. Some of the patients who developed venous thrombosis in the legs or who developed features suggesting mural thrombosis in the heart were then anticoagulated with heparin and warfarin sodium.

FIG. 1 Mean plasma clearance curves of ^{125}I . Patients with deep vein thrombosis compared with normals. - - - - no deep vein thrombosis; — deep vein thrombosis.

TABLE I Percentage plasma clearance of ^{125}I . Means, standard deviations, and values of 't' for daily percentage of initial plasma samples for patients with and without deep vein thrombosis

Days	Deep vein thrombosis		No deep vein thrombosis		t
	Mean	SD	Mean	SD	
0	100	—	100	—	—
1	51.7	13.3	53.2	11.8	0.5
2	35.0	11.3	39.0	10.3	1.4
3	25.7	9.9	27.9	8.7	0.9
4	20.0	8.8	22.1	8.2	0.9
5	16.3	7.7	17.7	6.4	0.8
6	13.7	6.6	14.4	5.6	0.4
7	11.2	5.6	12.0	4.9	1.8
8	9.5	5.3	10.1	3.9	0.4
9	7.5	4.4	8.5	3.4	1.0
10	6.5	4.1	7.7	2.9	1.2

Results

Of the 72 patients considered, 20 were shown by limb counting to develop a deep vein thrombosis in the leg. This incidence of 28 per cent compares with that found in previous studies (Nicolaidis *et al.*, 1971; Murray *et al.*, 1970) which reported findings on smaller numbers of patients.

Fig. 1 and Table 1 demonstrate the fall in radioactivity in the plasma of patients with and without evidence of deep vein thrombosis of the legs. It can be seen that the means of plasma ^{125}I -labelled fibrinogen clearance are very similar whether or not deep vein thrombosis occurs in the legs. The standard deviations are large, indicating considerable overlap between the two groups.

The plasma ^{125}I -labelled fibrinogen clearance curve was compared in all patients with the praecordial or heart ^{125}I -labelled fibrinogen clearance curve. If there is no accumulation of fibrinogen in the heart, these two curves should be identical, the praecordial radioactivity being merely a reflection of blood radioactivity. In all but 5 patients the daily praecordial percentage was greater than the daily plasma percentage, indicating that an accumulation of fibrinogen was occurring in the heart. In 4 of the 5 patients the percentage radioactivity in excess in the plasma was marginal and within the experimental limits of the study.

Fig. 2 and Table 2 show the mean and standard deviation of the praecordial percentage minus the plasma percentage for each day. The patients are divided into two groups, those with and those without deep vein thrombosis. Though the patients with deep vein thrombosis tended to have lower values, statistically there was no significant difference between the two groups for any particular day.

On the basis of the difference between heart and plasma percentage, patients were put into two groups, those with differences of greater than 25 per cent on the second day and those with less than 25 per cent. These groups were designated major and minor heart accumulators respectively. Fig. 3 and Table 3 show the mean and standard deviation of the plasma ^{125}I clearance curves for these two groups. It can be seen that major heart accumulation is associated with greater rates of plasma ^{125}I clearance. Using *t*-tests it was shown that for each day a significant difference existed between the two groups.

Urinary excretion of ^{125}I over the first 24 hours after injection was measured in 40 patients. The mean excretion was 20 μCi

FIG. 2 Change of heart accumulation of ^{125}I fibrinogen in patients with and without deep vein thrombosis. For key, see Fig. 1.

TABLE 2 Means, standard deviations, and values of '*t*' for daily differences between percentage of initial heart count and percentage of initial plasma samples in patients with and without deep vein thrombosis

Days	Deep vein thrombosis		No deep vein thrombosis		<i>t</i>
	Mean	SD	Mean	SD	
0	0	—	0	—	—
1	25.3	19.4	26.6	27.0	0.2
2	24.3	15.3	27.3	33.0	0.5
3	23.2	17.4	25.8	24.6	0.9
4	22.3	16.2	22.2	20.9	0.5
5	17.1	12.7	19.4	18.5	0.4
6	13.2	10.9	16.7	15.1	0.9
7	12.6	11.6	14.4	13.8	0.5
8	10.6	10.0	12.0	11.9	0.4
9	8.6	8.2	10.7	10.8	1.0
10	6.3	4.6	10.0	10.3	1.3

(27% of the given dose in those patients where a standard was retained). Considerable individual variation was observed, the standard deviation being 17 μCi (13%). In the 24 patients in whom 10-day urine collections were made the mean total excretion was 92 μCi (94%), standard deviation 29 μCi (17%). Patients were then divided into two groups, those who excreted more than 20 μCi ^{125}I in the first 24 hours after injection and those who excreted less than 20 μCi . The plasma ^{125}I clearances of these two groups are shown in Fig. 4 and Table 4. On each day there was a difference between the groups; some of these differences were found not to be significant on t-testing.

Discussion

The first object of this study was to decide whether, after myocardial infarction, the presence or absence of a deep vein thrombosis can be inferred from examination of the slope of the plasma clearance of ^{125}I -labelled fibrinogen.

When deep vein thrombosis occurs endogenous and ^{125}I -bound exogenous fibrinogen will be consumed locally in the thrombotic process. The increased removal of fibrinogen from the blood under such circumstances should be indicated by a steep decline in plasma radioactivity. Fig. 1 shows that the mean and standard deviation of clearance from plasma of ^{125}I -labelled fibrinogen in the 72 patients studied are similar whether or not deep vein thrombosis has occurred in the legs.

It seemed possible that the plasma ^{125}I -labelled fibrinogen clearance could also be dependent on other factors and that changes so caused might mask changes in clearance after deep vein thrombosis. The possibility that, after myocardial infarction, fibrinogen is consumed in the heart has been investigated.

Fig. 2 shows that in the great majority of patients daily praecordial percentage radioactivity is greater than plasma percentage radioactivity during the 11 days after myocardial infarction. During the first 3 days the radioactive accumulation in the heart rises to a maximum. Heart accumulation is similar whether or not deep vein thrombosis has occurred.

Fig. 3 and Table 3 show that major heart accumulation is associated with a significant increase in plasma ^{125}I clearance. This effect will make its mark whether or not deep vein thrombosis has occurred and is one factor masking any changes thrombosis might have on plasma ^{125}I clearance.

^{125}I -labelled fibrinogen may accumulate in

FIG. 3 Mean plasma clearance curves of ^{125}I . Patients with major heart accumulation compared with patients with minor heart accumulation. (Major accumulation is defined as a difference on the second day of more than 25 between heart and plasma percentages, the first day's measurements in each case being taken as 100%.) — — — heart-plasma < 25 per cent; — — — heart-plasma > 25 per cent.

the heart for two reasons. It may accumulate in the infarct itself or in the overlying pericardium, being concerned with inflammatory processes taking place. Alternatively it may be present in mural thrombosis.

We have assumed that extreme fibrinogen accumulation in the heart is likely to be associated with the presence of mural thrombosis. In 4 patients the percentage radioactivity minus percentage plasma radioactivity was greater than 75 on the second day after injection. Two of these patients died and necropsy revealed extensive mural thrombus in both.

TABLE 3 Percentage plasma clearance of ^{125}I . Means, standard deviations, and values of 't' for daily percentage of initial plasma samples for patients with major* and minor heart accumulation

Days	> 25 per cent		< 25 per cent		t
	Mean	SD	Mean	SD	
0	100	—	100	—	—
1	50.7	10.3	57.2	7.4	3.0
2	33.5	7.8	41.0	7.3	4.0
3	24.3	7.3	31.3	6.8	4.0
4	18.8	7.2	24.9	5.8	3.8
5	14.5	5.3	20.5	5.2	4.5
6	12.1	4.7	16.7	4.7	3.8
7	9.9	4.0	13.9	4.0	3.8
8	8.1	3.8	11.9	3.6	3.9
9	6.8	3.5	9.7	3.0	3.5
10	5.9	3.2	8.6	2.8	3.3

* Major accumulation defined as a difference on the second day of more than 25 between heart and plasma percentages, the first day's measurements in each case being taken as 100 per cent.

The thrombus was carefully removed from the heart in one patient and was found to contain 10 per cent of the given dose of radioactivity.

It became apparent from the urinary ^{125}I excretion measurements that there was considerable variation from patient to patient and to a lesser degree from batch to batch of fibrinogen. Urine radioactivity represents free iodide and will depend to a certain extent on renal function (Regoezi, 1971) but is also affected by the stability of the binding of the ^{125}I to the fibrinogen. In one particularly poor batch (which was immediately withdrawn by the Radiochemical Centre) an excretion of 64 μCi was found in 24 hours in one patient and 13 μCi in 7 hours in another patient. The effect on plasma ^{125}I clearance was considerable, causing a very steep decline. Fig. 4 and Table 4 examine whether urinary excretion in the first 24 hours after injection of ^{125}I fibrinogen has any effect on plasma ^{125}I clearance. Greater urine excretion is seen to be associated with increased clearance when compared with lower excretion, but the daily difference in plasma percentage between the two groups is not always significant on t-testing. This lack of significant difference can partly be explained by the fact that both groups contained major heart accumulators. One effect of this is to give a wide range in plasma percentages leading, particularly in the lower urinary excretion group, to a steeper mean plasma clearance than otherwise would occur. It seems reasonable to conclude that

FIG. 4 Mean plasma clearance curves of ^{125}I . Patients grouped according to urinary excretion in μCi during the first 24 hours after injection. — — — excretion < 20 μCi ; — — — excretion > 20 μCi .

TABLE 4 Plasma clearance of ^{125}I . Means, standard deviations, and values of 't' for daily percentages of initial plasma samples for patients grouped according to urinary excretion in microcuries of ^{125}I in first 24 hours after injection

Days	< 20 μCi		> 20 μCi		t
	Mean	SD	Mean	SD	
0	100	—	100	—	—
1	49.8	10.7	59.0	8.5	2.8
2	34.2	9.4	42.1	8.2	2.7
3	25.5	9.2	32.0	8.4	2.2
4	20.1	8.6	24.9	8.0	1.7
5	15.8	6.3	18.9	6.8	1.4
6	12.5	5.3	16.4	6.0	2.0
7	10.7	4.6	13.6	6.0	1.7
8	8.9	3.9	11.5	4.8	1.8
9	7.9	3.7	9.4	4.1	1.1
10	6.6	3.0	9.2	3.8	2.0

plasma clearance may well be affected by variations in the stability of ^{125}I binding after injection into the patient whether or not fibrinogen consumption in the body is increased.

The above remarks concerning heart accumulation of fibrinogen pertain, of course, only to patients with myocardial infarction. However, it seems possible that a comparable situation is present, perhaps to a lesser extent, in postoperative patients. Excess fibrinogen consumption may occur around tissues traumatized at operation. It would be interesting to see if in a large number of postoperative patients excess plasma ^{125}I -labelled fibrinogen clearance correlated with the development of deep venous thrombosis.

It might be considered that the patients studied are, because of the means by which they were selected, not representative of the spectrum of patients with myocardial infarction. It could be argued that milder cases without clear-cut clinical features or abnormalities in their admission electrocardiogram would not be studied. Certainly patients who did not survive till the morning after admission could not be included. The hospital mortality rate for the patients studied was 12.5 per cent and this figure does not seem excessive nor does it indicate that the patients studied had more severe myocardial infarction than average patients. Even if this criticism is valid it remains true that for many patients with myocardial infarction measurement of plasma ^{125}I -labelled fibrinogen clearance is of no value in the diagnosis of deep venous thrombosis of a leg.

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