Upsala J Med Sci 78: 191–199, 1973

Diagnosis of Venous Thrombosis in the Lower Limbs

A Comparative Study between ^{125}I-fibrinogen Test, Strain Gauge Plethysmography and Phlebography

E. BERGQUIST, D. BERGQVIST, A. BRONGE, S. DAHLGREN and T. HALLBÖÖK

Department of Surgery, University Hospital, Uppsala and Lund, and Department of Diagnostic Radiology, University Hospital, Uppsala, Sweden

ABSTRACT

Three methods of thrombosis diagnosis were compared in 97 patients: ascending phlebography, the ^{125}I-fibrinogen test, and strain gauge plethysmography. The fibrinogen test showed the highest frequency of thromboses and plethysmography the lowest. Phlebography gives a morphological diagnosis, but is not so reliable in muscular, superficial and deep femoral veins. It makes great demands on the X-ray department and is therefore seldom suitable as a screening method. It will continue to be the reference method for the diagnosis of thrombosis. The fibrinogen test measures the radioactive uptake, is simple and suited for screening examinations and sequential studies, but the risk of hepatitis must be remembered. The clinical relevance of positive fibrinogen test is discussed. We believe that calf vein thrombi may grow and reach the size where embolization is possible. Plethysmography measures the function of the deep venous system. It can be used for screening examinations and sequential studies. The thrombi diagnosed interfere with venous function and lie proximally to the calf. The method is valuable in acute iliofemoral thromboses. On the basis of diagnostic discrepancies between fibrinogen test and phlebography in dextran-treated patients the possibility is discussed that thrombi formed in a dextran milieu may lyse more rapidly than other thrombi.

INTRODUCTION

Several studies have shown that the clinical diagnosis of thrombosis is very inaccurate (8, 14, 19, 20, 28, 31, 35, 42). Thrombotic disease is of great significance, especially in view of its two complications: the acute, and frequently fatal, pulmonary embolus, and the chronic post-thrombotic syndrome. It is therefore important to develop and test diagnostic methods based on objective criteria, which are more reliable than subjective clinical assessment. This is true both in practical clinical work and in the investigations of the incidence of thrombosis and in the study of different methods for the prophylaxis of thrombosis. Phlebography is an established and reliable method, but is hardly suitable for screening investigations of any great extent, nor is it often applicable to sequential studies in the same patient over long periods of time. Methods which satisfy these requirements, however, have been developed during recent years: various plethysmographic techniques (16, 17, 22, 40, 41), the ^{125}I-fibrinogen test (2), and the ultrasound technique (18, 33, 43).

The purpose of this study was to compare three fundamentally different methods used for the diagnosis of thrombosis: phlebography, the ^{125}I-fibrinogen test, and strain gauge plethysmography.

MATERIAL

Ninety-seven patients (14 men and 83 women) of average age 72.1 ± 12.6 years (33–93 years), were admitted to the study. Sixty-four underwent a von Bahr operation for transcervical fracture of the femur, and 33 a McLaughlin operation for trochanteric fracture of the femur. These patients also formed part of a larger series, in which the early administration of dextran 70 or of dicoumarol were studied as methods for the prophylaxis of venous thrombosis (7).

METHODS OF DIAGNOSIS OF THROMBOSIS

^{125}I-fibrinogen test

The ^{125}I-fibrinogen test was carried out using the method described by Atkins & Hawkins (2). Radioactivity was measured with a mobile scintillometer containing a NaI crystal, a photo-amplifier and a round brass collimator of 8 cm in diameter, connected to an impulse calculator with a time-clock. The day before the investigation, the thyroid uptake of free ^{125}I was blocked by the administration of KI capsules by mouth. 150 mg KI was given daily for 3 weeks after the injection of ^{125}I-labelled fibrinogen. On the first day of the examination, which was usually one of the first post-operative days, the patient was given ^{125}I-labelled fibrinogen containing a specific radioactivity of about 50–100 μCi, as an intravenous injection. The fibrinogen was obtained from hepatitis-free blood donors, since in production it cannot be

Table I. *Technically successful and unsuccessful examinations with the ^{125}I-fibrinogen test and strain gauge plethysmography*

Percentages shown in parentheses

	Total number of investigated legs	Successful tests	Unsuccessful tests
^{125}I-fibrinogen test	174	150 (86.2)	24 (13.8)
Strain gauge plethysmography	108	86 (79.6)	22 (20.4)

separated from the hepatitis virus (15). Initially, background radioactivity was recorded and then measurements were taken over the heart and at eight points on both lower limbs, lying between the inguinal region and the medial melleolus. These eight points were marked so that the measurement was made at the same sites at each examination. The radioactivity at each site was related to the activity over the heart and expressed as a percentage. When the activity fell in relation to the background activity, the intravenous injection of ^{125}I-fibrinogen was repeated, and this usually occurred after 10–14 days.

An increase of 15% or more in the percentage activity between two consecutive points was used as a diagnostic criterion of thrombosis. This increase had to be present for two or more consecutive examinations.

Strain gauge plethysmography

The venous volume and the venous emptying of the lower leg were measured by venous occlusion plethysmography. A modification of Whitney's strain gauge plethysmographic technique was used (24). Latex gauges filled with mercury were arranged around the thickest part of the calf and the narrowest part of the ankle, and were placed at exactly the same sites at each examination. An air occlusion cuff was placed above the knee and measurements were carried out with the patient supine, with the calf suspended about 20 cm above the level of the manubrium sterni. Both legs were examined at the same time. The venous volume was defined as the volume increase in that part of the leg under the latex gauge when an occlusion pressure of 50 mm Hg was applied to the occlusion cuff. The venous volume was expressed in ml/100 ml tissue. Venous emptying was defined as the most rapid reduction in the volume of the calf and ankle after quick deflation of the pressure in the occlusive cuff to 0 mmHg and this was expressed in ml/min/100 ml tissue. The diagnostic criteria of thrombosis used were those proposed by Hallböök & Göthlin (23). In most cases the examinations were carried out together with the ^{125}I-fibrinogen test, usually on alternate days until phlebography became possible.

Table II. *Distribution of the three methods of diagnosis (Phlebography, Strain gauge plethysmography, and the ^{125}I-fibrinogen test)*

Investigation	Number of patients
^{125}I-fibrinogen test/plethysmography/phlebography	25
^{125}I-fibrinogen test/phlebography	32
^{125}I-fibrinogen test/plethysmography	6
Phlebography/plethysmography	9
Plethysmography	2
^{125}I-fibrinogen test	11
Unsuccessful tests	12
	97

Phlebography

Phlebography was carried out on the fractured leg only using a standardized ascending technique (7, 9), on an average 15.5±3.3 days post-operatively.

The phlebographic criteria for the dignosis of thrombosis were the same as those used by other authors (4, 26, 28).

Post-mortem

The three patients who died all underwent post-mortem examination.

RESULTS

Of the 97 original patients in the series, the examinations were technically unsatisfactory in 12, and these were therefore excluded. Seven of these cases underwent plethysmography, and 6 of the ^{125}I-fibrinogen test, i.e., both examinations were unsatisfactory in one case. Table I shows the number of successful and unsuccessful examinations, using both these methods. Two patients were successfully examined with plethysmography alone, and eleven patients with ^{125}I-fibrinogen alone. Two of the latter group died, leaving 72 patients (10 men and 62 women) who were satisfactorily examined with two or more methods, and who can be used for a comparison of the methods. The sub-division of these patients into the various methods is shown in Table II.

Each method was compared with the other two, and the result of the comparison is shown in Tables III, IV and V. Phlebography was performed on the fractured leg only, while the other two examinations were performed bilaterally. As a result, the figures given in Tables III and IV show the numbers of patients examined, while the figures in Table V show the number of legs examined. In this comparison, which is based only on whether the examinations were positive or negative, the ^{125}I-fibrinogen

Table III. *Comparison of the* ^{125}*I-fibrinogen test and phlebography in 57 patients*

	^{125}I-fibrinogen test	
Phlebography	+	–
+	14	4
–	7	32

Total number of patients: 57.
Agreement between methods in 80.7% and disagreement in 19.3%.

test and phlebography show 80.7% agreement, plethysmography and phlebography show 70.6% agreement, and the ^{125}I-fibrinogen test and plethysmography show 66.1% agreement. The ^{125}I-fibrinogen test was more often positive than phlebography, while both the ^{125}I-fibrinogen test and phlebography were more often positive than plethysmography.

Six of the 7 patients in whom the ^{125}I-fibrinogen test was positive and phlebography negative, were given prophylactic treatment against thrombosis with dextran 70. In addition, 1 patient treated with dextran (No. 2 in Table VI) showed two changes in activity in the ^{125}I-fibrinogen test, only the proximal of which corresponded to the thrombosis detected by phlebography. In Table IV and V, in which the results of plethysmography are compared with those of the other two methods, in these patients showing a discrepancy between the methods the number receiving dextran 70 and dicoumarol is approximately equal.

The results of the ^{125}I-fibrinogen test and of plethysmography both indicated a thrombosis on the left side with obstruction of venous outflow in one of the deceased patients (No. 13 in Table VI). Autopsy revealed a thrombosis in the deep venous system including the femoral vein on the left side, and a massive pulmonary embolus which was immediately fatal. The other two deceased patients were examined with the ^{125}I-fibrinogen test alone, with negative results, and autopsy showed no thrombosis or embolus.

Table VI shows a total of 40 patients in whom one or more examinations showed a positive result which, using the criteria we adopted, indicates the presence of a thrombosis. This table thus includes all the discrepancies in Tables III, IV and V.

None of the methods of examination gave rise to any complications.

Table IV. *Comparison of strain gauge plethysmography and phlebography in 34 patients*

Number of thromboses localised to lower leg only, shown in parentheses

	Strain gauge plethysmography	
Phlebography	+	–
+	4 (2)	9 (6)
–	1	20

Total number of patients: 34.
Agreement between methods in 70.6% and disagreement in 29.4%.

DISCUSSION

In comparing the three methods examined here, it is important to recognise just what the methods do in fact measure, and what are their limitations. Phlebography shows the morphological extent of thrombosis, and assessment of the passage of the contrast medium allows us to obtain some conception of the conditions of blood flow in the venous system. It is probable that small thromboses particularly in the muscular veins and superficial vessels of the lower leg, and in the deep femoral vein, often escape recognition by phlebography (11, 34).

The ^{125}I-fibrinogen test measures the uptake of the iodine-labelled fibrinogen which is built into thrombi in the course of their formation (3). Recently published results also indicate that "old thromboses" (days) may contain metabolically active tissue with a selective uptake of fibrinogen (11). A number of comparisons have been published between the ^{125}I-fibrinogen test and phlebography, and the correlation between the two methods is good, and

Table V. *Comparison of strain gauge plethysmography and* ^{125}*I-fibrinogen test in 31 patients*

Number of thromboses localised to lower leg only is shown in parentheses. Table shows number of legs examined

	^{125}I-fibrinogen test	
Strain gauge plethysmography	+	–
+	6 (5)	1
–	20 (17)	35

Total number of patients: 31.
Agreement between methods in 66.1% and disagreement in 33.9%.

Table VI. *Summary of patients in whom one of the diagnostic methods showed positive results, i.e., a thrombosis*

Figures in column for the ^{125}I-fibrinogen test refer to the point on the leg where the thrombosis is situated according to this method. Localisation of the points may be seen in Fig. 1.

ATV Anterior tibial vein; PTV Posterior tibial vein; Fib.V Fibular vein; Pe.V Peroneal vein; Po.V Popliteal vein; FV Femoral vein; DFV Deep femoral vein; SV Sural vein

No.	Age	Sex	Op. leg	X-ray localisation	Max. uptake with ^{125}I-fib. test Right	Left	Plethysmography Right	Left	Comments
1	87	F	Left	PTV	neg	567	—	—	
2	82	F	Right	PFV	167	neg	—	—	Increasing values 1. 67 neg on day for X-ray. Dextran 70.
3	86	F	Right	PTV	neg	neg	—	—	Increasing tendency 6. (max. 14%).
4	76	F	Right	neg	6	neg	—	—	X-ray 6 days after last scan. Dextran 70.
5	88	M	Left	neg	neg	45	—	—	X-ray 4 days after last scan. Dextran 70.
6	78	F	Left	PTV, PeV	56	6	—	—	
7	87	F	Left	FV	6	36	—	—	
8	88	F	Right	FV	neg	neg	—	—	X-ray 8 days after last scan. Increased uptake 3.
9	54	F	Right	PeV	6	neg	—	—	
10	75	F	Left	neg	6	neg	—	—	
11	89	M	Right	FibV, FV	167	neg	—	—	
12	82	F	Left	PeV	6	6	—	—	
13	69	F	Right	—	neg	67	neg	pos	Mors day 14. Autopsy: massive DVT. Pulmonary embolism.
14	77	F	Right	—	67	neg	neg	neg	Scan pos. days 12–16. Distal thrombosis.
15	84	F	Right	—	6	neg	neg	neg	Scan pos. days 12, 13. Distal thrombosis.
16	91	M	Right	—	neg	6	neg	pos	Scan normal last day. Plethysmography reversible slow empt.
17	76	M	Right	—	neg	5	neg	neg	Scan pos. days 7–11. Distal thrombosis.
18	93	F	Right	—	67	67	neg	neg	Distally located thromboses.
19	76	F	Left	PoV, PTV, FV	—	—	neg	pos	
20	60	F	Right	PeV, PoV	—	—	pos	pos	
21	77	F	Right	PTV, ATV, PoV	—	—	pos	neg	
22	66	F	Right	PeV	—	—	neg	neg	Distal thrombosis.
23	59	F	Left	neg	neg	neg	pos	neg	Pos. plethysmography days 11, 12. Difficult to explain.
24	56	F	Right	neg	3	neg	neg	neg	Scan. pos. days 4, 7. Dextran 70.
25	65	F	Right	FV	357	578	pos	pos	
26	59	F	Left	PTV, PoV, FV	7	67	pos	neg	Distal thrombosis. High uptake 1 from beginning, Lysis?
27	80	F	Left	neg	7	neg	neg	neg	Distal thrombosis days 8–17 with tendency to lysis?
28	68	F	Right	neg	5	neg	neg	neg	Distal thrombosis days 6–9. Scan neg on day for X-ray. Dextran 70.
29	86	F	Left	SV, FV	neg	neg	neg	neg	No hindrance of venous emptying. Scan not perfect.
30	57	F	Left	neg	67	67	neg	neg	Distal thrombosis.
31	80	F	Right	FV	1	neg	neg	neg	Not total occlusion.
32	65	M	Right	PTV, PeV	67	57	neg	neg	Distal thrombosis.
33	80	F	Right	neg	7	neg	pos	neg	Scan and plethysmography neg. on day for X-ray.
34	65	F	Left	PeV	467	567	neg	neg	No hindrance of venous emptying in deep venous system.
35	77	F	Right	PeV	neg	neg	neg	neg	Distal thrombosis. No hindrance of venous empt. Scan not perfect.
36	82	F	Right	neg	7	neg	neg	neg	Distal thrombosis. Dextran 70.
37	72	F	Left	PeV	neg	6	neg	neg	Distal thrombosis.
38	74	M	Right	PeV	6	neg	neg	neg	Distal thrombosis.
39	66	F	Left	neg	8	neg	—	—	
40	65	M	Right	neg	neg	6	neg	neg	Distal thrombosis.

greater than 90% in several studies (27, 28, 34, 39). In these studies, it has not been stated when the phlebography was carried out in relation to the positive fibrinogen test, but the high degree of agreement suggests that the examinations were carried out closely together. Milne et al. (31), however, found only 78% agreement, and Browse (12) 80%.

The ^{125}I-fibrinogen test more often gives positive results than does phlebography. In the literature, a positive ^{125}I-fibrinogen test often means deep vein thrombosis. According to our experience, however, the method is also capable of diagnosing superficial thrombosis. The commonest diagnostic criterion of thrombosis with the ^{125}I-fibrinogen test is an increase of 15% or more in radioactivity compared with the adjacent measurement point, and which remains present for at least two consecutive examinations (10, 11, 25, 34, 45). Wood et al. (46) and Nicolaides et al. (37), used a 20% increase as the criterion, and Murray et al. (32) used 30%. If the 20% criterion is used in our series, the ^{125}I-fibrinogen group will contain four less patients with thrombosis. One of these, according to phlebography, had no thrombosis, while the other three had thrombosis demonstrable by phlebography and/or plethysmography. An increase of 15% or more, therefore, appears to be a reasonable criterion for the diagnosis of thrombosis. Browse et al. (11) suggest as an additional criterion an increase in three adjacent points of more than 5% as compared with the corresponding points on the other leg. The application of this criterion does not alter the results in this series.

The following sources of error in the ^{125}I-fibrinogen test have been named by various authors: varices, haematoma, inflammatory states (34), and oedema (11). The effect of varices and oedema can be excluded if preoperative measurements are carried out, and this point is emphasised by Becker et al. (5), among others. Preoperative examinations are difficult to perform in patients who have sustained a fracture of the neck of femur, and examinations are, of course, not possible before trauma. Preoperative examinations were not performed in this series, and the radioactivity at point 1 is therefore difficult to estimate. High values at the first examination were not regarded as evidence of thrombosis, since in these cases it may have been due to haemorrhage at the fracture site, as well as to the trauma of operation. If, on the other hand, increasing activity was shown for several days postoperatively, after low initial values, this was regarded as evidence of a proximally situated thrombosis. Higher values are more often seen at point 1 than at other sites, and Flanc et al. (19) consider this to be due to the proximity of the femoral artery with its high blood flow.

Strain gauge plethysmography is a method for the quantitative assessment of the functional state of the deep venous system, based on measurements of volume changes in the lower leg (venous volume and venous emptying) (16, 23, 40, 41). A diagnosis of thrombosis made with this method implies the existence of a thrombosis of such an extent and so localised, that it restricts the venous outflow from the leg, and that the thrombosis is situated proximally to the latex gauges.

Of the 23 legs showing a negative result with plethysmography and a positive result with phlebography and/or the ^{125}I-fibrinogen test, 20 can be explained by the distal situation of the thrombosis at the time of examinations. Despite the fact that the latex gauges are placed at the ankle, the possibility of demonstrating changes in the deep veins of the leg is low because of the generally well-developed superficial venous system in the distal part of the leg. Phlebography was negative (i.e., a good flow), in one case (No. 24), and the peak at point 3 in the ^{125}I-fibrinogen test was of short duration. Heie the explanation could be a minor superficial thrombosis. In one case (No. 31), the radiological examination showed a thrombosis in the femoral vein which was not causing occlusion, indicating that the thrombus was not producing any essential interference with venous outflow. However, the ^{125}I-fibrinogen test showed increasing activity at point 1 in this patient. Again, one case (No. 29) had thromboses in both the sural and the femoral veins on phlebography, but there was good passage of the contrast medium past the thrombi.

One plethysmographic result was falsely positive on comparison with radiology and the ^{125}I-fibrinogen test, a discrepancy which we were unable to explain (No. 23). In this series, consisting of old patients who had undergone operation on the hip, there were, however, a number of technical difficulties in carrying out the plethysmographic examinations, a fact which may also explain the high incidence of unsuccessful examinations.

Four patients were negative with ^{125}I-fibrinogen test but showed thrombosis on phlebography. In two of these (Nos. 29 and 35), the ^{125}I-fibrinogen test cannot be considered completely satisfactory from the technical viewpoint, but the discrepancy is nevertheless difficult to explain. Both patients showed a negative result with plethysmography. One patient (No. 3) showed a negative result with the ^{125}I-fibrinogen test from the beginning, but with a tendency to increase (maximum 14%) at point 6 on the 10th, 13th and 14th days. The radiologically demonstrable thrombus was situated in the posterior tibial vein, about 15 cm distal to the knee, which corresponds to point 6. In the last patient (No. 8), phlebography was carried out as late as 8 days after the ^{125}I-fibrinogen test was completed, and then showed a thrombosis in the femoral vein. On the last day of the ^{125}I-fibrinogen test the patient showed an increase of more than 15% at point 3, and it is possible that this was the first day of the thrombosis. The possibility must also be considered that a small, older, inactive thrombus was present.

As regards the ^{125}I-fibrinogen examinations, 8 patients (Nos. 2, 4, 5, 24, 28, 30, 33 and 36) show "false" positive results in comparison with phlebography. Patient No. 2 is not shown as a discrepancy in Table II since she had two localisations of thrombosis (points 1 and 6, 7), the proximal one of which agrees with the results of phlebography. Seven of these 8 patients had been given dextran 70 for prophylaxis against thrombosis (Nos. 2, 4, 5, 24, 28, 33 and 36). Two of these seven dextran-treated patients underwent phlebography 6 days after the end of ^{125}I-fibrinogen examination in one case and 7 days after in the other (Nos. 2 and 4). Both had positive uptakes during the whole period of the ^{125}I-fibrinogen examination. The day on which phlebography was carried out was the same as in the rest of the patients. Four of the patients treated with dextran (Nos. 5, 24, 28, and 33) showed diminishing ^{125}I-fibrinogen uptake, and the phlebography was negative. One patient (No. 36) showed a positive result with the ^{125}I-fibrinogen test on the same day that phlebography was negative. One patient (No. 33) showed evidence of thrombosis both by the ^{125}I-fibrinogen test and plethysmography, but both of these examinations were negative on the day of phlebography. In 3 patients (Nos. 2, 4, and 5) plethysmography was not carried out, and in the other 3 (Nos. 24, 28, and 36) it was negative, indicating that the thromboses were functionally unimportant. One patient (No. 30) who was treated with dicoumarol had positive ^{125}I-fibrinogen test till the day before phlebography. On the very day of phlebography the test was negative.

These figures appear to speak in favour of an increase in the rate of disappearance of formed thrombi in the presence of dextran. The frequency of pulmonary embolism is clearly reduced when dextran prophylaxis is used, as shown by Bygdeman et al. (13) in a larger comparative series. None of the patients showing a discrepancy had any clinical signs of pulmonary embolism. A number of investigations suggest that there is a change in the structure of thrombi formed in the presence of dextran. Thus, sodium morrhuate thrombi in rabbits, formed after the infusion of dextran 70, are less mechanically tenacious than thrombi formed in control animals (1). Plasma clots in dogs treated with dextran 75 showed a different structure from those in control dogs (21). In the presence of dextran, the fibrin coagulum formed *in vitro* shows a considerably coarser structure than control coagula, when examined with the scanning electron microscope, and the rate of plasminolysis of fibrin plaques formed in the presence of dextran is significantly increased (44). It is possible, therefore, that thrombi formed in a dextran milieu lyse more easily than do other thrombi. Becker & Schampi (6) compared the effect of dextran 70 and electrical stimulation of the calf muscle as methods of prophylaxis against thrombosis. Phlebography and the ^{125}I-fibrinogen test were both used as diagnostic methods, and complete agreement was found between the two methods in the control and electrically stimulated groups, but there was a discrepancy in the dextran-treated group. Twenty-three legs were studied by both methods, and in 6 legs the ^{125}I-fibrinogen test was positive, while phlebography was negative. On the day of phlebography, which was on average seven days postoperatively, the fibrinogen test had returned to normal in all cases. Kakkar et al. (27) noted spontaneous lysis within 72 hours in 14 out of 40 thromboses, positive to the ^{125}I-fibrinogen test, in untreated postoperative patients.

It may be seen from Table VI that most of the thromboses in this series diagnosed by the ^{125}I-fibrinogen test and/or phlebography were situated distally. It is debatable to what extent distally-situated thromboses can be dangerous as regards the formation of emboli. Kakkar et al. (27) found that the thromboses localised in the calf which were diagnosed by the ^{125}I-fibrinogen test were not associated with pulmonary embolism, but that pul-

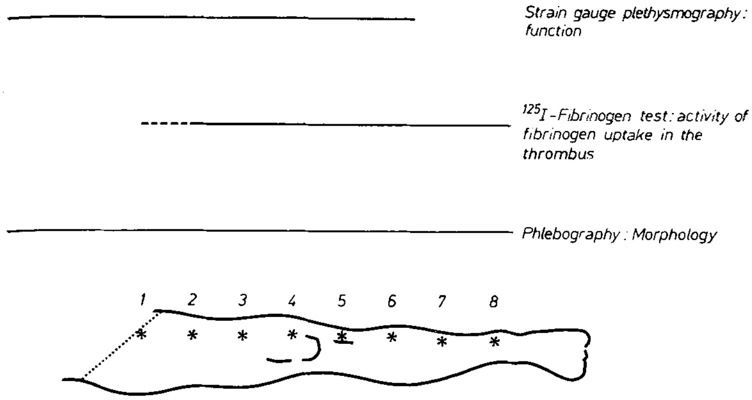

Fig. 1. Diagrammatic representation of the principles of the three methods and their diagnostic range. The points on the leg correspond to the points at which radioactive uptake is measured in the ^{125}I-fibrinogen test. The interrupted line corresponds to point 1, and indicates the difficulty of interpretation of the uptake pattern at this point in patients who have undergone hip surgery.

monary embolism did occur in four out of nine patients in whom thrombosis extended up to the popliteal and femoral veins. Only one definite pulmonary embolus occurred in our series, and this was immediately fatal (Patient No. 13). The peak level for thrombosis in the ^{125}I-fibrinogen test occurred at points 6 and 7, in this case, but the patient also showed a high uptake at point 1, which was, however, present from the first day of the examination. It is impossible to say to what extent this high uptake was due to thrombosis or to haematoma. The reduction of flow on plethysmography, however, is in favour of a relatively proximal localisation of the thrombus. Subsequent post-mortem examination showed thromboses in the deep venous system of the leg, including the femoral vein.

Flanc et al. (19) discuss the significance of high radioactive counts of short duration in the calf, and are of the opinion that they are due either to accumulations of blood in soleal sinusoids or to small thromboses which are rapidly dealt with by the patient's own fibrinolytic system. Nicolaides et al. (35 and 36) consider that thromboses form in the sinusoids of the soleus and then may propagate proximally. Maurer et al. (29) found a similar extension in seven out of 44 thromboses in the calf, in a group of patients with myocardial infarction, one thrombus extending up to the femoral vein.

Mavor et al. (30), in a study of 122 patients with early thromboembolic disease, diagnosed by ileofemoral phlebography and lung scanning with ^{131}I-labelled macroaggregate of human serum albumin, found negative results to the ^{125}I-fibrinogen test in 80%. However, the radio-active fibrinogen was only injected when the diagnosis of pulmonary embolus or of occlusive venous thrombosis had been made. To provide an answer to the question of the clinical relevance of thromboses diagnosesd with the ^{125}I-fibrinogen test, a large-scale prospective investigation would be necessary, in the course of which assessment of the incidence of pulmonary embolism and of the post-thrombotic syndrome would be made after the lapse of a certain period of time. Thromboses diagnosed by plethysmography are probably more dangerous from both these viewpoints. The only patients in this series who suffered a pulmonary embolus had had the thrombosis diagnosed by plethysmography. This patient also showed appearances in the ^{125}I-fibrinogen test typical of thrombosis.

This comparison between three different techniques for the diagnosis of thrombosis shows that all three methods are useful, but that each has its specific value and limitations. Phlebography is a reliable diagnostic method, but often gives incomplete filling of muscular veins and of the deep femoral vein. The techniques is refined, and its interpretation demands experience. To use this technique widely in the diagnosis of thrombosis places great demands on the X-ray diagnostic department. It is true that we used the method for the diagnosis of thrombosis in studies of prophylaxis against thrombosis (7, 9), but it cannot be regarded as a screening method. It can usually only be used for an isolated examination in the presence of very particular indications, in the same patient over a period of time.

The ^{125}I-fibrinogen test is easy to use and is a reliable method. It is highly suitable for screening examinations involving large numbers of patients and for sequential studies on the same patient. Its main sphere of usefulness is in the diagnosis of recent thrombi which take up fibrinogen, and therefore the method should be of particular value in prospective studies. Moreover its reliability is considerably reduced when diagnosing older thrombi. The dose of radiation which is used is low, and should not be harmful even for young patients. With a careful choice of fibrinogen donors, it should be possible to keep the incidence of hepatitis at a very low level. The clinical relevance of the thromboses revealed by the ^{125}I-fibrinogen test is a matter for debate.

Plethysmography, like the ^{125}I-fibrinogen test, is highly suitable for screening examinations and for the serial investigations of deep venous function in any one patient. It is a bloodless procedure, and without any discomfort to the patient, and furthermore requires no preparatory treatment. With this method it is possible to detect thromboses of sufficient magnitude to reduce venous volume (either by the thrombosis itself or by venous stasis), and to reduce venous flow. This condition is satisfied mainly by thrombosis in the ileo-femoral veins, and is commonly associated with complications. However, the method is not reliable in the diagnosis of minor muscular vein thromboses or superficial thromboses, or those that lie distally in the lower leg. Plethysmography is an excellent technique for the diagnosis of thromboses of acute onset in the deep venous system.

The spheres of usefulness of the three methods are shown diagramatically in Fig. 1.

REFERENCES

1. Ah-See, T., Arfors, K.-E., Bergqvist, D. & Tangen, O.: The effect of dextran prophylaxis in experimental thrombosis. To be published.
2. Atkins, P. & Hawkins, L. A.: Detection of venous thrombosis in the legs. Lancet *II:* 1217, 1965.
3. —— The diagnosis of deep-vein thrombosis in the legs using ^{125}I-fibrinogen. Brit J Surg *55:* 825, 1968.
4. Bauer, G.: A venographic study of thrombo-embolic problems. Acta Chir Scand, Suppl. *61*, 1940.
5. Becker, J., Bergqvist, D. & Dahlgren, S.: Trombosdiagnostik med J^{125}-märkt fibrinogen. Läkartidn *69:* 2315, 1972.
6. Becker, J. & Schampi, B.: The incidence of post-operative venous thrombosis of the legs. A comparative study on the prophylactic effect of dextran 70 and electrical calf-muscle stimulation. Acta Chir Scand. In press.
7. Bergquist, E., Bergqvist, D., Bronge, A., Dahlgren, S. & Lindquist, B.: An evaluation of early thrombosis prophylaxis following fracture of the femoral neck. A comparison between dextran and dicoumarol. Acta Chir Scand. *138:* 689, 1972.
8. Borgström, S., Greitz, T., van der Linden, W., Molin, J. & Rudics, I.: Anticoagulant prophylaxis of venous thrombosis in patients with fractured neck of the femur. Acta Chir Scand *129:* 500, 1965.
9. Bronge, A., Dahlgren, S. & Lindquist, B.: Prophylaxis against thrombosis in femoral neck fractures—a comparison between dextran 70 and dicoumarol. Acta Chir Scand *137:* 29, 1971.
10. Browse, N. L. & Negus, D.: Prevention of postoperative leg vein thrombosis by electrical muscle stimulation. An evaluation with ^{125}I-labelled fibrinogen. Brit Med J *3:* 615, 1970.
11. Browse, N. L., Clapham, W. F., Croft, D. N., Jones, D. J., Thomas, M. L. & Williams, J. O.: Diagnosis of established deep vein thrombosis with the ^{125}I-fibrinogen uptake test. Brit Med J *4:* 325, 1971.
12. Browse, N. L.: The ^{125}I-fibrinogen uptake test. Arch Surg *104:* 160, 1972.
13. Bygdeman, S., Svensjö, E. & Tollerz, G.: Prevention of venous thrombosis. Lancet *II:* 419, 1970.
14. Coon, W. W. & Coller, F. A.: Clinopathologic correlation in thromboembolism. Surg Gynec Obstet *109:* 259, 1959.
15. Cronberg, S., Belfrage, S. & Nilsson, I. M.: Fibrinogen transmitted hepatitis. Lancet *I:* 967, 1963.
16. Dahn, I.: Venous occlusion plethysmography in clinical routine. Scand J Clin Lab Invest, Suppl. *99:* 138, 1967.
17. Eiriksson, E.: Plethysmographic studies of venous diseases of the legs. Acta Chir Scand, Suppl. *398*, 1968.
18. Evans, D. S. & Cockett, F. B.: Diagnosis of deep-vein thrombosis with an ultrasonic Doppler technique. Brit Med J *II:* 802, 1969.
19. Flanc, C., Kakkar, V. V. & Clarke, M. B.: The detection of venous thrombosis of the legs using ^{125}I-labelled fibrinogen. Brit J Surg *55:* 742, 1968.
20. Gibbs, N. M.: Venous thrombosis of the lower limbs with particular reference to bed-rest. Brit J Surg *45:* 209, 1957
21. Gollub, S. & Schaefer, C.: Structural alteration in canine fibrin produced by colloid plasma expanders. Surg Gynec Obstet *127:* 783, 1968.
22. Hallböök, T.: Klinisk användning av strain gauge pletysmografi vid kärlsjukdomar i nedre extremiteterna. Thesis. Swedish text, Lund. 1970.
23. Hallböök, T. & Göthlin, J.: Strain gauge plethysmography and phlebography in diagnosis of deep venous thrombosis. Acta Chir Scand *137:* 37, 1971.
24. Hallböök, T., Månsson, B. & Nilsén, R.: A strain gauge plethysmography with electrical calibration. Scand J Lab Clin Invest *25:* 413, 1970.
25. Hills, N. H., Pflug, J. J., Jeyasingh, K., Boardman, L. & Calnan, J. S.: Prevention of deep vein thrombosis by intermittent pneumatic compression of calf. Brit Med J *I:* 131, 1972.
26. Hjelmstedt, Å. & Sundström, R.: Deep venous thrombosis following fractures of the tibial shaft. A phlebographic study of 40 patients one to two weeks after injury and after fracture union. Acta Chir Scand *126:* 211, 1963.
27. Kakkar, V. V., Howe, C. T., Flanc, C., Clarke, M. G.:

Natural history of postoperative deep-vein thrombosis. Lancet *II:* 230, 1969.
28. Lambie, J. M., Mahaffy, R. G., Barber, D. C., Karmody, A. M., Scott, M. M. & Matheson, N. A.: Diagnostic accuracy in venous thrombosis. Brit Med J *II:* 142, 1970.
29. Maurer, B. J., Wray, R. & Shillingford, J. P.: Frequency of venous thrombosis after myocardial infarction. Lancet *II:* 1385, 1971.
30. Mavor, G. E., Walker, M. G., Dhall, D. P., Mahaffy, R. G., Duthie, J. S., Gaddie, J. & Reid, G. F.: Peripheral venous scanning with ^{125}I-tagged fibrinogen. Lancet *I:* 661, 1972.
31. Milne, R. M., Griffiths, J. M. T., Gunn, A. A. & Ruckley, C. V.: Postoperative deep venous thrombosis. A comparison of diagnostic techniques. Lancet *II:* 445, 1971.
32. Murray, T. S., Lorimer, A. R., Cox, F. C. & Lawrie, T. D. V.: Leg-vein thrombosis following myocardial infarction. Lancet *II:* 792, 1970.
33. Myhre, H. O.: Ultrasound examination for deep vein thrombosis. J Oslo City Hosp *21:* 178, 1971.
34. Negus, D., Pinto, D. J., le Quesne, L. P., Brown, N. & Chapman, M.: ^{125}I-labelled fibrinogen in the diagnosis of deep-vein thrombosis and its correlation with phlebography. Brit J Surg. *55:* 835, 1968.
35. Nicolaides, A. N., Kakkar, V. V., Field, E. S. & Renney, J. T. G.: The origin of deep vein thrombosis: a venographic study. Brit J Radiol *44:* 653, 1971*a*.
36. Nicolaides, A. N., Kakkar, V. V. & Renney, J. T. G.: The soleal sinuses: origin of deep-vein thrombosis. Brit J Surg *57:* 860, 1970.
37. Nicolaides, A. N., Kakkar, V. V., Renney, J. T. G., Kidner, P. H., Hutchison, D. C. S. & Clarke, M. B.: Myocardial infarction and deep-vein thrombosis. Brit Med J *I:* 432, 1971*b*.
38. Nylander, G.: Phlebographic diagnosis of acute deep leg thrombosis. Acta Chir Scand, Suppl. *387:* 30, 1967.
39. Pinto, D. J.: Controlled trial of an anticoagulant (Warfarin sodium) in the prevention of venous thrombosis following hip surgery. Brit J Surg *57:* 349, 1970.
40. Sakaguchi, S., Tomita, T., Endo, I. & Ishitobi, K.: Functional segmental plethysmography: A new venous function test (preliminary report). J Cardiovasc Surg *9:* 87, 1968.
41. Sakaguchi, S., Tomita, T., Endo, I. & Ishitobi, K.: Functional segmental plethysmography. Clinical application and results. Angiology *21:* 714, 1970.
42. Sevitt, S. & Gallagher, N. G.: Prevention of venous thrombosis and pulmonary embolism in injured patients. A trial of anticoagulant prophylaxis with phenindione in middle-aged and elderly patients with fractured necks of femur. Lancet *II:* 981, 1959.
43. Sigel, B., Poply, G., Wagner, D., Boland, J., Mapp, E. & Feigl, P.: A Doppler ultrasound method for diagnosing lower extremity venous disease. Surg Gynec Obstet *127:* 339, 1968.
44. Tangen, O., Wik, K. O., Almqvist, I. A. M., Arfors, K-E. & Hint, H. C.: Effects of dextran on the structure and plasmin induced lysis of human fibrin. Thromb Res *I:* 487, 1972.
45. Williams, H. T.: Prevention of postoperative deep-vein thrombosis with perioperative subcutaneous heparin. Lancet *II:* 950, 1971.
46. Wood, E. H., Prentice, C. R. M. & McNicol, G. P.: Association of fibrinogen–fibrin-related antigen (F.R.-antigen) with postoperative deep-vein thrombosis and systemic complications. Lancet *I:* 166, 1972.

Received October 9, 1972

Address for reprints:
Docent Sven Dahlgren
Kir. klin.
Kärnsjukhuset
Skövde
Sweden