Diagnostic and therapeutic aspects of deep vein thrombosis

Claes Lagerstedt

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Abstract

51 out-patients presenting with calf-vein thrombosis were randomized to treatment with heparin for five days or heparin with subsequent warfarin for three months. Among 23 patients in the warfarin-group no recurrence occurred, whereas 8 of the 28 patients (29%) in the non-warfarin group had recurrent thrombo-embolism during the first 90 days. It is concluded that patients with symptomatic calf-vein thrombi should be treated with both heparin and oral anticoagulation.

In a prospective study of X-ray contrast media, post-phlebographic reactions occurred in 7 of 19 patients (37%) investigated with a high-osmolality contrast medium metrizoate whereas no such reaction occurred among 24 patients investigated with a low-osmolality contrast medium iohexol. Thus, low-osmolality contrast media should preferably be used at phlebography.

396 out-patients with suspected venous thrombosis were investigated with the $^{99m}$Tc-plasmin test, physical examination and phlebography. The plasmin test has a high sensitivity (95%) but a low specificity (47%), and was frequently abnormal when clinical signs of inflammation were present. Clinical signs could not accurately predict if thrombosis was present, although subpopulations of patients with high or low probability of venous thrombosis could be identified.

112 patients with suspected DVT were investigated with thermography. Both sensitivity and specificity were low (77% and 66% respectively) and thermography therefore seems not to be useful in the diagnosis of symptomatic venous thrombosis.

Long-term sequelae after a first episode of venous thrombosis are mostly mild as long as 6 years after the diagnosis. Venous function correlated to the extension of the thrombus but not to subjective symptoms. Clinical signs at diagnosis could not predict the late outcome. During the six years of follow-up, 28% of the patients had recurrent thrombosis.

Key words

Venous thrombosis, anticoagulants, phlebography, venous insufficiency, isotope tests
From the Departments of Internal Medicine and Clinical Physiology

Diagnostic and therapeutic aspects of deep vein thrombosis.

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Diagnostic and therapeutic aspects of deep vein thrombosis

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Lund 1992
To
Maria
Anna-Maria and Carl-Emil
This thesis is based on studies reported in the following papers referred to in the text by their respective Roman numerals:

I  Albrechtsson U, Fagher B, Lagerstedt C, Lárusdóttir H, Olsson CG, Westling H and Öqvist B.

II  Wallin L, Albrechtsson U, Fagher B, Lagerstedt C, Olsson CG, Westling H and Öqvist B.

III Lagerstedt C, Olsson CG, Fagher B, and Öqvist B.

IV Lagerstedt C, Olsson CG, Fagher B, Öqvist B, and Albrechtsson U.

V Lagerstedt C, Olsson CG, Fagher B, Norgren L and Tengborn L.
Recurrences and late sequelae after first-time DVT - relation to initial signs. Submitted to Phlebology 1992
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Introduction and aims of the present work

Deep vein thrombosis (DVT) is a common disease, present in approximately 10% of bedridden patients in a general medical ward, (Kirkegaard 1987), in 20-30% of postoperative patients (Bergqvist and Lindblad 1985), and in 40-50% of patients with hip fracture or stroke (Powers et al 1989, Prins et al 1989). However, only a small minority of these patients have any symptoms. The incidence of venous thrombosis found at autopsy was reported to be 60%, as compared with 15% for pulmonary embolism causing or contributing to death (Havig 1977). As it has been estimated that as few as 1-2% of all thrombi are localized in the upper extremities, the following discussion is confined to thrombosis of the deep veins in the lower extremities.

Symptomatic DVT is also frequent among out-patients. According to official Swedish hospital admission statistics, approximately 3,900 patients were treated for DVT as the primary diagnosis in 1989, and a further 3,200 patients were treated for pulmonary embolism as the primary diagnosis. At our hospital, a university hospital serving a population of 220,000, approximately 160 patients are hospitalized annually because of venous thrombosis, and 100 patients because of pulmonary embolism (70/100,000 and 45/100,000, respectively), figures of approximately the same order as those found elsewhere (Anderson F et al 1991). Symptoms commonly associated with venous thrombosis are swelling, pain on walking and on palpation, oedema, increased skin temperature, and induration of the leg.

The present work was begun in 1981 because we wished to evaluate the $^{99m}$Tc-plasmin test in a large series of patients with suspected DVT, and to compare the results with clinical signs and symptoms. Phlebography was used as the reference method; as thermography had shown promising results as a screening-test for DVT, it was compared to the other diagnostic methods.

Earlier findings of a high incidence of post-phlebography thrombosis we thought to be due to the use of high-osmolarity contrast media. Therefore, as one part of the investigation, a double-blind comparison was performed between a conventional high-osmolarity contrast medium, metrizoate, and a low-osmolarity contrast medium, iohexol.

When the work on the studies reported in this thesis began, it was assumed that a pathological plasmin test result in a case of DVT was due to specific binding of plasmin to the thrombus. However, later investigations showed that plasmin accumulates non-specifically, and therefore $^{99m}$Tc-plasmin was subsequently replaced by $^{99m}$Tc-albumin for the screening of DVT.
To evaluate the need of anticoagulant therapy in calf-vein thrombosis, patients with confirmed calf-vein thrombi were randomized to receive warfarin treatment or not after initial heparin treatment.

To assess whether it is possible to predict the development of chronic venous insufficiency, long-term sequelae after DVT were evaluated by interview, clinical examination, and footvolumetry and compared with initial clinical findings and phlebography in a group of patients with a first episode of DVT.

Abbreviations

DVT = deep vein thrombosis
Historical aspects

The physicians of antiquity believed inhaled air to be transported in the arteries, a view that persisted as scientific truth until Harvey (1628) described the circulation of blood and the function of the venous valves. With the description of the capillaries by Malphighi, it became clear how the blood moved from the arteries to the veins. On the basis of his findings with the newly invented microscope, Malphighi (1686) described the fibrin network of clotting blood. He emphasized the movement of blood to prevent clotting. He also described embolism: "While the network is carried along by the flow of the fluid remainder of the blood, it may reasonably be expected to become readily entangled in the recesses and irregular prominences of the chambers of the heart or in the bifurcation of vessels; there it is compacted by the ceaseless impact of the remaining blood, as occurs in rivers".

Virchow (1856) emphasized the role of mechanical factors in thrombosis, and postulated three factors of importance: changes in the flow of blood, changes in the composition of the blood, and changes in the vessel wall. From autopsy findings he concluded that pulmonary emboli originated from venous thrombi: "dass nämlich in allen Fällen, wo alte, primäre Gerinnsel in der Lungenarterie gefunden würden, bei genauem Untersuchung die Ursprungsstelle in den Venen sich nachweisen lasse, dass also Lungengerinnsel nie ohne Venengerinnsel vorkommen, und dass die Existenz der ersteren ein sicheres Beweis für das Vorkommen der letzteren sei". Virchow's concept of venous thrombosis and pulmonary embolism is still valid.

Before the introduction of phlebography, physical examination was the only method of diagnosing venous thrombosis. Swelling, oedema and tenderness of the calves are common in deep vein thrombosis. Some signs have been claimed to be more or less specific for venous thrombosis such as an increased heart rate after an operation or delivery (Mahler 1895), an inexplicable increase in body temperature under the same circumstances (Michaelis 1911), tenderness of the sole of the foot or in the calf (Övre 1929), increased skin temperature and delayed cooling on exposure (Pilcher 1939), increased resistance or pain in the calf on dorsiflexion of the foot (Homans 1944), or unilateral pitting oedema (McLachlin et al 1962). However, with phlebography as a reference method, clinical signs have not been found to be reliable; in patients with suspected deep vein thrombosis, the frequency of DVT was 55% when four or more signs of thrombosis were present, and 34% if only 1-3 signs were present (Haeger 1969).
Phlebography was first used in anatomical research. Various oils were tried as contrast media (e.g. bismuth oil, olive oil, camphor oil, and iodinated fatty acids), but they were found to induce fat embolism or thrombosis in animals. A phlebographic technique using a water-soluble solution of strontium bromide injected percutaneously with the patients in a sitting position was found to be feasible (Berberich and Hirsch 1923), but unfortunately it was painful and produced local thrombosis. Other water-soluble preparations such as lithium iodide, lithium bromide and sodium bromide were also tried, but pain, thrombi and anaphylactic reactions were frequent complications. The general opinion at the time was that angiographic investigations on humans were only experimental because of excessive risks to the patients. Perabrodil, introduced for urography in 1934, turned out to be less toxic and was also used for vascular investigations. Phlebography was introduced in clinical practice at the beginning of the 1940s (dos Santos 1938, Bauer 1942).

Until the beginning of the 1940s, patients with venous thrombosis were strictly immobilized with the feet elevated. Bandaging and warm dressings were used to combat inflammation. Cardiac stimulants, sodium citrate, leeches, blocking of the sympathetic system by anaesthetics, or ligation of the vein were utilized. The mean time in hospital (General Maternity Hospital in Stockholm 1930-39) for patients with venous thrombo-embolism was almost two months, and 6% of the patients died of pulmonary embolism (Zilliacus, 1946). When heparin was introduced it was used both for treatment of established DVT and as a prophylactic agent in patients undergoing major surgery (Crafoord 1937, Murray and Best 1938, Zilliacus 1946). With the advent of heparin, the duration of hospitalization for DVT decreased to approximately a week. In calf-vein thrombosis, progression to the femoral vein was observed in most patients before heparin was introduced, whereas treatment with heparin prevented proximal extension of the thrombus (Bauer 1942, 1959). In Sweden, heparin was administered in intermittent intravenous injections four times daily in most cases, therapy was combined with physical exercises and the patients were not confined to bed (Bauer 1964).

Dicoumarol is a hemorrhagic agent causing sweet clover disease in cattle by inhibiting the effect of vitamin K. After its isolation by Link in 1941, dicoumarol was initially used both for prophylactic purposes and for the treatment of thrombosis (Lehmann 1942, Bruzelius 1944, Link 1959). Since their anti-thrombotic effect is measurable only after 1-2 days, dicoumarol and other vitamin K antagonists have mostly been used as secondary prophylaxis together with initial heparin treatment or alone as primary prophylaxis in patients at high risk of thrombosis. The annual incidence of bleeding during long-term oral anticoagulation has been reported to be around 4% (Forfar 1979).
The first randomized study of anticoagulant therapy was performed in patients with pulmonary embolism. However, as heparin demonstrated a dramatic effect both on mortality and on recurrent embolism (Barrit and Jordan 1960), the study was terminated after only 35 patients had been included and heparin became the agent of choice for the treatment of pulmonary embolism. No additional studies with an untreated control group have been performed, either in pulmonary embolism or deep vein thrombosis. Therapy has usually taken the form of heparin given intravenously in hospital, followed by a period of oral anticoagulation of three to six months in order to prevent recurrence. Heparin can be administered intravenously, as intermittent injections or as continuous infusion, and subcutaneously as intermittent injections twice daily. The antithrombotic effect of heparin, and the incidence of bleeding in conjunction with its use (7-14% during short-time therapy with heparin), would seem to depend more on the dose than on the route of administration (Morabia 1986, Hirsch 1991).

During the early part of this century, induration and ulceration in the lower extremity was commonly considered to be due almost entirely to primary varicose veins, with syphilis as a differential diagnosis (Zilliacus 1946). When epidemiological studies showed patients with venous ulcers to be characterized by a high frequency of previous thrombosis (Birger 1941, Gjöres 1956), and that patients with thrombosis very frequently developed venous insufficiency with chronic swelling and leg ulcers (Bauer 1942), it was generally accepted that previous thrombotic episodes constituted the main cause of venous insufficiency. The term post-thrombotic syndrome was used synonymously with venous insufficiency. However, the diagnosis of DVT in these early investigations was made without objective confirmation in most cases, and may therefore be less reliable.
Diagnostic methods

Clinical diagnosis

Impaired venous outflow and an inflammatory reaction around the thrombus induce swelling, oedema, tenderness, induration and pain. Symptoms and signs of DVT are non-specific, and in several studies the predictive value of clinical diagnosis has been found to be poor (Haeger 1969, Nicolaides et al 1971, Cranley et al 1976). Other investigators have reported clinical signs to be useful in discriminating between calf and proximal DVT, since clinical signs are more frequent in proximal than in distal DVT (Singer 1980, Jefferey et al 1980, Molloy et al 1982). These reports notwithstanding, survey findings showed that almost half of the physicians approached depended on signs and symptoms alone for the diagnosis of DVT (Prentice et al 1982). Despite their unreliability, signs and symptoms continue to be used as a basis for further investigation with objective methods. We therefore evaluated clinical signs and symptoms in suspected DVT, and also tried to identify a combination of signs capable of predicting high or low probability of DVT.

Present results

Clinical diagnosis of DVT was evaluated with phlebography as the reference method (III). Of 396 patients with suspected DVT referred from the emergency department for investigation, 307 underwent physical examination, a $^{99m}$Tc-plasmin test and phlebography. Mean age was 66 years among patients with DVT and 58 years among those without, and of the 307 patients, 37% were males. A careful medical history was taken, with special emphasis on any previous thrombo-embolism and on current symptoms (Table I). A history of previous thrombo-embolism was more common in patients with DVT than in those without ($p<0.01$). Symptoms compatible with pulmonary embolism tended to be more frequent among patients with DVT, though the difference was non-significant ($p=0.06$). Medication with anticoagulants or oestrogens, or a first-degree relative with thrombo-embolism, was reported equally often by patients with DVT as by those without.
Table I. Clinical data in patients with suspected DVT and their predictive value (per cent of patients with the symptom that has DVT).

<table>
<thead>
<tr>
<th></th>
<th>No DVT %</th>
<th>DVT %</th>
<th>Predictive value %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms compatible with pulmonary embolism</td>
<td>9</td>
<td>17</td>
<td>55</td>
</tr>
<tr>
<td>History of thrombo-embolism</td>
<td>23</td>
<td>40</td>
<td>55</td>
</tr>
<tr>
<td>Male sex</td>
<td>33</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>Use of anticoagulants</td>
<td>2</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>First degree relative with DVT</td>
<td>23</td>
<td>23</td>
<td>42</td>
</tr>
<tr>
<td>Medication with oestrogen</td>
<td>7</td>
<td>5</td>
<td>37</td>
</tr>
</tbody>
</table>

In studies on DVT, Kirkegaard (1982) found the reported incidence of DVT to be higher among women than among men when the study was based on clinical diagnosis (Gjöres 1956, Coon et al 1973), but higher among men in studies based on phlebographic diagnosis (Nyländer and Olivecrona 1976, Kirkegaard 1980, Lindhagen et al 1985). In the present study, more women than men were investigated on the suspicion of DVT, but more men eventually turned out to have DVT at phlebography, and more men than women had proximal DVT. Thus, in our series, women more often consulted for DVT-like symptoms than did men, a female preponderance was also reported previously (Widmer 1978).
At the physical examination, each leg was divided into 12 segments, each of which was checked for the presence of such clinical signs as pitting oedema, swelling, erythema, increased skin temperature, increased consistency, calf and thigh circumferences, and Homan's sign (table II).

<table>
<thead>
<tr>
<th>Clinical sign</th>
<th>DVT %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitting oedema</td>
<td>80</td>
</tr>
<tr>
<td>Side difference in thigh circumference &gt; 25 mm</td>
<td>62</td>
</tr>
<tr>
<td>Side difference in calf circumference &gt; 20 mm</td>
<td>59</td>
</tr>
<tr>
<td>Increased consistency</td>
<td>57</td>
</tr>
<tr>
<td>Increased skin temperature</td>
<td>49</td>
</tr>
<tr>
<td>Homan's sign</td>
<td>42</td>
</tr>
<tr>
<td>Hematoma</td>
<td>41</td>
</tr>
<tr>
<td>Exudate in the knee joint</td>
<td>23</td>
</tr>
</tbody>
</table>

Table II. Predictive value of clinical signs in patients with suspected DVT

Pitting oedema turned out to be the most useful sign, as has also been found by others (McLachlin 1962). It had a predictive value of 80% with a sensitivity of 73%.

The overall likelihood of DVT was scored on a 5-point scale (0-4), where 0 = definitely not DVT, 1 = probably not DVT, 2 = uncertain, 3 = probably DVT, 4 = definitely DVT (Table III).

<table>
<thead>
<tr>
<th>Physical examination</th>
<th>Score</th>
<th>DVT %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely DVT</td>
<td>4</td>
<td>81</td>
</tr>
<tr>
<td>Probably DVT</td>
<td>3</td>
<td>47</td>
</tr>
<tr>
<td>Uncertain</td>
<td>2</td>
<td>41</td>
</tr>
<tr>
<td>Probably not DVT</td>
<td>1</td>
<td>26</td>
</tr>
<tr>
<td>Definitely not DVT</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

Table III. Comparison between clinical score and phlebography in 307 patients
When the investigator, after physical examination of the patient, felt certain that DVT was not present (score 0) he was correct in 91% of the cases and when he felt confident that the patient had DVT (score 4) he was correct in 81% of cases. Thus, it seems possible on the basis of history and physical examination to discern one group of patients with a low probability of DVT and one group of patients with a high probability of DVT. If the patients in these two groups had been treated on the basis of signs and symptoms, 10% would have been treated unnecessarily and 4% of the patients with DVT would have received no treatment. However, these groups comprise only 32% of the patients, and in the majority of cases the clinical diagnosis is considerably more uncertain. Inevitably some kind of symptoms from the leg must be present before a patient is referred for further investigation, but in view of the high incidence of DVT in patients with few signs of DVT (score 1), reported symptoms of obscure nature should be regarded as strong indicators for further investigation to exclude the possibility of DVT.

We also tried to identify a combination of signs and symptoms capable of predicting the likelihood of DVT. The presence or absence of the clinical signs was noted in each of twelve segments of the leg. With the aid of discriminant analysis (SPSS statistical package), a discriminant function was constructed on the basis of variables from medical history, symptoms and signs. To predict whether a patient has DVT, the value of each variable was multiplied by a coefficient, the aggregate of the products for all variables yielding an index that predicts to which group the patient belongs (Table IV).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Discriminant function coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitting oedema</td>
<td>(number of segments) x 0,120</td>
</tr>
<tr>
<td>Increased consistency</td>
<td>&quot; &quot; &quot; ) 0,166</td>
</tr>
<tr>
<td>Erythema</td>
<td>&quot; &quot; &quot; ) 0,097</td>
</tr>
<tr>
<td>Tender venous string</td>
<td>&quot; &quot; &quot; ) 0,105</td>
</tr>
<tr>
<td>Side difference in calf circumference</td>
<td>(mm) 0,014</td>
</tr>
<tr>
<td>Exudate in knee joint</td>
<td>(no = 0, yes = 1) -0,585</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>(days) -0,123</td>
</tr>
<tr>
<td>History of DVT</td>
<td>(no = 0, yes = 1) 0,555</td>
</tr>
<tr>
<td>Sex</td>
<td>(male = 1, female = 2) -0,609</td>
</tr>
<tr>
<td>Constant</td>
<td>0,173</td>
</tr>
</tbody>
</table>

Table IV. Discriminant function for predicting the presence or absence of DVT on the basis of symptoms and signs
The results are summarized in Figure 1.

Figure 1. Discriminant analysis of clinical signs for diagnosis of DVT based on 260 patients x = DVT, o = No DVT

As can be seen from Fig. 1, the groups with and without DVT overlap, though it is possible to select a group with a high probability of DVT and a group with low probability of DVT. If, for instance, an index value of $> 1.5$ is chosen to indicate DVT and an index value of $<-1.5$ is chosen to exclude DVT, $31/34$ patients with indices $> 1.5$ and $21/21$ patients with indices $< -1.5$ will be correctly classified. With these limits, $25\%$ of the patients are discernible as high- or low-risk cases. Other limits could be chosen, however, and as this distribution was calculated retrospectively, its value needs to be validated in a prospective series of patients.

**Phlebography**

In the diagnosis of DVT, phlebography is still the reference method and "gold standard", despite the development of various screening methods. However, there are a number of
problems with phlebography, one of which is a tendency for contrast media to induce endothelial damage and even thrombosis. Reports of the occurrence of thrombotic complications in conjunction with the use of phlebography began to appear already at the time of its introduction (Kemp 1940, Homans 1942). When tri-iodinated contrast media were introduced in 1958, they were thought to be harmless in this respect and the use of phlebography increased rapidly. Although Werner and Otto (1962) reported that 4% of the patients undergoing phlebography subsequently presented with symptomatic DVT or superficial phlebitis, the problem was considered to be a minor one (Williams 1973). However, during a pilot study of $^{99m}$Tc-labelled streptokinase compared with $^{125}$I-fibrinogen for the detection of DVT, Albrechtsson and Olsson (1976) found one third of patients with normal phleograms to have pathological isotope test results at follow-up, the presence of DVT or phlebitis with narrowed and tortuous veins being confirmed by new phleograms. High-osmolarity contrast media were known to cause extensive damage to the endothelium of rat aorta, whereas a low-osmolarity contrast medium (metrizamide) caused only minor effects (Almén 1973). In two prospective studies, a pathological fibrinogen uptake test result was often obtained when a high-osmolarity medium was used (meeglumine metrizoate 280mgI/mL, 1.46 Osm/kg), whereas a low-osmolarity medium (metrizamid, 0.46 Osm/kg) caused no such reaction (Albrechtsson and Olsson 1979a, 1979b). A high incidence of post-phlebography DVT with high-osmolarity contrast media has also been reported by others (Bettman and Paulin 1977, Ritchie et al 1977, Laerum and Holm 1981). Thus, a high osmolarity seemed to induce damage to the venous endothelium, which could give rise to thrombi.

**Present results**

The disadvantages of metrizamide included its high cost and its lack of stability upon autoclaving. Therefore we compared the second-generation, low-osmolar compound iohexol at a concentration of 240 mg I/mL (0.50 Osm/kg) with meeglumine metrizoate at a lower concentration than previously used, 200 mg I/mL (1.0 Osm/kg) (I). Forty-three patients with suspected DVT and a normal $^{99m}$Tc-plasmin test result were randomized with respect to testing with metrizoate or iohexol. Subjective reactions during or after injection were somewhat more common in patients examined with metrizoate, though the difference was non-significant. Of 19 patients in the metrizoate-group, seven manifested late reactions after phlebography such as oedema, superficial phlebitis, pain on walking or a pathological isotope test result, as compared with none of the 24 patients in the iohexol group ($p=0.002$). Of four patients who underwent repeat phlebography, DVT was present in one, evidence of phlebitic reaction in two, and a superficial thrombus was found in the fourth.
The results of the studies of four contrast media with different osmolality have been summarized in Figure 2. It is clear that the osmolarity of the contrast medium is an important determinant of the pathological isotope test result, high osmolarity being associated with phlebitis and thrombosis.

Figure 2. Mean values for side differences in $^{125}\text{I}$ activity before phlebography and 3 and 5 days after phlebography. Per cent values refer to counts per minute in per cent of heart activity.
The clinical significance of post-phlebography DVT has been questioned (May 1979, Schmitt 1979). In a comparison between meglumine metrizoate and metrizamide in 51 patients undergoing elective phlebography before operation for varicose veins, biopsies were taken from the dorsal foot vein and from the distal portion of the long saphenous vein (Berge et al 1981). Only 8% of the patients in the metrizoate group manifested biopsy evidence of thrombosis, as compared with none in the metrizamide group. However, confidence limits were wide and biopsy may be an insensitive method of detecting venous thrombosis. Different measures to eliminate post-phlebography reactions such as elevation of the leg to empty the contrast or flushing with saline or heparin might reduce the incidence of adverse reactions. In all likelihood, many of the thrombi induced by phlebography eventually dissolve spontaneously. The frequency of clinically relevant post-phlebography DVT was reported to be 2-4% (Hirsch 1979, Hull et al 1981a). These figures should probably be regarded as underestimates where high-osmolar contrast media are concerned, as in many cases post-phlebography DVT may well have been previously overlooked.

Currently low-osmolarity contrast media such as iohexol, ioxaglaxate, iopamidol or iopromide dominate the market for vascular contrast media in Sweden; low-osmolarity contrast media have been used routinely for phlebography and other vascular investigations at our hospital during the last decade. Switching to low osmolarity contrast media has also been reported to reduce the incidence of general adverse reactions to 25%, that of severe reactions to 20%, and that of very severe reactions to 10% of the corresponding figures for high-osmolarity contrast media (Grainger and Dawson 1990). However, low-osmolarity contrast media are more than three times as expensive as high osmolarity media in Sweden. In the USA, the corresponding price ratio remains as high as 15 to 1, which has led to proposals that low-osmolarity contrast media should be reserved for high-risk patients (Hirschfeld 1992).

**Thermography**

Thermography is a truly non-invasive method, and as such is an attractive alternative for screening purposes. Thermography in the diagnosis of DVT was initially suggested by Soulen and coworkers (1972) who followed patients during fibrinolytic treatment. Diagnostic criteria were proposed by Cooke and Pilcher (1974, 1978).

In the present study (II), thermography was performed by a specially trained laboratory technician and was only available during office-hours. In all, 112 patients were investigated both by physical examination, thermography and phlebography. The thermographs were
scored on a 5-point scale (0 to 4) where 0 = Normal, 1 = Patchy or mottled pattern, 2 = Doubtful pattern, 3 = Diffuse area of raised temperature and/or loss of prepatellar coolness but also mottled appearance, and 4 = diffuse increase of temperature and/or loss of prepatellar coolness. The sensitivity of thermography was low, 77% if a score range of 2-4 was considered to indicate DVT and only 66% if the range was limited to score 3-4, the respective specificities were 67% and 68% (II). These figures are similar to those of clinical diagnosis by the thrombosis team, which was based on symptoms and signs. As compared with findings in previous investigations of thermography (Cooke and Pilcher 1974, Bergqvist et al 1977, Watz et al 1979), both sensitivity and specificity were lower in our study, a discrepancy for which there may be several possible explanations. In the study of Cooke and Pilcher, most of the patients were screened for postoperative DVT. Among such patients, causes of an increase in leg temperature other than DVT should be less common than in our patients referred from an emergency department where differential diagnosis includes infection, trauma and other types of inflammation. The proportion of patients with DVT was lower in our study than in the study of Bergqvist and coworkers, which may indicate that their series included a larger proportion of patients with proximal or occlusive DVT both of which are easier to detect. Other investigators have reported results similar to those of the present study. Thus, sensitivity was reported to be 74% - 85%, and specificity 81 - 42% in studies of consecutive out-patients with suspected DVT (Ritchie et al 1979, Andersson S 1986, Holmgren et al 1990).

Skin temperature can also be measured with a thermotransducer, which is moved along the medial aspect of each leg; a side difference of 0.7°C in four segments being considered to be pathological. The thermo-profiles obtained yield more objective criteria for diagnosis than does the thermocamera technique used in our study. Sensitivity has been reported to be somewhat higher with the thermotransducer than with the thermocamera, but at the cost of a low specificity (Andersson S 1986, Hamberg et al 1987, Stevenson et al 1990, Holmgren et al 1990). Combining clinical data with temperature profiles was found to raise specificity somewhat (Andersson S, 1986).

Liquid crystals can also be used for thermography. The detectors are placed on the legs and temperature differences between the legs are registered with a Polaroid camera. The accuracy of this method in suspected DVT has been reported to be approximately the same as that of temperature profiles (Thomas et al 1989). In postoperative patients screened for DVT, the sensitivity was considerably lower, 33% and the specificity higher, 87% (Kjaer et al 1988).
To sum up, thermography or temperature profiles alone would not seem to be useful as single screening methods, since both sensitivity and specificity are too low to either confirm or rule out the presence of DVT. It is possible that investigators who have reported good results with these methods have interpreted the results together with symptoms and signs, in which case essentially two methods have been used together. However, objective criteria are hard to use in such situations, and the performance of the method depends on the individual doing the evaluation.

**Isotope tests**

**Earlier results**

Radio-isotope test for the detection of DVT have either been designed to examine the patency of the venous system (radionuclide venography) or have been based on incorporation or entrapment of a radiopharmaceutical within the thrombus. Patients confined to bed postoperatively manifested a reduced venous flow-rate when investigated with isotope injected in the foot veins (Payling-Wright et al 1951, Jönsson 1951). With the gamma camera, venous flow could be visualized by injection of $^{99\text{m}}$Tc-macroaggregated albumin in the foot veins (Rosenthal 1971), regions with impaired outflow indicating the presence of venous thrombosis (Ryo et al 1976, Hayt et al 1977). However, sensitivity and specificity were low, and since the isotopes are injected in the foot veins, there seems to be little advantage over venography (Gomes et al 1982).

The principle of utilizing a labelled substance that is accumulated at or in the thrombus was first investigated with $^{131}$I-fibrinogen. An accumulation of radioactivity after intravenous injection was found in experimental thrombi in rabbits (Hobbs and Davies 1960). However, an increased uptake of the isotope was also seen in other inflammatory processes such as healing of wound fractures and haematoma (Hobbs 1962). The method was soon applied in humans, especially for studies of postoperative DVT (Nanson and Palko 1965, Atkins and Hawkins 1965). To enable patients to be followed for a longer period postoperatively, $^{125}$I-fibrinogen was employed, which has a longer half life and a lower energy level than $^{131}$I-fibrinogen. An increase of radioactivity postoperatively in one leg as compared to the contralateral leg or to previous measurements in the ipsilateral leg, was found to indicate DVT (Flanc et al 1968, Negus et al 1968). For the investigation of postoperative DVT, $^{125}$I-labelled fibrinogen was administered before surgery, and the patient was examined several times postoperatively. Under these conditions, high sensitivity and specificity were
reported for the $^{125}\text{I}$-labelled fibrinogen uptake test with phlebography as a reference method (Kakkar 1972). Initially, the fibrinogen uptake test was regarded as unsuitable in the diagnosis of established DVT, since the thrombus had already formed and incorporation of fibrinogen into the thrombus could not be expected. (Flanc et al 1968). However, when the method was investigated in these patients it was found to be sensitive but with a rather low specificity (Browse 1971, Kakkar 1972, Olsson 1980, Hull et al 1981b). A disadvantage is that the test result is not available until 24 - 48 hours after the injection of labelled fibrinogen. Other substances have therefore been introduced to improve the diagnostic efficiency. A mixture of streptokinase and plasminogen labelled with $^{131}\text{I}$ failed to detect experimental thrombi (Ouchi and Warren 1962); and streptokinase or urokinase labelled with $^{131}\text{I}$ or $^{99m}\text{Tc}$ were also found to be unsuitable (Darte, Olsson and Persson 1977, Weir et al 1976).

A stable complex can be formed between porcine plasmin and $^{99m}\text{Tc}$ (Persson and Darte 1977). After intravenous injection, radioactivity was found to accumulate around experimental thrombi in rabbits (Darte, Olsson and Persson 1977). In human patients, 20 MBq of $^{99m}\text{Tc}$-labelled plasmin is injected intravenously, and the activity measured in 12 equidistant points on each leg. A side difference with at least 3% greater activity at three or more adjacent points in the symptomatic leg was considered pathological (Olsson 1979). In a series of consecutive out-patients with suspected DVT, the sensitivity was found to be 98% and the specificity 56% for DVT, phlebography being used as a reference method.

Present results

Our own study in a large series of patients (III) confirms that the $^{99m}\text{Tc}$-plasmin test has a high sensitivity (95%) for DVT. The predictive value of a negative test result was 91%, and that of a positive test was 49%, findings in accordance with those of others (Olsson 1979, Deacon et al 1980, Adolfsen et al 1982, Edenbrandt et al 1982, Jesperson et al 1983, Hustvedt et al 1984, Aronen et al 1985). The $^{99m}\text{Tc}$-plasmin test was pathological in approximately 90% of cases when any of the following signs of inflammation were present: erythema, increased skin temperature, increased calf circumference, induration or pitting oedema. The predictive value increased with the number of leg points manifesting significant uptake. Thus, the presence of DVT was confirmed by phlebography in 66% of cases where significant uptake was found at five or more points, but only in 29% of cases where significant uptake was found at fewer than five points.
Side difference in $^{99m}$Tc-activity follows an exponentially declining curve (III). The time till normalization of the test depends on the extension of the thrombus; the median time to normalization of the test was short in calf-vein thrombosis but as long as six months in femoral-vein thrombosis. Thus, in some patients with proximal DVT, the plasmin test result will remain abnormal for a long time. These findings are similar to those of Edenbrandt and coworkers (1986b). However, post-thrombotic changes per se do not necessarily cause a pathological test result, since patients with post-thrombotic changes at phlebography had the same frequency of pathological plasmin tests as patients with normal findings at phlebography (III).

The rationale for using radioactively labelled proteins such as fibrinogen, plasmin and activators of fibrinolysis was the notion that they would be selectively incorporated into a thrombus or adhere to its surface, when a high ratio between radioactivity in the thrombus and the blood would be expected. The clinical usefulness of $^{125}$I-fibrinogen and $^{99m}$Tc-plasmin seemed to prove the concept to be correct. However, since plasmin is rapidly bound to a physiological inhibitor in the circulation (Moroi and Aoki 1976), it might be suspected that the complex does not bind to a thrombus. In vitro, plasmin in complex with $\alpha_2$-antiplasmin was bound to the surface of an experimental thrombus (Tengborn et al 1982). However, this could only be demonstrated when the concentrations of $^{99m}$Tc-plasmin were much higher than these used in the investigations of patients (Edenbrandt 1986a).

The blood-thrombus ratio was determined in an animal model for $^{99m}$Tc-labelled plasmin, fibrinogen, macro-aggregated albumin, albumin-microcolloid, serum albumin, sulphur colloid, pertechnetate, erythrocytes, $^{111}$In-leucocytes, and $^{111}$In-platelets. None of these labelled reagents yielded a ratio between thrombus activity and blood activity of more than 2.2 (Ståhlberg et al 1984). In addition, a close relationship was reported between uptake of $^{99m}$Tc-plasmin and $^{99m}$Tc-erythrocytes when these were compared in patients with DVT (Edenbrandt et al 1984). Therefore, it seems evident that the diagnostic performance of plasmin is not related to a specific binding to the thrombus but rather reflects haemodynamic changes secondary to venous stasis and inflammation. This is probably also true for $^{125}$I-fibrinogen. The thrombus/blood ratio for $^{125}$I-fibrinogen, when injected before the formation of a thrombus, was reported to be 5 in a rabbit model (Ståhlberg et al 1984) and 4 in humans (Browse et al 1971). This is somewhat higher than the ratio for plasmin but probably not high enough to explain the accumulation of radioactivity in DVT, which is probably dependent on the same mechanisms as plasmin. Moreover, radioactivity as detected by a handheld detector, is highly dependent on the distance to the thrombus. Only part of
the radioactivity that is located in a thrombus in a deep vein reaches the detector, due to energy losses through tissue attenuation and thrombus-detector distance, while a much higher percentage of the activity is recorded from superficial vessels (Bernstein 1981). It was suggested that a reason why the $^{125}\text{I}$-fibrinogen uptake test results first becomes pathological after two days is that criteria used for diagnosis of DVT are less efficient than those used in the plasmin test (Edenbrandt 1986a).

Even if the $^{99m}\text{Tc}$-plasmin test does not depend on specific binding of plasmin to the thrombus, the test can still be used as a screening test to exclude the presence of thrombi. However, since albumin could be used as well, not only being commonly used for other investigations but also being cheaper, it has now replaced plasmin (Bornhov et al 1988). Probably $^{99m}\text{Tc}$-albumin could also be used for screening asymptomatic patients postoperatively or patients with prolonged bedrest.
Anticoagulant therapy

Heparin treatment

The duration of heparin treatment for DVT varies. In North America, heparin has usually been given for 7-14 days (Hull et al 1986, Coffman JD 1982), oral anticoagulation being started after 3-4 days of heparin treatment. In Europe, oral anticoagulation is usually begun at the same time as heparin, and heparin has been stopped when oral anticoagulation has become effective (i.e. after 3-6 days). Results from a randomized study showed a 9-day course of heparin not to be superior to a 4-day course, when warfarin is given concomitantly (Gallus et al, 1986).

Oral anticoagulation

After the initial hospital treatment with heparin, oral anticoagulation has been commonly continued for a period of weeks to months on an out-patient basis. Evidence of the need to continue anticoagulation treatment is scarce, and there is no agreement as to the optimum duration of treatment. The frequency of recurrence after DVT or pulmonary embolism was found to be highest during the first weeks after diagnosis and to decrease progressively over the first three years (Coon and Willis 1973). Treatment with anticoagulants, having been found to reduce the risk of recurrence, was recommended to be continued for at least four months, a conclusion based on findings in a retrospective study where clinical features were used for the diagnosis of recurrent thromboembolism (Coon and Willis 1973). In a prospective study where patients with confirmed DVT were randomized to treatment with oral anticoagulants for six weeks or six months after the initial heparin therapy (O'Sullivan 1972), no difference in recurrence rate was observed between the two groups. In a randomized study comparing warfarin and heparin as prophylaxis after initial heparin treatment, warfarin was found to be more effective than heparin in preventing recurrences (Hull et al 1979). Only patients with proximal DVT had any recurrences and it was concluded that the risk of recurrence was low in calf DVT irrespective of treatment. However, most of the calf-vein thrombi in that study were found by fibrinogen scanning of asymptomatic patients after surgery, in contrast to symptomatic patients with proximal DVT.
Recurrence of thrombo-embolism

Present results

We have tried to determine whether it is necessary to continue anticoagulation in symptomatic calf-vein thrombosis after initial heparin therapy (IV). We chose to study patients with isolated calf-vein thrombi without apparent continuing risk factors for recurrence. After initial treatment with heparin intravenously for five days, the patients were randomly allocated to oral anticoagulation treatment with warfarin for three months (n = 23) or to no treatment (n = 28). Recurrence of thrombo-embolism was found in 29% of the patients in the non-warfarin group (7 cases of DVT and 1 case of pulmonary embolism), as compared with none in the warfarin group.

The findings raise the question whether there were any special reasons for the high recurrence rate in the non-warfarin group. A history of a previous thrombotic episode was present in six patients of whom three had a recurrence. However, even if all patients with previous DVT are excluded, there would still be five recurrences among 22 patients (23%) in the non-warfarin group, as compared with no recurrence among 20 patients given warfarin (p = 0.05, Fisher's test).

Within the non-warfarin group, patients with later recurrences had a higher pain score at the end of heparin treatment than had patients without recurrence. If pain really predicts a higher risk of recurrence, it might be argued that heparin continued for 8 or 10 days might have reduced the recurrence rate. However, Coon and Willis (1973) found that, although insufficient anticoagulant treatment was correlated with the risk of recurrence during the acute phase in hospital, no such correlation was found at follow-up. Therefore, it seems unlikely that prolongation of heparin for a few days would have prevented the later recurrences.

During heparin therapy the plasma concentration of antithrombin III decreases (Blombäck et al 1963, Marciniak and Gockerman 1977), while it increases during treatment with oral anticoagulants (O'Brien 1977, Andersson G et al 1984). The decrease during heparin therapy was suggested to explain recurrences of the non-warfarin group (Huisman 1985). However, the plasma concentration of antithrombin III is normalized within 1-3 days after heparin is stopped. Since the recurrences were spread out over a considerable span of time after treatment, this explanation would seem improbable.
As neither age nor gender distribution differed between the warfarin and non-warfarin groups, such factors can not explain the higher recurrence rate in the non-warfarin group.

Need for treatment of calf-vein thrombosis

Calf-vein thrombosis has been claimed to be harmless and to require no treatment (Huismann 1985). One of the arguments for this point of view has been that in many cases calf-vein thrombi dissolve spontaneously, and that only 20-30% extend into proximal venous segment (Kakkar et al 1969). However, this conclusion was based on findings in patients screened for postoperative, mostly asymptomatic thrombi. Such thrombi may have a different natural course than thrombi in symptomatic patients, since we know that although 20-30% of patients have postoperative DVT after elective general surgery, only 1-2% have manifest symptoms (Lindhagen et al 1984, Gallus 1990). As the patients in the study of Kakkar and coworkers were only followed while in hospital, it is not known whether any of them had complications after discharge from hospital. It has been common among surgeons not to treat calf-vein thrombi (Lotke et al 1984). One reason is the increased risk of bleeding during the postoperative period, another being that the risk of pulmonary embolism is lower in asymptomatic calf-vein thrombosis than in symptomatic, proximal DVT (Moser and Le Moine 1981). On the other hand, a high incidence of pulmonary embolism (33%) in calf DVT was reported by Moreno-Cabral and coworkers (1976). Calf-vein thrombi were considered to be the most frequent source of pulmonary embolism both in clinical studies (Browse and Lea Thomas 1974) and in autopsy series (Havig 1977). It has been repeatedly found that the vast majority of venous thrombi start in the calf veins and spread proximally (Rössle 1937, Frykholm 1939, Nicolaides et al 1971, Havig 1977). Emboli that are lethal, however, arise in most cases from the iliofemoral segments (Sevitt and Gallagher 1961). It therefore seems logical to prevent the progression of the thrombus with anticoagulants to prevent the risk of dangerous embolism.

In one study, which has been frequently cited as evidence that calf-vein thrombi should not be treated, impedance plethysmography was used for the diagnosis and monitoring of DVT (Hull et al 1985). Hull and co-workers had previously found impedance plethysmography to be both sensitive and specific for proximal DVT, whereas calf DVT is not detected (Hull et al 1981b). They studied patients who had been referred because of a suspected DVT, but with an initially normal impedance plethysmography. In the first group, 311 patients were randomized to follow-up with repeated impedance plethysmography during 14 days in order to detect any calf-vein thrombi that progressed proximally. In the second group 323 patients were investigated with the $^{125}$I-fibrinogen uptake test in order to detect any calf-vein
thrombi missed at impedance plethysmography. In the first group, proximal DVT developed within 14 days in six patients and within 12 weeks in another five patients. In the second group, 30 patients had phlebography verified DVT. There ought to have been the same frequency of DVT in both groups at presentation. Therefore, it can be estimated that there should have been 29 patients with an unrecognized DVT in the first group and that 38% of them progressed, being detected by impedance plethysmography. This figure probably is an fair estimate of the risk of extension without treatment in symptomatic DVT. Hull and coworkers concluded that, since none of the patients that were followed by repeated impedance plethysmography died from thrombo-embolism and since only 3.5% (11/311) of the patients had a confirmed DVT, this was a safe and cost-effective approach. It should be borne in mind however, that only 14% of all patients screened eventually turned out to have DVT.

The policy of monitoring patients with symptoms of DVT, but with normal impedance plethysmography, and withholding treatment unless impedance plethysmography becomes abnormal has been advocated as cost-effective and safe (Hull et al 1985, Huismann et al 1986). However, in a recent report of 381 consecutive patients with suspected DVT, impedance plethysmography findings were pathological in only 18% of cases. Of the remaining patients, who were followed without treatment, ten episodes of confirmed thrombo-embolism, including four cases of fatal pulmonary embolism, occurred during follow-up (Prandoni et al 1991). Thus, there is always a risk of life-threatening complications if adequate treatment is withheld in DVT. There is also evidence that a thrombus sometimes propagates very quickly along a vein (Doig and Browse 1971). Heparin and oral anticoagulation should therefore be given to all patients with a confirmed, symptomatic DVT unless strong contraindications are present.

**Long-term sequelae after DVT**

Early investigations of sequelae after DVT showed complications to be frequent (Birger 1941, Bauer 1942, Gjöres 1956). In those patients series, however, as objective diagnosis was not available at the time of DVT there is some doubt as to the aetiology of the venous insufficiency. In a study where diagnosis was based on findings at phlebography, little correlation was found between severity of the thrombus at phlebography and late symptoms and signs (Browse et al 1980). Lindhagen and coworkers (1984), investigating patients 3-5 years after postoperative screening with the $^{125}$I-fibrinogen uptake test, found the same frequency of clinical signs of chronic venous insufficiency, 22%, in legs with a previous pathological test result as in those with a normal test. Lindhagen and coworkers (1985) also investigated patients who had been referred for phlebography 5-8 years earlier because of
suspected DVT, and found clinical signs of chronic venous insufficiency in 49% of patients with a previous DVT and in 41% of those without previous DVT. Thus, chronic venous insufficiency was twice as frequent among patients with clinical signs of DVT as in patients without such signs, irrespective of whether or not the patient had actually had a DVT.

Present results

We reasoned that the findings of Lindhagen and coworkers might be explained if the venous insufficiency was related to inflammatory reaction rather than to the presence or absence of DVT. As clinical signs at the time of diagnosis are related to the degree of inflammation around the thrombus, late outcome in terms of venous insufficiency might be expected to be related to the intensity of clinical signs. However, we found no such relationship. Thus, it does not seem possible to predict future venous insufficiency from findings at physical examination at the time of DVT diagnosis. On the other hand, phlebographic extension of the thrombi correlated with the degree of chronic venous insufficiency as well as with foot volumetric variables.

Patients with proximal DVT manifested more numerous clinical signs, a higher recurrence rate and a lower venous function at foot volumetry than those with distal thrombi. Thus, it would seem logical to diagnose and treat calf-vein thrombi before progression to proximal veins occurs. The incidence of severe venous insufficiency was low in our series, and none of the patients with DVT had developed an ulcer at follow-up. Moreover, there was no clear relationship between the patient's symptoms and the results of objective investigation. On the basis of our results, fibrinolytic therapy seems questionable. Although it can achieve thrombolysis in a high percentage of fresh thrombi, it has not been convincingly demonstrated that the long-term outcome in terms of venous function is better than that of treatment with anticoagulants (Sidorov 1989, Verstraete 1990). Although heparin and oral anticoagulants do not prevent venous insufficiency in patients with proximal DVT, they are associated with fewer acute side effects than in fibrinolytic therapy which causes cerebral bleeding in about 0.5% of cases (Wilcox et al 1988), and may increase the risk of lethal pulmonary embolism (Holmström et al 1990, Grimm et al 1990). The use of fibrinolytic therapy should probably be restricted to serious thrombotic complications (i.e. massive pulmonary embolism or phlegmasia). A noteworthy finding in the present studies were that there was no correlation between the patient's own grading of symptoms from the legs and the degree of chronic venous insufficiency (V). Venous function in patients without DVT was poor as compared with reference values, as has also been found by other investigators in similar studies (Browse et al 1980, Lindhagen et al 1984). The reason for this may be that, as pain
or swelling of the leg are more common symptoms among patients with venous insufficiency, such patients are more likely to be investigated on the suspicion of DVT.

Defective fibrinolysis has been associated with DVT (Korninger et al 1984, Juhan Vague et al 1987, Tabernero et al 1989, Engesser et al 1989). An increased concentration of endothelial cell-related level of plasminogen activator inhibitor (PAI-1) has been reported to be a marker of defective fibrinolysis (Nilsson et al 1985). If endogenous fibrinolysis is related to the break-down and recanalization of thrombi, a relationship might be expected to exist between the concentration of levels of plasminogen activator inhibitor and venous function might be expected. Therefore, we measured plasminogen activator inhibitor activity at follow-up but found no differences between patients with DVT and those without, nor was there any relationship between PAI-1 and clinical signs of venous insufficiency or the foot-volumetric variables. This is in accord with the findings by Edenbrandt and coworkers (1986b) of no relationship between fibrinolytic activity and the time to normalization of the $^{99m}$Tc-plasmin test result in patients with DVT. Thus there is no evidence that endogenous fibrinolysis affects long-term results. As PAI-1 is an acute phase reactant (Jansson et al 1989), it is possible that the degree of shut-down of the fibrinolytic system at the time when the thrombus is fresh is a determinant of outcome, but no data on this are available.

**General discussion**

In the diagnosis of DVT, phlebography continues to be the reference method after more than 50 years, and it is also the most widely available method for diagnosis. However, phlebography is not without considerable disadvantages. It is to some extent invasive, sometimes painful, involves the administration of contrast media and can not be performed in all patients. Although post-phlebography thrombosis does not seem to be a problem with modern low-osmolarity contrast media (I), there is still a risk of general and circulatory reactions, and of renal toxicity. In addition, phlebography may fail to detect thrombi in the calf, and the deep femoral vein is often not visualized (Olsson 1979). Phlebography cannot be easily repeated and it cannot be performed at the bedside. Therefore, there is a need for other diagnostic methods, especially simple screening-procedures.

Plethysmography was used early on as a screening method for DVT. In Sweden, mostly strain-gauge plethysmography has been used, whereas in North America and Holland impedance plethysmography is common. Plethysmography has a rather high sensitivity in proximal DVT (85-95%), but a much lower sensitivity in distal DVT. Even large, proximal but non-occluding DVT may be missed with this method. Since a proximal extension seems to
The fibrinogen uptake test was the first and most widely used isotope method for the diagnosis of DVT. It has primarily been used for the evaluation of different methods of preventing thrombo-embolism in surgery, but has also been used for the diagnosis of established DVT. The reported sensitivity of the fibrinogen uptake test in proximal DVT has varied from one study to another (Olsson 1979, Hull 1981). The performance of the $^{125}$I-fibrinogen test seems to be similar to that of the $^{99m}$Tc-plasmin test and also to indifferent molecules such as $^{99m}$Tc-albumin. The advantages with isotope tests are a high sensitivity and a simple test procedure, and the disadvantages are the isotope handling and low specificity. As fibrinogen is no longer available owing to the risk of spreading AIDS, and plasmin is no longer marketed, $^{99m}$Tc-albumin is currently used. Isotope-labelled antibodies to fibrin and to activated platelets on the surface of the thrombus are being investigated in animals but so far these methods have not been evaluated for use in humans (Oster and Som 1990, Knight 1991).

Thermography shows low sensitivity and low specificity (II) and does not seem to be a useful as a screening method in suspected deep venous thrombosis.

Ultrasonography has many attractive features since it is non-invasive, has no known side-effects and permits visualization of the thrombus. However, both sensitivity and specificity have been reported to be low for Doppler ultrasonography (Sigel et al 1972, Sandler et al 1984). With the development of Duplex scanning and colour Doppler techniques, both the sensitivity and the specificity have been reported to be high for proximal DVT (Lensing et al 1989, Woolson et al 1990). The drawbacks are that the sensitivity for calf-vein thrombi is low and that the performance of ultrasonography is highly dependent on the skills of the operator.

Preliminary reports indicate that magnetic resonance imaging could be used for the diagnosis of DVT, but the cost is high and method is not widely available.

With regards to biochemical markers of DVT, several promising methods such as FDP, $\beta$-thromboglobulin, FPA have been tried but not found to be useful. Recently, assays using monoclonal antibodies against cross-linked human fibrin degradation fragments, especially D-dimer, have been investigated for the diagnosis of DVT. They were found to have a reasonably good sensitivity and specificity when RIA-methods are used, whereas latex rapid
tests were found to be less reliable (Ott et al 1988, Bonameaux et al 1989). Possibly D-dimer could be used for the diagnosis of DVT in symptomatic patients, but further evaluation is necessary.

Combinations of non-invasive tests may reduce the need of phlebography. Thermography or temperature profiles together with plethysmography have been found useful by some investigators, as have plethysmography and isotope scanning by others. Probably a combination of leg ultrasound for proximal DVT together with leg scanning for distal DVT and D-dimer might reduce the number of phlebograms that are necessary to perform.

Study IV yielded strong evidence that treatment of calf-vein thrombosis is of benefit to the patient. Not only do anticoagulants have a rapid effect on the symptoms, but they also prevent extension of the thrombus, long-term postthrombotic sequelae seem to be fewer in calf-vein DVT, and the recurrence rate also seems to be lower (V). As long as we cannot predict which thrombi are innocuous, all DVT should be treated unless contraindications are present. Therefore, we need diagnostic methods which can detect calf-vein DVT.
Conclusions

From the finding in these studies (I-V) the following conclusions may be drawn:

Low-osmolarity contrast media such as iohexol appear to be safe and do not induce thrombi at phlebography, though their high cost is a problem.

Thermography would not appear to be effective as a screening method for deep venous thrombosis.

The $^{99m}$Tc-plasmin test is a rapid and sensitive test for deep venous thrombosis. However, the specificity is low due to non-specific accumulation of radioactivity in the leg. The test result is rapidly normalized in calf-vein thrombosis but not in proximal thrombosis.

Symptomatic calf-vein thrombi are associated with a high recurrence rate if treated for five days with heparin only, and the use of oral anticoagulation after initial heparin therapy is necessary.

The long-term development of venous insufficiency can not be predicted from clinical signs at the time of DVT diagnosis.

During follow-up after a phlebography performed because of suspected deep venous thrombosis, signs of venous insufficiency were more frequent among patients with a diagnosed thrombus than among those with normal phlebography findings. There was also a correlation between clinical signs, extension of the thrombus at phlebography and foot volumetric variables. No correlation was found between these measures and the patient's subjective symptoms, however. Their was no relationship between the concentrations at follow-up of plasminogen activator inhibitor and venous function or recurrence rate.

Recurrences after a first episode of deep venous thrombosis are common - 28% of patients develop new thrombi during the first six years.
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Sammanfattning på svenska

Bakgrund

I Sverige vårdas årligen knappt 4 000 patienter på sjukhus på grund av venös trombos och drygt 3 000 på grund av lungemboli (huvuddiagnos). I många fall finns en utlösande faktor t ex operation, benbrott, hjärtinfarkt, infektion etc, men ofta är den utlösande orsaken okänd. Ärfilig benägenhet att utveckla trombos på grund av brist på vissa blodproteiner förekommer men förklarar endast en liten del av trombosfallen, den viktigaste riskfaktorn tycks vara tilltagande ålder. Venös trombos drabbar oftast benen; endast ca 2% av patienterna drabbas av amputembris. Trommbildningen börjar vanligtvis i foten eller vaden och kan sedan sprida sig längre upp på benet. Mindre tromber i benen förekommer utan att ge symptom och de kan lösas upp spontant. En del av tromberna växer till och kan ge symptom som t ex svullnad, ödem, smärta och värmeökning av hud. Emellertid är sådana symptom ospecifika och förekommer även hos patienter som har andra typer av inflammationer. En fruktad komplikation till ventrombos är lungembolism, som innebär att en del av tromben bryts loss och fortsätter med blodflödet till lungan. Stora embolier kan ge livshotande symptom medan små kan förekomma utan symptom.


I slutet av 30-talet lyckades man framställa röntgenkontrastmedel som gick att använda för kärlundersökningar. Genom att spruta kontrast i en ven på fotryggen (flebografi) kunde man
få en bild av kärlet och eventuella tromber framträdde som ursparningar i kontrasten. Flebografi blev en allmänt använd metod under 50- och 60-talen. 1976 påvisades från vår klinik att de då använda röntgenkontrastmedlen hade kärlirriterande egenskaper och att det var vanligt att små tromber uppstod som en komplikation till undersökningen. Genom att använda ett lågosmolärt kontrastmedel (metrizamid) kunde denna komplikation undvikas. Metrizamid var emellertid dyrt och delvis besvärligt att handha och eftersom det framfördes att de beskrivna komplikationerna saknade klinisk betydelse, fortsatte de flesta röntgenologer att använda konventionella kontrastmedel men i lägre koncentrationer.

Eftersom flebografi är kostsam, kan vara svår att genomföra och/eller tolka och dessutom ofta är en besvärlig undersökning för patienten, har andra diagnostiska metoder prövats, i Lund bland annat $^{99m}$Tc-plasmin testet. Plasmin är ett fibrinolytiskt enzym som kan bryta ner fibrin i tromber. $^{99m}$Tc märkt plasmin injicerat intravenöst ger en ökad aktivitet i den symptomgivande sidan vid ventrombros. Man hade hoppats att plasmin skulle binda sig specifikt till tromben men senare undersökningar har visat att så inte är fallet. Anledningen att man ändå kan påvisa tromber är att plasminet ackumuleras i det sjuka benet sekundärt till inflammation och venös stås. En annan metod som hade visat lovande resultat i tidigare studier var termografi, där man använder en värmekamera för att detektera temperaturskillnader på benen.

Syfte

Vi ville undersöka om iohexol, ett lågosmolärt röntgenkontrastmedel som lanserats för att ersätta metrizamid, ger upphov till postflebogafisk trombos. Vi önskade också utvärdera klinisk diagnostik, termografi och $^{99m}$Tc-plasmin-testet i en större serie av patienter med misstänkt trombos och använda flebografi som referensmetod. Vi ville också undersöka om långtidsbehandling med antikoagulantia är nödvändig vid små vad tromber samt vilka komplikationer och symptom som föreligger på lång sikt efter en ventrombros.

Egna resultat

I arbete I jämförde vi ett lågosmolärt kontrastmedel, iohexol, med ett konventionellt högosmolärt kontrastmedel, metrizoat, i utspädd form. 43 patienter med misstänkt ventrombros men med normalt isotoptest undersöktes med flebografi. Efter denna undersökning följdes patienterna med upprepade isotoptester, dessa visade signifikant högre upptag i metrizoat- gruppen. Av 19 patienter som undersöktes med metrizoat fick 7 komplikationer efter undersökningen. Fyra patienter undersökte med förnyad flebografi, som visade kärlretning i två fall, ytlig flebit i ett fall och tromber i djupa vener i ett fall. Ingen av de 24 patienterna
som undersökt med iohexol hade någon reaktion efter undersökningen. Vid flebografi bör alltså lågosmolära kontrastmedel användas för att undvika risk för att undersökningen i sig ger upphov till trombos.

I arbete II redovisas en studie av 112 patienter med misstänkt trombos, som undersökt med termografi. Vi fann att både sensitivitet och specificitet för trombos var låga (77% resp 66%) och termografi kan därför varken säkert bekräfta eller utesluta om trombos förelåg. Metoden är därför inte användbar för diagnostik vid misstänkt venös trombos.

I arbete III jämfördes $^{99m}$Tc-märkt plasmin och klinisk diagnostik vid misstanke om venös trombos. Totalt undersöktes 396 patienter varav 307 också genomgick flebografi. På basen av symptom och kroppsundersökning graderades trombosmisstanken på en skala från 0 till 4 där 0 = säkert ej trombos och 4 = säkert trombos. När undersökaren bedömde att ventrombos säkert förelåg (score 4) var diagnosen riktig i 80% av fallen och när undersökaren var säker på att trombos ej förelåg (score 0) hade han rätt i 90% av fallen. Vid misstänkt ventrombos är det möjligt att på basen av kliniska symptom urskriva en grupp med hög sannolikhet och en grupp med låg sannolikhet för trombos. Även för dessa grupper är dock osäkerheten så stor att objektiv diagnostik är nödvändig. Majoriteten av fallen (68%) bedömdes som osäkra (score 1-3) och av dessa hade endast 37% trombos. Det finns därför ett behov av objektiva metoder för att fastställa diagnosen vid misstänkt trombos.

Genom att spruta $^{99m}$Tc-märkt plasmin intravenöst och mäta med en detektor över benen kan man påvisa sidoskillnader i $^{99m}$Tc aktivitet. Metoden är enkel, snabb och finner ca 95% av alla tromber. Isotopupptaget är emellertid ospecifikt och testet blir patologiskt vid tecken på inflammation i benet såsom rodnad, värmeökning och ödem. Den förhöjda isotopaktiviteten beror till största delen på venös stås och inflammation. ($^{99m}$Tc-albumin har visat sig ackumuleras i benen på samma sätt som plasmin och används nu rutinmässigt eftersom det är billigare och lättare tillgängligt). Ett normalt plasmin test utesluter trombos med hög säkerhet medan ett patologiskt test bör föranleda fortsatt utredning med flebografi för att bekräfta diagnosen.

I arbete IV undersöktes behovet av antikoagulantiabehandling vid vad trombos. Många har hävdats att små tromber i vaden är ofarliga och inte alls behöver behandlas eftersom man menat att de oftast löses upp spontant, medan andra behandlat med heparin med eller utan efterföljande Waranbehandling. Eftersom antikoagulantiabehandling inte är ofarlig utan medför en liten risk för allvarlig blödning (3-4% per år) ville vi undersöka om Waranbehandling är nödvändig eller om fem dagars heparinbehandling är tillräcklig vid okomplicerad