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***Observations of the Natural History and Long-term Outcomes
of Deep Venous Thrombosis***

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***A thesis submitted to the University of Dublin, Trinity College, for the
Degree of Doctor of Philosophy.***

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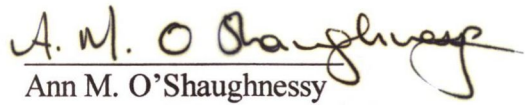
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DECLARATION

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Ann M. O'Shaughnessy

SUMMARY

One hundred above knee deep vein thromboses (DVT) from 89 patients (11 bilateral thrombosis) were examined to determine the dynamic status of the thrombi in the first year and to determine the long-term clinical outcome at three years. The patients in the study included patients with a terminal illness, with a previous history of DVT or with reversible risk factors. The mortality rate in this study was 14%. The majority of deaths occurred as a result of an underlying primary disease (e.g. cancer) and 3% died from a pulmonary embolism (PE). The treatment regime followed was carried out by a number of referring physicians from different specialities, independent of any input from the Vascular Laboratory. The initial treatment regime differed among the patients. Some physicians preferred to treat with the more established regime of intravenous (IV) heparin and bed rest instead of the more recent treatment of subcutaneous low molecular weight (SC LMW) heparin and early mobility. The duration of anticoagulant therapy also varied with most physicians treating the patient for six months regardless of their risk factors. A number of symptomatic and asymptomatic events (PE's, extension of thrombi, new DVT's) were recorded in the follow-up period especially in the initial and late phase. The asymptomatic events were diagnosed by duplex ultrasound and it is thought that probable additional asymptomatic events may have occurred but closer time intervals between duplex ultrasound scanning would be required to document them.

In the acute stage, it is important to assess the level of organisation of newly diagnosed DVT to determine its stability. The degree of organisation of a thrombus is determined by its echogenicity appearance on duplex ultrasound; however, there are many pitfalls in the subjective criteria used to describe echogenicity. The use of standardised computerised ultrasound images gives an objective and quantitative method of determining the echogenicity of thrombus. This method was used to study the natural history of the 100 acute thrombi during the first year. The grey scale median (GSM) of individual thrombi was measured at various intervals over a one-year period and the mean GSM values were calculated for each visit. The thrombi were then divided into groups – those that fully resolved, those that partially recanalised and those that remained occluded at one year. The GSM values of the groups were compared.

GSM measurement was found to be useful in the early stages of thrombus assessment to give a description of the stability or degree of organisation of the thrombus. The use of the individual GSM values over time was useful to study the thrombi individually; however, the dynamic process that occurred in the first year was not reflected in the mean group values.

The lower extremity venous segments differ with respect to their contribution to the post-thrombotic syndrome and similarly individual venous segments differ in respect to their tendencies to recanalise or to remain occluded. The subsequent course of residual abnormalities following an acute DVT can

vary within individual venous segments. The pattern of response of the acute DVT within the individual venous segments was examined and the differences were investigated. The anatomical segments involved in the patients at one year (N = 63) were examined and the anatomic and hemodynamic information at each individual site was compared.

The majority of the DVT's were multi-segmental with a total number of 171 proximal sites involved. Initially a greater number of segments were occluded than partially thrombosed. The occluded segments were predominately in the superficial femoral (SFV) and popliteal veins (PV). At one year, the thrombi had fully resolved in 60% of the venous segments, 27% remained partially recanalised and 13% were totally occlusive. The venous segments that resolved within the first six months had a higher valvular competence rate than those that resolved from six months to one year. The SFV and PV had a higher incidence of valvular incompetence than the external iliac (EIV) and common femoral vein (CFV). All venous segments that were partially resolved at one year were found to have valvular incompetence. The SFV had the highest incidence of total occlusion at the end of one year. The high rate of occlusion in the SFV may be influenced by local venous hemodynamic factors. Often competent collateral pathways were visualised on ultrasound running parallel to the occluded SFV. No retrograde flow was found in these collateral pathways

Sixty-three patients were followed up to a mean of three years. The initial risk factors were compared with the long-term outcome to determine if an underlying venous disease in the contralateral limb was an indication of a more severe long-term clinical outcome. Clinical examinations and duplex studies, including reflux studies were performed at yearly intervals and the patients were classified using the CEAP classification. The patients were divided into two groups. Those without and those with a history of a contralateral DVT and the ipsilateral and contralateral limbs were compared.

There was a significant difference in the incidence of symptoms between the ipsilateral limbs ($P > 0.01$) and the contralateral limbs ($P > 0.001$) for both groups. There was no significant difference between the incidence of superficial reflux between the ipsilateral and contralateral limbs but the deep venous system and perforators were involved more often in the ipsilateral limbs. For group 1 (i.e. no history of a contralateral DVT) only 10% of the patients had no evidence of venous dysfunction in their ipsilateral or contralateral limbs at the time of the final examination and all had reversible risk factors. In patients who had a mild clinical outcome (CEAP score 1-3), 64% of them had a normal contralateral limb and the remaining 36% of them had mild to moderate disease. Eighty percent of patients with the most severe clinical outcome (CEAP > 3) had mild to moderate venous disease on their contralateral limb and had non-reversible risk factors. All the patients in group II (i.e. with a history of a contralateral DVT) had evidence of mild to severe disease bilaterally.

In conclusion, the diagnosis and treatment of DVT continues to be a major clinical problem. There is still some confusion as to the type and length of

treatment needed and to the long-term prognosis of a DVT. Little consideration is given to asymptomatic events with physicians' dependant on unreliable clinical symptoms to determine if recurrences occur. Venous hypertension, which is the primary cause of the post-thrombotic syndrome, can derive from primary as well as post-thrombotic venous reflux. There were a significant number of patients presenting with an acute DVT who had an underlying venous disease in the uninvolved contralateral limb. Patients with primary venous reflux are more likely to develop an ipsilateral post-thrombotic limb following an acute DVT. The level of venous dysfunction on the contralateral limb is an indication of the severity of disease developing in the ipsilateral limb. The initial risk factors of the patients have an influence on the final clinical outcome.

1. INTRODUCTION

Venous disease had been known to exist since ancient times and reference to it can be found in early Egyptian and Greek writings. The rate of deep vein thrombosis (DVT) has been estimated to affect more than 250,000 patients per year in the USA and is treated by nearly all specialities in medicine. There are 300,000 to 600,000 hospitalisations associated with DVT or pulmonary embolism (PE) yearly (Consensus 1992). DVT is associated with an increased mortality rate, especially in the elderly and has considerable health care costs. Treatment of DVT involves anticoagulation but confusion still exists as to the correct duration of treatment. It is also thought that the level of anticoagulation achieved with present therapeutic regimes may be inadequate as there continues to be a high recurrence rate.

The long-term prognosis of the patient with a DVT is complicated by three main factors: - death, post-thrombotic syndrome (PTS) and recurrences (Leizorovicz 1998). Even when treated a small percentage of patients die from a pulmonary embolism, but more likely the major causes of death are from the underlying diseases that are associated with thromboembolism, including cancer (Peterson 1999). Chronic venous disease is one of the most serious long-term outcomes of DVT. The incidence of the post-thrombotic syndrome following a DVT has been well documented (Meissner *et al* 1998; O'Shaughnessy *et al* 1997; O'Shaughnessy *et al* 1997). It is known that the PTS occurs in 60-70% of cases when patients are monitored between five and 10 years after conservative treatment of DVT (Meissner 1995; O'Shaughnessy *et al* 1997; Saarinen *et al* 1995). However, 20-30% of limbs have no signs or symptoms following a DVT and 32% of the contralateral limbs, without DVT, have positive signs and symptoms (Meissner *et al* 1993; Taheri *et al* 1993; Heldal *et al* 1993). The question why some patients develop a post-thrombotic limb while others remain asymptomatic remains unanswered.

Serial duplex examination has become the method of choice for studying the natural history of DVT (O'Shaughnessy *et al* 1996; O'Shaughnessy *et al* 1997; van Gemmeren *et al* 1991; Meissner *et al* 1998, Johnson *et al* 1996). It has proven to be an effective diagnostic tool for the assessment of the status of an acute venous thrombosis in the lower extremity and to assess its effects on long-term venous function. One of the advantages of duplex scanning is that it can give information on the morphology of a thrombus. The ability to characterise a thrombus and to determine whether it represents an acute or chronic process has important implications in the treatment of deep vein thrombosis.

The degree of organisation of a thrombus is determined by its echogenicity appearance on duplex ultrasound. Whereas this has been proven to be a reliable method of assessment, it is subjective and depends greatly on the expertise and experience of the operator. Recent studies have shown that computer-based assessment of atherosclerotic plaque characteristics are a

more objective operator-independent method for determining plaque echodensity and the identification of high-risk lesions (Ramaswami *et al* 1999; Gronholdt *et al* 1998). In a similar manner, by using commercially available computer software, the ultrasound image of a thrombus can be captured, standardised and a measure of its grey scale median obtained. Since the level of echogenicity is directly related to the degree of organisation of a thrombus, this can be used as an objective method to describe the stage of organisation.

Differences are observed both between individuals with DVT as well as between different segments of the lower extremity veins. Individual difference in response of the fibrinolytic system is an important factor in the long-term outcome following a DVT ((Killewich *et al* 1997). Also, individual venous segments in the lower extremity seem to respond in a different way to the presence of a thrombus. The anatomical site of reflux appears to be important in determining the development of clinical signs and symptoms (Johnson *et al* 1996, Markel *et al* 1992, Labropoulos *et al* 1996, Haenen *et al* 1998). Patients with significant reflux in the popliteal and the calf perforators develop the most severe clinical symptoms. However, venous insufficiency can develop from primary as well as from post-thrombotic causes. Therefore it is important in long-term studies to include the contralateral limb to determine if the patient has an underlying venous disease (Linder *et al* 1986).

The CEAP (Clinical, Etiology, Anatomic, Pathophysiologic) classification provides a uniform means of classifying and grading the severity of the clinical findings (Beebe *et al* 1995). The classification addresses the clinical, etiologic, anatomic and pathophysiologic mechanisms and requires objective testing to support these diagnoses. The CEAP classification does not take into account the past history of the patient; however, it is known that the initial risk factors for the development of a DVT have strong influence on the long-term outcomes. Therefore, the initial risk factors need to be included when examining the long-term clinical symptoms.

The purpose of this study was to document the dynamic status of deep vein thrombosis within the first year and to study the long-term clinical outcome of the patient up to a three-year period. The lower extremity venous system was divided into anatomical segments that were examined sequentially by duplex ultrasound to obtain anatomic and hemodynamic information of each individual site. The proximal veins of the lower extremity were investigated to see if, in the presence of an acute thrombus, a pattern of response exists within the individual sites and to determine if some of the venous segments are more likely to recanalise or remain occluded. Examination of the level of venous dysfunction after three years was classified according to the CEAP classification. Both the ipsilateral and contralateral limbs were included in the study to determine if the presence of venous disease in the contralateral limb had implications in the long-term clinical outcome

2. LITERATURE REVIEW

2.1. INTRODUCTION

Venous insufficiency of the lower extremities is one of the commonest vascular disorders. Most venous disease is either a result of problems in one of two mechanisms - venous thrombosis or venous incompetence.

In 1846 Virchow first introduced the term "thrombus" which he defined as a "real coagulation of the blood at a certain fixed spot". He formulated the famous triad for the pathogenesis of venous thrombosis - stasis, changes in the vessel wall and changes in the blood (Virchow 1846).

There are three possible causes of venous thrombosis postulated: 1) a primary lesion in the intima involving the endothelium which produces an inflammatory reaction and then thrombosis; 2) a slowing or other abnormality of flow resulting in the adhesion of formed elements to the intima leading to thrombosis; 3) an increase of blood coagulability from changes in the physical and/or chemical properties of the formed elements of the plasma.

The natural history of deep vein thrombosis (DVT) and pulmonary embolism (PE) is almost exclusively drawn from hospital patients. Little is known of their prevalence in the community, though they certainly occur and may be under diagnosed.

The most serious complication of a DVT in the acute phase is pulmonary embolism. Pulmonary emboli are emboli from a point of origin that enter into a systemic vein and cross into a pulmonary artery causing obstruction that may result in immediate death.

A post-thrombotic limb is the most serious late complication of a DVT. Two major sequelae of DVT are obstruction to outflow due to the presence of residual thrombus and reflux due to valvular damage. After a venous thrombosis subsides, the clot may gradually organize occluding the vein or it may recanalise slowly destroying the valves. The valvular damage allows for retrograde flow within the vein that eventually leads to symptoms of oedema, development of pigmentation due to hemosiderin, dermatitis and induration and ultimately ulceration.

2.2. VENOUS ANATOMY

The function of veins is to return the blood from the capillaries throughout the body to the heart. In general veins are larger and more numerous than the arteries and their walls are thinner. Vein walls consist of the adventia, media and intima. The adventia is the outermost coat of the vessel consisting of loose connective tissue and longitudinal collagenous fibers. The media

consists mainly of smooth muscle running in a circular direction. The muscle bundles are separated by collagenous fibers running in a longitudinal direction. The intima consists of a thin basement membrane with irregular polyhedral endothelial cells situated on the internal surface (Williams *et* Warwick 1997).

The nutrition of the vessel wall is supplied by vasa vasorum, which compose an arterio-venous circulation in the wall of the vessel. Capillaries from nearby arterioles carry blood to the tissues of the vein wall while small venules drain it away. Occasionally these venules drain into the lumen of the vessel itself (Figure 2.1).

Veins contain valves that are bicuspid. Each cusp consists of a thin layer of collagen with endothelial cells covering both of its surfaces and contains a variable amount of smooth muscle. There is an increase in muscle fibers in the media at the base of the cusp of the valve, making the vein wall thicker. The function of a valve is to allow flow in one direction only and reduce the transmission of intravenous pressure in a retrograde direction (Fegan 1967).

There are two sets of veins in the body, the pulmonary and the systemic veins. The pulmonary veins contain arterial blood that they return from the lungs to the heart while the systemic veins are those veins in the general circulation. Only veins in the lower extremity are described in this section.

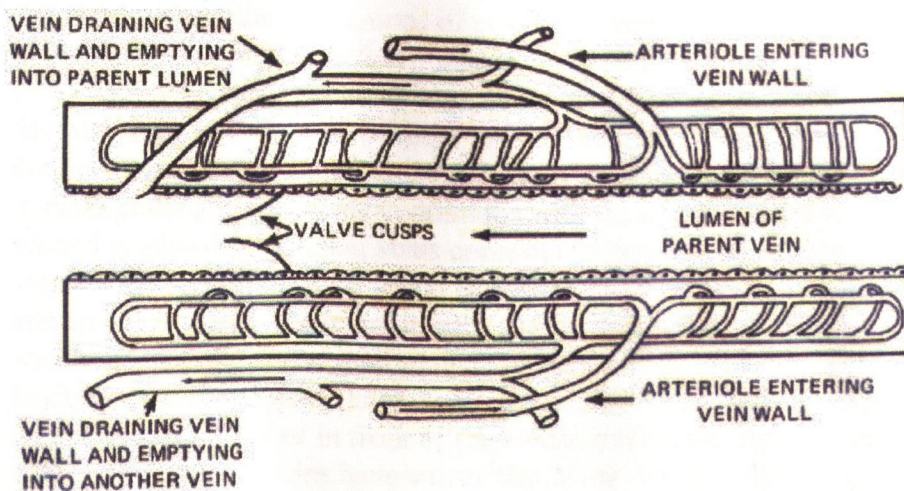


Figure 2.1: Patterns of blood vessels in vein wall.

2.2.1 Veins of the foot:

The deep veins of the foot are the deep plantar venous arch and the medial and lateral plantar veins. The deep plantar venous arch runs from the proximal end of the first interosseous space, where it is continuous with the venae comitantes of the dorsalis pedis artery, across the foot to the base of the fifth metatarsal, accompanying the deep plantar arterial arch. It receives the deep metatarsal veins and tributaries from the surrounding muscles and is continuous at its lateral end with the lateral plantar veins that run back across the sole.

The medial plantar veins run from the medial end of the deep plantar venous arch along the medial edge of the sole to join the lateral plantar veins below the medial malleolus and form the posterior tibial veins. The plantar vein receives numerous tributaries from the surrounding muscles, and from the superficial tissues of the sole. They have frequent valves that allow only proximal blood flow (Pegum *et al* 1967).

The superficial veins of the dorsum are the dorsal venous arch, the marginal veins and the anterior vein of the leg. The dorsal venous arch lies over the proximal ends of the metatarsal bones. On the medial side it runs back along the medial side of the dorsum to become continuous with the long saphenous vein in front of the medial malleolus. On the lateral side it runs below the lateral malleolus and becomes continuous with the short saphenous vein. The arch receives the dorsal metatarsal veins, the marginal veins, and tributaries from the superficial tissues of the sole. The anterior vein arises from the distal part of the dorsal venous arch and runs back across the dorsum of the foot and up the anterior aspect of the leg.

In the foot, there are two groups of perforator veins - one in the dorsum and the other in the sole of the foot. There are those that connect the superficial veins with deep veins on the dorsum of the foot (the venae comitantes of the dorsalis pedis artery). Two of these are constant, and connect the ends of the dorsal venous arch with the point at which the venae comitantes of the dorsalis pedis artery become continuous with the anterior tibial veins. The second group of perforating veins connects the superficial veins with the deep veins of the sole. These are found at both margins of the foot and in the first interosseous space. There are usually five on the medial border of the foot, of which the most posterior is large and constant in site. This connects the junction of the medial and lateral plantar veins with the medial end of the dorsal venous arch, just in front of the medial malleolus. Approximately 50% of these perforating veins have valves that allow blood to flow only from the deep to the superficial veins (Pengum *et al* 1967; Williams *et al* Warwick 1997; Dodd *et al* Cockett 1976).

2.2.2 Deep venous system in the calf:

The deep veins of the leg are the venae comitantes of the arteries: - the anterior and posterior tibial veins, the peroneal veins, the popliteal veins and

the intra-muscular veins. The veins are duplicate in the calf and run parallel to the arteries. They contain many valves that allow for only proximal flow (Figure 2.2).

The anterior tibial veins are formed by a continuation upward of the venae comitantes of the dorsalis pedis artery. They accompany the anterior tibial artery, passing between the tibia and fibula to the upper interosseous membrane where they form, with the junction of the post tibial and peroneal veins, the popliteal vein. The anterior tibial veins receive tributaries from the muscles of the anterior compartment of the leg and several perforating veins.

The posterior tibial veins are formed by the junction of the medial and lateral plantar veins below the medial malleolus. They run upwards, parallel to the artery, between the superficial and deep groups of flexor muscles of the leg. They receive many tributaries from the surrounding muscles and many perforating veins.

The peroneal veins arise from the postero-lateral aspect of the calcaneum to run behind the inferior tibio-fibular joint, and upwards between the flexor hallucis longus and tibialis posterior. They receive tributaries from the surrounding muscle and perforating veins and join the posterior tibial veins and then the anterior tibial veins at the lower border of popliteus to form the popliteal vein.

The popliteal vein ascends through the popliteal fossa, crossing superficially from the medial to the lateral side of the popliteal artery to the tendinous aperture in the Adductor magnus, where it becomes the femoral vein. It is often re-duplicated, especially below the knee-joint line. It receives the intra-muscular veins from the gastrocnemius muscle and usually the short saphenous vein.

The intra-muscular veins of the leg are the gastrocnemius and soleus veins. These intra-muscular veins are compressed and emptied when the muscles contract, providing the pumping action which aids venous return. The gastrocnemius veins drain the heads of the gastrocnemius and join the popliteal vein. The soleus muscle contains a variable number of wide, thin walled veins called sinuses, which run the length of the muscle. In the lower half of the leg these drain by short vessels into the posterior tibial veins. The deep flexor muscles are drained by short vessels that join the posterior tibial and peroneal veins at intervals. The upper half of the soleus drains into both the posterior tibial and peroneal veins.

2.2.3 Superficial veins of the calf:

The superficial venous system in the lower extremity consists of the long (great) saphenous and the short (small) saphenous veins, their tributaries, and the communicating veins connecting them. The long saphenous vein commences in front of the tip of the medial malleolus, as the continuation of the medial limb of the dorsal venous arch of the foot and runs upwards in

front of the medial malleolus, inclines posteriorly, crossing the medial surface of the tibia, runs along the medial aspect of the calf and passes behind the medial condyle of the tibia into the thigh. It has two main tributaries in the leg - the anterior vein and the posterior arch veins. The anterior vein arises from the distal part of the dorsal venous arch of the foot, runs up the anterior aspect of the leg lateral to the anterior border of the tibia where it usually joins the long saphenous just below the tibial tuberosity. The posterior arch vein begins behind the medial malleolus occasionally communicating with the constant most posterior perforating vein on the medial border of the foot. It runs upwards to join the long saphenous vein just below the knee.

The short saphenous vein begins at the lateral malleolus as the continuation of the lateral limb of the dorsal venous arch. It ascends along the lateral border of the Achilles tendon and along the mid line of the posterior aspect of the leg. It perforates the deep fascia in the lower part of the popliteal space and usually terminates in the popliteal vein between the heads of the Gastrocnemius muscle, although the junction may be at any level above the joint line. In approximately one quarter of cases the short saphenous vein does not join the popliteal vein but joins the deep veins in the thigh (Dodd *et* Cockett 1976). Before it perforates the deep fascia it gives off a communicating branch, the Giacomoni vein, which passes upward and inward to join the long saphenous vein in the upper thigh. The short saphenous has a number of valves present varying from three to nine with one always at the termination in the popliteal vein.

2.2.4 Perforating veins of the calf:

The perforating veins of the leg all have valves that allow blood flow only from the superficial to the deep veins. They are typically associated not with the saphenous veins, but with their tributaries and may conveniently be divided into four groups according to the deep veins with which they are connected (Dodd *et* Cockett 1976).

The anterior tibial group of perforating veins connects the anterior vein of the leg with the anterior tibial veins. There is a variable number, from three to ten, of which three are constant. The lowest is at the level of the ankle joint, the second is about halfway up the leg and often called the mid-crural vein. The third is at the point at which the anterior vein of the leg curves medially to cross the anterior border of the tibia.

The posterior tibial perforating veins connect the posterior arch vein with the posterior tibial veins, running in the transverse inter-muscular septum. They can be divided into lower, middle and upper groups. The total number of posterior tibial perforating veins may be as high as sixteen, but the usual figure is five or six. The lower group is found in the lower third of the leg. The middle group is found in the middle third of the leg, and the veins pierce the deep fascia behind the medial border of the tibia. In the upper group there are one or two, piercing the deep fascia just behind the medial border of the tibia.

On the posterior surface of the leg there are a group of soleal perforating veins that join the veins of the soleus and gastrocnemius muscles. These often leave the communicating veins joining the short saphenous to the long saphenous vein.

The peroneal group of perforating veins are found along the line of fusion of the deep fascia with the posterior inter-muscular septum. Two are constant, the lateral ankle perforating vein at the junction of the middle and lower thirds of the leg and the other one just below the neck of the fibula.

2.2.5 Veins of the thigh:

The deep veins of the thigh are: the upper part of the popliteal vein, the femoral vein and the profunda femoral vein. The popliteal and femoral vein may be duplicated. The profunda vein communicates with the femoral where it joins the plexus in the adductor canal and also about five centimetres below the inguinal ligament where the two vessels join. These veins receive tributaries from the surrounding muscles and perforating veins, of which the termination of the long saphenous vein is the largest (Figure 2.2).

The upper part of the popliteal vein lies on the lateral side of the popliteal artery at the hiatus in adductor magnus, where it becomes the femoral vein. The femoral vein crosses behind the femoral artery from lateral to medial in its course through the adductor canal and femoral triangle. It receives numerous muscular tributaries and just below the inguinal ligament it is joined by the profunda femoris and then the long saphenous vein. The femoral vein may have four to five valves, the commonest site being distal to the point of entry of the profunda vein and at or just distal to the inguinal ligament. Surgeons generally prefer the term the 'superficial femoral vein' for the deep vein from the adductor hiatus to its junction with the profunda, corresponding to the surgical terminology of the arteries, the profunda being considered as a separate major vein (Mavor *et* Galloway 1967). This term will be used in this study to distinguish the thigh region of the femoral vein.

The superficial veins of the thigh are the long saphenous vein and its tributaries. The long saphenous enters the thigh behind the medial femoral condyle and runs up the medial aspect of the thigh. It arches slightly forward to join the femoral vein just below the inguinal ligament. Its postero-medial tributary runs from the posterior aspect of the thigh to join the long saphenous vein usually at the level of the junction of the middle and upper thirds of the thigh or higher. The antero-lateral tributary of the long saphenous vein begins at the lateral side of the upper leg, runs upwards on the antero-lateral aspect of the knee and then obliquely, across the anterior aspect of the thigh, to join the long saphenous vein at any point between the mid-point of the thigh and the saphenofemoral junction. The long saphenous vein is joined at the saphenofemoral junction by the superficial circumflex iliac, superficial epigastric and the superficial external pudendal veins before it passes through the saphenous opening. In the long saphenous vein, the

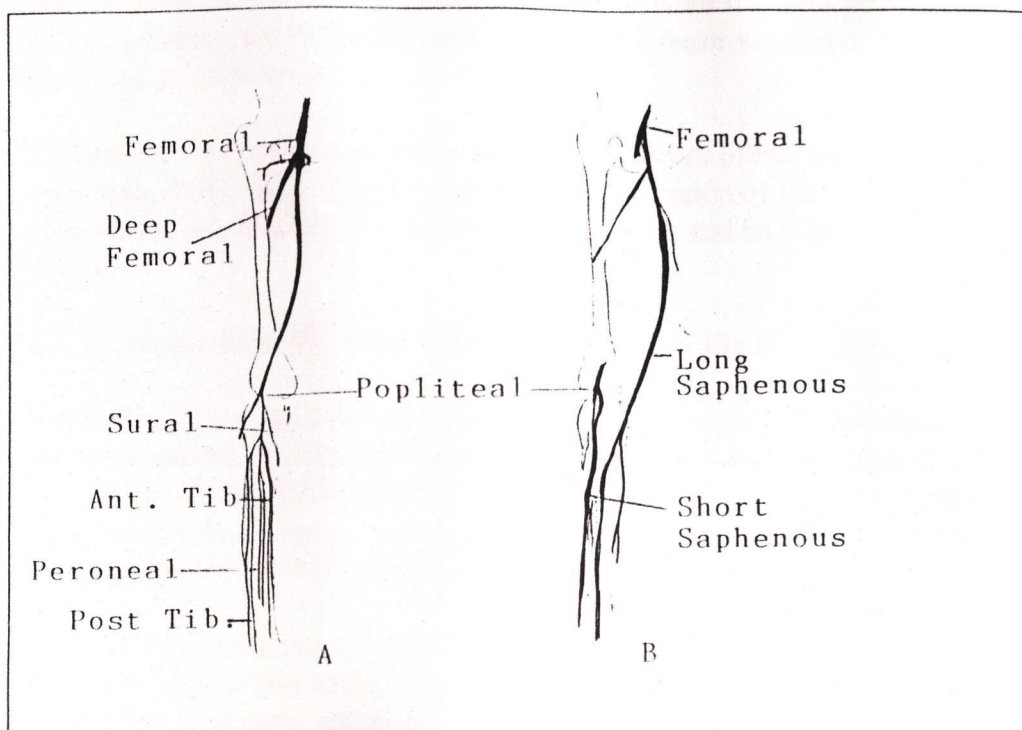


Figure 2.2: Venous anatomy of the lower extremity.
(A): Deep venous system; (B): Superficial venous system.

number of valves is more numerous in the thigh than in the calf and can vary from two to six with a constant valve at the termination of the vein.

The perforating veins in the thigh connect the long saphenous vein with the femoral vein in the lower, mid and upper (Hunter's) adductor canal. There are three other perforating veins. Two are connected with the antero-lateral tributary of the long saphenous vein and one where the postero-medial tributary of the long saphenous vein crosses the tendons.

2.2.6 The pelvic and abdominal veins:

The external iliac vein commences at the termination of the femoral, beneath the inguinal ligament and ascends along the brim of the pelvis terminating by uniting with the internal iliac to form the common iliac vein. On the right side it lies at first along the inner side of the external iliac artery, but as it passes upward gradually inclines behind it. On the left side it lies on the inner side of the artery. It receives the deep epigastric and deep circumflex iliac veins and a small pubic vein.

The internal iliac vein is formed by the venae comitantes of the branches of the internal iliac artery. It lies first on the inner side, then behind the internal iliac artery and terminates opposite the sacro-iliac articulation by uniting with the external iliac to form the common iliac vein. This vessel has no valves.

The common iliac veins pass obliquely upward toward the right side and terminate where the two sides unite to form the inferior vena cava. No valves are found in these veins.

The inferior vena cava passes upwards along the front of the vertebra on the right side of the aorta, and perforates the central tendon of the diaphragm, entering the pericardium. It terminates in the lower and back part of the right auricle.

2.2.7 Collaterals of the deep venous circulation of the lower leg:

The collateral venous channels of the lower limb are important in regard to the acute and chronic symptoms of venous thrombosis and their capabilities have direct clinical implications in the long-term prognosis following a deep vein thrombosis. Venous occlusion can be divided into lower segment or femoro-popliteal thrombosis and upper segment or iliofemoral thrombosis.

Cadaver studies by Mavor and Galloway from 22 dissections found that the profunda femoris vein had a direct communication with the popliteal vein in 39% of the specimens and an additional 48% via one of the latter's tributaries (Mavor *et al.* 1967). Thus, in 86% of limbs the profunda vein is a potential bypass collateral to the femoro-popliteal. In only one leg, the profunda had no connection with the venous plexus of the popliteal fossa and was incapable of acting as a collateral channel. Venae comitantes of the popliteal and femoral arteries were found in every instance; therefore, in every limb there was a potential bypass of the femoral popliteal segment. Also, the long saphenous system provides a constant long bypass because of its communications with deep veins above and below the knee (Figure 2.3).

Collateral channels become enlarged and more direct and linear when compared to their size in normal limbs. The valves may remain competent even in the presence of such marked enlargement. The enlarged collaterals may be mistaken for the original or a recanalised main channel.

The collaterals in the upper segment consist of two groups - the ipsilateral and the contralateral or crossover collaterals. The ipsilateral collaterals include; internal iliac vein and its tributaries; ascending lumbar veins bypassing the common iliac on the same side; venae comitantes of the external and common iliac arteries opening into the ascending lumbar vein or inferior vena cava; and lateral femoroiliac circle formed by the medial femoral circumflex and deep circumflex iliac veins. The cross over collaterals connect the internal iliac vein or its tributaries on the obstructed side with the internal iliac system of the other side, so that the venous drainage of one leg ultimately returns by way of the contralateral iliofemoral segment (Figure 2.4). The contralateral or crossover collaterals include the superficial, scrotal or vulval plexuses connecting the superficial epigastric and superficial pudendals, tributaries of the long saphenous veins of each side, or Inguino-axillary anastomoses; visceral, i.e. bladder, prostate, and broad ligament plexuses; and

the presacral plexus. For these veins to act as collateral channels they may dilate to a size that renders their valves incompetent.

When venous occlusion is limited to the lower segment, the collateral circulation is adequate and evidence of general venous stasis absent. However, with iliofemoral venous thrombosis the collateral venous circulation is inadequate, and the morbidity of the leg is generally severe (Mavor *et* Galloway 1967).

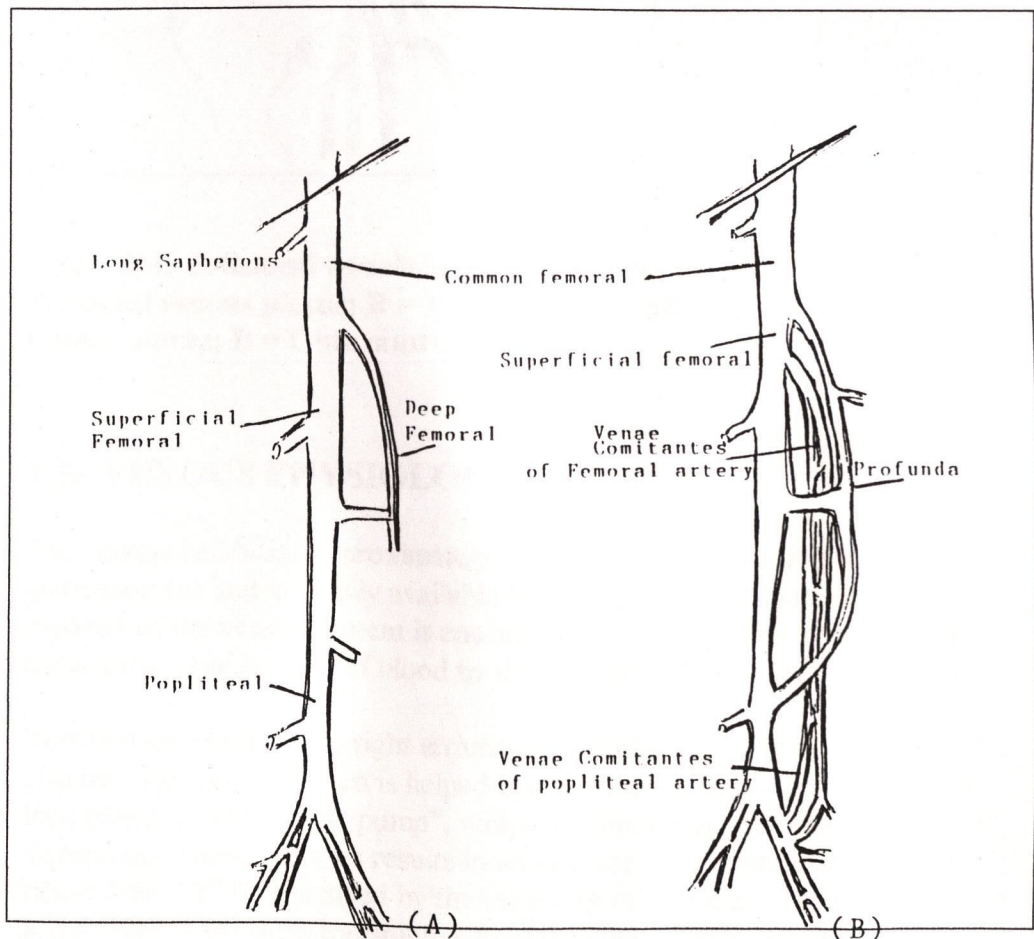


Figure 2.3: The deep venous system of the lower limb.
A: Classical anatomy. B: Collateral pathways.

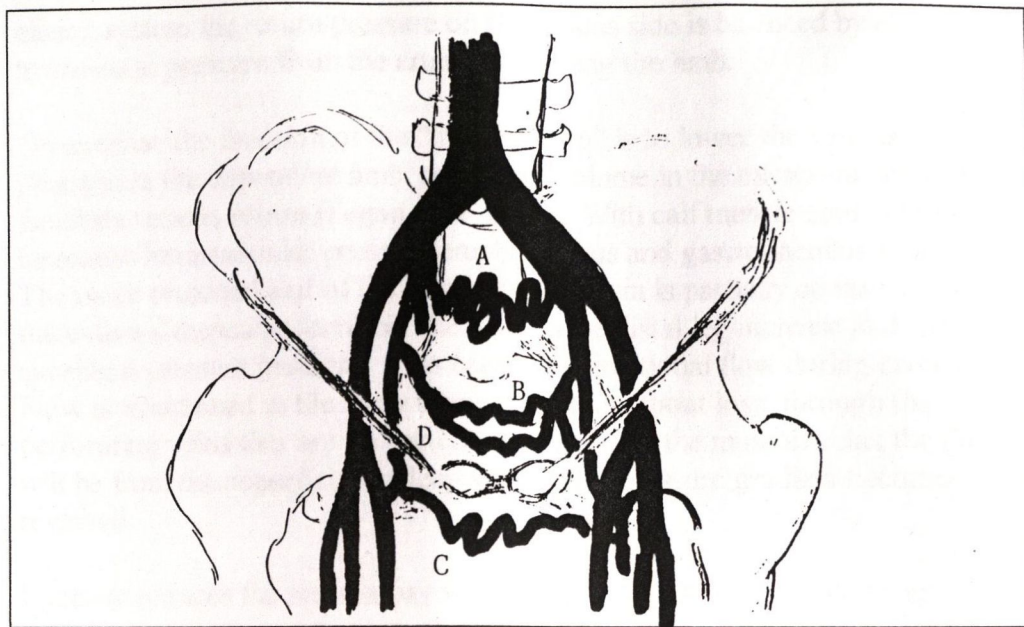


Figure 2.4: Collateral vessels in the case of iliac obstruction. (A = Presacral venous plexus; B = Visceral venous plexus; C = Suprapubic venous plexus; D = Obturator vein).

2.3. VENOUS PHYSIOLOGY

The venous bed holds approximately 70-75% of the circulating blood at any given moment and is readily available for sudden increase in diameter. The capacity of the venous system is enormous; it is a slow-flow system that can transport a large volume of blood to the heart at very low pressure.

Veins return blood to the right atrium and therefore must work against gravity. The venous return is helped by the pumping action of the calf and foot muscles, "the muscle pump", which compress the deep veins. Contraction of the muscles results in an increase in pressure that thrusts the blood forward. This is aided by the *vis a tergo* (the force from behind) which is the positive pressure transmitted from the capillaries to the venous bed and the *vis a fronte*, which is the negative pressure within the thorax causing a sucking action during inspiration.

In the horizontal plane, the hydrostatic pressure will be equal at all points. At rest venous flow is phasic and is dominated by respiratory movements, decreasing during inspiration and increasing with expiration. A Valsalva manoeuvre will cause the intra-abdominal pressure to change and flow will stop completely.

Venous pressure on standing would be equal to the distance from the foot to the right atrium or about 100 mmHg due to the hydrostatic pressure of a column of blood extending to the right atrium. Since the vascular system is a

closed system the return pressure on the venous side is balanced by an equal hydrostatic pressure from the arteries supplying the limb.

On exercise the function of the "muscle pump" is to lower the venous pressure in the dependent limb, reduce the volume in the exercising area and facilitate venous return (Fegan *et al* 1964). With calf muscle contraction, the increased intramuscular pressure empties soleus and gastrocnemius veins. The more proximal end of the posterior tibial vein is partially compressed by the external muscular force but the veins in the distal leg increase in diameter causing a pressure gradient. This causes unidirectional flow during exercise. Flow is maintained in the deep venous system, without loss, through the perforating veins that are protected by valves. As the muscles relax the flow will be from the superficial to deep veins as the pressure gradient becomes reversed.

Exercise reduces the ambulatory venous pressure. On resting following exercise the pressure returns to the level before exercise. The venous flow patterns and direction during exercise are dependent upon the competence of the valves. In the foot flow is normally directed from the deep to the superficial system while in the lower leg flow is in the opposite direction - superficial to deep. The most common failure of the venous system is valvular incompetence which results in symptoms ranging from varicose veins to severe ulceration of the lower limb. Studies have shown that a deficiency of the calf muscle pump is significant to the severity of venous ulceration and in the post-thrombotic limb there is a minimal drop in venous ambulatory pressure during exercise (Cranley 1975).

2.4. RISK FACTORS FOR DVT

There are a number of well-established risk factors for thromboembolism. Venous stasis is an important contributory factor. Any situation where venous stasis occurs (e.g. airplane journey, decreased cardiac output, prolonged bed rest etc.) can cause the development of a thrombus, especially in a patient with other contributing factors (Rosendaal 1993).

2.4.1 Thrombophilia:

Inherited deficiencies of antithrombin and of the vitamin K-dependent anticoagulants protein C and S are linked to a high risk of venous thrombosis, including pulmonary embolism. The condition is only prevalent in western and eastern Caucasians. Estimates of its prevalence have ranged widely from 1:350 to 1:30-40 000. The prevalence is 3-5% in the Netherlands, 5% in Sweden and 2% in Austria or about one person in 400 in the European population (Greaves *et al* Preston 1993).

Congenital predisposition to thrombosis should be considered in patients who have an unexplained episode of thrombosis below the age of 40, recurrent

DVT, and a positive family history. The evidence suggests that they are responsible for approximately 2-5% of venous thromboembolism occurring in adults below the age of 45 years (Greaves *et al* Preston 1993). The frequency of congenital thrombophilia in consecutive patients with confirmed venous thrombosis is approximately 8% (European Consensus Statement 1992).

The recommended screening tests are complete blood count including platelets, Antithrombin III, Protein C, Protein S and fibrinogen/thrombin clotting time, activated partial thromboplastin time (APTT), and anticardiolipin antibody.

2.4.2 Surgery:

Local and systemic activation of the clotting cascade begins during surgery. This activation, coupled with local trauma caused by surgery, may contribute to the development of DVT following surgery. Also, stasis caused by bed rest or poor mobility and with secondary activation of coagulation may be the cause a later DVT following surgery and the risk may extend beyond hospitalization.

Extensive surgical procedures, orthopedic surgery, surgery for malignant disease or those who sustain major trauma are at risk for developing venous thromboembolic disease (Pineo *et al* 1995). The degree of risk increases with age, obesity, malignancy, prior history of venous thromboembolism, varicose veins, and thrombophilic states.

Total hip replacement (THR) is considered a high-risk procedure and is associated with a fatal pulmonary embolism rate of 1 - 10% (Murray *et al* 1996). Pulmonary embolism is still the largest single cause of postoperative mortality following total hip replacement (Stewart *et al* 1990).

Approximately 50% of patients undergoing elective total hip replacement develop thrombi in the deep veins of the leg. The location of the wound might be one factor contributing to the high incidence of DVT in the operated leg although, development of thrombi in the contralateral leg suggest the possibility that mediators generated and acting during the operation are the initiating event (Stewart *et al* 1990).

In patients having vascular reconstructive surgery and, in particular amputation, there is a moderate risk of DVT despite the application of standard prophylactic measures (Fletcher *et al* Bastiste 1997).

Recent studies have shown that patients with venous wall thickening detected prior to surgery have a greater risk of developing postoperative proximal DVT (Cracowski *et al* 1998). Venous wall thickening is usually associated with the DVT sequelae and may be a more accurate way than clinical history of evaluating whether the patient had a previous DVT.

2.4.3 Medical:

Immobilized patients with chronic illness are all at risk to develop a DVT. Contributing factors include advancing age, venous stasis due to immobilization and the activation of blood coagulation.

Without prophylaxis 50-80% of patients with hemiplegia develop DVT, usually involving the paralysed limb, due to the absence of a functioning calf muscle pump. The incidence of proximal vein thrombosis in patients who do not receive prophylaxis is approximately 15 - 25%. The risk of death from pulmonary embolism after stroke is approximately 13% (Leclerc 1995).

2.4.4 Oral Contraceptive/Hormone Replacement Therapy (HRT):

In 1995, wide public coverage was given to the results of an epidemiological study, suggesting an increased risk of thromboembolism with the use of oral contraceptives containing desogestrel or gestodene compared to the use of "older" contraceptives (Carnall 1995). This risk is small and the risk with the use of oral contraceptives is still substantially less than the risk of such events in pregnancy. The risk of venous thromboembolism is likely to be greater in women with other predisposing factors.

There is an increased risk of deep venous thrombosis or pulmonary embolism in women taking hormone replacement therapy and is greater than those taking oral contraceptives. The risk is estimated between 16 and 23 excess cases per 100,000 women per year and about 6 per 100,000 for pulmonary embolism. The risk seems to be restricted to users in their first year of treatments; after this period the risk is similar to that of non-users (Gutthann *et al* 1997).

2.4.5 Gynecology and obstetrics:

During pregnancy there is a gradual fibrinolytic and blood coagulation change which may cause thrombus formation. The risk of DVT is higher post-partum than ante-partum. The risk of DVT is 0.13/1000 in the ante-partum period and 0.61-1.5/1000 in post-partum patients. PE is a leading cause of maternal mortality (European Consensus Statement 1992).

2.4.6. Malignant disease:

The association of thromboembolic events and malignant disease is well established. Otherwise healthy patients who have an initial episode of idiopathic venous thromboembolism, or 22% of patients who have an idiopathic PE, have approximately a 10% incidence rate of harboring cancer. In patients with recurrent idiopathic deep venous thrombosis this risk is even higher (17%) (Ihnat *et al* 1998).

2.4.7 Age:

Age is the most important general factor. The likelihood of thrombosis increases with age. Thrombosis is rare in children. Over 40 years of age a DVT following elective surgery may affect 25 - 30% of patients and the risk rises to 60 - 80% after the age of 65 years (Rosendaal 1993).

2.4.8 Sex:

Women have a significantly greater fibrin plate lysis than men (Lacroix *et al* 1996); however, autopsy studies have shown no relationship between sex and the incidence of venous thrombosis (Hunter *et al* 1941).

2.5. SITES AND INCIDENCE OF THROMBOSIS

There are two views on the origin of deep venous thrombi. Thrombus may originate in the calf veins only and propagate to the thigh or thrombi may arise in the ilio-femoral channel and leg vein thrombi form through retrograde extension. The likelihood is that thrombi begin at one or more of several sites. Approximately 40% of the thrombi in the ilio-femoral segment appear to be independent of any calf vein thrombosis (Browse *et Thomas* 1974). Popliteal vein thrombi can be isolated but are more often continuous with post-tibial thrombi. Femoral thrombi can occur with or without calf vein thrombosis. Thrombi in the profunda may or may not be associated with thrombus in the common femoral or iliac veins and iliac thrombosis may be continuous or independent. Approximately 0.9% of patients have bilateral deep vein thrombosis (Browse *et Thomas* 1974; Nix *et Troillett* 1991).

The calf has been found to be the commonest site of deep-vein thrombosis. The valve pockets and the veins of the soleus muscles have been shown to be the points of origin of many venous thrombi (Labropoulos *et al* 1999). Thrombi originating in the intramuscular veins, which drain into the posterior tibial and peroneal veins, can easily extend. Thrombi in the calf rarely result in fatal emboli and often resolve spontaneously.

In 1995, the International Consensus Statement on the Prevention of Venous Thromboembolism stated that the rate of DVT each year is 160 per 100,000 in the general population. The rate of PE is 20 per 100,000 for symptomatic non-fatal PE and 60 per 100,000 for fatal PE (European Consensus 1992).

2.6. SUPERFICIAL THROMBOPHLEBITIS

Superficial thrombophlebitis usually involves the long saphenous or one of its tributaries and almost always results from trauma. It is invariably painful and is characterized by a redness over the thrombosed vein which is tender to touch.

Until recently, superficial thrombophlebitis was considered a self-limiting benign disease without a significant incidence of morbidity or mortality. However, recent studies have shown that superficial thrombophlebitis can extend into the common femoral vein in approximately 8.6% of cases, of which 10% embolised to the lung (Jorgensen *et al* 1993; Bendick *et al* 1995; Blumenberg *et al* 1998). Also, the incidence of hypercoagulable states in patients with superficial thrombophlebitis can be up to 35% (Yucel *et al* 1992; Hanson *et al* 1998).

2.7. DEEP VEIN THROMBOSIS (DVT)

Deep vein thrombosis may or may not produce leg symptoms (Barnes *et al* 1975). Up to 50% of patients have no sign or symptoms in their legs and only 50% of patients with leg symptoms are found to have a DVT when investigated (Bergqvist 1990). The symptoms, if present, are swelling, the degree of which is directly related to the extent of thrombosis, and pain and tenderness of the limb. Cyanosis may develop if the venous outflow is sufficiently obstructed. This is known as "phlegmasia cerulea dolens". The limb becomes gangrenous due to the inability of arterial blood flow to enter, which leads to almost total loss of fluid into the limb causing shock and death.

A major complication of an acute DVT is pulmonary emboli. Not all deep vein thrombosis give rise to pulmonary emboli (approximately 10%) and proximal thrombi pose the greatest risk (Moser *et al* LeMoine 1981).

2.8. PULMONARY EMBOLISM (PE)

The clinical manifestations of a PE are characterized by sudden onset of chest pain associated with dyspnea, followed by pleuritic pain on breathing. The effect of an embolism depends on the size of the embolus and on the cardiovascular state of the patient (Browse 1974).

The majority of pulmonary embolisms originate in the deep veins of the legs and are a complication of acute DVT. In a small minority of cases, the thrombus may originate from other sites - more proximal veins, indwelling venous cannulae or the wall of the right ventricle - and even more rarely the embolus is not made of thrombus but of tumour, fat or amniotic fluid. Over half of patients with PE who have a DVT will have asymptomatic legs (Smith *et al* 1994). Usually, only part of the thrombus embolises and 50-70% of patients will have evidence of residual thrombus in the lower extremity when they present clinically with PE (Smith *et al* Iber 1989).

Thrombi isolated to the calf vein often resolve spontaneously and rarely result in emboli. The reasons for this is not entirely clear but it may be that calf vein thrombi are more securely attached and are more susceptible to rapid spontaneous resolution. However, whether calf vein thrombi fail to embolise

or merely give rise to small, clinically unapparent emboli remains an unanswered question. The risk associated with isolated calf vein thrombosis is that they may propagate to involve the proximal veins of the thigh (Meibers *et al* 1988; O'Shaughnessy *et Fitzgerald* 1997). It has been shown that, on subsequent venous duplex ultrasound examinations, up to 32% will propagate into the proximal veins and that propagation invariably occurs before embolisation (Moser *et LeMoine* 1981; Philbrick *et Becker* 1988; O'Shaughnessy *et Fitzgerald* 1997).

Patients with respiratory symptoms and diagnosed isolated calf vein thrombosis have a high prevalence of PE (Passman *et al* 1997). Autopsy studies reveal that 13-15% of patients with fatal pulmonary embolism have deep venous thrombosis confined to the calf veins (Giachino 1988). Other studies report a 26-30% incident of clinically significant PE in patients with thrombi confined to the deep veins of the calf (Browse *et Thomas* 1974; Smith *et Iber* 1989).

Of patients with a proven pulmonary embolus, 80-90% have a major predisposing risk factor. They are a major cause of morbidity and mortality and are commonly diagnosed at post-mortem (Sevitt *et Gallagher* 1961).

As PE is a frequent cause of death, immediate treatment is essential. Untreated pulmonary emboli tend to recur and their clinical outcome is poor. Massive and acute pulmonary embolisms, which cut off more than 80% of the pulmonary arterial flow, are fatal in a few minutes. Those that are massive but not immediately fatal (between 60 - 80% obstruction of the pulmonary arterial flow) may justify thrombolytic therapy.

2.9. CHRONIC VENOUS DISEASE (CVD)/ POST THROMBOTIC SYNDROME (PTS)

Recurrent thromboembolism and post-thrombotic syndrome (PTS) are the most important long-term complications of DVT. It is difficult to predict the late sequelae of deep vein thrombosis, as severe manifestations of the PTS often do not develop for years after an episode of acute DVT. Browse *et al* concluded that the development of the post-thrombotic syndrome was "totally unpredictable" (Browse *et al* 1980). The ability to predict the severity of chronic venous disease (CVD) after an acute DVT is limited, although studies suggest that the natural history appears more important than the presenting features of the event (Meissner *et al* 1998).

The PTS arises from two sequelae of DVT; 1) persistent obstruction to outflow from residual organized thrombus and 2) damage to the venous valves with resultant reflux of blood. The clinical manifestations are namely swelling, hyperpigmentation and ultimately ulceration. However, some patients with symptoms have no documented DVT (Taheri *et al* 1993). The Edinburgh vein study, which studied 1,566 people in a random sample of the

population found that lower limb symptoms such as heaviness, tension, aching, feeling of swelling, restless legs, cramps, itching and tingling which are often attributed to varicose veins are extremely common in the general population whether or not varices were present (Bradbury *et al* 1999).

Many investigators have found that the extent of thrombosis on initial presentation has a close relationship between the ultimate clinical outcomes. Valvular reflux is the dominant mechanism leading to a post-thrombotic limb (venous obstruction is more commonly associated with venous claudication). However, it is not clear whether reflux results from direct damage to the valves or is caused by other mechanisms, such as dilation of the vein, as reflux can be found in segments without previous thrombosis (Killewick *et al* 1989; Markel *et al* 1992). The development of reflux occurs before or simultaneously with complete recanalisation. Deterioration of normal valve function is rarely observed once complete recanalisation occurs.

In addition to the presence of reflux, the anatomical sites of reflux are important in determining the signs and symptoms (Meissner 1995; Labropoulos *et al* 1996). Investigations with Continuous Wave (CW) Doppler and later duplex ultrasound, showed an association between abnormalities in the popliteal and tibial veins and the severity of the PTS (Schmidt *et al* 1987; Van Bemmelen *et al* 1990; Markel *et al* 1992; Meisser *et al* 1993; Johnson *et al* 1996). These studies also demonstrated a lack of association between iliofemoral vein reflux and disease severity (Saarinen *et al* 1995).

Often the clinical sequelae will have some contribution from superficial venous incompetence. Distal reflux in combination with reflux in the superficial veins is more harmful than reflux confined to the deep veins, even when such reflux extends throughout the deep venous system (Labropoulos *et al* 1994). Insufficiency of the superficial, perforating or deep veins of the legs is a risk factor for venous ulceration. The pattern of venous insufficiency and the greater the degree of venous insufficiency, the greater the risk of a venous ulcer developing (Consensus 1992).

Early recanalisation can preserve valve function but it is not known why some valves remain protected during thrombus formation and recanalisation while others do not (Meissner *et al* 1993). The posterior tibial veins appear to be more resistant to the development of valvular insufficiency. This may be due to the large number of valves in these veins. Individual differences in the fibrinolytic system may also play an important part in preserving valve function. Meisser *et al* noted that females tend to recanalise more rapidly and to have a lower incidence rate of severe post-thrombotic skin manifestations, but gender is not independently predictive of ultimate CVD classification (Meisser *et al* 1998).

Little is known about the long term clinical and hemodynamic sequelae of isolated calf vein thrombosis. There are conflicting reports on the incidence of chronic venous insufficiency following calf vein DVT. Reports vary from

indicating few early complications and adverse sequelae at three years, to one third of patients showing evidence of mild to moderate venous valvular insufficiency and even that calf DVT's seem to cause late symptoms as often as more proximal DVT (Saarinen *et al* 1995; O'Shaughnessy *et al* Fitzgerald 1997; Masuda *et al* 1998; McLafferty *et al* 1998). Valvular reflux is rarely found in the affected calf vein at three years; however, reflux may be found in adjacent uninvolved veins in approximately 30% of the cases (Masuda *et al* 1998).

Ambulatory venous hypertension leads to venous ulceration. The microcirculatory regulatory mechanisms are disturbed in the skin adjacent to venous ulcers. Lymphatic function in the limbs of patients with chronic venous insufficiency is abnormal. The most common location of venous ulcers is in the region of the medial malleolus which is where the initial portion of the long saphenous vein lies. The second most common site is laterally in the area drained by the short saphenous vein. The perforator veins have their greatest concentration in these areas. It is nearly always possible to find an incompetent perforator in the vicinity of a venous ulcer.

2.10. CLINICAL CLASSIFICATION OF CHRONIC VENOUS DISEASE (CVD)

Variations in the way chronic venous disease has been reported from study to study has lead to confusion in interpreting results. An International Consensus Committee in 1995 developed reporting standards for acute and chronic venous disease under the auspices of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery (NA-ISCVS/SVS) (Beebe *et al* 1995). This classification has contributed to the uniform presentation of diagnosis and results of treatment.

The standards for CVD include a classification system that is based on the clinical signs, the causes, the presence of reflux or obstruction, and the anatomic sites of these abnormalities.

Classification has been developed under the following headings:

C: Clinical signs (Grade 0-6) supplemented by (A) for asymptomatic and (S) for symptomatic presentation. Symptoms include aching, pain, congestion, skin irritation and muscle cramps.

E: Etiologic classification - There are three categories of venous dysfunction: congenital, primary and secondary. These categories are mutually exclusive.

A: Anatomic classification - The anatomic extent of venous disease whether in the superficial, perforating or deep venous system. Disease may involve one, two or all three systems.

P: Pathophysiologic dysfunction - reflux or obstruction, alone or in combination

Chronic venous dysfunction scoring provides a numerical base for scientific comparison of limb condition and evaluation of results of treatments. This is based on the anatomic score, the clinical score and the disability score. The anatomic score is the sum of the anatomic segments, each scored as one point. The clinical score is the sum of the values assigned to the signs and symptoms.

This classification provides a standard for uniformity in reporting and assessing different modalities of diagnosis and treatment (See APPENDIX I).

2.11. PREVALENCE & SOCIO-ECONOMIC ASPECTS OF CVD

It is known that in approximately 11 - 37% of patients veins will return to normal following a DVT (Johnson *et al* 1995; Haenen *et al* 1998); however, approximately two thirds of patients with a DVT will develop valvular incompetence (Markel *et al* 1992). PTS occurs in 60-70% of cases when patients are monitored between five - 10 years after conservative treatment of deep vein thrombosis (Markel *et al* 1992; Johnson *et al* 1996; Meissner 1995; O'Shaughnessy *et al* Fitzgerald 1997). The severity of clinical features has been noted to increase with time after DVT (Welch *et al* 1996). The prevalence of incompetent perforators and their calf to thigh ratio increase linearly with the clinical severity of chronic venous disease (CVI). Both the prevalence of deep vein incompetence and the ratio of superficial and deep to superficial increase linearly with CEAP classification. Incompetence involving all systems increases in prevalence with the severity of CVI (Delis *et al* 1998).

Chronic venous insufficiency affects up to 4% of the population with over 80% of cases as a result of DVT (Johnson *et al* 1996). The remaining cases are due to varicose veins. Recent studies suggest that of patients with PTS, 25-30% of effected extremities have no problems, 15 - 30% develop hyperpigmentation and 3 - 5% progress to ulceration (Johnson *et al* 1996).

Assessment of the prevalence of ulcers has a number of pitfalls. Reports vary in whether the prevalence is the number of patients with a condition at that time or whether they present with the condition over a period of time. There is also variation in the definitions of the description, site and duration of ulcers (Callam 1992; European Consensus 1992). From various studies it can be concluded that the point prevalence of active leg ulceration, excluding isolated toe and forefoot lesions, is 0.1 - 0.2% of the population. In developed countries 1% of the adult population are likely to develop leg ulceration, although only a fifth of them will exhibit open ulceration at a single point in time (Callam 1992; Consensus 1992; Ruckley 1995).

Approximately 57-80% of leg ulcers are due to venous disease (Callam 1992). Women appear to be slightly more prone to ulceration and there is a marked increase in the prevalence of chronic leg ulceration with age.

Chronic venous insufficiency afflicts over seven million people in the United States alone with over 500,000 with leg ulceration. The Riverside study conducted in London suggests that the nursing costs alone of leg ulceration in Great Britain amount to between £100 million and £140 million annually (Bosanquet 1992). Additional indirect costs arise from leg ulcer disease e.g. time lost from work, permanent disability and early retirement (Taheri *et al* 1993). Ulcer care varies from country to country. Care may be provided by community nurses or by a number of various medical specialists ranging from dermatologists, vascular surgeons to medical doctors. For many patients poor results are achieved, with healing rates of 20 - 30% after 12 weeks using crepe bandaging (Bosanquet 1992).

2.12. DIAGNOSIS

2.12.1 Clinical evaluation:

The diagnosis of DVT, based on clinical signs and symptoms alone is notoriously inaccurate - 50% of patients with a suspected DVT on clinical bases will not have a DVT and 50% of patients without clinical evidence of DVT will have a significant thrombus (Barnes *et al* 1975).

2.12.2 D-dimer:

D-dimer concentration is a useful test in patients suspected of having venous thromboembolism. D-dimer is a specific degradation product of cross-linked fibrin that is released when the endogenous fibrinolytic system attacks the fibrin matrix of fresh venous thromboemboli. The test is non-specific, raised values can be found in many other conditions, especially in the post-operative period, which is a high-risk time for thromboembolism. However, measurements of D-dimer may be used to exclude the diagnosis and combined with other non-invasive tests is extremely valuable. Caution must be taken as normal values tend to vary with age. Also, it is not known how long it takes for a DVT to become sufficiently organized that it no longer releases D-dimer. Further investigations are needed.

The test can be used in combination with other methods (Bernardi *et al* 1998). Most studies suggest D-dimer to be used in conjunction with ultrasound testing especially in those centres where calf veins are not imaged. This allows for a reduction in repeat ultrasound examinations (Bernardi *et al* 1998).

2.12.3 Isotopic perfusion lung scan:

Probability lung scans are useful in the diagnosis of patients suspected of having pulmonary embolism. However, perfusion defects due to other pulmonary disease can be confused with pulmonary embolism. If these scans

are indeterminate and a more definitive diagnostic study is needed pulmonary angiography is conclusive in over 90% of patients; however, it carries some risk of morbidity and mortality.

Documentation of DVT in patients with indeterminate probability lung scans increase the likelihood of PE to greater than 90% and provides sufficient indication alone for anticoagulation.

2.12.4 Venography:

Venography, also known as phlebography, was first described by Berberich and Hirsch in 1923, and remained the “gold standard” for diagnosing venous thrombosis for a number of years (Berberich *et al* Hirsch 1923).

Venographic technique varies from institution to institution. Generally, venography is performed on a tilting table, tilted 30-45 degrees. A contrast solution is injected into a dorsal vein of the foot on the leg to be examined (Nix 1988). Thrombi are identified when contrast material outlines a thrombus as a filling defect and/or the absence of a known vein, associated with collateral circulation. The thrombosis severity is appreciated by its volume and location.

The most common complication from venography is the pain experienced by many patients at the time of contrast injection and in some instances superficial thrombophlebitis of the injected vein (Albrechtsson *et al* Olsson 1976). The risks of an allergic reaction to venography have been greatly reduced since the introduction of low osmolar contrast medians (Thomas *et al* 1984).

2.12.5 Duplex Ultrasound:

For a number of years now, venography, the “gold standard” for the detection of DVT, has been challenged by sonography (Lessing *et al* 1989; Baxter *et al* 1990; Muller *et al* 1992). Real time B-mode imaging has been enhanced by the addition of mean frequency colour coded duplex sonography and has proved to be a highly accurate, non-invasive method for the diagnosis of DVT (O’Leary *et al* 1988; Nix *et al* 1991). In recent years, the introduction of power Doppler has greatly enhanced the diagnosis. It is especially useful in the imaging of calf veins (van Bemmelen *et al* 1989; Baumgartner *et al* 1998). Doppler ultrasound with colour flow mapping has made it possible to monitor changes in the extent of the thrombus and can be used in trials to assess the efficacy of different therapeutic regimes (Polak 1991).

2.12.5.1 Principals of ultrasound:

There are two types of waves: - longitudinal and transverse, depending on whether the displacement is across or along the direction of travel. If across the direction of travel the wave is called transverse and if along the direction of travel the wave is called longitudinal. Sound waves are longitudinal waves.

Both types of waves have a common set of characteristics. The distance traversed by a simple cycle is called the wavelength and is expressed in millimetres. The time taken to form a cycle is called the period and the frequency is the number of cycles that occur in one second, measured in hertz. Ultrasound refers to those waveforms with frequencies above the audible range of hearing i.e. $>20,000$ Hz.

The speed of a wave travelling through a medium is called the propagation velocity and it is expressed in meters per second. The propagation velocity depends on the bulk modulus (stiffness) and the density (mass per unit volume) of the medium. Gases carry waves more slowly than fluids and fluids more slowly than solids. This is why a coupling gel is needed in clinical applications to allow for wave propagation between the ultrasound transducer and the skin surface. The ability of a material to promote or impede the formations of a wave depends on the product of its material density and the propagation velocity and is called the characteristic impedance. A material carrying a wave also converts some energy into heat. This energy loss is called absorption (Burns 1987).

If the medium is a mixture of materials with varying densities and velocities of propagation (impedance), reflection will occur where two interfaces meet. The amount of energy reflected is determined by the magnitude of the characteristic impedance change between the two interfaces. Scattering occurs when acoustic interfaces are very small. The scattering energy radiates in all directions.

The energy loss of a wave travelling through a medium is called attenuation. This energy loss is due to reflection and scatter as well as absorption of energy by the medium. Higher frequencies are more severely attenuated than lower frequency waves (Zwiebel 1986).

2.12.5.2 Transducers:

Transducers change one form of energy to another. Ultrasound transducers convert mechanical energy into electrical energy and *visa versa*. Transducers are made of materials called ferroelectric which have piezoelectric properties. Piezoelectric literally means "pressure electric". A pressure field (i.e. an ultrasound wave) applied to one of these transducing materials causes an electric field to be generated within the crystalline material. If the pressure is rhythmic, the electric field will change in a corresponding rhythmic manner as well.

The transducer is made to vibrate at its natural resonant frequency by applying an electrical pulse. This sets up a vibration of the transducer surfaces, the frequency of which is determined by the physical dimensions of the transducer. The energy is released as a mechanical ultrasound wave which is longitudinal in nature. As these waves are formed and radiate away, the duration of the transducer vibration (or ringing) after excitation is a function of the speed of which the vibrational energy is removed from the

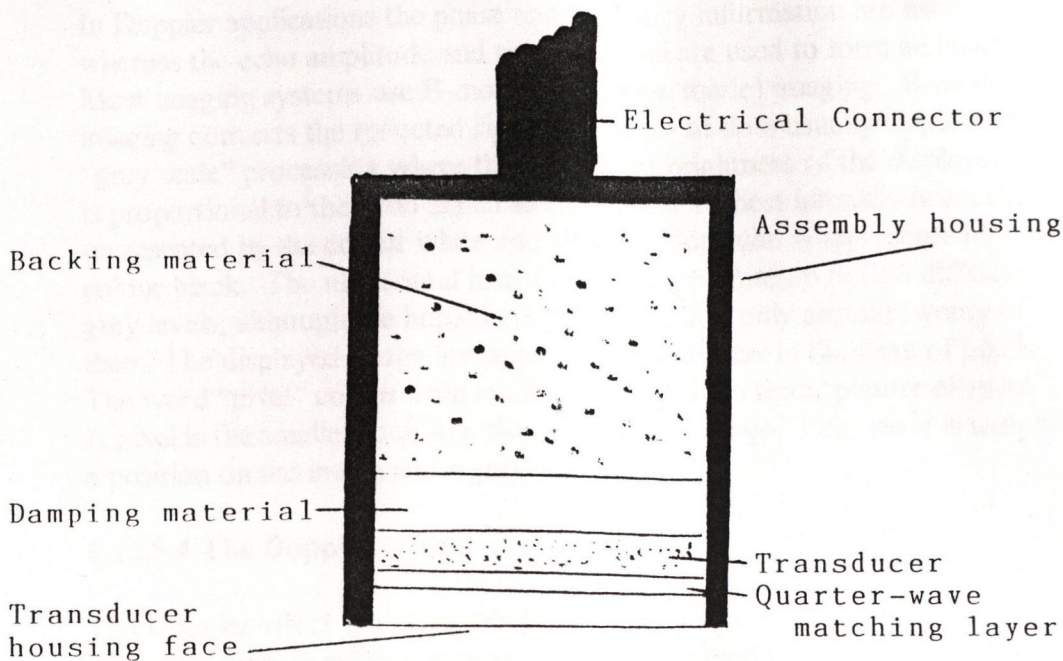


Figure 2.5: The principle components of a transducer.

transducer. A damping material, which is usually an epoxy substrate containing a metal powder, is placed on the back of a transducer and produces a highly energy-absorbent medium. The end result is a very short envelope of ultrasonic vibration. When selecting the appropriate transducer for application the optimal frequency choice is determined by the tissue depth of the vessel under examination. Therefore, for superficial vessels an eight to ten MHz transducer is used whereas for deeper vessels e.g. abdominal, a three MHz transducer would be used.

2.12.5.3 B-mode imaging:

The vibration, or ultrasound wave, travels through a medium to an echo source within the medium and an echo returns to the transducer. The frequency of the echo causes a rhythmic squeeze to the transducer of the same frequency value. This oscillating pressure produces an oscillating output voltage. This information is transmitted firstly into a receiver that will amplify and shape the signal that represents the echo and then into a display that permits the operator to see the returning signal (Burns 1987; Zwiebel 1986).

The echo carries the following information:

1. The time of arrival which can be translated into range or distance.
2. The amplitude of the echo that can be transcribed into relative signal strength.
3. The frequency of the echo which can be related to echo-source velocity.
4. The phase shifts that result from different reflecting conditions.

In Doppler applications the phase and frequency information are used whereas the echo amplitude and time of arrival are used to form an image. Most imaging systems use B-mode (Brightness mode) imaging. B-mode imaging converts the reflected signal to a series of dots usually employing “grey scale” processing where the intensity of brightness of the displayed dots is proportional to the echo signal strengths. The highest intensity is usually represented by the colour white and absence of an echo is represented by the colour black. The ultrasound instruments can generate up to 256 different grey levels, although the human eye can distinguish only around twenty of them. The displayed image is mapped onto the display in the form of pixels. The word “pixel” comes from an abbreviation of the term “picture element”. A pixel is the smallest unit of a two dimensional image. Each pixel is assigned a position on the image and a grey-scale value.

2.12.5.4 The Doppler effect:

The Doppler effect is a change in the frequency of echo signals that occurs whenever there is relative motion between the sound source and the reflector (e.g. red blood cells). The Doppler equation states that this frequency shift is proportional to the velocity of the moving object and the transmitted frequency, and inversely proportional to the velocity of ultrasound in tissue:

$$Df = \frac{2vfo\cos \Theta}{c}$$

Where:

Df is the Doppler frequency shift (difference between the transmitted and received frequency); v is the velocity of the moving cells; fo is the initial frequency; c is the speed of ultrasound in tissue (1,540 m/sec); Cos Θ is the cosine of the angle between the ultrasound wave and blood flow.

(Note: If $\Theta = 0$, $\cos \Theta = 1$ Max Doppler shift; If $\Theta = 90$, $\cos \Theta = 0$ No Doppler shift. In practice the angle is approximately 30 - 60 degrees).

If the direction of the moving object is toward the source then the reflected frequency is greater than the transmitted frequency giving a positive Doppler shift, and if the direction is away from the source, the reflected frequency is less than the transmitted frequency, giving a negative Doppler shift. Doppler shift information can be converted to velocity information as the resultant frequency is related to the velocity of all reflectors and scatters within the sound beam. The resultant Doppler frequency, which is the difference between the transmitted and reflected frequency, is in the audible range (Burns 1987). The output can be heard on headphones or can be applied to spectral analysis systems.

2.12.5.5 CW (Continuous wave) Doppler:

These are the simplest and least expensive Doppler devices. In a CW Doppler instrument the signal is continuously emitted and received. Two transducers are used in a single housing for simultaneous transmitting and receiving. The returning signals can be tested for shifts in phase. This yields direction information of the reflector. Within the CW Doppler system however, it is uncertain where the echo sources are located and interrogation of a single small region of interest is not possible.

2.12.5.6 Pulsed Doppler:

In pulsed Doppler systems a burst of coherent ultrasound is transmitted into the tissue. The receiver operates for a short time interval at a specified time following each transmission of the burst. This allows for a selection of Doppler signals originating only from a particular depth for display. This is called range gating. After being on for a short time the receiver and analyser are turned off again. The gate or "sample volume" position can be adjusted by the operator to select Doppler signals from any distance.

Since the primary target for Doppler application is the red blood cell, which is small in size, with this small target and scattering of energy in all directions, the amount of energy that can reach the transducer is usually very low. Such small signals not only limit the range of Doppler signals that are possible to detect from vessels, but also limit the useful depth at which Doppler can be used. Typically, we can use imaging at a much greater depth in the tissues than Doppler.

2.12.5.7 Doppler display:

The Doppler shift signal is in the audible frequency range therefore, for some applications adequate clinical interpretations can be made by simply listening to the signals.

The Doppler signal is a complex signal containing many individual frequency components. To display this complex signal a digital technique using fast Fourier transform (FFT) analysis is used. A FFT analysis is carried out on the digitised signal segment, giving the relative magnitude of each frequency component in the signal. The output is displayed on a screen where the magnitude of the signal at each frequency is encoded in display brightness. This process goes on continuously, producing a display of the frequency spectrum of the signal in real-time. The spectral display depicts Doppler frequency on the vertical axis, time on the horizontal axis and the relative amount of signal at a given frequency and time as a shade of grey. The frequency scale is more often displayed as a velocity scale. Velocity is calculated using the Doppler equation as the speed of sound, the ultrasound frequency and the Doppler angle are known. This mode of display is called a blood velocity spectrum and can combine forward - and reverse-flow spectral analysis (Burns 1987; Zwiebel 1986).

2.12.5.8 Duplex imaging - imaging plus Doppler:

Imaging and Doppler information are combined to offer both anatomical information about organ or vessel architecture and blood flow information. In most systems the two-dimensional real-time image is used to locate the anatomy of interest, and then the imaging is turned off while the Doppler portion of the machine operates. Other systems automatically switch between the real-time image and the Doppler function with the real time updating at a slow but still effective rate.

2.12.5.9. Colour flow:

Colour flow imaging was first developed by Quantum Medical Systems (Powis 1988). Real time colour flow mapping is an expansion of the Duplex technique. In traditional Duplex scanning flow information is taken from a single sample volume, whereas colour imaging displays, in real time, the flow throughout the vessel lumen. Each pixel is interrogated and assigned a colour based on velocity and direction of flow. Generally, flow away from the transducer is red and flow toward it is blue. The higher the velocity, the lighter the colour. White is associated with the highest velocities detected (Kremkau 1991).

The pulse echo information is used to produce an ordinary grey-scale image whilst the Doppler shift information from all or part of the scan area is superimposed as a colour image. Colour flow simplifies detection of vessels and allows for a rapid survey of flow.

The transducers used for colour flow mapping are the same type as those used for pulse echo imaging. However, since many blood vessels run parallel to the skin surface, an angular wedge or more likely an electronically steered beam is used to give a non-perpendicular insonation of the flowing blood. Although it is not ideal to use the same transducer for pulse echo imaging and Doppler, since the latter requires longer pulses, the convenience of a single probe for accessing the tissues of interest is usually considered to justify the compromise.

2.12.5.10 Phantoms:

The performance of the duplex system can be evaluated using flow and imaging phantoms. A phantom is a device that mimics the human body with respect to beam transmission properties of the modality of concern. Ultrasound phantoms must have representative speeds of sound, ultrasound attenuation coefficients and scatter levels for the tissues being mimicked. For testing ultrasound Doppler equipment a phantom must also have vessels containing flowing fluids.

However, the use of phantoms every day before scanning is not practical as they are time consuming and require considerable expertise to operate. In most centres the ultrasound machines self-test once the power is turned on.

For each application there are pre-set programs which pre-set the ultrasound frequency, the sensitivity settings, the sample volume size and brilliance and contrast of the display - all of the technical factors that affect the outcome. Quality assurance programs are a necessity in each laboratory to insure consistence in results. Also, the machine must be serviced on a regular basis to determine drifts in the equipment.

2.12.5.11 Venous duplex scanning:

Venous duplex scanning, as first described by Talbot in 1982, is based on the fact that veins easily collapse under light compression (Talbot 1982). The diagnosis of a DVT is made by the incompressibility or limited compressibility of the vein, but visualization of the thrombus is the most specific diagnostic criterion. The method is non-invasive which makes it ideal for serial examinations. There is only one reported complication of a pulmonary embolism during compression ultrasound (Perlin 1992).

An advantage of ultrasound is that it may show conditions that mimic deep vein thrombosis such as haematomas, abscess and ruptured Baker's cyst (Borgstede *et al* 1992; Gardner *et al* 1995; Lawson *et al* 1995).

As the duplex system can visualize the thrombus, information on the morphology of the thrombus is also obtained. The ability to characterize blood clots and, more specifically, to determine whether they represent an acute or chronic process has important clinical implications in the treatment of deep vein thrombosis (O'Shaughnessy *et al* 1996, O'Shaughnessy *et al* 1997).

The principal criterion used to estimate the age of a thrombus is by its echogenicity. Interpretations on the echogenicity of a thrombus are based on in vitro studies of blood clot echogenicity under duplex ultrasound. These studies showed that fresh clots are anechoic soon after thrombosis under high resolution imaging and echogenicity increases over time with organization and lamination (Coelho *et al* 1982; Frimerman *et al* 1994; Peter *et al* 1986).

Red cell lysis proceeds from the peripheral portions of the blood clots toward the more central areas over time. The process is seen as a centre of reduced echogenicity surrounded by a more echogenic ring (Peter *et al* 1986). Results of studies by Shung *et al* showed the echogenicity of thrombus increases rapidly following the initiation of clotting (Shung *et al* 1984). Fresh thrombi less than six hours old are less echogenic whereas older thrombi are usually more echogenic. These studies suggest that an estimation of the organisation of a thrombus from its echogenicity would be possible in a clinical setting (Shung *et al* 1984; Shung *et al* 1986; O'Shaughnessy *et al* 1996).

When using duplex ultrasound to diagnose a DVT, the echogenicity changes are defined by visual inspection of the images. However, this is a nonspecific

qualitative description and is subjective depending on the expertise of the interpreter (Shung *et al* 1984).

In extensive multilevel venous thrombosis the stage of organisation of the clot can be different at each level according to the developmental direction of the deep thrombosis, ascending from the femoropopliteal area or descending from the iliac vein.

2.12.6 Reflux studies:

Duplex ultrasound is the ideal method to study the post-thrombotic limb as it is accurate in detecting residual thrombus and the presence of reflux. It allows for the investigation of individual veins to obtain anatomic and hemodynamic information. As it is non-invasive it is also ideal for serial examinations (O'Shaughnessy *et Fitzgerald* 1997).

Recently, duplex ultrasound has been shown to be a better method than venography to measure reflux (Neglen *et Raju* 1992). Colour Doppler facilitates visualization of the vein and assessment of directional flow within the vein. However, many variations in the techniques and reporting criteria have led to conflicting results. Different patient positions and techniques to elicit reflux have been used (Welch *et al* 1996). The position of the subject can be either lying flat, sitting or standing. Stimulus used to provoke reflux vary from a Valsalva's maneuver to manual or pneumatic compression. There is also a problem in the definition of reflux. There is no consensus about the definition which ranges from 0.5 second to more than two seconds; however, it is generally accepted that most studies now use > 1 second.

Standing reflux assessment with duplex ultrasound with the use of a pneumatic cuff was first described in 1989 (van Bemmelen *et al* 1989; Johnson *et Strandness* 1997). Pneumatic cuffs on the thigh, calf, ankle and the transmetatarsal region of the foot are inflated and then rapidly deflated while simultaneously insonating the venous segment proximal to the cuff. This technique was found to be an accurate assessment of the sites and duration of reflux in the lower extremity (Czerdarczuk *et al* 1992; Johnson *et Strandness* 1997).

2.13. THERAPY

The condition of pulmonary embolism and deep vein thrombosis are considered the same disease therefore the anticoagulant treatment should not differ. The inhibition of thrombus propagation, the restoration of patency of the thrombosed veins, the prevention of pulmonary embolism and the preservation of venous valvular competence to avoid chronic venous insufficiency are the ultimate goals of treatment. Untreated, proximal leg vein thrombosis poses a risk of pulmonary embolism in the region of 50% (Moser *et LeMoine* 1981). Statistics appear to conflict as many emboli go

undetected. Untreated pulmonary embolism tend to recur and their clinical outcome is poor. Therefore it is important to first of all prevent venous thrombosis.

2.13.1 Prophylaxis:

Prophylaxis is used to prevent DVT. This includes, reducing venous stasis by pneumatic compression or graduate compression stockings and reducing blood coagulability using heparin or oral anticoagulants. Patients should be classified into high, medium and low risk of developing thromboembolism and be treated accordingly (European Consensus Statement 1992; Anderson *et al* 1992; Pineo *et al* 1995).

Low risk patients may receive prophylaxis; however, most receive graduated compression only. In moderated risk patients the use of low dose heparin or low molecular weight heparin is recommended. All high-risk patients should receive prophylaxis. Prophylaxis should be initiated before operation in all groups and continued for seven to 10 days (Hull *et al* 1992; Hull 1995; Antiplatelet Trialists' Collaboration 1994).

2.13.2 Treatment of an established DVT:

The therapeutic approach for the patients with established DVT includes prevention of acute embolic complication of the thrombus as well as the long-term sequelae of venous obstruction.

2.13.2.1 Heparin and warfarin:

Until the 1930's, patients with deep vein thrombosis were treated with bed rest, elevation of the leg and elastic bandages. In 1937, the preventive effect of heparin was demonstrated independently by Crafoord and Murry *et al* and has been used as the initial anticoagulant for the treatment of venous thrombosis since (Crafoord 1937; Murray *et al* 1937). The first oral anticoagulants, the vitamin K antagonist dicoumarol, was introduced into clinical practice by Lehmann and Allen *et al* in 1942, and these two therapeutic principles, heparin followed by an oral anticoagulant, have thereafter remained the basis for treatment of venous thrombosis (Lehmann 1942; Allen *et al* 1942).

Clinical management of patients experiencing a first idiopathic deep venous thrombosis or pulmonary embolism is controversial. Current treatment recommendations include heparinization for five to seven days followed by three months oral anti-thrombotic therapy with warfarin, adjusting the dosage to an international normalized ratio (INR) between 2.0 to 3.0. Oral anticoagulants are initiated at the start of heparinization and once therapeutic range (i.e. INR 2-3) is reached, heparin can be stopped (five to ten days).

For optimum therapeutic efficacy and safety, the dose of heparin should be adjusted at least daily (Mercuro *et al* 1993). Because of the daily laboratory

measurement needed for such adjustment, as well as continuous intravenous (IV) administration, most patients with deep vein thrombosis were treated in hospital.

In the past decade, low-molecular weight heparins (LMWH) have been developed. LMWH have a longer plasma half-life, less variability in the anticoagulant response to fixed doses, and a more favorable antithrombotic to haemorrhagic ratio. Hull *et al* showed that LMWH was at least as effective as continuous IV heparin with a 90% reduction in incidence of major bleeding and a 50% reduction in mortality (Hull *et al* 1992; Hull 1995). A fixed dose related to body weight of LMWH is given subcutaneously twice daily for the initial treatment of pulmonary embolism and DVT (Prandoni *et al* 1992; Simonneau *et al* 1997; Downing *et al* 1998). LMWH have also shown to be an effective form of prophylaxis (Bergqvist *et al* 1988; Leizorovicz *et al* 1994).

LMWH have two advantages. Firstly, weight-adjusted dosing obviates the need for dose adjustments on the basis of laboratory tests. Secondly, the subcutaneous administration of LMWH allows the patient to be fully ambulant and allows early discharge from hospital or the patient may even be treated at home (Partsch *et al* 1992; Partsch *et al* 1996; Buller *et al* 1998).

Low molecular heparins are more expensive than unfractionated heparin; however, cost savings are likely through savings in laboratory testing, consumables and staff time. It has not been determined if a prolonged use of LMWH is more effective in preventing the post-thrombotic sequelae. Subcutaneous heparin is used throughout pregnancy, as heparin does not cross the placenta.

Oral anticoagulant therapy is selected for long-term prophylaxis with initiation at the start of heparinization. Starting with oral anticoagulant alone is not sufficient because of the delay of 3-5 days until this treatment becomes effective (Brandjes *et al* 1992). Oral anticoagulation is necessary to maintain the antithrombin status, depending on the duration of the high-risk condition for recurrent thromboembolism. Maintenance of an INR level between 2.0 and 3.0 throughout oral anticoagulation therapy will minimize the rate of incomplete DVT resolution (Caprini *et al* 1999).

Controversy exists regarding the duration of anticoagulant therapy that varies from four to six weeks to up to six-months (Chesterman 1995; Schulman 1996). Some studies suggest that short-term therapy has similar outcomes to long-term therapy, except in cancer patients (AbuRahma *et al* 1998).

For patients with a second thromboembolic event, optimal duration of treatment is not known (Schulman 1996). After a third episode or in the presence of a hereditary thrombogenic abnormality (deficiency of antithrombin, protein C or S activated protein C resistance) most physicians favor long-term anticoagulation. Anticoagulant prophylaxis may prevent venous thrombotic events in individuals with a hereditary protein C deficiency

reducing morbidity; however, it is not known if anticoagulant prophylaxis will also reduce mortality (Allaart *et al* 1995). The use of low dose anticoagulants needs to be evaluated in a large prospective study. A study is being carried out under the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial to evaluate the efficacy of prolonged treatment with low-dose warfarin in the secondary prevention of venous thromboembolism (Ridker 1998).

Complications secondary to warfarin are an important consideration. The number of major haemorrhages induced by oral anticoagulants would exceed that of clinical pulmonary emboli prevented (beyond one year) amongst factor V carries over the entire range of duration of anticoagulation (one to five years) (Sarasin *et al* 1998). The cost aspect must also be considered.

There is also controversy regarding treatment for isolated calf vein thrombosis and there is no consensus regarding treatment. Sawyer *et al* suggested in 1964 that thrombi isolated to the calf veins would not need to be treated in active patients (Sawyer *et al* 1964). However, recent studies have shown that calf vein DVT may not be as benign as previously thought (Smith *et al* 1994; Passman *et al* 1997).

2.13.2.2 Thrombolytic therapy:

Thrombolytic agents, such as Streptokinase or Urokinase, have the advantage of higher lysis rate of venous thrombi. Thrombolytic therapy may be considered in selected patients who sustain acute recent massive venous thrombosis or massive pulmonary embolism in the absence of contraindications to thrombolytic therapy.

The efficacy of fibrinolysis in DVT depends on the age and organization of the thrombus as well as its location. Indication for lysis therapy is defined according to duration of clinical symptoms (less than seven days). However, studies have shown that organization of thrombus can occur as late as the 11-15th day and suggests the efficacy of late lysis therapy (Scheffler *et al* 1998).

The risk of hemorrhage must be taken into account (Fletcher *et al* 1984). Contra-indications to thrombolytic treatment are a haemorrhagic disease, a blood pressure superior to 20 mmHg for the maximum, a cerebral vascular accident less than 2 months old, a gastro-duodenal ulcer in evolution, a renal or hepatic insufficiency, a surgical operation of less than 10 days, a dacron prosthesis, a recent cardiac massage and pregnancy.

Studies suggest that thrombolysis may preserve vein function after DVT and may reduce the long-term potential for recurrent DVT and post-thrombotic syndrome (Cho *et al* 1998).

2.13.2.3 Vena cava filter:

The indications for vena cava filters are contraindications for anticoagulants, the presence of proven PE despite adequate anticoagulation, or complications of anticoagulation. The source of emboli must be proven to be from the leg or pelvic veins. The filter is passed, under radiographic control, via the internal jugular vein or the femoral through the right atrium and lodged in the inferior vena cava below the renal veins (McCollum 1987). There are few complications which usually result from inaccurate placement, occlusion at the venous insertion site, thrombosis of the inferior vena cava, new ipsilateral DVT and occasionally tears in the inferior vena cava (Blebea *et al* 1999; McCollum *et al* 1987; Dardik *et al* 1997). Filters prevent the migration of large emboli and have been shown to be safe and effective both in the infrarenal, and less commonly in the suprarenal, portion of the inferior vena cava (Greenfield & Proctor 1998). The common indications for a suprarenal filter include vena cava thrombosis to or above the level of the renal veins.

The use of vena cava filters has also been expanded to include prophylactic use in high-risk patient population (Dardik *et al* 1997). The risk of hemorrhagic complications must be weighed against the risk of recurrent thromboembolic events. Since the reported risk of hemorrhagic complications in patients with cancer who undergo anticoagulation therapy is highly variable, some studies suggest that an IVC filter should be in the primary treatment method of thromboembolism in patients with malignant disease (Cohen *et al* 1991). However, others suggest that most patients with malignant disease can be effectively treated with anticoagulation alone (Ihnat *et al* 1998).

2.13.2.4 Thrombectomy:

Thrombectomy is recommended for phlegmasia cerulea dolens that threatens the limb of the patient or in cases where medical therapy is contraindicated. Venous thrombectomy, with the specific goal of preventing the post-thrombotic syndrome, is to be proposed only to ambulatory patients with a good life expectancy. The clot age must be evaluated by history and duplex Doppler scanning and must be less than seven days.

There are few studies available that provide long-term follow-up following venous thrombectomy in preventing the development of the post-thrombotic syndrome. In selected cases, thrombectomy should yield better long-term results with the removal of the thrombus (Juhan *et al* 1997)

2.13.3 Treatment of the post-thrombotic limb:

There is little medical management to offer for venous insufficiency. Treatment usually requires that lifestyle be adapted, use of external compression or support, rest and elevation (Arcelus *et al* Caprini 1996). In 1968, Kistner first described the clinical use of valve reconstruction for deep vein reflux (Kistner 1968; Kistner 1985). Patients must be carefully selected and surgery can only be performed if a competent valve can be demonstrated

in the thigh. These procedures are still in the development stage, but early results are encouraging (Eriksson *et al* 1985; Taheri 1998; Trevivan *et al* Jamieson 1996).

Venous bypass can be performed to improve venous function in patients with post-thrombotic occlusion. Usually, the superficial femoral vein is bypassed using the 'non-affected' long saphenous vein. Synthetic grafts in the venous system have been less successful than in the arterial system. This is attributed to the low flow, low pressure characteristics of the venous system which predispose to thrombosis. This procedure must be performed to strict criteria and very often the extent of disease is either too diffuse to permit a successful bypass or too well collateralised to warrant the procedure (McMullin 1990; Eklof *et al* 1998).

Surgical procedures for venous disease are not a popular option as yet. The numbers of patients in various studies are low and long-term results vary. Very few patients fit the criteria for surgery, and there is the fear that reconstruction could result in severely incapacitating the patient.

2.14. RECURRENT DVT

Despite treatment many patients suffer from recurrent thromboembolic events in the months after initial deep venous thrombosis.

The clinical belief is that three months of oral anticoagulation is sufficient to prevent recurrences while longer periods increase venous thromboembolism. However, rates of recurrent venous thromboembolism after cessation of anticoagulation are halved when oral anticoagulant therapy is given for six months rather than six weeks, suggesting that longer-term therapy may provide a better benefit to risk ratio for some patients. Recent studies show that up to 24% of patients with idiopathic venous thromboembolism suffered recurrent events within two years after drug cessation (Ridker 1998).

Significant controversy exists in the medical community regarding the overall treatment of deep venous thrombosis. The long-term risk for recurrent DVT and the incidence of the post-thrombotic sequelae after long-term anticoagulant therapy have been widely debated.

The Research Committee of the British Thoracic Society considered medical versus post-operative patients and concluded that the incidence of recurrence and non-resolution was significantly higher in the medical group of patients who were given short-term anticoagulation (Research Committee 1960). Long term evaluation of mortality rate, recurrent venous thromboembolism, blood monitoring tests efficacy and thrombus propagation are open issues (Volteas *et al* 1996; O'Shaughnessy *et al* Fitzgerald 1997).

A Prevention of Recurrent Venous Thromboembolism (PREVENT) trial has been designed to evaluate the efficacy of prolonged treatment with low-dose warfarin in the secondary prevention of venous thromboembolism (Ridker 1998). This trial will include patients with and without factor V Leiden carriers.

The recurrence rate in studies varies from around 6.4%; however, with the use of ultrasound that has detected clinically asymptomatic recurrences, it is thought that the recurrence rate may be much higher. Recanalisation appears to be a dynamic process with lysis and re-thrombosis occurring as competing events early after DVT.

3. METHODS AND MATERIAL

3.1. PATIENT SELECTION

One hundred proximal deep venous thromboses were analysed from 89 patients (45 males, 44 females, 11 bilateral thromboses). The mean age of the patient population was 62 years (Range 22 - 94 years). The patients presented consecutively to the Vascular Medicine Unit, in James Connolly Memorial Hospital. All patients were referred with a clinically suspected deep vein thrombosis or were at high risk for a DVT and were diagnosed with an acute proximal (above knee) deep vein thrombosis by duplex ultrasound scanning. Their predisposing factors, clinical symptoms and duration of symptoms prior to the initial examination were recorded. The patients were referred by a variety of physicians and were treated by their referring physicians independently from the Vascular Laboratory. Their therapy regime was documented at each follow-up visit. Once the presence of an acute DVT was confirmed by duplex scanning and the patient met with all inclusion criteria an informed consent was obtained.

3.2. INCLUSION/EXCLUSION CRITERIA

Patients were included in the study if their deep vein thrombosis was acute, was at or above the knee and could be clearly imaged on ultrasound. The site of thrombosis in the proximal deep veins was not a factor. The patients were included in the study even in the end stages of a major illness and/or with a history of a previous DVT.

All the deep venous system had to be adequately imaged, including the calf veins. Patients were asked to be available for follow-up for up to a three-year period.

3.3. EQUIPMENT

Venous duplex examinations were performed with an Acuson 128xP/10 duplex scanner that combines B-mode imaging, pulsed Doppler spectral analysis and colour flow. The machine performed a self-test each time the power was turned on and was serviced on a regular basis to minimise drifts in the equipment. Prior to each examination the controls were pre-set to customise for the venous scanning protocol (see Appendix II). These pre-set settings and the same magnification size of the image were maintained during image capture. Individual scans often-required different control settings during scanning as patient size and individual image quality varied, so settings

were adjusted accordingly. However, an effort was made to make the scanning controls as consistent as possible, especially during image capture.

A 7.5 MHz linear array probe (transducer) was used for scanning. Occasionally a 5 MHz curved probe was used for greater depth penetration during scanning; however, when capturing an image for computer analysis only the 7.5 MHz probe was used.

Computer analysis was performed using a Power Macintosh 7100/80av computer and commercially available software - Adobe Premiere TM and Adobe Photoshop 4.0 TM

3.4. DUPLEX SCANNING

All venous duplex scans were performed by the same Vascular Technologist who was fully accredited and has had many years experience of venous scanning. Supervision and clinical advice was available from a vascular physician when necessary. Bilateral scanning was performed on each patient. At the patients initial Duplex scan (using the protocol for assessing DVT's as described below) the anatomical site and extent of the deep vein thrombosis was noted. The diameter and overall length of the thrombus was measured and an estimation of its bulk was recorded. Follow-up scans were performed at one week, one month, six months, at one year and each subsequent year after that. Reflux studies were also performed at each follow up visit.

Due to the difficulty of examining the common iliac vein, both at the initial examination and on follow-up visits, the study only included the external iliac veins, the common femoral veins, the superficial femoral veins and the popliteal veins. The calf veins were examined at each follow-up visit but were not included in the analysis of results due to the large number of segments involved.

3.4.1 Duplex venous scanning protocol for DVT:

Venous scanning was performed with the patient in the supine position and the leg to be examined externally rotated from the hip with the knee slightly flexed (Figure 3.1). Ultrasound coupling gel was applied to the limb under examination. The scan commenced in the groin area in a longitudinal scanning plane section (i.e. the probe position parallel to the vein) with pulsed-Doppler examination of the common femoral vein. The patient was then asked to perform a Valsalva manoeuvre to assess the phasic response of the Doppler signal and to determine competency of the vein. Imaging of the iliac veins and inferior vena cava (IVC) was then attempted by moving cephalad, along the line of the iliac veins, up to the mid line of the abdomen.

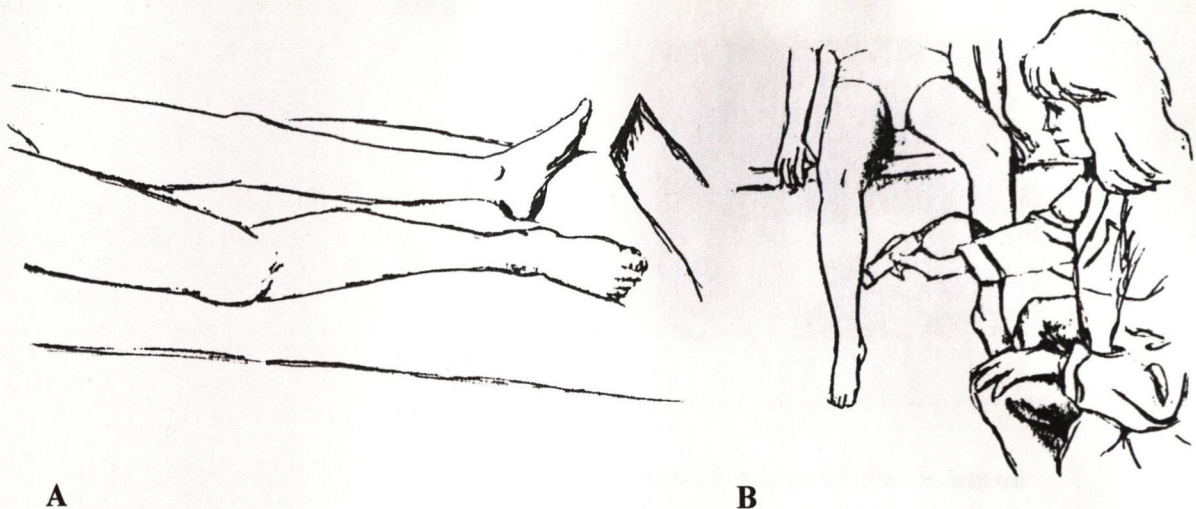


Figure 3.1: Patient positioning for DVT scanning.

A: Supine position for femoral and popliteal veins. B: Sitting with the legs dependant for scanning of the calf veins.

This was not always successful due to the presence of bowel gas that obscured the image. However, if an iliac thrombosis was suspected, the patient was then instructed to fast from 12 mid-night and return the following day for additional scanning. This made imaging of the IVC and iliac veins more successful.

Returning to the groin area and using a transverse scanning plane, (i.e. probe positioned perpendicular to the vein) the common femoral was imaged. A light pressure was applied to the ultrasound probe to compress the vein (Figure 3.2). The probe was then moved along the line of the femoral vein on the medial aspect of the thigh, compressing at regular intervals. The common femoral, profunda and superficial femoral vein were all examined in this position. The probe was then returned to the groin area and the long saphenous vein examined, also in a transverse scanning plane, and followed along the medial thigh to the knee level.

With the patient in the same position, the probe was placed in the popliteal space and the popliteal vein was examined. Imaging was performed in the transverse plane and the veins compressed at regular intervals. The probe was firstly moved cephalad along the posterior thigh to the point not examined in the previous position and then back into the popliteal space and down the upper posterior calf examining the popliteal vein along its length. The gastrocnemius muscle veins and the short saphenous vein were also examined in this position.

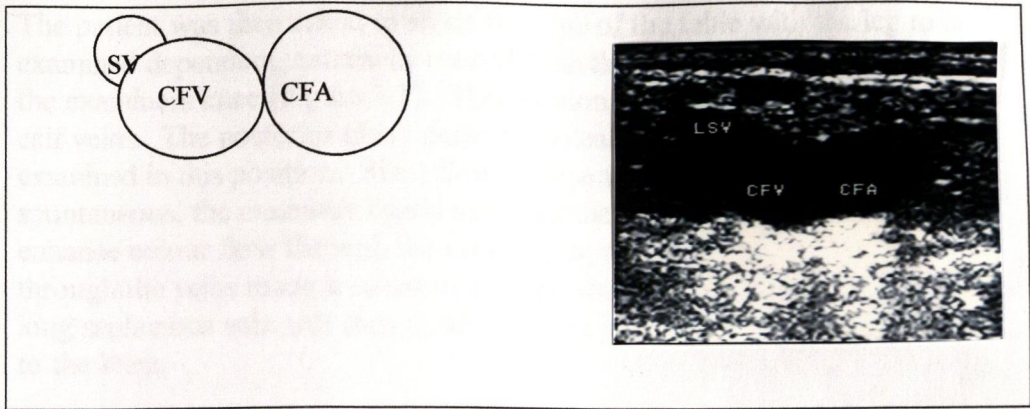


Figure 3.2(a): Normal cross sectional ultrasound image of the common femoral artery (CFA), the common femoral vein (CFV) and the long saphenous vein (SV)

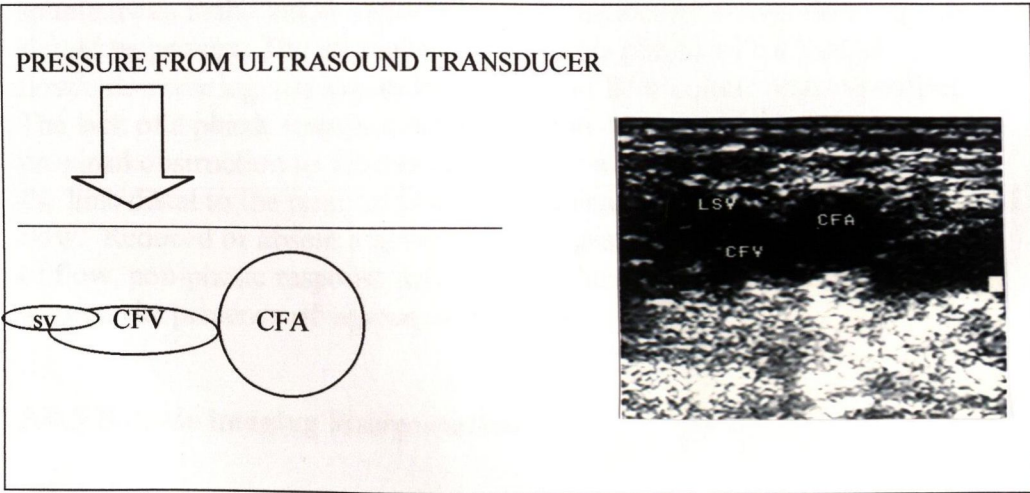


Figure 3.2(b): Applying pressure with the ultrasound transducer the CFV and SV begin to compress.

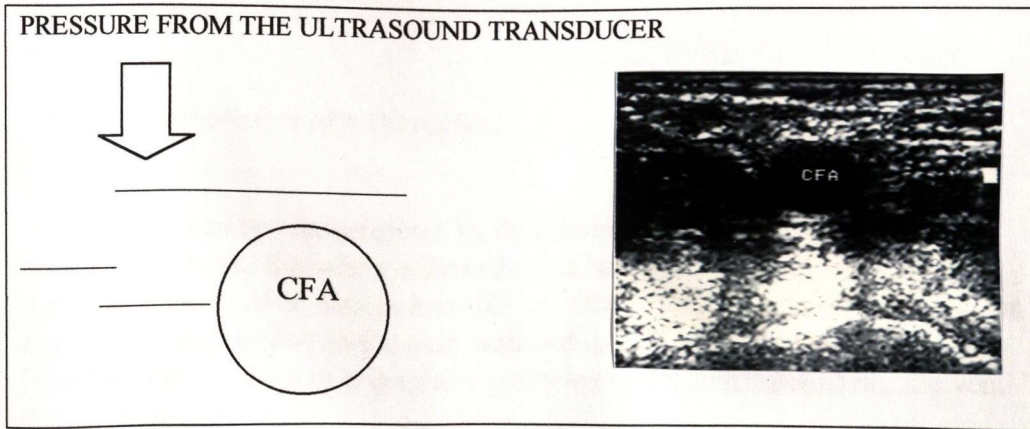


Figure 3.2(c) Further pressure causes the veins to fully compress.

The patient was then asked to sit on the edge of the table with the leg to be examined dependent, externally rotated from the knee and lightly resting on the examiners knee (Figure 3.1). This position enhanced visualisation of the calf veins. The posterior tibial, peroneal, soleal and perforator veins were all examined in this position. Since flow in these veins was not often spontaneous, the examiner lightly squeezed the foot at regular intervals to enhance colour flow through the veins during scanning. Enhancing the flow through the veins made it easier to visualise them. In the same position, the long saphenous vein was then examined from just above the medial malleolus to the knee.

3.4.2 Doppler/Colour flow interpretation:

Venous flow is non-pulsatile; however, it may contain pulsatile characteristics in the presence of venous hypertension. Flow is normally spontaneous in the larger veins therefore Doppler and colour flows signals should be present. The normal venous signal is phasic with a loss of flow/colour during inspiration and a return of flow/colour with expiration. The lack of a phasic response in the common femoral veins suggests a proximal obstruction to venous outflow. In a normal vein, compression of the limb distal to the point of Doppler examination will cause augmentation of flow. Reduced or absent augmentation suggests a distal occlusion. Absence of flow, non-phasic response and loss or reduction of augmentation, all suggest the presence of venous obstruction.

3.4.3 B-mode imaging interpretation:

A normal vein completely collapses with light compression of the ultrasound probe (Figure 3.2). Thrombus was said to be present within a vein when echogenic material was visualised within its lumen and/or by the incompressibility or partial compressibility of the vein and by lack of blood flow in the area.

3.4.4 Characteristics of a thrombus:

A thrombus can be characterised by its echogenicity appearance on ultrasound. Acute thrombus is described as having a low echogenic appearance and can be almost invisible on ultrasound scanning. The thrombus may be poorly attached to the vein wall and can be seen to float freely in the bloodstream. When a vein is totally occluded by an acute thrombus, the vein is very often dilated.

As a thrombus becomes organised over time its echogenicity increases. Chronic thrombus is described as being brightly echogenic and can be seen

more clearly on ultrasound. However, if a vein was totally occluded, then as the thrombus organises the vein wall contracts and the vein becomes difficult to visualise, as its echogenicity appearance is the same as the surrounding tissue. If the organised thrombus is not fully occluding the veins, it can become densely fibrous and take on the appearance of calcified plaque with irregular borders (Figure 3.3).

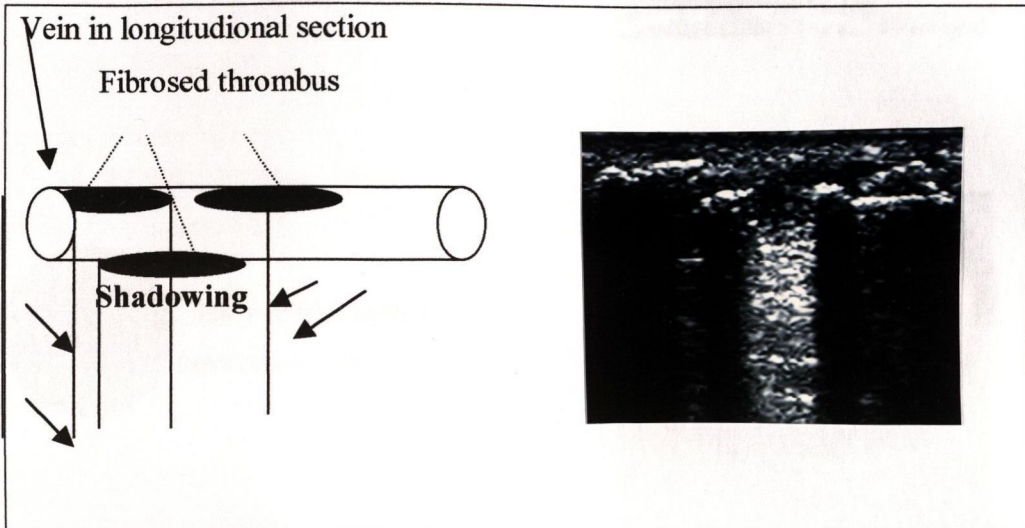


Figure 3.3: Fibrosed thrombus is brightly echogenic and causes shadowing similar to the appearance of calcified plaque.

From previous studies, the early stages of organisation of a thrombus were found to follow distinct patterns of organisation that can be seen on the ultrasound image (O'Shaughnessy *et al* Fitzgerald 1996). The process of early organisation is as follows:

1. Acute/fresh thrombus - mainly anechoic
2. Early cellular infiltration from the vein wall - increasing the echogenicity
3. More advanced cellular infiltration characterised by a low echogenic centre surrounded by a more brightly echogenic ring
4. Complete inflammatory cell infiltration - thrombus becomes more homogenous with a further increase in echogenicity (Figure 3.4).

Following these early stages the thrombus may then lyse, start to recanalise slowly over time or fibrose and remain occluded. These changes can be seen on the ultrasound image:

Lysis - before flow is established small anechoic areas are noted within the thrombus. With time these areas may become channels for venous flow.

Permanent occlusion - the thrombus will over time become more fibrosed increasing the echogenicity until the original vein becomes difficult to distinguish from the surrounding tissue.

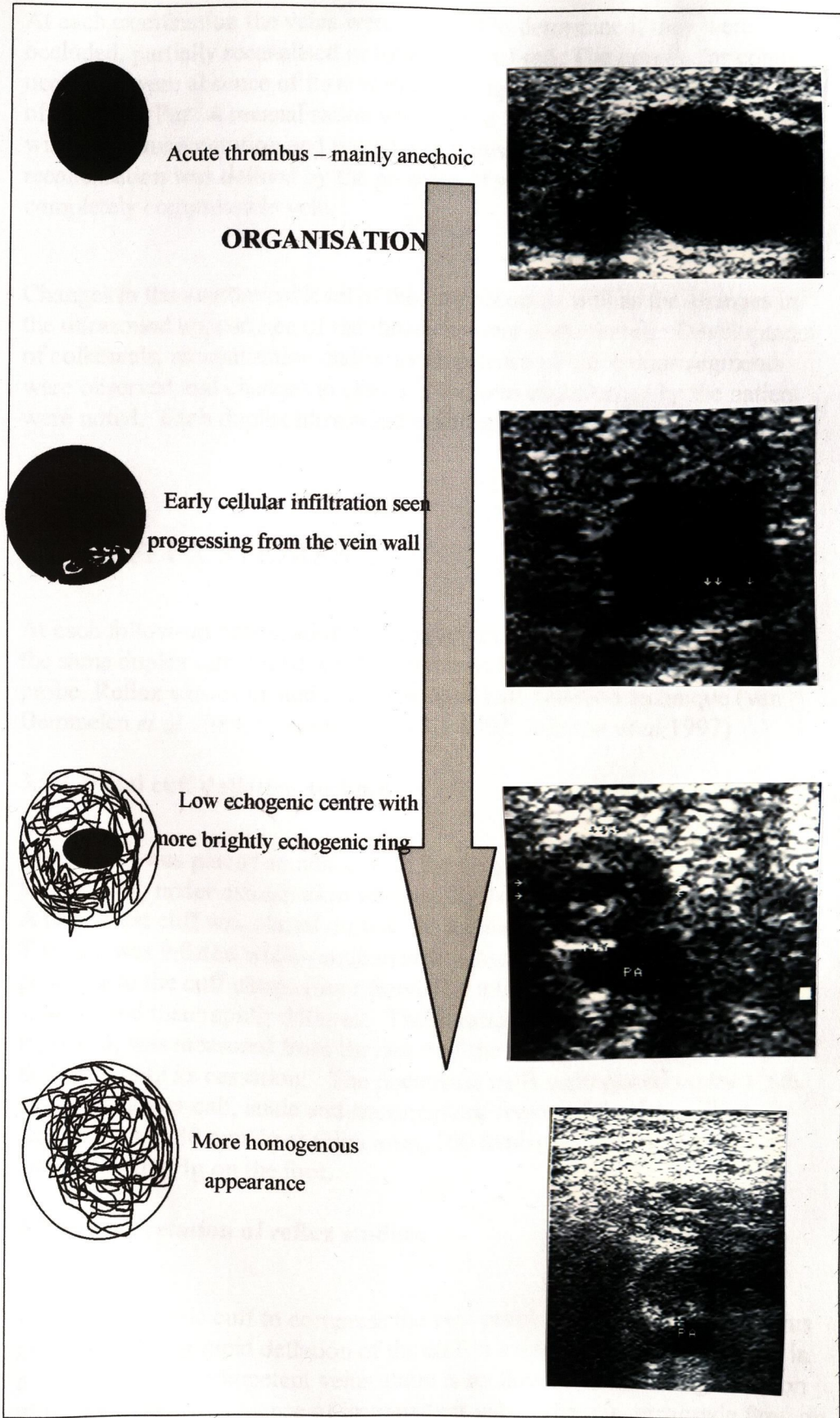


Figure 3.4: The changes in echogenicity appearance in the early stages of organisation of a thrombus – as the organisation progresses the echogenicity increases.

At each examination the veins were assessed to determine if they were occluded, partially recanalised or totally recanalised. The criteria for complete occlusion were absence of flow with distal augmentation and incompressibility of the vein. Partial recanalisation was defined by normal or diminished flow with distal augmentation and partial incompressibility of the vein. Complete recanalisation was defined by the presence of spontaneous phasic flow and a completely compressible vein.

Changes in the anatomical level of the thrombosis as well as the changes in the ultrasound appearance of the thrombus were documented. Development of collaterals, recanalisation and/or incompetence of the venous segments were observed and changes in clinical symptoms experienced by the patient were noted. Each duplex ultrasound examination was recorded on video.

3.5. REFLUX STUDIES

At each follow-up examination bilateral reflux studies were performed with the same duplex ultrasound machine (Acuson 128xP) using the 7.5 MHz probe. Reflux was evaluated using the distal cuff deflation technique (van Bemmelen *et al* 1989; Czeredarczuk *et al* 1992; Johnson *et al* 1997).

3.5.1 Distal cuff deflation technique:

The patient was placed standing, with the weight borne on the contralateral leg. The leg under examination was slightly externally rotated from the hip. A pneumatic cuff was placed around the leg distal to the vein being studied. The cuff was inflated while simultaneously insonating the venous segment proximal to the cuff using colour flow. The inflation was maintained for three seconds and then rapidly deflated. The duration in seconds of venous reflux, if present, was measured from the onset of the retrograde flow following cuff deflation, until its cessation. The pneumatic cuffs were placed on the thigh, upper and lower calf, ankle and transmartial region of the foot. The cuff was inflated to 80 mmHg at thigh level, 100 mmHg at calf and ankle levels and to 120 mmHg on the foot.

3.5.2 Interpretation of reflux studies:

Using a pneumatic cuff to compress the vein proximally the venous flow was monitored during rapid deflation of the cuff to assess valvular competence in a vein. In normal, competent veins, there is no flow reversal during deflation of the cuff. In the presence of incompetent valves there is retrograde flow on deflation of > 1 second. The greater the time interval of reverse flow, the more severe the reflux.

3.6. COMPUTER ANALYSIS

3.6.1 Method of computer analysis:

At each duplex ultrasound examination a cross sectional grey scale image of the proximal end of the thrombus was frozen and captured on videotape. Care was taken to assess the same segment of thrombus at each examination using anatomical reference points at the most proximal end of the thrombus. The frame to be analysed was then transferred onto the computer. The image was captured from video using Adobe Premiere™ and transferred to a Power Macintosh 7100/80av for analysis. Adobe Photoshop™ was used to standardise the image and calculate the grey scale median (GSM). The same technologist performed all the GSM analysis. The image was firstly cropped to include only the image of the artery, vein and surrounding tissue. The thrombus in the vein was then outlined and a histogram of its grey scale content obtained before standardisation. The image was standardised by taking blood as the darkest level (black = 0) and the brightest area of perivenous tissue as the brightest level (white = 255). The grey values of all the pixels then change according to the new linear scale defined by the reference values for blood and tissue. A histogram of the standardised image was taken to ensure all pixels from 0 to 255 were included.

Once the image was standardised, the thrombus was outlined and a histogram obtained for the selected area (Figure 3.5). The numerical values below the histogram displayed the statistical information about the selected area (i.e. the thrombus):

- (a) The Mean - the average brightness value.
- (b) Standard deviation - how widely the values vary.
- (c) Median - the middle value in the range of colour values (GSM).
- (d) Pixels - the total number of pixels in the selected area.

3.6.2 Reproducibility studies:

To determine the reproducibility of the image analysis 20 images were selected at random and analysed repeatedly over a period of five days by the same technologist. The mean GSM was calculated for each sample and the standard error of the mean of all twenty samples was calculated

3.6.3 GSM Analysis:

The GSM value was calculated for each thrombus at each consecutive scan during the first year. The initial GSM values were compared to the age of the

patient, the bulk of the thrombus and to the duration of symptoms to determine if a relationship existed between them.

At one week follow up the patients were divided into those with an initial GSM value of < 20 (poorly organised) and those with an initial value of > 20 (more advanced organisation) to determine the early changes in the organisation process.

An overall mean value of GSM for all the thrombi was calculated at each follow-up visit up to one year and the overall mean values were compared. The patient population were subsequently divided into groups according to their outcome at one year as follows:

Group I: Thrombi that recanalised fully

Group II: Thrombi that partially recanalised with some residual thrombus remaining

Group III: Thrombi that fibrosed and the vein remained totally occluded at one year.

The GSM values of the three groups were compared to determine if the changes in GSM over time could give an indication of the long-term outcome i.e. successful lysis, permanent occlusion or recanalisation with residual thrombus.

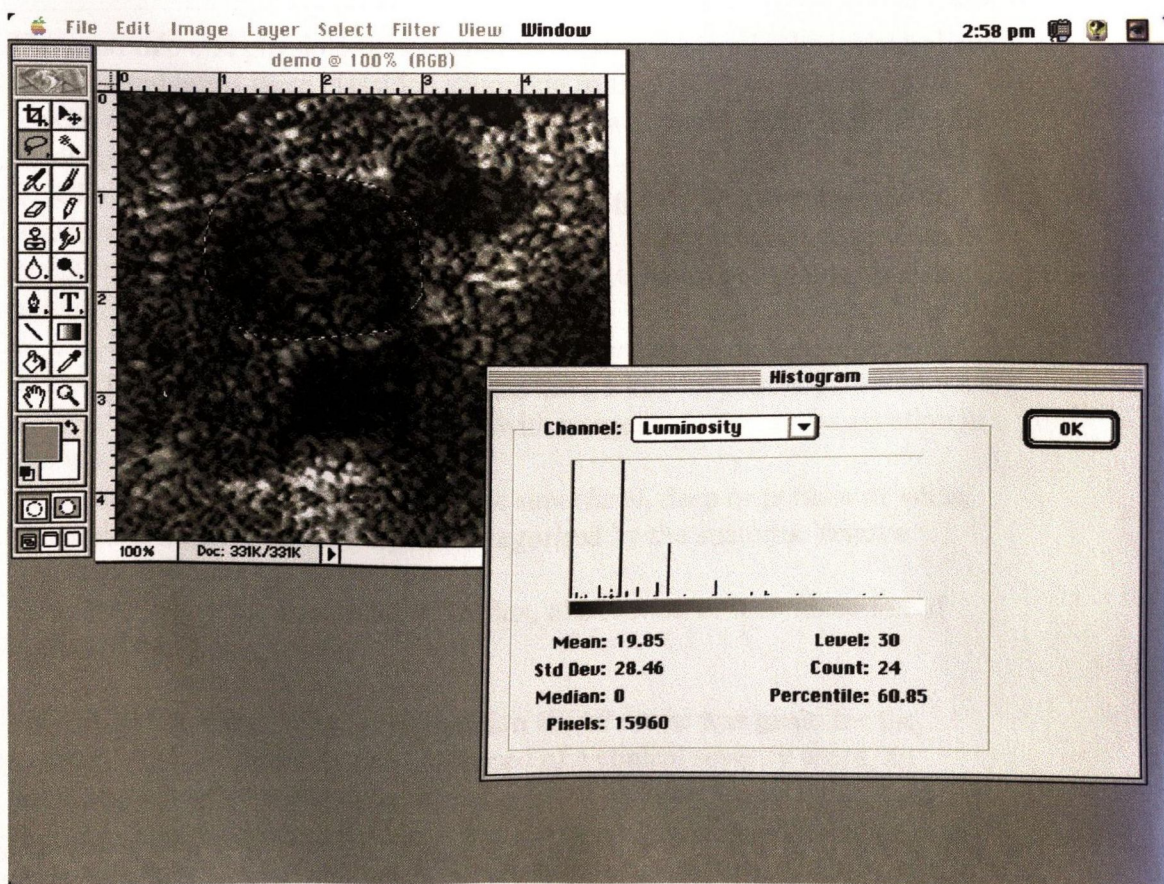


Figure 3.5. Ultrasound image analysis using Adobe Photoshop™. The thrombus totally occluding the popliteal vein is outlined and a histogram is obtained. The statistical information is displayed below the histogram.

3.7. ANALYSIS OF ANATOMICAL SITES

The patterns of response to an acute DVT in different anatomical venous segments throughout the first year were examined. At the initial examination, the anatomical distribution of thrombi, were grouped according the individual venous segments involved and the patterns of response within these segments were recorded. The venous segments were examined to determine if certain segments were more inclined to lyse successfully, to partially recanalise or remain occluded. The competence and timing of recanalisation of each segment was recorded to determine if certain venous segments were more likely to develop incompetence than others.

3.8. LONG-TERM RESULTS & CEAP CLASSIFICATION

A total of 63 patients were followed up to a mean period of three years. The patients were divided into two groups: group I – patients without a history of a contralateral DVT and group II - patients with a history of a contralateral DVT. The patient symptoms, venous systems involved (i.e. deep, superficial or perforator) and the anatomical site of venous dysfunction were compared in the ipsilateral and contralateral limbs for the two groups.

The anatomic and physiologic status of the venous system in the ipsilateral and contralateral limbs were classified according to the CEAP classification (Beebe *et al* 1995; Appendix 1). Classification was made under the following headings:

C: Clinical signs, grade 0 – 6, where limbs in higher categories have more severe manifestations of chronic venous disease. The presence or absence of symptoms was identified by the letters S (symptomatic) or A (asymptomatic) positioned after the letter C.

E: Etiologic classification i.e. congenital, primary or secondary which are mutually exclusive. Secondary problems have a known pathologic cause such as thrombosis. No patients presented with congenital venous classification in this study.

A: Anatomic distribution involving the superficial, deep or perforator veins, either alone or in combination, and categorised by the anatomic venous segments involved.

P: Pathophysiologic dysfunction – reflux, obstruction or a combination of both reflux and obstruction.

An overall subjective venous dysfunction CEAP score was given for the ipsilateral limb. This score was composed of a clinical severity score, an anatomical severity score and a disability score as experienced by the patient. For simplicity the anatomical score was given for overall superficial, deep or perforator involvement and not for the individual anatomical sites.

The CEAP total scores were subdivided as follows: CEAP score = 0. No visible sign of venous disease; CEAP score 1 –3 inclusive. Mild to moderate venous disease; CEAP score >3. Severe venous disease.

The two groups were then compared according to the total CEAP score on the ipsilateral limb and the ipsilateral and contralateral limbs were compared. The initial predisposing factors for each of the CEAP scores were then analysed to determine if the initial risk factors could give an indication of the severity of the long-term clinical symptoms.

3.9. STATISTIAL ANALYSIS

The mean value, standard deviation and range of values were calculated for each series of data.

The standard error of the differences between the means in the reproducibility studies was calculated from the formula:

$$= \sqrt{\frac{(SD1)^2}{n1} + \frac{(SD2)^2}{n2} + \frac{(SD3)^2}{n3} + \dots}$$

Where SD Standard deviation of series 1,2,3, etc
n = number in each series

Confidence intervals were used to present the data as estimates of results that would have been obtained if the total population were studied. This method has been recommended for medical studies (Gardner *et al* 1986).

The correlation coefficient is measured on a scale of +1, through 0, to -1. Complete correlation between two variables is measured by 1 and complete absence of correlation is measured by 0.

The correlation coefficient, r is calculated by the following formula:

$$r = \frac{\sum (x - \bar{x})(y - \bar{y})}{\sqrt{\sum (x - \bar{x})^2 \sum (y - \bar{y})^2}}$$

Where $\bar{x}$ and $\bar{y}$ are the mean of x and y observations.

It is important to note that correlation is not causation. There may or not be a causative connection between the two correlated variables.

The standard error of the correlation coefficient was also obtained. To test the deviation of r from 0, or nil correlation the t test was used :

$$t = \frac{r \sqrt{n-2}}{\sqrt{1-r^2}}$$

The t table is entered at $n-2$ degrees of freedom.

The regression equation representing how much y changes with any given change of x was used to construct a 'regression line' on a scatter diagram. A 'straight line' correlation was presumed i.e. the relationship between the two variables is expressed graphically by a straight line.

The regression equation is as follows:

$$y = a + bx$$

Where y = dependant variable; x = independent variable
 a signifies the distance above the base line at which the regression line cuts the vertical y axis.

b = regression coefficient – the amount by which a change in x must be multiplied to give a corresponding average change in y (Altman *et* Gardner 1988).

To compare the frequency of observations the Fisher exact test was used.

4. RESULTS

4.1. PATIENT POPULATION

4.1.1 Patient population at initial examination:

The patient population in this study included those with a terminal illness, those with a history of a previous DVT and those with reversible risk factors. The patients presented consecutively to the vascular laboratory and were diagnosed with acute proximal deep vein thrombosis by duplex ultrasound scanning. There were 100 proximal venous thromboses analysed from 89 patients (45 males, 44 females, 11 bilateral thromboses). The mean age of the patient population was 62 ± 18 years (Range 22 - 94 years).

Most patients presented initially with a combination of risk factors. Patients with a previous history of DVT (both ipsilateral and contralateral) were included in this study. Twenty nine patients (33%) had a history of a previous DVT; six (7%) had a history of a stroke; 15 (17%) had a known malignancy; 12 (13%) suffered a recent injury; 13 (15%) were post surgery; 19 (21%) smoked; 19 (21%) had varicose veins; 20 (22%) were on long-term bed rest and four (5%) were on hormone replacement therapy (Figure 4.1). Three patients were factor V Leiden carriers; however, as only a small number of patients in this study had a thrombophilia screen, coagulation abnormalities that may have been present in this patient population could not be included in the risk factor assessment.

The presenting clinical symptoms on initial examination were as follows: 24 with suspect pulmonary embolism (17 positive V/Q scans, one negative and six not performed); 19 patients had lower limb swelling only, 12 with tenderness only and 52 with both tenderness and swelling. Of the 11 patients with bilateral thrombosis, three patients presented with unilateral leg pain and swelling; three with a PE and unilateral pain and swelling; and one with a PE only (all V/Q scans positive). The mean duration of symptoms prior to examination was 5.79 ± 4.29 days (Range one - 21 days) (Appendix III).

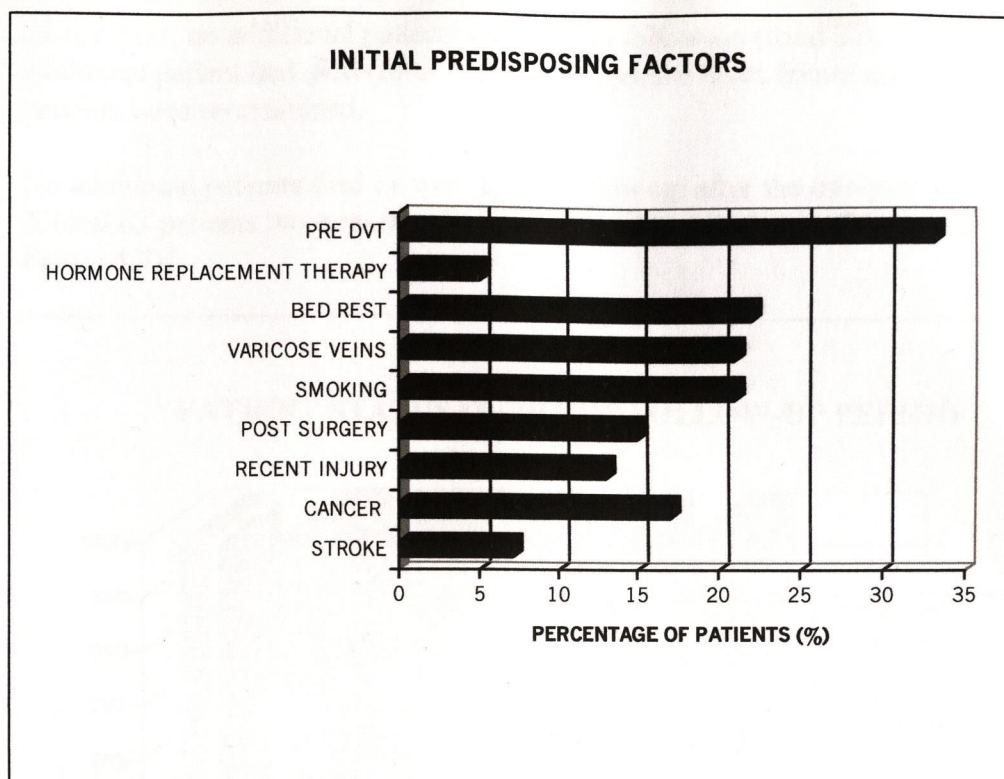


Figure 4.1: The initial predisposing factors for the patient population.

4.1.2. Patient population at follow-up visits:

A significant mortality rate has long been associated with DVT and a number of patients died during the follow-up period. In addition, a number of patients did not show for various follow-up visits and some were permanently lost to follow-up.

At one week follow-up 27 patients did not return for the follow-up examination and one patient had died from lung cancer. A total of 72 patients were re-examined.

At one-month follow-up examination, nine additional patients had died (total 10). The causes of death were as follows: seven from cancer and two from pulmonary embolism. Eighteen patients were lost to follow-up and 11 did not return for their one-month appointment. Sixty-one patients were re-examined.

At six months there were 23 patients who were lost to follow-up and seven patients did not return for this visit. An additional three patients had died (total 13) - two patients died from cancer and one patient, who had recurrent PE's, had died from a PE shortly after the one-month follow-up visit. Fifty-seven patients were re-examined.

At one year, no additional patients were lost to follow-up (total 23). One additional patient had died (total 14) from congestive heart failure and 63 patients were re-examined.

No additional patients died or were lost to follow-up after the one-year visit. A total 63 patients were re-examined over the subsequent years (Figure 4.2; Figure 4.3).

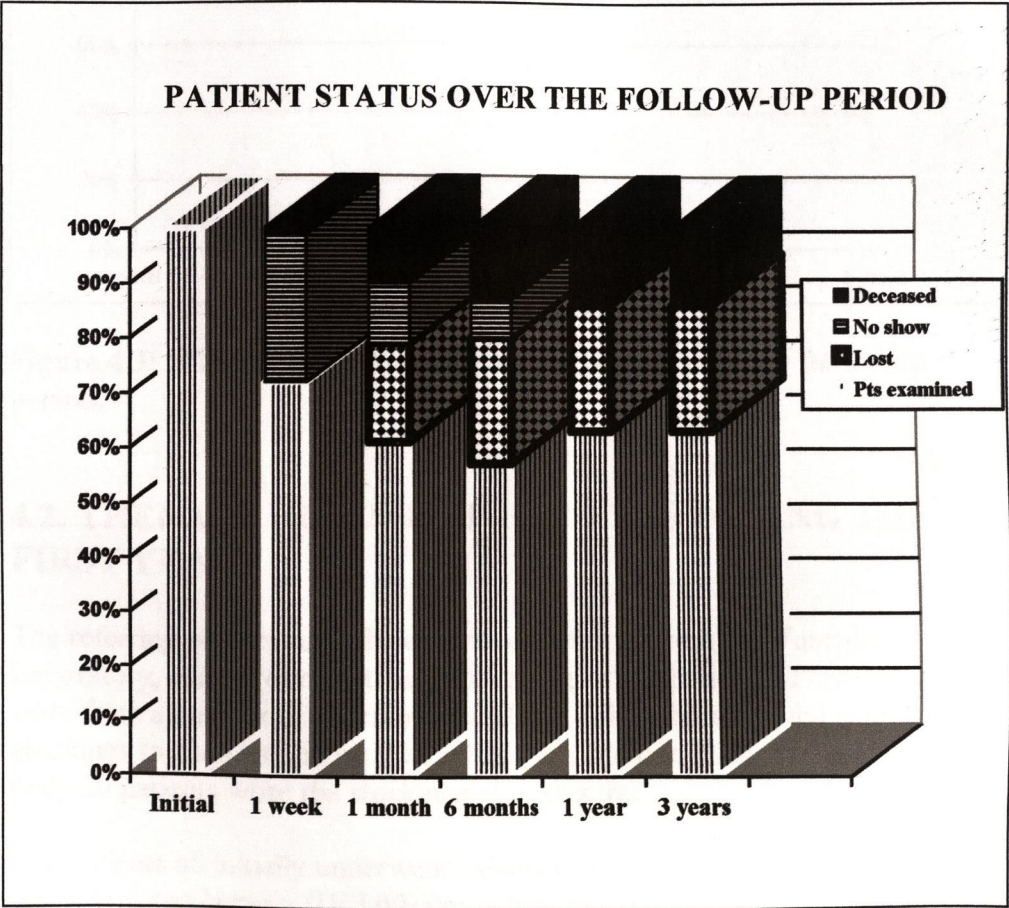


Figure 4.2: The percentage of patient over the follow-up period that were examined, that did not return for their visits, that were lost to follow-up and that died.

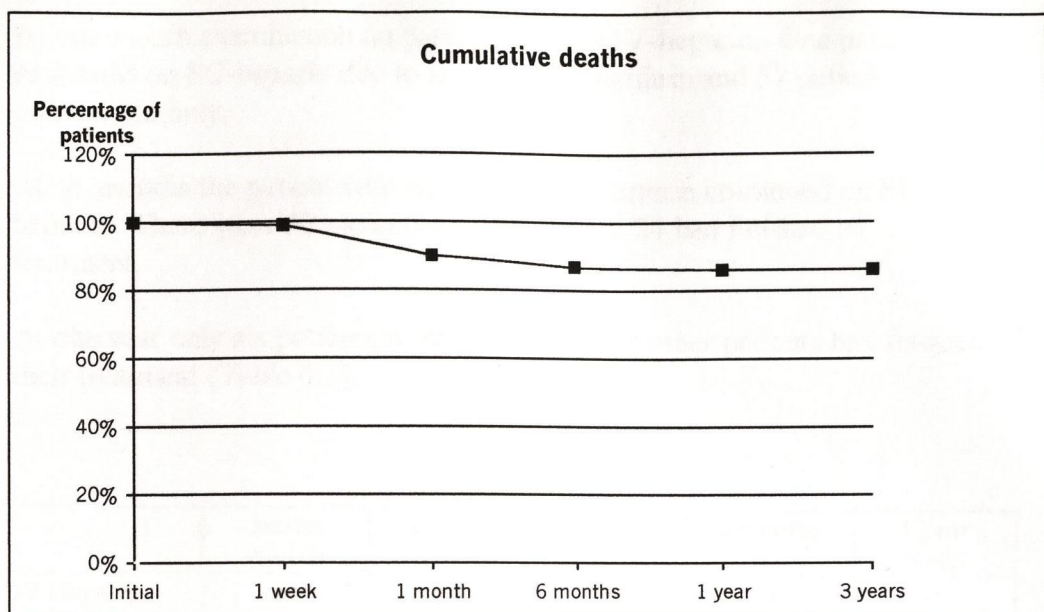


Figure 4.3: The percentage of cumulative deaths over the follow-up period.

4.2. THERAPY REGIME OF PATIENTS DURING THE FIRST YEAR

The referring physicians, independent of any input from the Vascular Laboratory, carried out the treatment regime of the patients. These physicians were from a number of different specialities. The laboratory did supply elastic stockings to each patient on their initial visit, but compliance of use was low. Only 20 patients wore the stockings as instructed.

The patients all initially underwent treatment with either intravenous unfractionated heparin (IV UFH) or subcutaneous low molecular weight heparin (SC LMWH). All patients were treated with warfarin, following heparin treatment, except for one patient who was allergic to warfarin. No patients required re-hospitalisation for bleeding complications during the follow-up period.

Sixty-four patients had commenced therapy before their initial scan. There were 36 on IV heparin, 11 of which had commenced warfarin also. Twenty-four patients were being treated with SC heparin two of which were also on warfarin. Four patients were on warfarin only.

At one week 14 patients were on IV heparin, nine of which were also on warfarin. Thirty-five patients were being treated with SC heparin, 16 of which were also on warfarin. There were 23 patients on warfarin only. Of those patients treated with SC heparin only one was treated as an outpatient, 10 were allowed full mobility in the hospital with early discharge (two - three days) and the remaining patients were treated in hospital on bed rest.

At one-month examination no patients were on IV-heparin. One patient continued on SC-heparin due to an allergy to warfarin and 57 patients were on warfarin only.

At six months the patient who was allergic to warfarin continued on SC heparin. There were 32 patients on warfarin and 24 had finished all treatment.

At one year only six patients were on warfarin, all other patients had finished their treatment (Table 4.1).

	Initial N=100	1 week N = 72	1 month N = 61	6 months N=57	1 year N=63
IV Heparin ..with warfarin	25 11	5 9	0 0	0 0	0 0
SC Heparin ..with warfarin	22 2	19 16	1* 0	1* 0	0 0
Warfarin only	4	23	57	32	6
No Treatment	36	0	3	24	57

(* Patient allergic to warfarin)

Table 4.1: The treatment regime of the patients during the first year showing the number of patients who were on no treatment and those been treated with IV heparin, SC heparin or warfarin at each examination.

4.3. FINDINGS ON DUPLEX EXAMINATION DURING THE FIRST YEAR (SYMPTOMATIC/ASYMPTOMATIC EVENTS)

4.3.1 Initial findings:

All patients were diagnosed with an acute DVT using duplex ultrasound scanning. Bilateral scanning was performed on each patient according to the venous scanning protocol. The same vascular technologist carried out all examinations.

At initial examination the size and bulk of the thrombus, as well as the most proximal site of thrombus, varied from patient to patient. Many of the thrombi were anatomically multi-level but their most proximal sites were as follows: inferior vena cava (IVC) - one; iliac veins - 30; common femoral vein - 33; superficial femoral vein - 30 and popliteal vein - six.

The size or bulk of each thrombus ranged from small isolated thrombi to those that occluded the length of the deep venous system in the lower extremity. By measuring the diameter and length of the thrombus, an estimation of the size of each thrombus was made. The mean volume of thrombus was $73.2 \pm 36.8 \text{ cm}^2$ (Range 9 - 160cm²). There were 18 thrombi that were partially occlusive and 82 were totally occlusive.

4.3.2 One-week follow-up:

At one-week a total of 72 patients were examined. Four patients had PE's during the first week. Two of these patients had a Greenfield filter inserted shortly after their scan and the patients had no further symptoms. Two patients (one post-stroke and the other with a history of malignancy) had developed phlegmasia. Both of these patients died shortly after the 1-week follow-up visit. Three patients had extensions of their thrombi, two were asymptomatic and one patient had a PE. One extension was a retrograde extension, extending from the common femoral vein to the popliteal and the other two were from the common femoral up to the common iliac veins. Two thrombi had fully resolved returning the vein to normal under ultrasound. These were small, isolated thrombi one located in the common femoral and one in the popliteal vein. These two patients did not have pulmonary symptoms during the follow-up period. There were 36 thrombi that were totally occlusive and 34 were partially occlusive. Of the 34 thrombi that were partially occlusive, 23 of these had been totally occlusive at the initial examination.

4.3.3 One-month follow-up:

At one month (N = 61), one patient had stopped taking warfarin against medical advice and developed a symptomatic extension from the popliteal vein up to the common femoral vein. A patient with a malignancy and bilateral thrombi developed phlegmasia and died shortly after the follow-up visit. There was one extension from the common femoral vein to the common iliac vein that was asymptomatic and the proximal tip of the thrombus was mobile. Eleven thrombi had fully resolved, 18 were totally occlusive and 32 were partially occlusive. Of those that were partially occlusive, 11 had been totally occlusive at the previous visit.

4.3.4 Six months follow-up:

At six months (N = 57) there was one symptomatic new DVT after the patient had completed warfarin treatment. Sixteen thrombi were fully resolved, 16 were totally occlusive and 25 were now partially recanalised. Three thrombi which had been partially occluded at the previous examination were found to have re-occluded indicating new asymptomatic events, within the follow-up time.

	1 week	1 month	6 months	1 year
Symptomatic events	2 x phlegmasia 3x PE's 1x extension + PE	1 x extension 1 x phlegmasia	1 x New DVT	2 x New DVT
Asymptomatic events	2 x extension (1 retrograde)	1 x extension	3 x re-occlusion	4 x re-occlusion
Deaths	1 x CA	7 x CA 2 x PE	2 x CA 1 x PE	1 x CHF

Table 4.2: The number of symptomatic and asymptomatic events detected by duplex ultrasound over the period of one year. The highest number of events occurred in the initial phase of treatment and at one year.

4.3.5 One-year follow-up:

At one year (N = 63) there were two symptomatic new DVT's - both patients had completed their treatment before developing symptoms. Four thrombi that had been partially occlusive were re-occluded indicating asymptomatic recurrences. Twenty-one thrombi had fully resolved, 18 were totally occlusive and 24 had partially recanalised (Table 4.2).

4.4. GSM RESULTS

At each duplex ultrasound examination during the first year, a cross sectional grey scale image of the proximal end of the thrombus was frozen and captured on videotape. Each image was then transferred to a computer, standardised and the grey scale median (GSM) was calculated.

4.4.1 Reproducibility studies:

To determine the reproducibility of the image analysis 20 images were selected at random and analysed each day, over a five-day period to determine the variation in calculation of the GSM. The same vascular technologist performed the computer analysis in a blind fashion. The GSM for each image obtained on five consecutive days and the calculated mean and standard deviations for each image were obtained (Table 4.3). The standard error (SE) of the difference between the means was calculated to be equal to 5.72.

	GSM measured on day					Mean	SD
	1	2	3	4	5		
Case 1	2	0	0	0	1	0.6	0.89
Case 2	35	31	33	32	36	33.4	2.07
Case 3	28	31	30	31	32	30.4	1.004
Case 4	0	2	2	2	0	1.2	1.095
Case 5	34	34	37	37	32	34.8	2.16
Case 6	4	2	1	5	4	3.2	3.28
Case 7	35	32	32	33	32	33.8	2.16
Case 8	47	53	55	50	53	51.6	6.2
Case 9	2	0	4	4	0	2	2
Case 10	29	31	34	33	31	31.6	1.95
Case 11	25	26	26	29	28	26.8	1.6
Case 12	45	50	48	46	49	47.6	2.07
Case 13	18	18	14	14	20	16.8	2.4
Case 14	0	0	0	0	0	0	0
Case 15	3	3	0	1	4	3	1.9
Case 16	4	4	0	1	1	2	1.87
Case 17	23	14	32	32	32	26.6	8.05
Case 18	33	32	32	32	32	32.2	0.44
Case 19	31	31	30	29	33	30.8	2
Case 20	26	26	26	28	28	26.8	1.095

Table 4.3: The results of measuring the GSM of twenty imaged over five consecutive days and the calculated mean and standard deviation of each sample.

4.4.2 GSM - Initial results:

The GSM value measured on the initial scan varied considerably as expected due to the various levels of organisation that can be seen on an initial duplex examination (Figure 4.4) (Appendix IV). The mean GSM was 18.02 ± 16.68 (Range 0 - 72).

The initial GSM values were compared to the duration of symptoms of the patient (Figure 4.5). Two patients had symptoms for 21 days before seeking medical attention and had high GSM values indicating more advanced organisation of the thrombus. Comparing the duration of clinical symptoms with the initial GSM value a strong correlation was obtained, correlation coefficient $r = 0.302$ which was highly significant ($P = 0.002$). However, the majority of patients had their clinical symptoms for seven days or less and no relationship was found between the duration of symptoms when < 7 days and the initial GSM value. The correlation coefficient for the patients with symptoms for seven days or less was found to be 0.05 and the P value = 0.67 (Figure 4.6).

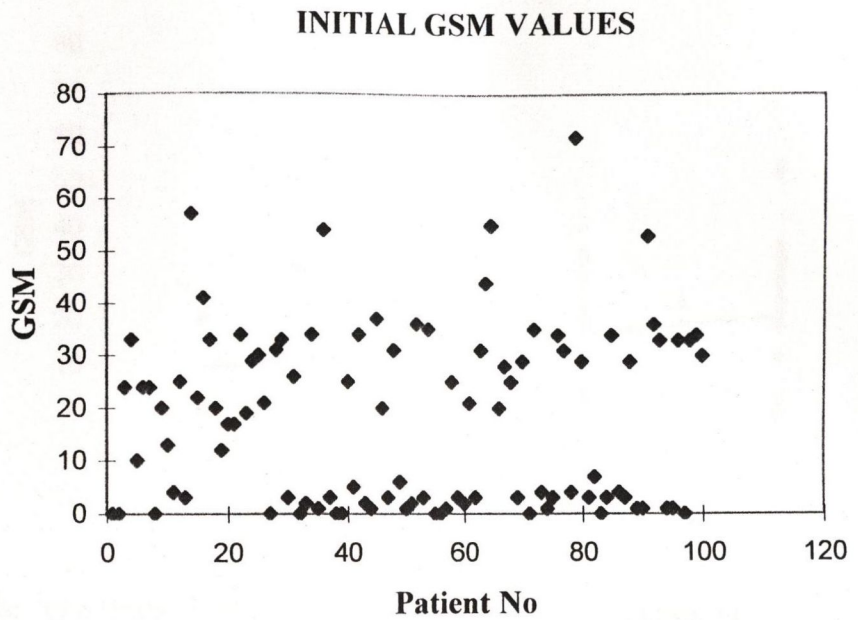


Figure 4.4: The GSM values measured at the patient's initial examination showing a wide variation in GSM values.

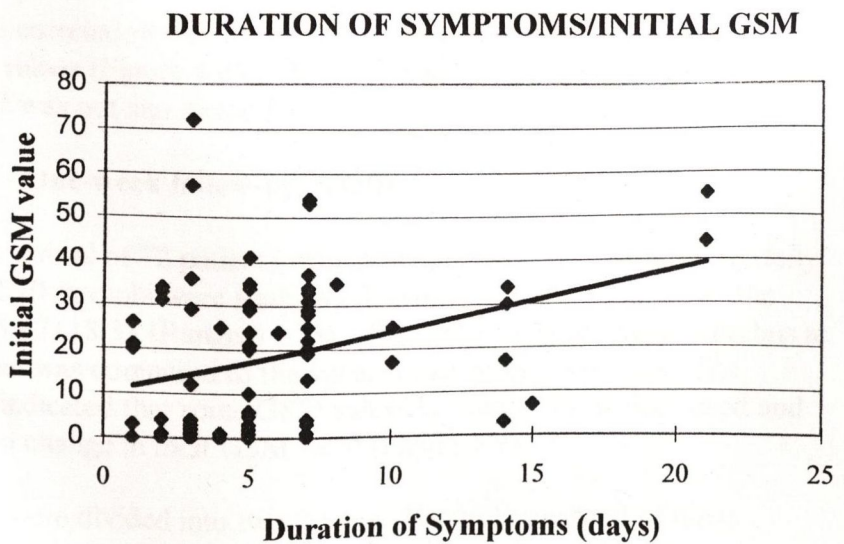


Figure 4.5. The initial GSM values compared to the duration of symptoms before the initial examination showing a positive correlation.

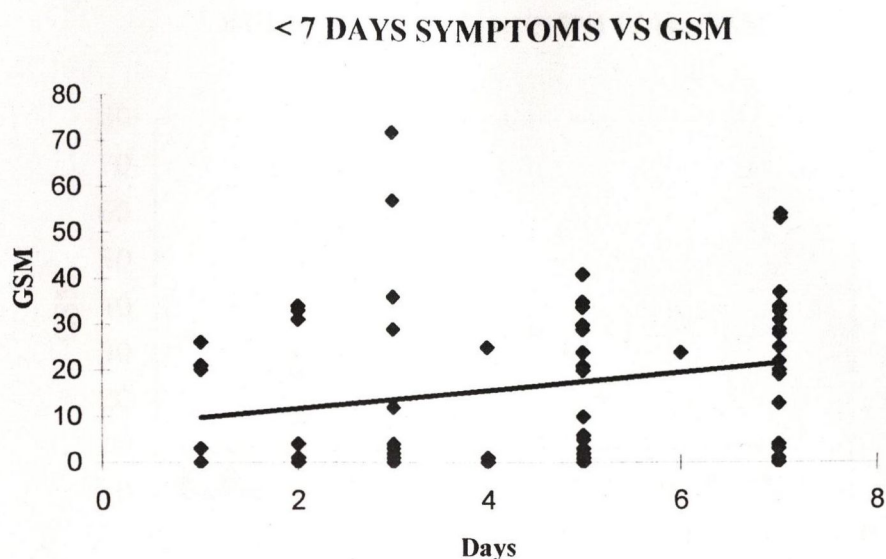


Figure 4.6. The initial GSM values compared to the duration of symptoms when the symptoms were < 7 days. There was a low correlation $r = 0.05$, which was not significant $P = 0.67$.

No relationship was found between the initial GSM values when compared to the size of the thrombus (Figure 4.7). The correlation coefficient was calculated to equal 0.01 and was not significant $P = 0.89$.

Similarly, no correlation was found between the age of the patient and the initial GSM values (Figure 4.8). The correlation coefficient was calculated to be 0.007 and was not significant $P = 0.9$.

4.4.3 GSM – One-week follow-up results:

At one week a total of 72 patients were re-examined. Two thrombi had fully resolved and 70 thrombi were analysed. The mean GSM calculated at one week was 25.87 ± 18.33 (Range 0 - 75). The GSM value for each thrombus at the initial scan was compared to the value at one-week follow-up. The comparison indicated that some GSM values increased, some decreased and others had no change in their GSM value (Figure 4.9).

The patients were divided into two groups. Group I consisted of those patients on initial examination with thrombi in the early stages of organisation (i.e. $GSM < 20$). There were a total of 32 thrombi in this group. An increase in GSM was expected due to an increase in echogenicity with organisation. The one-week follow-up GSM values were compared to the initial GSM values and 13 showed no significant change in their GSM value, two had a reduction in GSM and 17 had an increase in GSM as expected (Figure 4.10.).

BULK OF THROMBUS/INITIAL GSM

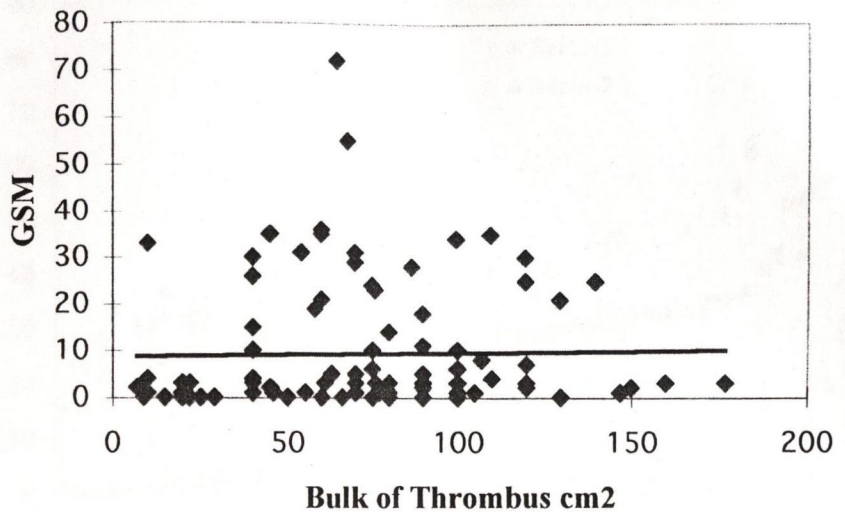


Figure 4.7: The initial GSM values compared to the bulk of the thrombus with the regression line indicating no correlation.

AGE/ INITIAL GSM

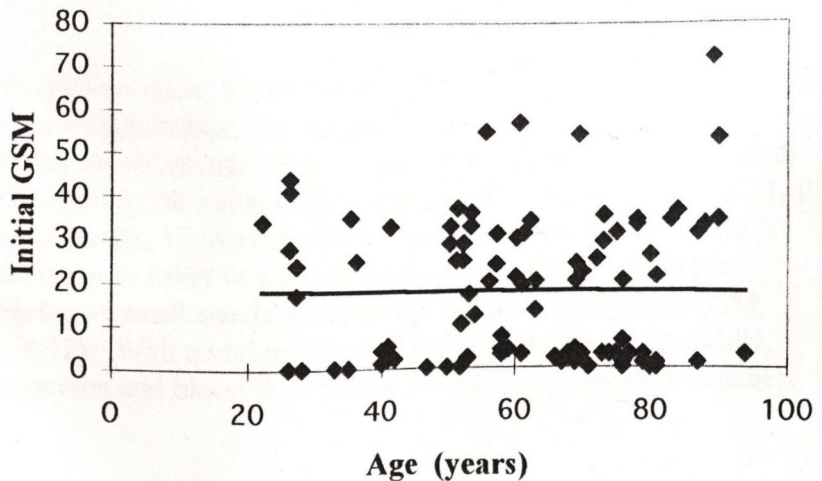


Figure 4.8: The initial GSM values compared to the age of the patient with the regression line indicating no correlation between the two.

INITIAL AND 1 WEEK FOLLOW-UP GSM VALUES

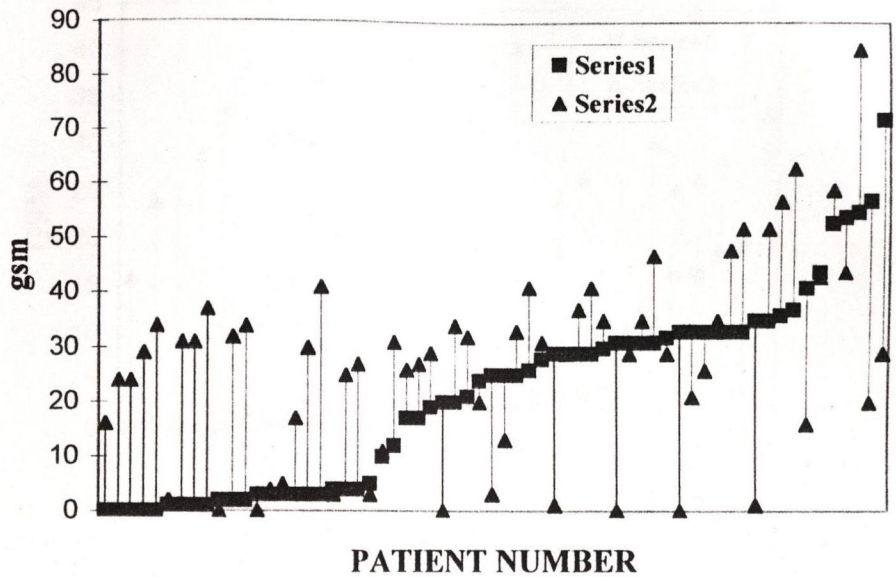


Figure 4.9: The GSM values measure initially and at one-week follow-up showing some values increasing, some decreasing and some having no change in their GSM value. (Series 1 = Initial GSM values; Series 2 = 1 week follow-up values).

Those thrombi with an initial higher GSM value >20- Group II, i.e. in a more advanced stage of organisation initially, were then examined and were compared to their values at one week. There were a total of 36 thrombi in this group. Comparing the initial GSM value at follow-up showed that 11 did not change significantly, 12 increased in value and 13 decreased (Figure 4.11). The decrease in value was due to small areas of lysis within the thrombi appearing as small anechoic areas that reduced the overall GSM value (Figure 4.12). With additional time, if these areas lyse successfully, recanalisation occurs and blood flow will be detected in these new channels.

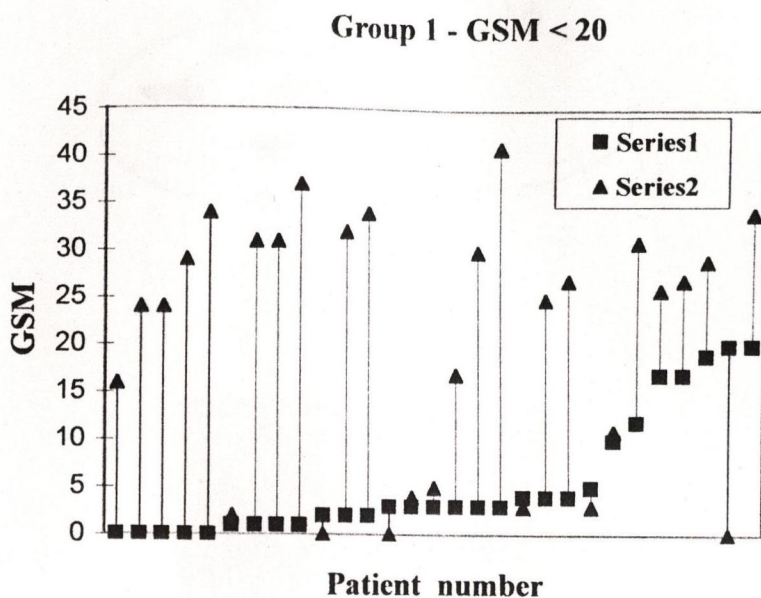


Figure 4.10: The changes in GSM values during the first week for Group 1 (i.e. initial GSM values < 20).

Series 1 = Initial values; Series 2 = 1 Week follow-up values.

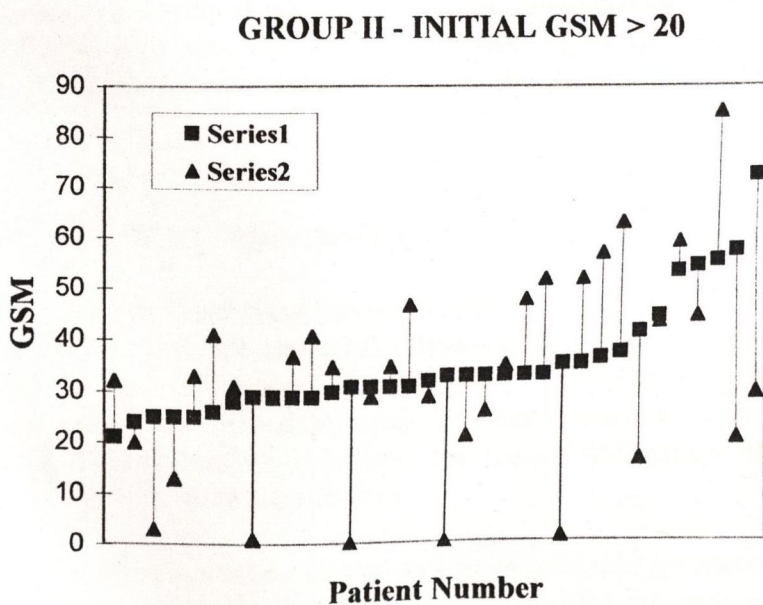


Figure 4.11: The changes in GSM values during the first week for Group II (i.e. Initial GSM values > 20).

Series 1 = Initial values; Series 2 = 1 Week follow-up values.

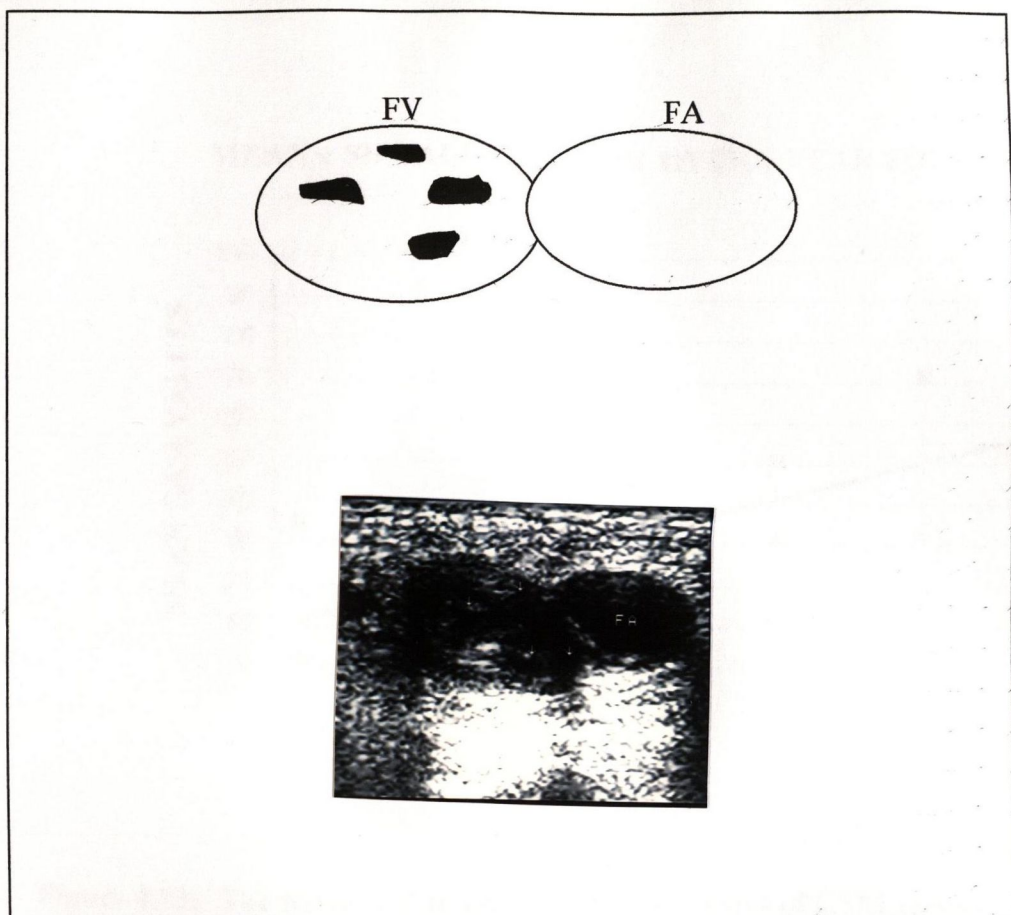


Figure 4.12: Cross sectional image of a femoral artery (FA) and vein. The vein is occluded with thrombus and there are small anechoic areas present (indicated by arrows). These are areas of lysis within the thrombus. With time, these areas may form channels recanalising the vein.

4.4.4. Changes in GSM values during the first year:

As already stated, the initial mean value of GSM (N = 100) was 18.02 ± 16.68 (Range 0 – 72) and the one week follow-up mean value of GSM (N = 70) was 25.87 ± 18.33 (Range 0 – 75). A total of 50 thrombi were analysed at one-month follow-up. The GSM values continue to fluctuate with some increasing and some decreasing as before. The mean GSM value at one month was 31.14 ± 19.75 (Range 0 - 96).

A total of 41 GSM values were calculated at six months and the mean value of GSM for the group was 52.11 ± 19.94 (Range 16 - 90). At one year a total of 42 GSM values were calculated. The mean GSM value was 64 ± 25.51 (Range 29 - 137)(Figure 4.13). There was a positive correlation coefficient for the changes in GSM over time, $r = 0.95$ which is statistical significant, $P = 0.04$.

MEAN $\pm$ SD VALUES OF GSM OVER 1 YEAR FOLLOW-UP

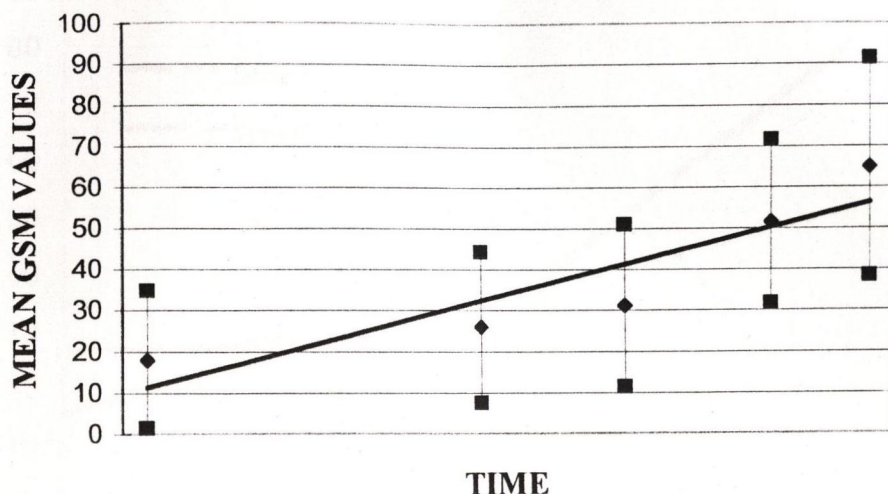


Figure 4.13: The mean and standard deviation values of GSM measured during the one-year follow-up period. There was a positive correlation between mean GSM and time as expected.

The patients were divided into groups as follows: Group I – thrombi that fully resolved during the first year; Group II – thrombi that were partially recanalised at the end of the first year; Group III – thrombi that were totally occlusive at the end of the first year.

Group I: Twenty -one thrombi had fully resolved over the one-year period. The GSM values before resolution were compared to the mean of the groups listed below and no significance difference was found.

Group II: There were 24 patients whose thrombi had partially recanalised at the end of the first year. The mean GSM values for this group were as follows: 18.86 ± 16.2 at initial examination, 33.2 ± 20.9 at one week, 37.2 ± 18.6 at one month, 44 ± 15.2 at six months and 53.7 ± 23.1 at one year.

Group III: There were 18 thrombi that were totally occlusive at one year. The mean GSM values for this group were 26.6 ± 17.3 at the initial examination, 25.6 ± 15.9 at one week, 28.9 ± 18.8 at one month, 56.7 ± 25.9 at six months and 84.3 ± 19.7 at one year.

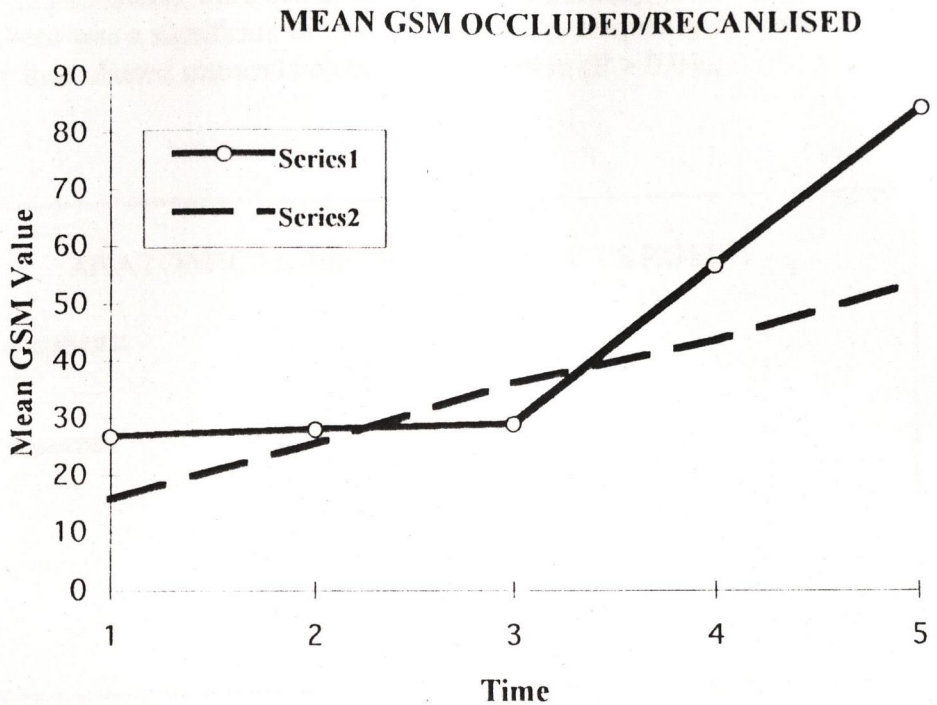


Figure 4.14: A comparison of the mean GSM values for those veins that were occluded at one year and those that were partially recanalised. There is no significant difference between the groups until after the six-months examination. Series 1 = Group III; Series 2 = Group II.

The mean GSM values of Group II and Group III were compared (Figure 4.14). There was no significant difference between the groups until after six months when the permanently occluded venous segments showed higher GSM values than those that partially recanalised.

4.5. RESPONSE OF THE ANATOMICAL SITES DURING THE FIRST YEAR

The pattern of response to an acute DVT in the individual venous segments throughout the first year was examined. In the 63 patients who were examined at one year the anatomical distribution of thrombus at their initial examination varied. The majority of thrombi involved multiple anatomic segments with only four isolated thrombi occurring, three in the common femoral vein and one in the popliteal vein. The most common distribution of thrombus extended throughout the lower extremity i.e. from the femoral to

the calf (Table 4.4). The numbers of segments involved at each site were as follows: external iliac vein (EIV) - 18; common femoral vein (CFV) - 41; superficial femoral vein (SFV) - 55; and popliteal vein (PV) - 57. Initially a total of 122 segments were occluded and 49 were partially thrombosed (Table 4.5). There was a significant difference between the frequency of occluded to partially thrombosed segments on initial examination ($P > 0.01$).

ANATOMICAL DISTRIBUTION OF THROMBI		
Single segment:	CFV	3
	PV	1
Multi-segment	EIV-CFV	0
	EIV-CFV-SFV	2
	EIV-CFV-SFV-PV	15
	CFV-SFV	1
	CFV-SFV-PV	19
	SFV-PV	17
	PV-Calf	4

Table 4.4: The anatomical distribution of thrombi at initial examination of those patients followed to one year showing the number of single and multi-segments involved. (EIV = external iliac vein; CVF = common femoral vein; SFV = superficial femoral vein; PV = popliteal vein)

	Occluded	Partially Thrombosed
EIV	8	10
CFV	16	25
SFV	47	8
PV	51	6
TOTAL	122	49

Table 4.5: The number of segments at each site that were occluded or partially thrombosed ($P > 0.01$) at the initial examination for those patients followed to one year.

At one year follow-up the thrombus had fully resolved in 103 segments; 94% (17) of the EIV; 78% (32) of the CFV; 42% (23) of the SFV and 54% (31) of the PV (Table 4.6). Of these, 63 segments were found to be competent without reflux flow and 40 were incompetent with reflux flow > 1 sec. The time involved for individual segments to fully recanalise varied from one week to one year. Segments that resolved within the first six months had a higher

frequency of valvular competency than incompetency ($P > 0.006$). The segments that resolved after six months had a higher incidence of incompetency to competency (31:13) but this was not statistically significant. The distribution comparing competent with incompetent segments and the time for complete recanalisation is shown in Figure 4.15 and Table 4.7.

Site	No of Segments	Resolved	Partial	Occluded
EI	18	17 (94%)	0	1 (6%)
CVF	41	32 (78%)	8 (20%)	1 (2%)
SFV	55	23 (42%)	12 (22%)	20 (36%)
PV	57	31 (54%)	26 (46%)	0
TOTAL	171	103 (60%)	46 (27%)	22 (13%)

Table 4.6: The outcome at one year showing the number (and percentage) of segments at each anatomical level that resolved, partially resolved or remained occluded.

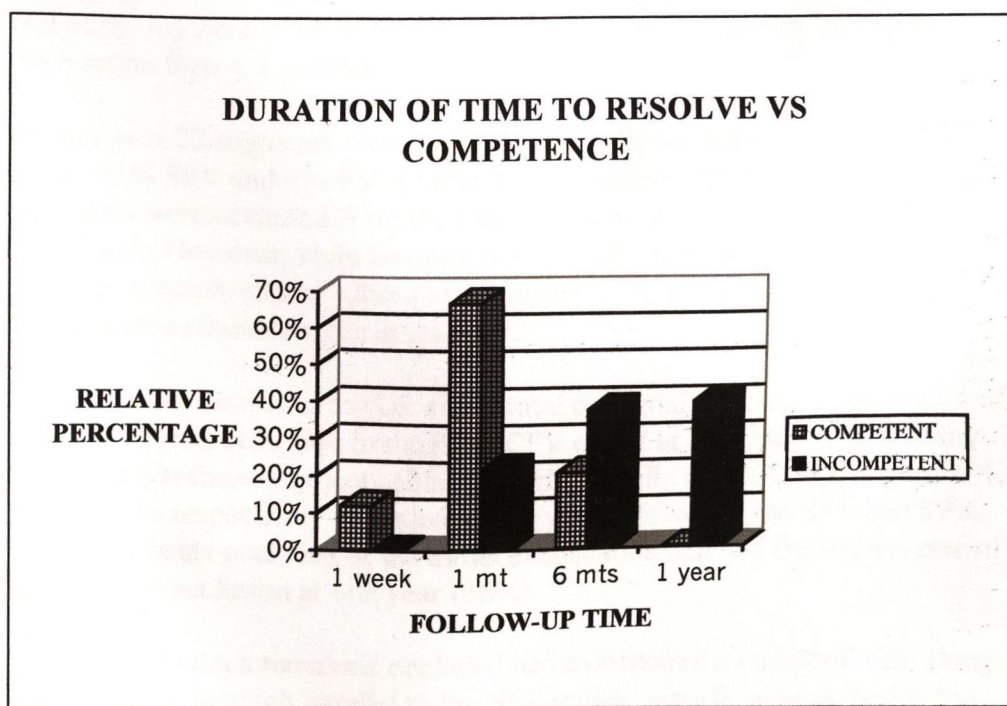


Figure 4.15: The relative percentage of competent and incompetent segments vs. the duration of time for the segments to resolve completely.

COMPETENT SEGMENTS					
Duration of time to resolve					
SITE	1 week	1 month	6 months	1 year	TOTAL
EIV	2	9	5	0	16
CFV	3	21	3	0	27
SFV	1	9	4	0	14
PV	2	3	1	0	6
TOTAL	8	42	13	0	63

INCOMPETENT SEGMENTS					
Duration of time to resolve					
SITE	1 week	1 month	6 months	1 year	TOTAL
EIV	0	1	0	0	1
CFV	0	2	3	0	5
SFV	0	2	2	5	9
PV	0	4	10	11	25
TOTAL	0	9	15	16	40

Table 4.7: The duration of time taken for a thrombus to fully resolve for all the segments vs. the competence of the segment at one-year follow-up. The table shows that in the segments that were competent the thrombi had fully resolved by six months; whereas, in the segments that are incompetent the thrombi generally took longer to resolve.

A total of 46 segments had partially resolved thrombi at one year with the following distribution: 0 EIV; 20% CFV; 22% SFV; and 46% PV (Table 4.6). All of the segments that were partially resolved were found to be incompetent with reflux flow > 1 second.

At one year 22 segments were found to be totally occluded (6% EIV; 2% CFV; 36% SFV and 0% PV) (Table 4.6). Fourteen of these venous segments were occluded from their initial examination throughout the follow-up period. However, eight thrombi were initially totally occlusive then partially recanalised and subsequently re-occluded by one-year follow-up. All of these re-occlusions were in the SFV.

The initial occlusion status (i.e. either total or partial) was not an indication of the rate of total occlusion in the EIV, CFV or PV at one year. The majority of thrombi in these segments either partially or fully recanalised with only 6%, 2% and 0% respectively occluded at one year. However, the SFV had 89% of the segments occluded at the initial examination and had the highest rate of maintaining occlusion at one year (36%).

Fifteen SFV which remained occluded had evidence of a collateral vein along the length of the thigh parallel to the SFV, either superficial to or beside the superficial femoral artery (Figure 4.16). Some of these collateral veins were visualised at the one-week follow-up period and the remainder were established by the one-month examination and remained present throughout the follow-up period. No retrograde flow was demonstrated in these collateral veins.

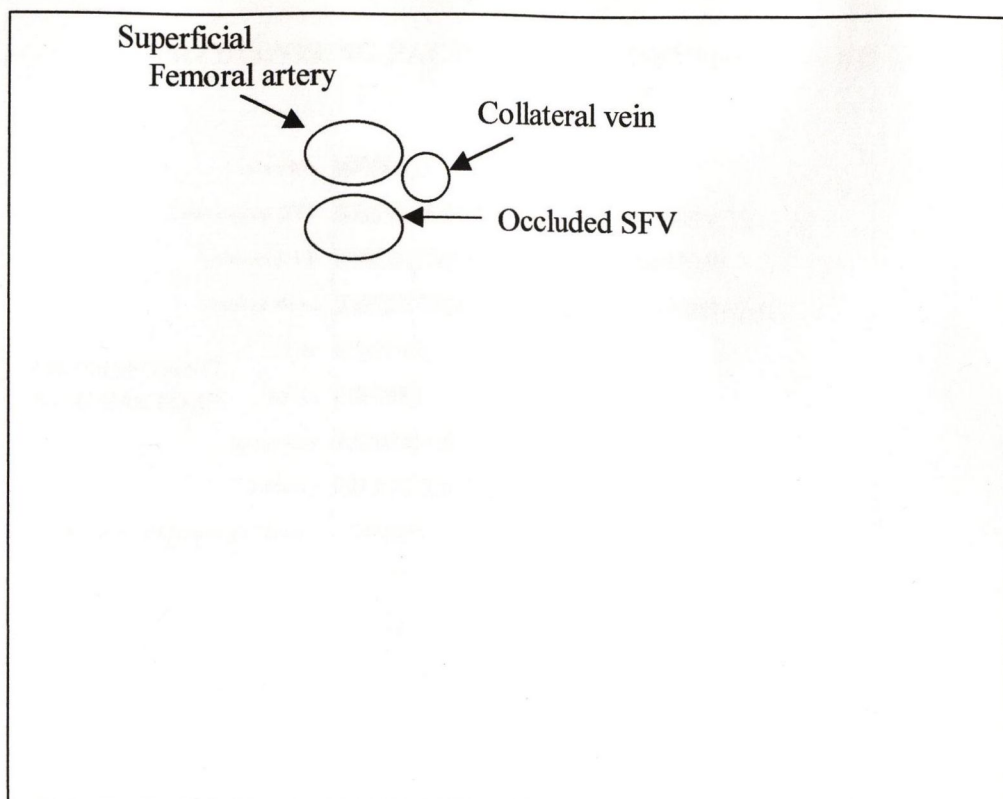


Figure 4.16: X-sectional ultrasound image of the superficial femoral artery (SFA) and vein (SFV). The superficial femoral vein is occluded with thrombus and a collateral vein (CV) is visible running parallel to the artery. No retrograde flow was demonstrated in the collateral vein.

4.6. LONG-TERM RESULTS

4.6.1 Patient population:

A total of 63 patients were followed for a mean period of three years (Range 2 - 6 years). These patients consisted of 34 males and 29 females of mean age 62 years (Range 22 - 94 years). Most of these patients had a combination of risk factors. Three patients (5%) had a previous history of a bilateral DVT. A total of 16 limbs (25%) had a history of an ipsilateral DVT and 17 (27%) had a history of a contralateral DVT. The predisposing factors of the patients are shown in Figure 4.17.

PREDISPOSING FACTORS OF PATIENTS ON LONG-TERM FOLLOW-UP

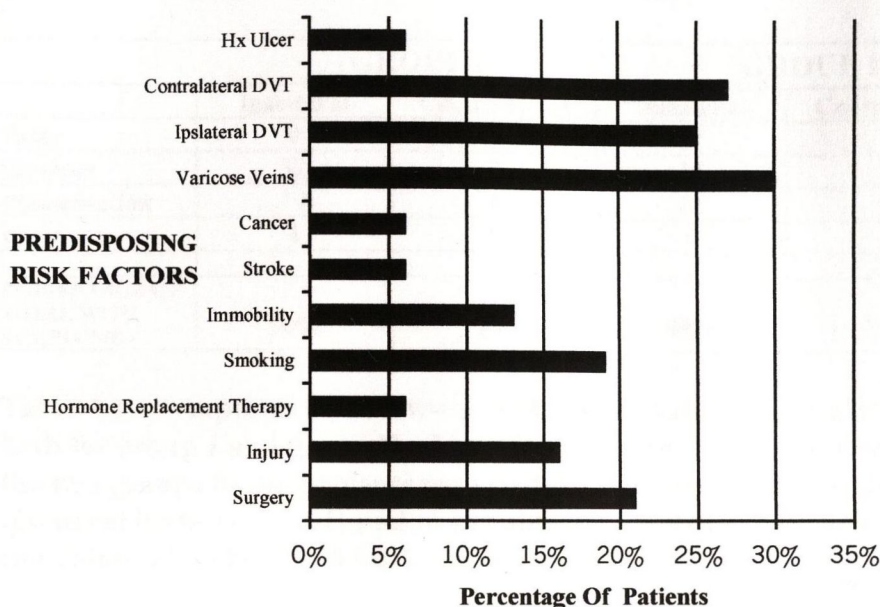


Figure 4.17: The percentage of initial predisposing factors for the patients that were seen on long-term follow-up.

The patients were divided into two groups: group I consisted of patients without a previous clinical history of a contralateral DVT (N = 46) and group II consisted of patients with a clinical history of a contralateral DVT (N = 17).

4.6.2 Signs and symptoms:

The symptoms at final examination included aching, pain, oedema, pigmentation and ulcer. Only one patient complained of pain in both lower extremities. No underlying cause (e.g. arterial disease) was established for this. The symptoms on follow-up in the ipsilateral and contralateral limbs for group I and II are shown in Table 4.8. All ulcers had healed at the time of final examination. There is a significant difference between group I and group II in the number of patients with symptoms on their ipsilateral limb ($P > 0.01$) and the number with symptoms on their contralateral limb ($P > 0.001$).

	GROUP I		GROUP II	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Pain	0	0	1	1
Oedema	32	3	14	10
Pigmentation	14	4	11	8
Ulcer	4	0	0	0
PERCENTAGE OF TOTAL WITH SYMPTOMS	56%	2%	88%	71%

Table 4.8: Symptoms on follow-up in the ipsilateral and contralateral limb for group I and group II. There is a significant difference between the two groups in the percentage of patients with symptoms in their ipsilateral limbs ($P > 0.01$) and in patients with symptoms in their contralateral limbs ($P > 0.001$).

4.6.3 Duplex results:

Duplex ultrasound identified sites of reflux and/or obstruction in the ipsilateral and contralateral limbs and are shown in Table 4.9. There is no significant difference between the percentage of abnormalities the ipsilateral limbs in group I and II; however, there is a significant difference in the percentage of abnormalities present in the contralateral limbs between the two groups ($P > 0.001$).

The anatomical sites of venous dysfunction involving the superficial, perforator and deep venous systems in the ipsilateral and contralateral limbs for both groups are shown in Table 4.10. In group I, there is no significant difference in the incidence of superficial system involvement between the ipsilateral and contralateral limb; however, there is a significant difference in the incidence of deep venous systems ($P > 0.001$) and perforators involvement ($P > 0.05$). For group II, there is no significant difference in involvement of the superficial or perforator between the ipsilateral and contralateral limb but there is a significant difference in the incidence of deep venous system involvement ($P > 0.04$). Comparing group I and group II there is no significant difference between the incidences of venous dysfunction in the ipsilateral limbs, but in the contralateral limb there is a higher incidence of deep venous and perforator involvement for group II.

GROUP I					GROUP II			
	None	Reflux	Obstruction	Both	None	Reflux	Obstruction	Both
Ipsilateral	13%	33%	2%	52%	0	53%	0	47%
Contralateral	57%	39%	4%	0	11%	65%	24%	0

Table 4.9: The percentage of ipsilateral and contralateral limbs with reflux, obstruction, a combination of both reflux and obstruction or no venous abnormalities for both groups. There is no significant difference between the percentage of abnormalities in the ipsilateral limbs between group I and II; however, there is a significant difference in the percentage of abnormalities present when the two contralateral limbs are compared ($P > 0.001$).

GROUP I				GROUP II		
	Superficial	Deep	Perforator	Superficial	Deep	Perforator
Ipsilateral limb	48%	89%	48%	47%	88%	59%
Contralateral limb	37%	17%	26%	41%	71%	59%
	NS	$P > 0.01$	$P > 0.05$	NS	$P > 0.04$	NS

Table 4.10: The number of ipsilateral and contralateral limbs involving the superficial, deep and perforator venous systems for both groups.

The anatomical sites of venous incompetence or obstruction in the ipsilateral and contralateral limbs are shown in Table 4.11. Most patients had multiple sites of reflux and/or obstruction. The most frequent anatomical sites involved in both the ipsilateral and contralateral limbs for both groups were the long saphenous veins, the superficial femoral veins, the popliteal veins and the calf perforators.

PERCENTAGE OF LIMBS				
	GROUP I	GROUP I	GROUP II	GROUP II
	Ipsilateral	Contralateral	Ipsilateral	Contralateral
Telanglectase/ Reticular veins	4%	2%	6%	6%
LSV AK	37%	22%	35%	47%
LSV BK	22%	13%	41%	29%
SSV	17%	0%	0%	0%
Non-saphenous	2%	0%	0%	0%
Iliac external	2%	0%	0%	0%
Femoral Common	9%	4%	18%	0%
Femoral Deep	4%	2%	6%	0%
Femoral Superficial	59%	15%	88%	53%
Popliteal	70%	22%	94%	59%
Cureal	17%	2%	6%	6%
Muscular	15%	2%	12%	6%
Perforator-thigh	6%	4%	6%	0%
Perforator -calf	43%	33%	59%	41%

Table 4.11: The anatomical sites of venous dysfunction (either reflux or obstruction) in the ipsilateral and contralateral limb for both groups. (LSV AK = Long saphenous veins above knee; LSV BK = Long saphenous vein below knee; SSV = Short saphenous vein)

4.6.4 CEAP Classification:

The two groups of patients were divided according to their total CEAP score on the ipsilateral limb. The subdivisions were as follow: CEAP = 0 no venous disease; CEAP 1-3 inclusive, mild to moderate venous disease; CEAP > 3 severe venous disease. The CEAP scores of the ipsilateral and contralateral limbs were compared for group I and group II and are shown in Table 4.12. The initial predisposing were compared to the classification according to the CEAP score and is shown in Figure 4.18

CONTRALATERAL LIMB														
GROUP I								/ GROUP II						
Ipsilateral Limb CEAP Score	0	1	2	3	4	5	6	0	1	2	3	4	5	6
0 (N = 6)	6													
1 - 3 (N = 22)	14	3	1						1	1	1	1		
> 3 (N = 35)	7	5	4	3	0	2	1	1		1	1	4	3	3

Table 4.12: The CEAP total score for the ipsilateral and contralateral limbs on follow-up for the two groups.

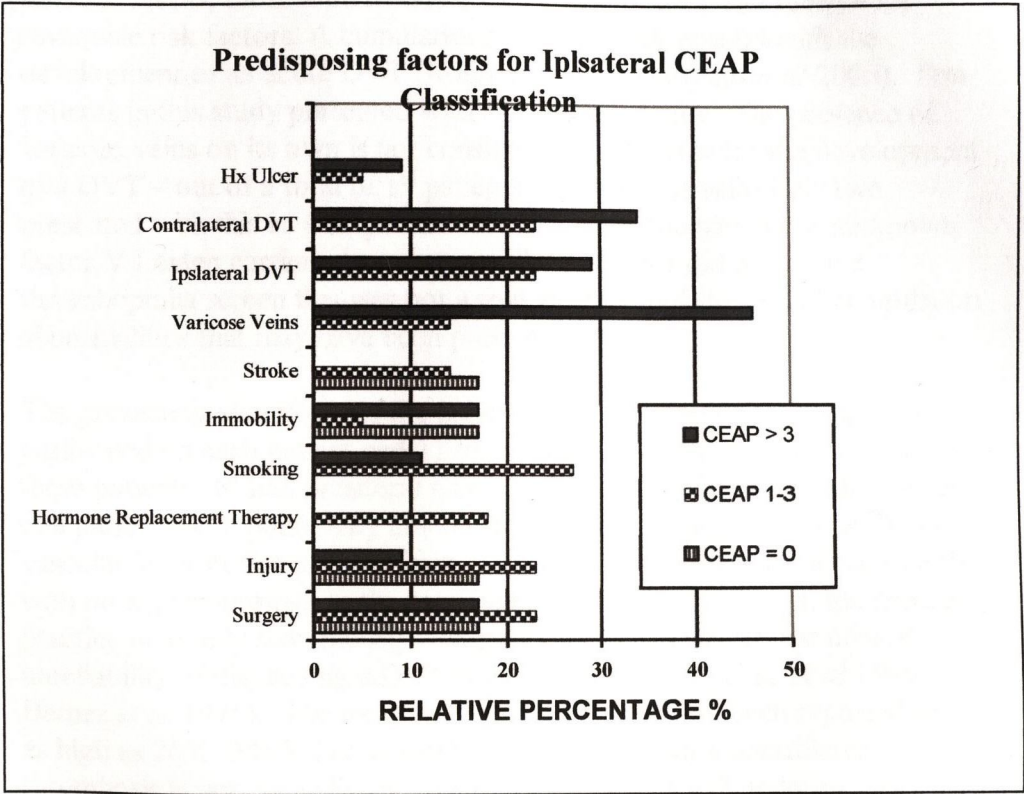


Figure 4.18: The relative percentage of initial predisposing factors for the patients according to the CEAP classification of the ipsilateral limb.

5. DISCUSSION

The patient population in this study were typical of the type of patients who present with an acute deep vein thrombosis (DVT), including those with a terminal illness, those with a history of a previous DVT and those with reversible risk factors. A cumulative risk score is associated with the development of an acute DVT (Rosendaal 1993; Motykie *et al* 2000). Few patients in this study presented with a single risk factor. The presence of varicose veins on its own is not considered a risk factor for the development of a DVT – out of a total of 19 patients with varicose veins only two presented with this as a single risk factor. Only three patients were known factor V Leiden carriers; however, as all the patients did not have a thrombophilia screen this was not a true indication of the rate of coagulation abnormalities that may have been present.

The presenting symptoms of the patients varied. Bilateral scanning was performed on each patient and 11 bilateral thromboses were diagnosed. Of these patients, 10 had unilateral pain and swelling of the lower extremity and one patient had a pulmonary embolism (PE) with no leg symptoms. Many vascular laboratories only perform bilateral scanning in the presence of a PE with no leg symptoms. In the presence of unilateral symptoms, the general practice is to only scan the leg with symptoms, even though the clinical unreliability of diagnosing a DVT is well established (Blebea *et al* 1999; Barnes *et al* 1975). The incidence of bilateral DVT has been reported to be as high as 26% (Markel *et al* 1992). Many argue that a contralateral thrombosis is not clinically significant, as the patient will undergo treatment with anticoagulants anyway. Occasionally, an acute DVT has been diagnosed in the asymptomatic limb without the presence of a DVT on the symptomatic side. Therefore, it is advisable, that bilateral duplex examination should be performed in patients with suspected pulmonary embolism, bilateral leg symptoms or with major risk factors for DVT (Love *et al* 1996; Nix *et al* Troillett 1991).

A significant mortality rate has been long associated with DVT. Before the use of anticoagulants the mortality was as high as 50% for pulmonary embolism. With treatment the one-year mortality rate for pulmonary thromboembolism ranges from 3 - 9% (MacIntyre *et al* 1982; Peterson 1999). However, more often the cause of death following a DVT is related to the primary underlying disease associated with venous thromboses. In this study at one year 14% of the patients had died. The rate of deaths from PE was 3% and the majority of deaths were due to cancer. These results are consistent with other studies (Prandoni *et al* 1998; Wakefield 2000).

Previous studies have shown that anticoagulation is necessary for the prevention of morbidity and mortality (Schulman 1996; Ginsberg 1996). All patients were treated with heparin, either intravenous unfractionated heparin (IV UFH) or subcutaneous low molecular weight heparin (SC LMWH), followed by warfarin. The treatment regime followed was carried out by a

number of referring physicians from different specialities, independent of any input from the vascular laboratory. The results indicate that there is still some confusion regarding the treatment and long-term prognosis of DVT. There was no indication as to why some patients were treated with IV heparin while others were treated with SC heparin. SC heparin has been shown to be at least as effective as IV heparin and is becoming the treatment method of choice as it encourages both early mobilisation and early discharge from hospital (Buller *et al* 1998; Hull 1995; Hull *et al* 1998; Koopman *et al* 1996; Prandoni *et al* 1992; Leizorovicz *et al* 1994; Levine *et al* 1996). The patient mobility does not seem to have been a factor in deciding whether SC or IV heparin was used in this study. Many physicians seem to prefer the use of IV heparin as it is a long established treatment.

The patients were supplied with elastic stockings on their initial examination; however, compliance of use was low and no comment could be made as to the advantages of elastic compression during the follow-up period.

All patients received warfarin following heparin. The use of anticoagulant therapy following a DVT is standard. However, the optimal duration of therapy continues to be controversial (Leizorovicz 1998; Ginsberg 1996; Sarasin *et al* 1998; Schulman *et al* 1995; Schulman *et al* 1997; AbuRahman *et al* 1998). Several studies have tried to stratify patients into groups that should receive short-term anticoagulation (3 to 8 weeks) versus long-term (3 – 12 months) (Research Committee 1960). A balance has to be obtained between the risk of a major haemorrhage with anticoagulation and the risk of recurrences. It was found that physicians generally treated patients with anticoagulants for at least six months with 56% of patients seen at six months still on warfarin. The duration of anti-coagulants did not seem to take into account the risk factors of the patient. The majority of patients had completed their warfarin therapy at one year including those with a previous history of recurrent DVT's.

The natural course of venous thromboembolism is one of recurrence (Prandoni *et al* 1998; AbuRahma *et al* 1998). There is a high risk for the development of new thrombi as the anticoagulation achieved is often inadequate. Patients with proximal deep vein thrombosis, who receive inadequate anticoagulation therapy, have a risk of recurrent venous thromboembolism that approaches 50%; however, this risk is reduced to about 4% with treatment of oral anticoagulants (Hull *et al* 1998). It has been reported that there is a higher rate of recurrent thromboembolism events in patients treated with anticoagulants for 4 weeks as opposed to 12 weeks (Hull 1995).

The recurrence rate for both symptomatic and asymptomatic events in this study was 20% in the first year. The recurrence rate in studies varies from 1% to 38% (Prandoni *et al* 1998; AbuRahma *et al* 1998; Hull *et al* 1998). This discrepancy is largely due to the study methods used. Trials vary in their initial treatment regimes i.e. SC or IV heparin, the inclusion/exclusion criteria of patients and the follow-up times (Koopman *et al* 1996; Prandoni *et al*

1992). Recurrences may be diagnosed with infrequent diagnostic tests or only take into account those recurrences that are symptomatic. As seen in this study, recurrences can occur without the development of new clinical symptoms. Studies need to be carried out with close intervals using duplex scanning to determine the exact rate of recurrences. The timing of the follow-up scans over the period of one year in this study was possibly too far apart and a number of additional events may have been missed.

Natural history studies have shown that complete occlusion may alternately partially recanalise and subsequently re-occlude before complete recanalisation (O'Shaughnessy *et al* Fitzgerald 1997; O'Shaughnessy *et al* Fitzgerald 1997; Killewich *et al* 1989; Meissner *et al* 1993; Meissner 1995). How often these re-occlusions occur is not known and closer follow-up examinations would be needed to determine the rate of these events. An acute thrombus can develop when in contact with an older thrombus as a result of the slow rate of flow through partially recanalised veins (Caprini *et al* 1999). If a new thrombosis occludes a flow channel in a previous baseline thrombus it is not likely to result in a significant change in the obstruction to venous outflow and will be unlikely to cause additional symptoms. Patients with restricted outflow will continue to suffer from a swollen limb and therefore may not present with additional clinical symptoms in the event of a new DVT. Clinical assessment of an acute DVT is difficult to ascertain and is even more difficult to determine for a recurrent DVT. Yet, physicians continue to presume that in the absence of clinical symptoms during treatment the DVT is stable. This is unreliable and only the use of objective testing can determine the stability of the thrombus during hospitalisation and beyond.

Duplex ultrasound has become the preferred diagnostic test for DVT of the lower extremities as it allows for direct imaging of major venous segments. It is an ideal method for follow-up studies as it is non-invasive and has become the method of choice in natural history studies (O'Shaughnessy *et al* Fitzgerald 1996; Talbot *et al* Oliver 1992; Ramaswani *et al* 1999; Elatrozy *et al* 1998; Tablot 1982). A thrombus can be imaged under ultrasound so its organisation can be evaluated. In addition, Doppler and colour flow can be used to study the hemodynamics of venous flow and the development of reflux can be documented in the individual venous segments in the lower extremity (Haenen *et al* 1998; O'Shaughnessy *et al* Fitzgerald 1996; O'Shaughnessy *et al* Fitzgerald 1997; Kilewich *et al* 1997; Johnson *et al* Strandness 1997). In addition, with the use of video recording it is possible to compare the changes in events over time.

The initial sites of an acute DVT can vary considerably between patients. Very often the thrombus will involve many venous segments as was found in this patient population with 96% of thrombi involving multi-segments and only 4% involving a single segment. This is not surprising as the more extensive the thrombus present, the more likely the patient is to have clinical symptoms and therefore undergo diagnostic testing. This would account for the small number of single segment thrombi within this group of patients.

Studies have shown that lower extremity venous thrombi are dynamic structures, especially during the first few weeks after the initial diagnosis (O'Shaughnessy *et al* Fitzgerald 1996; van Gemmeren *et al* 1991; Meissner *et al* 1998; Strandness *et al* 1983; vanHaarst 1996; Killewich *et al* 1989; Caps *et al* 1999). The risks of embolisation or propagation and the incidence of detectable new thromboses are especially high during the first few weeks of therapy (Caps *et al* 1999). The findings on duplex examination showed that within the first month of treatment there were a number of symptomatic ($N = 7$) and asymptomatic events ($N = 3$). That symptomatic events do occur during the initial phase of treatments was expected, especially in terminally ill patients. However, the asymptomatic events are of more concern, as the physician is unaware of them. The number of events was highest in the initial phase of treatment and also at one year ($N = 6$).

Identifying an acute thrombus in the presence of chronic thrombus using ultrasound can be difficult and there is some confusion between studies in the description of a thrombus. Certain studies describe the "age" of a thrombus, which is based on the clinical duration of time the thrombus is present. Other studies suggest that by measuring the diameter of a deep venous thrombus the age of the clot can be calculated as a vein dilates in the presence of an acute, occlusive thrombus (van Gemmeren *et al* 1991). The "stage of organisation" of thrombus is based on its echogenicity appearance. The echogenicity appearance gives information on the degree of organisation of a thrombus but cannot determine its age (Fobbe *et al* 1991).

Previous studies have shown that B-mode ultrasound imaging can be used qualitatively to investigate blood clot changes over time in vivo and in vitro (O'Shaughnessy *et al* Fitzgerald 1996; Peter *et al* 1986; Barzilai *et al* Eisen 1989). These studies show that blood clot echogenicity increases as a thrombus becomes more organised and is an accurate determination of the degree of organisation (Hull *et al* 1998). This information is used in clinical ultrasound examinations to assess the organisation of a thrombus and to differentiate between an acute or chronic event.

In a clinical setting, one of the major problems in the criteria used to determine the organisation of a thrombus is that they are subjective. The echogenicity appearance can be altered by instrument settings for power, dynamic range, grey scale etc. and the description of the morphology can vary from laboratory to laboratory. It is important to show that these subjective changes are real and potentially quantifiable. Computer analysis of standardised ultrasound images to measure the degree of echogenicity has been proven to be a useful method in the evaluation of atherosclerotic plaques (Ramaswami *et al* 1999; Elatrozy *et al* 1998). In a similar manner, this method was applied to measure the echogenicity of a venous thrombus. A quantifiable measurement of echogenicity, the grey scale median (GSM), was obtained which is related to the degree of organisation of the thrombus and can be used to describe the change in the thrombus over time.

In the presence of a long thrombus, the thrombus may be in different stages of organisation along its length. The proximal end of the thrombus was selected for analysis, as the organisation at the proximal end is a good indicator of the stability of the thrombus. On follow-up examinations care was taken to assess the same area of the thrombus so the changes in GSM could be accurately determined. Reproducibility studies showed that there is little variation in measurements, when performed by the same operator, as the machine and images are standardised.

On initial examination thrombi were found to be in various stages of organisation indicated by the considerable variation in the initial GSM values. These values were not related to the size of the thrombus or to the age of the patient. The GSM values were related to the duration of clinical symptoms of the patient especially in patients who had symptoms for longer periods of time. However, when the duration of symptoms was for less than seven days as the majority of patients had, there was no correlation between GSM values. In some patients with a short duration of clinical symptoms the thrombi were found to be in an advanced stage of the organisation process. The unreliability of clinical symptoms as a measure of the organisation of a thrombus has been well reported (O'Shaughnessy *et al* 1996; Hull *et al* 1998). The level of organisation is more likely related to the individual tissue response of the patient.

Decisions regarding therapy are continually being made based on clinical symptoms alone. This is especially relevant when selecting patients for thrombolysis. The indication for lysis therapy is defined according to the duration of clinical symptoms (usually less than seven days). However, as these results show, even with patients with less than seven days symptoms, the thrombus can be in an advanced stage of organisation and these patients would possibly have a poorer response to this method of treatment. Likewise, late organisation can occur suggesting the potential efficacy of late lysis therapy (Scheffler *et al* 1998). Computer assisted analysis of the echogenicity may allow for better selection of patients for thrombolysis. Strategies for identifying patients who might benefit would increase the cost-effectiveness of such therapy.

Previous studies of changes in morphology over time have shown that the organisation process follows distinct patterns and only vary in the time period in which these processes occur (O'Shaughnessy *et al* 1996). Many thrombi remained unchanged during the first week even though the patients' symptoms may have reduced. It was possible to identify thrombi were unstable (i.e. remaining poorly organised and/or mobile) and those that were stable (i.e. adhered and organising) by the change in their GSM values during the first week. This information could be used to reduce the risk of DVT beyond hospitalisation. Thrombi that are slow to organise, or are mobile, can be more closely monitored before discharging the patient.

The dynamic process of a thrombus is reflected in the measured GSM values at the follow-up examinations. As the process of organisation of a thrombus

advances the echogenicity of the thrombus increases therefore, the mean GSM value at each examination would be expected to increase also. This increase was documented; however, there is a large standard deviation at each level due to the variability of individual patient response. Individual GSM values were seen to fluctuate, increasing and decreasing, as the state of the thrombus changed. An increase in value indicated an increase in organisation of the thrombus, whereas a decrease was due to low echo areas with the development of lysis. In the early follow-up period, individual measurements of GSM were useful to describe these changes and to determine the stability of the thrombus; however, the overall mean value of GSM at each follow-up examination did not reflect the dynamic process occurring.

The GSM values of thrombi which fully lysed in the early stages were not significantly different than those thrombi which recanalised slowly over time or those that fibrosed and remained occlusive. Therefore, using GSM values it was not possible to predict which thrombi would spontaneously lyse.

Thrombi that ultimately fibrosed and remained occluded were not identifiable by their GSM values until after the six months follow-up period. At that time, thrombi which were fully occlusive remained so, and their mean GSM value was greater than those that partially recanalised.

Recanalisation of thrombosed venous segments does not occur universally and the measurement of mean GSM did not identify thrombi that finally recanalised, either fully or partially. Since often the process alternates between occlusion and recanalisation, this is not surprising.

Venous segments respond differently to the presence of an acute thrombus over time. Initially a greater number of venous segments were found to be occluded than partially thrombosed (122: 49). This is particularly evident for the superficial femoral and popliteal veins. The external iliac and common femoral had a higher incidence of partial occlusive thrombus. In some cases, this was due to a non-adhered tip extending into the common femoral and external iliac vein from an occlusive thrombus in the superficial femoral vein. With time, these non-adhered tips became more organised and either shrank back into the main thrombus or became attached to the vein wall. In the remaining cases, a higher incidence of partial occlusions in the common femoral vein was possibly influenced by flow from patent profunda femoral and long saphenous veins.

The first response of the endogenous fibrinolytic system to the presence of thrombus in a vein is to stimulate lysis (O'Shaughnessy *et al* 1996; Killewich *et al* 1989; Meissner *et al* 1993). Lysis has been observed as early as one week and as many as 50% of cases of DVT will undergo complete resolution within 6 months (Killewich *et al* 1989; Killewich *et al* 1997; Meissner *et al* 1993; vanRamshorst *et al* 1992; Caprini *et al* 1995). Similarly, in this study 51% of the venous segments had fully resolved by six months - 5% (8) of the segments had resolved by one week, a further 30% (51) by one

month and an additional 16% (28) by six months. By one year, 60% (103/171) of the venous segments had completely resolved.

Some venous segments, 13% (22/171), remained occluded at one year. It is possible that this represents a failure of the endogenous fibrinolytic system in some patients (Killewich *et al* 1997). The anatomical site of occlusion may also be a factor. The superficial femoral veins had the highest incidence of total occlusion at one year while partial to full recanalisation was more common in the external iliac, common femoral and popliteal veins.

The influence of flow from the long and short saphenous veins may affect the recanalisation of the popliteal and common femoral veins. Similarly the alternative pathways for flow around the superficial femoral vein may determine the higher rate of occlusions. It is known that collateral vessels rapidly open around an area of occlusion, providing an immediate avenue for venous outflow from the acutely obstructed limb (Killewich *et al* 1989). There are many collateral pathways around the superficial femoral vein. Cadaver studies have shown that an extensive system of veins provides communication between the distal superficial femoral and popliteal vein and the profunda femoral vein (Mavor *et al* Galloway 1967). In other studies using venography, collateral vessels connecting the profunda femoris system with the popliteal vein were present in all cases of femoral vein obstruction (Raju *et al* Fredericks 1991). Many of the deeper collateral pathways were not successfully imaged on ultrasound; however, some collaterals were imaged which were found consistently parallel to the superficial femoral artery. These were not duplicate superficial femoral veins as they were not present on the initial examination. The collateral vessels that were observed by duplex ultrasound established rapidly after the acute event that suggests they are pre-existing pathways in the surrounding tissue. Mavor and Galloway observed that the extent to which each collateral enlarged varied in individual persons and all had competent valves venographically (Mavor *et al* Galloway 1967). In this study no retrograde flow was observed in these collateral veins suggesting the presence of valves. However, the veins were small and valves would be difficult to image. Further studies need to be carried out to investigate collateral pathways.

Superficial femoral-popliteal vein harvest results in minimal mid-term to late term lower-extremity venous morbidity despite outflow obstruction (Masudo *et al* 1992; Wells *et al* 1999). This implies that the clinical outcome for occlusion with efficient collaterals may be a better outcome than an incompetent venous system. However, it is not known why some patients develop collaterals while others fail, even in the presence of a totally occluded vein. If the development of collaterals could be assisted, some therapeutic potential may be obtained.

Complete occlusion may alternately partially recanalise and re-occlude before complete recanalisation. In this study venous segments that were occluded at six months remained occluded. However, four veins that were partially

recanalised up to six months did re-occlude after this period. All these re-occlusions occurred in the superficial femoral vein.

Valvular incompetence is one of the leading causes in the development of the post-thrombotic syndrome (Johnson *et al* 1996; Markel *et al* 1992; Haenen *et al* 1998; Meissner *et al* 1993; Meissner 1995; Meissner *et al* 1998; Strandness *et al* 1983). One of the problems in trying to determine the cause of reflux following a DVT is that there is a lack of information regarding the competence of the vein before the acute event. It is well established that the clinical diagnosis of DVT is unreliable and it is thought that the true prevalence of DVT may be underestimated in the population. The lack of a clinical history may not necessarily mean that the patient has not had a previous event. In fact, often evidence of an old thrombus has been detected during duplex ultrasound scanning in patients without a prior clinical history of a previous DVT.

The time to complete recanalisation appears to be an important factor in the determination of valvular reflux and it is thought that rapid resolution of the thrombus may preserve valvular function (Markel *et al* 1992; Meissner *et al* 1993). The venous segments that resolved within the first six months had a higher competence rate than those that resolved from six months to one year; however, the ideal time for resolution is unknown (Markel *et al* 1992). Closer follow-up visits would be needed to determine optimal timing for resolution.

Recanalisation can occur a long time after an acute DVT (Markel *et al* 1992). Whether the delayed process of re-establishing a venous lumen by recanalisation is true lysis or some other process is unclear but it is unlikely that they are the same process. Late recanalisation may be due to the growth and development of neovascularization within the obstruction (Killewich *et al* 1997; Wakefield *et al* 1999). By whatever means the vessel lumen is re-established the vein generally becomes incompetent and reflux develops.

Complete recanalisation may not occur and 27% (46/171) of the venous segments were found to be only partially resolved at one year. The presence of residual thrombus can be demonstrated by duplex ultrasound but assessment of its physiological effect is more difficult. All veins with residual thrombus were incompetent at one year.

The ipsilateral and contralateral limbs were compared to assess the long-term clinical outcome of the patients. It was necessary to divide the patients into two groups; group I consisted of those patients without a history of a contralateral DVT and group II those with a history of a contralateral DVT or bilateral post-thrombotic limbs. Of the 63 patients on long-term follow-up, 25% had a history of an ipsilateral DVT and 27% had a history of a contralateral DVT (5% bilateral); however, these were not always confirmed by objective testing. Also, the history of an occult DVT cannot be ruled out in either limb.

The clinical manifestations of the post-thrombotic syndrome are hyperpigmentation, oedema, pain and ulceration (Linder *et al* 1986). There was a significant difference in the incidence of symptoms in the contralateral limbs between group I and group II ($P > 0.001$). This is not surprising as the contralateral limb in group II is post-thrombotic. However, on the ipsilateral limbs there is also a significant difference in the incidence of symptoms between group I and group II ($P > 0.01$). This indicates that patients with bilateral disease are more likely to develop symptoms on follow-up.

Post-thrombotic manifestations develop as a result of combined deep and superficial venous reflux, the extent of venous reflux, recurrent deep venous thrombotic events and persistent deep venous occlusion (O'Shaughnessy *et al* 1997; Meissner *et al* 1993; LeSiege *et al* 1992; Browse *et al* 1980). The presence of reflux, obstruction or a combination of both was confirmed by duplex scanning and reflux studies. In both groups, the ipsilateral limbs had a higher incidence of combined reflux and obstruction (due to residual thrombus) than in the contralateral limb. However, the contralateral limbs in group I had an incidence of reflux similar to that in the ipsilateral limb. As these patients had no clinical history of DVT in their contralateral limb, degenerative changes not related to the DVT, probably led to the development of reflux.

It has previously been reported that the sites of venous dysfunction are not always related to the sites of DVT (Johnson *et al* 1996; Welch *et al* 1996; LeSiege *et al* 1992; Lapropoulos *et al* 1996). Chronic venous insufficiency (CVI) can result from a primary as well as a post-thrombotic cause although occult thrombosis cannot be excluded. For both groups of patients, in the ipsilateral and contralateral limbs, the most common sites of venous dysfunction were the long saphenous veins, the superficial femoral veins, the popliteal veins and the perforator veins.

The anatomical site of reflux is important as the most severe symptoms are found in patients with incompetence in the distal deep and superficial veins (Johnson *et al* 1996; Lapropoulos *et al* 1996; LeSiege *et al* 1992; Strandness *et al* 1983; Taheri *et al* 1993; Welch *et al* 1996). Superficial venous incompetence may occur in the post-thrombotic limb due to concurrent thrombosis, increased venous pressure resulting from proximal venous obstruction or reflux, pressure transmission through incompetent perforator veins or degenerative changes occurring in the superficial veins that are unrelated to the thrombotic event (Meissner 1995; Meissner *et al* 2000). It has been reported that approximately 22% of limbs with DVT have related superficial thrombosis concurrent that may account for the development of reflux in some of the long saphenous veins (Meissner *et al* 2000). However, there is no significant difference in the incidence of superficial venous system involvement between the ipsilateral and contralateral limbs in group I suggesting an underlying venous disease as a more likely cause of reflux. Long saphenous reflux in the uninvolved extremity contralateral to a DVT develops at a background rate of approximately 15% over 8 years (Evans *et al* 1998; Meissner *et al* 2000). This is likely related to degenerative changes

within the vein as it has a similar rate to the prevalence of reflux in the general population. All limbs with a history of DVT had a higher incidence of deep venous system involvement.

The CEAP classification provides for a uniform means of classifying and grading the severity of the clinical findings and is a useful method in any long-term study (Beebe *et al* 1996). The classification addresses the clinical, etiologic, anatomic and pathophysiologic mechanisms and requires objective testing to support these diagnoses. In group II, there was a similar distribution of CEAP scoring between the ipsilateral and contralateral limbs. In group I, six limbs had a CEAP score of zero on both sides. Of the patients who had mild to moderate disease on the ipsilateral limb (CEAP 1 – 3), 64% of them had a normal contralateral limb and the remaining 36% had mild to moderate disease. In the patients who had severe venous disease (CEAP score > 3) only 20% had normal contralateral limbs and the remaining 80% had mild to severe disease. This means that the severity of the disease on the contralateral limb was related to the severity of the post-thrombotic changes recorded on the ipsilateral limb. These results indicate that patients with non-thrombotic venous disease on the contralateral limb are more likely to develop symptoms in the ipsilateral limb.

The CEAP scoring system does not take into account the past history of the patient; however, risk factors play an important part in the long-term prognosis. The risk of developing a post-thrombotic limb is higher among patients with permanent risk factors than among patients who have suffered trauma or are post-operative (Chesterman 1995; Prandoni *et al* 1998). The six patients who had bilateral normal venous systems on follow-up all had reversible risk factors. Patients with a history of varicose veins or a previous history of DVT, either contralateral or ipsilateral, had a higher final CEAP score. It should be noted that in those patients with a history of previous DVT only five had this as a single risk factor.

The clinical manifestations of CVI are often referred to as the post-thrombotic syndrome. Patients with recurrent DVT's are a high risk for the development of the post thrombotic syndrome (Prandoni *et al* 1998). However, a prior episode of DVT is not a prerequisite for developing the syndrome (Lapropoulos *et al* 1996). Venous hypertension, which is a universal element of the syndrome, can derive from primary as well as post-thrombotic venous reflux. The presence of reflux in the uninvolved contralateral limb suggests an underlying venous disease that may be further aggravated by the development of thrombus and leads to a more severe clinical outcome for the patient. Other factors also play a role in the pathogenesis of CVI. The initial risk factors for the development of a DVT has a strong influence on the long-term outcome.

In conclusion, the diagnosis and treatment of DVT continue to be a major clinical problem. Little consideration is given to the long-term outcome when treating an acute DVT. The natural history of a thrombus during the first year is a dynamic process that was reflected in the variations of measurements of

GSM values. Even though the GSM values could not predict the long-term outcome for the patients, it is a useful objective method to describe the level of organisation of a thrombus.

Individual venous segments react differently to the presence of thrombus. The timing of resolution was an important factor in maintaining competency of a venous segment. The site and extent of reflux is an established factor in the development of a post-thrombotic limb. The hemodynamics involved with an obstruction in the deep venous system is less well understood. The most common site of permanent occlusion was the superficial femoral vein. The site of occlusion and the development of a collateral circulation need further investigation.

A significant number of patients presenting with an acute DVT have an underlying venous disease in the uninvolved contralateral limb. Patients with contralateral venous reflux are more likely to develop an ipsilateral post-thrombotic limb following an acute DVT and the level of venous dysfunction on the contralateral limb is an indication of the severity of disease developing in the ipsilateral limb. The initial risk factors of the patient also influenced the long-term clinical outcome.

6. CONCLUSIONS

- The use of computer analysis to determine the GSM allows for an objective method of description of the organisation of a thrombus and would be a useful method for use in multi-centre studies.
- The measurement of GSM in long-term follow-up studies was useful to determine the stability of a thrombus and to demonstrate that the process of organisation was still active. However, measurement of mean GSM of the total group did not reflect these changes because of the individual variations.
- The lower extremity venous segments differ with respect to their contribution to the post-thrombotic syndrome. Similarly, the venous segments differed in their tendencies to recanalise or remain occluded.
- Thrombus resolution was common in the external iliac, common femoral and popliteal veins with the popliteal vein most likely to have valvular incompetency.
- The timing of resolution appears to be an important factor in maintaining competency as there was a higher frequency of competency in segments that resolved within the first six months than those that resolved after six months.
- The most likely site of permanent occlusion was found to be the superficial femoral vein; however, very often this obstruction was by-passed with a collateral system.
- No retrograde flow was observed in the collateral pathways but the presence of valves were not identified by duplex ultrasound.
- The rate of recurrence may be higher than previously thought but only the use of objective testing at close intervals will determine its true rate.
- A major determinant for the evolution of the post-thrombotic syndrome is previous venous disease.
- The symptoms of a post-thrombotic limb were more severe when there was evidence of venous disease on the contralateral limb and the severity of the symptoms was related to the severity of the disease in the contralateral limb.
- In cases where there was no evidence of venous disease on the contralateral limb the patient was less likely to develop PTS in the ipsilateral limb.
- The initial predisposing factors had an influence on the long-term clinical outcome.

7. REFERENCES

- AbuRahma AF, Stickler DL, Robinson PA. A prospective controlled study of the efficacy of short-term anticoagulation therapy in patients with deep vein thrombosis of the lower extremity. *Journal of Vascular Surgery* 1998. 28: 630 - 670.
- Albrechtsson U, Olsson CG. Thrombotic side-effects of lower-limb phlebography. *Lancet* 1976. 1: 723 - 724.
- Allaart CF, Rosendaal FR, Noteboom WM, Vanderbroucke JP, Briet E. Survival in families with hereditary protein C deficiency, 1820 to 1993. *British Medical Journal* 1995. 311: 910 - 913.
- Allen EV, Barker NW, Waugh LM. A preparation from spoiled sweet clover (3, 3'-methylent-bis(4-hydroxcommarin) which prolongs coagulation and prothrombin time of the blood: a clinical study. *JAMA* 1942. 120: 1009 - 1015.
- Altman DG, Gardner MJ. Calculating confidence intervals for regression and correlation. *British Medical Journal* 1988. 296: 1238 - 1242.
- Anderson FA, Brownell Wheeler H, Goldberg RJ, Hosmer DW, Forcier A. The prevalence of risk factors for venous thromboembolism among hospital patients. *Archives of Internal Medicine* 1992. 152: 1660 - 1662.
- Antiplatelet Trialists Collaboration. Collaborative overview of randomised trials of antiplatelet therapy - III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *British Medical Journal* 1994. 308: 235 - 246.
- Arcelus JJ, Caprini JA. The use of external pneumatic compression for the management of chronic venous insufficiency. *International Angiology* 1996. 15: 32 - 36.
- Barnes RW, Wu KK, Hoak JC. Fallibility of the clinical diagnosis of venous thrombosis. *JAMA* 1975. 234: 605 - 607.
- Bauer GA. A roentgenological and clinical study of the sequelae of thrombosis. *Acta Chir Scand Supplement* 1942. 74: 1 - 110.
- Barzilai B, Eisen HE. Intravascular thrombosis: definitive detecting by quantitative tissue characterization in vitro. *Journal of Clinical Ultrasound* 1989. 17: 579 - 584.

Baumgartner I, Braunschweig M, Triller J, Mahler F. Power-based colour coded duplex sonography for evaluation of calf veins. *International Angiology* 1998. 17: 43 - 48.

Baxter GM, McKechnie S, Duffy P. Colour Doppler ultrasound in deep venous thrombosis: a comparison with venography. *Clinical Radiology* 1990. 42: 32 - 36.

Beebe HG, Bergan JJ, Bergqvist D, Eklof B, Eriksson I, Goldman MP, Greenfield LJ, Hobson RW, Juhan C, Kistner RL, Labopoulos N, Malouf GM, Menzoian JO, Moneta GL, Myers KA, Neglen P, Nicolaides AN, O'Donnell TF, Perrin M, Poter JM, Raju S, Rich NM, Richardson G, Schanzer H, Smith PC, Strandness DE, Sumner DS. Classification and grading of chronic venous disease in the lower limbs. A consensus statement. *International Angiology* 1995. 14: 197 - 201.

Bendick PJ, Ryan R, Alpers M, Bielman S, Burr MO, Glover JL. Clinical significance of superficial thrombophlebitis. *Journal of Vascular Technology* 1995. 19: 57 - 61.

Berberich J, Hirsch S. Die rontgenologische Darstellung der Arterien und Venen im lebenden Menschen. *Klin Wsch* 1923. 49: 2226.

Bergqvist D, Matzsch T, Burmark US, Frisell J, Guilbaud O, Hallbook T, Horn A, Lindhagen A, Ljungner H, Ljungstrom KG, Onarheim H, Risberg B, Tornegrent S, Ortenwall P. Low molecular weight heparin given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis. *British Journal of Surgery* 1988. 75: 888-891.

Bergqvist D. Fatal postoperative pulmonary embolism: a major problem. In *Thrombosis Clinical Practice and Perspectives*. Editors: D. Bergqvist, K Burnand, VV Kakkar, M Rutllant, M Samama, E Wenzel. Publ Oxford Communications 1990.

Bernardi E, Prandoni P, Lensing AW, Agnelli G, Buazzaloca G, Scannapieco G, Piovello F, Verlato F, Tomasi C, Moia M, Scarano L, Girolami A. D-dimer testing as an adjunct to ultrasonography in patients with clinically suspected deep vein thrombosis: prospective cohort study. *British Medical Journal* 1998. 317: 1037 - 1040.

Blebea J, Kihara TK, Neumyer MM, Blebea JS, Anderson KM, Atnip RG. A national survey of practice patterns in the non-invasive diagnosis of deep venous thrombosis. *Journal of Vascular Surgery* 1999. 29: 799 - 806.

Blebea J, Wilson R, Waybill P, Neumyer MM, Blebea JS, Anderson KM, Atnip RG. Deep venous thrombosis after percutaneous insertion of vena caval filters. *Journal of Vascular Surgery* 1999. 30: 821 - 829.

Blumenberg RM, Barton E, Gelfand ML, Skudder P, Brennan J. Occult deep venous thrombosis complicating superficial thrombophlebitis. *Journal of Vascular Surgery* 1998. 27: 338 - 343.

Borgstede JP, Clagett GE. Types, frequency and significance of alternative diagnoses found during duplex Doppler venous examinations of the lower extremities. *Journal of Ultrasound in Medicine* 1992. 11: 85 - 89.

Bosanquet N. Costs of venous ulcers: from maintenance therapy to investment programs. *Phlebology* 1992. Suppl 1: 44 - 46.

Bradbury A, Evans C, Allan P, Lee A, Ruckley V, Fowkes FGR. What are the symptoms of varicose veins? Edinburgh vein study cross sectional population survey. *British Medical Journal* 1999. 318: 353 - 356.

Brandjes DPM, Heijboer H, Buller HM, et al. Acenocourmarol and heparin compared with acenocoumarol alone in the initial treatment of proximal vein thrombosis. *New England Journal of Medicine* 1992. 327: 1485 - 1489.

Browse NL, Thomas ML. Source of non-lethal pulmonary emboli. *Lancet* 1974: 258 - 259.

Browse NL, Clemenson G, Thomas ML. Is the postphlebotic leg always postphlebotic ? Relation between phlebographic appearances of deep vein thrombosis and the late sequelae. *British Medical Journal* 1980. 281; 1167 - 1170.

Buller HR, Kraaijenhagen RA, Koopman MWW. Early discharge strategies following venous thrombosis. *Vascular Medicine* 1998. 3: 47 - 50.

Burns PN. The physical principles of Doppler and spectral analysis. *Journal of Clinical Ultrasound* 1987. 15: 567 - 590.

Callam M. Prevalence of chronic leg ulceration and severe chronic venous disease in western countries. *Phlebology* 1992. Suppl 1: 6 - 12.

Caprini JA, Arcelus JJ, Hoffman K, Size G, Lauback M, Traverso CI, Coats R, Finke N, Reyna JJ. Venous duplex imaging follow-up of acute symptomatic deep vein thrombosis of the leg. *Journal of Vascular Surgery* 1995. 21: 472 - 476.

Caprini JA, Arcelus JJ, Reyna JJ, Motykie GD, Mohktee D, Zebala LP, Cohen EB. Deep vein thrombosis outcome and the level of oral anticoagulation therapy. *Journal of Vascular Surgery* 1999. 30: 805 - 812.

Caps MT, Meissner MH, Tullis MJ, Polissar NL, Manzo RA, Zierler BK, Chandler WL, Strandness DE. Venous thrombus stability during acute phase of therapy. *Vascular Medicine* 1999. 4: 9 - 14.

- Carnall D. Controversy rages over new contraceptive data. *British Journal of Medicine* 1995. 311: 1117 - 1118.
- Chesterman CN. After a first episode of venous thromboembolism. *British Journal of Medicine* 1995. 311: 700 - 701.
- Cho JS, Martelli E, Mozes G, Miller VM, Gloviczki P. Effects of thrombolysis and venous thrombectomy on valvular competence, thrombogenicity, venous wall morphology and function. *Journal of Vascular Surgery* 1998. 28: 787 - 798.
- Coelho JC, Sigel B, Ryva JC, Machi J, Renigers SA. B-mode sonography of blood clots. *Journal of Clinical Ultrasound* 1982. 10: 323 - 327.
- Cohen JR, Tenenbaum N, Citron M. Greenfield filter as primary therapy for deep venous thrombosis and/or pulmonary embolism in patients with cancer. *Surgery* 1991. 109: 12 - 15.
- Consensus paper on venous leg ulcers. The Alexander House Group. *Phlebology* 1992. 7: 48 - 58.
- Cracowski JL, Bosson JL, Baloul F, Moirant C, Hunt M, Merloz P, Carpentier P, Franco A. Early development of deep-vein thrombosis following hip fracture surgery: the role of venous wall thickening detected by B-mode ultrasonography. *Vascular Medicine* 1998. 3: 269 - 274.
- Crafoord C. Preliminary report on post operative treatment with heparin as a preventive of thrombosis. *Acta Chir Scand* 1937. 79: 407 -426.
- Cranley JJ. *Vascular Surgery*; Volume II. Peripheral Vascular Diseases. Publ. Harper & Row, 1975.
- Czeredarczuk M, Branäs CC, Weingarten MS. Duplex imaging and distal cuff deflation to measure venous reflux time. *Journal of Vascular Technology* 1992. 16: 284 - 287.
- Dardik A, Campbell KA, Yeo CJ, Lipsett PA. Vena cava filter ensnarement and delayed migration: an unusual series of cases. *Journal of Vascular Surgery* 1997. 26: 869 - 874.
- Delis KT, Ibegbuna V, Nicolaidis AN, Lauro A, Hafez H. Prevalence and distribution of incompetent perforating veins in chronic venous insufficiency. *Journal of Vascular Surgery* 1998. 28: 815 - 825.
- Dodd H, Cockett FB (Eds). *The pathology and surgery of the veins of the lower limb* (2nd Ed). Churchill Livingstone, Edinburgh 1976.

- Downing LJ, Strieter RM, Kadell AM, Wilke CA, Greenfield LJ, Wakefield TW. Low-dose low-molecular-weight heparin is anti-inflammatory during venous thrombosis. *Journal of Vascular Surgery* 1998. 28: 848 - 854.
- Eklof BG, Kistner RL, Masuda EM. Venous bypass and valve reconstruction: long-term efficacy. *Vascular Medicine* 1998. 3: 157 - 164.
- Elatrozy T, Nicholaides A, Tegos T, Zarka AZ, Griffin M, Sabetai M. The effect of B-mode ultrasonic image standardization on the echodensity of symptomatic and asymptomatic carotid bifurcation plaques. *International Angiology* 1998. 17: 179 - 186.
- Eriksson J, Almgren B, Nordgren L. Late results after venous valve repair. *International Angiology* 1985. 4: 413 - 417.
- European Consensus Statement. Prevention of venous thromboembolism. Under the Auspices of Cardiovascular Disease Educational and Research Thrust and St. Mary's Hospital Medical School. *International Angiology* 1992. 11: 151- 159.
- Evans CJ, Allan PL, Lee AJ, Bradbury AW, Ruckley CV, Fowkes GR. Prevalence of venous reflux in the general population on duplex scanning: The Edinburgh Vein Study. *Journal of Vascular Surgery* 1998. 28: 767 - 776.
- Fegan WG, Fitzgerald DE, Beesley WH. A modern approach to the injection treatment of varicose veins and its applications in pregnant patients. *American Heart Journal* 1964. 68: 757 - 764.
- Fegan G. *Varicose Veins*. 1967. Publ Heinemann Med Books Ltd.
- Fletcher AP, Alkjaersig N. Thrombolytic therapy: problems and prospects. *International Angiology* 1984. 3: 405 - 413.
- Fletcher JP, Batiste P. Incidence of deep vein thrombosis following vascular surgery. *International Angiology* 1997. 16: 65 - 68.
- Fobbe F, Ruhnke-Trautmann M, von Gemmeren D, Harmann CA, Kania U, Wolf KL. Age determination of venous thrombi by ultrasound. *Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr* 1991. 155: 344 - 348.
- Frimerman A, Miller HI, Hallman M, Laniado S, Keren G. Intravascular ultrasound characterization of thrombi of different composition. *American Journal of Cardiology* 1994. 73: 1053 - 1057.
- Gardner MJ, Altman DG. Confidence intervals rather than P values: estimation rather than hypothesis testing. *British Medical Journal* 1986. 292: 746 - 750.

Gardner NL, Zwolak RM, Musson A, LaBombard FE, Zaweski J. Baker's cysts and other incidental calf pathology identified by duplex during DVT examination. *Journal of Vascular Technology* 1995. 19: 69 - 72.

Giachino A. A relationship between deep-venous thrombosis in the calf and fatal pulmonary embolism. *Canadian Journal of Surgery* 1988. 31: 129 - 130.

Ginsberg JS. Management of venous thromboembolism. *New England Journal of Medicine* 1996. 335: 1816 - 1828.

Greaves M, Preston FE. The diagnosis and clinical management of thrombophilia. *Vascular Medicine Review* 1993. 4: 117 - 131.

Greenfield LJ, Proctor MC. Suprarenal filter placement. *Journal of Vascular Surgery* 1998. 28: 432 - 438.

Gronholdt ML, Nordestgaard BG, Wiebe BM, Wilhjelm JE, Sillesen H. Echo-lucency of computerized ultrasound images of carotid atherosclerotic plaques are associated with increased levels of triglyceride-rich lipoproteins as well as increased plaque lipid content. *Circulation* 1998. 97: 34 - 40.

Gutthann SP, Rodriguez LA, Castellsague J, Oliart AD. Hormone replacement therapy and risk of venous thromboembolism: population based case-control study. *British Medical Journal* 1997. 314: 796.

Haenen JH, Janssen MC, van Langen H, van Asten WN, Wollersheim H, Heystraten F, Skotnicki SH, Thien T. Duplex ultrasound in the hemodynamic evaluation of the late sequelae of deep venous thrombosis. *Journal of Vascular Surgery* 1998. 27: 472 - 478.

Hanson JN, Ascher E, DePippo P, Lorensen E, Scheinman M, Yorkovich W, Hingorani A. Saphenous vein thrombophlebitis (SVT): A deceptively benign disease. *Journal of Vascular Surgery* 1998. 27: 677 - 680.

Heldal M, Seem E, Sandset PM, Abildgaard U. Deep vein thrombosis: a 7 year follow-up study. *Journal of Internal Medicine* 1993. 234: 71 - 75.

Hull RD. Anticoagulant treatment. *International Angiology* 1995. 14: 32 - 44.

Hull RD, Raskob GE, Pineo GF, Green D, Trowbridge AA, Elliott G, Lerner RG, Hall J, Sparling T, Brettell HR, Norton J, Carter CJ, George R, Merli G, Ward J, Mayo W, Rosenblood D, Brant R. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *New England Journal of Medicine* 1992. 326: 975 - 982.

Hull RD, Pineo GF, Stein P. Heparin and low-molecular-weight heparin therapy for venous thromboembolism. The twilight of anticoagulant monitoring. *International Angiology* 1998. 17: 213 – 224.

Hunter WC, Sneed VD, Robertson TD, Snyder GAC. Thrombosis of the deep veins of the leg: its clinical significance as exemplified in 351 autopsies. *Archives of Internal Medicine* 1941. 68:1.

Ihnat DM, Mills JL, Hughes JD, Gentile AT, Berman SS, Westerband A. Treatment of patients with venous thromboembolism and malignant disease: should vena cava filter placement be routine? *Journal of Vascular Surgery* 1998. 28: 800 - 807.

Johnson BF, Manzo RA, Bergelin RO, Strandness DE Jr. Relationship between changes in the deep venous system and the development of the post-thrombotic syndrome after an acute episode of lower limb deep vein thrombosis: a one - to-six year follow-up. *Journal of Vascular Surgery* 1995. 21: 307 - 312.

Johnson BF, Manzo RA, Bergelin RO, Strandness DE Jr. The site of residual abnormalities in the leg veins in long-term follow-up after deep vein thrombosis and their relationship to the development of the post-thrombotic syndrome. *International Angiology* 1996. 15: 14 - 19.

Johnson BF, Strandness DE Jr. Ultrasound and venous valvular reflux. *Journal of Vascular Investigations* 1997. 3: 108-113.

Jorgensen JO, Hanel KC, Morgan AM, Hunt JM. The incidence of deep venous thrombosis in patients with superficial thrombophlebitis of the lower limbs. *Journal of Vascular Surgery* 1993. 18: 70 - 73.

Juhan CM, Alimi YS, Barthelemy PJ, Fabre DF, Riviere CS. Late results of iliofemoral venous thrombectomy. *Journal of Vascular Surgery* 1997. 25: 417 - 422.

Killewich LA, Bedford GR, Beach KW, Strandness DE Jr. Spontaneous lysis of deep venous thrombi: rate and outcome. *Journal of Vascular Surgery* 1989. 9: 89 - 97.

Killewich LA, Macko RF, Cox K, Franklin DR, Benjamin ME, Lilly MP, Flinn WR. Regression of proximal deep venous thrombosis is associated with fibrinolytic enhancement. *Journal of Vascular Surgery* 1997. 26: 861 – 868.

Kistner RL. Surgical repair of a venous valve. *Straub Clinical Procedures* 1968. 34: 41 - 43.

Kistner RL. Deep venous reconstruction (1968 - 1984). *International Angiology* 1985. 4: 429 - 433.

Koopman MMW, Prandoni P, Piovella F, Ockelford PA, Brandjes DP, van der Meer J, Gallus AS, Simonneau G, Chesterman CH, Prins MH, Bossuyt PM, de Haes H, van der Belt AG, Sagnard L, D'Azeman PD, Buller HR for the Tasman Study Group. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. *New England Journal of Medicine* 1996. 334: 682 – 687.

Kremkau FW. Principles of colour flow imaging. *Journal of Vascular Technology* 1991. 15: 104-111.

Labropoulos N, Leon M, Nicolaides AN, Sowade O, Volteas N, Ortega F, Chan P. Venous reflux in patients with previous deep venous thrombosis: correlation with ulceration and other symptoms. *Journal of Vascular Surgery* 1994. 20: 20 - 26.

Labropoulos N, Delis K, Nicolaides AN, Leon M, Ramaswami G. The role of the distribution and anatomic extent of reflux in the development of signs and symptoms in chronic venous insufficiency. *Journal of Vascular Surgery* 1996. 23: 504 - 510.

Labropoulow N, Giannoukas AD, Nicholaides AN, Veller M, Leon M, Volteas N. The role of venous reflux and calf muscle pump function in non-thrombotic chronic venous insufficiency. Correlation with severity of signs and symptoms. *Archives of Surgery* 1996. 131: 403 – 406.

Labropoulos N, Webb KM, Kang SS, Mansour A, Filiung DR, Size GP, Buckman J, Baker WH. Patterns and distribution of isolated calf deep vein thrombosis. *Journal of Vascular Surgery* 1999. 30: 787 - 793.

Lacroix KA, Bean C, Box L, Wagner K. A study of the fibrinolytic response in healthy men and women following a brief exposure to venous occlusion. *Thrombosis Research* 1996. 81: 133 - 143.

Lawson DW, Choroszy CJ, Belanger ES, Buckley FO, Sweetland RC, Murzic WJ. Large Hematomas as a cause of pseudothrombophlebitis. *Journal of Vascular Technology* 1995. 19: 181 - 184.

Leclerc JR. Venous thrombosis prophylaxis in medical patients. *Vascular Medicine Review* 1995. 6: 263 - 268.

Lehmann J. Hypoprothrombinaemia produced by methylece-bis- (hydroxycoumarin) its use in thrombosis. *Lancet* 1942. 1: 318

Leizorovicz A, Simonneau G, Decousus HD, Boissel JP. Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep venous thrombosis: a meta-analysis. *British Medical Journal* 1994. 309: 299 - 304.

Leizorovicz A. Long-term consequences of deep vein thrombosis. *Haemostasis* 1998. 28: S3: 1 – 7.

LeSiege CJ, McKean SC, Persson AV. Importance of valvular incompetence after acute deep venous thrombosis. *Journal of Cardiovascular Surgery* 1992. 33: 710 – 713.

Lessing AW, Prandoni P, Brandjes D, Huisman PM, Vigo M, Tomasella G, Krekt J, ten Cate JW, Huisman MV, Buller HR. Detection of deep vein thrombosis by real-time B-mode ultrasonography. *New England Journal of Medicine* 1989. 320: 342 - 345.

Levine MN, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, Ginsberg J, Turpie AG, Demers C, Kovacs M, Geerts W, Kassis J, Desjardins L, Cusson J, Cruickshank M, Powers P, Brien W, Haley S, Willan A. A comparison of low-molecular weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep vein thrombosis. *British Medical Journal* 1996. 316: 95 – 99.

Linder DJ, Edwards JM, Phinney ES, Taylor LM, Porter JM. Long-term hemodynamic and clinical sequelae of lower extremity deep vein thrombosis. *Journal of Vascular Surgery* 1986. 4: 36 – 42.

Love M, Blebea B, Strothman G, Bodenham R. Bilateral duplex scanning for deep venous thrombosis is unnecessary in symptomatic patients. *Journal of Vascular Technology* 1996. 20: 217 – 220.

Markel A, Manzo RA, Bergelin RO, Strandness DE Jr. Valvular reflux after deep vein thrombosis: incidence and time of occurrence. *Journal of Vascular Surgery* 1992. 15: 377 - 384.

Markel A, Manzo RD, Bergelin RO, Strandness DE Jr. Pattern and distribution of thrombi in acute venous thrombosis. *Archives of Surgery* 1992. 127: 305 – 309.

Masuda EM, Kistner RL, Ferris EB. Long-term effects of superficial femoral vein ligation: thirteen-year follow-up. *Journal of Vascular Surgery* 1992. 16: 741 – 749.

Masuda EM, Kessler DM, Kistner RL, Eklof B, Sato DT. The natural history of calf vein thrombosis: Lysis of thrombi and development of reflux. *Journal of Vascular Surgery* 1998. 28: 67 - 74.

Mavor GE, Galloway JMD. Collaterals of the deep venous circulation of the lower limb. *Surgery, Gynecology and Obstetrics* 1967. 125: 567 – 571.

MacIntyre D, Banham SW, Moran F. Pulmonary embolism: long-term follow-up. *Postgraduate Medicine Journal* 1982. 58: 222 – 225.

McCollum C. Vena cava filters: keeping big clots down. *British Medical Journal* 1987. 294: 1566.

McLafferty RB, Moneta GL, Passman MA, Brant BM, Taylor LM, Porter JM. Late clinical and hemodynamic sequelae of isolated calf vein thrombosis. *Journal of Vascular Surgery* 1998. 27: 50 - 57

McMullin GM. Surgical treatment of the postphlebotic limb. *Vascular Medicine Review* 1990. 1: 69 - 83.

Meibers DJ, Baldrige ED, Ruoff BA, Karkow WS, Cranley JJ. The significance of calf muscle venous thrombosis. *Journal of Vascular Technology* 1988. XII: 143 - 149.

Meissner MH. The effect of recanalization of venous thrombi on valve function. *Vascular Medicine Review* 1995. 6: 143 - 152.

Meissner MH, Manzo RA, Bergelin RO, Markel A, Strandness DE Jr. Deep venous insufficiency: the relationship between lysis and subsequent reflux. *Journal of Vascular Surgery* 1993. 18: 596 - 608.

Meissner MH, Caps MT, Zierler BK, Polissar N, Bergelin RO, Manzo RA, Strandness DE Jr. Determinants of chronic venous disease after acute deep venous thrombosis. *Journal of Vascular Surgery* 1998. 28: 826 - 833.

Meissner MH, Caps MT, Zierler BK, Bergelin RO, Manzo RA, Strandness DE Jr. Deep venous thrombosis and superficial venous reflux. *Journal of Vascular Surgery* 2000. 32: 48 - 56.

Mercuro G, Cherchi A. Deep venous thrombosis and insufficiency: treatment. *International Angiology* 1993. 12: 53 - 57.

Moser KM, LeMoine JR. Is embolic risk conditioned by location of deep venous thrombosis. *Annals of Internal Medicine* 1981. 94: 439 - 444.

Motykie GD, Caprini JA, Arcelus JL, Zebala LP, Lee CE, Finke MN, Tamhane A, Reyna JJ. Risk factor assessment in the management of patients with suspected deep vein thrombosis. *International Angiology* 2000. 19: 47 - 51.

Muller C, Muller R, Andros G, Salles-Cunha S. Pitfalls in the comparison of phlebographic and ultrasonic-based diagnosis in the evaluation of the lower extremity. *Journal of Vascular Technology* 1992. 16: 136 - 139.

Murray DW, Britton AR, Bulstrode CI. Thromboprophylaxis death after total hip replacement. *Journal of Bone and Joint Surgery* 1996. 78B: 863 - 868.

Murray DWG, Jacques LB, Perret TS, Best CH. Heparin and the thrombosis of veins following injury. *Surgery* 1937. 2: 163 - 187.

Neglen P, Raju SA. A comparison between descending phlebography and duplex Doppler investigation in the evaluation of reflux in chronic venous insufficiency: a challenge to phlebography as the 'gold standard'. *Journal of Vascular Surgery* 1992. 16: 687 - 693.

Nix ML. Venography. *Journal of Vascular Technology* 1988. XII: 105 - 109.

Nix ML, Troillett RD. The use of color in venous duplex examination. *Journal of Vascular Technology* 1991. 15: 123 - 128.

Nix ML, Troillett RD, Nelson CL, Ferris EJ, Lavender R, Barnes RW. Is bilateral duplex examination necessary for unilateral symptoms of deep vein thrombosis? *Journal of Vascular Technology* 1991. 15: 296 - 298.

O'Leary DH, Kane RA, Chase BM. A prospective study of the efficacy of B-scan sonography in the detection of deep venous thrombosis in the lower extremities. *Journal of Clinical Ultrasound* 1988. 16: 1 - 8.

O'Shaughnessy AM, Fitzgerald DE. Organization patterns of venous thrombus over time as demonstrated by duplex ultrasound. *Journal of Vascular Investigations* 1996. 2: 75 - 81.

O'Shaughnessy AM, Fitzgerald DE. Natural history of proximal deep vein thrombosis assessed by duplex ultrasound. *International Angiology* 1997. 16: 45 - 49.

O'Shaughnessy AM, Fitzgerald DE. The value of duplex ultrasound in the follow-up of acute calf vein thrombosis. *International Angiology* 1997. 16: 142 - 146.

O'Shaughnessy AM, Fitzgerald DE. Implications of duplex ultrasound morphological findings in the future management of acute DVT and development of the post-phlebotic syndrome. *Journal of Vascular Investigations* 1997. 4: 177 - 182.

Partsch H, Oburger K, Mostbeck A, Konig B, Kohn H. Frequency of pulmonary embolism in ambulant patients with pelvic vein thrombosis: a prospective study. *Journal of Vascular Surgery* 1992. 16: 715 - 722.

Partsch H, Kechavarz B, Mostbeck A, Kohn H, Lipp C. Frequency of pulmonary embolism in patients who have iliofemoral deep vein thrombosis and are treated with once- or twice-daily low-molecular -weight heparin. *Journal of Vascular Surgery* 1996. 24: 774 - 782.

Passman MA, Moneta GL, Taylor LM, Edwards JM, Yeager RA, McConnell DB, Porter JM. Pulmonary embolism is associated with the combination of isolated calf vein thrombosis and respiratory symptoms. *Journal of Vascular Surgery* 1997. 25: 39 - 45.

Pegum JM, Fegan WG. Anatomy of venous return from the foot. *Cardiovascular Research* 1967. 1: 241 - 248.

Perlin SJ. Pulmonary embolism during compression US of the lower extremity. *Radiology* 1992. 184: 165 - 166.

Peter DJ, Flanagan LD, Cranley JJ. Analysis of blood clot echogenicity. *Journal of Clinical Ultrasound* 1986. 14: 111 - 116.

Peterson KL. Acute pulmonary thromboembolism. *Circulation* 1999. 99: 1280 - 1283.

Philbrick JT, Becker DM. Calf vein thrombosis. A wolf in sheep's clothing? *Archives of Internal Medicine* 1988. 148: 2131 - 2138.

Pineo GF, Hull RD, Raskob G. Prevention of venous thrombosis in general surgery and orthopedics. *Vascular Medicine Review* 1995. 6: 185 - 192.

Polak JF. Doppler ultrasound of the deep leg veins. A revolution in the diagnosis of deep vein thrombosis and monitoring of thrombolysis. *Chest* 1991. Suppl 4: 165-172.

Powis RL. Colour flow imaging: understanding its science and technology. *Journal of Diagnostic Medicine* 1988. 4: 236 - 245.

Prandoni P, Lensing AW, Buller HR, Carta M, Cogo A, Vigo M, Casara D, Ruol A, ten Cate JW. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. *Lancet* 1992. 339: 441-445.

Prandoni P, Lensing AWA, Prins MR. Long-term outcome after deep venous thrombosis of the lower extremities. *Vascular Medicine* 1998. 3: 57 - 60.

Ramaswani G, Tegros T, Nicolaides AN, Dhanjil S, Griffin M, Al-Kutoubi A, Belcaro G, Lewis J, Wilkins R, Davies MJ. Ultrasonic plaque character and outcome after lower limb angioplasty. *Journal of Vascular Surgery* 1999. 29: 110 - 121.

Raju S, Fredericks R. Venous obstruction: an analysis of one hundred thirty-seven cases with hemodynamic, venographic and clinical correlations. *Journal of Vascular Surgery* 1991. 14: 305 - 313.

Research Committee of the British Thoracic Society. Optimum duration of anticoagulation for deep vein thrombosis and pulmonary embolism. *Lancet* 1960. 1: 1309 - 1312.

Ridker PM. Long-term, low-dose warfarin among venous thrombosis patients with and without factor V Leiden mutation: rationale and design for the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial. *Vascular Medicine* 1998. 3: 67 - 73.

Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet* 1993. 353: 1167 - 1173.

Ruckley CV. Socio-economic impact of chronic venous insufficiency and leg ulcers. *Phlebology* 1995. Suppl 1: 1107 - 1109.

Saarinen J, Sisto T, Laurikka J, Salenius JP, Tarkka M. Late sequelae of acute deep venous thrombosis: evaluation five and ten years after. *Phlebology* 1995. 10: 106 - 109.

Sarasin F, Bounameaux H. Decision analysis model of prolonged oral anticoagulant treatment in factor V Leiden carriers with first episode of deep vein thrombosis. *British Medical Journal* 1998. 316: 95 - 99.

Sawyer PN, Schaefer HC, Domingo RT, Wesolowski DA. Comparative therapy of thrombophlebitis. *Surgery* 1964. 55 : 113 - 122.

Scheffler P, Leipnitz G, Braun B, Jung F, DeLa Hamette D, Kramann B, Wenzel E. Thrombus formation in deep venous thrombosis. A clinical approach to diagnosis and control of lysis efficacy. *International Angiology* 1998. 7: 207-213.

Schmidt C, Schmitt J, Scheffmann M. Hemodynamics of the postphlebotic syndrome. *International Angiology* 1987. 6: 187 - 192.

Schulman S. Anticoagulation in venous thrombosis. *Journal of the Royal Society of Medicine* 1996. 89: 624 - 630.

Schulman S, Rhendin AS, Lindmarker P, Carlsson A, Larfars G, Nicol P, Loogna E, Svensson E, Ljungberg B, Walter H. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Group. *New England Journal of Medicine* 1995. 332: 1661 - 1665.

Schulmann S, Granqvist S, Holmstrom M, Carlsson A, Lindmarker P, Nicol P, Eklund SG, Nordlander S, Larfars G, Leijdt B, Linder O, Loogna E, Walter H, Viering S, Hjorth M, Boberg J, the Duration of Anticoagulation Trial Study Group. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. *New England Journal of Medicine* 1997. 336 : 393 - 398.

Sevitt S, Gallagher N. Venous thrombosis and pulmonary embolism: a clinico-pathological study in injured and burned patients. *British Journal of Surgery* 1961. 48: 475 - 489.

Shung KK, Fei DY, Yuan YW, Reeves WC. Ultrasound characterization of blood during coagulation. *Journal of Clinical Ultrasound* 1984. 12: 147 - 153.

Shung KK, Fei DY, Ballard JO. Further studies on ultrasound properties of blood clots. *Journal of Clinical Ultrasound* 1986. 14: 269 - 275.

Simonneau G, Sors H, Charbonnier B, Page OY, Laaban JP, Azarian R, Laurent M, Hirsch JL, Ferrari E, Bosson JL, Mottier D, Beau B. A comparison of low-molecular weight heparin with unfractionated heparin for acute pulmonary embolism. *New England Journal of Medicine* 1997. 337: 663-669.

Smith LL, Iber C. Venous duplex ultrasound in the diagnosis of pulmonary embolism. *Journal of Vascular Technology* 1989. XIII: 227 - 230.

Smith LL, Knoedler J, Hollerman JJ. Calf vein duplex imaging in the work-up of patients with clinically suspected pulmonary embolism. *Journal of Vascular Technology* 1994. 18: 9 - 13.

Stewart GJ, Lachman JW, Alburger PD, Ziskin MC, Philips CM, Jensen K. Intraoperative venous dilation and subsequent development of deep vein thrombosis in patients undergoing total hip or knee placement. *Ultrasound in Medicine & Biology* 1990. 16: 133 - 140.

Strandness DE Jr, Langlois Y, Cramer M, Randlett A, Thiele BL. Long-term sequelae of acute venous thrombosis. *JAMA* 1983. 250: 1289 - 1292.

Talbot SR. Use of real-time imaging in identifying deep venous obstruction. A preliminary report. *Bruit* 1982. 6: 41 - 46.

Talbot SR, Oliver MA. Thrombus identification and characterization. In: *Techniques of Venous Imaging*. Talbot & Oliver, Appleton & Davis, Inc. Pasadena, California 1992. Chapt. 5: 37 - 58.

Taheri SA. Surgical treatment of deep venous insufficiency. *International Angiology* 1998. 3: 281 - 282.

Taheri SA, Weaver TA, Schultz RO. Genetic alterations in chronic venous insufficiency. *International Angiology* 1993. 12: 1 - 4.

Thomas ML, Keeling FP, Piaggio RB, Treweek PS. Contrast agent induced thrombophlebitis following leg phlebography: iopamidol versus meglumine iothalamate. *British Journal of Radiology* 1984. 57: 205 - 207.

Trevivian AJ, Jamieson WG. Air plethysmography (APG) changes that occur following valve reconstruction for chronic venous insufficiency. *Journal of Vascular Technology* 1996. 20: 23 - 24.

van Bemmelen PS, Bedford F, Beach K, Strandness DE Jr. Quantitative segmental evaluation of venous valvular reflux with duplex ultrasound scanning. *Journal of Vascular Surgery* 1989. 10: 425 - 431.

van Bemmelen PS, Bedford G, Strandness DE Jr. Visualization of calf veins by color flow imaging. *Ultrasound in Medicine & Biology* 1990. 16: 15 - 17.

VanGemmeren D, Fobbe F, Ruhnke-Trautmann M, Hartmenn CA, Gotzen R, Wolf KJ, Distler Q, Schulte KL. Diagnosis of deep leg vein thrombosis with colour-coded duplex sonography and sonographic determination of the duration of the thrombosis. *Journal of Cardiology* 1991. 80: 523 - 528.

VanHaarst EP, Liasis N, van Ramshorst B, Moll FL. The development of valvular incompetence after deep vein thrombosis: a 7 year follow-up study with duplex scanning. *European Journal of Vascular and Endovascular Surgery* 1996. 12: 295 - 299.

VanRamshorst B, van Bemmelen PS, Hoeneveld H, Faber JAJ, Eikelboom BC. Thrombus regression in deep venous thrombosis: quantification of spontaneous thrombolysis with duplex scanning. *Circulation* 1992. 86: 414 - 419.

Virchow RI. Uber die Verstopfung der Lungenarterie Froriep's Notizen N; 1846. 794.

Volteas SK, Kalodiki E, Nicolaidis AN. Low molecular weight heparins in the initial treatment of deep vein thrombosis. *International Angiology* 1996. 15: 67 - 74.

Wakefield TW. Treatment options for venous thrombosis. *Journal of Vascular Surgery* 2000. 31:613 - 620.

Wakefield TW, Linn MJ, Henke PK, Kadell AM, Wilke CA, Wroblewski SK, Sarkar M, Burdick MD, Myers DD, Strieter RM. Neovascularization during venous thrombosis organization: a preliminary study. *Journal of Vascular Surgery* 1999. 30: 885 - 893.

Welch HJ, Young CM, Semegran AB, Iafrati MD, Mackey WC, O'Donnell TF. Duplex assessment of venous reflux and chronic venous insufficiency: The significance of deep venous reflux. *Journal of Vascular Surgery* 1996. 24: 755 - 762.

Wells JK, Hagino RT, Bargmann KM, Jackson MR, Valentine RJ, Kakish HB, Clagett GP. Venous morbidity after superficial femoral popliteal vein harvest. *Journal of Vascular Surgery* 1999. 29: 282 – 291.

Williams PL, Warwick R. Gray's Anatomy. 38th Edition. Editors Williams & Warwick. Publ. Churchill Livingstone 1995.

Yucel EK, Eggin TK, Waltman AC. Extension of saphenous thrombophlebitis into the femoral vein: demonstration by color flow compression sonography. *Journal of Ultrasound in Medicine* 1992. 11: 285 - 287.

Zwiebel WJ. *Introduction to Vascular Ultrasonography*. Second Edition. Edited by WJ Zwiebel. Publ. WB Saunders Co. London 1986.

8. APPENDIX

8.1 APPENDIX I

THE CEAP CLASSIFICATION

CEAP = clinical manifestations, etiologic factors, anatomic involvement and pathophysiologic features.

1. Scoring of Venous dysfunction:

Anatomical Score		1 Point Each	
	Superficial		_____
	Deep		_____
	Perforator		_____
	Subtotal		_____

Clinical Score	0 Points	1 Point	2 Points	
Pain	none	moderate not requiring analgesics	severe, requiring analgesics	_____
Oedema	none	mild/mod	severe	_____
Venous Claudication	none	mild/mod	severe	_____
Pigmentation	none	localized	extensive	_____
Lipoder-matosclerosis	none	localized	extensive	_____
Ulcer size	none	<2cm	>2cm	_____
Ulcer duration	none	< 3 mts	> 3mts	_____
Ulcer recurrence	none	once	more than once	_____
Ulcer number	none	single	multiple	_____
		Subtotal		_____

Disability Score	0 points	2 points	3 points
	Asymptomatic	Symptomatic, can function without support device	Unable to work even with support device
		Subtotal	_____

Venous Diagnosis:

Clinical: (C0 - C6)

- Class 0** No visible or palpable signs of venous disease
- 1** Telangiectases or reticular veins
- 2** Varicose veins
- 3** Oedema
- 4** Skin changes ascribed to venous disease
- 5** Skin changes with healed ulceration
- 6** Skin changes with active ulceration

NOTE: The presence or absence of symptoms such as pain or aching denoted by the additional "S" for symptomatic or "A" for asymptomatic to modify the class category

Etiological (E_c, E_p, or E_s)

- E_c** Congenital
- E_p** Primary, with undertermined cause
- E_s** Secondary with known cause - Post-thrombotic, post-traumatic etc.

Pathophysiological (P_R, P_O, P_{R,O})

- P_R** Reflux
- P_O** Obstruction
- P_{R,O}** Both reflux and obstruction

Anatomical (As, Ap, or Ar)

As = Superficial

- 1 Telangiectases/reticular veins
- 2 LSV - above knee
- 3 LSV - below knee
- 4 SSV
- 5 Non-saphenous

Ap = Deep

- 6 Inferior vena cava
- 7 Iliac - common
- 7 Iliac - internal
- 9 Iliac - external
- 10 Pelvic - gonadal, broad ligament, other
- 11 Femoral - common
- 12 Femoral - deep
- 13 Femoral - superficial
- 14 Popliteal
- 15 Cural - anterior tibial, posterior tibial, peroneal (all paired)
- 16 Muscular - gastrocnemial, soleal, other

Ar = Perforating

- 17 Thigh
- 18 Calf

EXAMPLES:

1. Telangiectases = C_{1(S or A)}
2. Varicose veins, asymptomatic = C_{2-A} EpAsPr
3. Active ulcer, incompetent long saphenous vein and perforators =
C_{6-S}EpAs,Pr
4. Healed ulcer, skin changes, post-thrombotic with pain, deep and
superficial reflux =
C_{4,5-S}EsAs,dPr

(Reference: Beebe *et al* 1995)

8.2 APPENDIX II

DUPLEX SETTINGS

The Acuson 128xP system can be customized for a particular application. The system contains a variety of application specific programs to make selecting scanning parameters consistent. These pre-set values can be set to optimise venous scanning. The following parameters are pre-set:

2-D Transit power: The transit power allows for the adjustment of the power for the ultrasound beam that is transmitted into the body of the patient. The machine is usually set at 0 dB which is the maximum output.

2-D log compression: Log compression changes the way the dynamic range is displayed. Images are displayed by assigning different shades of black and white to different levels of sound intensity. The available levels of black and white comprise the grey scale. The log compression was set at 60dB

Pre-processing: Pre-processing allows for sharpening the edges in an image from smooth, to moderately sharp to crisp borders. Pre-processing was set to 1 for venous scanning which is the level for moderately sharp borders.

Persistence: Persistence helps to bring out subtle differences in tissue texture and can be set for rapidly changing anatomical structures to slow-moving structures. The levels of persistence are labelled 0 to 5, where 0 level is for rapidly changing anatomical structures and 5 is for slow-moving structures. The persistence level is set at 2 for venous scanning.

Post-processing: The post-processing curve sets the relationship between the echo amplitude and the displayed grey or colour level. For venous scanning this is set at 6 for high contrast.

The Depth Gain Compensation (DGC): The DGC curve allows for the enhancement of specific areas of interest by increasing or decreasing the amplification of echoes at different depths. It compensates for losses in signal strength as the ultrasound passes through anatomical structures. The field of view is set into eight zones with slide-pot control for each zone located to the right of the screen. All eight controls are set midline for venous applications.

A 7.5 MHz linear array probe was used for scanning. Occasionally a 5 MHz curved probe was used for greater depth penetration during scanning; however, when capturing an image for computer analysis only the 7.5 MHz probe was used.

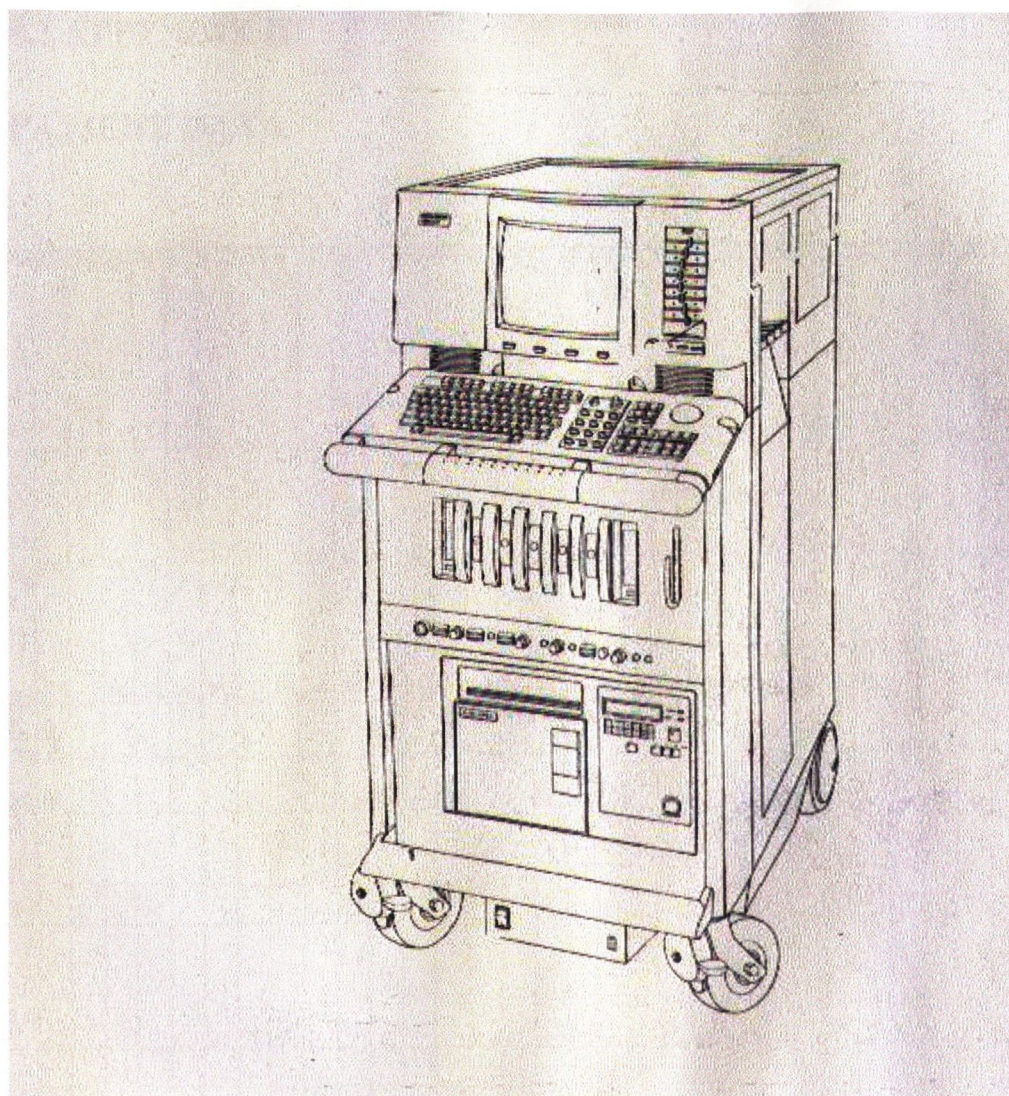


Figure 8.1: The Acuson 128xP/10

8.3 APPENDIX III

PATIENT DATA

No	sex	age	PRE DVT	CVA	CA	INJ	SURG	SMOK	Factor V	VV	Immobility	HRT/CONT	PE	V/Q	Tenderness	Swelling	Dur of symptoms
1	F	81					x								x	x	7
2	F	76					x									X	3
3	M	69						X							X	X	5
4	M	53						X					X	NP			2
5	M	52			X								X	NP		X	5
6	M	27			X											X	5
7	M	57				X				X					X	X	6
8	F	28						X	X			X			X	X	4
9	F	63			X			X							X		7
10	F	63			X			X							X		7
11	M	69									X		X	Y			3
12	M	72			X			X							X		4
13	M	61	X							X					X	X	7
14	F	60					X	X							X	X	3
15	M	70		X												X	7
16	M	26					X								X	X	5
17	M	50							X				X	Y			7
18	F	69			X										X	X	5
19	F	54	X												X	X	3
20	M	27	X												X	X	10
21	M	53					X								X	X	14
22	F	83	X								X				X		2
23	M	61									X				X	X	7
24	F	73	X								X						5
25	M	60	X				X								X	X	14
26	M	60						X					X	Y	X	X	5
27	M	47	X			X									X		5
28	F	57						X			X				X	X	7
29	M	41									X				X		7
30	M	77	X								X				X	X	7
31	F	80					X									X	1
32	M	76	X													X	2
33	M	41	X					X								X	3
34	F	62				X									X	X	14
35	F	81		X												X	2

36	M	69			X									X	X		7
37	M	68	X					X		X					X		3
38	F	33			X			X						X			3
39	M	50								X			X	Y			2
40	F	52	X											X	X		7
41	M	41			X									X	X		5
42	M	22	X		X			X						X	X		7
43	F	53	X					X							X		3
44	F	67		X	X								X	Y		X	7
45	F	51								X				X	X		7
46	F	56	X							X				X	X		5
47	M	73						X					X	NP			3
48	F	75								X				X			7
49	M	76								X				X	X		5
50	M	76								X							5
51	F	42	X										X	Y	X		5
52	F	53	X									X				X	3
53	M	70	X							X						X	14
54	M	73	X		X									X			8
55	F	80								X			X	Y			1
56	F	35			X									X	X		7
57	F	87	X		X								X	Y			4
58	M	51			X									X	X		10
59	F	79								X			X	N			1
60	F	66						X						X	X		3
61	M	81						X						X	X		1
62	F	94	X		X					X					X		5
63	M	87			X					X				X	X		2
64	F	26						X				X		X	X		21
65	M	55													X		21
66	F	76	X										X	Y	X	X	1
67	M	26			X									X	X		7
68	M	36			X									X			7
69	F	74								X				X	X		5
70	F	54	X		X									X	X		5
71	M	26			X									X	X		1

72	M	35			X		X											X			5
73	M	40											X	Y	X						7
74	M	40											X	Y	X			X			7
75	M	75											X	Y	X			X			5
76	F	90							X												5
77	M	61	X					X													7
78	F	59													X			X			2
79	F	89	X					X							X			X			3
80	M	52			X										X			X			7
81	F	58			X										X			X			5
82	F	58			X										X			X			15
83	F	71	X									X	Y	X				X			5
84	M	79		X			X		X						X			X			3
85	F	78	X									X	NP					X			7
86	M	58			X				X						X			X			3
87	F	75		X											X			X			1
88	M	50					X					X	Y	X				X			3
89	F	69							X									X			5
90	F	69							X									X			5
91	F	90	X						X						X			X			7
92	M	84							X						X			X			3
93	F	88							X						X			X			7
94	M	79							X			X	NP								3
95	M	79							X			X	NP								3
96	F	78										X	Y								7
97	F	52						X							X			X			7
98	M	53				X									X			X			7
99	F	72						X				x	Y								7
100	f	64	x									X	Y								5
MEAN		62																MEAN			5.79
SD		18	TOTAL															SD			4.29344803
			Pre DVT	CVA	CA	INJ	SURG	SMOK	FACTOR V	VV	IMMOB	HRT/OCP	PE								
			TOTAL	29	6	15	12	10	19	3	15	20	4	24							
												V/Q Positive (Y) = 17						Tenderness only = 12			
												V/Q Negative (N) = 1						Swelling only = 19			
												V/Q Not performed (NP) = 6						Tenderness & swelling = 52			

8.4 APPENDIX IV

GSM DATA

No	GSM VALUES							
	initial	1 week	1 mt	6 mts	1 year			
1	0	34	34	70	70		NS =	No Show
2	0	16	35	R	R		L =	Lost
3	24	20	76	76	78		R =	Resolved
4	33	48	D	D	D		D =	Deceased
5	10	11	32	NS	60			
6	24	NS	30	33	35			
7	24	20	33	49	78			
8	0	NS	R	R	R			
9	20	NS	3	D	D			
10	13	NS	0	D	D			
11	4	25	5	D	D			
12	25	13	27	32	50			
13	3	4	0	16	50			
14	57	20	32	90	100			
15	22	75	59	24	29			
16	41	16	L	L	L			
17	33	35	40	50	55			
18	20	0	NS	38	62			
19	12	31	L	L	L			
20	17	26	18	30	36			
21	17	27	18	22	63			
22	34	22	35	83	83			
23	19	29	47	27	29			
24	29	29	39	47	33			
25	30	59	59	55	60			
26	21	32	35	L	L			
27	0	1	2	NS	137			
28	31	35	44	44	48			
29	33	21	44	80	72			
30	3	5	42	50	70			
31	26	41	L	L	L			
32	0	24	21	58	50			
33	2	NS	NS	41	40			

34	34 NS		2	85	115
35	1	0 L	L	L	
36	54	44 NS		65	50
37	3 NS		3	85	70
38	0	29	33	40	50
39	0 NS		1 L	L	
40	25	3	38	32	48
41	5	3 NS	NS	R	
42	34 NS	R	R	R	
43	2	34 NS	NS	R	
44	1	37 R	R	R	
45	37	43 NS		52	86
46	20 NS	NS		48	34
47	3	0 R	R	R	
48	31 NS		47	55	60
49	6 NS	L	L	L	
50	1 NS	NS	NS		90
51	2	32 R	R	R	
52	36	57	51	33	70
53	3	41	41	61	70
54	35	1	29 NS		50
55	0	3 R	R	R	
56	0 R	R	R	R	
57	1 NS		31	35 D	
58	25 NS	D	D	D	
59	3	29	42 R	R	
60	2 R	R	R	R	
61	21	4	1	30 R	
62	3	17 NS		64	70
63	31	0 L	L	L	
64	44	43 NS		54	94
65	55	85	25	59	84
66	20	34 D	D	D	
67	28	31	31	70	90
68	25	33	50	58 R	
69	3 NS	L	L	L	

70	29	1	L	L	L			
71	0	2		21	68	90		
72	35	52		26	L	L		
73	4	3	R		R	R		
74	1	31		22		27	R	
75	3	NS	L		L	L		
76	34	NS	L		L	L		
77	31	30		27	NS		29	
78	4	27		19	R	R		
79	72	29	R		R	R		
80	29	37		33	L	L		
81	3	30	D		D	D		
82	7	D	D		D	D		
83	0	NS	L		L	L		
84	3	NS	D		D	D		
85	34	NS	L		L	L		
86	4	NS	D		D	D		
87	3	NS	NS		L	L		
88	29	41	L		L	L		
89	1	NS	D		D	D		
90	1	NS	D		D	D		
91	53	NS	L		L	L		
92	36	NS	L		L	L		
93	33	0	L		L	L		
94	1	31	L		L	L		
95	1	2	L		L	L		
96	33	26		54		50	72	
97	0	24	R		R	R		
98	33	52	D		D	D		
99	34	36		24	R	R		
100	30	35		96	R	R		
MEAN	18.02	25.8714286		31.14	52.1135135	64.0238095		
SD	16.675743	18.3310313		19.7546275	19.9411392	25.5133758		

PRESENTATIONS

1. Determining the stage of organisation and natural history of venous thrombosis using computer analysis.

Presented by: Ann M O'Shaughnessy

Winner of the International Union of Angiology Prize.

13th Congress of the European Chapter of the International Union of Angiology, Rhodes, Greece, May 1999.

2. The use of computer analysis as an objective method to determine the organisation of a deep vein thrombosis.

Presented by: AM O'Shaughnessy

Winner of the SVT prize.

8th Annual General Meeting of the Society for Vascular Technology of Great Britain and Ireland. Leicester, England, November 1999.

3. The use of computer analysis in the study of the organisation process of deep vein thrombosis.

Presented by: AM O'Shaughnessy

Cavan Venous Forum, Cavan. November 1999.

4. The use of computer analysis to study the natural history of DVT.

Presented by: AM O'Shaughnessy

19th World Congress of the International Union of Angiology. Ghent, Belgium May 2000.

5. DVT - an audit during the first year following an acute event.

Presented by: AM O'Shaughnessy

19th World congress of the International Union of Angiology. Ghent, Belgium. May 2000.

PUBLICATIONS

1. O'Shaughnessy AM, FitzGerald DE. Determining the stage of organisation and natural history of venous thrombosis using computer analysis. *13th Congress of the European Chapter of the International Union of Angiology*. Editor: EA Bastounis. Publ: Monduzzi Editore, International Proceedings Division. Italy 1999. 229 -233.

2. O'Shaughnessy AM, Fitzgerald DE. Determining the stage of organisation and natural history of venous thrombosis using computer analysis. *Interernational Angiology* 2000. 19: 220 -227.

3. O'Shaughnessy AM, Fitzgerald DE. The value of computer analysis in predicting the long-term outcome of deep vein thrombosis. *International Angiology* 2000. 19: 308 -313.
4. O'Shaughnessy AM, Fitzgerald DE. An audit of the clinical and sub-clinical changes in the first year following an acute DVT. *International Angiology* 2000. (In Print).
5. O'Shaughnessy AM, Fitzgerald DE. The patterns and distribution of residual abnormalities between the individual proximal venous segments following an acute deep vein thrombosis. *Journal of Vascular Surgery* 2001. 33: 379 – 384.
6. O'Shaughnessy AM, Fitzgerald DE. The underlying factors influencing the development of the post-thrombotic limb. *Journal of Vascular Surgery* 2001. (In Print).