VENOUS THROMBOEMBOLISM

MEDICAL GRAND ROUNDS

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CASE REPORT 1

[redacted]

PRESENT ILLNESS:

This was the 2nd [redacted] admission for this 37 year-old lady. 30 days before admission she had had a vaginal delivery of her 5th child without complications. Following delivery she was on oral contraceptive pills. During previous pregnancies she had a history of swelling and venous varicosities in the left leg. Two days prior to admission she noted increasing swelling, increasing pain, temperature and erythema of the left leg and left groin, preceeded by a 1 week history of left lumbar low back pain. There was no chest pain, dyspnea, cough or hemoptysis.

PHYSICAL EXAM:

Showed a pleasant lady in moderate distress who was afebrile and had normal vital signs. *Chest:* Clear without rubs. *Heart:* Showed the PMI to the right of the midclavicular line with normal 1st and 2nd sounds. There was no S3, no S4. There was a II/VI systolic ejection murmur at the left lower sternal border. There were no rubs. *Abdomen:* Soft without mass or tenderness. *Extremities:* Demonstrated a normal right leg. The left leg was warm. It was tender and erythematous. There was 2+ pitting edema at the ankle. The left leg 6 inches above the knee was 20 inches in circumference while the right leg at the same point was 18 inches in circumference.

LABORATORY:

Hemoglobin 11.4, hematocrit 35, white count 11,900, 86 polys, 14 lymphs. Arterial blood gases; Ph 7.44, PCO_2 27, PO_2 81. Chest x-ray was normal. Fibrin split products were greater than 10 and less than 40 and EKG demonstrated transient ST T changes that resolved upon subsequent cardiogram.

HOSPITAL COURSE:

1. Thrombophlebitis: She was begun on i.v. heparin therapy, 8,000 units q4h, giving a Lee White clotting time in the range of 30 minutes. Subsequent venograms demonstrated normal right venous collecting system in the lower extremity, the left lower extremity had deep vein thrombosis with the thrombus extending from the popliteal vein through the superficial femoral vein into the common iliac. Her lung scan was negative. She received heparin therapy i.v. for 9 days without complications. Her hemoglobin remained stable at 11.5, her guaiacs were repeatedly negative and UA was repeatedly negative for hematuria. The leg was elevated, she was kept at bed rest and all oral contraceptive pills were discontinued. During hospitalization coumadin was begun with a prothrombin time finally obtained at 20.5 versus her control at 12, on a 5mg per day dose. Gynecology consult fitted her for a diaphragm and suggested tubal ligation upon discontinuation of anticoagulation therapy in the future.

PATHOGENESIS OF DEEP VEIN THROMBI

Most deep vein thrombi probably originate in the deep veins of the calf and then extend into the popliteal and ileofemoral system according to autopsy studies (6), phlebographic studies (22) and ^{125}I fibrinogen leg scans in postoperative patients (28). The site of thrombus formation in the presence of a slowed venous stream seems to depend on a disturbance of normal laminar flow at valves, angulations, diluted sinuses or areas of compression. There is frequently a nidus of platelets at the site of origin of a thrombus in an area of stasis such as under a venous valve pocket. However, the nidus usually appears to have developed on top of a normal intima, suggesting that platelets silted in the regional eddy currents aggregate when traces of thrombin form due to local or systemic hypercoagulability (6). This is in contrast to a primary platelet nidus that occurs at sites of injury to endothelium resulting in exposed collagen or on foreign surfaces such as artificial heart valves. Such a mechanism may account for the few venous thrombi that do not seem to originate in calf veins (25).

The nidus of thrombus may propagate proximally until large enough tributary is reached to wash out activated coagulation factors. The final outcome is a balance of stasis, hypercoagulability (meaning sufficient activated coagulation factors) and the fibrinolytic mechanism. Leg veins have less potential for release of plasminogin activators than other veins (7). A pulmonary embolus occurs when the friable head of the forming thrombus propagates into a large enough vein and breaks off.

HYPERCOAGULABILITY

Predisposing factors

In a non-specific sense hypercoagulability refers to any state in which there is an increased tendency for thrombosis to occur. In my experience it is rare to be able to document pulmonry embolism in the absence of one or more of the following predisposing factors:

Precipitating Factors in Thromboembolism

Stasis:	Cardiac arrhythmia
	Congestive heart failure
	Dehydration
	Immobilization
	Myocardial Infarction
	Obesity
	Varicose Veins
Blood Vessel Wall Injury:	Fracture
	Operation
	Trauma
Hypercoagulability:	Cancer
	Hemolytic Anemia
	Oral Contraceptives
	Polycythemia
	Pregnancy
	Previous venous thromboembolism

Handin (139) reviews the multitude of data suggesting an association between oral contraceptives, deep venous thrombosis and pulmonary emboli but points out that no completely acceptable prospective study confirms this association. Vorherr (138) illustrates that the chance for a woman to die from abortion, pregnancy or delivery or during the puerperium is ten to thirty-fold higher than that of a non-pregnant woman ingesting the pill to die from thromboembolism.

Activated Coagulation factors

In a more specific sense hypercoagulability can be defined as the presence of activated coagulation factors within the blood (21) (See Figure 1). Exposed collagen, certain lipids or other contact activators can initiate the intrinsic coagulation cascade (16). Whether the chain proceeds to the conversion of prothrombin to thrombin is likely the result of the balance between the rate of activation and the level of naturally occuring inactivators. The naturally occuring antithrombin III requires about 20 minutes for complete neutralization of thrombin *in vitro* (71). Antithrombin III inactivates both thrombin and Xa by reaction of their active serine center with the reactive arginine site of antithrombin III. The other activated factors in the intrinsic coagulation system XIIa, XIa, and IXa all have an active serine center responsible for their enzymatic action. Rosenberg predicted that antithrombin III would inactivate all the enzymatic coagulation factors with an active serine center and that heparin would accelerate the inactivation (71). This has been confirmed for XIa and IXa (71).

There are satisfactory methods for measuring antithrombin III. Families with dominantly inherited deficiencies of antithrombin III have been identified and affected members are plagued with recurrent venous thromboembolism starting at about age 20 (13). Von Kaulla and Von Kaulla (11) found antithrombin III levels depressed in non-familial venous thromboembolism and proposed this as a means of identifying a hypercoagulable state. However in a larger series there was no deficiency of anti-thrombin III in patients with recurrent venous thromboembolism (14). There are no satisfactory methods for measuring activated coagulation factors including thrombin. However the result of thrombin action, the release of fibrinopeptides from fibrinogen, and the formation of fibrin monomer can be detected.

Fibrinopeptide A (FPA).

Nossel, *et. al.* (15) have developed a radioimmunoassay to detect minute amounts of FPA. FPA has a half life of about 5 minutes and its presence would indicate ongoing thrombin generation. However, the assay is very tedious to perform and is so sensitive that elevations can occur with minimal departure from the most gentle blood drawing technique.

FIGURE 1

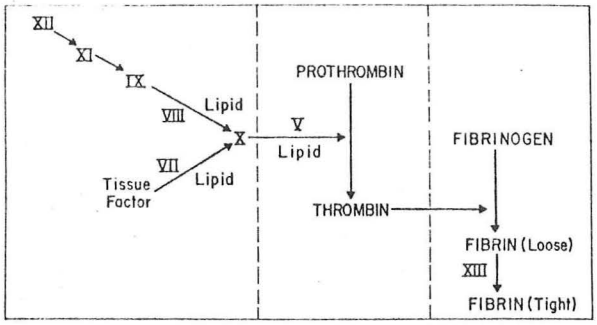

Figure 1. The Soluble Coagulation Mechanism.
All steps subsequent to the activation of factor XI require calcium. Factor XII = Hageman, XI = PTA, IX = PTC, VIII = AHF, X = Stuart, VII = proconvertin, V = proaccelerin, XIII = fibrin stabilizing factor.

Soluble fibrin complexes (SFC)

The subject of SFC has been reviewed extensively by Bang (21). Fibrin monomer (FM) ordinarily polymerizes with itself to form insoluble fibrin clots, but can form soluble complexes with fibrinogen or fibrin degradation products (fdp) both early (X^o) and late (Y, D, E). These SFC can be detected by means of a paracoagulation test such as the Serial Dilution Protamine Sulfate (SDPS) test (17) or by fibrinogen gel chromatography (FGC) (18). In the SDPS test protamine sulfate is thought to dissociate the complexes allowing the FM to spontaneously polymerize forming visible strands or gels (17). With fibrinogen gel chromatography the heavier SFC come out earlier than fibrinogen in the elution volume (18).

Unfortunately SFC can also be formed from early fdp (X^o) and these soluble complexes behave identically to those of FM in both the SDPS test and fibrinogen gel chromatography. The presence of SFC therefore can represent either ongoing thrombosis with formation of soluble fibrin monomer complexes or fibrinolysis with formation of soluble complexes of early fdp (X^o) (17). Gurewich (160) believes that the SFC detected clinically are the result of lysis of large thrombi. His SDPS test was positive in most large symptomatic deep vein thrombi confirmed with phlebography, whereas the SDPS test was rarely positive in asymptomatic postoperative calf vein thrombi detected by ^{125}I fibrinogen and confirmed with phlebograms. However in our experimental animal studies in dogs the Wessler model of hypercoagulability caused by homologous serum infusion induces a very positive SDPS test in the absence of gross thrombosis formation (142).

NATURAL HISTORY OF DEEP VEIN THROMBOSIS

Most asymptomatic deep vein thrombi that develop postoperatively and are detected by the very sensitive ^{125}I fibrinogen technique do not propagate above the knee and lyse spontaneously without sequallae with ambulation and no anticoagulation (28).

Modern physicians sometimes are skeptical about the need to treat deep thrombophlebitis with heparin, for they know of no controlled trial where half the patients were randomized to a placebo and are aware of reports of bleeding complications up to 28%. In 1942 Gunner Bauer reported his experience with early but symptomatic deep thrombosis confined to the calf veins on phlebography before and after heparin became available.

Treated with Heparin	NO	YES
Number of cases	32	38
Thrombosis remained localized	8 (25%)	38 (100%)
Thrombosis propagated to thigh (Phlegmasia alba dolens)	24 (75%)	0
Pulmonary infarct or embolism	11 (34%)	0
Thrombosis of the other leg	10 (31%)	0
Deaths from thrombotic complications	2 (6%)	0
Average time hospitalized in bed	43 days	6.4 days

Bauer retrospectively reviewed 41 patients who were treated at the Mariestad Hospital 10-15 years earlier for total deep thrombosis of the leg:

40 still had leg swelling and heaviness.
36 had indurated skin.
26 had leg ulcers.

Post-thrombophlebitic syndrome

Mavor and Gallaway (24) divide the deep venous system into the upper ileofemoral segment above the junction of the profunda femoris with the superficial femoral vein and the lower femoropopliteal segment. Collateral circulation for the ileofemoral system is inadequate and obstruction here leads to marked swelling of the thigh. Thrombotic occlusion limited to the lower femoropopliteal system does not cause clinical venous insufficiency because of the extensive collateral system connecting with the profunda femoris to bypass the popliteal vein. Despite marked enlargement the collaterals retain competent valves. Bauer (22) reports that when a thrombosed femoral vein recanalizes severe post-thrombophlebitic circulatory disturbance arise whereas this is not the case if the process has never extended upward to the popliteal vein. Tibbutt's experience is similar (126).

Leg Ulcers

Bauer (22) performed phlebography on 25 patients with leg ulcers of unknown cause. In 23 an old total thrombosis had been present in the deep passages of the leg. The other two had varicose veins. Phlebograms in 25 patients with varicose veins showed deep thrombosis in one and only the two had leg ulcers.

Phlegmasia Cerulea dolens

Phlegmasia Cerulea dolens is a condition in which total or near total occlusion of the venous outflow tract produces massive edema of the extremity and a characteristic violaceous discoloration of the skin. This extensive venous obstruction with the possible contribution of reflex arterial spasm ultimately leads to ischemic necrosis. Shock associated with about 1/3 of the cases is attributed to pooling of blood in the affected extremity (134). Boyd and Clark (23) reviewed 149 cases from the literature and included six cases from Lehey Clinic with the following bleak prognostic figures:

Complication	Number	(Per Cent)
Death	43	28%
Gangrene	81	52%
Surgical Amputation	38	25%
Spontaneous Amputation	7	5%
Pulmonary Embolus	20	13%
Venous sequelae	24	16%

Risk of Pulmonary Embolism

When symptomatic deep thrombophlebitis was the primary problem and was confirmed by liberal use of phlebography clinical evidence of pulmonary embolism before treatment was present in 59 (6%) of Bauer's 937 patients (93) and 6 of 52 (11%) patients studied by Kistner, *et. al.*(32). In the latter study routine lung scans showed perfusion defects in 52% of the remaining patients. The defects changed on serial scans suggesting that they were asymptomatic pulmonary emboli.

There is increasing evidence that the risk of pulmonary embolism is the least when thrombosis is confined to the calf and is greatest when it extends above the knee and into the ileofemoral system (25, 28, 29, 32, 45, 126). Kakkar, *et. al.* (28) studied 132 patients having elective surgery with the ^{125}I fibrinogen technique. Forty patients had increased counts going down the leg. Venography confirmed thrombi in all but one. Nine had increased counts extending into the popliteal and femoral areas. Four of these had clinical evidence of pulmonary emboli; whereas none of the other patients did. Beckering and Titus (29) examined femoral and popliteal veins in 93 unselected autopsies. thrombi were absent in thigh veins in 68 and only 6 (9%) had pulmonary emboli. Thrombi were present in thigh veins in 25 and 10 (60%) had pulmonary emboli. Superficial thrombophlebitis of the long saphenous system may extend into the deep system saphenous system may extend into the deep system (34) and is frequently associated with asymptomatic pulmonary emboli (32).

There is very little information available on untreated symptomatic deep thrombophlebitis. Villasanta (33) reviewed the literature and found 163 cases of antepartum thrombophlebitis that was not treated with anticoagulants. Twenty-six patients developed a pulmonary embolus (16%) and 21 died (13%). Bauer's (22) thirty-two patients with symptomatic thrombophlebitis progressing in the hospital before the days of heparin had pulmonary embolus or infarction in 11 patients (31%) and deaths from thrombotic complications in two (6%).

Influence of anticoagulation on the natural history of deep thrombophlebitis

When deep vein thrombosis progression under anticoagulation treatment is examined at various time intervals with phlebograms the thrombus appears loose in the first week. Over the next 14 days it becomes adherent to the vein wall and retracts (30). If an adherent thrombus completely obstructs a calf vein alone it usually lyses over several months (30, 32). On the other hand tibial fractures with unrecognized calf vein thrombi not treated with anticoagulants have a 50% incidence of residual thrombi in the calf veins when phlebograms are performed 2-3 years later (26). With more extensive thrombosis of deep veins above the knee there is rarely any spontaneous lysis (6 of 96 patients from several series) evident on repeat phlebograms 5-10 days later in patients treated with either heparin (120, 121, 122, 123) or arvin (121, 126).

In patients with residual thrombi after initial treatment Kakkar, *et. al.* (31) performed repeat phlebograms 6-12 months later. Eight patients had received oral anticoagulants for 6-9 months and seven showed complete recanalization, though none had demonstrable venous valves. Six patients had not received oral anticoagulation and only one of these completely recanalized. Eight patients had shown complete clearance with the initial treatment (six of these had streptokinase) and were not treated with subsequent anticoagulation. All eight had completely patent veins 6-12 months later and valves were normal on the phlebograms of five.

DIAGNOSIS OF DEEP VEIN THROMBOPHLEBITIS

Clinical diagnosis

Clinical diagnosis of deep vein thrombophlebitis appears to be incorrect about as often as it is correct whether compared with autopsy (35), phlebographic (36) or ^{125}I fibrinogen confirmation (38). Calf tenderness by direct pressure, by dorsiflexion of the foot (Homan's sign) or by low inflation pressure of a blood pressure cuff (Lowenberg's sign) are all false signs as often as they are correct. Unilateral calf swelling or skin temperature change are more reliable in some series (35).

Phlebography

Phlebograms are accepted (mostly by faith) as the most reliable diagnostic tool for deep thrombophlebitis. They appear to be most reliable when performed by the ascending technique with contrast media hand injected through a vein in the dorsum of the foot and the patient in the semi-erect position without weight bearing (41, 42). The technique undoubtedly misses some small thrombi in the deep veins of the calf and could miss thrombi that originate in the pelvic veins. However these do not appear to be significant problems because of the infrequency with which pelvic vein thrombi occur in the absence of ileofemoral thrombi and the infrequency with which pulmonary emboli arise from thrombi confined to small calf veins (112). In 72 patients with suspected deep thrombophlebitis Bauer found normal phlebograms in 15, did not anticoagulate these 15 and no further thromboembolism developed. Corrigan, *et. al.* performed phlebograms on 102 patients suspected of having pulmonary embolism. Phlebograms were normal in 44 and they did not anticoagulate despite lung scan abnormalities in 14. None of the patients had recurrence of pulmonary embolism. The phlebograms did not induce thrombophlebitis in patients not subsequently anticoagulated nor did they appear to dislodge thrombi and cause pulmonary embolism. Despite the safety, other than possible allergic reactions, phlebograms are inconvenient and usually painful to the patient. Three other techniques will be compared with phlebograms as the gold standard.

^{125}I Fibrinogen Leg Scans

Table 1 tabulates the comparisons of the ^{125}I fibrinogen technique with phlebograms in postoperative situations. The ^{125}I fibrinogen scan is very sensitive and there were no incidents of false-negative tests. It is difficult to know whether a positive ^{125}I fibrinogen test in the presence of a negative phlebogram is a false positive or whether the fibrinogen technique is just more sensitive in detecting small thrombi in the deep veins of the calf.

On the other hand, as indicated in Table 2, when ^{125}I fibrinogen leg scan has been utilized in the situation of suspected pulmonary embolism or in long-established major deep vein thrombophlebitis, there are very frequent false negatives and false positives. In experimental animals (52) ^{125}I fibrinogen is taken up more readily in clots that are formed after the administration of ^{125}I fibrinogen, but it is taken up to some extent in thrombi that are already formed. However, the usefulness in suspected deep thrombophlebitis or pulmonary embolism appears limited. Also ^{125}I fibrinogen leg scans are very unreliable above the mid-thigh level. Some conditions produce high levels of leg radioactivity in the absence of deep venous thrombosis. These include superficial thrombophlebitis, hematomas, healing wounds and fractures, ulceration, cellulitis, arthritis and gross edema (112).

In the absence of availability of ^{125}I fibrinogen ordinary ^{131}I MAA used for lung scans can be injected through a needle on the dorsum of the foot. Duffy, *et. al.* (54) found delayed leg clearance of ^{131}I in 18 of 21 patients with abnormal phlebograms and rapid clearance in 9 of 10 patients with normal phlebograms.

Ultrasound or Doppler Venous Flow Studies

Rushmer and associates introduced the transcutaneous Doppler flow detection technique in 1966 (56). The device senses blood flow by the shift in frequency produced back scatter of the high-frequency sounds from moving red blood cells. In venous disease the transducer is placed over the vein in question. Compression below this area produces an augmentation sound if the vein is patent. As indicated in Table 3, several different groups have found very good correlation between the Doppler examination and phlebograms. However, some investigators such as Milne (61) found only a 60% agreement and our own personal experience is similar. Most investigators have found it to be more reliable in detecting calf vein thrombosis. I find it most useful as suggested by Yao (62) in evaluation of swollen legs. A normal Doppler examination correctly predicted a normal phlebogram in all but 2 of 15 patients. Also the Doppler was abnormal in all but 2 of 35 patients with positive phlebograms in the situation of a swollen leg. It is surprising how many swollen legs are not due to obstructed major deep vein channels when they are investigated thoroughly. However, even in detecting large thrombi in the iliofemoral system, the thrombus has to virtually completely occlude the lumen before this test becomes abnormal.

TABLE 1

REFERENCE	TYPE OF PATIENT	I-125-FIBRINOGEN + / PHLEBOGRAM -	I-125-FIBRINOGEN - / PHLEBOGRAM +	TOTAL AGREEMENT / TOTAL COMPARISONS
FLANK ET AL BRIT J SURG 1968	POSTOP	1/8 (13%)	0/17 (0%)	24/25 (96%)
NEGUS ET AL BRIT J SURG 1968	POSTOP MAJ SURG	2/31 (6%)	0/24 (0%)	53/55 (96%)
MILNE ET AL LANCET 1971	POSTOP MAJ ABD SURG	7/17 (29%)	0/18 (0%)	30/35 (86%)

TABLE 2

REFERENCE	TYPE OF PATIENT	I-125-FIBRINOGEN + / PHLEBOGRAM -	I-125-FIBRINOGEN - / PHLEBOGRAM +	TOTAL AGREEMENT / TOTAL COMPARISONS
FLANK ET AL BRIT J SURG 1968	SUSPECTED DVT	6/10 (60%)	6/26 (23%)	24/36 (67%)
KAKKAR ARCH SURG 1972	SUSPECTED DVT	13/28 (46%)	12/74 (16%)	77/102 (75%)
MAVOR ET AL LANCET 1972	PULMONARY EMBOLISM	6/32 (19%)	38/40 (95%)	28/72 (39%)
MAVOR ET AL LANCET 1972	MAJOR DVT		34/50 (68%)	16/50 (32%)
BROWSE ARCH SURG 1972	SUSPECTED DVT	19/	26/	150/195 (77%)

TABLE 3

REFERENCE	TYPE OF PATIENT	DOPPLER + / PHLEBOGRAM -	DOPPLER - / PHLEBOGRAM +	TOTAL AGREEMENT / TOTAL COMPARISONS
EVANS & CROCKETT BRIT MED J 1969	SUSPECTED DVT	0/25 (0%)	3/13 (23%)*	35/38 (92%)
SIGEL ET AL ARCH SURG 1970	SUSPECTED DVT OR PE	20/83 (24%)	15/165 (9%)	213/248 (86%)
MILNE ET AL LANCET 1971	POSTOP ABD SURG	7/17 (41%)	7/18 (39%)	21/35 (60%)
YAO ET AL LANCET 1972	SWOLLEN LEGS ONLY	2/15 (13%)	2/35 (6%)	46/50 (92%)
STRANDNESS & SUMNER ARCH SURG 1972	SUSPECTED ACUTE DVT	2/12 (17%)	3/41 (7%)	48/53 (91%)**

* Includes unspecified number of patients with positive I-125-fibrinogen leg scans without phlebograms.

** This study was evaluated per patient rather than per exam.

Evans (60) reported the usefulness of ultrasound examination as an emergency procedure in the situation of suspected massive pulmonary embolism. In 11 patients who collapsed and had the clinical diagnosis of probable massive pulmonary embolism made, ultrasound examination demonstrated the presence of peripheral venous occlusions in 7. In all 7 massive embolism was subsequently confirmed. In 4 patients whose venous flow was normal, three died within 24 hours and at postmortem no embolism was apparent. In the fourth who survived subsequent lung scans showed no perfusion defects.

Impedance Plethysmography

The impedance plethysmography technique is based on the principle that changes in blood volume within the leg change the impedance to a small 100 microamp current applied between two circumferential electrodes on the leg. Most of the reports used the methods originally described by Wheeler (66) looking for the maximal respiratory variations in impedance. Normally the variation is at least 0.2% of the baseline impedance with maximum respiratory efforts. Johnston and associates (69) proposed a new method of inflating a small blood pressure cuff on the midthigh to 250 mm Hg allowing the impedance to change for 10 seconds and then suddenly releasing the cuff. The return to baseline impedance is then measured for the next 2 seconds; the return to baseline within 2 seconds should be at least 70% of the change induced by the cuff.

In Table 4 one of Wheeler's several articles on the subject is included where he reports a very low incidence of false negatives and no false positives with the technique. However, his analysis omits 19 patients with equivocal findings in the calf on phlebography. Several other investigators have been unable to reproduce his results using his methods. However, Johnston, *et. al.* (69) using their thigh-cuff-release method found a very low incidence of false positives and a 28% incidence of false negatives with the technique. However, in all instances in which the impedance plethysmography was normal the phlebogram was abnormal only in the calf veins. When there was major deep vein thrombophlebitis involving the iliofemoral or popliteal systems, the impedance plethysmography was abnormal in all 14 instances. Personal communication with Dr. Ken Moser in La Jolla, California, indicates that he also finds the impedance plethysmography using a thigh-cuff-release method to be very reliable in identifying major deep thrombophlebitis.

Wheeler (70) reports that in 22 patients who had the suspicion of pulmonary embolism confirmed by pulmonary angiograms or lung scans 20 (91%) of the patients had abnormal impedance plethysmograms in one or both legs.

This technique appears very promising. It appears to correctly identify the most important deep thrombophlebitis, that in the iliofemoral or popliteal system and has objective criteria upon which to decide it it is abnormal.

Table 4

REFERENCE	CRITERIA	IMPEDANCE + / PHLEBOGRAM -	IMPEDANCE - / PHLEBOGRAM +	TOTAL AGREEMENT / TOTAL COMPARISONS
WHEELER ET AL SURGERY 1971	RESPIRATORY VARIATION	0/29 (0%)	2/27 (7%)	54/56 (96%)*
DMOCHOWSKI ET AL ARCH SURG 1972	RESPIRATORY VARIATION	6/13 (46%)	1/16 (6%)	22/29 (76%)**
JOHNSON ET AL AM J SURG 1974	RESPIRATORY VARIATION	1/39 (3%)	24/28 (86%)	42/67 (63%)
JOHNSON ET AL AM J SURG 1974	THIGH CUFF RELEASE	3/38 (8%)	9/32 (28%)	58/70 (83%)

* Omits 19 patients with equivocal findings in calf on phlebography.

** Omits 14 limbs with phlebographic evidence of old venous disease without recent clot.

In summary the ^{125}I fibrinogen technique is very sensitive and accurate in identifying asymptomatic developing calf vein thrombi but is unreliable in identifying well established thrombophlebitis with or without associated pulmonary embolism. It also may take 24-96 hours to become positive. Injection of the same material used for perfusion lung scans and immediately detecting delay of transit in a leg looks worth further comparison with phlebograms. In our local experience Doppler venous flow studies have end points that are too subjective to be reliable. The impedence plethysmographic technique looks promising because of accuracy when thrombi are located in the popliteal or ileofemoral system, the regions from which pulmonary emboli are more likely to occur.

ANTICOAGULATION WITH HEPARIN

Mechanism of action

A major effect of heparin is that it greatly accelerates the rate of inactivation of thrombin and Xa by the natural inhibitor, antithrombin III (72), which has been shown to be identical with heparin cofactor (72). The negatively charged heparin combines with the positively charged lysyl residues of antithrombin III and probably induces a conformational alteration of the inhibitor that renders its reactive site arginine more accessible to the active center serine of thrombin (71, 75). Heparin also accelerates the neutralization of other serine proteases (Xa, XIa, and IXa), thus inhibiting virtually every enzymatic step of the intrinsic coagulation cascade as well as inhibiting the action of thrombin on fibrinogen according to Rosenberg (71). Heparin also has an anti-thromboplastic effect but its affect on platelet aggregation is controversial in different reports (Joist and Mustard in 71). Heparin has an anti-serotonin action in animals (78) but whether this is beneficial in humans is not clear.

Heparin Variability

Commercial heparins vary considerably in chemical composition (87). In the standard USP biological assay using frozen sheep plasma ten commercial preparations varied from 140-183 units/mgm. However, beef lung heparin and porcine mucosa heparin give the same dose response curve in dogs when I.V. dose/kg is plotted against clotting time, activated PTT or lipoprotein lipase activity. However, in the presence of arterial catheters gut heparin accelerated the primary phase of platelet thrombus formation in dogs (Kwaan and Hotem in 71) and was associated with thrombosis of the arteries cannulated in man (88), whereas this did not occur with lung heparin. In blood samples from normal volunteers given I.V. heparin, gut heparin significantly shortened the time required for ADP induced platelet aggregation in Chandler's loop and was associated with a significantly longer time for lysis of the white thrombus compared to control sample. In volunteers given lung heparin platelet changes in the opposite direction were seen. Protamine sulfate given I.V. to the volunteers neutralized approximately 25 per cent more heparin units derived from gut than from lung.

Evidence that a minimal heparin effect prevents thrombi

A heparin dose producing a Lee White clotting time at least 1½ - 2X the average control prevented thrombi development or propagation in 48/50 (95%) of animals with attempted thrombus induction by the Wessler homologous serum stasis model (86, 77, 91) or a current application method (78, 79). Of the 35 thrombi that were formed 34 (97%) had clotting times less than 1½ - 2X control. In the study by Zucker, *et. al.* (91) using 2X an average normal clotting time was just as reliable as using 2X that dog's control clotting time. Also when thrombi formed the activated PTT was < 52 sec in 17 of 18 rabbits and only 1 of 20 with APTT ≥ 52 sec developed thrombi.

In a human study (77) using APTT goal of 60-100 sec to monitor continuous heparin therapy there were 5 recurrences in 162 cases of thromboembolism. The mean APTT of 49 sec in the recurrences was significantly different from the mean of 66 in those without recurrences. Of the 19 patients who had APTT < 50 sec on 3 consecutive days 4 had recurrence of thromboembolism.

Method of administration and bleeding complications

Salzman, *et. al.* (90) recently reported the only prospective randomized comparison of intermittent intravenous heparin with and without laboratory control versus continuous intravenous heparin with laboratory control. The laboratory control goal was an APTT of 50-80 sec (3 hr after last dose if on intermittent). Major bleeding was 7 times more frequent with intermittent than with continuous infusion of heparin ($p < .05$). Attempted control with APTT did not prevent bleeding with intermittent heparin. However the therapeutic goal was achieved only 44% of the time and 4 of the 6 major bleeds were associated with an APTT > 110 sec. Perhaps all this means is that attempted control gets a patient in the "therapeutic range" no more often than occurs by chance with a reasonable arbitrary dose. Other series show 4-14% incidence of major bleeding with continuous heparin, especially when there was a high incidence of clotting times > 60 min (135). Bleeding caused death in 3 of 595 patients in three series utilizing continuous heparin (77, 83, 135). In other series there was 0-10% incidence of major bleeding utilizing intermittent intravenous heparin (93, 92, 80). Bleeding was rarely massive enough to cause death (5 of 1,269 patients). Bauer's (93) large series of 937 patients had no major bleeding and only 1.5% incidence of minor bleeding. The major difference between his and other series is that even though he gave high doses of 15,000 units he gave them only 2-4 times per day at most and always omitted doses at night except for the 1st 24 hours in pulmonary embolism. All other series with higher rate of bleeding complications with intermittent intravenous heparin stick to a rigid schedule of injections of 4-6 hours around the clock.

ANTICOAGULATION WITH ORAL ANTICOAGULANTS

Vitamin K is essential for post ribosomal modification of blood clotting protein prothrombin, factors VII, IX, and X. Warfarin interferes with minor Vitamin K dependent structural modification of prothrombin responsible for calcium binding, which is essential for the physiologic conversion of prothrombin to thrombin (97, 98, 99). Deykin (100) showed that the antithrombotic effect of Coumadin was delayed by about 7 days and did not correlate with any of the factors coumadin is known to effect, such as factor 2 (prothrombin), factor 7, factor 9 or factor 10. It is interesting that patients with hereditary antithrombin III deficiency increase their antithrombin III activity to normal when on coumadin therapy (13). With this information it would appear better to initiate anticoagulation with heparin and to continue it for about a week after the onset of Coumadin therapy. If this is done one has to be careful, as shown by Moser, *et. al.* (101) to check the prothrombin time at least 5 to 6 hours after an IV heparin dose. Shortly after an IV heparin dose the prothrombin time is affected markedly and after subcutaneous heparin there is a minor continuous prolongation of the prothrombin time.

The laboratory control of oral anticoagulants is usually done with the prothrombin time. Some claim that the thrombo test is a better test because it is sensitive to depression of factor 9 to which the prothrombin time is not sensitive, and factor 9 is affected by Coumadin. However, Sevitt and Ennis (102) found no advantage of the thrombo test over the prothrombin time. Using the prothrombin time they found that if the prothrombin time was less than one and one half times normal there was no protection against thrombi. If the prothrombin time was one and a half to two times normal there was some protection against thrombi but not invariably. If the prothrombin time was greater than 2 times normal there was always protection against thrombosis. Prolongation of the prothrombin time more than this gave no advantage and led to a greater frequency of bleeding. They had 600 patients (elderly) with fractures of the hips on oral coagulants followed with prothrombin times. There was significant thrombosis in only 4 of 22 necropsies, and all 4 of the patients had prothrombin times less than twice normal most of the time. Unfortunatley, 25% of the hemorrhages occurred when the prothrombin time was less than twice normal which is the goal necessary to achieve in order to prevent thrombosis. Therefore, if you prevent thrombosis with Coumadin you will have somewhere between a 15 and a 20% instance of hemorrhage, approximately a 10% instance of major hemorrhage but will rarely have a fatal hemorrhage.

Any number of drugs or other factors interact with oral anticoagulants and alter the necessary dose. Table 5 from Dalen's monograph (3) summarize common drugs or factors.

TABLE 5

DRUGS AND FACTORS INTERACTING WITH ORAL ANTICOAGULANTS

Drugs		Factors	
Potentiators	Inhibitors	Potentiators	Inhibitors
Alcohol	Antacids	Hepatic disorders	Edema
Anabolic steroids	Antihistaminics	Diarrhea, steatorrhea	Hyperlipemia
Chloral hydrate	Barbiturates	Malnutrition: low protein, decreased vitamin C, cystine	Diabetes mellitus
Chloramphenicol	Corticosteroids		
Clofibrate	Ethchlorvynol		
Dilantin	Glutethimide (Doriden®)	Fever	
Enzymes: bromelain, papain	Griseofulvin	Congestive heart failure	
Glucagon	Vitamin K, dietary (fish, fish oils, broad leaf vegetables)	Visceral carcinoma, especially pancreatic	
Hepatotoxins: carbon tetrachloride	Placidyl	Prolonged hot weather	
Mefenamic acid	Haloperidol (Haldol®)	Radioactive compounds, x-radiation	
Methylthiouracil	Mepbromate		
Narcotics, prolonged use	Mineral Oil		
Oxyphenbutazone			
Phenylbutazone			
Phenyramidol			
Quinine			
Quinidine			
Salicylate (more than 1 gm daily)			
Sulfonamides			
Thyroid hormones			

Recurrence of Pulmonary Embolism in Patients Treated with Anticoagulants

It is difficult to come up with a representative figure for the incidence of recurrence of pulmonary embolism during or after anticoagulation treatment for thrombophlebitis or pulmonary embolism. Almost all series are based on clinical diagnoses. Recent series base the original diagnosis on lung scans or angiograms but recurrence are usually clinical diagnoses. Methods, doses, and duration of heparin differ. Therapeutic goal and duration of coumadin differ or are not stated. Aggeler and Kismin (136) reviewed the literature from 1945 to 1967 and found usually less than 5% occurrence of pulmonary embolism during anticoagulation treatment for either thrombophlebitis or pulmonary embolism. See Table 6. Byrne's (137) high incidence of fatal pulmonary embolism (18.6%) in his 979 cases of thrombophlebitis was associated largely with concomitant cardiac disease. The mortality rate in patients treated with anticoagulants was 32% in those with heart disease and 4% in those without.

Corrigan, *et. al.* (45) utilized both phlebography and lung scans in 102 patients suspected of having pulmonary embolism. Only patients with thrombi evident on phlebography were anticoagulated. Heparin initiation was followed by coumadin for 12 weeks. If the residual thrombi were below the knee (minor DVT) there was no recurrence of pulmonary embolism. Pulmonary embolism recurred despite anticoagulation in 5 of 32 patients who had residual thrombi above the knee (major DVT) on phlebography.

		PHLEBOGRAPHY		
	PATIENTS	NORMAL	MINOR DVT	MAJOR DVT
LUNG SCAN				
NORMAL	45	30 (67%)	9	6
LOW PROBABILITY	24	10 (43%)	6	8
HIGH PROBABILITY	33	4 (13%)	11	18
ANTICOAGULATION		NONE	HEPARIN →	COUMADIN
RECURRENCE OF PULMONARY EMBOLISM		NONE	NONE	5

Corrigan, *et. al.*, Brit J Surg 1974

A similar study needs to be done in thrombophlebitis without initial pulmonary embolism.

TABLE 6

Occurrence, Recurrence, or Progression of Venous Thrombosis; Recurrence of Pulmonary Embolism; and Incidence of Hemorrhagic Complications in Patients with Thromboembolism Treated with Anticoagulant Drugs

Author	Year	No. Patients	Type of Patients	Type of anticoagulant			Venous Thrombosis, %	Pulmonary Embolism, %		Thromboembolism,[a] %	Hemorrhagic Complications, %			
				Heparin	Oral	Oral and Heparin		Total	Fatal		Mild	Moderate or Severe	Fatal	Total
Patients Treated for Venous Thrombosis														
Barker *et al.*[12]	1945	138	Surgical		X		1.4	0	0	1.4	3.6	0.7	0	4.3
Allen *et al.*[5]	1947	352	Surgical		X[b]				0	1.4	3.4	1.8	0.1	5.2[c]
Cosgriff *et al.*[30]	1948	96	Mixed			X	7.3	3.1	0	10.4				
Coon *et al.*[31]	1958	359	Mixed		X[d]	X[e]	1.7	2.5	0.8	4.2	12.4	2.8	0	15.2[c]
Byrne [27]	1960	118	Mixed	X	X	X		>18.6	18.6	>18.6				
Patients Treated for Pulmonary Embolism														
Barker *et al.*[12]	1945	180	Mixed		X		0	0	0	0	2.8	1.1	0	3.9
Allen *et al.*[5]	1947	44	Medical		X		0	2.3	0	2.3	0.66	1.0	0	1.66
Allen *et al.*[5]	1947	329	Surgical			X			0	0.9	3.4	1.8	0.1	5.2[c]
Cosgriff *et al.*[30]	1948	107	Mixed			X	2.8	2.8	0	5.6				
Ochsner *et al.*[125]	1951	60	Surgical			X		>11.7	11.7	>11.7		3.7	0	>3.7
Coon *et al.*[34]	1958	152	Mixed		X[d]	X[e]	0	7.9	2.6	7.9	12.4	2.8	0	15.2[c]
Barritt and Jordan [13]	1960	54	Mixed			X		1.9	0	5.6			1.9	7.5
Schatz and Lang [154]	1966	443	Mixed		X			1.3	0.9	>1.3		2.2	0.7	
Patients Treated for Thromboembolism														
Bruzelius [21]	1945	113	Surgical		X		2.6	4.4	0	7.1	5.3	7.1	0.9	12.4
Marks *et al.*[100]	1954	1135	Mixed			X	0	0	0	0				
Crane [40]	1957	391	Surgical	X			6.1	5.1	1.0	11.2			0.5	3.3
Fuller *et al.*[62]	1960	394	Mixed	X		X		10.2	2.3	>10.2	4.8	0.2	0	5.0
Donaldson *et al.*[52]	1961	473	Mixed	X	X	X			1.1	24.9				
Bauer [14]	1964	937	Surgical	X			2.6[f]	0.9[f]	0.7[f]	3.5[f]	1.5			1.5
Aaro *et al.*[1]	1966	47	Obstetric	X		X	0	0	0	0				
Husni *et al.*[87]	1967	15	Obstetric			X	0	6.6	0	6.6				

[a] Some authors gave results only when anticoagulant therapy was adequate.
[b] "In most instances."
[c] Statistics regarding hemorrhagic complications for venous thrombosis and pulmonary embolism were combined.
[d] 35% of patients.
[e] 65% of patients.
[f] Some occurred after cessation of treatment.

PROPHYLAXIS FOR POST-OPERATIVE VENOUS THROMBOPHLEBITIS

Wessler (111) has summarized the rationale for the use of low dose heparin in postoperative states.

> "Circumstantial evidence strongly suggests that during and after operation a state of hypercoagulability, not previously present, is initiated, but that it remains non thrombotic so long as the rate of factor Xa neutralization exceeds its rate of generation. Because this neutralization reaction rate depends on the inhibitor concentration, the latter becomes rate-limiting. Thus, as the inhibitor becomes increasingly utilized, a point will be reached at which some factor Xa will escape its inhibitor, combine with lipid, calcium ion, and factor V, and rapidly generate large quantities of thrombin that once formed cannot be prevented by low doses of heparin from converting fibrinogen to fibrin. It is, in essence, the presence of small amounts of plasma heparin which augments severalfold the rate of normal factor Xa neutralization before the development of hypercoagulability that may prevent venous thrombosis in patients undergoing operation."

One μg of antithrombin III (Heparin cofactor) by neutralizing 32 units of factor Xa indirectly prevents the generation of 1600 NIH amounts of thrombin. To neutralize this amount of thrombin 1000 μg of the inhibitor are required. Thus more heparin is required to block the thrombin fibrinogen reaction via the inhibitor than is required to neutralize factor Xa (111).

Kakkar early this year (112) reviewed the subject of deep vein thrombosis and its prevention. I have reproduced two of his tables and in Table 7 shows that in all instances reported low dose heparin significantly reduces the instance of postoperative deep venous thrombosis detected by the ^{125}I fibrinogen leg scan technique. In Kakkar's studies ^{125}I fibrinogen was used in over 2000 patients without a single case of clinical serum hepatitis. The huge randomized international multicenter trial organized by Kakkar (118) has now shown that the incidence of fatal postoperative death is significantly reduced by low doses of heparin (5000 u 2 hr pre-op and q 8 hr post-op for 7 days).

TABLE 7

Prophylaxis: Effect of Low Doses of Heparin on the Incidence of Postoperative Deep Venous Thrombosis (DVT) as Assessed in Controlled Clinical Trials

Study	Control group		Treated group		Statistical significance
	No. studied	DVT	No. studied	DVT	
Kakkar, Field and others (1971)[55]	27	7 (26%)	26	1 (4%)	$0.05 > P > 0.25$
Williams (1971)[56]	29	12 (41%)	27	4 (15%)	$0.02 > P > 0.01$
Gordon-Smith and others (1972)*[57]	50	21 (42%)	52	7 (13.5%)	$P < 0.003$
			48	4 (8.3%)	$P < 0.001$
Kakkar, Corrigan and others (1972)†[58]	39	17 (42%)	39	3 (8%)	$P < 0.001$
			133	13 (9.7%)	
			50	20 (40%)	
Nicolaides, Dupont and others (1972)[59]	122	29 (24%)	122	1 (0.8%)	$P < 0.000003$
Gallus and others (1973)[61]	118	19 (16%)	108	2 (2%)	$P < 0.003$

*A trial comparing two different regimens.
†Double-blind randomly allocated trial.

Incidence of Deep Vein Thrombosis (DVT) with Different Regimens of Low-dose Heparin in Patients Undergoing Total Hip Replacement

Study	Control group		Heparin group		
	No. studied	DVT	Regimen	No. studied	DVT
Kakkar et al. (1972)[58]	18	7 (38.8%)	b.i.d. $P > 0.05$	15	4 (26.6%)
Kakkar et al. (1974)	35	12 (34%)	t.i.d. $P < 0.01$	37	4 (10.8%)
Nicolaides et al. (1974)[65]	27	11 (40%)	t.i.d. $P = 0.00016$	25	1 (4%)
Dechavanne et al. (1974)*	20	8 (40%)	t.i.d. $P < 0.025$	20	1 (5%)

*Dechavanne M, Ville D, Viala J. J., Kher A, Faivre J., et al: Controlled trial of platelet anti-aggregating agents and subcutaneous heparin in prevention of postoperative deep vein thrombosis. Unpublished observations.

	Control	Heparin	P value
Number of Patients	2076	2045	
Deaths from all causes	100	80	
Autopsies performed	72%	66%	
Deaths due to Pulmonary Emboli	16	2	< 0.005
Pulmonary emboli contributing to death	6	3	
^{125}I fibrinogen detected DVT	24.6%	7.7%	< .005
DVT at necropsy	24	6	< .005
Rx for Clinical DVT Confirmed by ^{125}I fib or phlebography	122	23	< .005
Rx for clinically suspected P.E.	24	8	< .005
Death from hemorrhage	5	4	
Excessive blood loss during surgery	126	182	
Wound hematomas	117	158	< .01

A careful objective analysis of operative and postoperative bleeding in 1,475 of the patients showed no significant difference in the blood transfusion requirements or fall in the postoperative hemoglobin levels for a wide variety of operations. It seems clearly established that low dose heparin in a standard dose without laboratory control is both effective and safe in preventing postoperative venous thromboembolism.

Whether it is reasonable to give heparin to all postoperative patients is a judgement matter. It seems rational to use it at least in those operative situations in which an unusually high incidence of postoperative ^{125}I detected DVT has been identified (119).

Condition	Per Cent Positive ^{125}I fibrinogen
Recent pulmonary embolism	100%
Previous history of PE or DVT	68%
Varicose veins	56%
Obesity	46%
Age over 60	46%
Malignancy	41%

It should be pointed out that all of the studies in which low dose heparin is effective prophylaxis in hip surgery used heparin tid and are situations in which the fractured hip is replaced with the patient ambulating the first postoperative day (112, 119).

Kakkar (112) extensively reviewed the literature showing that other means of prophylaxis for venous thromboembolism are:

Effective but difficult or risky

Electrical stimulation of the calf during operation
Pneumatic cuffs that rhythmically squeeze the calf muscle
Passive dorsifexion of the foot with motor driven pedals
Oral anticoagulation started before surgery

Controversial

Dextran

Ineffective

Extensive measures to eliminate stasis including early ambulation
Aspirin and dipyridamole
Phenformin and Ethyloestranol
Oral anticoagulants started after surgery
Elastic stockings are also ineffective (117)

THROMBOLYTIC THERAPY IN DEEP VENOUS THROMBOPHLEBITIS

When phlebographically confirmed deep venous thrombophlebitis is treated with streptokinase and evaluated by repeat phlebograms about a week later there is complete or good lysis of the thrombus in 57% of 221 reported cases (120, 121, 122, 123, 124, 125, 126).

	N	Phlebographic clearing complete or good	Bleeding		Pulmonary Emboli	
			Minor	Major	Total	Fatal
Robertson '68	8	5	2	2		
Kakkar '69	10	6	3	1		
Mavor '73	40	34	10			
Tsapogas '74	19	10		3		
Astedt '74	33	17		3	2	
Tibbutt '74	18	15	15	1	1	1
Duchert '75	93	39	"common"		9	2
	221	126 (57%)			12 (5%)	3 (1.4%)

Minor bleeding was common. Major bleeding occurred in 10 of 128 instances in which it was quantitated, but was never the cause of death. Pulmonary embolism occurred in 5% and was the cause of death in 1.4%.

There are 3 randomized prospective studies utilizing repeat phlebograms at the completion of treatment in which the degree of lysis with streptokinase was compared to heparin or arvin.

	Complete or good phlebographic clearing		
	Streptokinase	Heparin	Arvin
Kakkar '69	6/10 (60%)	2/10 (20%)	1/10 (10%)
Tsapogas '73	10/19 (53%)	1/15 (7%)	
Tibbutt '75	15/18 (83%)		2/16 (13%)

Kakkar (31) using follow-up phlebograms 6-12 months later found preserved valves only if there had been complete lysis with the initial treatment and that complete lysis rarely occurred unless streptokinase was used within 72 hours of the onset of symptoms. Others (126, 122) frequently found complete or good lysis even when symptoms had been present more than 1-2 weeks, however the incidence of valve preservation was not commented upon. Tibbutt, *et. al.* (126) found in his 18 patients treated with streptokinase that despite 4 with complete lysis and 11 with substantial lysis, shown by phlebography at 96 hours, only 1 patient had a normal limb clinically at 3 month follow-up. This patient had thrombi confined to calf veins initially. None of the patients had oral anticoagulants during the three months following streptokinase.

THROMBECTOMY FOR ILEOFEMORAL DEEP VENOUS THROMBOPHLEBITIS

Thrombosis that extends into the iliofemoral system is more likely to lead to pulmonary embolism, is more likely to lead to severe post-thrombophlebitis symptoms in the leg, and is very unlikely to lyse spontaneously with anticoagulation therapy alone. Thrombectomy is an obvious direct approach to the problem. Reported series are variable as to the benefits, however. Kistner, *et. al.* (33) performed iliofemoral thrombectomy on 5 patients who had subsequent post-op venograms. If the thrombus was non-adherent at the time of surgery the follow-up phlebogram was patent. However, if the thrombus had been adherent at the time of surgery the post-op phlebogram showed that the vein was again occluded. Even the most avid proponents of theprocedure such as Mavor (130) admit a 60% instance of rethrombosis largely due to inadequate clearance of the thrombi at the time of surgery. Mahorner (132) reviewed the experience in various hospitals in New Orleans and found only 20 of 106 patients who had had thrombectomy who had persistent edema necessitating modification of activity. Heller, (127) reported that 10 of 33 patients who had thrombectomy had venous insufficiency to some degree following the operation. Only six patients had severe venous insufficiency. Available data suggests that a severe acute iliofemoral thrombosis of recent onset would likely benefit from thrombectomy if it is non-adherent to the vein wall.

Phlegmasia cerulea dolens has such an ominous prognosis (see natural history of DVT) that it seems reasonable to follow the recommendations of Fogarty, *et. al.* (134) even though it is based on favorable results with only 6 cases. He recommends proximal ligation of the highest venous involvement followed by thrombectomy assisted by a balloon tipped catheter and "milking" techniques. A relieving fasciotomy is indicated if one is unable to perform a thrombectomy.

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