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DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

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INTRODUCTION

The complications of acute venous thromboembolism (VTE), including deep venous thrombosis (DVT), pulmonary embolism (PE), and post-thrombotic syndrome, are important not only as the most common preventable causes of hospital death, but also as a source of substantial long-term morbidity.

Components of the pathophysiologic triad initially described by Rudolf Virchow remain applicable today. It now appears that many venous thrombi arise from the convergence of several risk factors against a background of an imbalance between coagulation and fibrinolysis. Similar factors defining the balance between recanalization of the venous lumen and recurrent thrombotic events may also be important determinants of long-term outcome after an episode of acute venous thrombosis.

EPIDEMIOLOGY

Incidence

The incidence of recurrent, fatal, and nonfatal VTE has been estimated to exceed 900,000 cases annually in the United States alone. This study also demonstrated higher age-adjusted rates in men than in women (134 versus 115 per 100,000, respectively).The total new VTE cases in the United States amounts to greater than 275,000. Estimates of VTE across the European Union were 684,019 cases of DVT, 434,723 cases of PE, and 543,454 VTE-related fatalities.

Populations Affected

Of the estimated 38 million patients discharged in 2003, 31% were considered to be at risk for VTE secondary to either major surgery or a medical illness. The incidence of VTE varies with the population studied, use of thromboprophylaxis, the intensity of screening, and the accuracy of the diagnostic test

Recurrence

Although VTE can be a devastating acute disease process, it may develop chronically, with 30% of patients experiencing a recurrence in a 10-year time span. Recurrences are more likely to be the same event type as the incident event type; that is to say, those in whom PE initially developed are more likely to have another episode of PE rather than DVT. In addition, the 7-day case fatality rate is significantly higher for recurrent PE than for recurrent DVT.

Mortality

The severity of PE has been shown in 30-year data from autopsy studies, which demonstrated a 26% incidence of PE in hospitalized patients, 9% of which were fatal. This translated into a 1% incidence of PE and a 0.36% incidence of death from PE in all hospitalized patients.

Risk Factors

There are numerous risk factors for venous thrombo-embolism (Table 1)

Surgery

Surgery constitutes a spectrum of risk that is influenced by patient age, coexistent thrombotic risk factors, type of procedure, extent of surgical

Table 1: Risk factors for venous thrombo-embolism	
Risk Factor	**Comments**
Age	Incidence of first VTE rises exponentially with age
Obesity	2-3 fold VTE risk if obese (BMI >30) May reflect immobility and coagulation activation
Varicose veins	1.5-2.5 fold risk after major general / orthopaedic surgery Low risk after varicose vein surgery
Family history of VTE	A history of at least one first degree relative having had a VTE at age <50 years or more than one first degree relative with VTE history regardless of age is an indicator of increased risk of first VTE
Thrombophilia	Low coagulation inhibitors (anti-thrombin, protein C or S) Activated protein C resistance (eg. Factor V Leiden) High coagulation factors Anti-phospholipid antibodies High homocysteine Elevated lipoprotein

trauma, length of the procedure, and duration of postoperative immobilization. The type of surgical procedure is particularly important. The overall incidence of DVT is approximately 19% in general surgical patients, 24% in elective neurosurgical patients, and 48%, 51%, and 61% in those undergoing surgery for hip fracture, hip arthroplasty, and knee arthroplasty, respectively. On the basis of these data, patients can be classified as being at low, moderate, or high risk for thromboembolic complications, as shown in table 2.

Other risk factors include: malignancy , hormonal therapy, acute illness , trauma ,immobility , pregnancy and venous catheters .

Table 2: Risk for Postoperative Deep Venous Thrombosis	
Category	**Characteristics**
Low	Age <40 yr, no other risk factors, uncomplicated abdominal/thoracic surgery
	Age >40 yr, no other risk factors, minor elective abdominal/thoracic surgery <30 min
Moderate	Age >40 yr, abdominal/thoracic surgery >30 min
High	History of recent thromboembolism
	Abdominal or pelvic procedure for malignancy
	Major lower extremity orthopedic procedure

From Hull RD, Raskob GE, Hirsh J: Prophylaxis of venous thromboembolism. Chest. 1986;89(Suppl):374S.

All components of Virchow's triad may be present in surgical patients—perioperative immobilization, transient changes in coagulation and fibrinolysis, and the potential for gross venous injury, as exemplified by hip arthroplasty.

PATHOPHYSIOLOGY

Virchow's Triad

As initially postulated by Virchow, three factors are of primary importance in the development of venous thrombosis: (1) abnormalities in blood flow, (2) abnormalities in blood, and (3) vascular injury. These tenets have subsequently been refined, and it currently appears that flow abnormalities determine the localization of venous thrombi, abnormalities in blood may include aberrations in both the coagulation and fibrinolytic systems, and biologic injury to the venous endothelium is potentially more important than gross trauma. It is also clear, however, that the origin of DVT is frequently multifactorial, with components of

Virchow's triad assuming variable importance in individual patients.

Activation of Coagulation

Activation of coagulation appears to be critical in the pathogenesis of DVT. The coagulation cascade functions through serial activation of zymogens in the intrinsic and TF pathways, with the ultimate generation of thrombin by the prothrombinase complex. Antithrombin and the thrombomodulin–protein C systems are the primary inhibitors of coagulation, whereas the fibrinolytic system serves to further limit fibrin deposition. Although the hemostatic system is continuously active, thrombus formation is ordinarily confined to sites of local injury by a precise balance between activators and inhibitors of coagulation and fibrinolysis. A prothrombotic state may result either from imbalances in the regulatory and inhibitory systems or from activation exceeding antithrombotic capacity.

NATURAL HISTORY

Thrombus Evolution as Determined by Noninvasive Studies

The results of noninvasive studies were found to normalize in 67% of patients by 3 months and in 92% by 9 months. Venous duplex ultrasonography, which permits individual venous segments to be observed over time, has further documented that recanalization does occur in most patients after an episode of acute DVT. In 21 patients monitored prospectively with duplex scanning, recanalization was evident in 44% of patients at 7 days and in 100% of patients by 90 days after the acute event. The percentage of initially involved segments that remained occluded decreased to a mean of 44% by 30 days and to 14% by 90 days

COMPLICATIONS

Pulmonary Embolism

PE, with its attendant mortality, is the most devastating complication of acute DVT. When associated with acute DVT, the majority of PE episodes may be clinically silent. In patients with symptomatic DVT, 50% to 80% have evidence of asymptomatic PE. Conversely, in those with symptomatic PE, asymptomatic DVT can be demonstrated in about 80% of cases. Approximately 90% of thromboemboli arise from the lower extremity veins, and inadequate treatment of proximal lower extremity venous thrombosis is associated with a 20% to 50% risk for clinically significant recurrent thromboembolism. Symptomatic PE may also complicate 7% to 17% of proximal upper extremity thrombi. The risk of death in patients with symptomatic PE is 18-fold higher than in patients with DVT alone. For almost 25% of PE patients, the initial manifestation is sudden death.

Pulmonary Hypertension

The development of chronic thromboembolic pulmonary hypertension (CTEPH) after acute PE has historically been thought to have been a rare occurrence that affected only 0.1% to 0.5% of individuals who survived the initial embolic event.[1] However, recent data have suggested that CTEPH occurs more often than previously suspected, with the disorder developing in 3.8% of individuals after acute PE. The most common symptom in patients with CTEPH is progressive exertional dyspnea, with worsening right ventricular failure, edema, chest pain, lightheadedness, and syncope developing as the disease progresses.

Post-thrombotic Syndrome

Though less dramatic than PE, development of post-thrombotic syndrome is the most important late complication of acute DVT, and it is responsible for a greater degree of chronic socioeconomic morbidity. As many as 29% to 79% of patients may have some degree of long-term

manifestations such as pain, edema, heaviness, or hyperpigmentation, but severe manifestations occur in only 7% to 23%, while ulceration occurs in 4% to 6% of patients. The severe manifestations of post-thrombotic syndrome are a consequence of ambulatory venous hypertension, which is determined by a combination of factors, including valvular reflux, persistent venous obstruction, and the anatomic distribution of these abnormalities

MORTALITY

DVT is associated with a high frequency of co-morbid medical conditions, and the rate of early death after lower extremity thrombosis is substantial during the first year after acute DVT and, at 3- and 5-year follow-up, demonstrated mortality rates of 30% and 39%, respectively. The mortality rate after acute DVT exceeds that in an age-matched population, and most deaths are related to malignancy or cardiovascular disease. Higher short-term mortality rates have been seen in patients with upper extremity DVT; these patients tend to be more ill and have an increased prevalence of metastatic malignancy. Six-month mortality may be as high as 48% in patients with upper extremity DVT versus 13% in those with lower extremity thrombosis.

CLINICAL FEATURES

The clinical manifestations of DVT are variable and may range from absence of symptoms to massive pitting edema and blanching (phlegmasia alba dolens) or a painful blue leg (phlegmasia cerulea dolens). The signs and symptoms currently attributed to acute DVT may include pain, edema, erythema, tenderness, fever, prominent superficial veins, pain with passive dorsiflexion of the foot (Homans' sign), and peripheral cyanosis. More often, the initial complaints are vague and can be attributed to a host of other causes. Up to 70% of patients with signs and symptoms compatible with DVT will not have the disease identified, and up to 50% of patients with acute DVT may lack any specific signs or symptoms.

In summary, basing the diagnosis of DVT on signs, symptoms, and risk factors remains notoriously inaccurate. With continued technologic advances in medicine, the skills most relevant to proper diagnosis appear to have shifted from clinical assessment to the clinician's ability to order the correct diagnostic testing.

Predictive Clinical Models

In 1997, Wells and associates developed and adopted a clinical model predicting the pretest probability of DVT based on ten predictors. Implementation of this model in symptomatic patients stratified them into high- and low-probability groups, in whom the overall prevalence of venous thromboembolism was found to be 75% and 3%, respectively. The Wells score was better at categorizing low-risk patients.

Table 3: Two Level DVT Wells score	
Clinical feature	**Points**
Active cancer (Treatment ongoing, within 6 months, or palliative)	1
Paralysis, paresis or recent plaster immobilization of lower extremities	1
Recently bedridden for 3 days or more or major surgery within 12 weeks requiring general or regional anaesthesia	1
Localised tenderness along the distribution of the deep venous system	1
Entire swollen leg	1
Calf swelling at least 3 cm larger than asymptomatic side	1
Pitting oedema confined to the symptomatic leg	1
Collateral superficial veins	1
Previously documented DVT	1
Alternative diagnosis at least as likely as DVT	-2
Clinical probability simplified score	
DVT likely	2 points or more
DVT unlikely	1 point or less

PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med. 2003;349:1227-1235.

Note: A score of 2 or higher indicates that the probability of deep venous thrombosis is high; a score of less than 2 indicates that the probability of deep venous thrombosis is low. In patients with symptoms in both legs, the more symptomatic leg is used.

In summary, we recommend the Wells clinical probability score in low-risk symptomatic patients combined with a negative D-dimer assay as adequate evaluation, and no further studies are needed. In high-risk patients, a B-mode duplex scan should be performed to further evaluate the patient.

D-Dimer

D-dimers are products of the degradation of cross-linked fibrin by plasmin. D-dimer blood levels reflect the presence of intravascular fibrin and are sensitive for the diagnosis of thromboembolism. When measured by enzyme-linked immunosorbent assay (ELISA), the reference standard, sensitivity for the diagnosis of DVT is as high as 97%. Elevated D-dimer values are also associated with disseminated intravascular coagulation, malignancy, postoperative states, preeclampsia, infection, and recent trauma. The specificity of D-dimer measurements diminishes with patient age.

Duplex Ultrasonography

Duplex ultrasonography is the diagnostic test of choice for the detection of DVT. The benefits of duplex ultrasonography over venography include a lack of radiation, portability, noninvasiveness, and relative cost-effectiveness. In addition, ultrasound has the ability to distinguish among nonvascular pathologies, such as inguinal adenopathy, Baker's cyst, abscess, and hematoma.

Diagnostic Criteria

Diagnostic criteria for DVT include an assessment of venous compressibility and intraluminal echoes using the B-scan image, venous flow characteristic using Doppler, and luminal color filling using color Doppler). Among these factors, venous incompressibility is the most widely used objective criterion for the diagnosis of DVT.

Methods of Prophylaxis

General Measures

Apart from the usual measures taken during the postoperative period such as adequate hydration and analgesia, it is important that patients start to ambulate as soon as and as much as possible. For patients who are immobile in bed, repeated active flexion-extension exercises of the ankle joints should be encouraged to enhance venous flow. The assistance

of nurses and auxiliary personnel is valuable to achieve good implementation of these actions.

Leg elevation has a dual physiologic effect: it reduces swelling and thereby improves venous return, and it reduces venous pressure by its gravitational effect.

Mechanical Prophylaxis

Elastic Compression Stockings

GCS reduce the cross-sectional area of the veins and increase the velocity of venous blood flow. This acceleration of blood flow depends on the pressure gradient applied from the ankle to the knee or thigh level. A pressure profile of 18 mm Hg at the ankle and 8 mm Hg at the upper portion of the thigh increases venous flow velocity up to 75%.In addition, GCS prevent intraoperative distention of the calf veins in patients receiving general anesthesia. It is important to differentiate GCS used for primary prophylaxis of DVT from therapeutic graduated stockings, which apply a pressure of 30 to 40 mm Hg at the calf and are used for the secondary prevention of PTS after DVT is diagnosed or as therapy once this syndrome arises.

Intermittent Pneumatic Compression

IPC of the lower limbs is the most extensively studied of the mechanical modalities of thrombosis prophylaxis and is considered the most effective of them. Basically, most IPC devices consist of pneumatic boots or garments that are wrapped around the legs. The boot or sleeve is connected to an electrical compressor that intermittently insufflates air to a preselected pressure. Hemodynamic studies have shown that uniform IPC might trap blood in the distal veins of the leg whereas intermittent sequential compression would not, thereby enhancing venous return.

Foot Compression Devices

Foot compression devices, also known as foot pumps, consist of inelastic slippers or boots with an air bladder in the area of the sole of the foot. This air chamber is rapidly inflated to a pressure up to 200 mm Hg over a 3-second period every 20 seconds. This plantar compression increases venous outflow and reduces stasis in the legs and therefore has been investigated for the prevention of DVT

Pharmacologic Methods of Prophylaxis

As mentioned earlier, hypercoagulability is a key risk factor for the development of VTE. Therefore, several pharmacologic agents with different anticoagulant actions have been evaluated for prevention of VTE during the past 40 years. These methods include subcutaneous unfractionated heparin (UFH) and LMWH, dextrans, and oral VKAs. More recently, promising new molecules that inhibit some specific components of the clotting cascade have been developed and are pending approval by health regulatory agencies.

Unfractionated Heparin

Low-dose (5000 units given 2 hours before surgery followed by 10,000 to 15,000 U/24 hr) subcutaneous UFH was the first pharmacologic agent to be widely investigated for the primary prevention of VTE in patients undergoing surgery. In a landmark multicenter international study, Kakkar and colleagues demonstrated that low-dose heparin significantly reduced the risk for both DVT and PE in general surgical patients, including fatal PE.

Low-Molecular-Weight Heparin

Although UFH represented the standard for pharmacologic prevention of VTE for more than a decade, in the 1980s a new group of heparin

fractions, generically known as LMWHs with an average molecular weight between 4000 and 8000 daltons, were developed and accepted for clinical use. These fractions have greater activity against factor Xa than against factor II, whereas these actions are similar with UFH. LMWHs have practical advantages in clinical use, including the possibility of a single daily injection without the need for laboratory monitoring, which makes them ideal for outpatient prophylaxis

Oral Vitamin K Antagonists

Coumarin derivatives such as warfarin act as VKAs. Synthesis of the active clotting factors II, VII, IX, and X requires carboxylation of glutamic acid residues, which is dependent on the presence of vitamin K. The amount of these carboxylated active clotting factors is reduced by the action of VKAs to produce a state of anticoagulation. For the past 50 years several VKAs have been used for the prevention and management of VTE. The most commonly used VKA in North America is warfarin. This product can be administered orally, either at fixed low doses that do not need laboratory monitoring or at adjusted doses with the goal of achieving a therapeutic level of anticoagulation by using the international normalized ratio (INR). A prolongation of the prothrombin time corresponding to an INR between 2.0 and 3.0 is considered adequate for VTE prophylaxis in high-risk patients

Table 4: Recommended Prophylaxis in Surgical Patients According to the Estimated Level of Risk

Risk Level	Prophylaxis Regimen
Low risk	Early and aggressive mobilization
Moderate risk	LMWH at low doses (<3400 U daily)
	Unfractionated heparin (5000 U twice daily)
	Elastic stockings (18-23 mm Hg) or IPC, especially in patients in whom anticoagulants are contraindicated
High risk	High-dose LMWH (>3400 U daily)
	Unfractionated heparin (5000 U every 8 hours)
	Elastic stockings (18-23 mm Hg) or IPC, especially in patients in whom anticoagulants are contraindicated
	Combination of high-dose heparin or LMWH with stockings or IPC
Highest risk	High-dose LMWH (>3400 U daily)
	Unfractionated heparin (5000 U every 8 hours)
	Elastic stockings (18-23 mm Hg at the ankle) or IPC, especially in patients in whom anticoagulants are contraindicated
	Combination of high-dose heparin or LMWH with stockings or IPC
	Warfarin for patients undergoing hip or knee arthroplasty (target INR of 2-3)
	Fondaparinux (2.5 mg daily)
	In patients undergoing major orthopedic or abdominal cancer surgery, consider extending prophylaxis with LMWH for 28-35 days

IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin.

TREATMENT

The objectives in treatment of acute DVT are to prevent thrombus extension, early recurrence, and death from PE. In addition, treatment should attempt to prevent late recurrences and long-term consequences such as the development of PTS and chronic pulmonary hypertension. Since the landmark paper by Barrit and Jordan approximately 60 years ago, anticoagulation remains the mainstay of VTE treatment. In most cases, the initial treatment of DVT and PE is similar. Indeed, as many as 20% to 25% of patients with symptomatic DVT have asymptomatic PE when routine imaging techniques are performed.

Initial Treatment of Deep Venous Thrombosis

Immobilization and Leg Elevation

Elevation of the legs and initial bed rest may provide some relief of pain and tenderness in patients with an acutely swollen leg because of DVT. However, this traditional approach has been challenged by recent studies showing that bed rest does not reduce the incidence of PE detected by routine lung scanning. Furthermore, pain and swelling improve more quickly in patients with early ambulation and leg compression than in those confined to bed rest.

Anticoagulation

Patients with VTE should be treated with anticoagulants as soon as the diagnosis is confirmed by objective imaging techniques. However, if clinical suspicion is very high, treatment should be initiated until the diagnosis can be confirmed. There are two options for the initial anticoagulant treatment of VTE: (1) intravenous or subcutaneous UFH and (2) subcutaneous LMWHs, whose main characteristics have already been described. The current recommended approach is to start heparin or LMWH and VKAs together at the time of diagnosis and to overlap them for 5 to 10 days, with UFH or LMWH discontinued when the prothrombin time, expressed as the INR, is within the target (2.0 to 3.0) for 2 consecutive days.

Unfractionated Heparin

Intravenous heparin given for 5 to 10 days and followed by oral anticoagulation is very effective in the treatment of DVT. However, this treatment modality requires hospital admission and repeated monitoring for adjustment of the heparin dose to achieve an activated partial thromboplastin time (aPTT) within a therapeutic range of 1.5 to 2.5 times control within 24 hours.

Low-Molecular-Weight Heparins

These heparin fractions have better bioavailability, more consistent response, and more predictable pharmacokinetics and pharmacodynamics than UFH when given subcutaneously. For these reasons, LMWHs do not require routine monitoring, other than a platelet count, when used for the treatment of VTE. Possible exceptions are patients with extreme weight or renal insufficiency. In these cases, determination of anti-Xa activity is recommended. In addition, LMWH's favorable pharmacodynamic properties make them suitable for once-daily administration.

Long-term Treatment of Deep Venous Thrombosis

After the initial therapy with LMWH or UFH, extended anticoagulation is required to prevent thrombus extension and recurrent VTE. The most commonly used agents for long-term anticoagulation or secondary prevention are VKAs such as warfarin or acenocoumarol. Because of the delayed onset of their anticoagulant effect, VKAs should be initiated at the

same time as heparin or LMWH and used simultaneously for at least 5 days. A therapeutic INR level of between 2.0 and 3.0 should be achieved 24 to 48 hours before heparin is discontinued. The usual starting dose of warfarin is 5 to 10 mg. In outpatients, 10 mg is more effective than 5 mg in achieving a therapeutic INR by the fifth day of treatment.

Although warfarin is the preferred approach for long-term anticoagulation in most patients, aPTT-adjusted doses of UFH or therapeutic weight-adjusted LMWH is indicated for some patients in whom VKAs are contraindicated, such as pregnant patients or those with cancer, for whom LMWH is more effective and safer than warfarin.

Duration of Secondary Prevention

The optimal duration of anticoagulant treatment of VTE remains controversial. The advantages of prolonging the duration of therapy should be weighed against the risk for bleeding complications.

According to the Seventh ACCP consensus statement, the recommended duration of anticoagulation for patients with a first episode of DVT secondary to a transient risk factor such as surgery or immobilization is 3 months.[] For patients with a first episode of idiopathic DVT, the recommended duration is between 6 and 12 months. In patients with cancer, LMWH is preferred over VKA for the first 3 to 6 months.

For patients with a first episode of DVT and documented antiphospholipid antibodies or who have two or more thrombophilic conditions, the recommended duration of VKA treatment is at least 12 months. Finally, for patients with two or more episodes of previous objectively documented DVT, indefinite treatment is suggested.

Elastic Stockings for the Prevention of Postphlebitic Syndrome

This syndrome may be manifested clinically as leg swelling or tiredness, leg pain, pigmentation, eczema, or frank ulceration of the skin. Brandjes and coworkers first reported in 1997 that the use of 30 to 40 mm Hg elastic thigh-length stockings for at least 2 years in those with symptomatic proximal DVT reduced the incidence of PTS by 50%.Prandoni and colleagues, who also found a 50% reduction in PTS sequelae by using, in this case, calf-length 30 to 40 mm Hg hose for 2 years in those with proximal DVT. They theorized that the calf hose were important because they improved the efficiency of the calf muscle pump. Partsch has demonstrated that ambulation and leg compression with bandages and later appropriate-strength hose improved pain and swelling in comparison to bed rest. He also postulated that this tactic may inhibit thrombus growth and decrease the incidence of PTS.

Initial Treatment of Pulmonary Embolism

Treatment of DVT and PE is similar because both conditions are clinical manifestations of the same disease: VTE. However, the mortality rate in patients with PE within 28 days of diagnosis is 17%, as opposed to 8% in patients with DVT. Moreover, patients with symptomatic PE have a fourfold risk of dying from recurrent VTE than do patients with DVT. Although outpatient treatment with subcutaneous LMWH has become common for the management of DVT, some questions remain regarding the efficacy and safety of outpatient treatment of PE. Current data indicate that outpatient treatment of PE is feasible, effective, and safe in selected patients.

For the initial treatment of acute nonmassive PE, subcutaneous LMWH and intravenous UFH are

recommended. As for treatment of DVT, VKA should start the first day of treatment and LMWH or UFH should be discontinued after 5 to 10 days when the target INR has been reached and remains stable.

Vena Cava Filters

The purpose of vena cava interruption procedures, including filters, is to prevent PE. These interventions are not a treatment or preventive measure for DVT. Vena cava filters are sometimes placed after massive PE when it is thought that further PE may be fatal or the patient has contraindications to fibrinolytic therapy. Inferior vena cava interruption procedures are often used as alternatives to anticoagulant therapy for the prevention of PE.

UPPER LIMB DVT

PRIMARY SUBCLAVIAN-AXILLARY VEIN THROMBOSIS

Epidemiology

Primary upper extremity deep venous thrombosis (DVT) is a rare disorder that occurs in 2 per 100,000 individuals per year. It is estimated that upper extremity DVT accounts for approximately 2% to 4% of all cases of DVT. Upper extremity DVT can be a relatively common occurrence in a hospital, with an estimated prevalence of 2 cases per 1000 hospital admissions.

Etiology

Venous thoracic outlet syndrome (TOS) is a condition that ultimately results in thrombosis or severe narrowing of the subclavian-axillary vein secondary to chronic extrinsic mechanical compression. This clinical syndrome has been referred to as “effort thrombosis” because of its association with young, otherwise healthy individuals who engage in activities requiring repetitive arm and shoulder motion. The venous pathology is a direct result of repetitive injury to the subclavian vein at the level of the costo-clavicular space, the most medial aspect of the thoracic outlet). The key anatomic structures contributing to compression of the subclavian vein and recurrent venous trauma are the first rib, the clavicle with its associated subclavius muscle and fibrous costocoracoid ligament, and the anterior scalene muscle and tubercle. A cycle of alternating post-traumatic inflammation and quiescence leads to perivenous fibrosis, endothelial injury, stasis of blood flow, and thrombosis. In many cases, compression of the subclavian-axillary vein may occur at the costoclavicular space without progression to thrombosis. This point is underscored by venographic studies evaluating the contralateral extremity in patients with confirmed subclavian-axillary vein thrombosis; although significant compression with provocative measures is visualized in 56% to 80% of contralateral limbs, the incidence of bilateral thrombosis is markedly less at 2% to 15%.

Clinical Findings

Venous TOS usually develops in young, healthy patients with few, if any, co-morbid conditions. The mean age at diagnosis is 32 years, with the majority of patients affected between the second and fourth decades. Traditionally, men have been reported to be affected more often than women; however, the largest series published to date (312 affected extremities) reported an equal gender ratio.[1] Individuals who perform strenuous or sustained upper extremity activities, whether athletic or occupational, are particularly prone to the development of subclavian-axillary vein thrombosis. The dominant arm is involved in the clear majority of cases. Upper extremity edema is the hallmark characteristic associated with subclavian-axillary vein thrombosis. The edema is often, though not

always, accompanied by pain and cyanosis of the affected extremity. Dilated superficial veins over the shoulder, neck, and anterior chest wall can often be visualized as collateral veins that accommodate to the increased venous hypertension (a pattern often referred to as “first rib bypass venous collaterals”).

The two most severe potential complications of subclavian-axillary vein thrombosis are pulmonary embolism and upper extremity phlegmasia cerulea dolens (venous gangrene). Fortunately, both are reported to occur relatively infrequently. The reported incidence of pulmonary embolism secondary to subclavian-axillary vein thrombosis is less than 12%.Furthermore, the small clot burden, as compared with iliofemoral DVT, may reduce the clinical impact of this entity. Venous gangrene is exceedingly rare and has been limited to case reports in patients with malignancy or an underlying hypercoaguable state. There have been no published reports of venous gangrene occurring secondary to venous TOS.

Diagnostic Evaluation

The diagnosis of subclavian-axillary vein thrombosis requires recognition of the clinical signs and symptoms just presented, followed by definitive imaging studies.

Duplex Ultrasound

Duplex ultrasonography is the first step in confirming a clinical suspicion of venous TOS. Recent technologic advances such as color-flow duplex, used in conjunction with indirect criteria suggesting the presence of an occlusion (evaluation for phasicity of flow with respiration and augmentation with compressive maneuvers), have led to markedly increased sensitivity (81% to 100%) while maintaining high specificity (82% to 100%).

Magnetic Resonance and Computed Tomographic Venography

Magnetic resonance venography (MRV) is another noninvasive imaging modality that has been used with increasing frequency for the diagnosis of venous TOS. The cost and time required for completion of the examination are substantial, and we have therefore continued to choose duplex ultrasound. With time and more accumulation of data, the role of MRV in patients with suspected subclavian-axillary vein thrombosis will be better defined.

Computed tomographic venography (CTV) shows high concordance with duplex ultrasound. When imaging of the extremity veins and pulmonary arteries is considered clinically indicated, CTV can be used to reliably diagnose DVT.

Venography

Venography remains the “gold standard” for the diagnosis of venous TOS and also plays a fundamental role in the current standard treatment of the condition. Invasive catheter-based imaging should be reserved for patients whose condition warrants an intervention. If thrombosis is visualized), thrombolysis of the subclavian-axillary vein can be initiated with this approach. Once thrombolysis is successful or in patients found to have a patent but severely narrowed subclavian-axillary vein, positional venography is performed. Positional venography involves a venogram of the subclavian-axillary vein segment performed in full adduction and then in 90 degrees of abduction with external rotation (“hand-on-head” position)). These positional images are helpful to confirm the presence of extrinsic compression of the subclavian vein at the level of the thoracic outlet.

Treatment

Anticoagulation Alone

Historically, treatment of acute primary subclavian-axillary vein thrombosis consisted of rest and elevation of the affected extremity, accompanied by a variable duration of systemic anticoagulation. Many authors have reported high rates of residual functional impairment after treating patients with venous TOS in this manner .

Thrombolytic Therapy

The early use of catheter-directed thrombolysis has emerged as the preferred initial management strategy in the modern treatment paradigm of venous TOS. Because subclavian-axillary thrombus is much more localized than lower extremity DVT, this approach usually lyses the subclavian-axillary vein clot quickly to restore luminal patency. If attempted within 14 days of the onset of symptoms, the results are generally reported to be excellent. Treatment with thrombolysis in patients with greater than 14 days of symptoms is possible, albeit with a decreased chance for successful re-establishment of luminal patency.

Surgical Decompression of the Thoracic Outlet

Patients with persistent stenosis or signs of extrinsic compression on positional venography after thrombolysis remain at significant risk for recurrent thrombosis with anticoagulation alone. In addition, if the underlying pathophysiology has not been addressed, adjunctive therapies such as balloon angioplasty or stent placement may provide satisfactory immediate results but lack sufficient durability to be used as definitive therapy. Multiple reports have confirmed that the radial force associated with either a self-expanding or balloon-expandable stent is not adequate to compensate for the compressive force between the first rib and clavicle; stent deformation, fracture, and thrombosis in this setting are the norm rather than the exception). Therefore, stents have no role in the treatment of venous TOS before surgical decompression.

Once subclavian-axillary vein patency has been restored and extrinsic compression has been demonstrated, first rib resection with external venolysis should be performed. Although some authors advocate deferring surgical decompression for 1 to 3 months after thrombolysis to allow healing of the venous endothelium and resolution of the acute inflammatory process, most now agree that decompression should take place during the same hospitalization as the thrombolysis to decrease the significant risk for reocclusion that may occur between thrombolysis and deferred surgery.

SECONDARY SUBCLAVIAN-AXILLARY VEIN THROMBOSIS

By the 1970s, secondary upper extremity DVT became increasingly associated with the use of central venous catheters for chemotherapy, bone marrow transplantation, dialysis, and parenteral nutrition. Secondary upper extremity DVT can also be seen in patients with nephrotic syndrome, mediastinal tumors, malignancy, local surgery or trauma, and hypercoagulable states.

The most common causes of secondary subclavian vein thrombosis are catheter-induced thrombosis, cancer, and congestive heart failure. However the vast majority are secondary to various types of venous catheters such as pacemaker wires, tunneled catheters, peripherally inserted central catheters, and subcutaneous ports. Catheter-related subclavian-axillary venous thrombosis can be a serious disease resulting in pulmonary embolism and postphlebitic

syndrome. In fact, catheter removal itself can be a cause of pulmonary embolism. As a catheter is removed, the fibrin sheath can break loose and embolise into the pulmonary circulation.

In various studies, approximately 33% to 60% of patients with catheter-related venous thrombosis are asymptomatic The incidence of pulmonary embolism in patients with catheter-related thrombosis is between 15% and 25%, a not insubstantial figure.. This risk for pulmonary embolism is higher after secondary than after primary upper limb venous thrombosis.

Treatment

The goal of treatment of secondary upper extremity DVT is to prevent pulmonary embolism and to achieve recanalization of the vein. Most patients with secondary upper limb DVT improve after removal of the venous catheter and institution of anticoagulation therapy. If a catheter causes extensive axillary vein thrombosis resulting in marked edema, thrombolytic therapy may be considered. However, in the vast majority of patients, removal of the catheter plus systemic anticoagulation for a period of 3 months is indicated. Patients with secondary upper limb DVT who may have contraindications to systemic anticoagulation, such as concurrent gastrointestinal bleeding, recent neurosurgery, or the presence of pulmonary embolism despite anticoagulation, may be candidates for SVC filter placement.

Pulmonary Embolism

Effective diagnosis is crucial as PE is a treatable condition and severe cases of PE can lead to collapse and / or sudden death. Some PEs are rapidly fatal, and in the majority of the fatal cases they are not clinically diagnosed prior to death. The outcome is dependent on the clot burden and the underlying cardiorespiratory function. Although DVT and PE are manifestations of the same disease process, mortality is significantly higher with PE. If left untreated, the prognosis for PE is poor. Even when treated, some patients develop chronic thromboembolic pulmonary hypertension due to fibrotic, occlusive organisation of thrombi/emboli and pulmonary vascular remodelling.

The symptoms and signs of PE are not specific and include dyspnoea, pleuritic chest pain (due to pleural irritation in pulmonary infarction), retrosternal chest pain (due to right ventricular ischaemia), cough and haemoptysis. In severe cases, the right ventricle fails leading to dizziness and/ or syncope. The signs include tachypnoea, tachycardia, hypoxia, pyrexia, elevated jugular venous pressure, a gallop rhythm, a widely split second heart sound, tricuspid regurgitant murmur, pleural rub, systemic hypotension and cardiogenic shock.

Clinical probability scores and D-dimers

Diagnosing PE is a diagnostic challenge because the symptoms and signs are common and not specific. The initial step for patients presenting with signs and symptoms of possible PE is to assess their likelihood of having a PE.

CT Pulmonary Angiogram

CTPA is the gold standard for detecting acute pulmonary embolus with a high sensitivity (83-100%)and specificity (89-97%).290-292 Assessment of right ventricular/left ventricular (RV/LV) ratio as seen during CTPA is a useful indicator of severity of PE in the acute situation

Table 4: Two Level PE Wells score	
Clinical feature	**Points**
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
An alternative diagnosis is less likely than PE	3
Heart rate greater than 100 beats per minute	1.5
Immobilization (for more than 3 days) or surgery in the previous four weeks	1.5
Previous DVT / PE	1.5
Haemoptysis	1
Malignancy (Treatment ongoing, within 6 months, or palliative)	
Clinical probability simplified score	
PE likely	More than 4 points
PE unlikely	4 points or less

Additional diagnostic predictive value can be achieved by combining a clinical prediction score with D-dimer testing. D-dimer concentrations are elevated in an acute clot due to the resulting activation of fibrinolysis. The negative predictive value of D-dimer is high; however its specificity for VTE is poor.

Isotope Lung Scintigraphy

Isotope lung scintigraphy may be considered if computed tomography pulmonary angiography is unavailable and the patient is clinically stable (*ie, no right heart strain and no hypotension)*, and is of most use in:

- patients with a normal chest X-ray and no underlying chronic lung disease
- patients with a contraindication for computed tomography pulmonary angiography
- pregnant women who have a normal chest X-ray

Treatment

Initial clinical assessment of a patient with suspected PE is essential to estimate the severity of PE as this may dictate treatment options. Patients presenting with cardiogenic shock or sustained systolic hypotension (systolic blood pressure <90 mmHg for >15 minutes) should be regarded as high risk PE with a 15% early (<30 days) mortality rate. Non-high-risk patients who are initially cardiovascularly stable, can be sub classified into low risk (PE with 30 day mortality <1%) or intermediate risk (PE with 30 day mortality 3-15%) based on evidence of myocardial injury and/or right ventricular dysfunction.

For the majority of patients, heparin therapy can be discontinued once therapeutic anticoagulation with a vitamin K antagonist has been established (usually 6-10 days) and the INR is ≥2

Given the potential for early improvement in haemodynamic function, however, such treatment could be considered within a trial setting or possibly in young patients deemed to be in the upper region of intermediate risk and at low risk for haemorrhagic complications.
Patients deemed to have low-risk PE are suitable for outpatient management or early discharge

High-Risk PE

Initial management of the shocked patient with PE includes haemodynamic (dobutamine, epinephrine) and respiratory (oxygen) support. Intravenous UFH is preferred to subcutaneous

LMWH in this situation as it is likely to achieve therapeutic levels more rapidly and can be adjusted more readily should thrombolytic therapy be necessary. Patients with high-risk PE should be managed in a coronary care unit or high dependency.