Review of therapeutic endovascular interventions in venous diseases

Essay

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Dedication

Dedicate this work to the two persons who in forehand dedicated me all their lives resulting in all what I have achieved and will ever achieve. They set example of sacrifice and love. My very beloved parents

Your forever grateful son

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Summary

Endovascular surgery is a minimally invasive discipline. The endovenous therapy was introduced in later 1980s and early 1990s, following the success of endovascular interventions in the arterial tree.

The main complications of DVT are Pulmonary Embolism and Post-Thrombotic Syndrome. Both are cause of mortality and long term morbidity. Both can be prevented by implying edovenous techniques.

Endovascular thrombolysis provides a good treatment modality to allow early removal of the thrombus and preserve valves integrity. The thrombolytic agent is delivered through the catheter directly to the thrombosed segment allowing more concentrated, focused and direct delivery of agent into the clot. A high success rate of 80 – 85 % is observed by this technique. Newer modality using a combination of mechanical removal of thrombus and chemical lysis was adopted to decrease lytic agents load and minimize bleeding complications.

Pulmonary embolism (PE) remains a major cause of mortality. The mainstay of treatment is anticoagulation. However, 5 to 8% of patients receiving therapeutic anticoagulation for PE experience PEs. Complications of anticoagulation also occur in up to 26% of patients. There are also some clinical situations when therapeutic anticoagulation is contra-indicated. Vena caval filters were developed to provide prevention of an embolus to reach the pulmonary vasculature. According to their durability filters are classified into permanent, temporary or retrievable. Careful attention to caval anatomy is vital to avoid any unexpected anomalies and to plan the best deployment point. The results of caval filter insertion and its effect to reduce PEs depends on medical co-morbidities and filter insertion indication. Some studies showed similar mortality rates between filter and no filter group. More careful inspection of these studies reveals PE related deaths were much less in filter group. The major complications of filter insertion are either thrombotic or due to filter migration.

Stents can be deployed in venous as well as arterial vasculature although different rules apply. Most of venous stenotic lesions are of fibrotic and neointimal hyperplasia in origin. Owing to this fact, rapid elastic recoil occurs nearly in all cases after angioplasty alone making stent deployment is a must. Stents should be at least 2 mms wider than the vein diameter to allow proper fixation to the less muscular vein wall. This technique now has become the gold standard in treating lower limb venous insufficiency with iliac vein stenosis replacing surgery. Similarly, May-Thurner syndrome now is treated mainly by stenting with primary patency around 75% in first year. Stenting of Superior vena cava and its major tributaries is also feasible but with less results in comparison to IVC and iliac veins.

Surgical stripping of varicose Saphenous veins is a traumatic procedure with consequent neovascularisation, recurrent varicosities, pain, long convalescence and scarring. In the last 10 years, three main methods of in-situ venous ablation have come to practice: foam sclerotherapy, radiofrequency ablation **(RFA)** and laser ablation. The three techniques depend on obliteration of the vein lumen and leaving it in situ. RFA and Laser ablation depend on duplex ultrasound guidance and use energy to obliterate the vein. The tumescent anesthesia is used to collapse the vein in addition to anesthetic effect. Both Laser and RFA showed comparable results with conventional stripping surgery. Hyperpigmentation, neuralgia and recanalization are the commonest complications. One of the advantages usually credited to Laser treatment is that the duration of the procedure is shorter than that for RFA. Trials comparing RFA to Laser demonstrated better primary obliteration and less postoperative pain and bruising with RFA.

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Introduction

Endovascular surgery is a minimally invasive discipline, where sheath is inserted and instruments and devices are introduced for treating vascular pathologies using the aids of newly developed imaging equipments. The endovenous therapy was introduced in later 1980s and early 1990s, following the success of endovascular interventions in the arterial tree. (Neglen & Raju, 2005)

Deep venous thrombosis **(DVT)** has been estimated to affect more than 250,000 patients yearly (Wakefield & Arbor, 2000). The complications of acute DVT as Pulmonary Embolism **(PE)** or Post-Thrombotic Syndrome are important not only as a preventable cause of mortality but also as a source of long term morbidity. (Silva, 1991)

This thrombus can be lysed endovascularly using catheter directed technique. Thrombus lysis spares the venous valves reducing the post-thrombotic syndrome with a success rate reaching 80 – 85 %. . (Comerota; et al., 2001) The thrombolytic agent is delivered through the catheter directly to the thrombosed segment which is safer and more efficient with fewer complications. (Comerota & Assi, 2005)

To avoid pulmonary embolism **(PE)**, a special filter can be introduced into Caval veins endovenously. Caval interruption is one of the earliest vascular procedures performed in 1893. (Rectenwald; et al., 2005)

Two more indications for Caval filter insertion were suggested more recently; the bed ridden massive trauma patient who is liable to develop DVT and PE. (Khanasarinia, 1995) and patients with malignancy who are hypercoagulable. (Lossef & Barth, 1995)

Central venous occlusion or stenosis developing after incomplete recanalization of DVT or secondary to venous stenosis due to external or internal cause leads to venous insufficiency. Unlike arterial occlusions or stenoses, angioplasty alone is less effective.

There is usually immediate elastic recoil after initial balloon angioplasty leading to early restenosis. (Walpole; et al., 1988) In order to overcome the immediate recoil and early restenosis, metallic stents placement is to keep the lumen patent and prevent the recoil. (Neglen & Raju, 2005)

Recently, venous angioplasty and stent placement has widely replaced venous bypass surgery and considered as the *"Initial method of choice"* for chronic iliofemoral venous obstruction. It is an effective treatment modality used in large veins especially Superior and Inferior Vena Cava **(SVC & IVC)** and their major tributaries. (Neglen & Raju, 2005)

Varicose veins are dilated tortuous superficial veins with incompetent valves. These dilated veins can be removed surgically or ablated either by Radio-frequency Endovenous Occlusion **(RF)** or Endovenous Laser Treatment **(EVLT)**. (Bergan, 2005)

Both techniques depend on energy delivery to the vein wall leading to its shrinkage, with nearly equal results. There is level 1 evidence that Radiofrequency Endovenous Occlusion **(RF)** is beneficial. (Rautio; et al., 2002) Also, reports show comparable results of Endovenous Laser Treatment **(EVLT)** with traditional stripping & ligation. Three years data on 499 limbs had EVLT, success rate reached 93.5% (Min; et al., 2003)

Aim of the work

This is an overview to highlight various endovascular techniques treating much venous pathology since their wide incidence among populations. The essay demonstrates updated results, indications and contraindications, complications and techniques.

Pathophysiology and Natural History of Deep Venous Thrombosis

Deep vein thrombosis (DVT) occurs when a thrombus, formed from elements of the blood, develops in the deep veins of the lower extremity. An understanding of the epidemiology, pathophysiology, and natural history of DVT is essential in guiding prophylaxis, diagnosis, and treatment.

Heamostasis

It is the mechanism by which blood loss is prevented. Any injury to a blood vessel provokes 3 mechanisms:

1 – Constriction of blood vessel by smooth muscle contraction

2 – Platelet plug formation and activation which secrete serotonin, growth factors, thromboxane A2

3 – Blood coagulation through a successive enzymatic activity to form thrombin needed for fibrinogen to form fibrin threads (Mackenna & Callander, 1997)

Clot begins to develop in 15 to 20 seconds if the trauma to the vascular wall has been severe and in 1 to 2 minutes if the trauma has been minor. More than 50 important substances that cause or affect blood coagulation have been found in the blood and in the tissues. Some that promotes coagulation, called *procoagulants,* and others that inhibit coagulation, called *anticoagulants*. In the blood stream, the anticoagulants normally predominate, so that the blood does not coagulate while it is circulating. But when a vessel is ruptured, procoagulants from the area of tissue damage become "activated" and override the anticoagulants, and then a clot develops. (Guyton & Hall, 2006)

For a clot to form, 3 essential steps needed : 1 – Formation of prothrombin activator, 2 - The prothrombin activator catalyzes conversion of prothrombin into thrombin., 3 - The thrombin acts as an enzyme to convert fibrinogen into fibrin fibers that enmesh platelets, blood cells, and plasma to form the clot. Prothrombin activator complex can be formed by either of two systems, known as intrinsic and extrinsic. Fig (1) (Barrett, et al; 2010)

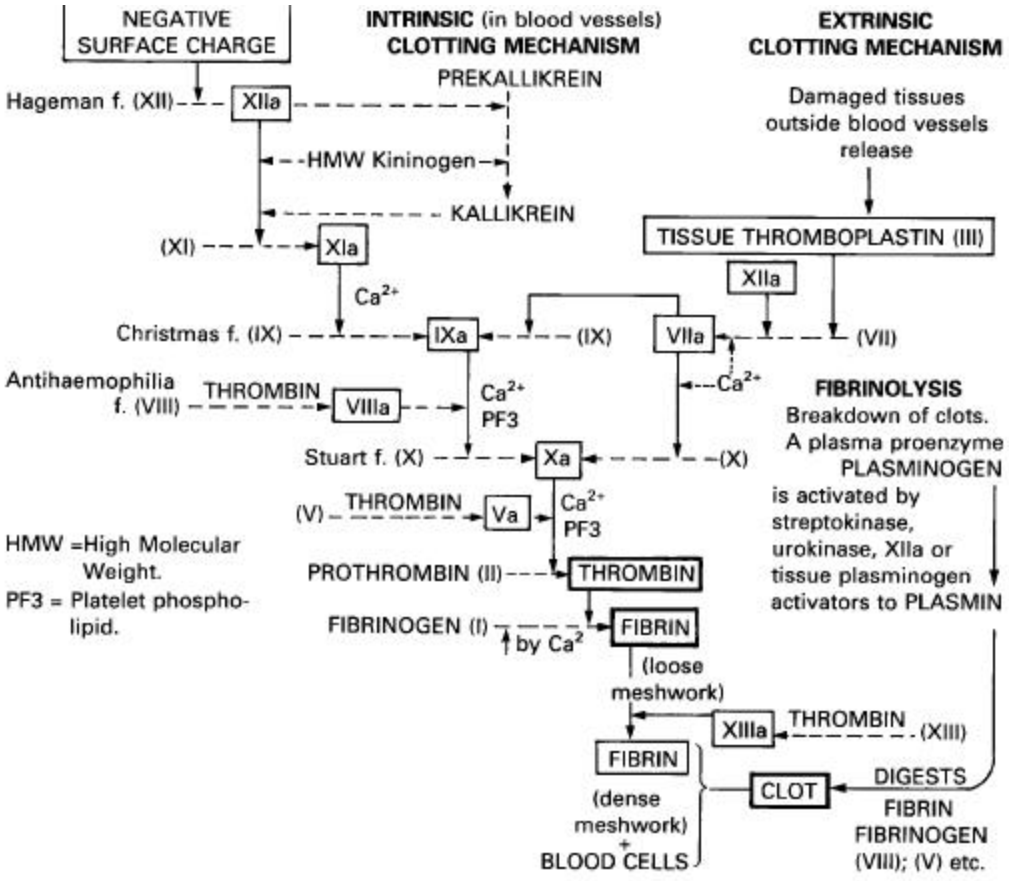

Fig (1): Intrinsic and extrinsic pathways of blood clotting, (Barrett, et al; 2010)

Once a clot has developed, continued flow of blood past the clot is likely to break it away from its attachment and cause the clot to flow with the blood; such freely flowing clots are known as emboli. Emboli that originate in the venous system or in the right side of the heart generally flow into the lungs to cause pulmonary arterial embolism. (Guyton & Hall, 2006)

The tendency of blood to clot is balanced in vivo by reactions that prevent clotting. **Antithrombin III** is a circulating protease inhibitor that binds to serine proteases in the coagulation system, blocking their activity as clotting factors. This binding is facilitated by **heparin,** a naturally occurring anticoagulant that is a mixture of sulfated polysaccharides. **Thrombomodulin,** a thrombin-binding protein formed by endothelial cells of most blood vessels. In circulating blood, thrombin is a procoagulant that activates factors V and VIII, but when it binds to thrombomodulin, it becomes an anticoagulant in that the thrombomodulin–thrombin complex activates **protein C**.

Activated protein C (APC), along with its cofactor protein S, inactivates factors V and VIII and inactivates an inhibitor of tissue plasminogen activator, increasing the formation of plasmin. (Barrett, et al; 2010)

The plasma proteins contain **plasminogen** that activated into **plasmin**. Plasmin is a proteolytic enzyme that resembles trypsin. Plasmin digests fibrin fibers and some other protein coagulants such as fibrinogen, Factor V, Factor VIII, prothrombin, and Factor XII. Therefore, whenever plasmin is formed, it can cause lysis of a clot. The injured tissues and vascular endothelium very slowly release a powerful activator called **tissue plasminogen activator (t-PA)** that eventually converts plasminogen to plasmin for thrombolysis. (Guyton & Hall, 2006)

Deep Venous Thrombosis

An abnormal clot that develops in a blood vessel is called a thrombus. Deep vein thrombosis (DVT) occurs when a thrombus develops in the deep veins of the lower extremity. Since many patients with acute DVT are asymptomatic, the true prevalence of DVT in the population is unknown. Some have suggested at least 2–3% of the population have experienced a DVT at some time in their life. DVT and pulmonary embolism (PE) represent the early manifestations of thrombus formation in the venous system, while venous stasis disease is late sequelae of acute DVT. (Welch, et al; 2005)

EPIDEMIOLOGY

Precise definition of the incidence of acute DVT is complicated by the clinically silent nature of most thromboses as well as by the nonspecific signs and symptoms. The incidence depends on the population studied, the intensity of screening, and the accuracy of the diagnostic tests employed. Most clinical trials and studies on the incidence of acute DVT have focused on specific inpatient groups, such as postoperative patients. Later epidemiologic data found that the overall average annual incidence of venous thromboembolism (VTE) was 117 per 100,000 (DVT, 48 per 100,000; PE, 69 per 100,000), with higher rates among men than women (130 vs. 110 per 100,000, respectively) .(Silverstein, et al; 1998) The incidence of PE decreased in the past decades, but the

incidence of DVT remained constant for males across all age strata, decreased for females younger than 55 years, and increased for women older than 60 years. (Mejssner & Strandness, 2005)

Venous thromboembolism is predominantly a disease of older age. In the absence of a central venous catheter9 or thrombophilia, venous thromboembolism is rare prior to late adolescence. Incidence rates increase exponentially with age for both men and women and for both deep vein thrombosis and pulmonary embolism. Incidence rates are somewhat higher in women during the childbearing years. (Heit, 2007)

Virchow's triad

Despite major advances in coagulation research, the basic etiologic factors in venous thrombosis can still be categorized by Virchow's triad originally described in 1856: (i) stasis of blood flow; (ii) injury to the vessel wall; and (iii) hypercoagulable blood. (Welch, et al; 2005)

Stasis

It is well accepted that surgical patients suffer periods of prolonged venous stasis in their lower extremities. The soleal sinuses may have the most profound stasis, and an autopsy study showed this location to be the principal site of venous thrombosis. (Gibbs, 1957)

Stasis itself, however, does not cause blood to clot when it is in contact with intact endothelium. Static blood does not clear activated coagulation factors, nor does it allow dilution of these activated coagulation factors by non activated blood. Additionally, inhibitors of the activated coagulation factors cannot effectively mix with the activated factors in static blood. Finally, increased blood viscosity can be present in areas of decreased blood flow. (Welch, et al; 2005)

In comparison with pulsatile flow, static streamline flow is associated with profound hypoxia at the depths of the venous valve cusps and may induce endothelial injury. The effects of hypoxia in cultured endothelial cells have been noted to include stimulation of cytokine production and leukocyte adhesion molecule expression, perhaps

accounting for the adhesion and migration of leukocytes observed in association with stasis. (Thomas, et al; 1983)

Venous stasis can result from immobility, or obstruction to blood flow. Immobility is seen most frequently during surgery and in the early postoperative course, as well as in advanced age and obesity. Extremities immobilized by splints or casts, or paralysis also cause stasis. Prevention of stasis due to immobility is the rationale behind the use of pneumatic compression boots in patients confined to bed. Obstruction to venous blood flow can take several forms. Intraluminal obstruction can result from a previous thrombus, intraluminal web, or a tumor, such as a renal clear cell cancer invading the inferior vena cava. Extraluminal extrinsic compression by tumors, a gravid uterus, or aortic aneurysm may result in stasis. Elevated venous pressure resulting from right heart failure will produce decreased venous flow in the periphery, leading to a high incidence of venous thrombosis in patients with congestive heart failure. Venous dilation can lead to stasis and perhaps endothelial damage. Venodilation occurs in pregnancy, in oral contraceptive use, and in varicose veins. (Welch, et al; 2005)

Vessel wall injury

Mechanical venous injury clearly plays a role in thrombosis associated with direct venous trauma, hip arthroplasty, and central venous catheters. Central venous cannulation is largely responsible for the increasing incidence of upper extremity thrombosis, whereas similar venous injury is presumably responsible for the observation that 57% of thrombi occurring after hip arthroplasty arise from the femoral vein rather than the usual site in the calf. (Mejssner & Strandness, 2005)

Thermal injury to the vein wall can result from electrocoagulation and the acrylic glue used in total hip replacement. Chemicals such as intravenous contrast agents and chemotherapeutic drugs injure endothelial cells. Circulating immune complexes and endothelial cell antibodies may result in endothelial cell injury. It is postulated that tobacco smoke may cause damage via the mechanism of immune complexes. Burns, blunt and penetrating trauma, varicose vein stripping, and indwelling venous catheters are other etiologies of vessel wall injury. (Welch, et al; 2005)

To study venous endothelial damage occurring in veins distant from the operative site, animal models have been developed evaluating both abdominal operations and total hip operations. Following the surgical procedure, canine jugular veins were excised to study the venous endothelium in a vein distant from the site of the operation. Endothelial damage occurred after abdominal operations, and more serious endothelial damage was found after total hip replacement. These endothelial lesions occurred as multiple micro-tears within the valve cusps, usually at the junction of small side branches to the main vein and act as nidus for thrombosis (Comerota, 2004)

Surgery causes release of humeral mediators, which produce venodilation, the action of which can be blocked by dihydroergotamine. This dilation is thought to be the cause of distant venous endothelial injury. (Welch, et al; 2005)

The normal venous endothelium is antithrombotic, producing prostaglandin I2 (PGI2, prostacyclin), glycosaminoglycan cofactors of antithrombin, thrombomodulin, and tissue-type plasminogen activator (t-PA). However, the endothelium may become prothrombotic under some conditions, producing tissue factor, von Willebrand factor, and fibronectin. It is conceivable that some thrombotic risk factors act through production of a procoagulant endothelium. Microscopic changes in the endothelial surface associated with greater endothelial permeability and leukocyte adhesion have been demonstrated in response to distant surgical injury. (Mejssner & Strandness, 2005)

Hypercoagulable states

A hypercoagulable state and stasis are well accepted in the etiologic theories of postoperative DVT. The role of venous injury in initiating thrombus formation, however, has received a little attention over the years. (Comerota, 2004)

Hypercoagulable states are either inherited or acquired. Primary or inherited hypercoagulable conditions represent discrete genetic mutation. They include inherited deficiencies of the naturally occurring anticoagulants, they include:

Protein C deficiency: Decreased circulating levels of protein C can be on a genetic or an acquired basis. Protein C deficiency is an inherited condition expressed in an autosomal dominant, while the acquired condition is seen in patients with liver failure, postoperative states, disseminated intravascular coagulation (DIC), and chronic renal failure.