1

Risk Factor for Pulmonary Embolism

Ufuk Çobanoğlu
The University of Yuzuncu Yil
Turkey

1.Introduction

Pulmonary embolism (PE) is a common disease with high morbidity and mortality, yet it is a disorder that is difficult to diagnose (Stein & Matta, 2010). 90% of the clinical PE originates from the proximal deep veins of the lower extremities. An ultrasonographic study involving patients diagnosed with pulmonary embolism detected thrombus in 29% of the deep veins (Anderson et al., 1991). Failure to demonstrate the presence of deep vein thrombosis (DVT) in many patients with pulmonary embolism results from the detachment of the emerging blood clot or the inability of ultrasonography to show minor clots (Anderson et al., 1991). Besides DVT, immobilization after fracture or surgical procedures, pregnancy, delivery and usage of estrogen containing oral contraceptives are the other predisposing factors for pulmonary emboli (Quinn et al., 1992). The predisposing factors were first described by Virchow in 1856 as consisting of three major phenomena (Table 1) (Anderson et al., 1991; Quinn et al.,1992): the "Virchow triad", that is, the triad of the three factors that induce the process of vascular clotting: endothelial injury, hypercoagulability and lower extremity stasis (Carson et al., 1992).

In 75% of pulmonary embolism cases, the acquired and/or hereditary factors that lead to one of these predisposing factors are detected; in half of the hereditary thrombophilia cases, an accompanying acquired risk factor is also present (White, 2003). Stasis in the lower extremities usually results from slow blood flow occurring in the patient groups with decreased mobility. In patients with endothelial injury, causes such as trauma and surgery trigger this process while hypercoagulation is a mechanism observed in cases of hereditary thrombophilia (White, 2003). Table 2 presents the acquired and hereditary risk factors.

2. Genetic risk factors

Among the hereditary risk factors leading to a predisposition to thrombosis, antithrombin deficiency was first shown to create predisposition to thrombosis in 1965, followed by the description of protein C deficiency in 1981 and protein S in 1984. These three deficiencies represent only 15% of hereditary thrombophilias. The description of the active protein C (APC) resistance by Dahlback et al in 1993 (Dahlback, 1995) and of the factor V Leiden mutation by Bertina in 1994 (Bertina, 1999) enabled elucidation of the etiology in 20% of patients with thrombosis and in 50% of families with thrombophilia. Similarly, hyperhomocysteinemia and a mutation in the prothrombin gene were shown to cause hereditary thrombophilia in 1994 and 1996, respectively (Makris et al., 1997). In patients with genetic thrombophilia, the predisposition to thrombotic and recurrent venous thromboembolism (VTE) in the early stages of life is increased.

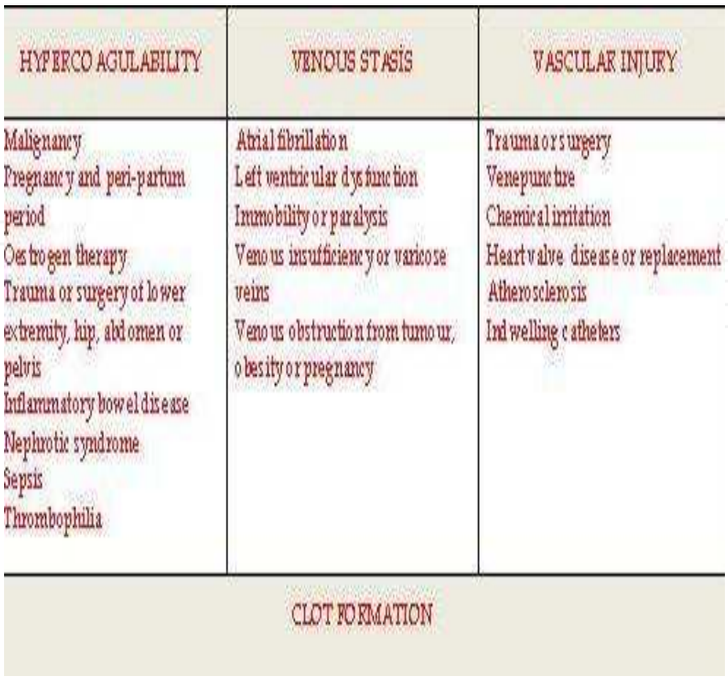


Table 1.Virchow's triad/ venous thromboembolism risk factors

Genetic risk factors	Acquired risk factors
Antithrombin III deficiency	Advanced age
Protein C deficiency	Obesity
Protein S deficiency	Long haul air travel
Activated Protein C resistance and	Immobilization
Factor V Leiden Mutation	Major surgery
Factor II G20210A Mutation:	Trauma
Hyperhomocysteinemia	Congestive cardiac failure / Myocardial
Increase in Factor VIII Levels	infraction
Congenital Dysfibrinogenemia	Smoking
Plasminogen deficiency	Stroke
Factor VII deficiency	Malignity/ Chemotherapy
Factor XII deficiency	Central venous catheter
Factor IX increase	Pregnancy/puerperality
	The use of Oral contraceptives and hormone replacement
	Previous pulmonary emboli and deep vein thrombosis
	Antiphospholipid syndrome
	Chronic obstructive pulmonary disease (COPD)
	Medical Conditions requiring hospitalization

Table 2. Risk factor for pulmonary embolism

2.1 Antithrombin III deficiency

Antithrombin III (AT III) deficiency is among the first described thrombophilias. It is one of the most important natural protease inhibitors and a glycoprotein that is synthesized in the liver, which exhibits anticoagulant efficacy through inhibition of thrombin and the other serine proteases (factor IX a, X a, XI a, XIIa and kallikrein). Owing to these properties, it is accepted to be one of the most potent physiologic inhibitors of the fibrin formation. There are two types of antithrombin III deficiencies: type I involves reduction in the synthesis while type II involves functional inactivity. Type I AT III deficiency is characterized by both a functional and an immunological reduction in AT III. Type II AT deficiency involves variant AT III molecules (Thaler & Lechner, 1981). When the serum concentration of antithrombin III is mildly decreased, factor Xa, IXa, XIa and XIIa and thrombin cannot be inactivated, leading to thrombus formation. In addition to congenital deficiency, the antithrombin level is also decreased in cases of diffuse intravascular clotting, oral contraceptive (OC) use, and liver and kidney diseases. In antithrombin III deficiency, thrombotic events occur mostly in the mesenteric and lower extremity deep veins, leading to an increased predisposition to pulmonary embolism. A trial detected a rate of AT III deficiency at 1/600 in healthy individuals (Tait et al., 1994). In another trial, this figure was 1.5% in patients diagnosed with VTE (Bauer& Rosenberg, 1991).

2.2 Protein C deficiency

Protein C (PC) is a glycoprotein synthesized in the liver. Its deficiency exhibits autosomal dominant or autosomal recessive inheritance. Protein C deficiency has two subtypes. Type I protein C deficiency: protein C antigen level is low due to genetic defect while the protein C activity is normal. Type II protein C deficiency involves the presence of an abnormal protein C molecule. Protein C antigen is normal while the protein C activity is low (Hoshi et al., 2007). Protein C is activated after the thrombin binds to the endothelial receptors. Activated PC binds to the factor Va and factor VIIIa and inactivates these factors, thereby inhibiting the clot formation.

In the general population, protein C deficiency prevalence is between 1/16000 and 36000. The fact that the protein C deficiency rate is 10% in patients with previous VTE below 40 years of age and that it increases the VTE risk 6-fold, protein C level should be investigated in all young patients with previous VTE (Folsom et al., 2002).

2.3 Protein S deficiency

Protein S is a glycoprotein that is vitamin K-dependently synthesized, exhibits an autosomal dominant inheritance and activates protein C as a cofactor. Protein S exhibits anticoagulant efficacy through both the inactivation of factor Va and factor VIIIa by Protein C that is activated as a cofactor and directly through inhibition of the interaction of prothrombin with factor Va and Xa; therefore, protein S deficiency is considered a significant risk factor for thrombosis formation (Bertina, 1999). Protein S deficiency has three subtypes. Type I protein S deficiency involves a reduction in the total protein S antigen level. The free protein S antigen level and activity is low. Type II protein S deficiency involves the presence of a functionally abnormal protein S molecule. The total and free protein S antigens are normal but the protein S activity is decreased. Type III protein S deficiency involves a normal total protein S antigen but a decreased free protein S antigen level and activity (Dykes et al., 2001). Protein S deficiency is observed at a rate of 0.03%-0.13 (Dykes et al., 2001) and 6% in

healthy individuals and families with thrombophilia (Bertina 1999). The trials performed demonstrated a 6 to 10-fold increased VTE risk in heterozygous Protein S gene carriers (Bauer& Rosenberg, 1991). As well as leading to thrombus formation in the deep (axillary, femoral etc), mesenteric, cerebral and superficial veins, it also causes PE and arterial thrombus formation. It is also one of the causes of recurrent VTE attacks. Pregnancy, OC or estrogen replacement use, nephritic syndrome, disseminated intravascular coagulation, HIV infection and liver diseases may also result in acquired protein S deficiency (Bauer& Rosenberg, 1991).

2.4 Activated protein C resistance and factor V Leiden mutation

In cases of activated partial thromboplastin time (aPTT) changes, an addition of activated Protein C to the plasma is expected to cause the prolongation of bleeding time. However, Dahlback et al detected no prolongation in some patients with VTE in 1993 (Dahlback, 1995); this phenomenon was described as the activated protein C resistance (APCR). Activated Protein C resistance is clearly associated with an increase in thrombosis incidence. The subsequent studies detected this phenotype in 20-50% of the patients with VTE (Dahlback, 1995). In many cases of hereditary APCR, aG→A transition causes translocation of the amino acids (glutamine and arginine) at 506 location in the position 1691 nucleotide as a result of the activated function of the point mutation in factor V (site of cleavage for the activated PC in the factor V molecule). This point mutation was first described in 1994 and named as Factor V Leiden (FVL), FVR Q or FV: Q (Rosendaal et al., 1995). Factor V mutation notably increases the predisposition to VTE, causes hypercoagulability and neutralizes activated PC-mediated resistance. The risk of VTE is increased 3 to 8-fold in individuals heterozygous for factor Leiden mutation; as for homozygous individuals, the increase in the thrombotic risk is 50 to 100-fold (Rosendaal et al., 1995). The incidence of factor V Leiden carriers is 1-15% in the population (Rosendaal et al., 1995). Factor V Leiden is present in 10-50% of the cases with VTE. Factor V Leiden abnormality results from a single mutation. In APCR without factor V Leiden mutation, the VTE risk is increased (Rosendaal et al., 1995).

2.5 Factor II G20210A mutation

A new genetic factor was discovered in the etiology of VTE in 1996. The G→A transition (Factor II G20210A) of the nucleotides at 20120 location in the region of the coagulation factor II gene not undergoing 3'-translation is associated with hyperprothrombinemia. G→A transition increased the prothrombin synthesis at the level of mRNA and protein synthesis. In heterozygous carriers of this mutation, the prothrombin level is increased 1.3-fold while it is increased 1.7-fold in homozygous carriers. The increase in the plasma prothrombin level results in a predisposition to thrombosis. This mutation was detected in 1-3% of the general population and 6-18% of the patients with VTE (Poort et al. 1996). Factor II G20210A diagnosis is only established by gene analysis. It is the second most common genetic abnormality, secondary to thrombophilia. In the case of factor II G20210A, there is no increase in the risk of VTE (Miles et al., 2001).

2.6 Hyperhomocysteinemia

It is the only hereditary cause of thrombophilia that has been proven to lead to arterial and venous thrombosis. Hyperthrombosis is believed to trigger the development of thrombosis via various mechanisms; there are in vitro studies showing that it affects the endothelial

cells by causing the formation of reactive oxygen forms, such as superoxide, hydrogen peroxide and hydroxyl radicals, it causes proliferative response by affecting the smooth muscle cells and increasing collagen production, it affects the clotting system by increasing tissue factor production in the monocytes, creating acquired APC resistance and increasing the synthesis of thromboxane in the platelets (Miletich et al., 1987). Hyperhomocysteinemia is an established risk factor for VTE and is usually associated with a 2 to 4-fold increased thrombotic risk. Plasma homocysteine concentration is affected by genetic and acquired factors and thus known as the mixed risk factor (Miletich et al., 1987). Vitamin B12, vitamin B6 and folate deficiency, advanced age, chronic renal failure and malnutrition involving anti-folic drug use represent acquired factors in hyperhomocysteinemia. Gene defects in two enzymes involved in the intracellular metabolism, methyltetrahydrofolate reductase (MTHFR) and cystathionine B-synthase (CBS) result in hyperhomocysteinemia and enzyme deficiency. Various mutations have been defined in methyltetrahydrofolate reductase and CBS to date; most are rare and lead to clinical outcomes in homozygous cases only. This condition is characterized by multiple neurological deficiency, physicomotor retardation, seizures, skeletal abnormalities, lens dislocation, premature arterial disease and VTE (Weisberg et al., 1999). Methyltetrahydrofolate reductase 677 C→T is associated with high-prevalence polymorphism in the general population and reduced enzyme activity in homozygous cases. Methyltetrahydrofolate reductase 1298 A→C is not considered to be associated with hyperhomocysteinemia and not considered a thrombotic risk factor.
However, MTHFR results in reduced enzyme activity and increased homocysteine levels in heterozygous cases of 677 C→T (Weisberg et al., 1999). 68-bp insertion in the cystathionine B-cynthase gene (844ins68) is a common mutation in various populations. This gene change has no effect on the risk of DVT or homocysteine levels. Hyperhomocysteinemia is not defined as a genetic abnormality for VTE but as an independent risk factor (Kluijtmans et al., 1997).

2.7. Increase in factor VIII levels

Factor VIII is an entity with a gene localized on the 10th chromosome, which activates the factor X by forming a complex with factor IXa and phospholipids in the coagulation cascade. The increase in factor VIII is included among the thrombotic risk factors since it further increases formation of thrombin from prothrombin by factor X activation (Schambeck et al., 2004). The increased factor was detected in 3-9.4% of healthy individuals and in 11.3% of patients with VTE (Schambeck et al., 2004). A high FVIII level was reported to increase the VTE risk approximately 5-fold compared to individuals with a normal level (Schambeck et al., 2004). In addition, the factor VIII level was demonstrated to be an independent risk factor for VTE (Kraaijenhagen et al., 2000) (21) and to be correlated with the PE recurrence (Kyrle et al., 2000).

2.8. Congenital dysfibrinogenemia

The impairment in the formation of fibrin from fibrinogen secondary to the changes in the structure of fibrinogen is called dysfibrinogenemia. Dysfibrinogenemia is a dominant disease group characterized by qualitative abnormal fibrinogen formation. Various fibrinogen abnormalities are assessed within this group. Approximately 300 abnormal fibrinogen have been defined (Schorer et al., 1995). The most common structural defects are detected in fibrinopeptides and their sites of cleavage. Each dysfibrinogenemia affects

thrombin time and clotting in a different way. While some dysfibrinogenemias do not have the effect of bleeding or thrombosis, some may cause abnormal bleeding and even thrombosis (Schorer et al., 1995).

2.9 Plasminogen deficiency

Plasminogen (plg) plays an important role in intravascular and extravascular fibrinolysis, wound healing, cell migration, tissue remodeling, angiogenesis, and embryogenesis (Castellino & Ploplis, 2005).

Plasminogen deficiency shows an autosomal dominant inheritance.

Plasminogen deficiency is classified into two groups: one is type I deficiency characterized by the parallel reduction of both activity and antigen, and the other is dysplasminogenemia (type II) characterized by reduced activity with a normal antigen level (Schuster et al., 2001).

Hypoplasminogenemia (type I plg deficiency): No significantly increased risk of deep venous thrombosis. In hypoplasminogenemia, or type I plg deficiency, the level of immunoreactive plg is reduced in parallel with its functional activity. The specific plg activity is normal.

Some further case reports and family studies had originally suggested that heterozygous hypoplasminogenemia might be a risk factor for venous thrombosis (Leebeek et al., 1989). The relationship between hypoplasminogenemia and venous thrombosis has more recently been called into question, mainly based on two lines of evidence. Dysplasminogenemia (type II plg deficiency): in dysplasminogenemia, or type II plg deficiency, the level of immunoreactive plg is normal (or only slightly reduced), whereas the specific functional plg activity is markedly reduced because of abnormalities in the variant plg molecule (Robbins, 1990).

2.10 Factor VII deficiency

Inherited factor VII (FVII) deficiency is the most widespread of the rare inherited bleeding disorders, with an estimated prevalence of 1 in 400 000 Caucasians (Mariani et al., 2005). It is characterized by a wide heterogeneity as regards clinical, biological and genetic parameters. Clinical features are extremely variable, ranging from mild cutaneo-mucosal bleeding to lethal cerebral haemorrhages, and are poorly correlated with residual FVII coagulant activity (FVII:C). Moreover, several patients remain asymptomatic (Aynaoğlu et al., 2010), even under conditions of high haemorrhagic challenge. Notably, in some rare cases, patients have a history of arterial (Escoffre et al., 1995) or venous (Mariani & Bernardi, 2009) thromboses. The mechanisms accounting for the association of FVII deficiencies with thrombosis remain unclear. FVII deficiency is characterized by a wide heterogeneity, even amongst those patients presenting with rare thrombotic events. In a few case reports, thrombosis can occur in "usual" sites, such as the deep veins of the lower limbs or pulmonary embolism, or in atypical sites, such as the sinus veins (Lietz et al., 2005). The first series of FVII deficiency associated with thrombosis included seven cases of venous thrombosis, localized primarily in typical sites (lower limbs and pulmonary embolism) (Mariani et al., 2005).

2.11 Factor XII deficiency

Severe FXII deficiency (FXII activity <1%) shows an autosomal recessive inheritance and patients are detected to have a prolonged aPTZ time. Despite this prolongation in the active partial thromboplastin time, patients do not have bleeding diathesis. In contrast, these

patients develop VTE and myocardial infarction. While the incidence of thrombosis secondary to factor XII deficiency was not well-established, it was reported to be 8% approximately (Goodnough et al., 1983).

2.12 Factor IX increase

Factor IX plays a key role in hemostasis; it is a vitamin K–dependent glycoprotein, which is activated through the intrinsic pathway as well as the extrinsic pathway (B. Furie & BC. Furie, 1988). Factor IX, when activated by factor XIa or factor VIIa-tissue factor, converts factor X into Xa and this eventually leads to the formation of a fibrin clot. This conversion is accelerated by the presence of the nonenzymatic cofactor factor VIIIa, calcium ions, and a phospholipid membrane (van Dieijen et al., 1981). In healthy individuals, factor IX activity and antigen levels vary between 50% and 150% of that in pooled normal plasma (B. Furie & BC. Furie, 1988; van Dieijen et al., 1981). Individuals who have high levels of factor IX (>129 U/dL) have a more than 2-fold increased risk of developing a first DVT compared with individuals having low levels of factor IX. The risk of thrombosis increased with increasing plasma levels of factor IX (dose response). At factor IX levels of more than 125 U/dL, an increase of the risk can already be observed compared with the reference category (factor IX levels ≤100 U/dL). Individuals with a factor IX level over 150 U/dL have a more than 3-fold increase in the risk of thrombosis when compared with the reference category.

3. Acquired risk factors

3.1 Advanced age

The VTE incidence increases linearly with the age. Above 50 years of age, the PE incidence was detected to be higher in women. This increase is also associated with other comorbidities (cancer, myocardial infarction) that increase with age (Stein et al., 1999).

3.2 Obesity

The risk of PE by obesity is correlated with the body mass index. While the relative risk of pulmonary embolism is 1.7 for those with a body mass index of 25-28.9 kg/m², it is increased 3.2-fold for those with a BMI ≥29 (Goldhaber et al., 1997). Obesity is correlated with VTE, particularly in women. It was reported to be an independent risk factor in women with a body mass index ≥ 29. However, there are controversial study results on this subject (Goldhaber et al., 1997).

3.3 Long haul air travel

Air travel is a risk factor for PE. In a trial by Lapostolle et al, severe pulmonary embolism was detected in 56 of 135.29 million passengers from 14 countries. The assessment of the results revealed a rate of 1.5 in one million cases in those flying more than 5000 km and a rate of 4.8 in one million cases in those flying more than 10000 km, leading to the reported result that PE risk was correlated with flight distance. Conditions that lead to hemoconcentration during air travel, such as dehydration, lower oxygen pressure and foot swelling are believed to induce venous stasis (Lapostolle et al., 2001).

3.4 Immobilization

Immobility is a condition that is most commonly observed in PE, which may concomitantly exist with other risk factors (Stein et al., 1999). Long-term absence of mobilization results in

a weakening of the muscles that provide an upward flow of the blood in the leg veins. The blood accumulates backwards; thus, among the activated platelets and clotting factors, thrombin in particular accumulates locally, leading to the formation of thrombus. Even if for a short time, for example one week, in the postoperative period, immobilization increases the risk of VTE (Stein et al., 1999).

3.5 Major surgery

Surgical intervention is one of the most significant acquired risk factors that cause PE. The decreased mobility during the operation, hypercoagulation secondary to local trauma and endothelial injury, the prothrombotic process that may be caused by the general anesthesia administered increase the risk of PE (Rosendaal, 1999). The presence of operation history within a 45-90 day period increases the risk of thromboembolism 6 to 22-fold (Rosendaal, 1999); 25% of these emboli occur after discharge from the hospital (Huber et al., 1992). Surgeries of the hip, knees, and the abdominopelvic region represent the most risky operations for venous thromboembolism development (Huber et al., 1992).

3.6 Trauma

Trauma is also a risk factor for PE development; the localization of the trauma is very important with respect to venous thrombus development (Geerts et al., 1996). VTE occurs in 50% of chest or abdomen traumas, 54% of head traumas and 62% of spinal cord injuries, and 69% of lower extremity orthopedic traumas (Geerts et al., 1996). The incidence of venous thromboembolism increases proportionally with time after the traumatic event. While the rate of PE confirmed by autopsy was 3.3% in those who survived less than 24 hours after trauma, this rate was 5.5% in those who survived up to seven days. PE was reported at a rate of 18.6% in individuals who survived longer (Geerts et al., 1996). Patients over 45, a requirement of more than three days bed rest, a previous history of VTE, fractures of the lower extremity, pelvis, spine, the development of coma and plegia, a requirement for blood transfusion and surgery further increase the risk of DVT and PE, therefore, effective and safe prophylactic anticoagulant treatment is recommended in traumatic patients unless contraindicated (Shackford et al., 1990).

3.7 Congestive cardiac failure/myocardial infraction

The presence of congestive cardiac failure or arrhythmia underlying heart disease further increases the risk of PE. In cardiac failure, the risk of mortality from PE is increased due to decreased cardiopulmonary reserve (Anderson & Spencer, 2003). The increase of factor VIII, fibrinogen and fibrinolysis in the acute phase following acute myocardial infarction leads to PE (Anderson & Spencer, 2003). Nearly all of the PEs occurring in acute myocardial infarction result from deep vein thrombosis in the lower extremity. Very rarely, they result from mural thrombi occurring in the infraction site in the right ventricle (Anderson & Spencer, 2003).

3.8 Smoking

Smoking may increase the risk of VTE through a number of mechanisms:

1. Smoking is a well established, potent risk factor for a number of diseases, including cancer and cardiovascular diseases (stroke and coronary heart diseases); these, in turn, are associated with an increased risk of VTE. Therefore, smoking might be associated with the risk of provoked VTE.

2. Smoking is associated with a higher plasma concentration of fibrinogen (Yanbaeva et al., 2007; Lee & Lip, 2003).
3. Smoking is associated with reduced fibrinolysis (Lee & Lip, 2003; Yarnell et al., 2000).
4. Smoking is associated with inflammation (Yanbaeva et al., 2007; Yarnell et al., 2000).
5. Smoking increases the viscosity of the blood (Yanbaeva et al., 2007; Lee & Lip, 2003).

3.9 Stroke

Most patients with acute ischemic stroke or intracranial hemorrhage survive the initial event. Early in-hospital mortality has been attributed not only to swelling of the brain and enlargement of hematoma but also to aspiration pneumonitis, sepsis, and severe heart disease (Brandstater et al., 1992). Pulmonary embolism after a stroke has received some attention, but the incidence is considered small. The incidence of clinical PE reported in the absence of heparin prophylaxis varies considerably, depending on the methodology of the studies. In the International Stroke Trial, the incidence was 0.8% at 2 weeks (International Stroke Trial Collaborative Group [ISTCG], 1997). Similarly, in a retrospective study of 607 patients who had acute stroke, PE was reported in 1% during the period of hospitalization (Davenport et al., 1996). However, prospective studies that focused specifically on venous thromboembolic complications reported incidences of clinically apparent PE of 10% to 13% (excluding pulmonary emboli identified in autopsy that were asymptomatic during life) (Warlow et al., 1972). In a retrospective study of 363 patients who did not receive heparin prophylaxis and entered a rehabilitation unit four weeks after stroke, 4% developed PE (confirmed by VQ scanning) on average 11 days after entering the unit (Subbarao & Smith, 1984). Only one small study has prospectively screened for PE by using VQ scintigraphy. Dickmann et al (Dickmann et al., 1988) studied a group of 23 patients 10 days after hemorrhagic stroke and found evidence of PE in 39%, though the proportion with symptoms was not stated. Autopsy studies show that half of the patients who die in hospital after the first 48 hours post stroke have evidence of PE, (McCarthy & Turner, 1986) which suggests that pulmonary emboli are often subclinical and/or unrecognized after stroke.

3.10 Malignity/chemotherapy

Cancer patients have a higher risk of complications and recurrence compared to patients without cancer. This risk is more marked especially in the pancreas, pulmonary disease, gastrointestinal system and mucinous carcinoma patients (Er & Zacharski 2006). Different mechanisms were proposed for the development of thrombotic predisposition in cancer patients. Development of procoagulant activity by the tumor products, coagulatory macrophage activation, endothelial cell injury and platelet activation secondary to interaction with the tumor cells are among these mechanisms. Some malignities (pancreas, colon, lungs and promyelocytic leukemias) systemically result in activation of the clotting system, leading to thrombotic complications. In cancer patients, the serum concentrations of the clotting factors, such as factors V, VIII, VII and fibrinogen are increased. Again, in these patients, local or systemic coagulation may occur secondary to vascular wall injury and factor X is activated (Falanga & Zacharski, 2005). The chemotherapeutical agents used for DVT after chemotherapy are significantly involved in this process due to the endothelial injury occurring in the vein to which these agents are administered (Nightingale et al., 1997).

3.11 Central venous catheter

Jugular, subclavian and femoral venous catheters lead to vascular injury and represent a focus for thrombus formation. Although less common, these patients may develop

symptomatic PE caused by the catheter-associated upper extremity thrombi (Haire & Lieberman 1992). In approximately 10-20% of the cases with pulmonary emboli, the emboli results from the thrombus in the site of the superior vena cava. Recently, upper extremity venous thrombus has been commonly known to occur as a result of invasive diagnostic and therapeutical procedures (intravascular catheter and intravenous chemotherapeutical agents) (Haire & Lieberman 1992).

3.12 Pregnancy/puerperality

Compared to the age-matched individuals, the risk of VTE is 5-fold higher in pregnant women. While 75% of the deep vein thrombi occur in the pre-delivery period, 66% of the PEs develop after the delivery. The risk is 20-fold higher in the postpartum period relative to the antepartum period (Kovacevich et al., 2000; Greer, 2003). Venous stasis secondary to dilated uterus in pregnancy, hormonal venous atonia, increased levels of thrombin and various clotting factors (fibrinopeptide A), increased platelet activation, decreased acquired protein S, antithrombin deficiency, the decreased APC response due to factor VIII increase are the risk factors. There are no trials using objective diagnostic techniques to show that cesarean section involves an additional thrombotic risk relative to normal delivery. The risk of a thrombotic event is higher in patients who are on mandatory bed rest due to premature action or preterm premature membrane rupture (Kovacevich et al., 2000). Since oral anticoagulation is risky for the fetus, low-molecule weight heparin treatment with a lower osteoporosis risk relative to the conventional heparin that will be maintained at least until puerperality appears to be an appropriate choice (Greer, 2003).

3.13 The use of oral contraceptives and hormone replacement

Oral contraceptive (OC) use was shown to increase the risk of PE approximately 3-7-fold. Oral contraceptives result in PE by increasing the levels of coagulation factors, such as prothrombin, factor VII, factor VIII, factor X and fibrinogen, and decreasing the levels of the coagulation factors, such as antithrombin III and protein S (Spitzer et al., 1996). Compared to the persons who are not on oral contraceptives, the risk was detected to be 3.4 for low-estrogen levonorgestrel and 7.3 and 10.2 for the 3rd generation progesterone desogestrel and gestodene (World Health organization [WHO], 1995). Third generation OC use increases the VTE risk particularly in Factor V Leiden mutation carriers and those with a positive familial history (Bloemenkamp et al., 1995). In women, hormone replacement therapy used in the postmenopausal period is reported to be a risk factor for PE (Cushman et al., 2004). This risk is higher in patients with coronary artery disease. The risk is higher at the start of treatment and disappears upon discontinuation of the hormone replacement therapy. The mechanism involved in the increase of thrombosis by estrogen alone or in combination with progesterone is not known. However, recent trials report that OCs cause a reduction in the sensitivity to activated protein C irrespective of the type of drug used and that this reduction is higher with 3rd generation monophasic OCs relative to 2nd generation drugs (Rosing et al., 1997).

3.14 Previous pulmonary emboli and deep vein thrombosis

Hospitalized patients with a history of pulmonary emboli have a significant risk of recurrence. More than 50% of patients with a history of venous thromboembolism undergoing surgery develop postoperative DVT if no prophylaxis is administered. The rate

of recurrence within 5 years after the first DVT is 21.5% (Hansson et al., 2000). Jeffrey et al (Jeffrey et al., 1992) detected the PE recurrence as 8.3% and reported that recurrence occurred mostly within the first week of treatment. In addition, mortality was 45% in these patients.

3.15 Antiphospholipid syndrome

Antiphospholipid syndrome (APS) characterized by arterial and venous thrombosis predisposition, repeated miscarriage and the presence of antiphospholipid antibodies is one of the leading causes of acquired thrombophilia. While the pathogenesis of the syndrome is not elucidated clearly, the negatively charged phospholipids and the phospholipid antibodies developing against the phospholipid protein complexes (lupus anticoagulant-LA and anticardiolipin antibodies-AKLA) are believed to be responsible for clinical manifestations. In AFS, the most important factor affecting mortality and morbidity is thromboembolic complications. Thromboses can both involve the arterial and the venous system and may be observed in each tissue and organ. The recurring tendency of the thromboses and the high risk of consecutive thrombotic complications involving the same system (for example, recurrent arterial thrombosis in a case with previous arterial thrombosis) are interesting. Approximately 2/3 of the cases develop venous thromboembolism and 1/3 develop arterial thrombosis. In venous thrombosis, DVT and PE rank first while ischemic cerebral attack ranks first in arterial thrombosis followed by myocardial infarction and digital thromboses. Thrombosis in abnormal regions is common in antiphospholipid syndrome (thrombosis in upper extremity veins, intra abdominal veins and the veins inside the head) (Hanly, 2003).

3.16 Chronic Obstructive Pulmonary Disease (COPD)

COPD is a major health burden worldwide. It is the fourth-leading cause of mortality, accounting for > 3 million deaths annually; and by 2020, COPD will be the third-leading cause of death, trailing only ischemic heart disease and stroke. Most COPD-related deaths occur during periods of exacerbation (Sapey & Stockley, 2006). Previous studies (Sidney et al., 2005) estimate that 50 to 70% of all COPD exacerbations are precipitated by an infectious process, while 10% are due to environmental pollution. Up to 30% of exacerbations are caused by an unknown etiology Sapey & Stockley, 2006). Exacerbations are characterized by increase in cough and dyspnea. A study (Sidney et al., 2005) suggests that patients with COPD have approximately twice the risk of PE and other venous thromboembolic events (VTE) than those without COPD. Since thromboembolic events can lead to cough and dyspnea (just like infectious events), PE may be another common cause of COPD exacerbations (Tapson, 2008). However, dissimilar to infectious etiologies, which are effectively treated by antimicrobials and systemic corticosteroids, thromboembolic diseases require anticoagulant therapy and significant delays in treatment are associated with poor outcomes (Hull et al., 1997). Owing to multiple perfusion and ventilation abnormalities frequently observed in COPD lungs (even in the absence of VTE), noninvasive diagnosis of PE using imaging modalities was a significant challenge until quite recently. With the advent of contrast-enhanced (multidetector) CT, it is now possible to reliably diagnose PE in COPD subjects with minimal discomfort or risk to the patients. The primary purpose of this review was to determine the reported prevalence of PE in patients with COPD who required hospitalization for their disease.

3.17 Medical conditions requiring hospitalization

The incidence of thromboembolic diseases in inpatients is reported to be different depending on the type of disease. While the risk is reported to be 3% in patients without risk factors, it is reported to be 50% in patients with previous VTE. Massive PEs account for 4-8% of inpatient mortality (Rubinstein et al., 1988). The VTE risk is higher in patients with neurological and cardiac diseases during hospitalization compared to other patient groups (Nicolaides et al., 2001). There are certain diseases that have been proven to increase the risk of venous thromboembolism complications; these include SLE, inflammatory intestinal diseases, nephritic syndrome, paroxysmal nocturnal hemoglobinuria, myeloproliferative diseases, Behcet's disease, Cushing syndrome and sickle cell syndrome. The number of DVT cases is larger in these diseases relative to the general population.

4. References

Anderson, FA. Jr., & Spencer, FA. (2003). Risk Factor for Venous Thromboembolism. *Circulation,* Vol.107, No. [Suppl I].I-9, (Jun), pp.(1-16), ISSN: (Print) 0009-7322, (Electronic)1524-4539.

Anderson, FA. Jr., Wheeler, HB., Goldberg, RJ., Hosmer, DW., .Patwardhan, NA., Jovanovic, B., Forcier, A., & Dalen JE. (1991). A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT study. *Arch Intern Med,* Vol.151, No.5, (May) pp.(933-938), ISSN: (Print) 0003-9926, (Electronic)1538-3679.

Aynaoğlu, G., Durdağ, GD., Ozmen, B., Söylemez, F. (2010). Successful treatment of hereditary factor VII deficiency presented for the first time with epistaxis in pregnancy: a case report. *J Matern Fetal Neonatal Med,* Vol.23, No.9, (Sep), pp.(1053-1055), ISSN: (Print) 1476-7058, (Electronic) 1476-4954.

Bauer, KA., & Rosenberg, RD. (1991). Role of antithrombin III as a regulator of in vivo coagulation. Semin Hematol, Vol.28, No.1, (Jan), pp.10-18, ISSN: (Print) 0037-1963, (Electronic)1532-8686.

Bertina, RM. (1999). Molecular risk factors for thrombosis. *Thromb Haemost,* Vol.82, No.2, (Aug), pp.(601-609), ISSN: (Print) 0340-6245, (Electronic) 0340-6245.

Bloemenkamp, KW., Rosendaal, FR., Helmerhorst, FM., Bumer, HR., & Voldenbroucke JP. (1995). Enhancement by factor V Leiden mutation of risk of deep vein thrombosis associated with oral contraceptives containing a third generation progestagen. *Lancet,* Vol.346, No.8990, (Dec), pp.(1593-1596), ISSN: (Print) 0140-6736, (Electronic)1474-547X.

Brandstater, ME., Roth, EJ., & Siebens, HC. (1992). Venous thromboembolism in stroke: literatüre revievv and implica- tions for clinical practice. *Arch Phys Med Rehabil,* Vol.73, No. (5-S) (Study Guide), (May), pp.(379-391), ISSN: (Print) 0003-9993, (Electronic) 1532-821X.

Carson, JL., Kelley, MA., Duff, A., Weg, JG., Fulkerson, WJ., Palevsky, HI., Schwartz, JS., Thompson, BT., Popovich, J., Jr., Hobbins, TE., Spera, MA., Alavi, A., & Terin ML. (1992). The clinical course of pulmonary embolism. *N Engl J Med,* Vol.326, No.19, (May), pp. (1240-1245), ISSN: (Print):0028-4793, (Electronic):1533-4406.

Castellino, FJ., & Ploplis, VA. (2005). Structure and function of the plasminogen/plasmin system. *Thromb Haemost,* Vol.93, No.4, (Apr), pp. (647–654), ISSN: (Print) 0340-6245, (Electronic) 0340-6245.

Cushman, M., Kuller, LH., Prentice, R., Prentice, R., Rodabough, RJ., Psaty, BM., Stafford, Rs., & Rosendaal, FR.(2004),. Estrogen plus progestin and risk venous thrombosis. *JAMA,* Vol. 292, No.13, (Oct), pp.(1573-1580), ISSN: (Print) 0098-7484, (Electronic) 1538-3598.

Dahlback, B. (1995). Inherited Thrombophilia: resistance to activated protein C as a pathogenetic factor of venous thromboembolism. *Blood,* Vol.85, No.3, (Feb), pp.(607-614), ISSN: (Print) 0006-4971, (Electronic) 1528-0020.

Davenport, RJ., Dennis, MS., Wellwood, I.,& Warlow, CP. (1996). Complications after acute stroke. *Stroke,* Vol.27, No.3, (Mar), pp.(415-420), ISSN: (Print) 0039-2499, (Electronic) 1524-4628.

Dickmann, U., Voth, E., Schicha, H., Henze, T., Prange, H., & Emrich, D. (1988). Heparin therapy, deep vein thrombosis and pulmonary embolism after intracerebral haemorrhage. *Klin Wochenschr*, Vol.66, No.23, (Dec), pp.(1182-183), ISSN: (Print) 0023-2173, (Electronic) 0023-2173.

Dykes, AC., Walker, ID., McMahon, AD., Islam, SI., & Tait RC. (2001). A study of protein S antigen levels in 3788 healthy volunteers: Influence of age, sex and hormone use, and estimate for prevalence of deficiency state. *Br J Haematol,* Vol.113, No.3, (Jun). pp.(636-641, ISSN: (Print) 00071048, (Electronic) 13652141.

Er, O., & Zacharski, L. (2006). Management of cancer-associated venous thrombosis. *Vasc Health Risk Manag,* Vol.2, No.4, (Dec), pp.(351–356), ISSN: (Print) 1176-6344, (Electronic) 1178-2048.

Escoffre, M, Zini, JM., Schliamser, L., Mazoyer, E., Soria, C., Tobelem, G., & Dupuy, E.(1995). Severe arterial thrombosis in a congenitally factor VII deficient patient. *Br J Haematol,* Vol. 91, No.3, (May), pp.(739–741), ISSN: (Print) 0007-1048, (Electronic) 1365-2141.

Falanga, A., & Zacharski, L. (2005). Deep vein thrombosis in cancer: the scale of the problem and approaches to management. *Annals of Oncology,* Vol 16, No.5, (May), pp.(696-701), ISSN: (Print) 0923-7534, (Electronic) 1569-8041.

Furie, B., & Furie, BC. (1988). The molecular basis of blood coagulation. *Cell,* Vol.53, No.4, (May), pp. (505-518), ISSN: (Print) 0092-8674.

Folsom, AR., Aleksic, N., Wang, L., Cushman, M., Wu, KK., & White, RH. (2002). Protein C, antithrombin, and venous thromboembolism incidence: a prospective population-based study. *Arterioscler Thromb Vasc Biol,* Vol.22, No.6, (Jun), pp.(1018-1022). ISSN: (Print) 1079-5642, (Electronic) 1524-4636.

Geerts, W., Jay, RM., Code, KI., Chen, E., Szalai, JP., Saibil, AE., & Hamilton, PA. (1996). A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med,* Vol.335, No.10, (Sep), pp.(701-707), ISSN: (Print):0028-4793, (Electronic):1533-4406.

Greer, IA. (2003). Prevention and management of venous thromboembolism in pregnancy. *Clin Chest Med,* Vol. 24, No.1, (Mar), pp.(123-137),ISSN: (Print) 0272-5231, (Electronic) 1557-8216.

Goldhaber, SZ., Grodstein, F., Stampfer, MJ., Manson, JE., Colditz, GA., Speizer, FE., Willett, WC., & Hennekens, CH. (1997). A prospective study of risk factors for pulmonary embolism in women. *JAMA,* Vol.277, No.8. (Feb), pp. (642-645), ISSN: (Print) 0098-7484, (Electronic) 1538-3598.

Goodnough, LT., Saito, H., & Ratnoff, OD. (1983). Thrombosis or myocardial infarction in congenital clotting factor abnormalities and chronic thrombocytopenias: a report of 21 patients and a review of 50 previously reported cases. *Medicine (Baltimore),* Vol.62, No.4, (Jul), pp. (248-255), ISSN: (Print) 0025-7974, (Electronic) 1536-5964.

Haire, WD., & Lieberman, RP. (1992). Thrombosed central venous catheters: restoring function with 6-hour urokinase infusion after failure of bolus urokinase. *J Parenter Enteral Nutr,* Vol.16, No.2, (Mar-Apr), pp. (129-132), ISSN: (Print) 0148-6071.

Hanly, JG. (2003). Antiphospholipid syndrome: an overview. *CMAJ,* Vol.168, No.13, (Jun), pp. (1675-1682), ISSN: (Print) 0820-3946, (Electronic) 1488-2329.

Hansson, P., Sorbo, J., Erikson, H. (2000). Recurrent Venous Thromboembolism After Deep Vein Thrombosis. *Arch Intern Med,* Vol.160, No.6, (March), pp.(769-774), ISSN: (Print) 0003-9926, (Electronic) 1538-3679.

Hoshi, S., Hijikata, M., Togashi, Y., Aoyagi, T., Kono, C., Yamada, Y., Amano, H., Keicho, N., & Yamaguchi, T. (2007). Protein C deficiency in a family with thromboembolism and identified gene mutations. *Intern Med,* Vol.46, No.13, (Jul), pp. (997-1003), ISSN:(Print) 0918-2918; (Electronic) 1349-7235.

Huber, O., Bounameaux, H., Borst, F., & Rohner, A. (1992). Postoperative pulmonary embolism after hospital discharge. An underestimated risk. *Arch Surg,* Vol.127, No.3, (Mar), pp. (310-313). ISSN: (Print) 0004-0010, (Electronic) 1538-3644.

Hull, RD., Raskob, GE., Brant, RF., Pineo, GF., & Valentine, KA. (1997). The importance of initial heparin treatment on long-term clinical outcomes of antithrombotic therapy: the emerging theme of delayed recurrence. *Arch Intern Med,* Vol.157, No.20, (Nov), pp. (2317–2321), ISSN: (Print) 0003-9926, (Electronic) 1538-3679.

International Stroke Trial Collaborative Group. (1997). The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet,* Vol.349, No.9065, (May), PP. (1569–1581). ISSN: (Print) 0140-6736, (Electronic)1474-547X.

Jeffrey, LC., Kelley, AM.,& Duff, A.(1992). The Clinical Course of Pulmonary Embolism. *N Engl J Med,* Vol.326, No.19, (May), pp.(1240-1245), ISSN: (Print) 0028-4793, (Electronic) 1533-4406.

Kluijtmans, LA., Boers, GH., Trijbels, FJ., van Lith-Zanders, HM., van den Heuvel, LP, & Blom, HJ. (1997). A common 844INS68 insertion variant in the cystathionine beta-synthase gene. *Biochem Mol Med,* Vol. 62. No.1, (Oct), pp. (23-25), ISSN: (Print)1077-3150, (Electronic) 1077-3150.

Kovacevich, GJ., Gaich, SA., Lavin, JP., Hopkins, MP., Crane, SS., Stewart, J., Nelson, D, & Lavin, LM. (2000). The prevalenee of thromboembolie events among women with extended bed rest prescribed as part of the treatment for premature labor or preterm premature rupture of membranes. *Am J Obstet Gynecol,* Vol.182, No.5 (May), pp.(1089-1092), ISSN: (Print) 0002-9378, (Electronic) 1097-6868.

Kraaijenhagen, RA., in't Anker, PS., Koopman, MMW., Reitsma, PH., Prins, MH., van den Ende, A., & Buller, HR. (2000). High plasma concentration of factor VIIIc is a major risk factor for venous thromboembolism. *Thromb Haemost,* Vol.83, No.1, (Jan), pp. (5-9), ISSN: (Print) 0340-6245, (Electronic) 0340-6245.

Kyrle, PA., Minar, E., Hirschl, M, Bialonczyk, C., Stain, M., Schneider, B., Weltermann, A., Speiser, W., Lechner, K., & Eichinger, S. (2000). High plasma levels of factor VIII and the risk of recurrent venous thromboembolism. *N Engl J Med,* Vol.343, No.7, (Aug), pp. (457-462), ISSN: (Print):0028-4793, (Electronic)1533-4406.

Lapostolle, F., Surget, V., Borron, SW., Desmaizieres, M., Sordelet, D., Lapandry, C., Cupa, M., & Arnet, F. (2001). Severe pulmonary embolism associated with air travel. *New Eng J Med,* Vol.345, No.11, (Sep), pp. (779-783), ISSN: (Print):0028-4793, (Electronic):1533-4406.

Lee, KW., & Lip, GY. (2003). Effects of lifestyle on hemostasis, fibrinolysis, and platelet reactivity: a systematic review. *Arch Intern Med,* Vol.163, No.19, (Oct), pp.(2368-2392), ISSN: (Print) 0003-9926; (Electronic) 1538-3679.

Leebeek, FW., Knot, EA., Ten Cate, JW., & Traas, DW. (1989). Severe thrombotic tendency associated with a type I plasminogen deficiency. *Am J Hematol,* Vol.30, No.1, (Jan), pp.(32–35),. ISSN: (Print) 1939-6163, (Electronic) 1939-6163.

Lietz, K., Kuehling, SE., & Parkhurst, JB. (2005). Hemorrhagic stroke in a child with protein S and factor VII deficiencies. *Pediatr Neurol,* Vol.32, No.3, (Mar), pp.(208–210), ISSN: (Print) 0887-8994, (Electronic) 1873-5150.

Makris, M., Rosendaal, FR., & Preston, FE. (1997). Familial thrombophilia: Genetic risk factors and management. J *Int Med Suppl,* Vol.740, (Jan), pp. (9-15), ISSN: (Print) 0955-7873, (Electronic) 0955-7873.

Mariani, G, & Bernardi, F. (2009). Factor VII Deficiency. *Semin Thromb Hemost,* Vol.35, No.4, (Jun), pp.(400-406), ISSN: (Print) 0094-6176, (Electronic) 1098-9064.

Mariani, G., Herrmann, FH., Dolce, A., Batorova, A., Etro, D., Peyvandi, F., Wulff, K., Schved, JF., Auerswald, G., Ingerslev, J., & Bernardi, F; International Factor VII Deficiency Study Group. (2005). Clinical phenotypes and factor VII genotype in congenital factor VII deficiency. *Thromb Haemost,* Vol.93, No.3, (Mar), pp.(481–487), ISSN: (Print) 0340-6245, (Electronic) 0340-6245.

McCarthy, ST., & Turner, J. (1986). Low dose subcutaneous heparin in the prevention of deep vein thrombosis and pulmonary emboli following acute stroke. *Age Ageing,* Vol.15, No.2, (Mar), pp.(84–88). ISSN: (Print) 0002-0729, (Electronic) 1468-2834.

Miles, JS., Miletich, JP., Goldhaber, SZ., Hennekens, CH., & Ridker, PM. (2001). G20210 A mutation in the prothrombin gene and the risk of recurrent venous thromboembolism. *J Am Coll Cardiol,* Vol.37, No.1, (jun), pp.(215–218), ISSN: (Print) 0735-1097, (Electronic)1558-3597.

Miletich, JP., Sherman, L., & Broze, GJJ. (1987). Absence of Thrombosis in Subjects with Heterozygous Protein C Deficiency. *N Engl J Med,* Vol.317, No.16, (Oct), pp.(991–996), ISSN:(Print):0028-4793, (Electronic):1533-4406.

Nicolaides, AN., Breddin, HK., Fareed, J., Goldhaber, S., Haas, S., Hull, R., Kalodiki, E., Myers, K., Samama, M., & Sasahara, A. (2001). Cardiovascular Disease Educational and Research Trust and the International Union of Angiology. Prevention of venous thromboembolism. International Consensus Statement. Guidelines

compiled in accordance with the scientific evidence. *Int Angiol,* Vol.20, No.1, (Mar), pp. (1-37), ISSN:(Print) 1061-1711, (Electronic) 1615-5939.

Nightingale, C.E., Norman, A., Cunningham, D., Young, J., Webb, A., & Filshie, J. (1997). A prospective analysis of 949 long-term central venous Access catheters for ambulatory chemotherapy in patients with gastrointestinal malignancy. *Eur J Cancer,* Vol.33, No.3, (Mar), pp.(398-403), ISSN: (Print) 0959-8049, (Electronic) 1879-0852.

Poort, SR., Rosendaal, FR., Reitsma, PH., & Bertina, RM. (1996). A common genetic variation in the 3'-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. *Blood,* Vol.88, No.10, (Nov), pp. (3698–3703), ISSN: (Print) 0006-4971, (Electronic) 1528-0020.

Quinn, DA., Thompson, BT., Terrin, ML., Thrall, JH., Athanasoulis, CA., McKusick, KA., Stein, PD., & Hales, CA. (1992). A prospective investigation of pulmonary embolism in women and men. *JAMA,* Vol.268, No.13, (Nov). pp. (1689-1696). ISSN: (Print) 0098-7484, (Electronic) 1538-3598.

Robbins, KC. (1990). Classification of abnormal plasminogens: dysplasminogenemias. *Semin Thromb Hemost,* Vol.16, No.3, (Jul), pp. (217–220), ISSN: (Print) 0094-6176, (Electronic) 1098-9064.

Rosendaal, FR. (1999). Risk factors for venous thrombotic disease. *Thromb Haemost,* Vol.82, No.2, (Aug), pp. (610-619), ISSN: (Print) 0340-6245, (Electronic) 0340-6245.

Rosendaal, FR., Koster, T., Vandenbroucke, JP., Reitsma, PH. (1995). High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). *Blood,* Vol.85, No.6, (Mar), pp.(1505–1508), ISSN: (Print) 0006-4971, (Electronic) 1528-0020.

Rosing, J., Tans, G., Nicolaes, GA., Thomassen, MC., van Oerle, R., van der Ploeg, PM., Heijnen, P., Hamulyak, K., & Hemker, HC. (1997). Oral contraceptives and venous thrombosis: different sensitivities to activated protein C in women using second and third generation oral contraceptives. *Br J Haematol,* Vol. 97, No.1, (Apr), pp. (233-238), ISSN: (Print) 0007-1048, (Electronic) 1365-2141.

Rubinstein, I., Murray, D., & Hoffstein, V. (1988). Fatal pulmonary emboli in hospitalized patients. An autopsy study. *Arch Intern Med,* Vol.148, No.6, (Jun), pp. (1425-1426), ISSN: (Print) 0003-9926, (Electronic) 1538-3679.

Sapey, E., & Stockley, RA. (2006). COPD exacerbations: 2. Aetiology. *Thorax,* Vol.61, No.3, (Marc), pp. (250–258), ISSN: (Print) 0040-6376, (Electronic)1468-3296.

Schambeck, C., Grossmann, R., Zonnur, S., Berger, M., Teuchert, K., Spahn, A., & Walter U. (2004). High factor VIII (FVIII) levels in venous thromboembolism: role of unbound FVIII. *Thrombosis and haemostasis,* Vol. 92, No.1, (July), pp.(42-46), ISSN: (Print) 0340-6245, (Electronic) 0340-6245.

Schorer, AE., Singh, J., & Basara, ML. (1995). Dysfibrinogenemia: a case with thrombosis (fibrinogen Richfield) and an overview of the clinical and laboratory spectrum. *Am J Hematol,* Vol.50, No.3, (Nov), pp.(200-208), ISSN: (Print) 1939-6163, (Electronic) 1939-6163.

Schuster, V., Zeitler, P., Seregard, S., Ozcelik, U., Anadol, D., Luchtman, JL., Meirc, F., Mingers, AM., Schambeck, C., & Krelh, HW. (2001). Homozygous and compound-heterozygous lype I plasminogen deficiency is a common cause of ligneous conjunctivitis. *Thromb Haemost,* Vol.85, No.6, (Jun), pp.(1004-1010), ISSN: (Print) 0340-6245, (Electronic) 0340-6245.

Shackford, SR., Davis, JW., Hollingsworth-Fridlund, P., Brewer, NS., Hoyt, DB., & Mackersie, RC. (1990). Venous thromboembolism in patient with major trauma. *Am J Surg,* Vol.159, No.4, (Apr), pp.(365-369), ISSN: (Print) 0002-9610, (Electronic) 1879-1883.

Sidney, S., Sorel, M., Quesenberry, CP Jr., DeLuise, C., Lanes, S.,& Eisner MD. (2005). COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest,* Vol.128, No.4, (Oct), pp.(2068–2075), ISSN: (Print) 0012-3692, (Electronic) 1931-3543.

Spitzer, WO., Lewis, MA., Heinemann, LA., Thorogood, M., & MacRae, KD. (1996). Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. Transnational Research Group on Oral Contraceptives and the Health of Young Women. *Br Med J,* Vol.312, No.7023, pp. (83-88), ISSN: (Print) 0959-8138, (Electronic) 1468-5833.

Stein, PD., Huang, HI., Afzal, A., & Noor, HA. (1999). Incidence of acute pulmonary embolism in a general hospital: relation to age, sex, and race. *Chest,* Vol.116, No.4, (Oct), pp.(909-913), ISSN: (Print) 0012-3692, (Electronic) 1931-3543.

Stein, PD., & Matta, F. (2010). Acute pulmonary embolism. *Curr Probl Cardiol,* Vol.35, No.7, (Jul), pp.(317-376), ISSN: (Print) 0146-2806, (Electronic)1535-6280.

Subbarao, J., & Smith J. Pulmonary embolism during stroke rehabilitation. (1984). *IMJ Ill Med J,* Vol.165, No.5, pp.(328-332), (May), ISSN: (Print) 0019-2120, (Electronic) 0019-2120.

Tait, RC., Walker, ID., Perry, DJ., Islam, SI., Daly, ME., McCall, F., Conkie, JA., & Carrell, RW. (1994). Prevalence of antithrombin deficiency in the healthy population. *Br J Haematol,* Vol.87, No.1, (May), pp.(106-112), ISSN: (Print) 0007-1048, (Electronic) 1365-2141.

Tapson, VF. (2008). Acute pulmonary embolism. *N Engl J Med,* Vol.358, No.11, (Mar), pp.(1037–1052), ISSN: (Print):0028-4793, (Electronic):1533-4406.

Thaler, E., Lechner, K. (1981). Antithrombin III deficiency and thromboembolism. *Clin Haematol,* Vol.10, No.2, (Jun), pp.(369-90), ISSN: (print) 0308-2261, (Electronic) 0308-2261.

van Dieijen, G., Tans, G., Rosing, J., & Hemker, HC. (1981). The role of phospholipid and factor VIIIa in the activation of bovine factor X. *J Biol Chem,* Vol.256, No.7, (Apr), pp. (3433 3442), ISSN: (Print) 0021-9258, (Electronic) 1083- 351X.

Warlow, C., Ogston, D., & Douglas, AS. (1972). Venous thrombosis following strokes. *Lancet,* Vol.1, No.7764, (Jun), pp.(1305–1306), ISSN: (Print) 0140-6736, (Electronic) 1474-547X.

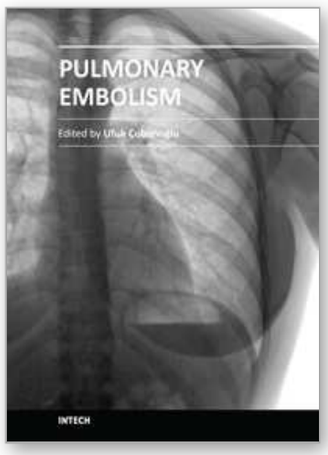
Weisberg, I., Tran, P., Christensen, B., Sibani, S., & Rozen R. (1998). A second genetic polymorphism in methylenetetrahydrofolate reductase (MTHFR) associated with decreased enzyme activity. *Mol Genet Metab*, Vol.64, No.3, (Jul). Pp.(511–512), ISSN: (Print)1096-7192, (Electronic) 1096-7206.

White, RH. (2003). The epidemiology of venous thromboembolism. *Circulation,* Vol.107, No. (23 Suppl 1), (Jun), pp.(14-18), ISSN: (Print) 0009-7322, (Electronic)1524-4539.

World Healt organization collaborative study of cardiovascular disease and steroid hormone contraception. (1995). Effect of different progestagens in low oestrogen oral contraseptives on venous thromboembolic disease. *Lancet,* Vol.346, No.8890, (Dec), pp.(1582-1588), ISSN: (Printed) 0140-6736, (Electronic)1474-547X.

Yanbaeva, DG., Dentener, MA., Creutzberg, EC., Wesseling, G., & Wouters, EF. (2007), Systemic effects of smoking. *Chest,* Vol.131, No.5, pp.(1557-1566), ISSN: (Print) 0012-3692, (Electronic) 1931-3543.

Yarnell, JW., Sweetnam, PM., Rumley, A., & Lowe, GD. (2000). Lifestyle and hemostatic risk factors for ischemic heart disease : the Caerphilly Study. *Arterioscler Thromb Vasc Biol,* Vol.20, No.1, (Jan), pp.(271-279), ISSN: (Print) 1079-5642, (Electronic)1524-4636.



Pulmonary Embolism
Edited by Dr. Ufuk Çobanoğlu

ISBN 978-953-51-0233-5
Hard cover, 236 pages
Publisher InTech
Published online 14, March, 2012
Published in print edition March, 2012

Pulmonary embolism is a serious, potentially life-threatening cardiopulmonary disease that occurs due to partial or total obstruction of the pulmonary arterial bed. Recently, new improvement occurred in the diagnosis and treatment of the disease. The aim of this disease is to re-review pulmonary embolism in the light of new developments. In this book, in addition to risk factors causing pulmonary embolus, a guide for systematic approaches to lead the risk stratification for decision making is also presented. In order to provide a maximum length of active life and continuation of functional abilities as the aim of new interventional gerontology, the risk factors causing pulmonary embolus in elderly individuals are evaluated, and the approach to prevention and treatment are defined. The risk of the development of deep vein thrombosis and pulmonary embolism, combined with obesity due to immobility, the disease of this era, irregular and excessive eating, and treatment management are highlighted. Non-thrombotic pulmonary emboli are also covered and an attempt is made to constitute an awareness of this picture that can change the treatment and prognosis of the disease to a considerable extent. In addition to the pathophysiological definition of pulmonary embolus, the priority goal of quick and definitive diagnosis is emphasized, and diagnostic strategies are discussed in the book. A numerical analysis of the vena cava filters, which is a current approach to prevent pulmonary emboli recurrences, is presented in the last chapter.

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen