

## PULMONARY THROMBOEMBOLISM AND ROLE OF FACTOR V LEIDEN IN ITS DEVELOPMENT - REVIEW OF LITERATURE

Lazović Biljana,<sup>1</sup> Milić Rade,<sup>2</sup> Detanac A. Dženana,<sup>3</sup> Detanac S. Džemail,<sup>3</sup>  
Mulić Mersudin,<sup>4</sup> Žugić Vladimir<sup>5</sup>

<sup>1</sup> University clinical center “Zemun”, Belgrade, Pulmonary Ward, Serbia

<sup>2</sup> Military Medical academy, Clinic for lung disease, Belgrade, Serbia

<sup>3</sup> General Hospital, Novi Pazar, Serbia

<sup>4</sup> State University Novi Pazar, Serbia

<sup>5</sup> Clinic for lung diseases, Clinical center of Serbia, Belgrade, School of medicine, University of Belgrade, Serbia

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**Abstract:** Pulmonary embolism (PE) and deep vein thrombosis (DVT) are associated with considerable morbidity and mortality, and for as much as twenty-five percent of PE patients the primary clinical appearance is unexpected death. Diagnosis of PE is based on clinical suspicious at first, but sometimes its diagnostics can be extremely difficult. Newly increased interest in an inherited thrombophilic states has been provoked by the discovery of several common inherited abnormalities, i.e. the prothrombin (PT) gene G20210A, Factor V Leiden (FVL) mutation (Arg506Gln), hyperhomocystenemia and homocysteinuria, Wein-Penzing defect, Sticky Platelet Syndrome (SPS), Quebec platelet disorder (QPD) and Sickle Cell Disease (SCD). PE incidence rates increase in recent years. The only explanation at this moment is increased awareness of PE, especially after any kind of surgery, immobile state or unexplained shortness of breath.

**Key words:** Inherited thrombophilic states, venous thromboembolism, pulmonary embolism.

### INTRODUCTION

Venous thromboembolic disorders (VTE) are serious disorders with high morbidity and mortality rates. Many genetic and acquired risk factors were identified to cause VTE (1).

Thrombophilia is the term given to abnormal blood coagulation condition leading to hypercoagulability status. People with hypercoagulability are at risk of developing thrombosis, especially venous thromboembolic disorders (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a

significant cause of morbidity and mortality in many countries with an annual incidence of 1/1000 (2, 3). Many genetic and acquired risk factors for the development of VTE were identified. In fact, the WHO expert group (1996) defined thrombophilia as a tendency to develop VTE that may be genetically determined, acquired or both (4). Genetic factors include activated protein C resistance (APC-R) associated with Factor V, Prothrombin G20210A mutation associated with high levels of prothrombin, genetic deficiencies of proteins C, S and antithrombin, and others. Acquired risk factors include lupus anticoagulants, pregnancy, the use of contraceptives, major surgeries, cancer, inflammations, and others. This review article focuses on the epidemiology of APC-R/FVL as the most common risk factor for PE in 20-40% patients (5).

### HEMOSTASIS

Normal human hemostasis is a balanced system which, on one hand, prevents excessive bleeding from any injured site, while on the other hand maintains blood circulation inside intact blood vessels by inhibiting intravascular coagulation. A healthy hemostatic process involves proteins called the plasma clotting factors (enzymes). These enzymes circulate in the blood in an inactive form, and get activated in case of vessel injury. In summary, when a blood vessel is injured, the coagulation cascade is initiated by the release of tissue factor (thromboplastin) and the exposure of intravascular collagen, which activates clotting factors VII and XII, respectively. These clotting factors activate other clotting factors in a stepwise procedure ending

up with the formation of a fibrin clot. A fibrin clot, in association with platelets, form a plug that blocks the injured blood vessel, preventing bleeding and allowing for wound healing. After healing, the fibrin clot is dissolved by the enzyme plasmin in a process called fibrinolysis. The whole process is under careful supervision by three main proteins that circulate normally in the blood; namely protein C (and its active form activated protein C; APC), protein S (PS) and antithrombin (AT). These so-called “natural anticoagulants” monitor the processes of coagulation and fibrinolysis in order to prevent excessive clotting. Abnormalities in clotting factors may lead to bleeding problems (hemophilia), while abnormalities in the natural anticoagulants may lead to hypercoagulability and thrombosis, with certain exceptions in both (5-8).

### APC-R/FVL

**Factor V Leiden (rs6025)** is a variant (mutated form) of human factor V (one of several substances that helps blood clot), which causes an increase in blood clotting (hypercoagulability). With this mutation, protein C, an anticoagulant protein (which normally inhibits the pro-clotting activity of factor V), is not able to bind normally to Factor V, leading to a hypercoagulable state, i.e., an increased tendency for the patient to form abnormal and potentially harmful blood clots. Factor V Leiden is the most common hereditary hypercoagulability disorder amongst ethnic Europeans. It is named after the Dutch city Leiden, where it was first identified in 1994 by Prof R. Bertina under the direction of (and in the laboratory of) Prof P. Reitsma (7, 8, 9).

Together, protein C and S deficiencies and antithrombin III comprise between 5 percent and 10 percent of all DVT cases. Factor V Leiden is responsible for many more, between 20 percent and 40 percent. Normally, APC should inactivate clotting Factor V (FV) and therefore slow down the coagulation process. About 3 percent of the general population has this gene alteration, also called a mutation. Dahlbäck and al. called this phenomenon “APC resistance”, and they originally thought this could be due a deficiency in a yet unknown protein that co-helps APC in inactivating FV (5). It is about a missense point mutation in the FV gene and nucleotide replacement. Because of the amino acid change in FVL, APC can no longer inactivate FV efficiently, but FV retains its coagulation capabilities and therefore carriers of FVL develop hypercoagulability which may clinically manifest as VTE episodes. Later studies showed that people with FVL were at higher risk of developing VTE (10-fold in heterozygous carriers and 30 to 140-fold in homozygous carriers) (9, 10, 11). Additionally most homozygotes for FVL were reported to get at least one VTE event in their life time

(12, 13). This explains the great clinical and scientific consideration this mutation had appealed and the hundreds of studies conducted on its prevalence and risk for developing VTE in almost every part of the world.

Interesting thing is that clinical symptoms in patients with the factor V Leiden mutation are variable. Some patients could never experience thrombosis, whereas other patients suffer recurrent and severe thrombotic events. Because of this marked variance, lifelong anticoagulation may not be necessary for all individuals with factor V Leiden mutation. Lifelong anticoagulation should be reserved for patients who experience two or more thrombotic events or a single life-threatening thrombosis (14).

### DISTRIBUTION OF THE COAGULATION FACTOR V

Distribution of the coagulation factor VR506Q (FV Leiden) mutation, which is known to be a cause of VTE, is often seen in Caucasians, whereas the mutation has not been reported in other population, in fact the prevalence was almost zero in other ethnic groups (15, 16). Therefore, its development is of historical significance. A group of scientists got a perception that FVL has occurred once in the past time in one European Caucasian person. Anthropology proposes that Caucasoid populations who settled in Europe were diverted from Mongoloid populations (who moved to East Asia) around 32 thousands of years ago; therefore FVL should have appeared sometime earlier than 32,000 years ago (17-20). It was suggested that the mutation occurred in Europe first, and then spread to other parts of the world. The rarity of FVL in the French and Spanish Basque populations, which are thought to be the oldest ethnic groups in Europe of Paleolithic origin, has also suggested FVL to occur outside Europe first (21, 22). Lucotte et al proposed that FVL expanded in Europe during the Neolithic period, from a probable Anatolian center of origin in Turkey, which has occurred around 10,000 years ago (23). This may explain the highest prevalence of FVL in East Mediterranean countries, and that the prevalence decreases when radiating away from this region towards Europe or other parts of the world. Still, more genetic and molecular studies may be needed to detect certain genetic loci or markers that may help in following the movement of carriers of FVL in the Mediterranean region to definitely determine the exact location where FVL might have occurred first.

### CONCLUSION

DVT has been focused on and recognized by medical professionals and by general citizens. In medical professionals, mechanical compressions, malignant di-

seases, lower limb operations, sedentary postures for long periods and central vein catheters cause VTEs, and DVT often results in fatal pulmonary thromboembolism, which is unacceptable in the modern diagnostic and medical treatment. We cannot fight against hereditary factors, but if one is to have lung thromboembolism, it is necessary to have hematological testing.

### Abbreviations

**PE** — Pulmonary embolism  
**DVT** — deep vein thrombosis  
**PT** — prothrombin  
**FVL** — Factor V Leiden

**SPS** — Sticky Platelet Syndrome  
**QPD** — Quebec platelet disorder  
**SCD** — Sickle Cell Disease  
**VTE** — Venous thromboembolic disorders  
**APC-R** — activated protein C resistance

### DECLARATION OF INTEREST

The authors declare that there are no conflicts of interest.

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### Sažetak

## PLUĆNA TROMBOEMBOLIJA I ULOGA FAKTORA V LEIDEN U NJENOM NASTANKU — PREGLED LITERATURE

Lazović Biljana,<sup>1</sup> Milić Rade,<sup>2</sup> Detanac A Dženana,<sup>3</sup> Detanac S Džemail,<sup>3</sup> Mulić Mersudin,<sup>4</sup> Žugić Vladimir<sup>5</sup>

<sup>1</sup> University clinical center "Zemun", Belgrade, Pulmonary Ward, Serbia

<sup>2</sup> Military Medical academy, Clinic for lung disease, Belgrade

<sup>3</sup> General Hospital, Novi Pazar, Serbia

<sup>4</sup> State University Novi Pazar

<sup>5</sup> Clinic for lung diseases, Clinical center of Serbia, Belgrade, School of medicine, University of Belgrade, Serbia

Plućna embolija (PE) i duboka venska tromboza (DVT) su povezani sa značajnim stepenom mortaliteta i morbiditeta, a za 25% PE pacijenata prvi klinički znak je neočekivana smrt. Dijagnoza PE zasnovana je na kliničkoj sumnji u prvom koraku, ali ponekad je i određivanje same dijagnostike izuzetno otežano. U poslednje vreme dosta pažnje se posvećuje urođenim stanjima trombofilije, koja su bila najviše izazvana otkrićem nekoliko čestih naslednih abnormalnosti, npr gen za protrombin (PT) G20210A, mutacija za faktor V Le-

iden (FVL) /Arg506Gln), hiperhomocisteinemija i homocistinurija, Wein-Penzing defekt, Sindrom lepljivih Trombocita (SPS), poremećaj trombocita – Kvebek (QPD) i anemija srpastih ćelija (SCD). Incidencija PE beleži značaj porast u poslednjih par godina. Jedno od mogućih rešenja je proširena svest o pojavi PE, posebno nakon bilo kakvih oblika hirurgije, stanja nepokretnosti i neobjašnjivog gubitka daha.

**Ključne reči:** nasledna trombofilna stanja, venska tromboembolija, plućna embolija.

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### Correspondence to/Autor za korespondenciju

Biljana Lazovic

University clinical center "Zemun", Belgrade, Serbia

Vukova 9, Zemun, 11070 Belgrade

Email: lazovic.biljana@gmail.com