



Thrombosis and Thrombophilia

What is Thrombosis?

Normal clotting is essential for stopping blood loss after an injury. But abnormal clotting or *thrombosis* means clotting when there is no apparent injury. An abnormal clot in a blood vessel is called a *thrombus*, and it may completely plug the vessel. For example, a thrombus may plug an artery that provides blood to the heart muscle, causing a heart attack, or *acute myocardial infarction*. Another may plug a large leg vein, causing *deep venous thrombosis (DVT)*. Pieces of venous clots may break off, travel to the lungs or brain, and plug an artery. These pieces are called *emboli*. An *embolus* that travels to the brain causes a stroke. One that goes to the arteries in the lungs is called a *pulmonary embolism (PE)*, often fatal. This is an article about venous thrombosis. Many good articles on arterial thrombosis may be found on the web site of the American Heart Association.

What Are the Symptoms of Venous Thrombosis?

Deep venous thrombosis: symptoms of DVT include pain, swelling, discoloration of the affected area in the leg, and skin that feels warm. But up to 50% of DVTs produce minimal symptoms. Because muscle strains, skin infections, and inflammation of superficial veins (phlebitis), give symptoms similar to those of deep vein thrombosis, the condition may be difficult to diagnose without ultrasound or magnetic resonance imaging (MRI).

Pulmonary embolism: Blockage of the *main pulmonary artery* in the lung by an embolus may be fatal. In non-fatal PE, symptoms include shortness of breath, a feeling of apprehension, rapid pulse, sweating, and sharp chest pain that worsens with deep breathing. Some patients may cough up bloody sputum. Others may develop very low blood pressure and faint. Anyone experiencing these symptoms should call for assistance and get to the hospital as soon as possible. Heart attack, severe bronchitis, and pneumonia may mimic pulmonary embolism.

Effective treatment for DVT or PE is available provided the symptoms are recognized early.

What is Thrombophilia?

Thrombophilia is a condition or a disorder that increases the risk of thrombosis. For example, elevated *cholesterol* levels double the risk of a heart attack. Risk factors are *acquired* throughout life; others are *inherited* at conception.

Some *acquired* risk factors that are related to *venous thrombosis* are listed in table 1.

Table 1: Acquired venous thrombosis risk factors and the risk of a thrombotic event

Factor	Risk
Large leg bone fractures	80% possibility
Previous clot in a leg vein	50% possibility
Hip, knee, GYN, or prostate surgery	50% possibility
Chronic antiphospholipid antibody (see below)	30% possibility
Various types of cancer	20-fold increased risk
Birth control pills (30 mg)	4-6-fold increased risk
Pregnancy	3-5-fold increased risk
Hormone replacement therapy (5 mg)	2-4-fold increased risk
Vitamin B ₆ , B ₁₂ , or folic acid deficiency, causing homocysteine increase in blood	2-7-fold increased risk

Some *inherited* risk factors that are related to *venous thrombosis* are listed in table 2.

Table 2: Inherited thrombosis risk factors and risk of a thrombotic event

Factor	Prevalence	Risk
APCR: heterozygous FVL mutation	3-8% of Caucasians, Arabs, and Hispanics	2-8x
APCR: homozygous FVL mutation		80x
Prothrombin G20210A heterozygotes	2-3% of Caucasians, Arabs, and Hispanics	2-6x
Antithrombin heterozygotes	1 in 2000-5000	10-24x
Protein C heterozygotes	1 in 300	6.5x
Protein S heterozygotes	1%	1.6 to 11.5x
Double heterozygote	Unknown	80x
Triple heterozygote	Unknown	Unknown

Chronic Antiphospholipid Antibody and Homocysteine

The conditions in table 1 are self-explanatory except for *chronic antiphospholipid antibody and homocysteine*.

Antiphospholipid antibodies, sometimes named lupus anticoagulants, are blood proteins that appear following a viral infection or during the course of a chronic inflammatory condition like arthritis or cancer. About half of patients who have lupus erythematosus develop antiphospholipid antibodies, however the proteins are detected in many other conditions or even with certain drugs. They are common, detectable in 1 to 2% of people, but most disappear after six weeks. Those that persist confer a 30% risk of a venous or arterial thrombotic event.

Clinical scientists identify antiphospholipid antibodies through a complicated series of laboratory analyses performed at specialty laboratories. When the test is negative but the symptoms imply the antibody is there, the physician may choose to repeat the test after a few weeks. Likewise, if the test is positive, a repeat test is required to confirm the diagnosis. Antiphospholipid antibodies are not inherited so there is no need to test the kindred of patients with the protein.

Homocysteine is a normal blood component that becomes elevated in people who are not getting enough folic acid, vitamin B₆, or vitamin B₁₂. Homocysteine may be measured in most

clinical laboratories. The higher the level, the greater the risk for a thrombotic event. Dietary inclusion of the vitamins usually rectifies the situation.

Mendelian Inheritance

The mutated genes for thrombophilia risk factors listed in table 2 are inherited in a *simple Mendelian dominant* fashion. Everyone has two copies of a gene, one from each of their parents. It takes only one copy carrying the mutation to increase the risk for abnormal blood clotting. If we get a normal gene from one parent and a mutated gene from the other, we are *heterozygous* for the mutation. This means that one of the two genes is abnormal. If we get abnormal genes from each parent, we are *homozygous*, with two abnormal genes. Homozygous mutations are often fatal.

If one parent is heterozygous for a risk factor and the other is normal, each child has a 50% chance of inheriting the mutation. Each sibling of a person who is heterozygous has a 25% chance of being heterozygous. Whenever a person is discovered to be either heterozygous or homozygous, all close relatives should be tested for the mutation.

Antithrombin, Protein C, and Protein S

Diminished coagulation *control proteins* cause one form of thrombophilia. Since 1972, laboratory scientists have identified three such clot-controlling proteins, named *antithrombin*, *protein C*, and *protein S*. The data in table 2 show that inherited deficiencies are rare but confer a severe clotting risk. Very few cases of *homozygous* antithrombin, protein C, or protein S deficiency have been described. A homozygous deficiency is usually fatal.

Laboratory tests for these proteins are widely available, however the tests are invalid when patients have recently suffered a thrombotic event or when they are on Coumadin or heparin anticoagulants.

Factor V Leiden and Prothrombin 20210

Both factor V Leiden and prothrombin 20210 are “gain of function” mutations that affect blood-clotting factors, factor V (five) and prothrombin, in such a way that they are more active than normal. The factor V Leiden mutation is fully described in a separate article on this uabcoag.net web site. Both are quite common in Caucasians, Hispanics, and Arabs, but uncommon among Africans and absent from Asians.

Treatment

For people with thrombophilia, doctors may prescribe protective *anticoagulant* (blood-thinning) therapy during unavoidable periods of increased risk. For example, a patient with protein S deficiency may be instructed to use *heparin* injections for a few days after major surgery.

Patients who have had a blood clot may be placed on long-term anticoagulant therapy such as Coumadin pills. Some thrombophilia sufferers who have experienced a clot may need to take Coumadin indefinitely. This well-known drug requires monthly laboratory monitoring. Please read more information on Coumadin this web site.

For more information, contact the UAB Coagulation Service

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