Is There a Genetic Relationship Between Arterial and Venous Thrombosis?

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ABBREVATIONS: ASVD = atherosclerotic vascular disease; DVT = deep venous thrombosis; GAIT = Genetic Susceptibility to Thrombosis; PE = pulmonary embolus; VTE = venous thromboembolic event.

INDEX TERMS: acute coronary syndrome; atherosclerotic vascular disease; deep vein thrombosis; lipids; myocardial infarction; pulmonary embolism; stroke; venous thromboembolic disease.

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LEARNING OBJECTIVES

1. Correlate the clinical pathologic manifestations with the type of thrombosis (arterial vs venous).
2. Compare and contrast the most important risk factors, the nature of the clot, and the target for therapeutic prevention and treatment for arterial and venous clot formation.
3. Summarize the data suggesting a link between arterial and venous thrombosis.

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Thromboembolic disease is the leading cause of morbidity and mortality in the developed world.[1] Arterial thrombosis is the most common underlying cause of acute myocardial infarction, non-hemorrhagic cerebrovascular accidents, and peripheral vascular disease. Pathological manifestations of venous thrombosis largely include deep venous thrombosis (DVT) and/or pulmonary embolus (PE). While arterial thromboembolic events are the foremost cause of death and disability, venous disease also plays an important role. DVT affects approximately two million Americans annually while PE is the most common cause of preventable hospital death accounting for 60,000 deaths in the United States annually.[2]

Medical textbooks and epidemiological studies characteristically consider arterial and venous thromboembolic disease as distinct entities, each with their own pathophysiological basis, unique risk factors, and distinct therapeutic regimens.[3-6] Arterial clots typically occur in an injured vessel and the most common cause of vascular damage in the arterial system is atherosclerotic vascular disease (ASVD).[3] The risk factors for arterial thrombosis are therefore considered the same as those for ASVD. Arterial clots occur in a high flow, high shear environment and these clots, also called white clots, are rich in platelets. Prevention and treatment of arterial thrombosis is often aimed at platelet inhibition. While vascular injury can promote the formation of venous clots, stasis and changes in blood composition (thrombophilia) are the most important risk factors for venous clot development.[3] Venous clots occur in a low flow system. They are rich in fibrin that is enmeshed with red blood cells and are referred to as red clots. Inhibition of fibrin formation is the mainstay of prevention and treatment of venous thrombosis. It is often reported that the risk factors for arterial and venous thrombosis largely differ.[5,6]

Is this distinction between arterial and venous thrombosis artificial? Is it a by-product of the fact that these entities often occur in different clinical settings and that they are treated differently and by different physician specialists? Have research and epidemiological studies, in evaluating arterial and venous disease as separate entities, perpetuated this segregated approach? Is it possible or perhaps likely that arterial and venous thromboembolic events actually represent different presentations of the same disease? While it is appreciated that

one may provoke the other as either can activate the hemostatic system, is the relationship between these entities in fact, more intimate?[3] One important consideration supporting a close link is the well appreciated concept that both arterial and venous thrombosis are complex multi-factorial traits in which multiple genetic and acquired risk factors interact to determine risk.[4,6,7] Do the risk factors for arterial and venous thrombosis share more in common than previously realized? If so, are there common genetic and acquired components? Indeed, recent studies, including a select few discussed below, have demonstrated a close association between these entities at a variety of levels. Specifically it has been shown that 1) arterial and venous thrombosis share common risk factors, 2) individuals that suffer idiopathic VTE are at a markedly increased risk of suffering a significant cardiovascular event, 3) individuals that suffer idiopathic VTE have an increased incidence of atherosclerotic vascular disease, and 4) those that suffer idiopathic VTE have a significantly higher incidence of metabolic syndrome.

The risk factors reported to be common to both arterial and venous thrombosis and that represent significant hazard for the development of each entity include increasing age and weight, smoking, exposure to estrogen, and the presence of diabetes. It has also been shown that high HDL cholesterol levels are associated with a decreased risk of venous thrombosis while elevated triglyceride and/or total cholesterol levels convey an increased risk. [8,9] Other risk factors reported to be common to both arterial and venous thrombosis include the presence of antiphospholipid antibodies, dysfibrinogenemia, hyperhomocysteinemia, and elevated levels of fibrinogen, lipoprotein (a) and factor VIII.[10,11]

A number of studies published recently have reported a strong link between arterial and venous thromboembolic disease. These studies have shown that patients who suffer an idiopathic venous thromboembolic event (VTE) are more likely to experience a significant arterial event than either the general population or those who suffered a provoked venous thrombosis. [12] In a 2005 study published in the *European Heart Journal*, of those who suffered their first idiopathic PE, 11% had a symptomatic arterial event with 12% mortality while those with a PE secondary to a known provocateur suffered a 4% rate of symptomatic arterial events with 4% mortality. Another study published in 2006 reported that 11% of those who suffered an idiopathic VTE had a symptomatic arterial event with 8% mortality compared to 4% in the secondary VTE group with a 3% mortality rate. Likewise, Prandoni and others reported a 60% higher risk of suffering arterial events in those with idiopathic VTE than the cohort with VTE secondary to well-established risk factors after adjusting for age, hypertension, smoking, gender, and the presence of diabetes.[13] Cardiovascular events therefore represent a major cause of morbidity and mortality in those individuals also at risk for idiopathic PE. This link supports a strong connection between arterial and venous thrombosis.[12] Given these reports, idiopathic PE can be considered an independent risk factor for cardiovascular disease.

In a recent study reported in the *New England Journal of Medicine*, patients with idiopathic VTE who were asymptomatic for atherosclerosis were studied using carotid ultrasound.[14] Carotid plaques are considered a reliable indicator of atherosclerosis elsewhere in the circulation, in subjects without symptomatic athersclerosis. Forty-seven percent of those individuals with idiopathic VTE had carotid plaque compared to twenty-seven percent with secondary DVT and thirty-two percent of controls. [14] After noting this association between spontaneous VTE and atherosclerotic disease, the authors hypothesized that either one induces the other or else they share common risk factors.

There is an apparent association between metabolic syndrome, characterized by insulin resistance or glucose intolerance, hypertension, atherogenic dyslipidemia, central obesity, and the development of idiopathic VTE. [15] It is well-established that those with metabolic syndrome are at significantly increased risk for the development of cardiovascular events. These individuals are also at risk for suffering spontaneous VTE. Ageno demonstrated that patients with idiopathic VTE had a higher incidence (51%) of metabolic syndrome than those without VTE (35%) or those that suffered VTE with known provocateur. [15] Should individuals with metabolic syndrome be more likely to receive thromboprophyaxis in situations of increased thrombotic risk than those without metabolic syndrome?

One of the strongest pieces of evidence in favor of a link between arterial and venous thrombosis is the Genetic Suseptibility to Thrombosis (GAIT) study. [16] This family-based study of the genetics of thrombosis in a Spanish population was initiated to determine the heritability of thrombosis. Three hundred and twenty-eight individuals in 21 extended pedigrees were evaluated using a novel computer assisted adaptation of a multivariate threshold model. The authors concluded that more than 60% of the variation in susceptibility to common thrombosis is attributable to genetic factors. What makes this study unusual is that both

venous and arterial thromboembolic events were included in the analysis. When venous and arterial thrombosis were jointly analyzed as two distinct traits, the genetic correlation between these entities was not significantly different from one, and this strongly suggests that arterial and venous thromboses are highly genetically correlated. That is, many of the same genes are involved in the pathogenesis of arterial and venous disease.

The recent studies cited suggest that arterial and venous thrombosis represent different manifestations of the same disease and that the underlying process is driven by a common set of genes. [15,16] The implications of these findings are significant with potential impact on many different areas of medicine from basic research to the various patient treatment regimens in current use. Transgenic and knock-out murine models evaluating thrombotic risk should evaluate risk of *both* arterial and venous disease, as should large family studies using genome wide linkage analysis. On a more practical note, the close link demonstrated between arterial and venous thrombosis suggests that patients who suffer idiopathic VTE should be closely evaluated for risk of all cardiovascular events and that individuals with atherosclerotic vascular disease should be monitored or in some circumstances provided prophylaxis for VTE. Future trials are needed to determine whether the long-term management of VTE should include prophylaxis against arterial cardiovascular events.

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