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Is Peripheral Artery Disease a Hypercoagulable Disorder?

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Peripheral artery disease (PAD) affects more than 200 million individuals worldwide, and is associated with substantial cardiac and limb morbidity and all-cause mortality. Despite its prevalence and well described adverse outcomes, the pathobiology of PAD is incompletely understood. Conventional risk factors for PAD include demographics, such as older age and male sex, environmental exposure to tobacco smoke, and traditional cardiovascular risk factors, including hypertension, diabetes mellitus, and chronic kidney disease.

Observational data from the Atherosclerosis Risk in Communities (ARIC) study cohort noted increased plasma levels of hemostatic markers, such as fibrinogen, von Willebrand factor (VWF), and coagulation factor VIII (FVIII) in subjects with PAD.[1] Circulating biomarkers of inflammation and endothelial cell activation are also associated with PAD.[2,3] Markers of platelet activity, including platelet aggregation and monocyte platelet aggregates, are increased in patients with PAD and may contribute to PAD pathogenesis.[4,5] Recent genetic studies of patients with PAD provide novel insights into potential pathophysiologic mechanisms. A recent Genome-Wide Association Study (GWAS) of PAD in the Million Veteran Program (MVP) identified 18 novel PAD risk factor loci, including a gene coding for factor V Leiden – suggesting a pathogenic role of hypercoagulability in PAD.[6]

In this issue of ATVB, Dr. Small and colleagues use Mendelian randomization to provide additional support for the relationship between hypercoagulability and PAD.[7] Mendelian randomization was first proposed in 1986 as a study design that leverages the random assignment of genetic variants to eliminate confounding and reverse causality, thereby improving causal inferences.[8] The basis of this approach is that individual genotypes are randomly assembled at the time of conception in a process governed by Mendel's law of independent assortment, in which inheritance of alleles of different genes are independent of one another. Since an individual's genotype remains fixed thereafter, it is independent of acquired exposures that confound the development of disease. In a sufficiently large cohort, measured and unmeasured confounders are expected to be balanced between individuals with and without a particular allele of interest. Therefore, Mendelian randomization studies are considered to be a "natural randomization", with genotype as the random treatment assignment. In order to explore the relationship between risk factor and disease, a successful Mendelian randomization study requires an established association between a risk allele, which serves as the instrumental variable, and a risk factor, such as the level of circulating

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hemostatic factors. Demonstration of a relationship between the risk allele and the outcome of interest, such as PAD, provides evidence to support a causal relationship between the risk factor and the outcome. Of course, the validity of this approach depends on the assumption that variants of interest are unrelated to any other factors that could confound the association between the exposure and the outcome.

To examine the genetic contribution of hypercoagulability to PAD, Dr. Small and colleagues selected genetic variants previously associated with circulating levels (FXI, VWF, fibrinogen) and activity (FVII, FVIII) of hemostatic factors.[7] The authors evaluated associations between variants associated with each hemostatic factor and prevalent PAD in both trans-ethnic and European genetic ancestries from a recent PAD GWAS in the MVP. A Bonferroni p-value cut-off was used to determine the significance based on the number of hemostatic factors tested ($p<0.01$ [$p=0.05/5$]). The primary analysis identified a significant association between both FVIII (Trans-ethnic, odds ratio [OR] 1.41, $p=6.0\times10^{-7}$; European, OR 1.34, 2.7×10^{-5}) and VWF (Trans-ethnic, odds ratio [OR] 1.28, p=0.007; European, OR 1.40, 4.8×10^{-4}) with PAD. In contrast, no significant association was observed between FVII, FXI, and fibrinogen and the outcome of PAD. The authors conducted a number of sensitivity analyses to test the robustness of their findings related to FVIII and VWF. The overall findings remained significant in MR Egger, weighted median and mode-based sensitivity analyses. However, leave-one-out analysis demonstrated that the associations of FVIII and VWF with PAD did not meet statistical significance when the lead variant of the ABO locus was excluded. While the ABO locus explained the majority of the variance for both FVIII and VWF, it is impossible to untangle the pleiotropic effect(s) of ABO on thrombosis. In multivariable mendelian randomization analysis using genetic instruments for FVIII and VWF, FVIII maintained a nominally significant effect on PAD in the trans-ethnic population. FVIII was no longer significant for the European population, and VWF was no longer significant in either the trans-ethnic or the European cohort.

Although intriguing, the study has notable limitations. The number of trans-ethnic PAD cases, a combination of both African and Hispanic genetic ancestries, was substantially lower (30%) than the number of PAD cases of European genetic ancestry. As noted by the authors, VWF is bound to inactive FVIII in the blood, protecting it from degradation. Based on the interdependence of these two factors, it is challenging to determine independent contributions of each hemostatic factor to the outcome of PAD. Regulation of hemostatic factor levels is complex, and genetic instruments that explain too little of the variation in the risk factor can bias causal estimates in Mendelian randomization; thus, estimates of the casual effect size must be interpreted with caution. Next, the endpoint of PAD was dependent on a clinical diagnosis of PAD. The impact of misclassification of patients with subclinical PAD would likely bias the results towards the null. Since many patients with PAD have concomitant coronary artery disease (CAD), the findings herein could alternatively reflect a relationship between hemostatic factors and disease in other vascular beds. Finally, hemostatic factors may not be related to the initial pathobiology of atherosclerotic PAD itself, but to superimposed thrombotic events that lead to clinically evident progression of disease.[9]

Although the findings of the present study are not conclusive, the authors provide intriguing data to support a link between coagulation factors, FVIII and VWF, and the development of PAD. The role of hypercoagulability in the pathobiology of PAD is further supported by recent pathology data and large clinical trials. A pathological series of 239 arteries from patients with critical limb ischemia (CLI; the most severe phenotype of PAD) found that the majority of the lower extremity arteries have luminal thrombi not associated with atherosclerosis, raising the likelihood of embolic phenomenon or in situ thrombosis.[10] Two large multinational clinical trials of anticoagulation with a factor Xa inhibitor reduced clinical events in PAD.[11,12] Rivaroxaban, a factor Xa inhibitor, modulates a direct downstream target of activated FVIII, thereby limiting thrombin generation and coagulation. In a subgroup analysis of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, the addition of very low-dose rivaroxaban to low-dose aspirin in patients with PAD was associated with a lower risk of major adverse limb events, including acute limb ischemia, chronic limb ischemia treated with revascularization, and major limb amputation than aspirin alone.[13] In the Vascular Outcomes Study of Aspirin Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD (VOYAGER PAD) trial, rivaroxaban anticoagulation reduced the risk of the composite of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or cardiovascular death in patients with undergoing peripheral revascularization for PAD.[14] Altogether, these data further support the hypercoagulable state of PAD.

Unfortunately, clinical implications of this Mendelian randomization analysis remain elusive and several questions remain. First, emerging therapies targeting FVIII and/or VWF are not yet ready for prime time. Second, it remains unknown whether *early* modulation of other hemostatic factors (e.g. Factor Xa inhibitor) would yield clinically important reductions in the incidence of PAD. Even if it did confer a benefit, currently available antithrombotic therapy is associated with significant risks of major bleeding that may preclude its routine use for PAD prophylaxis. Third, the relative contributions of other risk factors, including platelet activity, environmental exposures, traditional cardiovascular comorbidities, and genetics to PAD pathogenesis still require further study. Ultimately, this manuscript provides important data to justify additional investigation into the hypercoagulability in the pathobiology of PAD. We are hopeful that these data, and others like it, may help us define new targets for PAD prevention and treatment.

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