Race and Venous Thromboembolism: Nature or Nurture?

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Conventional teaching is that a racial gradient exists for the frequency of venous thromboembolism (VTE) in the United States. Asian-Americans have the lowest risk, and African-Americans have the highest risk. Hispanic Americans and Americans of European ancestry have an intermediate list, with Hispanics having less frequent VTE than those of European but non-Hispanic heritage. The most apparent paradox is that African-Americans have the highest rate of VTE, even though they rarely carry the prothrombin gene mutation or Factor V Leiden mutation, two genetic abnormalities that predispose to VTE. Based upon genetic profiling (nature), one might have predicted that African-Americans would have a low rate of VTE. In one study, when compared to European-ancestry individuals and adjusting for age and gender, African-Americans had a 30-60% higher incidence of VTE than European-Americans.¹ This finding suggests that environmental and socioeconomic factors and perhaps healthcare disparities (nurture) play an important role in determining the risk of developing VTE.

In New York City, 578 consecutive out-of-hospital fatal PE cases were investigated by the Office of the Chief Medical Examiner.² All underwent autopsy, toxicology, microbiology, and genetic testing. Race-adjusted incidence rates per 100,000 people per year were as follows: blacks 3.73, whites, 1.15, and Hispanics, 0.93. The percent of PE deaths compared with the New York City population was as follows: blacks (58% versus 25%), whites (25% versus 35%), and Hispanics (16% versus 28%). Obesity was 2.5 to 3-fold higher in fatal PE cases than in the New York City population as a whole.

The observation of race correlating with VTE frequency has been accepted with little disagreement or critique. One compelling cross-sectional study challenges existing dogma and shows that the topic is far more complex than initially thought. This observational study compared data from individuals enrolled in seven U.S. Centers for Disease Control (CDC)
Thrombosis and Hemostasis Centers from 2003 to 2009. Demographic characteristics were compared between whites (N=2002) and African-Americans (N=395) who had objectively diagnosed VTE. There is no overall population denominator in this study, so that the rate of VTE cannot be compared between races. However, in this study which included only patients with established VTE, the total number of VTE events was marginally but significantly greater among whites. Whites had more “DVT only” and more “DVT + PE” than African-Americans. In contrast, African-Americans had about twice the rate of “PE only” compared with whites.3

With respect to thrombophilia in this CDC study, Factor V Leiden occurred in 1.5% of African-Americans versus 14.7% of whites. The prothrombin gene mutation was present in only 0.3% of African-Americans compared with 3.6% of whites. Rates of the antiphospholipid syndrome and of deficiency of antithrombin, protein C, and protein S were similar in both groups. Other notable findings were that a higher proportion of African-Americans were female (71% versus 61%). African-Americans had a higher proportion of HIV and sickle cell disease, whereas whites had a higher proportion of surgery, trauma or infection. African-Americans also had a higher proportion of idiopathic DVT and idiopathic PE compared with whites, who more often had secondary, provoked VTE.

These findings about DVT versus PE rates, coupled the consistent observation about low rates of factor V Leiden and prothrombin gene mutation in African-Americans, raise several questions that recur when evaluating other studies of race and VTE. First, is DVT actually the same illness as PE, and can we justify lumping DVT and PE together under the umbrella of VTE? Second, is the biochemistry of venous thrombosis different in African-Americans compared with whites? Do African-Americans have venous thrombi that are less likely to adhere to the wall of the pelvic and deep leg veins and consequently more likely to embolize to
the pulmonary arteries? Third, does the low rate of factor V Leiden and the prothrombin gene mutation in African-Americans in this CDC study provide at least a partial explanation for the divergent rates of PE and DVT that were observed?

Factor V Leiden confers resistance to activated protein C. The “Leiden Paradox”, named and popularized by Henri Bounameaux of Geneva, Switzerland, is that patients with VTE and factor V Leiden have a rate of “PE only” that is about half the rate of patients without factor V Leiden. This means that those patients with VTE who do not have factor V Leiden are more likely to suffer isolated PE (as compared with isolated DVT) than those who have inherited the genetic predisposition to VTE. Similar to factor V Leiden, certain acquired VTE risk factors also confer increased resistance to activated protein C and cause more isolated DVT than isolated PE. These include oral contraceptive use, pregnancy, the postpartum state, and obesity.

So far, we have addressed primarily “Nature,” the genetic predisposition sorted by race, and its possible relationship to the anatomical location of the venous thrombosis (Table 1). However, to understand the profound connection between race and VTE, one must probe “Nurture” (acquired, environmentally important risk factors) (Table 2) along with “Nature” (genetics).

Acquired risk factors for VTE and its pathophysiology (especially the interplay of inflammation, hypercoagulability, and endothelial injury) are similar to acute myocardial infarction and atherothrombosis. They include obesity, hypertension, diabetes mellitus, cigarette smoking, and hypercholesterolemia. Triggers for hospitalization for VTE also include certain conditions associated with an intense inflammatory state: infection, erythropoiesis-stimulating agents, and blood transfusion. One line of reasoning is that African-Americans constitute a minority population subjected to health disparities and at risk for a disproportionate
burden of acquired risk factors, making them especially vulnerable to developing VTE.

In this issue of Circulation, three large prospective study databases are examined to test the association of race with VTE. The cohorts together accumulated an impressive 438,090 person-years experience and uncovered 916 incident VTE events (302 in blacks) with a denominator of 51,149 individuals (including 17,318 blacks). The three cohorts were: Atherosclerosis Risk in Communities (ARIC) (15,792 participants including 4,266 blacks), the Cardiovascular Health Study (5,888 participants including 924 blacks), and the REasons for Geographic and Racial Differences in Stroke (REGARDS) (30,239 participants, including 12,128 blacks). The years of recruitment for these cohorts ranged from 1987 through 2007. Follow-up extended from 2001 to 2010. Geographic location varied as well as recruitment age and eligibility to participate. The Cardiovascular Health Study included subjects age 65 years or older. ARIC enrolled subjects ages 45 to 65 years, and REGARDS enrolled subjects age 45 years or older. Only ARIC permitted enrollment of subjects with active cancer. Only the Cardiovascular Health Study excluded wheelchair bound subjects at baseline.

Given the variability in the design and magnitude of these cohorts, perhaps it is not surprising that the association of race with VTE in risk factor-adjusted models differed in each cohort. In the Cardiovascular Health Study, blacks had a statistically significant 81% excess rate of VTE than whites. In ARIC, blacks trended toward more VTE than whites, with a 21% excess rate of VTE, a difference that approached but that did not achieve statistical significance. When ARIC data were normalized for age and sex distribution, the racial difference became statistically significant. In REGARDS, blacks in the Southeast had a significantly higher VTE rate than whites, but this observation did not hold true in the rest of the United States.

There is, however, one big surprise. In contrast to prior epidemiologic studies, PE
incidence was not higher in blacks than whites in ARIC, the Cardiovascular Health Study, or REGARDS.

Puzzlement results from trying to harmonize the results of three large epidemiologic studies with radically different designs. One fact does remain secure. We must concede that there are no unshakable tenets when studying the relationship between race and VTE.

Several fundamental questions emerge:

1. Can we continue to justify lumping VTE as a combination of DVT alone, PE alone, DVT presenting symptoms plus PE found incidentally, and PE presenting symptoms with DVT found incidentally? Or are these distinct illnesses?

2. Can we define race on the basis of how a subject self-identifies?

3. Can we consider genetics (nature) based upon a handful of clinically available thrombophilic tests? Or should we progress to a more sophisticated multilocus, population-based, prospective genetic analysis? For example, in the Physicians’ Health Study cohort, 92 polymorphisms were genotyped from 56 candidate genes among 304 subjects who subsequently developed VTE. For idiopathic VTE, an N291S lipoprotein lipase gene polymorphism and a Q27E beta-2-adrenergic receptor gene polymorphism were associated with increased VTE risk.11

4. Can we devise a predictive epidemiologic model that guides us in the racial association with VTE by inventing a paradigm that integrates nature and nurture?

5. Can we reform our healthcare and socioeconomic systems to minimize disparities that lead to more hypertension, cigarette smoking, obesity, and diabetes among underserved groups and which, in turn, constitute a higher frequency of reversible risk factors for PE and DVT?
Figuring out the association between race and VTE will lead to better understanding of PE, DVT, genetic predisposition, and acquired risk factors. We have many gaps to fill. The epidemiology of this problem is ripe for new ideas and unconventional approaches. Our overarching goal is to prevent PE and DVT. We have only scratched the surface of what we can achieve with promotion of heart healthy lifestyle and elimination of reversible VTE risk factors.

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**Table 1. Nature**

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<th>Race</th>
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<tbody>
<tr>
<td>Genetic predisposition for hypercoagulability (factor V Leiden, prothrombin gene mutation)</td>
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<td>Acquired predisposition for hypercoagulability (antiphospholipid antibody syndrome)</td>
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<td>Inflammation (nature, nurture, or both?)</td>
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<td>Hypercholesterolemia (nature, nurture, or both?)</td>
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<td>Diabetes mellitus (nature, nurture, or both?)</td>
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**Table 2. Nurture**

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<td>Hypertension (nurture, nature, or both?)</td>
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<td>Cigarette smoking</td>
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<td>Immobility</td>
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<td>Healthcare disparities</td>
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