Commentary

The relationship between FV Leiden and pulmonary embolism

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Abstract

Pulmonary embolism (PE) is one of the leading causes of in-patient hospital deaths. As a consequence, the identification of hemostatic variables that could identify those at risk would be important in reducing mortality. It has previously been thought that deep vein thrombosis and PE are a single disease entity and would, therefore, have the same risk factors. This view is changing, however, with the realization that the prevalence of FV Leiden, a recognized genetic risk factor for deep vein thrombosis, may be a 'milder' genetic risk factor for PE. These observations suggest that PE is not only associated with a different set of risk factors, but may be reflective of a different clot structure.

Keywords: FV Leiden, genetics, pulmonary embolism, venous thrombosis

Introduction

Pulmonary embolism (PE), a potential lethal complication of venous thromboembolism (VTE), is a leading cause of in-hospital death and the prevalence of symptomatic pulmonary embolism has been estimated to be approximately 630,000 cases per year in the United States [1]. It has also been estimated that PE may be directly responsible for up to 100,000 deaths and a contributing cause in another 100,000 [1]. Despite these estimates, it has been commonly agreed that the true magnitude of PE is unknown. The pathogenesis of VTE/PE is multifactorial and frequently reflects the interplay between environmental, clinical and genetic factors. Although it has been long recognized that deficiencies in the anticoagulation proteins protein C, protein S and antithrombin III were often the consequence of underlying genetic defects, there was little interest in defining the genetics of VTE/PE. This view changed, however, when FV Leiden was described and subsequently shown to be associated with 18–20% of all idiopathic VTE cases [2,3].

FV Leiden is a consequence of a single G-to-A transition at nucleotide 1691 in the Factor V gene that results in the amino acid substitution of an arginine by glutamine [4,5]. This single nucleotide substitution is the only known mutation responsible for the FV Leiden genotype and a rapid molecular diagnosis can thus be easily made. A phenotypic diagnosis, which is commonly referred to as resistance to activated protein C, can also be made using findings from the clinical hematology laboratory [6]. The phenotypic diagnosis can be directly correlated with FV Leiden in approximately 90–95% of cases [7]. Since the initial description of FV Leiden, several studies have demonstrated that the prevalence of this mutation differs among the populations of the world, ranging from 5–12% of individuals of northern European descent to approximately 1% in those of African descent [7–9]. For example, in a case–control study of African-Americans with VTE, a FV Leiden prevalence rate of 1.2% was seen in both cases and controls [9]. Consequently, the association between FV Leiden and VTE varies according to ethnicity.

DVT = deep vein thrombosis; FV = factor V; PE = pulmonary embolism; VTE = venous thromboembolism.

FV Leiden and pulmonary embolism

As VTE was thought to represent a single pathological process, clinical investigators believed that the risk factors associated with deep vein thrombosis (DVT) were the same for PE. Manten *et al*. [10] hypothesized that FV Leiden would be more common in patients with PE since resistance to activated protein C may lead to the development of a larger, more extensive clot, which would lead to a subsequent increased risk for PE. To validate this hypothesis, Manten and colleagues [10] used a VTE clinical diagnosis to divide their study population of 279 patients into three groups. These comprised patients with DVT with no signs or symptoms of PE ($n = 211$), patients with PE with no signs or symptoms of DVT ($n = 45$), and patients who were clinically diagnosed as having both DVT and PE ($n = 23$). Acquired VTE risk factors, such as hospitalization and surgery, were similar among the three study groups . After adjusting for age and sex, the prevalence of FV Leiden was lowest in patients with PE (8.9%) and highest in patients with only DVT (17.5%). The prevalence for patients with both DVT and PE was 13.0%, intermediate between the two other groups. In comparison, the prevalence of FV Leiden in the control group was approximately 3.0%. These data demonstrate that the relative risk for PE in the individuals with FV Leiden was approximately three-fold while the risk for DVT was about seven-fold in the FV Leiden carriers [10]. In another study, Martinelli *et al*. [11] found that the 4.9% prevalence of FV Leiden in patients with isolated PE was about the same as that found in the controls. To more fully define these findings, Turkstra *et al*. [12] ascertained the FV Leiden prevalence in an unselected group of 92 patients who had an objectively confirmed diagnosis of PE. Of these, 67 presented with only a primary PE and the FV Leiden prevalence in this group was 7.4%. The FV Leiden prevalence in the remaining 25 patients, who had both DVT and PE, was 24.0%.

A related question raised by these studies is whether or not the FV Leiden prevalence was higher in cases that were associated with a fatal PE. Using autopsy material, Vandenbroucke *et al*. [13] divided autopsied individuals into two groups. The first consisted of a consecutive series of autopsies in which PE was described as an incidental finding; the majority of these patients had a major underlying disease. The second group consisted of a series of cases in which PE was the sole cause of death in individuals under the age of 70 with no known acquired risk factors for VTE. Although these investigators stated that they could not rule out selection bias in terms of patients autopsied, or technical bias due to the use of paraffin blocks, their results were nevertheless similar to the earlier findings. In the first autopsy series, the FV Leiden prevalence of 2.3% was comparable to that of the general population. The prevalence of 10% found in the second autopsy series reflected only a three-fold increase in risk, a relative risk below what would have been expected for DVT [13]. In addition to the work by Vandenbroucke and colleagues, three further studies by other investigators also used autopsy material to look at the relationship between FV Leiden and PE and found no association [14–16].

FV Leiden and the prothrombin G20210A variant

Since FV Leiden was first described, another DNA single nucleotide substitution, the prothrombin G20210A variant, has also been linked to an increased risk for VTE [17]. Meyer *et al*. [18] assessed the prevalence of both FV Leiden and the prothrombin G20210A variant in a series of 773 consecutive patients with an objective diagnosis of VTE. Similar to the other studies, the cases were divided into three groups comprising patients with DVT only, PE only, and DVT with PE. As in the earlier studies, this study found FV Leiden to be less common in the PE only cases than in the other two groups [18]. They did, however, find that the prevalence of the prothrombin G20210A variant was similar in the three groups. It was further noted that both mutations were present in 10 patients with DVT and in two patients with only PE [18]. In a similar study that also looked at both mutations, Margaglione *et al*. [19] analyzed 647 consecutive referred patients and 1,329 controls. They also found the prevalence of both mutations in patients with isolated PE to be comparable to those found in the controls. In analysis of autopsy material from 67 patients who died suddenly from PE, Kohlmeier *et al*. [20] also found the prevalence of prothrombin G20210A variant and FV Leiden to be similar to that found in the general population.

The relationship between PE and DVT

As noted by Bounameaux [21], the relationship between FV Leiden, DVT and PE represented a 'paradox' in that the published reports were not necessarily supportive of the concept that DVT and PE represented two clinical expressions derived from one disease, namely VTE. There are currently two prevailing hypotheses to explain the apparent paradox. In one, selection bias has been suggested as the cause, as most of the PE cases came from unselected patients while most of the information linking FV Leiden and DVT has come from central referral centers. The other hypothesis is that the paradox is actually a reflection of the clot structure and its location [10,21,22]. In support of the latter hypothesis, Bjorgell *et al*. [22] used phlebography in a prospective study to score the location and extent of DVT in 247 consecutive patients. The results were then correlated with the presence and absence of FV Leiden. These demonstrated that incidences of DVT in the iliofemoral veins occurred about eight-fold less in FV Leiden carriers than in non-carriers [22]. Their analysis did show, however, that FV Leiden was a true DVT risk factor below the iliofemoral segments. This finding is particularly

interesting because another study has reported that DVTs located in the iliofemoral vein segments are more likely to be associated with PE [23].

Conclusions

The above observations support earlier suggestions that clot location and size may be important determinants in defining the embolic risk [10]. As suggested by Manten *et al*. [10], these initial clot parameters may be influenced by different etiologic mechanisms (for example, stasis and genetics) and one such mechanism could lead to an inflammatory reaction that would amplify thrombin generation with the likely consequence of a more stable, adherent clot [10]. It could thus be further argued that the magnitude of the inflammatory response may not only be a primary factor in determining the embolic potential of the clot, but could also be an important factor in VTE pathogenesis in the absence of any prothrombotic genetic risk factors.

The clinical implications of these observations remain uncertain and the findings do not discount the prevailing belief that DVT and PE are a consequence of a single disease entity. They do suggest, however, that a better understanding of the disease is essential to ensure the accurate use of genetic information. One possible way forward is to initiate a prospective multi-center study based on the seminal work of Bjorgell *et al*. [22] that would include not only phlebography, but also a full hemostatic and genetic analysis.

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