REVIEW ARTICLE

# Factor V Leiden and Perioperative Risk

Brian S. Donahue, MD, PhD

Department of Anesthesiology, Vanderbilt University, Nashville, Tennessee

Factor V Leiden (FVL) is the most common known inherited cause of thrombophilia; it is present in approximately 5% of the Caucasian population. Although the risk of venous thrombosis associated with this polymorphism in various medical settings is well described, its effect on perioperative risk is only beginning to be explored. Specifically, there are few studies addressing the potential risks of FVL in the surgical population, in which both hemorrhagic and thrombotic complications convey substantial clinical and economic significance. There are speculations and unproven hypotheses regarding FVL in this population, and these therefore highlight the need to comprehensively address this issue. This review will describe the physiology of the FVL mutation, briefly clarify its risk in the nonsurgical setting, and assess current data regarding FVL in noncardiac and cardiac surgery. Finally, a summary of current clinical evidence and a plan for more detailed investigation of this potentially significant risk factor will be proposed.

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Hypercoagulable states describe a heterogeneous mix of clinical and inherited risk factors for thrombotic events and are significant contributors to adverse patient outcomes. Venous thrombosis is an important cause of morbidity in developed countries and affects approximately 2 individuals per 1000 each year (1–3). Although classic risk factors such as pregnancy, surgery, immobilization, malignancy, and estrogen use continue to be clinically important, many thrombotic episodes remain unexplained (4,5). The role of hypercoagulable states in the pathogenesis and prognosis of cardiovascular disease is established and becoming better understood (6–8).

With regard to venous thrombosis, investigators have recently identified many inherited deficiencies and genetic variants as risk factors (9). Rare inhibitor deficiencies, such as protein C, protein S, and antithrombin deficiencies, are easily identified by routine testing, but together they account for only approximately 10%–15% of all cases of venous thrombosis (10). Allelic variants in coagulation factor genes appear to account for a much larger fraction of cases; the prothrombin 20210 G/A polymorphism and factor V Leiden (FVL) (present in approximately 2% and 5% of Caucasians, respectively) account for approximately 50% of cases in the Caucasian population (10).

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Address correspondence and reprint requests to Brian S. Donahue, MD, 504 Oxford House, Department of Anesthesiology, Vanderbilt University, Nashville, TN 37232. Address e-mail to brian.donahue@vanderbilt.edu.

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Today, because genetic testing for inherited thrombophilias is becoming more commonplace, anesthesiologists are likely to see more genetic data listed on preoperative laboratory reports. This often leaves them wondering what effect this should have on perioperative management. FVL is a common inherited prothrombotic risk factor (11) in the Caucasian population; its physiologic significance is well characterized, and its testing is often part of a hematology evaluation for venous thrombosis. Yet the literature on the significance of FVL in the perioperative setting is unclear. The purpose of this review is to summarize the current evidence for FVL as a risk factor for perioperative complications, highlight some unresolved issues, and offer evidence-based recommendations for testing, practice, and future investigations.

## FVL: Physiology and Epidemiologic Risk

In the early 1990s, Svensson and Dahlback et al. (12,13) reported their results from population studies of patients with idiopathic venous thrombosis. They initially observed that a specific laboratory abnormality—resistance to activated protein C (aPC)—was present at a much more frequent rate in cases than in controls (14). This led the investigators to search for polymorphisms in regions of the factor V gene that coded for protein C cleavage sites (12). A single base substitution, adenosine for guanosine at position 1691, coded for a glutamine substitution for arginine at amino acid 506 and was identified in almost all of the cases (15). This mutated factor V protein was found to have normal procoagulant function *in vitro* but was


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resistant to inactivation by aPC, demonstrating that the mutation was responsible for the observed rate of aPC resistance in the studied population. The mutation was later found to have a carrier rate of 5%–10% in the Caucasian population. It was most common in Scandinavian and northern European ethnicities (16) and was termed *factor V Leiden*. Figure 1 depicts this role of FVL in the pathway of thrombin generation.

Subsequent epidemiologic studies have reported an increased risk of several thrombotic complications associated with FVL, such as recurrent venous thrombosis (17), cerebral sinus thrombosis (18–20), renal transplant rejection (21), venous thrombosis during pregnancy (22), and various obstetric complications (22–28). There is a much weaker association for FVL and arterial thrombosis or infarction: FVL appears to be principally a venous thrombosis risk factor (29). This may be due to the presence of an endogenous protein C inhibitor in platelets and the more dominant role that platelets play in arterial thrombosis (30–32). Although smaller reports in specific clinical subgroups have described some arterial thrombosis risk (33–41), these findings may reflect a common problem known as *publication bias*: the bias for studies with positive results to be published compared with studies with negative results, especially when the sample size is smaller (29,42). More comprehensive discussions of the clinical effect of FVL can be found in several excellent recent reviews (9,10,43–46).

The discovery of FVL and its 5% frequency in the Caucasian population marks an important watershed in our understanding of the genetics of thrombophilia (16,47,48). Before its discovery, most epidemiology regarding thrombophilia assumed that hypercoagulable states were monogenetic in origin. That is, a single factor deficiency (such as protein C, protein S, or antithrombin) was believed to be responsible for the observed thrombophilic phenotype. After the discovery of FVL, the understanding that multiple risk factors contribute to a clinical hypercoagulable state began to evolve (10,49). This newer model was more consistent with observations that most patients with FVL are asymptomatic and often must be exposed to an additional risk factor (pregnancy, immobilization, severe illness, or other genetic factors) to manifest the thrombophilic phenotype. This paradigm shift has fostered aggressive pursuits of polymorphism detection and the use of computerized technologies for rapid DNA analysis in an effort to characterize multiple genetic risk factors and their possible interactions (48).

## aPC Resistance

Resistance to the anticoagulant effect of aPC is the hallmark laboratory finding associated with FVL (11), and an understanding of its physiologic significance and the laboratory methodology is crucial. Protein C is converted to its biologically active form, aPC, by the thrombin-thrombomodulin complex on endothelium (50). aPC, together with its cofactor protein S, serves multiple anticoagulant and antiinflammatory functions, one of which is to inactivate factors Va and VIIIa by proteolytic cleavage at specific sites on the substrate proteins. aPC also indirectly increases fibrinolytic activity by decreasing thrombin generation and the subsequent formation of thrombin-activatable fibrinolysis inhibitor (TAFI) (51,52). This role of aPC in supporting fibrinolysis has been demonstrated in animal models of experimental thrombosis (53,54). Other activities of aPC include inhibition of inflammatory cytokine production by activated monocytes, reduction of leukocyte rolling on injured endothelium (a key initial step in leukocyte-mediated inflammation), and inactivation of plasminogen activator inhibitor-1 (55).

Resistance to aPC is measured in a laboratory by comparison of standard clotting times in the presence and absence of aPC. Normal plasma typically clots in approximately 28–35 s when exposed to a contact pathway activator, creating the standard measurement known as "activated partial thromboplastin time" (aPTT). When aPC is added to the plasma, the anticoagulant effect of aPC is revealed by an increase in aPTT, usually by a factor of 2.0 or more: to 70–100 s, for instance. This plasma is said to be sensitive to aPC. When the aPTT for a plasma sample is prolonged by aPC by a measurably lesser extent, such as by a factor of 1.5–1.7 (as is typical for FVL heterozygotes), the plasma is said to exhibit resistance to aPC. Many conditions can produce or influence resistance to aPC (56–61); some of these are listed in Table 1. Although the assay can be modified by using different substances (e.g., tissue factor or Russel viper venom) to initiate *in vitro* coagulation (62), a contact pathway activator, such as colloidal silica, is usually used as described previously. The aPC resistance assay can also be made very specific for detecting factor V mutations by prediluting the plasma sample with factor V-deficient plasma (60).

FVL is therefore one common cause of resistance to aPC in Caucasians. This is due to the loss of the principal aPC cleavage site, usually present at the arginine residue 506, on the factor V protein. Proteolysis of activated factor V by aPC is usually rapid, but the activated FVL molecule remains intact much longer because aPC cannot cleave it at its principal location (45,52). FVL heterozygosity differs considerably from a 50% factor V deficiency, because in the latter case all circulating factor V still remains sensitive to inactivation by aPC, whereas in the former, half of the factor V is resistant to aPC and is present in amounts sufficient to continue thrombin generation

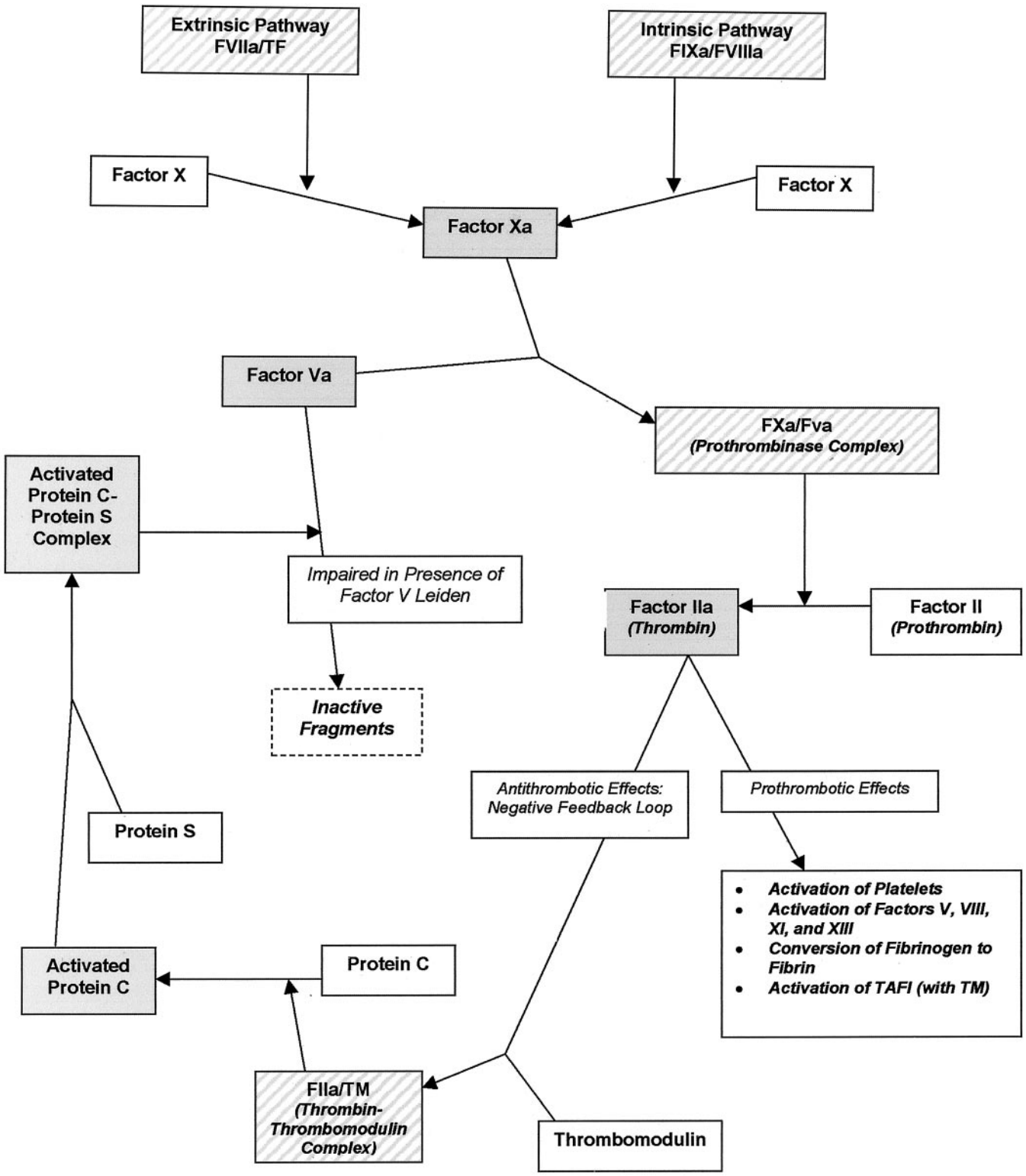


**Figure 1.** Feedback inhibition of thrombin generation: role of factor V Leiden. The inactivation pathway of factor V is impaired in the presence of the Leiden mutation, blocking an important inhibitory feedback loop that regulates thrombin generation. Hatched boxes represent activated coagulation factor complexes that require a phospholipid surface and calcium ions, shaded boxes represent activated coagulation factors, and open boxes represent unactivated factors or zymogens. TF = tissue factor; FVIIa = activated factor VII; FIXa = activated factor IX; FVIIIa = activated factor VIII; FX = factor X; FXa = activated factor X; FII = factor II (prothrombin); FIIa = activated factor II (thrombin); TM = thrombomodulin; TAFI = thrombin-activatable fibrinolysis inhibitor; FVa = activated factor V.

**Table 1.** Common Causes of Activated Protein C Resistance

| |
|---|
| Congenital |
| Factor V mutations |
| Arg506Gln (Leiden) |
| *HR2* haplotype |
| Arg506Thr (Cambridge) |
| His1299Arg |
| Family history |
| Non-O blood group |
| Female sex |
| Increased factor VIII:C levels |
| Acquired |
| Pregnancy |
| Age |
| Acute phase inflammation |
| Antiphospholipid antibody |
| Increased serum lipid levels |
| Increased body mass index |
| Increased blood pressure |
| Drugs |
| Aprotinin |
| Oral contraceptives |

despite the presence of aPC. This represents an important source of increased thrombin formation with FVL, because thrombin production is regulated by factor Va availability (45).

Resistance to aPC is not the only measurable prothrombotic abnormality observed in the plasma of FVL subjects. Additional effects of the FVL mutation on coagulation are listed in Table 2. Increased thrombin generation produces increased activation of TAFI, an important clot-stabilizing enzyme, and FVL subjects have demonstrated increased TAFI activity and lysis-resistant clots in laboratory assays of fibrinolysis (52). Also, the cleavage of factor VIIIa by aPC is normally facilitated by the prior cleavage of factor Va by aPC, a curious anticoagulant function of factor V (45). Hence, because factor Va cleavage by aPC is substantially reduced in the presence of FVL, subsequent cleavage of factor VIIIa is reduced.

The aPC resistance phenotype should be understood as a quantitative phenomenon: some patients are more resistant to aPC than others, and multiple factors (such as those in Table 2) can produce additive effects on aPC resistance (60). Clinical hypercoagulability, evidenced by the risk of venous thrombosis, also appears to be directly related to the degree of aPC resistance (60). For example, whereas patients heterozygous for FVL typically have aPC ratios of 1.6–1.8, rare patients who are homozygous for FVL have aPC ratios of 1.2–1.4. Such patients exhibit a lifetime risk of venous thrombosis that is approximately 5–10 times more than that of FVL heterozygotes, whose risk is approximately 5–10 times that of the noncarrier Caucasian population (9,44,46).

**Table 2.** Coagulation Abnormalities Observed in Patients with Factor V Leiden

| |
|---|
| Resistance to aPC |
| Increased factor Va levels |
| Increased thrombin generation |
| Decreased fibrinolytic capacity |
| Decreased aPC-mediated proteolysis of factor VIIIa |

Factor Va = activated factor V; aPC = activated protein C; factor VIIIa = activated factor VIII.

## FVL in Noncardiac Surgery

### *Venous Thrombosis*

Venous thrombosis often complicates the postoperative course, with a reported frequency as high as 36% even with anticoagulant management (63–65). In patients undergoing noncardiac surgery, many investigators have examined the effect of FVL as a potentially additive risk factor for this complication but have reported almost uniformly negative results (66–68). One of these studies (69) reported that FVL was not associated with an increased risk of postoperative venous thrombosis but was associated with an increased risk of pulmonary embolism. This finding was not confirmed in a large autopsy study of postoperative deaths caused by pulmonary embolism (70). Other authors have found that the risk of venous thrombosis after orthopedic surgery may be increased by the presence of the aPC resistance phenotype, which has multiple causes other than FVL, but the increase in clinically relevant predictive power provided by aPC resistance testing appears to be small (71).

From the current literature, it appears that the risk of venous thrombosis associated with joint replacement surgery and current postoperative management is large enough to overpower the relatively mild effect of FVL. Worth noting is that all patients in these studies received postoperative antithrombotic therapy. Therefore, although the natural history of FVL in the postoperative setting (i.e., in the absence of antithrombotic therapy) may not be known, such therapy constitutes standard practice, and routine preoperative screening has not been recommended in this population (72,73).

Negative findings have been reported in other postsurgical populations as well, although fewer studies are available and thrombosis rates are less frequent than for orthopedic surgery. Venous thrombosis after gynecologic surgery (74) was not associated with FVL in a retrospective case-control study, although all subjects had solid tissue malignancies, a condition that may carry more thrombosis risk than FVL and may limit the applicability of these results to other populations. Thromboembolic complications of artificial cardiac valves (75) do not appear to be associated with FVL. The relatively small populations in these studies

(74 and 148 subjects, respectively) and the approximately 5% incidence of FVL heterozygosity considerably limit the power to detect differences.

### *Arterial Thrombosis*

Whether FVL and aPC resistance are risk factors for perioperative arterial thrombosis is an important question, because postoperative ischemia is a serious postoperative complication (76). Unfortunately, the current literature contains studies that are not sufficiently powered to conclusively address this question. Kibbe et al. (77) recently reported their findings from a prospective randomized study of 3 anticoagulation regimens for peripheral artery bypass operations in 244 patients; this study showed no decrease in patency rates associated with FVL. The power of the study may have been improved if all patients had been receiving the same postoperative therapy. Foley et al. (78) reported an increased frequency of aPC resistance and FVL among patients with peripheral vascular disease when compared with the general population, but they did not observe a decrease in long-term graft patency rates among patients with FVL. This study population consisted of only 45 patients, 8 of whom were heterozygous for FVL.

Positive associations in subgroups were reported in a study of 262 patients undergoing peripheral revascularization procedures, in which aPC resistance and FVL were not significant contributors toward a composite thrombotic end point (7). Subgroup analysis revealed significant associations of aPC resistance (observed in 22% of subjects) with early graft occlusion and early thrombotic complications. FVL was associated with early postoperative cerebrovascular events and late peripheral bypass graft occlusion, but the very small sample size (FVL was present in 1 of 3 patients with cerebrovascular events and 2 of 11 patients with late graft occlusion) and lack of adjustment for multiple testing call the validity of these results into serious question. Furthermore, postoperative antithrombotic or antiplatelet therapy (in the form of aspirin, warfarin, or both) was not standardized and was not included as a possible covariate.

As is common with rare catastrophic events, case reports further complicate interpretation of the literature because of their inherent publication bias and the anecdotal nature of the clinical circumstances. Cases of thrombosis after noncardiac surgery have been associated with FVL in both adult (79–81) and pediatric (82) settings and are included here for completeness.

## FVL in Cardiac Surgery

### *Relevance of FVL to Cardiac Surgery*

Cardiac surgery is a particularly relevant setting for clarifying genetic hemostatic risks because of the difficulty in predicting which patients are at risk for transfusion (83–85). Postoperative thrombosis can be catastrophic (5–8), and the role of antifibrinolytic drugs in precipitating serious thrombotic events is controversial (86–91). Cardiac surgery patients are major consumers of the nation's blood supply (83,92,93)—a problem that is more than economic, because postoperative transfusion is linked with poorer patient outcomes (94–96). The morbidity and economic considerations of antifibrinolytic drugs and the duration of intensive care unit and hospital stay are also matters of significant importance (95,97–101). Before the current literature regarding FVL and cardiac surgery is outlined, it is important to first emphasize some relevant issues of coagulation physiology in this clinical setting.

### *Physiologic Disturbances Specific to Cardiac Surgery*

The hemostatic and inflammatory disturbances induced by cardiopulmonary bypass (CPB) are complex and produce activation of the inflammatory, complement, coagulation, and fibrinolytic systems. These multiple physiologic processes have been previously reviewed in detail (102–104). In our current understanding, thrombin generation remains central to the activation of the coagulation and fibrinolytic systems (104), and postoperative blood loss and transfusion correlate directly with thrombin generation during CPB (104–108). Platelets, activated by thrombin and CPB, are removed from circulation, and remaining platelets exhibit decreased responsiveness to thrombin (109). Fibrinolysis is activated during CPB by several mechanisms. Kallikrein, produced from contact activation, produces the active two-chain urokinase plasminogen activator (110). Kallikrein also releases bradykinin from high-molecular-weight kininogen, which in turn causes tissue plasminogen activator release from endothelium (111,112). Thrombin also stimulates the release of tissue plasminogen activator, the dominant plasminogen activator during CPB (113,114).

### *Protein C and Other Anticoagulant Systems During CPB*

Thrombin generation during CPB has potential relevance for patients with FVL and aPC resistance, because thrombin produces an anticoagulant effect through the protein C pathway (115–117). Thrombin, bound to thrombomodulin, activates protein C, which inactivates factors Va and VIIIa (118). Levels of total protein C decrease during CPB, probably as a result of hemodilution. Levels of aPC increase during CPB, probably a result of thrombin generation, and increase specifically after release of the aortic cross-clamp (116). Investigators have found correlations between the aPC/total protein C ratio in coronary sinus blood and myocardial performance on the first postoperative day, suggesting an important function of this

anticoagulant system in suppressing ischemia-induced inflammatory and cytotoxic effects (116). Earlier findings by the same group suggested that pediatric cardiac surgery patients with low perioperative levels of antithrombin and aPC, as well as patients with resistance to aPC, were at most risk for postoperative central venous thrombosis, an important contributor to early postoperative mortality (117).

Other anticoagulant systems, such as tissue factor pathway inhibitor (TFPI) (119,120), antithrombin (121–123), and heparin cofactor II (124–126), clearly play important roles during CPB, and a thorough discussion of the contribution of each is beyond the scope of this review. Also, evidence suggests important synergistic interactions between anticoagulant pathways in suppressing coagulation system activity (127,128). FVL patients who have experienced thrombosis have TFPI levels 39% less than those without thrombosis (129). Baseline thrombin generation *in vitro* is increased by the presence of FVL (130), suggesting that low TFPI or antithrombin activity may be a particularly substantial thrombosis risk factor in the presence of FVL.

## *FVL and Hemostasis After Cardiac Surgery*

Reports of the hemostatic effect of FVL in the cardiac surgery population are shown in Table 3. Until recently, only one rather small study found a nonsignificant trend toward decreased blood loss among FVL heterozygotes (58). Investigators measured blood product use among 13 cardiac surgery patients with FVL and 13 matched controls and noted only a trend toward decreased consumption of blood products among the FVL subjects.

The question of whether FVL patients are at decreased risk for blood loss was addressed directly in a larger study (135): this was one of the first studies to answer a key issue regarding FVL in the cardiac surgery population. Using multivariate regression techniques to account for known variables that affect surgical hemostasis, researchers found that FVL carriers had an average of 30% less blood loss after CPB. The magnitude of blood sparing associated with FVL was nearly the same as that provided by the antifibrinolytic drugs aprotinin and ϵ-aminocaproic acid. Furthermore, the chance of not receiving any blood product transfusion during hospitalization was 46% among FVL patients, compared with 28% for noncarriers, a finding that was significant on logistic regression accounting for other known transfusion risks.

## *FVL and Risks for Thrombosis*

Coronary bypass graft occlusion is an important clinical problem and often occurs despite optimal patient management (136,137). The frequency of vein graft occlusion may be as much as 10% within the first 10 days after surgery (138) and as frequent as 26% by the first year (136). More recent studies suggest that the long-term occlusion rate is quite variable among centers but approaches approximately 20% after 3–6 yr (139,140).

The unpredictability of vein graft occlusion has prompted investigators to consider patient-specific factors in the etiology, because prothrombotic states have been known to be risk factors for some time (141). In an earlier study, Eritsland et al. (131) reported their findings from 587 patients enrolled in a randomized trial of fatty acid supplementation and anticoagulant management. In these patients, whose aPC resistance status was known, no association was observed between graft occlusion at 1 yr and resistance to aPC. The relevance of these findings to FVL patients is limited, because these authors used a Russell viper venom time to measure resistance to aPC. This assay was later found to be insensitive in detecting FVL carriers (58,142).

The possible association of FVL with coronary artery bypass (CAB) graft occlusion was addressed by Moor et al. (132) in 1998. These authors performed coronary angiography on a population of 100 men 3 months after elective CAB surgery and reported graft occlusion in 45% of the FVL carriers (5 of 11) and in only 20% (18 of 89) of the noncarriers, a finding of borderline statistical significance ($P = 0.06$). Of note, all patients in this trial received postoperative aspirin therapy beginning on the day after surgery. These findings are mirrored by a later case report (143) describing complete CAB graft occlusion 1 mo after surgery in a patient with FVL and other prothrombotic risk factors, and successful management with repeat CAB and anticoagulation treatment. Because of the anecdotal nature of this report and the marginal findings in the study by Moor et al., overall conclusions regarding FVL and CAB graft occlusion are provocative, yet unclear: FVL may represent a contributory factor for early graft occlusion, but the magnitude of the effect and the possible interacting factors are unknown. Furthermore, because this study involved only men, the risk of CAB graft occlusion associated with FVL in women or in other populations and the possible interaction with other clinical variables or postoperative management options have not been investigated.

The risk of central venous thrombosis has been reported in a series of 20 affected pediatric patients after congenital heart repairs (117). These authors observed an association of low aPC and antithrombin levels with central vein thrombosis, an important contributor to death in 8 of the 20 patients. Also reported was the observation of resistance to aPC in 2 (17%) of 12 tested patients, a finding of unclear significance. Another underpowered study of FVL in pediatric patients undergoing congenital heart surgery (133) observed central vein thrombosis in 3 of 200 subjects, none of whom was found to carry FVL. However, these populations involved mostly children who had a broad spectrum of cardiac defects, and the surgical

**Table 3.** Existing Studies of FVL or APCR in Cardiac Surgery

| Study | Description | End points | Findings |
|---|---|---|---|
| Eritsland, 1995 (131) | Case-control study of 587 subjects enrolled in a randomized trial of anticoagulant management | CAB graft occlusion (arterial or saphenous vein grafts) at 1 yr | No significant effect of FVL on graft occlusion |
| Petaja, 1996 (117) | Descriptive report of 1591 pediatric CPB procedures | Central vein thrombosis, death | Uncertain association with APCR |
| Sweeney, 1997 (58) | 13 FVL patients and 13 matched noncarrier controls; measurement of APCR with and without aprotinin in FVL plasma and noncarrier plasma | Blood product use; APCR and effect of aprotinin | Nonsignificant trend toward decreased transfusion; APCR increased with aprotinin and increased further in FVL plasma |
| Moor, 1998 (132) | Case-control study of 100 males undergoing CAB grafting | Angiographic CAB graft occlusion at 3 mo | Borderline increased risk for FVL (OR = 3.29; $P = 0.06$) |
| Ong, 1998 (133) | Case-control study of 200 consecutive children undergoing CPB | Clinical thrombotic events | No association with FVL |
| Linden, 2001 (134) | Measurement of APCR during *ex vivo* CPB, with and without aprotinin in FVL blood and noncarrier blood | APCR and effect of aprotinin | APCR increased with aprotinin and increased further in FVL samples |
| Donahue, 2003 (135) | Multivariate analysis of blood loss and transfusion, including FVL as a risk factor | Chest tube blood loss, blood product use, risk of transfusion | Significant effect of FVL on postoperative blood loss and overall risk of transfusion |

FVL = factor V Leiden; APCR = activated protein C resistance; CAB = coronary artery bypass; CPB = cardiopulmonary bypass; OR = odds ratio.

interventions consisted of a wide range of procedures. These important considerations limit the applicability of the results to adults or to other cardiac surgery populations.

## *FVL and Antifibrinolytic Drugs*

Although antifibrinolytic therapy is a well studied modality for decreasing the hemorrhagic risk associated with CPB, much controversy has surrounded these drugs because of their possible prothrombotic risk (101,144,145). Attempting to characterize patients who are at risk for thrombosis when exposed to CPB and antifibrinolytic therapy has proven difficult. Aprotinin and the lysine analogs will be considered separately because of substantial differences in their pharmacology.

## *Aprotinin*

Because aprotinin is a known inhibitor of aPC, authors have addressed its effect in models of cardiac surgery. Sweeney et al. (58) observed that aprotinin induces resistance to aPC in normal plasma and exacerbates aPC resistance further in the plasma from FVL heterozygotes. The authors hypothesize that this doubly impaired anticoagulant function of aPC in the presence of FVL may account for the thrombosis observed in some clinical studies involving aprotinin. A similar laboratory finding—increased resistance to aPC in FVL plasma treated with aprotinin—was also observed in an *ex vivo* model of CPB, in which blood specimens from noncarriers and from FVL subjects were circulated in a bypass system (134). These authors used a slightly different aPC resistance assay that relied on activation of the patient's endogenous protein C by a snake venom and activated coagulation by Russel viper venom, a method mentioned previously. However, aprotinin induces a dose-dependent prolongation of aPTT in the absence of aPC (146). The standard cutoff value of 2.0 for the aPC ratio assumes a linear relationship of the aPC response and represents an assumption that may not be valid in the presence of prolonged baseline aPTT. The clinical significance of a decreased aPC ratio in the presence of aprotinin is therefore not clear.

Although these findings contribute to our understanding of the pharmacology of aprotinin, no clinical studies have documented an increased thrombotic risk of aprotinin in FVL patients undergoing cardiac surgery. Moreover, no studies have reported measuring an increase in aPC resistance in the blood of patients during CPB, rather than in blood to which aprotinin has been added *in vitro*. Many authors (147–149) have concluded that the CAB graft occlusion observed in earlier aprotinin trials was most likely a result of inadequate heparinization due to the use of celite-based activated clotting time, which is artificially prolonged in the presence of aprotinin.

Whether this potentially prothrombotic effect of aprotinin (inhibition of aPC) or the anticoagulant effects of aprotinin predominate in the presence of FVL has been addressed in a well documented case report

(150). These authors, using a thromboelastogram technique, reported that aprotinin produced a 30% increase in the r-time (time to initiation of clot formation) and a decrease in the $\alpha$-angle (rate of clot progression), with no measurable change in the maximum amplitude (a measurement of total clot strength), representing a definite anticoagulant effect of aprotinin. This anticoagulant effect persisted after the addition of either endothelial cells (a source of thrombomodulin to generate aPC) or celite (a contact pathway activator). Because aprotinin attenuates coagulation at multiple enzymatic steps (151), the results are somewhat expected. As the authors point out, these assays involved blood samples to which aprotinin was added, rather than specimens drawn from the patient during aprotinin therapy and CPB. Furthermore, inhibition of aPC by aprotinin occurs at concentrations of ≥500 kallikrein-inhibiting units per milliliter, levels not typically achieved in cardiac surgery (152–154). The authors conclude that although aprotinin can inhibit aPC, the anticoagulant effect of aprotinin appears to predominate in FVL plasma, and they recommend the use of aprotinin in this population when clinically warranted (150).

### *Lysine Analogs*

Tranexamic acid and $\epsilon$-aminocaproic acid have a much different pharmacologic profile than aprotinin, because their principal effect is inhibition of plasmin and plasminogen activators, whereas aprotinin has inhibitory effects on multiple enzyme systems (102,155). The literature appears void of studies of the thrombotic risks of lysine analogs in the FVL population. However, the possible interaction of FVL, antifibrinolytic therapy, and hypothermic circulatory arrest in precipitating thrombosis was recently highlighted by a startling case report. Authors described two lethal massive thrombotic events occurring after protamine administration in patients undergoing hypothermic circulatory arrest with $\epsilon$-aminocaproic acid (156). One of these patients was found to be a carrier of FVL. Presurgical screening was proposed, which generated some controversy because of its lack of demonstrated advantage in prospective trials (157). Later, the same group observed another massive thrombotic event in a third patient undergoing hypothermic arrest with $\epsilon$-aminocaproic acid, who was an obligate carrier of FVL as determined by testing family members (Dr. Linda Shore-Lesserson, Mt. Sinai Medical Center, New York, personal communication, 2002). Although there is an inherent anecdotal nature to these reports, they highlight the importance of balancing the need for definitive evidence against conscientious and prudent medical practice.

## Perioperative Risk of FVL: Summary and Unresolved Questions

The following conclusions can be drawn from the current data involving FVL in the perioperative setting:

1. Venous thrombosis after orthopedic or general surgery does not appear to be increased in the presence of FVL heterozygosity when patients are managed according to published protocols involving prophylactic anticoagulation. There is no evidence for altering perioperative management on the basis of the finding of FVL, nor is there evidence to support a role of preoperative screening for FVL or aPC resistance.
2. The role of FVL in arterial thrombosis and infarction after vascular surgery is less clear, but current literature suggests that there may be an increase in risk. On the basis of the literature, preoperative screening for FVL is unlikely to be of benefit, but screening for aPC resistance may identify patients at particular risk for earlier postoperative complications. Prudent recommendations include adherence to guidelines established by the American College of Cardiology/American Heart Association Task Force for management of patients at risk for perioperative ischemia (158), with decisions based on surgical urgency, patient history, clinical predictors, functional capacity, surgical risk, and specific invasive and noninvasive testing.
3. Cardiac surgery patients with FVL are likely to bleed less than noncarriers, and the degree of blood sparing may be equivalent to that associated with antifibrinolytic therapy.
4. Coronary bypass graft occlusion within the first few months after surgery may be increased in the presence of FVL. However, there is no evidence documenting the benefits of any targeted postoperative therapy to maintain graft patency in patients with FVL. Adherence to established guidelines (159) for maintaining graft patency, including the use of arterial conduits, postoperative antiplatelet therapy, antilipid therapy, lifestyle modifications, cardiac rehabilitation, and medical follow-up, may therefore have the greatest benefit in this potentially higher-risk group of patients.
5. The interaction of aprotinin at Hammersmith or half-Hammersmith doses with FVL is characterized mostly by an increase in anticoagulation, not by a hypercoagulable state. Early graft closure in FVL patients in the presence of aprotinin and risk factors for graft thrombosis remains a theoretical possibility without supporting or refuting evidence.

6. Little is reported on lysine analogs in the presence of FVL and CPB. Anecdotal evidence suggests the risk of a hypercoagulable state in the setting of circulatory arrest and profound hypothermia.

## Future Investigations

Several well conducted clinical studies are necessary to better clarify risk in the clinical situations listed previously. The risk for arterial thrombosis after both vascular surgery and cardiac surgery needs to be addressed in a large-scale, well controlled, prospective trial with sensitive clinical end-points and inclusion of other covariates. Early coronary graft occlusion and the need for repeat revascularization need to be studied as clinical end-points. The possible interaction of FVL with antifibrinolytic drugs, especially the lysine analogs, needs to be characterized. Novel methods of contact pathway inhibition are on the horizon, such as the aprotinin analog DX-88, a potent and specific inhibitor of kallikrein (160). Because kallikrein-induced fibrinolysis is a significant result of CPB (110–112), the potential interaction of this drug with FVL and other prothrombotic genotypes will need to be investigated. Each of these studies needs to include an evaluation of coagulation phenotypes, such as resistance to aPC, impaired fibrinolysis, and thrombin activation, as possible mechanisms by which FVL may be having a clinically apparent effect. Because prospective trials demonstrating the benefit of presurgical genotyping have yet to be performed, most current data do not support either preoperative screening for FVL or modification of anesthetic or surgical management on the basis of preoperative knowledge of a patient's factor V genotype. Genetic testing can be advocated only once the risks of a genotype are known and there is an evidence-based plan for decreasing the associated risks.

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