

Research article

## The relationship of the factor V Leiden mutation or the deletion-deletion polymorphism of the angiotensin converting enzyme to postoperative thromboembolic events following total joint arthroplasty

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### Abstract

**Background:** Although all patients undergoing total joint arthroplasty are subjected to similar risk factors that predispose to thromboembolism, only a subset of patients develop this complication. The objective of this study was to determine whether a specific genetic profile is associated with a higher risk of developing a postoperative thromboembolic complication. Specifically, we examined if the Factor V Leiden (FVL) mutation or the deletion polymorphism of the angiotensin-converting enzyme (ACE) gene increased a patient's risk for postoperative thromboembolic events. The FVL mutation has been associated with an increased risk of idiopathic thromboembolism and the deletion polymorphism of the ACE gene has been associated with increased vascular tone, attenuated fibrinolysis and increased platelet aggregation.

**Methods:** The presence of these genetic profiles was determined for 38 patients who had a postoperative symptomatic pulmonary embolus or proximal deep venous thrombosis and 241 control patients without thrombosis using molecular biological techniques.

**Results:** The Factor V Leiden mutation was present in none of the 38 experimental patients and in 3% or 8 of the 241 controls ( $p = 0.26$ ). Similarly there was no difference detected in the distribution of polymorphisms for the ACE gene with the deletion-deletion genotype present in 36% or 13 of the 38 experimental patients and in 31% or 74 of the 241 controls ( $p = 0.32$ ).

**Conclusions:** Our results suggest that neither of these potentially hypercoagulable states are associated with an increased risk of symptomatic thromboembolic events following total hip or knee arthroplasty in patients receiving pharmacological thromboprophylaxis.

### Background

Patients following total hip and knee arthroplasty are at a significant risk for thromboembolic complications. De-

spite modern prophylaxis against thromboembolism, studies still report a 10 to 40% frequency of deep venous thrombosis and a significant rate of pulmonary embo-

lism following total hip or knee arthroplasty [1–3]. The high incidence of thrombotic disease despite prophylaxis makes early detection imperative, as treatment with anticoagulation is highly effective [4, 5].

Both DVT and PE manifest few specific clinical signs or symptoms, making the clinical diagnosis neither sensitive nor specific [5–7]. A high index of suspicion based on risk stratification is necessary for the detection and appropriate implementation of diagnostic studies to identify this complication. The ability preoperatively to identify a subset of patients undergoing adult reconstructive surgery that are at a higher risk of developing thromboembolic complications would aid the clinician in making an accurate diagnosis and make possible further research to determine optimal regimes of postoperative detection and prophylaxis.

Until recently, the only known hypercoagulable states were several rare genetic disorders of the coagulation cascade (antithrombin III, protein C, and protein S deficiency), which accounted for only a small percentage of all patients with venous thrombosis [16]. In 1993, Dahlback et al. [17] described a previously unreported hypercoagulable state among members of three families that suffered from recurrent venous thrombosis. Further investigation revealed an autosomal-dominant inherited defect in the anticoagulant function of factor V resulting in resistance to the anticoagulant action of activated protein C (APC) [18]. Formal evidence for this association came from a large population-based patient-control study, the Leiden Thrombophilia Study, which followed 474 consecutive patients of less than 70 years of age with a first episode of objectively confirmed DVT [9]. Twenty-eight percent of patients in the study group and 5.7% of controls were found to be APC-resistant. Furthermore, it was estimated that these patients have a sevenfold greater risk of developing a DVT. The abnormal factor V that causes APC resistance was subsequently termed factor V Leiden. Later studies confirmed a seven- to-eightfold increased risk for patients heterozygous for the factor V mutation and an 80-fold increased risk in homozygous individuals [3,9]. Factor V Leiden is therefore the most common thrombophilic disorder described, 10 times more common than all the other genetic coagulopathies combined, with an estimated prevalence of 5% in the general population [9, 10, 15].

Although the majority of patients undergoing total hip and knee arthroplasty are subjected to similar perioperative risk factors that predispose to thromboembolism, only a subset of patients develop this complication. The objective of this study was to determine whether the FVL mutation or the deletion polymorphism of the ACE gene

is associated with a higher risk of developing a postoperative thromboembolic complication.

## Patients and Methods

### Patients

The presence of the Factor V Leiden mutation and the deletion-deletion polymorphism of the angiotensin converting enzyme gene were determined for 38 patients who developed symptomatic pulmonary embolism (30 patients) or proximal deep venous thrombosis (8 patients) following elective total hip or knee arthroplasty at our institution between February of 1997 and July of 1999. The prevalence of these genetic profiles was compared to a control cohort of 241 patients who had undergone similar procedures between November 1997 and March of 1998 at the same institution and whose postoperative course was not complicated by symptomatic thromboembolism using an unmatched case-control design. A total of 321 elective total hip and knee arthroplasties were performed during the time period that samples for the control group were collected, however 14 patients chose not to participate in the study and 7 patients were discharged to home prior to sample collection. An additional 59 patients who were clinically suspected of deep vein thrombosis but had a single negative duplex ultrasound of the lower-extremities were also excluded from the analysis.

Pulmonary embolism was diagnosed on the basis of clinical symptoms and signs combined with a high probability ventilation-perfusion scan in 20 of the 30, a positive pulmonary angiogram in 6, a positive high resolution chest CT in 2 and an intermediate probability ventilation-perfusion scan combined with a high clinical suspicion in 2. The 8 proximal deep venous thrombosis was diagnosed by duplex ultrasonography in seven and contrast venography in 1. Thirty-one of the 38 patients were treated with intravenous heparin followed by oral warfarin, five by placement of an inferior vena caval and oral warfarin and two by placement of an inferior vena caval filter followed by intravenous heparin and oral warfarin

Polymorphisms of the angiotensin converting enzyme have also been associated with a hypercoagulable state. The angiotensin converting enzyme (ACE) digests angiotensin I to angiotensin II (a potent vasoconstrictor) and is thus involved with the regulation of vascular tone. The angiotensin converting enzyme has also been shown to attenuate fibrinolysis and affect both platelet activation and aggregation [14]. The ACE gene has been found to have a polymorphism consisting of an insertion and a deletion of a 287 base pair fragment of intron 16 [13]. Patients may thus be of one of three separate genotypes; insertion/insertion, deletion/deletion or insertion/deletion. Patients with the deletion/deletion genotype have

been shown to have mean plasma ACE levels of approximately twice that of patients with the insertion/insertion genotype [13]. Thus patients with the deletion/deletion genotype may be at increased risk for thromboembolic events.

Demographic and operative information including relevant past medical history and the type of thromboembolic prophylaxis utilized was collected for the experimental and control groups as summarized in Table 1. Approval was obtained from the Institutional Review Board at our hospital prior to initiating this study and all patients signed informed consent prior to participating in the study.

**Determination of the Factor V Leiden Mutation**

Two-milliliter samples of whole blood were collected in buffered sodium citrate, and high molecular weight genomic DNA was obtained from the peripheral blood leukocyte fraction (QIAamp Blood Tissue Kit, Qiagen, Valencia CA). The factor V Leiden mutation is located in

exon 10, 11 nucleotides 5' of the start of intron 10 at nucleotide 1691, where an adenosine replaces guanidine [15]. A 169-base-pair DNA fragment of the factor V gene that includes nucleotide 1691 was amplified utilizing the polymerase chain reaction (PCR) with the forward primer 5'CATACTACAGTGACGTGGAC3' and the reverse primer 5'GACCTAACATGTTCTAGCCAGAAG3'. PCR was performed using a standard protocol as follows with a final volume of 50 µl; 5 µl 10X PCR buffer, 5 µl 2 mM dNTP, 5 µl forward primer (concentration 20 ng/ul), 5 ul reverse primer (concentration 20 ng/ul), 1.5 µl 50 mM MgCl, 0.25 µl Taq polymerase (5 U/µl), and 1 µl sample purified genomic DNA (concentration approximately 30 ng/µl) (PCR reagents, Gibco-BRL, Bethesda, MD). Thirty-five cycles of the polymerase chain reaction utilizing a microprocessor controlled thermal cycler (Perkin-Elmer, Norwalk, CT) were then performed to amplify the desired segment utilizing the following parameters; 94°C for denaturation for 45 seconds, 63°C for 60 seconds for annealing, and 72°C for 90 seconds for extension.

**Table 1: Demographic and Operative Data**

	<b>Study Group</b> N = 38	<b>Control Group</b> N = 241	<b>P Value</b>
<b>Mean Age (years)</b>	67	63	0.11
<b>Female Sex</b>	33 (87%)	171 (71%)	0.07
<b>Thromboembolic Prophylaxis</b>			0.79
Enoxaparin Sodium	37 (97%)	228 (95%)	
Warfarin	1 (3%)	13 (6%)	
<b>History of Prior Thromboembolism</b>	5 (13%)	3 (1%)	<0.001
<b>Family History of Thromboembolism</b>	3 (8%)	5 (2%)	<0.001
<b>Percent Ideal Body Weight</b>	139%	147%	0.23
<b>History of Smoking</b>	3 (8%)	20 (7%)	0.77
<b>Procedure</b>			0.21
Primary Total Hip Arthroplasty	10 (26%)	94 (39%)	
Primary Total Knee Arthroplasty	25 (66%)	113 (47%)	
Revision Total Hip Arthroplasty	1 (3%)	20 (8%)	
Revision Total Knee Arthroplasty	2 (5%)	14 (6%)	
<b>Preoperative Diagnosis: Hips</b>			0.71
Osteoarthritis	6 (55%)	75 (66%)	
Rheumatoid Arthritis	1 (9%)	4 (4%)	
Failed Implant	1 (9%)	20 (18%)	
Other	3 (27%)	15 (12%)	
<b>Preoperative Diagnosis: Knees</b>			0.8
Osteoarthritis	22 (81%)	101 (79%)	
Rheumatoid Arthritis	2 (7%)	7 (6%)	
Failed Implant	1 (4%)	14 (11%)	
Other	2 (8%)	5 (4%)	
<b>Estimated Blood Loss (milliliters)</b>	323	425	0.21
<b>Operative Time (minutes)</b>	128	145	0.24
<b>Anesthetic</b>			0.09
Neuraxial	30 (78%)	142 (59%)	
General	8 (22%)	99 (41%)	

The amplified 169-base-pair fragment was digested with 0.4 U of the restriction enzyme *Mnl* I (New England Bio Labs, Beverly, MA) at 37°C for 6-12 hours and the resulting fragments were subjected to electrophoresis on 4% Nu-Sieve GTG agarose gels (FMC Bioproducts, Rockland, ME) and the nucleotide bands visualized by ethidium bromide fluorescence and photography. Digestion yields three fragments (86, 46, and 37 base pairs) in the normal allele and two fragments (123 and 46 base pairs) in the mutant allele as the point mutation at position 1691 is associated with loss of the recognition site for *Mnl* I. Control digestions were performed with fragments amplified from cloned DNA with and without the factor V Leiden mutation.

#### **Determination of Angiotensin Converting Enzyme Polymorphisms**

The insertion/deletion genotype of subjects was performed using purified genomic DNA (prepared as above) and the polymerase chain reaction using the forward primer 5'CTGGAGACCACTCCCATCCTTTCT3' and the reverse primer 5'GATGTGGCCATCACATTCGTCAGAT3' as per Rigat et al [13]. PCR was performed using a standard protocol as follows with a final volume of 50 µl; 5 µl 10X PCR buffer, 5 µl 2 mM dNTP, 5 µl forward primer (concentration 20 ng/µl), 5 µl reverse primer (concentration 20 ng/µl), 1.5 µl 50 mM MgCl, 0.25 µl Taq polymerase (5 U/µl), and 1 µl sample purified genomic DNA (concentration approximately 30 ng/µl), and 5 µl dimethyl sulfoxide. Thirty-five cycles of the polymerase chain reaction utilizing a microprocessor controlled thermal cycler (Perkin-Elmer, Norwalk, CT) were then performed to amplify the desired segment utilizing the following parameters; 94°C for denaturation for 60 seconds, 63°C for 90 seconds for annealing, and 72°C for 90 seconds for extension. The PCR products were subjected to electrophoresis on 1.2% agarose gels and the nucleotide bands visualized by ethidium bromide fluorescence and photography. A 190-bp fragment characterizes the deletion polymorphism, while the presence of the insertion leads to a 490-bp fragment. Heterozygotes exhibit an intermediate band that is most likely a heteroduplex DNA fragment.

#### **Statistical Analysis**

Statistical analysis was performed using a two-tailed student's t test, Chi square analysis or Mann-Whitney U test where appropriate with a significance set at  $p = 0.05$ . Assuming an unmatched case control design with  $\alpha = 0.05$  and  $\beta = 0.80$ , post-hoc power analysis was performed to determine the minimum detectable relative risk detectable with the given sample size [24].

#### **Results**

A comparison between the experimental and control subjects revealed that they were of comparable age and sex (Table 1I). Operative indications, procedures and surgical variables were likewise similar in the two groups of patients (Table 1I). A significant difference was noted however in that the patients in the experimental group had a significantly higher percentage of patients with a personal or family history of thromboembolism ( $p < 0.001$  for both).

The Factor V Leiden mutation was present in none of the 38 experimental patients and in 3% or 8 of the 241 controls ( $p = 0.26$ . Odds ratio = 1 with 95% confidence interval 0-3.8). Post-hoc power analysis revealed that with the number of subjects available, the minimum detectable risk for the Factor V Leiden mutation being associated with a higher risk of thromboembolic complications was 5.9.

Similarly there was no difference detected in the distribution of polymorphisms for the Angiotensin Converting Enzyme gene with the deletion-deletion genotype present in 36% or 13 of the 38 experimental patients and in 31% or 74 of the 241 controls ( $p = 0.32$ . Odds ratio = 1.2 with 95% confidence interval 0.5-2.5). Post-hoc power analysis revealed that with the number of subjects available, the minimum detectable risk for the deletion-deletion polymorphism of the ACE gene being associated with a higher risk of thromboembolic complications was 2.7.

#### **Discussion**

Previous authors have examined the relationship between inherited hypercoagulable states and thromboembolism following total hip and knee arthroplasty with mixed results. Lowe et al. [19] found that the Factor V Leiden mutation was associated with an increased risk of deep venous thrombosis (as determined by routine bilateral ascending venography) in 480 European patients who had undergone total hip arthroplasty, however only 41 of the 120 patients with deep venous thrombosis had proximal thrombi. Svensson et al. [20] found that among a cohort of 100 Swedish patients who had undergone hip arthroplasty, female patients who were heterozygous for the factor V Leiden mutation had a four-fold increased risk of thrombosis. The authors felt, however, that based on their data, no definite association between the Factor V Leiden mutation and postoperative thrombosis could be made. In contrast, Ryan et al. [21] studied 825 patients who had routine bilateral ascending venography following total hip and knee arthroplasty and found that the prevalence of the Factor V Leiden mutation was no different between patients who did and did not have venographic evidence of deep venous thrombosis. Simi-

larly, Woolson et al. [22] studied 36 patients who had a proximal deep venous thrombosis after total hip arthroplasty (detected by routine pre-discharge compression duplex ultrasound) and found that the prevalence of the Factor V Leiden was no different in that population compared to 45 controls. In contrast to the aforementioned studies, the present report studied patients who had developed symptomatic thromboembolic events (the majority of which were pulmonary embolism) and were all treated with a uniform thromboembolic prophylaxis regime. Our results support the findings of others, that in patients receiving pharmacological prophylaxis against postoperative thrombosis, the Factor V Leiden mutation is not associated with an increased risk of symptomatic thromboembolism following total hip or knee arthroplasty.

While Phillip et al. [23] found no association between the Factor V Leiden mutation and deep venous thrombosis, they did find that the deletion-deletion genotype of the angiotensin converting enzyme was strongly associated with postoperative venous thrombosis in 85 patients who had undergone total hip arthroplasty (30 of whom had a thromboembolic event as detected by routine compression duplex ultrasound). They concluded that patients with the deletion/deletion genotype were at a 10-fold increased risk for a thromboembolic event following total hip arthroplasty as compared to patients with the insertion-insertion genotype. However, 12 of the 30 experimental subjects had isolated distal deep venous thrombosis (which is of questionable clinical significance) and only 10% had a pulmonary embolism. While the results of this study had encouraged us to screen our patient population for these polymorphisms, when utilizing a more relevant clinical endpoint (symptomatic pulmonary embolism or deep venous thrombosis) we were unable to confirm this association.

Due to the relative infrequency of symptomatic thromboembolic events while using pharmacological agents as prophylaxis, an unmatched case-control study design was employed. This type of study design has the advantage of increased statistical power for studying relatively rare events [24]. However, its disadvantages include the possibility that other variables that were not controlled for could have affected our results. The patients in both the case and control groups were operated on during overlapping time periods and were found to be demographically similar, and thus we do not believe that such confounding variables affected our results. Our power analysis reveals that a relatively strong association between these genetic profiles and postoperative thromboembolism (5.9 fold increased risk for the factor V Leiden mutation and a 2.7 fold increased risk for the deletion/deletion polymorphism of the angiotensin con-

verting enzyme gene) would have been required to detect a significant difference between the prevalence of these mutations in our case and control groups. Likewise, a larger number of patients would have been required to find a significant difference if a weaker association was assumed. However, no trend was detected in our data to suggest that such an association was present. Furthermore, such a weak association would make preoperative screening and identification of such patients not cost effective.

It was noted however, that a significantly greater percentage of patients who suffered a thromboembolic event had a personal or family history of thromboembolism ( $p = 0.001$  for both). The report by Woolson et al. [22] included similar findings. Although residual abnormalities of the deep venous system could account for the higher prevalence of a personal history of prior deep venous thrombosis or pulmonary embolism, the higher prevalence of a family history of thromboembolic events suggests that an as yet undescribed genetically determined hypercoagulable state or predisposition may be present in these patients.

## Conclusions

The objective of this study was to determine whether a specific genetic profile is associated with a higher risk of developing a postoperative thromboembolic complication. Although our results suggest that neither of these potentially hypercoagulable states are associated with an increased risk of symptomatic thromboembolic events following total hip or knee arthroplasty in patients receiving pharmacological thromboprophylaxis, an as yet undescribed genetically determined hypercoagulable state or predisposition may be present in these patients.

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