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The contribution of factor V Leiden and prothrombin G20210A mutation to the risk of central venous catheter-related thrombosis

CORNELIS J. VAN ROODEN
FRITS R. ROSENDAAL
A. EDO MEINDERS
JACQUES A. VAN OOSTAYEN
FELIX J. M. VAN DER MEER
MENNO V. HUISMAN

A B S T R A C T

Background and Objectives. The purpose of this study was to assess the incidence of central venous catheter (CVC)-related thrombosis and the contribution of two common inherited coagulation disorders (factor V Leiden, prothrombin G20210A mutation) to this complication in a large hospital population.

Design and Methods. In a prospective setting, patients were assessed daily for signs and symptoms suggestive of thrombosis. Routine Doppler-ultrasound was performed weekly in all patients until CVC removal. Doppler-ultrasound examinations were stored on videotape and assessed by two blinded observers. In the case of clinically suspected thrombosis the physicians followed routine diagnostic and therapeutic procedures. The presence of factor V Leiden and prothrombin G20210A mutation and other potential risk factors were assessed in all patients.

Results. In 252 consecutive patients the cumulative incidence of-CVC related thrombosis was 30% (clinically manifested thrombosis: 7%). The relative risk of factor V Leiden or prothrombin G20210A mutation for thrombosis was 2.7 (CI95% 1.9 to 3.8). In addition, a personal history of venous thrombosis was associated with CVC-related thrombosis, whereas the severity of thrombosis was affected by the absence of anticoagulants and the presence of cancer.

Interpretation and Conclusions. Thrombosis is frequently observed after central venous catheterization. Common inherited abnormalities in blood coagulation contribute substantially to CVC-related thrombosis. In view of physicians' reluctance to prescribe prophylactic anticoagulant treatment in vulnerable patients, *a priori* determination of common inherited and acquired risk factors may form a basis to guide these treatment decisions.

Key words: thrombosis, central venous catheter, thrombophilia, genetics, Doppler-ultrasound.

From the Department of General Internal Medicine (CJvR, AEM, MVH), Clinical Epidemiology (FRR), Hematology (FRR, FJMvdM) and Radiology (JAvO). Leiden University Medical Center (LUMC), Leiden, the Netherlands.

Correspondence: Dr. Menno V. Huisman, Department of General Internal Medicine, room B3-Q-84, Leiden University Medical Center (LUMC), PO Box 9600, 2300 RC Leiden, The Netherlands.
E-mail: m.v.huisman@lumc.nl

A central venous catheter (CVC) is commonly used for a variety of indications.[1] The benefit derived from these devices can be offset by thrombosis, which may be complicated by pulmonary embolism (PE) and CVC dysfunction.[2-4] Often, thrombosis may force premature CVC removal, which requires the insertion of a new CVC with the associated risk of complications (pneumothorax), and the need for anticoagulant treatment with its concomitant bleeding risk.

Reliable estimates of the incidence of CVC-related thrombosis among a large hospital population are lacking. Besides, in contrast to a large number of studies on the association of factor V Leiden and prothrombin G20210A mutation with deep vein thrombosis of the leg and pulmonary embolism,[5] studies investigating the association of these risk factors with CVC-related thrombosis are scarce.[6-9] Such data are relevant since they may indicate differences in thrombotic risk in patients who need to undergo central venous catheterization. Moreover, these data could assist clinicians in their decisions on anticoagulant prophylaxis.[10]

In a prospective setting we carefully assessed the incidence of CVC-related thrombosis in patients undergoing catheterization via the jugular or subclavian vein. We determined the contribution of the two most common prothrombotic inherited abnormalities in blood coagulation, factor V Leiden and prothrombin G20210A mutation, to CVC-related thrombosis in these patients. In addition all patients were assessed for other potential risk factors for CVC-related thrombosis.

Design and Methods

Patients and study design

This prospective study was performed at the Leiden University Medical Center (LUMC), a university hospital in The Netherlands. The study protocol was approved by our local medical ethical committee and all participating patients gave written informed consent.

Consecutive patients, aged 16 years or older, with a central venous catheter (CVC) in place for at least 48 hours were considered eligible to participate in the study. Central venous catheters could be inserted via the jugular or subclavian vein. Patients were recruited from the different departments throughout our hospital. Patients received a CVC for chemotherapy, for hemodynamic or perioperative monitoring, for fluid administration or for pharmacotherapy.

Patients with abnormal Doppler-ultrasound findings (performed within 48 hours after CVC insertion) were excluded if they had a history of a CVC at the same insertion site, or a history of an objectively confirmed thrombosis at the same insertion side, since these were regarded as pre-existing thrombosis. Patients who were unable to undergo serial Doppler-ultrasound evaluations were also excluded.

The decisions to give anticoagulant prophylaxis and, if so, the dosage, were at the discretion of the attending physicians. Post-operative patients, patients who were immobile or sedated, and patients with a long-term CVC (Port-a-cath®), who received prophylactic doses of nadroparin subcutaneously at a dosage between 2850 IU and 7600 IU daily were classified as receiving *prophylactic anticoagulant treatment*. A higher daily dosage of nadroparin, intravenous unfractionated heparin (prolonging the APTT by 2 to 2.5 fold) or oral vitamin K antagonist (INR: 2.0 – 4.0) were classified as *therapeutic anticoagulant treatment*.

Monitoring and follow-up

During their admission, all patients were examined daily by physicians for symptoms and signs suggestive of CVC-related thrombosis; i.e. pain, discoloration, local swelling or edema and visible collateral circulation. If patients were discharged from the hospital while their CVC was still in place, patients were seen in the outpatient clinic at least every three to six weeks. Clinical follow-up ended six weeks after removal of the CVC, or one year after insertion if the CVC was still in place. Patients with clinically suspected thrombosis were referred to our department of Radiology for Doppler-ultrasound examination. If no thrombosis was objectively identified by Doppler-ultrasound, patients underwent unilateral venography.

Separate from the clinical follow-up, all patients were examined serially for CVC-related thrombosis by Doppler-ultrasound by one ultrasonographer according to a standardized protocol. During admission, Doppler-ultrasound was performed within 48 hrs after the insertion of the CVC, and at least once a week until CVC removal. Outpatients were examined by Doppler-ultrasound every three to six weeks. Doppler-ultrasound examinations were performed bilaterally and the following venous segments were subsequently identified: the brachial, axillary, subclavian and jugular vein. All real-time examinations were coded and recorded on videotape. Recordings were assessed at least three months after discharge of the patient from follow-up by a panel of two blinded observers, experienced in Doppler-ultrasound evaluation. A third expert opinion was asked for, when needed. The outcomes of the screening Doppler-ultrasound examinations were not made known to the physicians responsible for clinical follow-up nor to the radiologists who performed the Doppler-ultrasound examinations or venography in the case of clinically suspected thrombosis, since it is routine clinical practice to diagnose and treat CVC-related thrombosis based on clinical signs and symptoms.

Blood samples were taken from all patients within the 48 hrs after catheterization. Factor V Leiden and prothrombin G20210A mutation and factor VIII:C (IU/dL) were determined by standard techniques as described previously.[11-13] Factor V Leiden and prothrombin G20210A mutation were analyzed by comparing carriers of the mutation to homozygous wild-type individuals. Factor VIII levels were categorized in levels over and under the 90th percentile of the distribution in this group of patients. In addition, established risk factors for venous thrombosis and CVC characteristics were assessed in detail in each patient.

Outcome measures

The primary end-point in this study was CVC-related thrombosis. Two types of thrombosis were distinguished, clinically manifest thrombosis and subclinical thrombosis. Clinically manifest thrombosis was defined as thrombosis objectively identified by Doppler-ultrasound or venography following signs or symptoms suggestive of CVC-related thrombosis, as noted by attending physicians. Subclinical thrombosis was defined as thrombosis demonstrated by screening Doppler-ultrasound in the absence of signs or symptoms.

A Doppler-ultrasound diagnosis of CVC-related thrombosis was made according to predefined criteria. For veins accessible to direct insonation, the criteria of non-compressibility, visualization of an echogenic intravascular mass and absence of respiratory phasicity were used (jugular, axillary and subclavian veins).[14-17] For veins inaccessible to direct insonication the criterion of mono-phasic flow (spectral Doppler) was used (middle

part of subclavian vein, brachiocephalic vein and superior vena cava) to detect occlusive thrombosis.[18]

Criteria for diagnosing by contrast venography included an intraluminal contrast filling defect of a venous segment or persistent non-filling of a venous segment in the presence of collateral circulation.[19] Possible complications associated with CVC-related thrombosis, pulmonary embolism (PE) and CVC dysfunction (occlusion) were carefully noted.

Statistical analysis

Cumulative incidences for subclinical thrombosis and clinically manifest thrombosis were calculated as the number of first events over the number of patients at baseline. The ratios of the cumulative incidences were the relative risks (RR). Ninety-five percent confidence intervals (CI95%) were based on standard errors for binomial distributions. The effects of risk factors that were likely to be associated were determined by restriction analysis.

Results

Patients

In the 18-month study period, 368 patients with a central venous catheter (CVC) were considered for enrollment. Informed consent was not obtained from 88 eligible patients. In nine patients, the attending physician did not allow us to recruit the patient. Fourteen patients met one of the exclusion criteria: inability to undergo Doppler-ultrasound (n = 9), an abnormal Doppler-ultrasound (performed within 48hrs after CVC placement) in patients with a history of a prior CVC at the same insertion site (n = 3), or a history of thrombosis on the same side prior to CVC insertion (n = 2). Thus, 257 patients were enrolled in the study protocol. Five patients were subsequently excluded from analysis: in one patient the determination of factor V Leiden and prothrombin mutation had failed, in three patients it was not possible to perform the scheduled Doppler-ultrasound because of prior hospital discharge, and one patient withdrew informed consent. Thus, complete data were obtained for analysis from 252 patients. The main characteristics of these 252 patients and their CVC are shown in Table 1.

Table 1. Baseline characteristics for 252 patients with a central venous catheter (CVC).

	Mean	*(range)*
Age (yr)	54	(16-88)
Height (m)	1.73	(1.47-2.04)
Weight (kg)	75	(43-140)
Body mass index (kg/m^2)	25	(16–41)
CVC in place (median days)	14	(2-365)
	Numbers (%)	
Sex		
Male	149	(59.1)
Female	103	(40.9)
Underlying Disease		
Medical conditions	170	(67.5)
Solid tumor malignancy	39	(15.5)
Hematologic malignancy	97	(38.5)
Infectious disease	13	(5.2)
Cardiopulmonary disease	11	(4.4)
Inflammatory disease	8	(3.2)
Other	2	(0.8)
Postoperative condition	82	(32.5)
Anticoagulant treatment		
No anticoagulants	107	(42.5)
Prophylactic dose	127	(50.4)
Therapeutic dose	18	(7.1)
Type CVC		
Single/double lumen	61	(24.2)
Triple/four lumen	86	(34.1)
Swan-Ganz catheter	69	(27.4)
Porth-a-cath®	35	(13.9)
Other	1	(0.4)
Location CVC		
Right side	164	(65.1)
Jugular vein	143	(56.7)

CVC-related thrombosis

Overall, 29.8% (75 out of 252) of patients developed CVC-related thrombosis (CI95% 24.1% to 35.4%). In 18 patients (7.1%) the thrombosis was clinically manifest, while in 57 patients (22.6%) subclinical thrombosis was demonstrated by routine Doppler-ultrasound.

Four patients (1.6%) developed pulmonary embolism (PE), objectively diagnosed by a high probability ventilation perfusion scintigram (n = 3) or abnormal helical CT (n = 1). In 12 patients (4.8%) one or more lumina of the CVC became occluded. Pulmonary embolism and CVC occlusion were not associated with clinically manifest thrombosis. Subclinical thrombosis was diagnosed in one patient with PE and in another patient with CVC occlusion.

Risk estimates for CVC-related thrombosis

Seventeen patients were heterozygous carriers of the factor V Leiden mutation (6.7%) and another 6 patients had heterozygous prothrombin G20210A mutation (2.4%). No patient was double heterozygous or homozygous. Thrombosis was diagnosed in 12 of the 17 patients with factor V Leiden (70.6%), as compared to in 63 of 235 patients who did not have the mutation (26.8%) (RR 2.6, CI95% 1.8 to 3.8). Thrombosis was diagnosed in 4 of 6 patients (66.7%) with

Table 2. The risk of central venous catheter (CVC)-related thrombosis in the presence or absence of inherited coagulation disorders (factor V Leiden and prothrombin G20210A mutation).

Factor V Leiden or Prothrombin G20210A mutation	*CVC-related thrombosis*		
	Yes	*No*	*Total*
Yes	16	7	23
No	59	170	229
Total	75	177	252

prothrombin G20210A mutation, whereas 71 thromboses were detected in 246 patients (28.9%) without the mutation (RR 2.3, CI95% 1.3 to 4.2). For patients with CVC-related thrombosis who had at least one of the mutations the relative risk was 2.7 (CI95% 1.9 to 3.8) (Table 2). The population-attributable risk of the mutations to thrombosis was 13.4%.

The risk estimates of other factors for CVC-related thrombosis are summarized in Table 3. In univariate analysis, a personal history of venous thrombosis was associated with an increased risk of CVC-related thrombosis. If patients with an inherited coagulation disorder were excluded from the analysis, a personal history of a venous thrombosis was still associated with an increased risk of CVC-related thrombosis (RR 2.3, CI95% 1.6 to 3.4). When the risk factor analysis was performed within the group of patients with inherited coagulation disorders (n = 23) or within the different groups of patients according to the underlying disease (cancer vs. no cancer) or anticoagulant-status (absence vs. presence), no other substantial contributors to CVC-related thrombosis could be identified.

With regard to clinically manifest thrombosis, a similar trend in relative risk was observed for the inherited coagulation disorders and a personal history of thrombosis. Three out of 23 patients (13%) with an inherited coagulation disorder, in all cases heterozygous factor V Leiden, developed clinically manifest thrombosis, as compared to 15 out of 229 (6.6%) patients without the mutation, (RR 2.0, CI 95% 0.6 to 6.4). The RR from a personal history of thrombosis was 2.3 (CI 95% 0.8 to 6.5). Other factors were also associated with the occurrence of clinically manifest thrombosis. The lack of anticoagulant therapy was strongly associated with an increased risk of clinically manifest thrombosis (RR 4.7, CI 95% 1.6 to 14), especially in cancer patients who underwent intensive chemotherapy. Among these patients, 14 of 98 without prophylaxis developed clinically manifest thrombosis (14.3%), whereas no patients among the group who received anticoagulants (n = 35) did so.

Table 3. Risk estimates for central venous catheter (CVC)-related thrombosis.

	Patients with thrombosis (%)	*Relative Risk (CI95%)*
Sex		
Male	39/149 (26.2%)	
Female	36/103 (35%)	1.3 (0.9–1.9)
Age (years)		
< 75	66/226 (29.2%)	
≥ 75	9/26 (34.6%)	1.2 (0.7–2.1)
Body mass index (kg/m^2)		
< 30	62/219 (28.3%)	
≥ 30	13/33 (39.4%)	1.4 (0.9–2.2)
Personal history of venous thrombosis		
No	60/224 (26.8%)	
Yes	15/28 (53.6%)	2.0 (1.3–3.0)
Active cancer treatment/intensive chemotherapy*		
No	34/114 (29.8%)	
Yes	41/138 (29.8%)	1.0 (0.7–1.5)
Major surgery/trauma°		
No	47/153 (30.7%)	
Yes	28/99 (28.3%)	0.9 (0.6–1.4)
Oral contraceptives/hormone therapy		
No	61/218 (28%)	
Yes	14/34 (41.2%)	1.5 (0.9–2.3)
Factor VIII: C (IU /dL)†		
< 290	64/227 (28.2%)	
≥ 290	11/25 (44%)	1.6 (1.0–2.5)
Family history of venous thrombo-embolism		
No	64/223(28.7%)	
Yes	11/29 (37.9%)	1.3 (0.8–2.2)
Insertion site		
Jugular vein	42/143 (29.4%)	
Subclavian vein	33/109 (30.3%)	1.0 (0.7–1.5)
Type of central venous catheter		
Single/Double lumen	20/61 (32.8%)	
Triple/Four lumen	29/86 (33.7%)	1.0 (0.6–1.6)
Swan-Ganz	18/69 (26.1%)	0.8 (0.5–1.4)
Port a cath®	8/35 (22.9%)	0.7 (0.3–1.4)
Other	0/1	Not calculated
Absence of anticoagulant treatment		
No	45/145 (31%)	
Yes	30/107 (28%)	0.9 (0.6 – 1.3)

**Including all patients with hematologic malignacies (n = 97) or solid tumors (n = 39) and two patients who had undergone stem cell transplantation for rheumatoid arthritis. °Including 82 post-operative patients and 17 patients with a primary medical condition who were operated on during the follow-up while the CVC was in place. †FVIII levels: cut off level is the 90th percentile.*

Discussion

In a large cohort of prospectively followed patients, we found a clear relationship between two thrombophilic mutations, factor V Leiden and prothrombin G20210A, and CVC-related thrombosis. Overall, in the presence of one of the two mutations the risk of CVC-related thrombosis increased almost three-fold. Factor V Leiden or prothrombin G20210A contributed to 13.4% of the thrombotic events. In addition, a personal history of thrombosis was associated with CVC-related thrombosis.

Reliable data concerning the association between inherited coagulation disorders and CVC-related thrombosis in adult patients are scarce and contradictory. In a study of patients undergoing bone marrow transplantation, a 54% frequency of clinically manifest thrombosis (seven of 13 patients) in patients who were heterozygous for factor V Leiden was reported, whereas in patients without factor V mutation a 10% risk was found (26 of 264 patients). The reported relative risk (Cox proportional hazard model) from this study was 7.7 (CI95%; 3.3 to 17.9).[6] In a smaller study in which 82 adult cancer patients with a CVC were evaluated, prothrombotic risk factors, including factor V Leiden, were not substantial predictors of clinically manifest thrombosis, although the data suggested that factor V Leiden increased the risk of thrombosis.[7] However, the statistical power of this study was limited because of the small numbers of patients with thrombosis and factor V Leiden.[7]

In one other study it was reported that factor V Leiden did not contribute to CVC-related thrombosis.[8] In this case-control study, the prevalence of factor V Leiden in patients with thrombosis (7.4%; two of 27 patients) was not observed to be higher than the prevalence in the general Western population (5%). The contribution of prothrombin G20210A mutation to CVC-related thrombosis was not assessed in these studies.[6-8]

In previous studies, clinically manifest thrombosis was used as a primary end-point.[6-8] Due to the systematic screening of our patients, we found a total of 75 cases with thrombosis (nearly 30%), which clearly enhanced the statistical power of our study. This figure indicates that clot formation is a common phenomenon after CVC placement, while patients are at high risk for progression to clinically manifest thrombosis and associated morbidity. Our results emphasize the need for implementation of adequate prevention strategies.[20] Although the overall frequency of CVC-related thrombosis was not reduced by anticoagulants, the severity of thrombosis was. Clinically manifest thrombosis was observed substantially more often in patients who received no anticoagulant prophylaxis, who were mainly patients with active cancer treatment.

Indeed, data from randomized controlled trials have supported the use of routine anticoagulant prophylaxis in patients with a CVC, which has resulted in consensus guidelines.[21-23] However, many clinicians are reluctant to prescribe anticoagulant prophylaxis routinely in patients with cancer and a CVC because of the low expected incidence of thrombosis and the fear of hemorrhage during anticoagulant prophylaxis.[10,24] Recently it was reported that only 10-20% of physicians routinely prescribe anticoagulant prophylaxis.[10,24]

Individual risk-assessment for CVC-related thrombosis, prior to the insertion of a CVC, could help clinicians in making decisions about prescribing anticoagulant prophylaxis in vulnerable patients who have a presumed increased risk of bleeding. From a clinical point of view, determination of factor V Leiden and prothrombin G20210A mutation may be useful in such individual risk assessment, since these risk factors can easily be determined before placement of the CVC. Future studies in which the effectiveness of individualized anticoagulant prophylaxis, after determination of common inherited and established acquired risk factors, are clearly required to assess the effectiveness of such a policy.

Factor VIII levels were generally high in our patients, reflecting the acute phase reactive nature of this procoagulant factor. Patients with the highest levels appeared to be at a slightly higher risk of thrombosis which further supports a prognostic role of a prothrombotic state in the occurrence of CVC-related thrombosis. In this study, all patients were examined systematically for thrombosis with serial Doppler-ultrasound. The reported sensitivity of criteria used for Doppler-ultrasound diagnosis of subclavian thrombosis ranged from 78 to 96%.[14-18] Thus, the rate of thrombosis we found in patients with a subclavian CVC could be an underestimation, but this would not have materially affected our risk estimates for prothrombotic abnormalities. The reported specificity of Doppler-ultrasound varied from 92 to 100%.[14-18] This precludes false labeling of patients with genetic abnormalities. Contrast venography, although the gold standard, is an invasive test and serial performance for screening is not feasible.

In conclusion, thrombosis frequently occurs after central venous catheterization. Common inherited coagulation disorders and a personal history of thrombosis contributed to CVC-related thrombosis and increased the risk almost three-fold. In vulnerable patients, the determination of these factors prior to CVC insertion could help clinicians to decide on anticoagulant prophylaxis. Future studies are needed to evaluate implementation of preventive strategies, including individual risk-assessment and subsequent

anticoagulant prophylaxis of high-risk patients versus long-term routine anticoagulant prophylaxis in all patients.

FRR, AEM, JAvO, FJMvdM and MVH were responsible for the concept of the study. CJvR, FRR, MVH analyzed and interpreted the results. All authors have drafted or critically revised the manuscript, and all authors approved the final version of the manuscript. We would like to thank all the participating patients, physicians and nurses for their co-operation; Mrs T.C. Visser-Oppelaar, Mrs P.J. Noordijk and Mr J. van der Meijden for laboratory assistance; and Dr S.G. Molhoek and Dr A.N. Scholten for evaluation of Doppler-ultrasound recordings. The authors indicated no potential conflict of interest.

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