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Reduced inhibition of activated prothrombin by heparin and venous thromboembolism: heparin resistance revisited

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Background and Objectives. We evaluated a new test, based on prothrombin activation by *Echis Carinatus* snake venom in the absence/presence of unfractionated heparin, in patients with venous thromboembolism (VTE).

Design and Methods. The test (*activated prothrombin heparin-inhibition test*) was performed in 555 unselected, unrelated patients who had suffered from at least one objectively confirmed VTE and the results were compared with those obtained in 408 healthy controls.

Results. In 71 (12.8%) of the 555 patients the results of the test, expressed as a normalized ratio, were below the cut-off. This compared with 19 (5% by definition) results below the cut-off in the control group. The crude OR for VTE in subjects with altered vs those with normal results was 3.00 (95% CI: 1.78-5.07). ORs did not significantly change after adjustment for age (2.86, 95% CI: 1.68-4.85) and age/sex (2.80, 95% CI: 1.64-4.77) by logistic regression. After adjustment for antithrombin III, fibrinogen and prothrombin levels the risk associated with altered results remained significantly high. The overall OR for VTE in females (3.22; 95% CI: 1.53-6.75) was higher than that in males (2.69; 95% CI: 1.27-5.69). However, for both sexes there was a sharp increase in the risk of VTE associated with altered results in patients aged less than 45 years (crude OR 9.61; 95% CI: 3.38-27.3).

Interpretation and Conclusions. Lower than expected thrombin inhibition by endogenous antithrombin action after full activation by heparin addition was found to be a common feature in patients who suffered from previous venous thrombotic events, and may reflect a hitherto unrecognized thrombophilic alteration.

Key words: risk factor, thrombophilia, antithrombin III, prothrombin, heparin.

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The risk of venous thromboembolism (VTE) is increased by factors that cause hypercoagulability and venous stasis (e.g. oral contraceptive use, pregnancy and postpartum state, surgery, trauma, prolonged immobilization) and by the presence of inherited and acquired abnormalities of the coagulation system (e.g. deficiencies of antithrombin III, protein C, or protein S, G1691A mutation in the factor V gene, G20210A mutation in the prothrombin gene, and the presence of antiphospholipid antibodies). Despite increasing knowledge about the coagulation process, many idiopathic or secondary thrombotic episodes remain unexplained, as they occur in the absence of any of the above-mentioned predisposing factors.[1,2]

A new test, based on prothrombin activation by *Echis Carinatus* snake venom in the absence/presence of unfractionated heparin, was recently designed.[3] In normal conditions the addition of heparin induces a prolongation of clotting time because of the antithrombin activity exerted by the antithrombin/heparin complex. We initially performed the test in some patients who suffered from VTE. Interestingly, in a far from negligible number of them, the addition of heparin did not result in the expected prolongation of clotting time. The new test is indicated as the *activated prothrombin heparin-inhibition test* throughout the paper. Results obtained with a test whose methodology was, at least in principle, similar to the one described in this study have recently been published as a case report.[4]

The aim of this study was to evaluate the clinical importance of the newly designed activated prothrombin heparin-inhibition test. The test was performed in 555 unselected patients who had suffered from at least one objectively confirmed VTE; the results were compared with those obtained in a large group of healthy controls.

Design and Methods

Patient group

All consecutive unrelated patients included in the records of our Department, who had been screened for thrombophilic states between September 1994 and December 1999 after experiencing at least one VTE were eligible for this study. Data regarding the presence of a family history of venous thrombosis and circumstantial triggering factors (recent surgery, trauma, immobilization, fracture, pregnancy/puerperium, oral contraceptives) at the first VTE were collected by personal interview (except for a few patients whose blood samples had been sent directly to our laboratory from other centers in our region).

Blood was collected from the antecubital vein into 0.129 mmol/L trisodium citrate; plasma was prepared by centrifugation for 20 min at 2,000 g at room temperature; aliquots of plasma and blood for DNA extraction were snap frozen and stored at –70°C. The screening for thrombophilia included the following tests: prothrombin time; activated partial thromboplastin time (aPTT); fibrinogen plasma levels, antithrombin III, protein C, protein S; activated protein C resistance (APCR) and a test for diagnosing lupus anticoagulant. Patients with altered APCR were screened for factor V Leiden mutation. Starting from February 1996, basal homocysteine level was also measured; G20210A mutation of the prothrombin gene was checked as of January 1998.

From the above mentioned group, 555 patients (characteristics reported in Table 1) were included in the present study, independently of the presence or absence of thrombophilic alterations, on the basis of the following inclusion criteria: a) objectively confirmed lower limb deep vein thrombosis (DVT) (compression ultrasonography or venography) and/or pulmonary embolism (lung scan); b) blood sampled at least 3 months after single or last thrombotic episode and 3 weeks after withdrawal of any antithrombotic treatment; c) normal liver function and no overt evidence of autoimmune or neoplastic disease; d) frozen blood and plasma aliquots available. Patients with lupus anticoagulant (LAC) were excluded.

Control group

Four hundred and eight apparently healthy subjects [male/female, 218/190; median age, 40 yrs (range, 10 to 79 yrs)] were used as a control group; they were from the same geographic area as the patients referred to our Center for thrombophilic screening and had no genetic relationship with them. Previous thromboembolic episodes had been ruled out by personal interview. Blood collection, plasma preparation, and storage were performed as described for the group of patients. Subjects with prolonged aPTT suggesting a possible LAC phenomenon were excluded.

Table 1 Characteristics of the 555 patients with previous venous thromboembolic episodes (VTE).

Number [total (M/F)]	555 (236/319)
Age, y [median (range)]	44 (11-91)
≤ 45 y, n (%)	297 (53.5)
> 45 y, n (%)	258 (46.5)
Age at first VTE, y [median (range)]	39 (10-89)
Time elapsed since last episode, mo [median (range)]	16 (3-120)
Type of episode	
DVT, n (%)	421 (75.3)
DVT + pulmonary embolism, n (%)	104 (18.7)
Pulmonary embolism, n (%)	30 (5.4)
Number of thrombotic episodes (n=539[§])	
One, n (%)	406 (7.53)
Two or more, n (%)	133 (24.7)
Familial history of venous thrombosis (n=474[§])	
Yes, n (%)	168 (35.4)
No, n (%)	306 (64.6)
Circumstantial risk factors at first episode (n=501[§])	
None, n (%)	174 (34.7)
Recent surgery, n (%)	58 (11.6)
Trauma/immobilization/fracture, n (%)	105 (21.0)
Pregnancy/puerperium, n (%)[#]	48 (51.0)
Oral contraceptives, n (%)[§]	104 (69.3)

[§]Number of patients for whom information was available; [#]women who had VTE during oral contraceptive use and postmenopausal women were excluded; [§]women who had VTE during pregnancy or puerperium and postmenopausal women were excluded.

Laboratory tests

The activated prothrombin heparin-inhibition test was performed as follows. Clot formation was started by adding, to 50 µL of undiluted plasma, either 100 µL of *Echis Carinatus* snake venom (Sigma Chemical Co, 0.5 µg/mL), NaCl (75 mmol/L) and $CaCl_2$ (2.5 mmol/L) (solution A) or 100 µL of solution A also containing 3 U/mL unfractionated heparin (Liquemin, Roche) (solution B). Automated analysis was performed on an ACL 6000/plus (Instrumentation Laboratory) within 2 h from thawing. Under these conditions, the intra- and

between-assay variations were less than 5%. In each run a normal plasma pool was tested and, to reduce the between-assay variation, results were expressed as follows:

$$\text{Normalized ratio} = \frac{(\text{clotting time}_{\text{SolutionB}} - \text{clotting time}_{\text{SolutionA}})_{\text{sample}}}{(\text{clotting time}_{\text{SolutionB}} - \text{clotting time}_{\text{SolutionA}})_{\text{pool}}}$$

The expected clotting time ranges in a normal plasma pool were 40-60 sec. with solution A (without heparin) and 100-150 sec. with solution B (with heparin).

All tests included in the thrombophilic screening (see Patient Group section) were performed using standard methods: prothrombin time (Recombiplastin, Instrumentation Laboratory, Milan, Italy); activated partial thromboplastin time (automated aPTT, Organon Teknika, Rome, Italy); fibrinogen according to the Clauss method (Fibrinomat, Biomerieux, Rome, Italy); antithrombin III activity (Antithrombin, Instrumentation Laboratory); protein C activity (Coamate Protein C, Instrumentation Laboratory); protein S activity (Protein S, Instrumentation Laboratory); activated protein C resistance, according to de Ronde and Bertina,[5] dilute Russel's viper venom time (LA-Test and LA-Check, Organon Teknika, Rome, Italy), factor V Leiden mutation,[6] plasma homocysteine,[7] and G20210A mutation of the prothrombin gene.[8]

In all patients and controls putative confounder variables (fibrinogen, antithrombin III and prothrombin) were re-measured in the same plasma aliquot that was used to perform the activated prothrombin heparin-inhibition test, on the same day. Prothrombin was measured by a one-stage clotting assay, using thromboplastin and factor II deficient plasma (Instrumentation Laboratory). The test was performed on a ACL 6000/plus and results were expressed as a percentage of the results from a normal plasma pool.

The technicians were at all times unaware of the origin of the sample (i.e., patient or control). The study protocol was approved by the local ethics committee, and all participants gave their informed consent for further blood tests to be performed on their frozen blood and plasma aliquots.

Statistical analysis

Continuous variables are presented as medians (range); the two-tailed t test was used to compare means. Pearson's correlation coefficients were calculated to determine the association between variables. Crude odds ratios (ORs) and 95% confidence intervals (CI) were calculated with the approximation of Woolf[9] as estimates of the relative risk for VTE. Adjustment for matching factors and potential confounding factors was performed by unconditional logistic-regression analysis with the SOLO software package (BMDP Statistical Software, Los Angeles, USA). Age, fibrinogen, antithrombin III and prothrombin were entered into the logistic regression as continuous variables. To assess a dose-response relation, we stratified the results of the activated prothrombin heparin-inhibition test and calculated ORs for the lower ranges relative to the highest range used as reference. In addition, ORs for males and females separately and for two different age groups (≤ 45 vs > 45 years) were calculated to assess possible risk differences between these subgroups. Fisher's exact test was used to compare the frequency of an altered activated prothrombin heparin-inhibition test in the patients according to the following characteristics: presence/absence of thrombophilic alterations, family history of thrombosis, more than one episode of VTE, circumstantial triggering factors. All *p* values less than 0.05 were considered to be statistically significant.

Results

The ratios of activated prothrombin heparin-inhibition test for individual patients and controls are shown in Figure 1. Some patients presented with high ratios of activated prothrombin heparin-inhibition test; we therefore did not see a difference in mean values between patients and controls (patients: mean ratio=1.14; SD=0.33; range, 0.38 to 2.67; controls: mean ratio=1.14, SD=0.24; range, 0.66 to 2.19). Because statistically significant sex-related differences in the activated prothrombin heparin-inhibition test ratio were observed both for patients and controls (Table 2), separate 5th percentiles were calculated for men (ratio cut-off value = 0.85) and women (ratio cut-off value = 0.79) in the control group to compute prevalences in the patient group. In 71 (12.8%) of the 555 patients the activated prothrombin heparin-inhibition test ratio was below the above-mentioned cut-offs (27/44 males/females), as compared with 19 (5% by definition) in the control group (10/9 males/females). The crude OR for VTE in subjects with an activated prothrombin heparin-inhibition ratio at or below the 5th percentile, as compared with those whose activated prothrombin heparin-inhibition ratios were above the cut-off values, was 3.00 (95% CI: 1.78-5.07). ORs did not change significantly after adjustment for age (2.86, 95% CI: 1.68-4.85) and age/sex (2.80, 95% CI: 1.64-4.77) by logistic regression (Table 3).

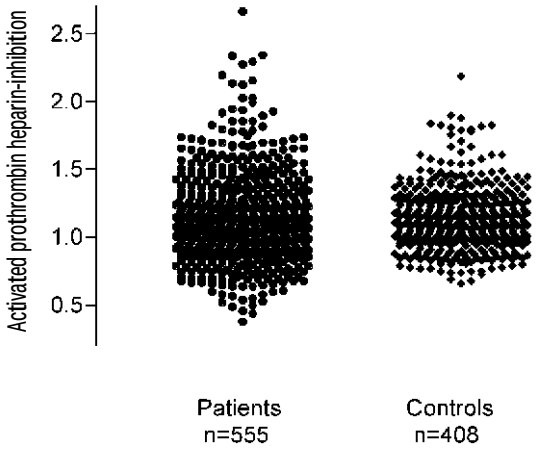

Figure 1. Individual ratio of the activated prothrombin heparin-inhibition test in 555 patients with VTE and in 408 controls.

Since activated prothrombin heparin-inhibition, as measured by our test, may be influenced by other variables, we assessed whether the observed association could be explained by the effects of some of these variables. Fibrinogen, antithrombin III and prothrombin levels were indeed significantly correlated ($p<0.0001$) with activated prothrombin heparin-inhibition ratios (Pearson's correlation coefficients were -0.432, -0.145 and -0.367, respectively). When we adjusted for fibrinogen, antithrombin III and prothrombin levels by logistic regression the ORs decreased; however, the risk associated with an altered activated prothrombin heparin-inhibition ratio was still significantly high (Table 3). The OR was 3.19 (95% CI 1.72-5.93) after adjustment for all the possible confounding variables and 3.16 (95% CI 1.74-5.74) after adjustment for antithrombin III, prothrombin and fibrinogen. Entering these variables into the logistic model as categorized variables (approximate tertiles) gave similar results as when they were entered as continuous variables.

ORs for two age groups and for males and females separately are shown in Table 4. The overall OR for VTE in females (3.22; 95% CI: 1.53-6.75) was higher than that in males (2.69; 95% CI: 1.27-5.69). Adjustment for age and other possible confounding variables did not significantly change the above-mentioned ORs. However, for both sexes there was a sharp increase in the risk of VTE (crude and adjusted for possible confounding variables) associated with reduced activated prothrombin heparin-inhibition ratio at an age less than 45 years (crude OR 9.61; 95% CI: 3.38-27.3).

Table 2. Median (range) results of the activated prothrombin heparin-inhibition test (ratio) in patients and controls.

	All	*Females*	*Males*	*p F vs M*
Patients	1.12 (0.38-2.67) n=555	1.08 (0.38-2.35) n=319	1.19 (0.50-2.30) n=286	<0.0001
Controls	1.12 (0.66-2.19) n=408	1.09 (0.66-2.19) n=190	1.16 (0.69-1.90) n=218	0.0006

Table 3. Risk of VTE associated with an altered activated prothrombin heparin-inhibition test.

Model	*OR*	*95%CI*
Crude	3.00	1.78-5.07
Age	2.86	1.68-4.85
Age, sex	2.80	1.64-4.77
Age, sex, fibrinogen	2.92	1.69-5.03
Age, sex, antithrombin III	2.51	1.46-4.31
Age, sex, prothrombin	2.64	1.46-4.79
Prothrombin, antithrombin III, fibrinogen	3.16	1.74-5.74
All variables	3.19	1.72-5.93

Table 4. Risk of VTE (OR and 95%CI) associated with an altered activated prothrombin heparin-inhibition test according to age and sex.

Age (years)	*Males*	*Females*	*Both sexes*
≤ 45	20.3 (2.65-154.8)	6.17 (1.80-21.1)	9.61 (3.38-27.3)
> 45	0.87 (0.34-2.24)	1.46 (0.56-3.82)	1.23 (0.64-2.36)
All ages	2.69 (1.27-5.69)	3.22 (1.53-6.75)	3.00 (1.78-5.07)

In order to evaluate the possibility of a dose-response relation, we stratified the patients and controls according to their activated prothrombin heparin-inhibition ratios and calculated ORs for VTE in the patients with a ratio in the lower classes as compared with those in the highest ratio class (>0.90). As Figure 2 shows, the risk of VTE did not increase significantly among subjects with an activated prothrombin heparin-inhibition ratio down to 0.71; the risk was, however, greatly increased for a ratio of 0.70 or less (OR 9.97; 95% CI 3.05-32.6). Though the χ^2 test for trend was statistically significant (20.389, $p<0.0001$), these results seem to indicate a threshold effect rather than a continu-

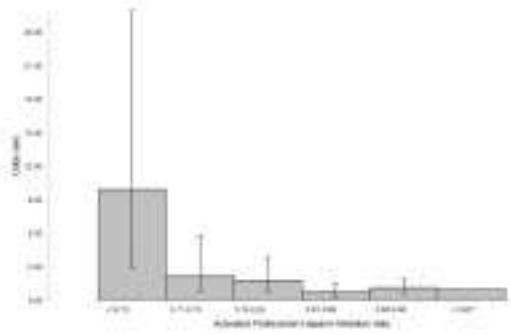

Figure 2. Risk of VTE (OR) according to activated prothrombin heparin-inhibition ratio strata. The reference category (OR=1) was subjects with an activated prothrombin heparin-inhibition ratio > 0.90 (*). The 95% CI are represented by error bars.

ous dose-response relation. Adjustment for age, sex, fibrinogen, antithrombin III and prothrombin did not significantly change the reported ORs. As mentioned above, no difference was seen in mean values between patients and controls, because of the number of patients with high ratios of the activated prothrombin heparin-inhibition test. This is in accordance with the finding that only very low values seem to be related to thrombosis and the absence of a dose-response pattern.

The prevalence of altered activated prothrombin heparin-inhibition tests was not statistically different in patients with or without a familial history of thrombosis (11.3 vs 12.7%) and in patients who had had only one or multiple episodes of VTE (13.6 vs 11.3%). No significant differences were found in patients who had suffered from VTE after surgery (10.9%) or during trauma/immobilization/fracture (8.1%) vs those with idiopathic VTE (12.1%). The prevalence of altered activated prothrombin heparin-inhibition tests was slightly higher in women who had VTE during pregnancy/puerperium (16.7%) than that in women who had VTE during oral contraceptive use (12.1%) and that in women with idiopathic VTE (14.3%). The differences, however, were not statistically significant.

Of the 555 examined patients, 185 had a diagnosed thrombophilic alteration (1 antithrombin III, 14 protein C and 8 protein S deficiency, 86 factor V Leiden mutation, 27 G20210A prothrombin mutation out of 360 tested, and 29 hyperhomocysteinemia out of 303 tested; 20 patients were carriers of double alterations: 2 cases with protein C deficiency and factor V Leiden mutation, 2 cases with protein S deficiency and factor V Leiden mutation, 6 cases with factor V Leiden and G20210A prothrombin mutations, 8 cases with factor V Leiden and hyperhomocysteinemia, 2 cases with G20210A prothrombin mutation and hyperhomocysteinemia). An altered activated prothrombin heparin-inhibition test was found in 11.9% of these patients (22 cases: 1 protein C and 3 protein S deficiency, 10 factor V Leiden mutation, 5 G20210A prothrombin mutation, 1 hyperhomocysteinemia, 2 factor V Leiden mutation and hyperhomocysteinemia) and in 13.2% of remaining patients in whom no thrombophilic alterations were found (49 cases, the difference was not statistically significant).

Repeated samples, taken on a different occasion from 31 of the 71 patients with an altered activated prothrombin heparin-inhibition test and 49 of those with a normal test were analyzed. Altered results were confirmed in 16/31patients; in no case were altered results obtained in subjects with a previously normal test. It was also possible to examine both parents of 3 young patients with confirmed altered results; an altered activated prothrombin heparin-inhibition test was recorded in one parent of 2 cases and in the third case the mother presented with a borderline value (not checked again as yet).

Discussion

The activated prothrombin heparin-inhibition test, adopted in the present study, was designed to assess the power of native antithrombin, once fully activated by addition of standard amounts of heparin, to inhibit the thrombin generated by prothrombin activation induced by *Echis Carinatus* snake venom. In this study we performed the test in a large series of patients with previous VTE, with or without identified thrombophilic alterations, in order to assess whether: a) altered results of the test were more frequent in this group than in healthy subjects, and b) the test might be used as screening to detect a pro-thrombotic tendency.

With a similar aim (to assess the anticoagulant effect of antithrombin/heparin complex), Makris and van Dreden[4] designed a different test, based on addition of purified human antithrombin and heparin to the activated partial thromboplastin time (aPTT) reagent. They found lower than expected aPTT prolongation after antithrombin+heparin addition in a woman who had suffered repeated episodes of VTE and also in her asymptomatic son. They concluded that the altered results of the test might be the expression of a still unrecognized familial thrombophilic condition.

In the present study we found a 12.8% preva-

lence of an altered activated prothrombin heparin-inhibition test in a large series of patients who had suffered from VTE, with an OR of 3.0 versus a comparable large series of normal controls. This finding seems to indicate that this alteration is a common and moderate risk factor for venous thromboembolism. This association seems to have a threshold rather than a dose-response relationship, the risk being greatly increased for an activated prothrombin heparin-inhibition ratio under 0.70 (OR = 9.97).

In principle, the results of the activated prothrombin heparin-inhibition test may be affected by several factors (e.g. the levels of prothrombin, antithrombin III and fibrinogen). In line with previous results,[8] high prothrombin levels in our population also increased the risk of thrombosis independently of the presence of the G20210A genetic variation in the prothrombin gene (OR = 2.20, 95% CI 1.29-3.78). Prothrombin levels may well be a factor influencing the results of the test, and indeed the ratios we obtained were significantly (inversely) correlated with the clotting prothrombin levels. We, therefore, adjusted for prothrombin levels by a logistic regression analysis; after correction for their confounding effect, it emerged that an altered activated prothrombin heparin-inhibition test remains a significant risk factor for VTE, even if to a lesser extent (OR = 2.64, 95% CI 1.46-4.79). We also investigated the effects of other variables, such as antithrombin III and fibrinogen levels, but did not find any significant influence on the crude OR.

Since the test was independent of prothrombin, antithrombin III and fibrinogen levels, it could be suggested that the different prevalences of altered results in patients and controls may be due to differences in the concentration of other heparin-binding proteins such as platelet factor 4 or histidine-rich glycoprotein, which compete with antithrombin for heparin.[10,11] Indeed, it has been suggested that the phenomenon of heparin resistance and heparin rebound is influenced by heparin binding by proteins not active on coagulation.[12-14]

The higher prevalence of the alteration of the test in patients compared with in controls could also be the result of a post-thrombotic effect. However, the relatively long median time elapsed since last episode (16 months) makes this explanation less likely. Moreover, dividing the elapsed time from the last VTE episode in tertiles, no differences in the prevalence of altered activated prothrombin heparin-inhibition test were found [prevalence in 1st tertile (blood sampled 3-9 months from the last VTE episode) = 9.7%; 2nd tertile (9-25 months) = 12.4%; 3rd tertile (> 25 months) = 16.2%).

Our results showed a stronger association between an altered activated prothrombin heparin-inhibition test and thrombotic events in women than in men. In fact, when men and women were analyzed separately, the risk of thrombosis associated with an altered activated prothrombin heparin-inhibition test was found to be significantly different. Even when different cut-off points in men and women were used, by calculating separately for men and women in the control group the 5th percentiles of the activated prothrombin heparin-inhibition test distribution, the OR was higher in women (OR: 3.22 vs 2.69).

The age of the investigated subjects seemed to play a decisive role in the results of the test since the VTE risk associated with an altered activated prothrombin heparin-inhibition test was significantly increased only for subjects below 45 years old (OR = 9.61, 95% CI 3.38-27.3). Altered results of the test were more frequent in VTE patients irrespective of the presence of other identified thrombophilic conditions.

Our results show that the alteration of the activated prothrombin heparin-inhibition test, even though in some cases transient, in many patients is persistent; in fact, it was confirmed in the majority of patients who could be re-examined using samples taken on a different occasion. Furthermore, a family pattern of the alteration is very likely, since in the few cases in which a family study was possible (3 patients with confirmed altered activated prothrombin heparin-inhibition test), clearly abnormal results were recorded in one parent of 2 patients and a borderline value was obtained in a parent of the third patient.

In conclusion, lower than expected thrombin inhibition by endogenous antithrombin action after full activation by heparin addition (the activated prothrombin heparin-inhibition test) was found to be a common finding in patients with previous venous thrombotic events. As this laboratory abnormality was not likely to be secondary to thrombosis it more probably reflects a hitherto unrecognized thrombophilic alteration, representing a common although moderate risk factor for VTE. The association of the test alteration with VTE was particularly marked in young subjects (< 45 years old) and in women, especially those who had experienced VTE during pregnancy/puerperium. The prevalence of the alteration was not different in patients who were or were not carriers of other identified thrombophilic conditions. Altered results of the test were to a large extent independent of the levels of prothrombin, antithrombin III and fib-

rinogen in the examined samples; however, we have no data on the possible effect of other heparin-binding proteins which can compete with antithrombin. Whether the results of the activated prothrombin heparin-inhibition test can be affected by the balance between free heparin and protein-bound heparin in plasma or by other unknown causes is a matter for further investigation.

Contributions and Acknowledgments

CL: designed the study, performed a large part of the blood coagulation tests reported, analyzed the data, wrote the draft version of the manuscript; LP: designed and carried out the new laboratory test; GP: contributed to the selection of patients and normal subjects investigated and to collection of blood samples, contributed to discussing the results and writing the paper; BL: performed the DNA analysis for factor V Leiden and prothrombin mutation in the patients investigated; ER: contributed to the selection of patients and normal subjects; SC: contributed to discussing the results and writing the paper.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Peer Review Outcomes

What is already known on this topic

Heparin resistance not dependent on antithrombin deficiency can be due to heparin binding by proteins not active on coagulation. Impaired anticoagulant effect of heparin has been reported anecdotally in a patient with venous thromboembolism (VTE).

What this study adds

The activated prothrombin heparin-inhibition test was carried out on a series of 555 patients with VTE, in order to add an overall plasma assay in the diagnostic panel employed for screening of thrombophilia. Impaired thrombin inhibition by endogenous antithrombin after heparin activation was present in 12.8% of the patients, independently of the presence of other thrombophilic traits.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Valerio de Stefano, who acted as an Associate Editor. The final decision to accept this paper for publication was taken jointly by Dr. de Stefano and the Editors. Manuscript received September 26, 2001; accepted November 26, 2001.

Potential implications for clinical practice

Thrombophilia can be detected in up to 50% of patients with VTE; an additional 10% of patients can be identified by the activated prothrombin heparin-inhibition test as carriers of a plasma alteration associated with an increased risk for VTE, as high as 9-fold in younger individuals. Further studies are needed to identify the factors leading to heparin-resistance.

Valerio de Stefano, Associate Editor