

# Primary Upper-Extremity Deep Vein Thrombosis: High Prevalence of Thrombophilic Defects

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Primary deep venous thrombosis of the upper extremity (UEDVT) is an unusual disorder. Limited data are available on the contribution of hypercoagulable status in the pathogenesis of this disease. This study aims to report the prevalence of inherited and acquired thrombophilic risk factors (TF) in patients with primary (effort-related and spontaneous) UEDVT. From 1993 to 2002, 31 patients (17 females, median age 38.8 years, range 16–60 years; and 14 males, median age 31.4 years, range 20–56 years) with primary UEDVT ( $n = 15$  effort-related and  $n = 16$  spontaneous) were referred for screening of hypercoagulable status. Nineteen (61.3%) patients had at least one coagulation abnormality. The most common acquired TF were antiphospholipid antibodies (31% lupus anticoagulant and 12.9% anticardiolipin antibodies). Factor V Leiden (12.9%) and prothrombin G20210A mutation (20%) were the most prevalent genetic risk factors. Five patients (16.1%) had high plasma homocysteine levels, and one patient (4.7%) had protein S deficiency. Effort-related UEDVT was associated with male gender ( $P = 0.04$ ) and younger age ( $P = 0.02$ ). There was no significant difference in the prevalence of acquired or inherited TF between patients with effort-related or spontaneous UEDVT. A local anatomic abnormality was detected in seven patients (22.5%), and the prevalence of TF was significantly lower within this group ( $P = 0.006$ ). The incidence of TF in patients without an anatomic abnormality was 75% (RR 5.25). This study found a high prevalence of an underlying thrombophilic status in spontaneous and effort-related UEDVT. Hypercoagulable status may play a significant role in both groups. Screening for local anatomical abnormalities and thrombophilia should be included in the evaluation of primary UEDVT. *Am. J. Hematol.* 76:330–337, 2004. © 2004 Wiley-Liss, Inc.

**Key words:** thrombophilia; Paget-Schroetter syndrome; deep venous thrombosis; upper extremity

## INTRODUCTION

Deep venous thrombosis of the upper extremity (UEDVT) is an unusual disorder, estimated to range from 1% to 4% of all cases of deep vein thrombosis [1]. However, this rate may be higher as many patients with UEDVT are asymptomatic. Moreover, it has become more prevalent over the past decades, associated to the increasing use of central venous catheters and the more common implantation of cardiac pacemakers. The clinical diagnosis of this entity is nonspecific and troublesome. Venography remains the standard method of diagnosis, but ultrasonography is the most acceptable noninvasive and available test employed.

Secondary UEDVT develops in patients with congestive heart failure, malignant disease, or drug

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abusers, or those implanted with pacemakers, catheters for chemotherapy, dialysis, and parenteral nutrition, and it accounts for most cases of UEDVT. The prevalence of catheter-related UEDVT ranges from 13% to 39% in patients with subclavian catheters and has been reported as high as 66% [2–4]. Primary UEDVT includes patients with effort-related thrombosis (called Paget-Schroetter syndrome) and with spontaneous UEDVT (where no underlying disease may be found).

Although studies in patients with lower-limb deep venous thrombosis (DVT) reported an overall rate of thrombophilic abnormalities ranging from 30% to 40%, very limited data are available on the prevalence of prothrombotic abnormalities in patients with UEDVT. Classically, primary UEDTV had been associated with the presence of anatomical abnormalities manifesting after thrombosis precipitated by compressive venous trauma. However, little is known about the contribution of hypercoagulability status in the pathogenesis of this syndrome.

Recent studies have reported a higher prevalence of hypercoagulable abnormalities than previously thought in patients with primary UEDVT. Some of them also incorporated cases with effort-related UEDVT and the prevalence showed range from 8% to 61.1% [5–8].

The aim of this study was to report the prevalence of inherited or acquired thrombophilic risk factors (TF) found in our population of patients with primary UEDVT, including cases with effort-related and with spontaneous upper-limb venous thrombosis evaluated in a single institution.

## MATERIALS AND METHODS

### Patients

From 1993 to 2002, 31 patients were referred to the Hemostasis and Thrombosis Department with a diagnosis of primary UEDVT, confirmed by ultrasonography in 25 patients and by venography in 6. All patients were interviewed, and a clinical evaluation was performed in order to determine predisposing risk factors and underlying disease. Patients with catheter-related thrombosis, pacemakers, history of cancer or other intercurrent disease, recent trauma, or iatrogenic vein manipulation were excluded from this study. Information about work-, sport-, or recreation-related activities or any unusual strenuous efforts made before the thrombotic event was carefully evaluated. All patients provided written informed consent before testing.

Patients with a history of vigorous or unusual exercise within 21 days prior to the thrombosis developing in the affected arm comprised the effort-related

UEDVT group. UEDVT was classified as spontaneous when no forceful activity of the limb had occurred before the onset of symptoms and no underlying disease or predisposing factor was found. Personal or family history of venous thrombosis was also recorded. All patients were referred to a thoracic surgeon for evaluation in order to identify the presence of any local anatomic abnormality in the thoracic outlet. Chest X ray and thoracic CT scan were performed in each patient. Patients went through a venography with different positions of the examined arm (dynamic venography) if the surgeon that evaluated the case considered it necessary.

### Laboratory Tests

Samples for coagulation tests were taken at least 2 months after the thrombotic event in order to avoid possible abnormal results associated with potential consumption of natural inhibitors or acute phase reaction of thrombosis. Protein C (PC) and protein S (PS) plasma levels were evaluated only if the patient was not under oral anticoagulation treatment at the time of evaluation.

Blood was withdrawn by antecubital vein puncture, collected in plastic tubes with 0.11 M sodium citrate (9:1), and centrifuged twice at 1500g for 15 min to obtain platelet-poor plasma (PPP). Aliquots were frozen and stored at  $-70^{\circ}\text{C}$  until use. Standard methods for DNA isolation were applied, and samples were stored at  $4^{\circ}\text{C}$ .

Lupus anticoagulant was assigned following SSC-ISTH criteria, based on APTT (PTT-LA, Diagnostica Stago, Asnières, France) and dRVVT (Russell's venom from Sigma Chemical Co., St. Louis, MO), including mixing studies and neutralization procedures [9]. Anticardiolipin antibodies were assayed using a commercial ELISA kit (The Binding Site, Birmingham, U.K.). Assays were calibrated against the Louisville reference. Results were expressed in antiphospholipid units for IgG (GPL) and IgM (MPL), applying the following criteria:  $<15$  units, negative; 15–20 units, low positive; 20–80 units, medium positive; and  $>80$  units, high positive [10].

Plasma homocysteine levels were measured using high-pressure liquid chromatography (HPLC) and a fluorescent detection system modifying a previously described method [11]. Criteria for the diagnosis of hyperhomocysteinemia were plasma levels above the media plus 2 SD, as assessed in 50 control subjects whose age ranged from 25 to 65 years. The cutoff level was  $14.6\ \mu\text{mol/L}$ . Activated protein C resistance (APCR) was evaluated by a modified technique (COATEST® APC<sup>TM</sup> Resistance V, Chromogenix-Instrumentation Laboratory SpA, Milan, Italy), with

values lower than 1.96 regarded as abnormal. Anti-thrombin (AT) and PC activities were determined by chromogenic assays (COAMATIC® antithrombin, Chromogenix-Instrumentation Laboratory SpA) and IL Test™ protein C (Instrumentation Laboratory SpA); normal ranges were as follows: AT, 80–140 U/dL; PC, 60–120 U/dL. PS activity was measured using a coagulation technique (IL Test™ protein S, Instrumentation Laboratory SpA). Free PS levels were measured by Laurell's method (using anti-human protein S from DAKO A/S, Glostrup, Denmark). Normal values for both PS activity and free protein were 60–120 U/dL.

Only patients showing abnormal APCR values were screened for factor V Leiden. DNA was amplified by PCR technique and digested as previously described [12]. Patients displaying hyperhomocysteinemia were screened for the MTHFR C→T677 mutation by PCR technique as originally described [13]. As from 1998, we included the identification of the G→A mutation of the prothrombin 20210 gene through DNA analysis by PCR allele specific technique [14].

### Statistics

Statistical analysis was performed using a chi-square ( $\chi^2$ ) or a Fisher test for bivariate analysis between categorical variables. The *t*-test was used to compare quantitative variables between groups.  $P < 0.05$  was considered statistically significant.

## RESULTS

### Patient Population

We evaluated 31 patients with UEDVT referred to our institution for thrombophilic studies. The group comprised 17 females with a median age of 38.8 years (range 16–60 years) and 14 males with a median age of 31.4 years (range 20–56 years). These 31 patients had a total of 34 diagnoses of UEDVT. Thrombus localization was as follows: 15 isolated subclavian, 10 axillary and subclavian, 7 isolated axillary, 1 brachial and axillary, and 1 brachial, axillary, and subclavian. In 22 episodes (64.7%), the dominant limb hand was the symptomatic side. Patients were not routinely tested for pulmonary embolism (PE), and none had signs or symptoms of PE.

All patients received unfractionated heparin or low molecular weight heparin followed by oral anticoagulation therapy for 6–12 months. One patient underwent surgical correction of extrinsic vein compression, and balloon angioplasty was performed after thrombolytic therapy in a second patient.

### Clinical Characteristics

Four (12.9%) out of the 31 patients had recurrent venous thrombosis. Two patients had a detectable local anatomic abnormality: a 44-year-old woman with a cervical rib who had a bilateral episode and a 29-year-old woman with a costal subclavian vein compressive abnormality who had homolateral recurrence. No coagulation abnormality was found in these two women. A 45-year-old man without an identified anatomical defect had bilateral UEDVT and a diagnosis of PS deficiency. All three cases were effort-related UEDVT. The fourth case was a 54-year-old man with chronic renal failure and spontaneous axillary vein thrombosis (unrelated to a hemodialysis catheter), developing a femoral deep vein thrombosis a week later and found to have lupus anticoagulant and high homocysteine levels.

Three patients were under hormonal treatment when the thrombotic event occurred (one under hormone replacement therapy [HRT] and the other two on oral contraceptives). The patient under HRT was a 60-year-old postmenopausal woman who had factor V Leiden mutation. One of the patients on oral contraceptives was a 16-year-old female with the prothrombin G20210A mutation, but the other one (a 28-year-old woman) had normal thrombophilic tests. Another patient was in the second month of pregnancy and had a diagnosis of transient lupus anticoagulant plus anticardiolipin antibodies. None of these females had a history of an unusual effort related to the onset of UEDVT symptoms.

Patients were classified into two groups as described above: spontaneous UEDVT and effort-related UEDVT. Clinical and laboratory features are shown in Table I. Sixteen patients had a single spontaneous thrombotic event, and 15 patients had a total of 18 episodes associated with identifiable effort activity. In five of these 15 patients was a confirmed history of strenuous physical activity related to competitive sports (swimming in 2; water-polo, karate, and gymnastics in 1 each). In the remaining 10 cases, unusual or vigorous occupational activity was associated with the event: heavy weightlifting in 6, and energetic floor washing, wall and ceiling cleaning, choir director, and tai chi practitioner in 1 each. Effort-related UEDVT was associated with male gender (relative risk [RR] 2.67, 95% confidence interval [CI] 1.06–6.70,  $P = 0.04$ ) and younger age ( $P = 0.02$ ). We found a nonsignificant difference between the spontaneous and the effort-related groups regarding a positive family history of DVT. Three out of 15 (20%) and 1 out of 16 (6.25%) patients had a positive family history of DVT within the effort-related and spontaneous UEDVT groups, respectively. These data

**TABLE I. Clinical Features and Laboratory Findings in Patients With Effort-Related or Spontaneous Upper-Extremity Deep Vein Thrombosis (UEDVT)**

	Effort-related UEDVT ( <i>n</i> = 15)	Spontaneous UEDVT ( <i>n</i> = 16)	<i>P</i> value
Median age: years (range)	30.1 (20–45)	40.5 (16–60)	0.02
UEDVT recurrence	3	0	
Sex: male/female	10/5	4/12	0.04
Dominant arm	11/18 episodes	11/16 episodes	
Local anatomical anomaly	4 (26.7%)	3 (18.7%)	NS <sup>a</sup>
At least one thrombophilic defect	8/15 (53.3%)	11/16 (68.7%)	NS
Combined thrombophilia	2 (13.3%)	3 (18.7%)	NS
Lupus anticoagulant	4 <sup>b</sup>	6 <sup>c</sup>	NS
Anticardiolipin antibodies	1	3	NS
Factor V Leiden	2	2 <sup>d</sup>	NS
Prothrombin G20210A <sup>e</sup>	1	2 <sup>d</sup>	NS
PS deficiency <sup>f</sup>	1	0	NS
High homocysteine levels	2	3	NS

<sup>a</sup>NS, not significant.

<sup>b</sup>One patient had both lupus anticoagulant and anticardiolipin antibodies.

<sup>c</sup>Two patients had both lupus anticoagulant and anticardiolipin antibodies.

<sup>d</sup>One patient had both factor V Leiden and prothrombin G20210A gene variant.

<sup>e</sup>Determined in 15 patients.

<sup>f</sup>Determined in 21 patients.

would be in agreement with our laboratory results where we did not find a significant difference in the prevalence of inherited thrombophilic abnormalities between both groups. On the other hand, we evaluated the presence of a positive family history of DVT in patients with and without a detectable anatomic anomaly. None of the seven patients with anatomical defects had a positive history, while the 4 patients with a positive family history of DVT were in the group without detectable anatomical abnormalities.

### Laboratory Results

In 12 (38.7%) out of the 31 patients, no thrombophilic defect was found. Nineteen patients (61.3%) had at least one coagulation abnormality. The thrombophilia form most frequently found was the presence of antiphospholipid antibodies: 10 patients (31%) had lupus anticoagulant, and 4 (12.9%) anticardiolipin antibodies (one had positive low IgM levels, two positive low IgG levels, and one moderate IgG anticardiolipin antibody titers). Three patients had both lupus anticoagulant and anticardiolipin antibody positive results. Antibody assays were repeated after 2 months in 6 patients, and titers normalized in 3.

Factor V Leiden mutation was the hereditary TF most frequently found. Four (12.9%) of 31 patients had an abnormal APCR test and were heterozygous for factor V Leiden mutation. All four had a single UEDVT episode. One case was the 60-year-old woman taking HRT, the other two were men aged 20 and 22 years with a proven history of strenuous effort (swimming and unloading heavy weights,

respectively), and the fourth case was a 49-year-old man with an spontaneous episode of UEDVT who carried both prothrombin G20210A and factor V Leiden mutations. Fifteen patients were evaluated for the prothrombin G20210A gene variant. The 3/15 (20%) heterozygous cases comprised a 16-year-old girl with a spontaneous UEDVT taking oral contraceptives, a 31-year-old man with effort-related UEDVT (heavy weightlifting), and the man described above with both factor V Leiden and prothrombin G20210A combined mutations. No homozygous individuals were found for these two frequent mutations.

Five patients (16.1%) had high plasma homocysteine levels. MTHFR C→T677 substitution was determined in all these cases: 2 patients had a normal genotype, 2 were heterozygous, and 1 was mutant homozygous. Two out of the original 5 had a diagnosis of chronic renal failure, and both had a combined diagnosis of hyperhomocysteinemia and lupus anticoagulant. Two other patients had effort-related UEDVT (water-polo and competitive karate), and the fifth case had spontaneous UEDVT.

Protein C and S activity and free protein S were measured in 21 patients not on oral anticoagulation treatment. The only one (4.7%) with a protein S deficiency was a 45-year-old man who had two episodes of UEDVT (bilateral), both related to occupational activities, but there was no history of thromboembolism in his first-degree family. None of these patients had PC or antithrombin deficiency.

There was no significant difference between patients with effort-related UEDVT and spontaneous thrombosis with respect to the prevalence of acquired

or hereditary thrombophilic abnormalities. Eight patients (53.3%) with effort-related UEDVT had at least one coagulation abnormality versus 11 patients (68.8%) with spontaneous UEDVT. Antiphospholipid antibodies were found in 4 patients with effort-related versus 7 with spontaneous UEDVT, and genetic coagulation defects were found in 4 patients with effort-related versus in 3 with spontaneous UEDVT.

Evaluation by a thoracic surgeon detected the presence of local anatomic abnormalities in seven patients (22.5%): 1 cervical rib, 2 clavicle fractures with callus formation, 2 costal subclavian vein compressive abnormalities, and 2 with some degree of vein compression after stress maneuvers where the precise anatomical defect could not be found. Only one of these 7 patients had a detectable coagulation abnormality versus 18 of the remaining 24 without any identifiable anatomic abnormality of the thoracic outlet. There was a higher percentage of patients with hypercoagulable status within the group without local anatomic anomalies (RR 5.25, 95% CI 0.84–32.70), which was statistically significant ( $P = 0.006$ ). Four of these 7 cases with an underlying mechanical abnormality carried out identifiable vigorous activity before the onset of symptoms (one each swimming, tai chi practice, washing floors, and unloading heavy weights).

## DISCUSSION

Upper extremity deep vein thrombosis is an uncommon condition. The incidence of primary UEDVT reported is 2 per 100,000 patients per year [15], but its prevalence has risen during the last few decades due to the increasing use of central venous catheters and transvenous cardiac pacing.

Von Schroetter first described effort-related thrombosis or “stress thrombosis” in 1884, and the entity of subclavian thrombosis was later defined as Paget-Schroetter syndrome [16]. This syndrome was first related to forced muscular abduction leading to vein compression and microtrauma of vessel intima by the subclavius muscle or the costocoracoid ligament. In the 1970s, additional cases of UEDVT were reported that involved other contributing anatomic variations of the structures comprising the thoracic outlet, such as cervical rib, anomalous musculofascial bands, hypertrophied venous valves, or aberrant pectoralis tendons [17,18]. This entity was found to occur typically in healthy young men, within the active age group, mainly in the dominant arm. A wide spectrum of physical activities preceding the thrombotic event have been reported and related to the pathogenesis of the Paget-Schroetter syndrome, including sports, i.e.,

strenuous and unusual recreational or working activities. There is no consensus in the literature about the exact time period the strenuous activity had to take place to consider the thrombosis to be effort-related. In our series, 13 out of 15 patients had a clear history of unusual or vigorous activity during the week before the diagnosis of UEDVT was made. In two cases (a tai chi practitioner and a woman who had energetically cleaned walls and a ceiling), the time from the activity to the diagnosis of UEDVT was 21 days. Because there was a clear relation between the physical work and the onset of symptoms of thrombosis, we considered all of them as effort-related UEDVT.

Although effort-related thrombosis had been previously considered the most common cause of UEDVT, a central venous catheter is currently the most common risk factor. In our series, we did not include patients with catheter-related UEDVT. Within the group with effort-related UEDVT, evaluation by a thoracic surgeon found a local anatomic anomaly in only 7 patients. The detection of uncommon anatomic defects, such as anomalous musculofascial bands, hypertrophied venous valves, or aberrant pectoralis tendons, is difficult and requires dynamical tests and trained personnel. Usually, the obstruction is position dependent and can only be evidenced performing provocative tests (i.e., Adson’s and Wright’s maneuvers) during venography examination. Moreover, in some cases, they are not easily detected in a first dynamic evaluation. We cannot rule out that some atypical anatomical abnormalities may have gone undiagnosed. Several studies have emphasized the importance of eradicating vein compression in patients with particular anatomical defects to reduce the risk of recurrent thrombosis. In our series, seven patients were found to have a local anatomic abnormality: 2 have fracture of clavicle with callus formation, but direct interaction with the subclavian vein could not be found. Four patients have some degree of vein compression with stress maneuvers, but the precise anatomic defect was not demonstrable and there was no clear indication for surgical evaluation by the surgeons that managed these cases. The last case had a cervical rib anomaly and was the patient that underwent surgical correction. Two of these 7 patients had recurrent venous thrombosis. One was a 44-year-old woman with a cervical rib that underwent surgical correction after both events. The other case is a 29-year-old woman with a complex costal abnormality who had a homolateral recurrence and is planning a surgical examination.

Pregnancy and oral contraceptive use are classic risk factors associated with thrombosis. In a series of 25 women with idiopathic UEDVT, one had

received ovarian stimulation, 3 were pregnant (all through the first two months of pregnancy), and 11 were using oral contraceptives [7]. In our series, three patients were under hormonal treatment and 1 was in the second month of pregnancy, all having spontaneous UEDVT.

The synergistic effect of multiple risk factors in the pathogenesis of thrombosis is well recognized [19], but the putative relationship between the onset of UEDVT and the presence of an underlying thrombophilic status has not yet been proven. This association has been more commonly evaluated during the last few years, when a number of publications warned about the prevalence of thrombophilic defects in patients with UEDVT.

The prevalence of coagulation abnormalities reported in the literature ranges from 8% to 61% (Table II). Because relatively few patients have been evaluated so far, most studies are retrospective and there are discrepancies in coagulation test results, analysis and comparison are still inconclusive. Ruggeri et al. [20] reported a congenital coagulation defect in only two out of 27 patients (7.4%) with upper-limb thrombosis and positive anticardiolipin antibodies in 4 cases (14.8%). Martinelli et al. [5] found an inherited hypercoagulable status in only three out of 36 patients (8%) with spontaneous UEDVT. This prevalence was similar to a control healthy group but significantly lower than a cohort of patients with lower-limb DVT (56%).

Prandoni et al. [6] identified a thrombophilic status in seven out of 27 patients (26%) with UEDVT, and Ellis et al. [8] demonstrated in a retrospective study the presence of an underlying thrombophilic status in 61% of patients with axillosubclavian thrombosis (11 out of 18 patients). Héron et al. [7] also reported a high prevalence of hypercoagulable status in a population of patients with idiopathic UEDVT compared to those with effort-related UEDVT [42% (13/31) vs. 15% (3/20)]. Leebeek et al. [21] recently found

thrombophilic defects in 32% of their population with UEDVT and the most frequently found coagulation abnormality was the presence of antiphospholipid antibodies (27%). A recent publication documented the prothrombin G20210A mutation in 12.5% of patients with primary UEDVT and increased thrombotic risk in fertile women using oral contraceptives [22].

In our study, the most common acquired thrombophilia found was the presence of antiphospholipid antibodies. Factor V Leiden mutation and prothrombin G20210A polymorphism were the most prevalent genetic risk factors, detected in 4 out of 31 (12.9%) and in 3 out of 15 (20%) patients, respectively. This prevalence is similar to that reported in lower-limb DVT [14,23]. However, we failed to observe any difference in the prevalence of these two genetic risk factors between the effort-related and the spontaneous UEDVT groups. These results may suggest that, in patients with effort-related UEDVT, the presence of hypercoagulable status may possibly contribute to the pathogenesis of thrombosis in addition to local trauma at the thoracic outlet. One of our patients has the coinheritance of both mutations, demonstrated to be associated with an increased risk of deep vein thrombosis. There is only one publication where both factor V Leiden and prothrombin G20210A mutations were diagnosed in a 31-year-old man with effort-related UEDVT at the workplace [24].

The prevalence of factor V Leiden and prothrombin G20210A mutations varies markedly between different countries. In Argentina, it is similar to the one reported for Southern Europe with a prevalence of 2.9% for the factor V Leiden mutation and 2.6% for the prothrombin G20210A gene variant [25]. In our series, only patients with abnormal APCR values detected with the modified APCR test were screened for factor V Leiden mutation. Several studies have evaluated the ability of the modified APCR technique (using undiluted and diluted samples in factor V depleted plasma) to discriminate between carriers

TABLE II. Prevalence of Thrombophilic Risk Factors in UEDVT—Review of Literature Data\*

	No. of patients (n)	Type UEDVT	AT (%)	PS (%)	PC (%)	Factor V Leiden (%)	Factor II G20210A (%)	Hcy (%)	APA (%)	Total (%)
Prandoni et al. [6]	27	All	3.7	3.7	7.4	7.4	NT	NT	3.7	26
Martinelli et al. [5]	36	Spontaneous	0	0	0	8.3	NT	5.6	0	14
Ruggeri et al. [20]	27	Not catheter-related	0	0	3.7	3.7	NT	NT	14.8	22
Héron et al. [7]	31	Idiopathic	0	7	0	15	0	0	29	42
	20	Effort-related	0	0	0	5	0	NT	10	15
Leebeek et al. [21]	41	All	2.4	0	0	4.9	0	NT	26.8	32
Hendler et al., present study	16	Spontaneous	0	0	0	12.5	12.5	18.7	56	68
	15	Effort-related	0	6.6	0	13.3	6.6	13.3	33.3	53

\*Abbreviations: Hcy, hyperhomocysteinemia; APA, antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies); NT, not tested.

and non-carriers of factor V Leiden mutation. Most of them demonstrated that the modified APCR test provides a clear-cut discrimination between normal wild type and carriers of factor V Leiden mutation that could obviate the necessity for genotyping subjects with a normal phenotype [26–28].

Several studies reported an increased evidence that hyperhomocysteinemia is a risk factor for venous thrombosis and that the association of this coagulation abnormality with other genetic or acquired thrombophilic defects further increased this risk. Reviewing the series published about prevalence of thrombophilic states in UEDVT, only the one by Martinelli et al. [5] evaluated plasma homocysteine levels and found hyperhomocysteinemia in 6% of patients with UEDVT and in 14% with lower extremities DVT. In our series, we found high plasma homocysteine levels in five patients (16%) with a combined diagnosis of hyperhomocysteinemia and lupus anticoagulant in two of them. The prevalence of this thrombophilic disorder was comparable with that observed in patients with lower extremities DVT.

The prevalence of pulmonary embolism (PE) in patients with UEDVT is controversial. Although, in the earlier reports PE was thought to be almost nonexistent, it has become increasingly prevalent. In a revision of nine studies (406 patients) with UEDVT, PE was detected in 52 (12.8%) and showed the highest risk in patients with catheter-related UEDVT [29]. However, most of these studies assessed for patients with symptomatic PE. Prandoni et al. [6] suggested a high prevalence of both symptomatic and asymptomatic PE in patients with UEDVT (36%), comparable with that observed in lower-extremity DVT. In a recent series by Héron et al., the screening for PE was performed in 26 out of 55 patients with UEDVT and results were positive in 11 (20%). However, they did not specify if patients were or not pulmonary symptomatic. In our series, we did not have pulmonary symptomatic patients and none had developmental symptoms or fatal pulmonary disease during the follow-up.

Although the prevalence of coagulation abnormalities is expected to be higher in patients with spontaneous thrombosis compared with those with effort-related UEDVT, we found no significant differences in the prevalence of acquired versus inherited thrombophilia. On the other hand, the prevalence of thrombophilic disorders found in our study is comparable to that observed in other cohorts of patients with lower-limb DVT. These findings suggest that hypercoagulable status may well play a significant role in both spontaneous and effort-related UEDVT and that screening for thrombophilic defects would be justified in both groups as routinely done in lower-limb thrombosis.

Furthermore, the proportion of patients with TF was significantly lower within the group with local anatomic anomalies compared with the group without anatomical defects ( $P = 0.006$ ). The incidence of coagulation abnormalities in the second group was 75%, for a RR of 5.25. This data suggested that hypercoagulability would not play a role in the pathogenesis of UEDVT associated with local anatomical defects but the presence of hypercoagulable status appears to be implicated when a non-anatomic abnormality is detected, both in the effort-related and in the spontaneous UEDVT group.

In conclusion, we found a high prevalence of underlying thrombophilic status in our population of patients with either spontaneous or effort-related UEDVT. As most of the latter also had a hypercoagulable status, a synergistic effect between mechanical and procoagulant risk factors is not unlikely. Both screening for local anatomical abnormalities (thoracic outlet syndrome) and a thrombophilic search should be included in the evaluation of patients with UEDVT.

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