Risk Factors and Management of Patients With Upper Limb Deep Vein Thrombosis*

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Study objectives: To determine the prevalence of endogenous and exogenous risk factors for venous thrombosis in patients with upper limb deep vein thrombosis (DVT), and to evaluate the risk of clinically detectable pulmonary embolus, recurrent DVT, and postphlebitic symptoms in these patients.

Design: A combined prospective and retrospective descriptive analysis of a cohort of patients with upper limb DVT compared with age- and sex-matched patients with lower limb DVT.

Setting: Internal medicine departments, and hematology and vascular surgery outpatient clinics at a tertiary-care university hospital.

Patients: Consecutive patients with “spontaneous” upper limb DVT diagnosed between 1989 and 1997 were studied. Twenty age- and sex-matched patients with lower limb DVT admitted to the hospital via the emergency department served as control patients.

Results: Eighteen patients with upper limb DVT were studied. An endogenous risk factor (thrombophilia) was present in 11 of 18 patients vs 8 of 20 control patients (p < 0.5 not significant).

In the upper limb group, nine patients had activated protein C resistance, four patients had anticardiolipin antibodies, and two patients had both forms of thrombophilia. Furthermore, 14 of the upper limb DVT patients were found to have an exogenous risk factor for thrombosis compared with 7 of the patients with lower limb DVT (p = 0.01), and 66.6% of patients with upper limb DVT had both an exogenous and an endogenous risk factor for thrombosis vs 15% of patients with lower limb DVT (p < 0.002). No clinically detectable pulmonary emboli occurred among the upper limb DVT patients. Three patients have minor postphlebitic symptoms. Two patients experienced recurrent DVT.

Conclusion: In the majority of patients with upper limb DVT that we studied in this relatively small study, exogenous (environmental) or endogenous risk factors for venous thrombosis, or a combination of both, were found. Furthermore, in our patients, these thromboses had a low propensity to cause clinically significant pulmonary embolus and did not cause significant postphlebitic symptoms. Finally, we suggest that anticoagulant therapy for these thromboses may be adequate and that thrombolytic agents and surgical intervention are not routinely indicated.

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Key words: anticoagulation; effort; Paget-Schroetter; thrombophilia

Abbreviations: aCL-Ab = anticardiolipin antibody; APCR = activated protein C resistance; DVT = deep vein thrombosis; PTT = partial thromboplastin time

S pontaneous thrombosis of the axillary or subclavian vein is a well-described syndrome.1 In keeping with Virchow’s time-honored dogma that thrombosis results from stasis, vessel wall abnormalities, or blood disorders, however, no thrombus can ever truly be defined as being “spontaneous.” Indeed, many have noted that specific risk factors exist for axillosubclavian vein thrombosis. These risk factors include external compression of the vein by a cervical rib or shoulder girdle tendon and the Paget-Schroetter or “effort” syndrome, where recurrent, vigorous exertion of an upper extremity results in endothelial damage to a proximal vein that is permissive for clot development.2 In fact, most series of patients with axillosubclavian deep vein thrombosis (DVT) report these abnormalities in nearly all patients in whom a more obvious etiologic factor such as a venous catheter or locally compressing tumor is present.

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absent. No studies have been performed to define the prevalence of inherited or acquired thrombophilias in patients with spontaneous upper limb DVT.

In this report, we analyze the risk factors for DVT present in a group of patients with upper limb vein thrombosis. We also discuss the treatment and clinical outcome of these patients.

**Materials and Methods**

We conducted a retrospective study of patients treated in the vascular surgery and hematology departments for a diagnosis of spontaneous axillosubclavian thrombosis from 1989 to 1997. Over this period, patients with a diagnosis of upper limb DVT were evaluated and treated in a uniform manner. The diagnosis was suggested by the findings of pain, swelling, and erythema of an upper extremity and was confirmed by noninvasive color duplex Doppler studies in 16 of 18 patients and by venography in 2 patients. Risk-factor assessment was performed by taking a detailed history, performance of tests for protein C antigen, protein S antigen and activity, activated protein C resistance (APCR), antithrombin III activity, lupus anticoagulant activity, and anticardiolipin antibodies (aCL-Abs). APCR was determined using a partial thromboplastin time (PTT)-based test in which the results of the partial PTT time test are compared before and after adding activated protein C to the test reaction (Coatest; Chromogenics; Molndal, Sweden). Protein C activity was measured using a chromogenic assay (Coamatic; Chromogenics; Molndal, Sweden). Protein C activity was measured using a chromogenic assay (Coatest; Deerfield, IL). Protein S activity was measured using protein S deficient plasma with the addition of CaCl₂ (Biopool; Biopool; Ventura, CA), and protein S free antigen was determined by enzyme-linked immunosorbent assay (Stago; Asnieres, France). Antithrombin III activity was measured using a chromogenic assay (Coamatic Antithrombin, Chromogenics). Lupus anticoagulant was tested for using an activated PTT-based assay (Actin FSL activated PTT reagent; Dade Behring, Marberg, Germany). aCL-Ab titers were determined by a semiquantitative enzyme-linked immunosorbent assay (REAADS; Med-Ox; Kanata, Canada). IgG and IgM aCL-Abs were measured. When the aCL-Ab test finding was positive, it was repeated after 6 weeks. A patient was regarded as aCL-Ab-positive if he had two positive test results. The thoracic inlet region was studied using CT for evidence of local anatomic abnormalities. Patients with catheter-related DVT or a history of trauma to the affected extremity were excluded from this study.

The patients were compared with 20 consecutive age- and sex-matched patients with popliteal or iliofemoral vein thrombosis admitted to our hospital via the emergency department. These patients were all screened for the presence of underlying thrombophilia using the same tests as those performed in the study patients. Statistical analysis was performed using a x² test with commercially available software (GraphPad Prism version 2; GraphPad Software; San Diego, CA).

**Results**

Eighteen patients with axillosubclavian vein thrombosis were treated at our institution from 1989 to 1997. The male to female ratio of the study group was 1:2. The patients’ ages ranged from 22 to 70 years, with a median age of 38 years. The presence of an exogenous risk factor for venous thrombosis was identifiable in 14 patients. Exogenous risk factors were as follows: pregnancy (four patients), estrogen ingestion (four patients), effort syndrome (five patients), and malignancy (one patient). No patients had anatomic abnormalities of the thoracic inlet, such as a hypertrophied scalenus anticus tendon or an obstructing tumor.

Thrombophilia was found in 61.1% of the patients: APCR alone in 38.9%, aCL-Abs alone in 11.1%, and both APCR and aCL-Abs in 11.1% of patients. No patients were found to have protein C, protein S, or antithrombin III deficiency.

Thirteen of the 18 patients had more than one risk factor for venous thrombosis. In two patients, there were two coexistent exogenous risk factors (effort and estrogen ingestion); in two others, there were two exogenous factors and an underlying thrombophilia (effort, estrogen ingestion, and APCR in both patients). Ten patients had a single exogenous risk factor and thrombophilia. Table 1 summarizes the risk factor profile and treatment outcomes of the two groups of patients.

Thirteen patients were treated with unfractionated dose-adjusted heparin followed by warfarin sodium for 3 to 6 months. A single patient received IV streptokinase followed by heparin and warfarin. The four pregnant patients were treated with a low molecular weight heparin (enoxaparin at a dosage of 1 mg/kg bid) for the duration of the pregnancy and received warfarin for 6 weeks thereafter.

**Treatment Outcomes**

All patients had resolution of their symptoms within 12 to 72 h. Imaging studies to detect pulmonary embolism were not performed routinely, but no patient developed a clinically significant pulmonary embolus; that is, no patient complained of chest pain or dyspnea, and no patient developed tachycardia, tachypnea, or hypotension.

Postphlebitic symptoms after a median follow-up period of 15 months have been limited to discomfort and prominence of superficial veins in three patients. In two of these patients, the mid-upper arm circumference of the affected extremity was 2 cm greater than that of the normal arm. Two patients have suffered recurrent venous thrombosis, one patient at the site of the original thrombosis, and the other in a lower extremity.

**Discussion**

Spontaneous thrombosis of the axillary or subclavian veins was first postulated as a cause of upper extremity pain and swelling by Sir James Paget in...
Von Schroetter demonstrated thrombotic occlusion of upper limb veins in 1884, and thus the syndrome of idiopathic upper limb venous thrombosis has come to be known as the Paget-Schroetter syndrome. More recently, the association between strenuous repetitive movement of the upper extremity and axillosubclavian thrombosis has been recognized and is known as effort syndrome. These patients often have anatomic variations of the structures comprising the thoracic inlet that may lead to compression of the subclavian vein. Such abnormalities include the presence of a cervical rib and hypertrophy of the scalenus anticus or subclavius tendons.

The causal relationship between an underlying thrombophilic tendency and upper limb venous thrombosis has not yet been defined. It has been noted, however, that a feature of hypercoagulable states may be the occurrence of thromboses at unusual anatomic locations in addition to a history of recurrent thromboses or a positive family history of thrombosis. In this retrospective study of patients presenting to a single institution with axillosubclavian thrombosis, we have been able to demonstrate the presence of an underlying thrombophilic state in > 60% of patients. This incidence is not statistically different than that of thrombophilia detected in unselected patients with venous thrombosis of the lower limbs in whom 40% had a procoagulable state. The only exogenous factor found to be significantly associated with upper limb DVT was effort, justifying the frequent use of the term effort syndrome to describe spontaneous axillosubclavian thrombosis.

Furthermore, we have shown the importance of the presence of an exogenous risk factor for thrombosis occurring either alone or together with a known thrombophilia. The concept of the synergistic effect of multiple risk factors for thrombosis is well recognized and is reinforced by our findings. Our findings differ from those of Martinelli et al, who have reported a significantly lower incidence of thrombophilia in upper limb vein thrombosis compared to leg vein thrombosis (10.8% vs 43.2%). These investigators did not indicate whether their patients had spontaneous thromboses or whether some were catheter associated, and this makes uncertain their conclusion that the pathogenesis of upper limb thrombosis in general differs from that of lower limbs.

Our results suggest that in addition to a careful history of physical exertion of the upper limbs and other exogenous causes of venous thrombosis, evaluation of patients should include imaging of the thoracic outlet and screening for an underlying hypercoagulable disorder. In keeping with the frequency of thrombophilia in venous thromboembolism in general, the abnormalities most likely to be encountered are APCR and the presence of aCL-Abs. The incidence of hyperhomocysteinemia and the G21020A mutation in the prothrombin gene

**Table 1—Demographic Data, Exogenous and Endogenous Risk Factors, and Treatment Outcomes of the Study Patients With Upper Limb DVT and the Age- and Sex-Matched Control Group**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Upper Limb DVT</th>
<th>Lower Limb DVT</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>18</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>Median age, yr (range)</td>
<td>38 (22–70)</td>
<td>40 (25–72)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>6/12</td>
<td>8/12</td>
<td>NS</td>
</tr>
<tr>
<td>Endogenous risk factor, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APCR</td>
<td>9 (50)</td>
<td>5 (25)</td>
<td>NS</td>
</tr>
</tbody>
</table>
aCL-Ab                            | 4 (22.2)       | 3 (15)         | NS      |
|APCR and ACL-Ab                   | 2 (11.1)       | 0 (0)          | NS      |
|Total                            | 11 (61.1)      | 8 (40)         | NS      |
|Exogenous risk factor, No. (%)    |                |                |         |
|“Effort”                         | 5 (27.7)       | 0 (0)          | 0.01    |
|Estrogen ingestion                | 4 (22.2)       | 2 (10)         | NS      |
|Pregnancy                         | 4 (22.2)       | 2 (10)         | NS      |
|Malignancy                        | 1 (5.5)        | 4 (20)         | NS      |
|“Effort” and estrogen             | 2 (11.1)       | 0 (0)          | NS      |
|Total                            | 10 (55.5)      | 7 (35)         | NS      |
|Combined risk factors, No. (%)    | 12 (66.6)      | 3 (15)         | < 0.002 |

*Statistical analysis was performed using χ² test; p < 0.02 was considered statistically significant; NS = not significant.
†Endogenous and exogenous.
(two other common causes of thrombophilia) in upper limb venous thrombosis are unknown.

Our observations on the treatment and outcome of patients with noncatheter-associated axillosubclavian suggest that a conservative approach (that is, treatment with anticoagulants alone without thrombolytic or surgical therapy) is appropriate in most patients. Anatomic abnormalities of the thoracic inlet should, however, be surgically corrected. In our experience, anticoagulation alone results in good short-term and long-term outcome. No patient had a clinically significant pulmonary embolus, and only three patients have postphlebitic symptoms. In one patient, the symptoms were significant functionally, requiring the patient to cease working as a physical therapist. These results suggest that more invasive treatments such as catheter-directed thrombolysis, angioplasty, or thrombectomy are unwarranted except in selected cases.12

In conclusion, we have found that in most of the patients studied in this relatively small cohort of patients with upper limb DVT, an underlying thrombophilic state is present. Most of the patients in our series also had an added exogenous risk factor for thrombosis, and a synergistic effect between multiple risk factors is likely. The detection of a hypercoagulable state in these patients is important for decisions regarding prophylactic anticoagulant therapy during high-risk periods, such as pregnancy and at the time of surgery or immobilization. We also suggest that a conservative approach to the treatment of axillosubclavian thrombosis with anticoagulation alone results in a good clinical outcome in most patients.

**REFERENCES**

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