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Original scientific paper

Thrombus Size is Associated with Etiology of Deep Venous Thrombosis – A Cross-Sectional Study

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A B S T R A C T

The aim of this study was to evaluate the impact of risk factors for deep vein thrombosis (DVT) on thrombus sizes in lower extremities. The size and extent of thrombus was scored according to International Consensus Committee for venous disease classification. After the diagnosis of DVT was established and its size scored, predominant risk factors for DVT in each patient were identified (malignant disease, thrombophilia, postoperative state, hormonal therapy, heredity, limb trauma, immobilization, others and unknown risk factors). The average thrombus score was 6 (95% CI 5.47–6.53). The analysis of thrombus size indicated that the largest thrombi were found in patients with malignancy. Their average score was 8.5 (95% CI 7–10) and was significantly higher than in patients with other risk factors for deep vein thrombosis. There was no significant correlation between numbers of days from the onset of symptoms to the moment of DVT diagnosis and thrombus score (r=–0.08, p=0.38). Age was very slightly correlated to thrombus size (r=0.19; p=0.046), while the gender did not have significant impact on thrombus score (p=0.074). The conclusion of our study was that etiology of thrombosis and particularly malignant diseases has the largest impact on venous thrombus size.

Key words: *deep vein thrombosis, DVT, ultrasonography, thrombus size, etiology, malignant disease, thrombophilia*

Introduction

Deep vein thrombosis is an age-related disease for which various risk factors are already identified: prolonged immobilization, cancer, thrombophilia, surgery, heredity, pregnancy and estrogen use, nephrotic syndrome, indwelling intravenous catheters. After diagnosis of deep venous thrombosis is made by ultrasound, its extent should be evaluated. Porter et Moneta on behalf of International Consensus Committee for venous disease introduced anatomical distribution and scoring after which the thrombus load can be determined[1]. Its determination is important because it may influence the course of therapy and possibly is related to DVT complications[2]. DVT may present in the whole spectrum of severity ranging from small subsegmental partial clot in posterior tibial veins to large multisegmental thrombi extending from illiac veins over femoral, popliteal to crural veins. Small clots usually produce mild symptoms while large ones present with swelled and painful leg[3]. Thrombus load and its relation to deep vein thrombosis complications was evaluated in many articles with often controversial conclusions[1,4–11]. Meissner found that popliteal location was more frequently associated with the development of deep vein thrombosis than other locations[8]. The extent of thrombosis was not evaluated in literature with the risk factors for DVT, but sporadically[1,10,12].

We hypothesized that various risk factors are associated with different thrombus score. Our intention was to evaluate the role of individual risk factors in size and location of DVT. Cancer causes hypercoaguable state that may produce high thrombus load, particularly if other risk factors such as surgery, indwelling catheters and chemotherapy are present[13–15].

Patients and Methods

Protocol

All patients with signs and symptoms suspected of deep vein thrombosis referred for Doppler examination from July 2003 to April 2004 entered the study. The pa-

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tients with ultrasonographically-confirmed first-time deep vein thrombosis of pelvis or lower extremities were included into the study.

Patient population

Hundred-twelve patients with diagnosed DVT were enrolled into the study. There were 52 (46%) males and 60 (54%) females. The mean age of males was 60 years (95% CI 55–64) and for females it was 61 years (95% CI 56–65, p=0.72).

Methods

Duplex examinations were performed in 15-degrees reverse Trendelenburg position with Aloka 640, with 7.5 MHz transducer. All deep and superficial venous segments from the inferior vena cava to the crural veins were imaged, and venous segments were classified as patent, partially occluded or completely occluded on the bases of standard ultrasound criteria which included compressibility and the presence of spontaneous or augmented Doppler and color flow[2,16,17]. Then, analysis of involvement of an each venous segment according to International Consensus Committee for venous disease classification was performed[1]. Six venous segments were taken for analysis: external illiac, common femoral, superficial femoral, profound femoral, popliteal and crural. For each segment a patient was assigned one point which was multiplied with the level of occlusion. The level of occlusion was scored as follows: 0 – patent vein, 1 – subsegmental nonocclusive thrombus, 2 – subsegmental occlusive thrombus, 3 – occlusive thrombus throughout the entire segment. Patent vein was defined by spontaneous biphasic flow and complete compressibility of the vein. The criteria for complete occlusion were absence of flow with distal compression and incompressibility of the vein. Nonocclusive thrombus was defined by normal or diminished flow with distal compression and partial incompressibility of the vein. The final result was a thrombus score or load[1]. With this scoring, the maximal number of points (thrombus score) was 18.

Exclusion criteria

The number of days since symptoms of DVT started to the time of diagnosis was recorded. The patients with symptoms lasting longer than 2 weeks were excluded from the study, because after that time, recanalization by patients´ own fibrinolysis usually started. Also, the patients with recurrent thrombosis were excluded, because we could not know the possible residual clot size. In the »intention-to-treat« analysis there were 185 patients while per protocol analysis included 112 subjects.

Risk factors analysis

Careful search for risk factors for DVT was made. The presence or absence of following risk factors for DVT was recorded: malignant disease, immobilization > 3 days, earlier DVT, pregnancy, hormone replacement therapy, smoking, obesity, varicose veins, family history

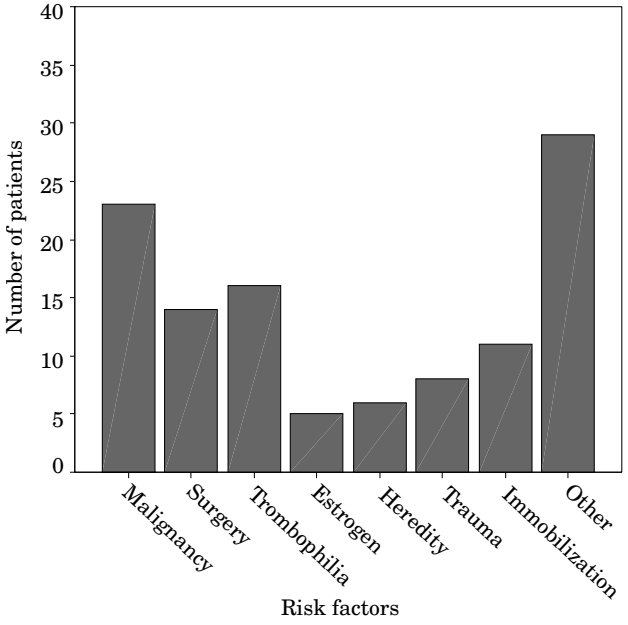

Fig. 1. Malignancy and thrombophilia were single most frequent risk factors in 112 patients with DVT.

of DVT, recent surgery, recent trauma, and myocardial infarction[18]. The incidence of risk factors is presented in Figure 1. In patients with malignancy (diagnosed within past 6 months), surgery, irradiation, chemotherapy are termed as cancer-related procedures and treated as one variable for statistical purposes. As the patients were followed for their INR levels and thrombus resolution the detection of malignancy after DVT was recorded. As smoking, obesity, varicose veins, myocardial infarction have only circumferential impact on DVT incidence, they were analyzed together[1,19]. Patients younger than forty years were analyzed for thrombophilia. The levels of antithrombin, protein C and S were measured[20]. Polymerase chain reaction for point mutation of factor V (Leiden) and factor II were performed[21]. The level of factor VIII was not determined because its true role in pathogenesis of thrombosis is not yet completely elucidated[22]. The assays on anticardiolipin antibodies and lupus anticoagulants were also done[14].

Statistical analysis

The data are presented as means and 95% confidence intervals. As distribution was normal, parametric statistics was used. ANOVA was used to compare thrombus load among various risk factors of thrombosis. Pearson coefficient of correlation was used to estimate relationship between thrombus score and number of days from the onset of symptoms and the detection of DVT. The level of significance was defined at 0.05, actual probabilities were presented in the text. Statistical analysis was performed with SPSS software (SPSS 11.5 Inc., Chicago, Illinois).

Results

Analysis of distribution of 251 occluded venous segments in 112 patients is presented in Figure 2. The most common affected segments were superficial femoral (88; 35%) and popliteal vein (59; 23%). The distribution of thrombus in each patient is presented in Table 1. Eighty--nine (79%) thrombi involved multiple anatomic segments and in 23 (21%) patients DVT was single-segmental.

The most frequent thrombus site was femoropoliteal (37/89; 42%), and ileofemoral (18/89; 20%). The average thrombus load was 6 (95% CI 5.47–6.53) (Table 1).

Analysis for thrombophilia indicated 6 patients with FV (Leiden) mutation, 2 patients with antiphospholipid antibodies, 2 patients with F II G20210A, and 4 patients with potentially serious thrombophilia (one with AT, one with PC and 2 with PS deficiency, but the level of deficiency was rather small in all four patients).

The patients were divided in 8 groups according to predominant risk factor for DVT (Figure 3). Analysis of variance (ANOVA – Tukey correction) has shown that cancer patients had significantly higher thrombus load than others (mean value 8.5; 95% CI 7–10) as shown in Figure 3.

There were 24 patients with cancer (8 breast, 5 gastrointestinal, 3 genitourinary, 4 hematological and 4 miscellaneous malignancies). Most patients had combined treatment: fourteen patients underwent surgery for malignancy, 9 patients were on chemotherapy, and 10 patients on radiation therapy.

TABLE 1
THE ANATOMIC DISTRIBUTION OF THROMBI SHOWING THE NUMBER OF SINGLE AND MULTI-SEGMENTS INVOLVED

Single segment thrombosis	Number of segments
CFV	10
SFV	10
PV	2
CV	1
Multisegmental thrombosis	
ILV + CFV +SFV + PFV +PV+CV	4
ILV +CFV+SFV+PV	7
ILV +CFV+SFV	18
ILV +CFV	6
CFV +SFV + PFV	8
SFV + PV	37
SFV + PFV + PV + CV	4
PV+CV	5

ILV – illiac vein, CFV – common femoral vein, SFV – superficial femoral vein, PFV – profound femoral vein, PV – popliteal vein, CV – crural veins

Pearson coefficient of correlation between thrombus score and the time interval from onset of symptoms and detection of thrombosis was – 0.08 (p=0.39). The majority of DVT were diagnosed during the first week. It is also obvious from Figure 4. that most DVT with high thrombus score were detected early in the course of disease. Age was only slightly correlated to thrombus score (r=0.19; p=0.046), while gender did not have significant impact on thrombus score (p=0.074).

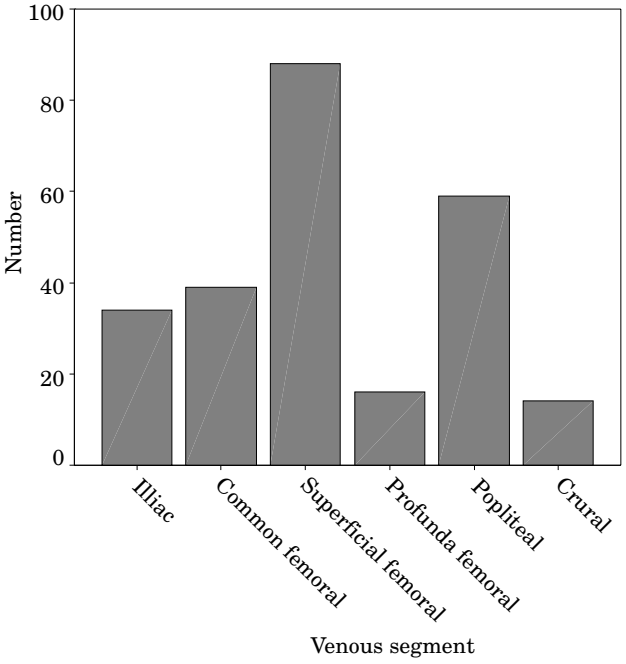

Fig. 2. Anatomical distribution of affected venous segments by deep vein thrombosis. The most common affected segments were superficial femoral and popliteal vein.

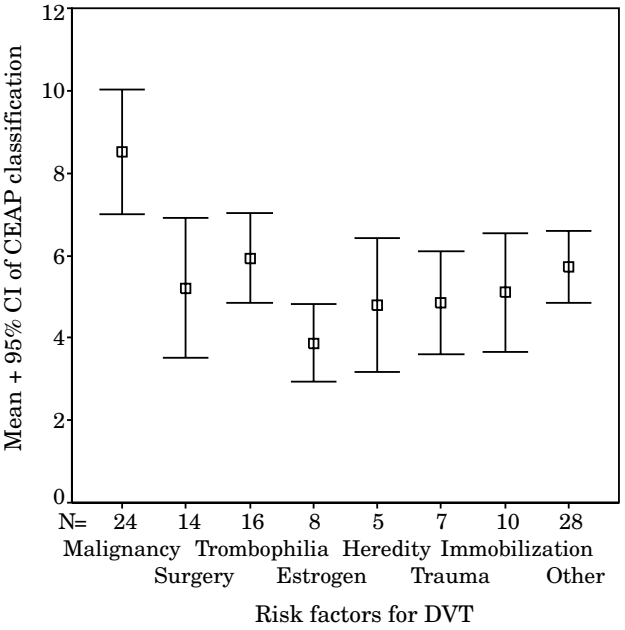

Fig. 3. The means and 95% confidence intervals are presented for risk factors for deep vein thrombosis. Malignancy had significantly higher score than other risk factors.

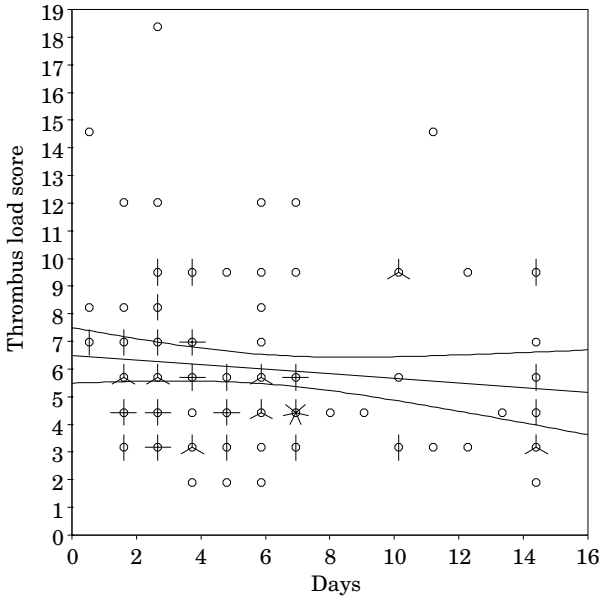

Fig. 4. There is no significant relationship between thrombus load score and days from onset of symptoms to diagnosis of deep vein thrombosis (r=–0.08, p=0.39).

Discussion

It is a challenge for any clinician to recognize a risk for DVT, and to stratify patients according their risk level to apply proper DVT prophylaxis. If DVT occurs, it is important to recognize short-term and reversible risks and avoid them in the future as well as lifelong risks since they require different therapeutic approach[13,23–25]. Beside risk factors, it is important to define the site and extent of deep vein thrombosis, because these parameters have predictive value in terms of possible thrombosis recurrence or embolism as well as development of postthrombotic syndrome[9–12,26,27].

Our finding of predominant affection of superficial femoral and popliteal segments is in accordance with findings from other studies[4,5,8,12].

Killewich et al in their study of thrombus load regression by natural fibrinolytic activity found in 19 patients 33% segments affected and that is similar to our results as they measured thrombus load in 5 segments. Our initial thrombus load was different from theirs 5.79±2.68 vs. 4.5±0.6 partly due to their small number of examined extremities and different classification. Besides, they had only 3 patients with malignancy[12].

Van Ramhorst analyzed 20 extremities with mean thrombus load of 5. Out of 80 potential segments they found 49 of them had intravascular occlusion. These results correspond to our findings but they did not refer to risk factors for DVT at all[10].

The study of Johnson about development of postthrombotic syndrome also found similar thrombus load, the risk factors were presented but not associated with thrombus load[9].

Meissner et al in their study of determinants of chronic venous disease after acute DVT followed 68 patients during 2 years. The initial thrombus load was 6.9±4.2. They found thrombosis of popliteal vein to be associated with increased risk of postthrombotic syndrome. They also identified risk factors for DVT without association with thrombus load[8].

In another study about coagulation, fibrinolysis markers and recanalization Meissner et al found in 71 patients initial thrombus load to be 5.1±4.7. Risk factors were analyzed but particular attention was paid to biochemical markers and their temporal changes in relation to thrombus load[5].

The common denominator of all these studies including ours, are similar initial thrombus scores and distribution of affected venous segments. The original contribution of our study is an attempt to associate thrombus load to risk factors for DVT.

In our study cancer was significantly better as predictor of thrombus load (mean value 8.5, 95% CI 7–10) than other risk factors.

Cancer and its treatments are well-recognized risk factors for venous thromboembolism (VTE). Evidence suggests that the absolute risk depends on the tumor type, the stage or extent of the cancer, and treatment with antineoplastic agents. Furthermore, age, surgery, immobilization, and other comorbid features will also influence the overall likelihood of thrombotic complications, as they do in patients without cancer. The role of hereditary thrombophilia in patients with cancer and thrombosis is still unclear, and screening for this condition in cancer patients is not indicated. Patients undergoing surgery for cancer have a higher risk of postoperative deep vein thrombosis (DVT) than those having surgery for nonmalignant diseases[13–15].

Cancer is a hypercoaguable state as reflected in increased levels of coagulation parameters (D-dimer, prothrombin fragment 1+2, thrombin-antithrombin and plasmin-antiplasmin complexes). Surgery and chemotherapy were also contributing factors to thrombus load and produce hypercoaguability of blood[13–15]. In this study we did not present coagulation parameter levels, because they have low positive predictive value for thrombosis[2,11,28]. Venous thrombus is a three-dimensional structure and it should be detected by imaging methods rather than coagulation assays.

The patients with thrombophilia did not exhibit high thrombus load. Analysis of particular types of thrombophilia has shown that there were only 4 patients with serious defect (2 with antiphospholipid antibody syndrome and 2 with combined positive heterozygous mutations for F V and F II) and this might explain relatively low initial thrombus load[29].

The lack of correlation between thrombus score and time of detection of thrombosis is somewhat surprising as there is a belief that thrombosis precipitates and increases slowly as a function of time, producing symptoms when venous outflow is obstructed[2,28]. Our results indicate that in most cases large thrombus load is generated

during short period of time, while in other cases it precipitates slowly and increases in time. In latter case, the pain in deep vein thrombosis is dull, unlike arterial thrombosis where pain is sharp and incapacitating, and patients affected do not ask medical examination.

The surgical patients had lower thrombus load probably because of hospital stuff surveillance and awareness of patients of possible postsurgical DVT. Low-molecular-weight heparins are used routinely as prophylaxis of DVT. In patients, where LMWH fail to prevent thrombosis their role on reduction of thrombus size remains to be elucidated.

The limitation of the study is its cross-sectional character. Its shortcomings were partly avoided as we followed all patients to keep INR levels within therapeutic limits and were able to detect malignancy that was occult at the onset of thrombosis[30]. Visualization of thrombus score would have been probably better with venography but its use to this purpose would be unethical. In conclusion, our results indicate that further studies exploring the association between etiology of thrombosis and thrombus score, particularly the rate of recanalization in various etiologies are necessary.

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VELIČINA TROMBA OVISI O ETIOLOGIJI DUBOKE VENSKE TROMBOZE – PRESIJEČNA STUDIJA

SAŽETAK

Cilj rada bio je procijeniti utjecaj rizičnih faktora za nastanak duboke venske tromboze (DVT) donjih ekstremiteta na veličinu tromba. Veličina i proširenost tromboze je ocjenjena prema klasifikaciji Međunarodnog kosenzus komiteta za bolesti vena. Nakon što je kod 112 bolesnika potvrđena DVT donjih ekstremiteta bojanim doplerom utvrđeni su predominatni čimbenici rizika koji su mogli dovesti do tromboze (maligna bolest, trombofilija, postoperativno stanje, imobilizacija, hormonska terapija, nasljedna sklonost trombozi, trauma, ostali i nepoznati faktori). Prosječna veličina tromba je bila 6 (95% CI 5.47–6.53). Analizom veličine tromba utvrđeno je da su trombi najveći kod bolesnika sa malignim bolestima. Njihova prosječna veličina iznosila je 8.5 (95% CI 7–10) i bila je statistički značajno veća nego kod bolesnika sa drugim faktorima rizika za nastanak tromboze. Nije postojala značajna korelacija između broja dana od početka pojave simptoma do detekcije tromboze (r=–0.08, p=0.39). Dob je pokazala niski stupanj korelacije sa veličinom tromba (r=0.19, p=0.046), dok spol nije imao utjecaja. Zaključak naše studije je da etiologija tromboze, a posebno maligna bolest ima najveći utjecaj na veličinu tromba.