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● Original Article ●

Predictors of Clinical Severity in Post-thrombotic Syndrome

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Abstract: Predictors of clinical severity in post-thrombotic syndrome (PTS) were examined in a retrospective study of 51 limbs in 45 patients at over 1 year following an acute episode of deep vein thrombosis (DVT). All patients underwent a treadmill walking test with near-infrared spectroscopy (NIRS), and the ambulatory venous retention index (AVRI) in each patient was obtained from serial deoxygenated hemoglobin changes determined by NIRS. The location and extent of thrombi at the onset of DVT were also identified by venography. Seventeen limbs were asymptomatic, 27 had mild symptoms, and 7 showed severe symptoms. The calculated AVRI was significantly associated with clinical symptoms of PTS. A univariate linear regression analysis was used to assess effects of several covariates on AVRI. Compliance with compression therapy, presence of thrombi in popliteal segments and thrombi in multiple segments showed a statistically significant correlation with AVRI. In a subsequent multiple stepwise regression analysis, involvement of thrombi in multiple segments was overridden by the other factors, suggesting that thrombi in the popliteal vein affect the clinical severity in PTS, and that compression therapy with elastic stockings is an effective treatment for patients with PTS. (J Jpn Coll Angiol, 2006, **46:** 177–183)

Key words: deep vein thrombosis, post-thrombotic syndrome, near-infrared spectroscopy, popliteal vein, compression stockings

Introduction

Deep vein thrombosis (DVT) has a comparatively high prevalence, affecting approximately 4% of the European and US populations,[1] whereas interest in the disease has been limited in Japan. Recent media publicity of so-called economy-class syndrome drove the interest in DVT to grow. In addition, post-thrombotic syndrome (PTS) is known as a chronic complication of DVT, and its pathologic features include retained thrombi,[2] reflux of venous blood due to damaged venous valves,[3, 4] and deteriorated calf muscle pump function.[5, 6] At the onset of DVT it is difficult to predict whether PTS will develop or aggravate during the clinical course, and clinical factors related to the severity of PTS have not been identified.

We studied venous return function during exercise in patients with venous diseases using near-infrared spectroscopy (NIRS), and found a significant correlation between clinical severity in patients with chronic venous insufficiency and the ambulatory venous retention index (AVRI) calculated from NIRS data.[7, 8] This study examined correlations between AVRI (closely related to PTS clinical symptoms) and various clinical parameters (including location of thrombi upon onset of DVT, and use of elastic stockings post DVT onset to identify what affect the severity of PTS.

Patients & Methods

The study was performed in PTS patients who visited the

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Department of Vascular Surgery at the University of Tokyo from January 1995 to March 1997. Patients in whom the location of thrombi at onset of DVT could be confirmed by venography were selected as subjects. Criteria for subject exclusion were 1) under 1 year since the onset of DVT, 2) possibilities of recurrence of DVT during observation periods, 3) past surgical procedures such as thrombectomy, 4) possibilities of developing chronic venous insufficiency of lower limbs prior to the onset of DVT, 5) presence of peripheral arterial disease, 6) no AVRI available due to difficulty in walking.

The study was performed on 51 limbs of 45 subjects (23 males and 22 females) in 17–81 years with the mean age of 54.6 years, with an average duration from the onset of DVT of 8.2 years (1–33 years). Clinical severity of PTS was classified as follows: no symptoms, class 0 in the CEAP classification;[9] mild symptoms, classes 1 to 3; and severe symptoms with skin changes such as pigmentation and ulceration, classes 4 to 6. Locations of thrombi were confirmed by venography at the onset of DVT, and classified as follows: iliac segment (common iliac, external iliac and common femoral veins), femoral segment (superficial femoral and deep femoral veins), popliteal segment (popliteal vein), and crural segment (tibioperoneal trunk or lower). The Patients were divided into 2 groups: a single-segment group in which thrombi developed in one of the above segments only, and a multiple-segment group in which thrombi were confirmed in two or more segments.

To evaluate ambulatory venous return function, all subjects were analyzed using NIRS during a treadmill walking test, and AVRI was calculated as a parameter of ambulatory venous return function based on serial deoxygenated hemoglobin (DeoHb) changes during exercise.[7] In brief, the optrodes of a NIRS (Shimadzu Co. OM-100A, Japan) were positioned on the posterior aspect of the calf. The light guide and the near-infrared detector were applied to the skin 4 cm apart longitudinally with a bandage. The treadmill waking test was done on the 12% gradient, at the speed of 2.4 km/h, for 5 minutes. DeoHb and oxygenated hemoglobin (OxyHb) were continuously measured by NIRS during rest exercise, and after exercise. AVRI was defined as rise from the bottom to the new plateau (R) / fall from the baseline to the bottom (E) (**Fig. 1**). E means the expulsion volume during exercise and R means venous retention. For comparison with the NIRS data, 31 limbs in 26 patients (15 limbs with no symptoms, 14 with mild symptoms, 2 with severe symptoms) were also evaluated by venous occlusion air plethysmography (APG, ACI medical, Inc., Sun Valley, Calif) according to the protocol described by Kalodiki et al.[10] Briefly, the patients were examined in the supine position, with the knee slightly flexed and elevated, the heel supported 15 cm above ground. A polyurethane cuff was inflated to 6 mmHg around the calf. After calibration, a thigh tourniquet was inflated to 70 mmHg. After the venous volume reached a plateau, the thigh tourniquet was deflated rapidly with the long saphenous vein at the knee compressed digitally. The decrease in volume is a result of venous outflow, and the venous volume (VV) and the 1-second venous outflow (V1) were obtained from the recording. The outflow fraction (OF) was then calculated as V1/VV X 100 (%). Regarding the use of compression stockings, an interview was performed to classify the subjects into regular-use and irregular-use groups: use of compression stockings 5 days/week or more, and less than 5 days/week, respectively.[11]

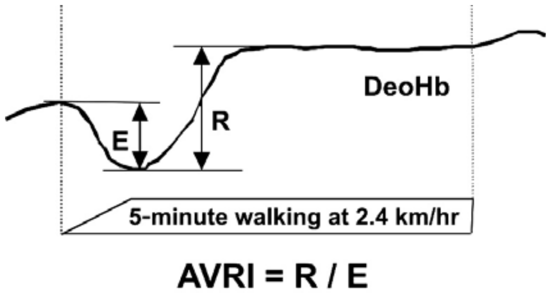

Figure 1 Definition of the ambulatory venous retention index (AVRI).
AVRI = rise from the bottom to the new plateau level (R) / fall from the baseline to the bottom (E). The less the expulsion during exercise (E), the more the venous reflux or retention (R), and therefore the greater AVRI, which indicates a higher severity of ambulatory venous insufficiency.

Correlation between AVRI, VV or OF and clinical severity in PTS was confirmed by Scheffe's F test, and then univariate analysis was used to assess correlations between AVRI and individual parameters. In addition, to exclude interactions among variables, multivariate analysis was performed with AVRI as the object variable. All data are shown

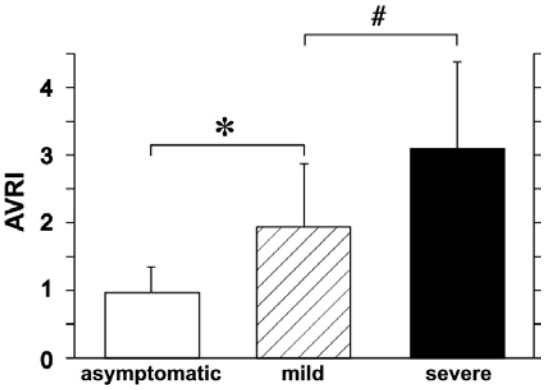

Figure 2 Relationship between AVRI and clinical severity in PTS.
The error bars represent standard deviations from mean values. There were significant differences among the groups (*p = 0.003, #p = 0.008).
AVRI: ambulatory venous retention index, asymptomatic: asymptomatic group, mild: mild group, severe: severe group

Table 1 Localization of inital thrombosis identified by venography

Site of thrombi	Number of limbs
Single segment	16 (31%)
Iliac	1
Femoral	3
Popliteal	1
Crural	11
Multisegment	35 (69%)
Iliac + femoral	6
Iliac + crural	2
Femoral + popliteal	1
Femoral + crural	2
Iliac + femoral + popliteal	4
Iliac + femoral + crural	1
Iliac + popliteal + crural	1
Femoral + popliteal + crural	14
Iliac + femoral + popliteal + crural	4

as averages ± standard deviation, and univariate linear regression analysis and multiple stepwise regression analysis were used for univariate and multivariate analysis, respectively, with $p < 0.05$ considered significant.

Results

No symptoms, mild symptoms and severe symptoms were confirmed in 17 limbs (33%), 27 limbs (53%) and 7 limbs (14%), respectively. Ulceration was observed only in two limbs. The locations of thrombi confirmed by venography in acute episodes of DVT are shown in **Table 1**: the single- and multiple-segment groups included 16 limbs (31%) and 35 limbs (69%), respectively. Regarding the use of elastic stockings, the regular-use and irregular-use groups included 29 limbs (57%) and 22 limbs (43%), respectively. AVRI values were 0.98 ± 0.36, 1.94 ± 0.93 and 3.10 ± 1.28 for limbs with no symptoms, mild symptoms and severe symptoms, respectively, showing a significant correlation with clinical severity in PTS (**Fig. 2**). VV or OF obtained from APG showed no correlation with clinical severity of PTS (VV: 79.7 ± 26.2, 80.7 ± 24.5, 101.1 ± 21.3 and OF: 28.3 ± 7.7, 26.8 ± 5.4, 29.4 ± 8.6 for limbs with no symptoms, mild symptoms and severe symptoms, respectively).

Univariate analysis: No significant correlations were found between AVRI and age, sex and presence of thrombi in the iliac, femoral and crural segments (**Table 2**). Regarding compression stockings, AVRI in the irregular-use group was significantly higher than that in the regular-use group. Significant correlations were also noted between AVRI and presence of thrombi in the popliteal segment and multiple segment groups compared with the single-segment group.

Multivariate analysis: Multiple stepwise regression analysis was performed to assess differences between the single- and multiple-segment groups, the presence of thrombi in the popliteal segment and use of compression stockings, with which a significant correlation of AVRI was found in the univariate analysis. The AVRI values for the single- and multiple-segment groups were not significantly different in the multivariate analysis, but significantly higher AVRI values were confirmed for thrombi in the popliteal segment ($p = 0.004$), and irregular use of compression stockings ($p = 0.02$).

Discussion

While the long-term prognosis for acute DVT requires further research, an early study showed that ulceration

Table 2 Univariate regression analysis of factors affecting AVRI

Variable	p value	95% confidence interval
Sex*	0.1806	(–0.196–1.013)
Age (year)	0.0569	(–0.036–0.001)
Mult#	0.0089	(0.218–1.449)
Iliac†	0.1439	(–0.162–1.078)
Femoral†	0.0935	(–0.096–1.187)
Popliteal†	< 0.0001	(0.604–1.646)
Crural†	0.4877	(–0.872–0.422)
Stockings‡	0.0036	(0.295–1.429)

AVRI: ambulatory venous retention index, *: male versus female, #: presence of thrombi at multisegment versus at single segment, †: presence of thrombi versus absence of that, ‡: regular compliance with stockings versus sporadic

developed in 80% of DVT patients over a 15-year period.[12] In recent studies,[2, 13-15] no symptoms, pigmentation and ulceration were observed in 20–59%, 13–37% and 2–5% of lower limbs with DVT, respectively. These data suggest that the incidence of serious PTS may have decreased due to treatment with anticoagulants and compression therapy. Intractable leg ulcer due to PTS, however, remains a concern. In the current study, no symptoms, class 4 symptoms and ulcer were confirmed in 17 limbs (33%), 5 limbs (10%) and 2 limbs (4%), respectively, consistent with other recent data.

To evaluate venous function in PTS patients, ultrasonography, ambulatory venous pressure (AVP) measurements and various plethysmography have been used, including air plethysmography. Some of their pros and cons are as follows: AVP measurements have been regarded as the gold standard for evaluation of chronic venous insufficiency. A correlation between AVP and venous stasis ulcer has been reported;[16] yet the invasiveness of the method inhibits repeated performance. Ultrasonography enables observation of occlusion and reflux of individual veins, while evaluation of the venous return function of entire limbs remains difficult with these data. In addition, calf muscle pump function cannot be evaluated since it is difficult to measure during walking using ultrasonography. APG measurements is commonly used to determine venous return function, enabling evaluation of muscle pump function and return function during tip-toe exercise.[17] Note that this is different from actual walking exercise. Moreover, in APG the venous filling index serves as a reflux index for the entire lower limbs, such reflux may be underestimated when occlusion remains in proximal veins such as an iliac or a femoral vein.[18] OF obtained from APG detects venous obstruction and is highly valued as a parameter of acute DVT.[10] Kalodiki et al.[19] reported that OF was useful in detecting past DVT, but they failed to examine all patients with venography at the acute DVT. Some patients with PTS could be excluded because over time the lysis of thrombi causes recanalization. Indeed, OF showed no correlation with clinical severity of PTS in this study. Therefore, APG may not be an appropriate evaluation method, given that reflex and occlusion may occur simultaneously in PTS. In contrast, NIRS can be used to measure the level of venous stasis in entire limbs during physiological exercise, regardless of whether reflex or occlusion is more closely associated with venous insufficiency.[7] Thus, NIRS is a very useful method for evaluation of severity in PTS with complex features.[7]

The factors involved in the onset of PTS have been widely examined, and some studies have included multivariate analysis.[20] Challenge is to establish the factors related to severity of PTS in a statistical manner. Comparison of the two groups with inclusion of certain factors and exclusion of one factor is possible, but a large number of subjects are needed for statistical significance using this method. Logistic regression analysis can be used only for two object variables, such as ‘alive’ and ‘dead’, and multiple linear regression analysis requires objective variables that are continuous and normally distributed. Since the severity of venous return insufficiency is classified into several levels and cannot be represented by continuous variables, neither of these analyses can be performed. Multivariate analysis is an alternative approach to exclude interactions among factors. Here we used this approach to examine individual factors thought to affect severity, using AVRI as the object variable that is a continuous variable and is significantly correlated with PTS severity. This analysis showed significantly higher AVRI values for the presence of a thrombus in the popliteal segment and irregular use of elastic stockings.

The correlation between thrombus location and PTS in patients with acute DVT has been studied extensively, but details differ from study to study due to differences in definition of location and various other biases. Using ultrasonography, Saarinen et al.[21] found no correlation between the location of thrombi and PTS in patients with acute phase DVT. Thrombus location was classified into only two regions: veins in the crural and the proximal veins. In contrast, Cohen et al.[22] showed that the incidence of PTS increased when a thrombus was located in the iliofemoral vein, but failed to examine popliteal and crural segment classifications. Strandness et al.[14] performed a prospective study in 65 limbs and reported a correlation between thrombi located in the popliteal vein or calf vein and prognosis of PTS, but again categories based on thrombi in popliteal and crural segments were not used. Monreal et al.[20] performed a logistic multivariate analysis in a 3-year prospective study of 84 limbs of patients with acute DVT, in which the lower extremity vein was divided into four segments, similarly to our study, and showed a correlation between thrombi in the popliteal vein and incidence of PTS, yet no correlation between incidence of PTS and extent of thrombi, similar to findings in our study. Franzeck et al.[11] found a low incidence of PTS in patients with DVT of the calf vein, based on a 12-year prospective study of 58 cases. Although findings regarding a correlation between the location of thrombi at the onset of DVT and development of PTS differ in the above studies, we consider that thrombi in the popliteal vein are of importance in this correlation. This may be because there is less collateral flow in the popliteal vein segment, although the iliac vein and the superficial femoral vein segments include the internal iliac vein and deep femoral vein, respectively. Poor prognosis is also observed in acute occlusion of the popliteal artery, and Moore et al.[23] emphasized the importance of popliteal vein function in showing that the popliteal venous valve works as “a gatekeeper for the calf muscle pump”. Our results support this suggestion, and we consider that treatment such as catheter-directed thrombolytic therapy in the acute phase should be used to prevent PTS development, because PTS may aggravate even after compression therapy or anticoagulant therapy in DVT patients with thrombi in the popliteal vein.

Compression therapy using elastic stockings is effective for chronic venous insufficiency and is widely used after the onset of DVT. Although mechanism underlying this therapy needs further clarification, it is thought to improve muscle pump function and microcirculation. Brandjes et al.[24] reported the effectiveness of compression stockings in reducing the incidence and rate of aggravation of PTS by 50% in a 2-year randomized study of 153 limbs. In our study, a significantly lower AVRI value was obtained with regular use of compression stockings, again showing the effectiveness of the therapy. We note that the subjects in the current study were patients for whom one year or longer had passed since onset of acute DVT; recanalization and reflux may occur within one year after onset, whereas significant changes in PTS symptoms are not evident one year after the onset of DVT. Despite that development of PTS has been reported to require more than three years.[25] Johnson et al.[2] found no difference in incidence of PTS symptoms between cases in which one and five years had passed since the onset of DVT. When NIRS was performed with elastic stockings, AVRI was frequently measured unsuccessfully because reduction in venous retention before exercise made a fall from the baseline to the bottom (E) smaller. Therefore, in this study NIRS was performed without compression stockings. We hypothesize that the reason for lower AVRI without compression in the patients with regular-use of stockings than those with irregular-use is the inhibition of venous dilation by long-term use of compression stockings or the promotion of recanalization by enhanced muscle pump function. Further investigation is required on this issue to verify this idea.

Finally, we note some limitations of the study. Firstly, the retrospective study design has the potential to introduce bias in the clinical severity of the subjects. Patients with no symptoms or mild symptoms are likely to suspend their visits to hospitals, therefore an incidence of symptoms and a rate of aggravation in the subjects may be higher than those for the entire patient population. Secondly, assessment of anticoagulant therapy at the onset of DVT was insufficient, and since the number of severe PTS cases appears to be decreasing, it is possible that anticoagulant therapy may contribute to prevention of PTS. In this study, it was difficult to collect the details of anticoagulant therapy, which may have affected the results. Thirdly, although the study was performed with the aim of examining correlations between various parameters and clinical severity in PTS, correlations of these parameters with AVRI were actually examined, for statistical reasons. Therefore, this difference from an actual correlation with clinical severity should be noted. Lastly, causative factors for severity in PTS makes the absence of previous our data significanct as the first evaluation of these factors.

Conclusions

A retrospective assessment of 51 limbs in PTS patients was performed to examine correlations between clinical parameters, such as thrombus location at the onset of DVT and compression therapy, and AVRI calculated using NIRS data, are significantly correlated with severity in PTS. Multivariate analysis showed that the presence of thrombi in the popliteal vein segment and the irregular use of elastic stockings were related to a higher AVRI. Therefore, use of compression stockings is recommended after the onset of acute DVT. In addition, further management of the condition is necessary because severe PTS may develop as a complication when only routine treatment is provided to acute DVT patients with thrombi in the popliteal vein.

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