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An association between residual vein thrombosis and subclinical atherosclerosis: Cross-sectional study

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ABSTRACT

Background: The association between venous and arterial thrombotic disorders is still unclear. We assessed the association between residual vein thrombosis (RVT) and subclinical atherosclerosis in a cohort of patients with unprovoked (or associated with weak risk factors) proximal deep-vein thrombosis (DVT).
Methods: In a multicenter cross-sectional study, consecutive patients over 40 years free from atherosclerotic disorders received the ultrasound assessment of the leg vein system and that of carotid arteries approximately three months after an episode of proximal DVT. In each center the evaluation was done by two independent assessors. The presence of RVT was defined as the incompressibility of at least 4 mm in either the popliteal or the common femoral vein, and that of subclinical atherosclerosis as the presence of increased (>0.9 mm) intima-media tickness (IMT) and/or carotid plaques.
Results: Out of 252 patients (mean age, 67; males, 53%; unprovoked, 77%), the presence of RVT was found in 139 (55.2%). An increased IMT was shown in 76 (54.7%) patients with and in 35 (31.0%) without RVT ($p < 0.001$). At least one carotid plaque was found in 80 (57.6%) patients with and in 36 (31.9%) without RVT ($p < 0.001$). After adjusting for the baseline characteristics, the odds ratio of subclinical atherosclerosis (increased IMT and/or carotid plaques) was 2.8 (95% CI, 1.6 to 4.7).
Conclusion: The ultrasound detection of RVT after an episode of proximal DVT that is either unprovoked or triggered by weak risk factors is associated with a higher prevalence of subclinical atherosclerosis. These findings may have implications for patient prognosis.

1. Introduction

In the last 15 years, the separate nature of arterial and venous thrombotic disorders has been questioned [1]. Arterial and venous thrombosis may share common risk factors [2], and may have a common origin in abnormalities of various blood constituents [3–5]. Patients with venous thromboembolism (VTE) are at an increased risk of subsequent arterial cardiovascular events over matched control individuals [6–15], the risk being definitely higher in those with unprovoked VTE [7,9,12–15]. The prevalence of subclinical atherosclerosis was also found to be higher in individuals with unprovoked VTE than in control individuals [16]. Finally, the ultrasound detection of residual vein thrombosis (RVT) has recently been shown to be a powerful and independent predictor of subsequent symptomatic atherosclerotic events [17].

In a cohort of patients with proximal deep vein thrombosis (DVT), unprovoked or triggered by weak risk factors, we assessed the occurrence of RVT, as shown by ultrasonography approximately three

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months after the acute event, and compared the prevalence of subclinical atherosclerosis between individuals with and without RVT.

2. Methods

A multicenter cross-sectional study was designed and conducted at nine third-level Angiology or Internal Medicine Centers in Italy between August 2014 and April 2016. Recruited patients gave their written informed consent, and the study protocol was approved by the Institutional Board of each participating Center. The study was conducted in accordance with the declaration of Helsinki.

2.1. Study population

Consecutive patients older than 40 with an episode of symptomatic proximal DVT, with or without clinical symptoms of pulmonary embolism, were eligible for the current investigation. Patients with DVT associated with major persistent or transient risk factors were excluded, as were those with previous symptomatic atherosclerotic disorders (such as acute myocardial infarction or angina, transitory ischemic attacks or stroke, peripheral artery disease) and those with recent (less than two years) episodes of ipsilateral DVT. Patients fulfilling these criteria were treated with either conventional or the newer anticoagulant drugs for at least three months.

2.2. Data collection

At the examination after three months (±two weeks), eligible patients were interviewed and then evaluated by two trained assessors blinded to each other.

The venous thrombotic event was categorized as being unprovoked or associated with weak risk factors of thrombosis (such as minor injury, arthroscopic or laparoscopic general surgery, short immobilization, long haul flight or estrogen therapy), and as being the first or a recurrent VTE episode. Additional information was also collected on risk factors for atherosclerosis: smoking habit (at least 10 cigarettes in a day within the past 30 days), obesity (body mass index ≥ 30), blood hypertension, diabetes mellitus or hyperlipidemia (based on the assumption of hypotensive, anti-diabetic or lipid-lowering drugs, respectively), family history of cardiovascular disease, use of statins or anti-platelet drugs.

Of the two assessors, the former investigated the proximal leg vein system in order to evaluate the presence of RVT. The latter investigated the carotid arteries in order to evaluate the presence of subclinical atherosclerosis as described below.

2.3. Ultrasound examination

The RVT was defined as the presence of a thrombotic burden of at least 4 mm in the transverse section under maximum compression in either the popliteal or the common femoral vein.

The ultrasound examination of carotid arteries was performed according to a standardized procedure [18]. IMT measurement was performed on the right and left common carotid arteries 1.0 cm proximal to the carotid bulb. An IMT value higher than 0.9 mm was considered positive [19]. The plaque was defined as a protrusion into the vessel lumen of at least 1.5 mm, as measured from the border between the adventitial and medial layer. The percentage of vessel obstruction was measured along the longitudinal axis and classified as stenosis < 20%, from 20 to 49%, from 50 to 69% and from 70 to 99% [18].

When more than one plaque was found, the highest obstruction degree was recorded, as well as the presence of bilateral lesions.

2.4. Statistical analysis

On the basis of the results of a pilot study, conducted in 50 patients, we estimated that a sample size of approximately 250 patients would result in a statistically significant odds ratio (OR) of subclinical atherosclerosis in individuals with as compared to those without RVT, as well as in a reasonably narrow confidence interval (CI) around the identified OR. All participating centers were asked to enroll patients until the estimated sample size was reached.

To compare the baseline characteristics between patients with and without RVT, we used the chi-square test for categorical variables and Student's *t*-test for continuous variables. The OR of asymptomatic atherosclerosis (with 95% CIs) was calculated with the use of the logistic regression, and adjusted for age, gender, risk factors of atherosclerosis, nature of DVT and clinical symptoms of PE.

The 95% CIs and p values were calculated according to the normal approximation of the binomial distribution. All calculations were performed with the use of SPSS software, version 22.0.

3. Results

3.1. Patients

Out of 427 consecutive patients with DVT referred to the participating centers during the study period, 70 were excluded for the presence of major risk factors of thrombosis, 49 because of a previous history of symptomatic atherosclerosis, 25 for age younger than 40, 17 for a recent previous ipsilateral DVT, and 14 for refusal of the informed consent. Therefore, we recruited 252 patients with proximal symptomatic DVT, which was unprovoked in 194, and associated with weak risk factors in the remaining 58 (estrogen therapy in 24, minor injury of the legs in 19, arthroscopic or laparoscopic general surgery in 9, short immobilization in 4, long haul flight in 2). The main demographic and clinical characteristics of the recruited patients are shown in Table 1.

3.2. RVT and subclinical atherosclerosis at the 3-month evaluation

The presence of RVT was detected in 139 (55.2%) patients. Patients with RVT had more frequently an unprovoked DVT (86.2% versus 73.5%, p = 0.01) and a DVT associated with clinical symptoms of PE (59.7% vs 27.4%; p < 0.001). Table 2 summarizes the main features of patients with and without RVT.

An IMT higher than 0.9 mm was detected in 111 patients (44%), while at least one carotid plaque was shown in 116 subjects (46%). Among subjects with RVT, 76 (54.7%) had an IMT higher than 0.9 mm, 80 (57.6%) had at least one carotid plaque, and 49 (35.3%) had bilateral lesions; among subjects without RVT, the corresponding features were 35 (31%), 36 (31.9%) and 18 (15.9%), respectively. The characteristics of the carotid plaque producing the greatest degree of obstruction are

Table 1
Main demographic and clinical characteristics of the recruited patients.

Features	Patients (N = 252)
Age (mean ± SD)	67.2 ± 12.8
Male sex	133 (52.8)
Type of event	
DVT only	130 (51.6)
DVT + PE	122 (48.4)
Nature of event	
Unprovoked	194 (77.0)
Provoked	58 (23.0)
DVT localization	
Popliteal only	101 (40.1)
Common femoral only	21 (8.3)
Popliteal and femoral	130 (40.1)
BMI ≥ 30	58 (23.0)
Blood hypertension	117 (46.4)
Diabetes mellitus	38 (15.1)
Hyperlipidemia	78 (31.0)

SD = standard deviation; DVT = deep vein thrombosis; PE = pulmonary embolism; BMI = body mass index.
Number in parenthesis indicates percentages.