

# Is the fibrotic parietal thickening a reliable parameter for diagnosing previous asymptomatic deep vein thrombosis?



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## Is the fibrotic parietal thickening a reliable parameter for diagnosing asymptomatic deep vein thrombosis?

AIM: Research of a starting point to debate about the possibility of identifying a unique sign of previous DVT.

MATERIAL OF STUDY: A retrospective study involving 202 outpatients with venous insufficiency of the lower limbs (CEAP classes C 4/6), classified according to the affected venous district. Patients positive for deep vein thrombosis (DVT) were subjected to Compression Ultra Sound test (CUS test) with measurement of the wall thickness at the point of formation of the thrombus and at fixed points of common femoral and popliteal veins used also in the patients with negative history of DVT

RESULTS: Among total group, only 19 patients (9.40%) had an history of DVT. No one of them had a superficial incontinence. The measurement of wall thickness in positive DVT history patients (group A) resulted in an average value of 1.10 mm (s.d.=0.06), while the average value obtained in negative DVT history (group B) was 0.55 mm (s.d.= 0.20). However, in 13 patients wall thickness was > 1mm (mean: 1.04 mm). The difference between the averages of group A and B was statistically significant ( $p < 0.05$ ).

DISCUSSION: In all positive DVT history patients and in 13 ones with negative history we found an increase in wall thickness, with a value > 1 mm. Can the wall thickening more than 1 mm be considered an indicator of previous DVT? Can it be considered a "marker" for thrombophilia status?

CONCLUSIONS: The usefulness of a sign of previous DVT (even if asymptomatic), detected during a routine Doppler ultrasound check of lower limbs, could be a warning bell to investigate thrombophilia status.

KEY WORDS: Chronic Venous Insufficiency, Duplex ultrasound, Hypercoagulability, Post-thrombotic Syndrome, Venous Thromboembolism

## Introduction

The aim of our study is to identify a measurable and reproducible parameter (like the carotid Intima-Media

Thickness (IMT) is for cardiovascular risk) useful to determine whether a patient developed a previous deep vein thrombosis; this could be useful especially in cases in which clinical history is negative, but the patient experiences symptoms and signs attributable to a post-phlebotic syndrome. In the international scientific literature there are no studies focused on this aspect of this syndrome.

The term postthrombotic syndrome (PTS) indicates a situation of chronic venous insufficiency, clinically manifested in patients with an history of deep vein thrombosis (DVT); PTS is the most common complication of DVT. 20% to 50% of patients with DVT develop PTS.

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Both the upper and lower limbs may develop this complication; however PTS in upper limbs does not exceed 15% of cases<sup>1</sup>.

Causes are not fully understood; however, two factors are certainly involved: the effect of inflammatory proteins and thrombus which contributes to valve destruction and the incomplete recanalization of venous vessels which leads to an altered blood drain<sup>2,9</sup>.

Various situations may occur:

1. Substituting Syndrome: failed lysis of the thrombus in presence of a pervious collateral circulation with consequent is the formation of compensatory superficial varicose veins;
2. Obstruction Syndrome: failed lysis of the thrombus without a collateral blood supply, with consequent obstruction to the venous blood outflow;
3. Recanalization syndrome: lysis of the thrombus and valvular destruction followed by impaired venous blood outflow and reduction of venous pressure during muscle pump work;
4. Mixed Syndrome:
  - a. recanalization + substitution,
  - b. obstruction + substitution<sup>3</sup>.

The lower limbs PTS is an high social costs disease, disabling, affecting the overall patient's quality of life.

The symptoms of PTS are characterized by feeling of heaviness in the lower limbs, pain, cramps, itching, numbness. Characteristic signs are: edema, dermal-liposclerosis, hyperpigmentation, venous ectasia, redness, ulcers<sup>5</sup>.

Signs and symptoms can be quantized with a score (except the ulcer, which is referred to as absent / present) from 0 (absent) to 3 (severe), as part of Villalta Score<sup>6-7</sup>. The sum of the scores gives the possibility to stage the disease: 0-4 = no disease, 5-9 = slight PTS, 10-14 = moderate PTS, > 15 = severe PTS.

## Materials and Methods

In our study we carried out a retrospective analysis on patients with chronic venous insufficiency of the lower limbs seen as outpatients at Vascular Pathology Ambulatory - Department of Endocrinology, Gastroenterology and Surgery of the Federico II University Hospital - Naples, from January 2011 to December 2013.

All outpatients, at the first visit, are routinely scheduled for pathology, address, telephone number, and email address. We contacted all patients with venous insufficiency of lower limbs, visited in the above indicated period, for a free control. After a preliminary visit, we asked to the patients, classified on the basis of symptoms and signs attributable to the CEAP C4 / C6, the willingness to undergo an ultrasound duplex control of the lower limbs. Among the 308 contacted patients, 223 were eligible and 202 gave their availability (126 female and 76 male). None of the patients called to visit had signs and symp-

toms attributable to DVT at the time of evaluation, but our study was done on a pool of patients who, according to the presented symptoms, and after the quantization of the CEAP score (and successively of Villalta score), could be regarded as potentially suffering from post-thrombotic syndrome.

All patients were evaluated by duplex ultrasound, using a 7.5 mHz linear probe, using an ESAOTE™ My Lab 40™: the reflux was considered pathological if, in Pulsed Wave mode, we obtained a reflux longer than 0,5 seconds<sup>8</sup> during the Valsalva maneuver in the standing position. We also performed a Compression Ultra-Sound (CUS) Test on the whole femoropopliteal venous axis and a systematic measurement of the wall thickness at pre-fixed segments of femoral and popliteal veins: immediately distal to the sapheno-femoral junction (for the femoral vein and in correspondence of the popliteal crease for the popliteal vein) and saphenous-popliteal junction<sup>9</sup>. Measurement also took place in the area of localization of previous thrombosis, in cases of a positive history for DVT. Measurement was performed in supine position; the probe was placed longitudinally to the vessel to be scanned, so that the major axis of the probe was parallel to the vessel; in this way we had the possibility to scan a relatively long tract of the vessel and evaluate the trend of the local wall thickness. The segment of the common femoral vein situated at 1 cm proximally (hemodynamically) from the sapheno-femoral junction and the segment of the popliteal vein situated at 1 cm distally to the origin of genicular veins, were used as points of screening.

In correspondence of wall thickness increasing area, the venous segments showed no residual intra-luminal thrombosis; the transition from the section with normal thickness, to the one with increased thickness is gradual, without any "step"; the surface of the thickened section does not show irregularities and appears to be essentially linear; these segments always showed a reflux, with an average duration of 1.27 (s.d. = 0.15) seconds, and an average flow rate of 18.24 (s.d. = 0.30) cm/s in the first second. After the hemodynamic study, patients were stratified according to the affected venous district.

Within each group, it was considered a subset of patients with an history of DVT (if present). The diagnosis of eventual previous DVT was formulated on anamnestic data and, if available, reports of previous Duplex US examinations performed at the time of onset of symptoms (if performed in other facilities). This means that our Duplex US examination was performed on veins not affected, at the time, from thrombotic events and / or on re-channelled veins.

## Results

Patients involved in this study showed the following distribution according to C.E.A.P classification: C4: 123

TABLE I - *Distribution of patients according to CEAP-C class.*

	CEAP C 4	CEAP C 5	CEAP C 6	Total
N. of patients	123 (60.89%)	33 (16.33%)	46 (22.78)	202

patients (60.89%), C5: 33 patients (16.33%), C6: 46 patients (22.78%). The average age of patients was 66.7 years (Table I)

After stratification, we found that 27 patients (13.36%) had valvular incontinence in the superficial venous circulation, 59 patients (29.20%) had valvular incontinence only in the deep venous circulation and 116 patients (57.44%) had both the superficial and the deep circulation affected.

Only 19 patients (group A) (9.40%) had an history of DVT (patients with no history of DVT were included in group B).

Among these 19 patients, according to the previous hemodynamic evaluation, 14 patients (73.68%) had a mixed valvular incontinence (superficial / deep), while 5 patients (26.32) had a valvular incontinence involving only deep venous system.

The measurement of wall thickness in patients with positive history for DVT resulted in an average value of 1.10 mm (s.d.=0.06).

The average value obtained from the measurement of wall thickness in the patients with no history of DVT (group B) was 0.56 mm (s.d.= 0.20 mm). However, in this group there is a subset in which 13 patients (6.44%) showed an higher (> 1 mm) wall thickness (mean: 1.07 mm; sd= 0.04). Of these, 8 patients showed both superficial and deep venous insufficiency, 3 only deep vein insufficiency and the remaining ones only superficial venous insufficiency (Table II).

We performed a z-test on mean values of the wall thickness among A and B groups, which resulted statistically significant ( $p < 0.05$ ); then, we performed a z-test on average values of wall thickness between the subset of B group with a thickness > 1 mm and B group itself, which resulted statistically significant; finally, we performed a z-test between mean values of wall thickness of A group and the subset of the B group, which resulted not statistically significant ( $p > 0.05$ ).

## Discussion

The majority of patients (57.44%) evaluated in this study suffered from a chronic venous insufficiency, with both superficial and deep circulation impairment. If we exclude the minority of patients with only a superficial venous incontinence, it is clear that 86,64% of our patients attributable to CEAP- C classes 4-6 were affected from deep venous incontinence.

Of these patients, we know, with certainty, that 19 suffered from DVT. This, however, does not exclude that patients with no history of DVT suffered from an asymptomatic/subclinical episode of DVT. Ciuti et al<sup>10</sup> reported an incidence of 16% of DVT in a cohort of asymptomatic patients at the time of admission to a Department of Internal Medicine; in Pennell et al.<sup>11</sup> is reported a 34% incidence of DVT in the asymptomatic limb, contralateral to the one affected by DVT, in patients at high risk for thrombosis and 16% for the contralateral limb ambulatory patients with DVT.

According to our observation, in all patients with a history of DVT we found an increase in wall thickness, with a value always greater than 1 mm.

In support of this observation, Forauer<sup>12</sup> et al examined the histological changes in the wall of the veins that

TABLE II - *Distribution of patients according to the affected venous district and history of DVT with average wall thickness.*

		Superficial Vein Insufficiency	Deep Vein Insufficiency	Superficial + Deep Vein Insufficiency	Mean Wall Thickness
Patients with history of DVT (A Group)	0	0	5 (2.46%)	14 (6.94%)	1.10 mm (s.d.=0.06)
Patients with no history of DVT with wall thickness < 1 mm	26 (12.87%)	26 (12.87%)	51 (25.26%)	94 (46.54%)	0.56 mm (s.d.=0.20)
no history of DVT (B Group)	Patients with no history wall of DVT and thickness > 1mm (B Group Subset)	1 (0.49%)	3 (1.48 %)	8 (3.96%)	1.07 mm (s.d.=0.04)



Fig. 1: Wall thickness (pathological) common femoral vein

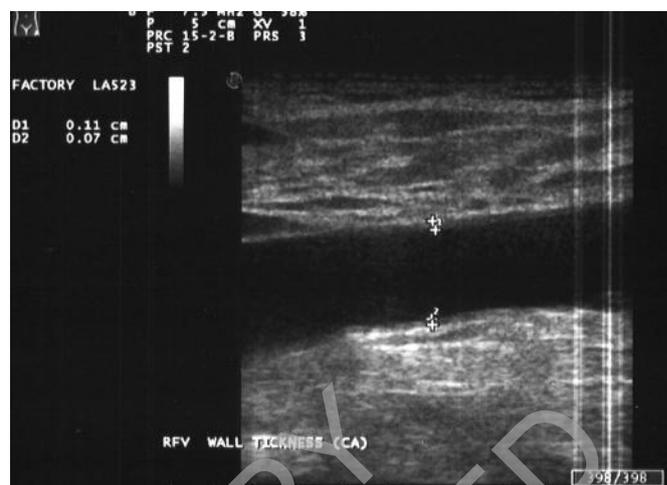


Fig. 3: Wall thickness (subset B patient) common femoral vein



Fig. 2: Wall thickness (not pathological) common femoral vein



Fig. 4: Wall thickness (pathological) common femoral vein 34 days post-DVT

have been affected by a thrombotic process induced by the insertion of a catheter. The inflammatory reaction, due to the presence of the thrombus immediately determines an endothelial reaction which stimulates, subsequently, a proliferation of smooth muscle cells of the wall with an increasing in thickness.

The difference between mean values of wall thickness between Groups A and B and between B Group and its subset is statistically significant. Group B includes a quota of 13 patients that, in theory, had to be included in A group if we consider their values of wall thickness.

## Conclusions

From this retrospective study we deduced that a medium/high severity lower limbs was chronic venous insufficiency, in a cohort of 202 outpatients, configure, approximately, as post-thrombotic syndrome in 10% of cases. This percentage, supported by medical history, can,

however, underestimate the actual value of the post-thrombotic syndromes, as there is the occurrence of asymptomatic DVT. The parietal fibrotic thickening which we constantly found in patients positive for previous DVT, could be considered a sonographic sign interpretable as a target of previous asymptomatic DVT. However, it would be interesting a follow-up of patients with symptomatic DVT to detect the evolution of the thrombus and the changes of the wall. This evaluation, at fixed intervals, could show us how the wall thickening changes over time, reaching the maximum value, then decreasing. This could give us information in order to determine "if" and "when" DVT occurred and what is its pathological state.

A sign of previous DVT, detected during a routine Doppler ultrasound check of the lower limbs, could lead to evaluate patients who never were symptomatic for DVT, with an increase in wall thickness, for thrombophilia, alerting the clinician to engage in diagnostic assessment and prophylactic measures to prevent a recurrence of DVT.

## Riassunto

Lo scopo di questo studio è quello di fornire un punto di partenza per discutere circa la possibilità di individuare un segno ultrasonografico suggestivo di pregressa Trombosi Venosa Profonda (TVP).

Abbiamo effettuato uno studio retrospettivo che coinvolge 202 pazienti ambulatoriali con insufficienza venosa degli arti inferiori (CEAP classi C 4/6), classificati in base al distretto venoso interessato. I pazienti positivi per TVP sono stati sottoposti ad un CUS test con misurazione dello spessore della parete nel punto interessato dal trombo e in punti specifici della vena femorale comune e della vena poplitea; tali punti sono stati utilizzati anche nei pazienti con anamnesi negativa per TVP

Dell'intera popolazione esaminata, solo 19 pazienti (9,40%) presentavano in anamnesi un episodio di TVP, e nessuno di essi aveva una incontinenza del circolo superficiale. La misurazione dello spessore parietale, a 1 cm di distanza prossimalmente (in senso emodinamico) all'ostio safeno-femorale e a 1 cm distalmente allo sbocco delle vene gemellari sulla vena poplitea, nei pazienti con anamnesi positiva (gruppo A) ha dato come risultato un valore medio di 1,10 mm (sd = 0,06), mentre il valore medio delle misurazioni eseguite nei medesimi punti ottenuto nei pazienti senza anamnesi di TVP (gruppo B) è stato pari a 0,55 mm (sd = 0,20). Tuttavia, in 13 pazienti con anamnesi negativa il valore medio dello spessore della parete è stato > 1mm (media: 1,04 millimetri). La differenza tra le medie del gruppo A e B è statisticamente significativa (p <0,05). La differenza tra la media dei valori misurati nel gruppo A e il sottogruppo della popolazione B con spessore parietale > 1mm non è statisticamente significativa. È lecito supporre che i pazienti del sottogruppo B avessero sofferto una trombosi venosa profonda asintomatica. Per questo motivo, la nostra ipotesi è che l'ispessimento parietale oltre 1 mm potrebbe essere considerato un indicatore di pregressa TVP. In linea con quanto supposto si potrebbe anche valutare di considerare l'ispessimento parietale "marker" per un maggior rischio di trombosi venosa profonda.

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