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ECHOGENICITY OF THROMBOTIC MASSES IN PATIENTS WITH VARICOSE VEINS OF THE LOWER LIMBS COMPLICATED BY ACUTE SUPERFICIAL VENOUS THROMBOSIS

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Summary.

Introduction. Previous studies have revealed that measuring thrombus echogenicity could be useful in managing patients with deep vein thrombosis of lower limbs. Our study aimed to analyse the echogenicity of thrombi in subjects with superficial vein thrombosis (SVT) and varicose veins.

Materials and methods. Duplex ultrasound was performed in 50 patients with varicose veins and SVT of both the trunk of the great saphenous vein and the subcutaneous tributaries. A series of images of the thrombi from the trunk and varicose tributaries were captured and analyzed in Adobe Photoshop®, CS6.0 (Adobe Systems, USA), and the grey scale median (GSM) thrombus echogenicity was determined using the „*lasso tool*" and „*histogram*".

Results. Varicose tributary thrombus had a significantly higher echogenicity compared to saphenous trunk thrombus: 69.2±17.2 (95% CI 64.4-74.2) *vs*. 46.4±14.8 (95% CI 42.2-50.6) GSM units, p<0.0001. GSM values in varicose branches demonstrated a strong positive correlation (*r*=0.79 [95%CI 0.65-0.87], p<0.0001) with the time since the onset of SVT, while the echogenicity of the thrombus in the trunk had only a moderate correlation (*r*=0.42 [95%CI 0.16-0.63], p<0.01). In the linear regression model, assessing the dynamics of echogenicity depending on the duration of SVT, the R^2 coefficient was three times higher for the tributaries – 0.54 *vs*. 0.18 for the trunk. Thrombus echogenicity increased with each day from the onset of the disease: by +3.4±0.4 GSM units in tributaries (p<0.0001) and by +1.7±0.5 GSM units in the trunk (p<0.01). There were no significant differences in GSM values in patients of different gender, age and body mass.

Conclusion. Significantly higher echogenicity of the thrombotic masses in the subcutaneous varicose tributary compared with that of the saphenous thrombus, as well as the strong positive correlation of echogenicity with SVT duration, point to the secondary character of involvement of the superficial vein trunks and centripetal progression of thrombosis.

Keywords: thrombus echogenicity, duplex ultrasound, superficial vein thrombosis, varicose veins.

Rezumat. Ecogenitatea maselor trombotice la pacienții cu varice primare ale extremităților inferioare complicate cu tromboză venoasă superficială acută.

Introducere. Cercetările anterioare au relevat că determinarea ecogenității trombului ar putea fi utilă în managementul pacienților cu tromboză venoasă profundă a membrelor inferioare. Studiul nostru a urmărit să analizeze ecogenitatea trombilor la subiecții cu tromboză venoasă superficială (TVS) și boală varicoasă.

Material și metode. Ultrasonografia duplex a fost efectuată la 50 de pacienți cu varice și TVS atât a trunchiului venei safene mari, cât și a tributarelor subcutanate. O serie vastă de imagini ale maselor trombotice din trunchiul safenian și din afluenții varicoși au fost capturate și analizate în Adobe Photoshop®, CS6.0 (Adobe Systems, SUA), iar ecogenitatea trombului exprimată în unități *grey scale median* (GSM) a fost determinată utilizând opțiunile „*lasso tool*" și „*histogram*".

Rezultate. Trombii tributarelor subcutanate varicoase au prezentat o ecogenitate semnificativ mai mare în raport cu masele trombotice din trunchiul safen: 69,2±17,2 (95% CI 64,4-74,2) *vs*. 46,4±14,8 (95% CI 42,2-50,6) unități GSM, p<0,0001. Valorile GSM de la nivelul venelor subcutanate varicoase au demonstrat o corelație pozitivă puternică (*r*=0,79 [95%CI 0,65-0,87], p<0,0001) cu timpul de la debutul TVS, în timp ce ecogenitatea trombului în trunchi a prezentat doar o corelație moderată (*r*=0,42 [95%CI 0,16-0,63], p<0,01). În modelul de regresie liniară, evaluând dinamica ecogenității în funcție de durata TVS, coeficientul R^2 a fost de trei ori mai mare pentru tributarele subcutanate – 0,54 *vs*. 0,18 pentru trunchiul venei safene mari. Ecogenitatea trombului a crescut în fiecare zi de la debutul TVS: cu +3,4±0,4 unități GSM în tributare subcutanate (p<0,0001) și cu +1,7±0,5 unități GSM în trunchi (p<0,01). Nu au fost identificate diferențe semnificative ce țin de valorile GSM la pacienții de gen, vârstă și masă corporală diferite.

Concluzie. Ecogenitatea semnificativ mai mare a maselor trombotice din tributarele varicoase subcutanate comparativ cu cea a trombului safenian, precum și corelația pozitivă puternică a ecogenității cu durata TVS indică asupra caracterului secundar al afectării trunchiurilor venoase superficiale și progresiei centripete a trombozei.

Cuvinte cheie: ecogenitatea trombului, ultrasonografie duplex, tromboză venoasă superficială, vene varicoase.

Резюме. Эхогенность тромботических масс у пациентов с варикозной болезнью нижних конечностей, осложненной острым тромбозом поверхностных вен.

Введение. Предыдущие исследования показали, что анализ эхогенности тромба может быть полезен при ведении пациентов с тромбозом глубоких вен нижних конечностей. Целью нашего исследования был анализ эхогенности тромбов у пациентов с тромбозом поверхностных вен (ТПВ) и варикозной болезнью.

Материалы и методы. Дуплексное ультразвуковое исследование было проведено 50 пациентам с варикозным расширением вен и ТПВ как ствола большой подкожной вены, так и подкожных притоков. Серия цифровых изображений тромботических масс в стволе и варикозных венах была проанализирована в программе Adobe Photoshop®, CS6.0 (Adobe Systems, США), определяя эхогенность тромба (в единицах GSM) с помощью функций «*lasso tool*» и «*histogram*».

Результаты. Тромб в варикозных притоках имел значительно более высокую эхогенность по сравнению с тромбом в стволе вены: 69,2±17,2 (95%CI 64,4-74,2) против 46,4±14,8 (95%CI 42,2-50,6) единиц GSM, p<0,0001. Значения GSM в варикозных подкожных ветвях продемонстрировали сильную положительную корреляцию (*r*=0,79 [95%CI 0,65–0,87], p<0,0001) со временем с момента возникновения ТПВ, в то время как эхогенность тромба в стволе показала лишь умеренную корреляцию (*r*=0,42 [95%CI 0,16-0,63], p<0,01). При построении модели линейной регрессии, оценивающей динамику эхогенности в зависимости от длительности ТПВ, коэффициент R^2 был в три раза выше для притоков – 0,54 в сравнении с 0,18 для ствола. Эхогенность тромба увеличивалась с каждым днем с момента начала заболевания: на +3,4±0,4 единицы GSM в притоках (p<0,0001) и на +1,7±0,5 единиц GSM в стволе (p<0,01). Не было выявлено значимых различий в значениях GSM у пациентов разного пола, возраста и массы тела.

Выводы. Значительно более высокая эхогенность тромботических масс в подкожных варикозных притоках по сравнению с эхогенностью тромба в стволе большой подкожной вены, а также сильная положительная корреляция эхогенности с продолжительностью ТПВ указывают на вторичный характер вовлечения венозных стволов и центростремительное прогрессирование тромбоза.

Ключевые слова: эхогенность тромба, дуплексное ультразвуковое исследование, тромбоз поверхностных вен, варикозное расширение вен.

Introduction.

Acute thrombosis of the superficial veins of the lower extremities occurring in subjects with pre-existing varicose vein disease, also called superficial thrombophlebitis (ST), is characterized by a varied incidence ranging from 3% to 11% in the general population [1, 2, 3]. Formerly considered a benign, self-limiting disease, acute ST is now regarded as a condition with an unpredictable clinical course. Moreover, publications from the specialized scientific literature highlight a surprisingly high rate of associated thromboembolic events [4, 5, 6, 7]. A timely diagnosis and prompt initiation of treatment seem to be the solutions to stop the progression of thrombosis and reduce the frequency of embolic complications. Current guidelines recommend duplex ultrasound (DUS) as the diagnostic method of choice for monitoring the clinical evolution and treatment of venous diseases [8]. However, the investigation protocol is basically focused on identification and characterization of pathological venous reflux, determination of the spectral Doppler waveform using calipers and diameter measurements [9]. When clinical symptoms of ST occur, DUS aims to confirm the presence of thrombosis in the superficial venous system with the specification of the extension of masses along the saphenous trunks and/or subcutaneous varicose tributaries, as well as to verify the patency of deep veins. One of the ultrasonographic characteristics of venous thrombotic masses is echogenicity, although its measurement is not routinely performed in real daily medical practice. The echogenicity changes throughout the course of ST, progressively amplifying as a result of fibrotic organization and transformation of the intraluminal blood clot. Therefore, evaluation by DUS could allow a rough estimation of the age of the thrombotic masses (fresh thrombus, organizing or old thrombus).

The aim of the present research was to study the initial evolution of the thrombotic process in the superficial venous system of the lower extremities in patients with pre-existing varicose veins by analyzing the relative echogenicity of thrombotic masses.

Material and methods.

Study was conducted at the Department of General Surgery „*Nicolae Anestiadi*" of „*Nicolae Testemitanu*" State University of Medicine and Pharmacy (Vascular Surgery Clinic, Institute of

Emergency Medicine; and General Surgery Clinic, Municipal Clinical Hospital „*Gheorghe Paladi*", Chisinau, Republic of Moldova), and included 50 adult patients, hospitalized during the period 2018-2020, with primary episode of ST of the lower limbs. As acute was considered thrombosis with duration of clinical manifestations up to and including 14 days. The diagnosis was confirmed in all cases by DUS performed with ultrasound scanners: Toshiba Nemio XG SSA-580A (Toshiba Corporation, Tokyo, Japan) and Mindray M9 (Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China), using the 7-12 MHz linear transducer. For the study were selected patients with thrombosis in both the trunk of the great saphenous vein and its varicose tributaries. The median value of thrombus echogenicity expressed in *gray scale median* (GSM) units was determined based on DUS results in order to compare the age of thrombotic masses at the level of the tributaries and in the saphenous trunk. Within the study to quantitatively assess the degree of echogenicity of thrombi in superficial veins, the method proposed by Zhao *et al.* for monitoring the resolution of deep vein thrombosis was used [10]. Multiple digital images of thrombosed veins at the saphenous trunk and tributary level were captured during DUS. For further analysis, images with the highest degree of resolution and reduced artifact („*noise*") were selected. The basic settings of the ultrasound scanner (dynamic range, frame rate, gain) were not changed during the entire study. The stored images were subsequently processed in Adobe Photoshop®, CS 6.0 (Adobe Systems, USA). After conversion of the images to grayscale, their contrast and brightness levels were standardized, setting the fluid blood in the lumen of the vein as a black reference point and the perivenous adventitia – as a white reference point. At the next phase, the edges of the intraluminal thrombus were outlined with the „*lasso tool*" and, using the „*histogram*" function, the median echogenicity value was determined. At the initiation stage of the investigation, 20 images of thrombotic masses were repeatedly evaluated by the same investigator to assess the degree of agreement between measurements.

All data obtained during the study were entered into the digital database created in Microsoft® Excel® 2016 MSO (16.0.13029.20450). Continuous variables are presented as median with interquartile range Q_1-Q_3 (25%-75% IQR). Mean values are accompanied by standard deviation (±SD) and 95% confidence intervals (95%CI). A difference plot (Bland–Altman) was used in analyzing the agreement between two different assays. The degree of correlation between two or more variables, reflecting the coordinated concomitant change of two assessed indicators, was determined on the basis of correlational analysis: *r* Spearman coefficient (in asymmetric distribution of data). The result of the analysis was interpreted according to widely accepted criteria in biomedical studies: negative or positive *r*-value from 0.1 to 0.2 was considered as weak correlation, from 0.3 to 0.5 – as moderate, from 0.5 to 0.7 – as strong and ≥0.8 – as very strong. Correlation was considered statistically significant at p-values <0.05 [11]. In case of determination of the existence of a true correlation between the variables, a linear regression model was constructed to study the influence of the explanatory variable on the dependent one. The model was considered statistically appropriate at values $p<0.05$ and coefficient $R^2>0.5$; whereas the degree of influence of the predictor variable was evaluated by the regression coefficient (*slope*).

The project of the scientific study was approved by the Research Ethics Committee of „*Nicolae Testemitanu*" State University of Medicine and Pharmacy, Chisinau, Moldova (favorable decision no.38 issued on 12.02.2018).

Results.

The study group included 32 (64%) women and 18 (36%) males. The age of the subjects ranged from 31 to 82 years, with the median value – 60 (25%-75%IQR 51-67) years. Duration of ST from onset of clinical signs to hospitalization constituted 6 (25%-75%IQR 4-10) days. The thrombus echogenicity expressed in GSM units ranged in the saphenous trunk from 21 to 91, and at the level of subcutaneous varicose tributaries – from 44 to 110.

The analysis of the degree of agreement between repeated measurements of echogenicity by the same evaluator using the Bland–Altman plot demonstrated an acceptable reproducibility of the method, the mean value of the difference being 0.45 (Figure 1).

Analysis of the digital images showed that thrombotic masses in varicose tributaries have significantly higher echogenicity compared to the thrombus in the saphenous trunk – 69.28±17.2 (95%CI 64.39-74.17) *vs*. 46.4±14.84 (95%CI 42.18-50.62) GSM units, respectively ($p<0.0001$). GSM values determined at the level of varicose veins showed a strong positive correlation (r_s=0.79 [95%CI 0.65-0.87], $p<0.0001$) with time from the onset of ST, while thrombus echogenicity in the saphenous trunk had only a moderate correlation with this variable (r_s=0.42 [95%CI 0.16-0.63], $p<0.01$). Respectively, in the linear regression model designed to assess the dynamics of the change in median echogenicity depending on the duration of ST, the coefficient of

determination R^2 was three times higher for the „tributary" curve: 0.54 *vs*. 0.18 – for the „trunk" curve (Figure 2).

Elaborated statistical models confirmed the progressive increase of thrombus echogenicity in superficial veins with each day after the onset of ST: by +3.43±0.45 GSM units in the tributary ($p<0.0001$) and by +1.75±0.52 GSM units in the trunk ($p<0.01$). No statistically significant differences were determined between GSM values in patients of different gender, age and body mass (data are not presented).

Discussion.

Depending on the amount of fibrin, thrombotic masses in the venous lumen analyzed ultrasonographically can present anechoic, hypo- or hyperechoic character. Based on the large experience with DUS examination of patients with deep vein thrombosis, it is well known that in the process of reorganization and natural transformation of thrombi their echogenicity progressively increases – from homogeneous hypoechoic intraluminal inclusions in the early period to heterogeneous and predominantly hyperechoic structures in the late stage [12, 13].

In the clinical context the data obtained during our study can be interpreted as evidence of the initial formation of thrombotic masses in varicose veins with their eventual extension and secondary involvement of the saphenous trunk. The much weaker correlation of saphenous trunk GSM values with days from the onset of ST indicates that after the occurrence of thrombosis in varicose tributaries the further progression of the thrombotic process has individual variability. This means that both the risk of the development of the truncular form of ST and the time needed for the thrombus to pass from the tributaries to the trunk, with the latter extending along

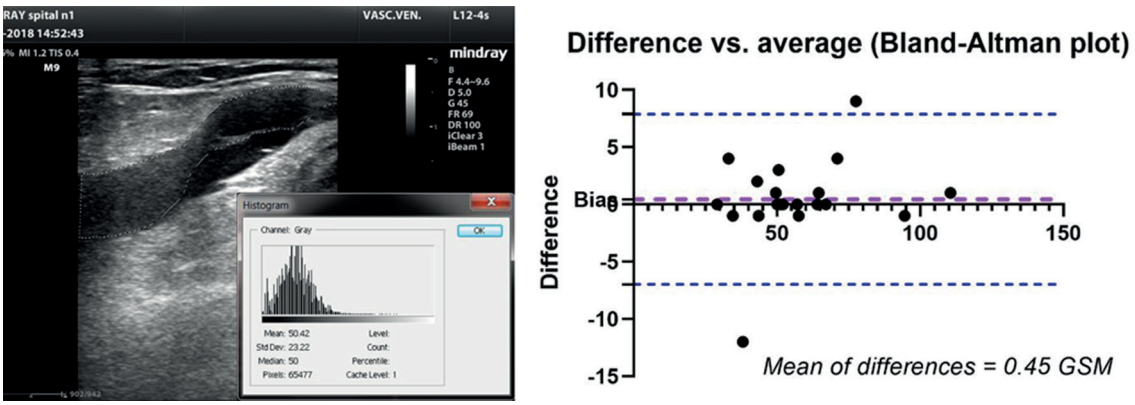

Figure 1. Echogenicity assessment of thrombotic masses using Adobe Photoshop® (left) and analysis of method reproducibility (right).

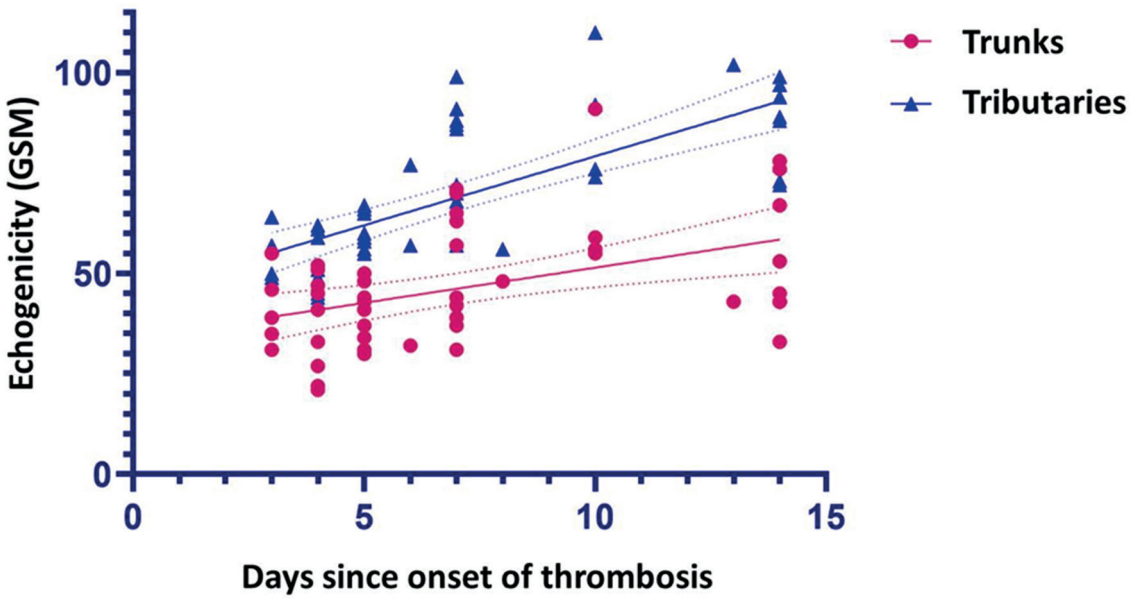

Figure 2. Linear regression curves (with 95%CI) demonstrating increasing echogenicity of thrombotic masses in varicose tributaries and saphenous trunk depending on the duration of disease.

the saphenous axis, differ from case to case, being influenced by factors that are yet to be identified.

There are a limited number of publications in the medical literature dedicated to assessing the ecogenicity of thrombotic masses in patients with deep vein thrombosis. Zhao *et al*. studied the echogenicity of thrombi within deep veins of lower limbs in 25 patients, reporting an initial median value of 59 GSM units, which occupies an intermediate position between the data obtained in our study for ST at the saphenous vein trunk level and tributaries [10]. In our cohort of patients with ST, the median echogenicity value calculated jointly for tributaries and trunks was almost identical to that established by Zhao *et al*. in deep vein thrombosis – 57.84±19.69 GSM units. Similar to current research, the authors did not observe any correlations between patient demographics and thrombus echogenicity. Conversely, the echogenicity growth rate of thrombotic masses reported by Zhao *et al.* is significantly lower, and constitutes only +0.36±0.23 GSM units per day. This difference can be explained by the slower progression of deep vein thrombosis and the fact that the dynamics of echogenicity in that study were evaluated on the background of curative doses of anticoagulants. Unfortunately, the mentioned article lacks data on the time since the onset of thrombosis, which makes more difficult the interpretation of the results. Another research study reported by Mazetto *et al.* demonstrated that the presence of thrombotic masses with very low echogenicity (<24 GSM units) in the lumen of deep veins is an independent risk factor for thrombosis recurrence, with a positive predictive value of 75% [14].

To the best of our knowledge, at the time of the study, there were no publications in the available literature on the analysis of thrombus echogenicity in patients with ST. Nevertheless, based on DUS data and quantitative analysis of thrombi echogenicity, our study confirmed the progression of ST from varicose tributaries to the trunk and secondary involvement of great saphenous vein, associated with the accelerated growth of the thrombus. Although the routine implementation of ecogenicity measurement in daily practice seems to be difficult from a methodological point of view, in our opinion, further research is needed in this direction to monitor the evolution of ST under the influence of different conservative treatment regimens.

Conclusions.

The significantly higher echogenicity of thrombotic masses in subcutaneous tributaries compared to that of great saphenous vein thrombus, as well as the strong positive correlation of echogenicity with ST duration, indicates the secondary nature of superficial venous trunk involvement and centripetal progression of thrombosis.

The results of the study were submitted in the abstract form to be considered for an e-poster presentation at the 2nd Venous Symposium Europe (Athens, October 30th - November 1st, 2025).

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