

ORIGINAL ARTICLE

Orthostatic-loading-induced transient venous refluxes (day orthostatic loading test), and remedial effect of micronized purified flavonoid fraction in patients with telangiectasia and reticular vein

Yurii T. TSUKANOV*, Aleksandr I. NIKOLAICHUK

Department of Surgical Diseases, Omsk State Medical University, Omsk, Russia

*Corresponding author: Yurii T. Tsukanov, Department of Surgical Diseases, Omsk State Medical University, ul. Lenina 12, 644043, Omsk, Russia.
E-mail: yutsokanov@mail.ru

ABSTRACT

BACKGROUND: Orthostatic loading can induce transient venous reflux (TVR). Among patients with telangiectasia and reticular varices, we determined the proportion that developed TVR after a day of orthostatic loading (DOL test), and investigated the remedial effects of micronized purified flavonoid fraction (MPFF).

METHODS: All 96 patients enrolled in this study had telangiectasia and reticular varices. Patients underwent duplex scanning (DS) in the morning and evening, and vein diameters were measured. Patients with detectable evening TVR were treated daily with MPFF (Daflon® 1000 mg; Servier, Suresnes, France) for 90 days, and then reassessed. Patient quality of life (QOL) was evaluated using the Chronic Venous Insufficiency Questionnaire (CIVIQ-20).

RESULTS: At baseline, patients had telangiectasia (45.8%), reticular varices (13.5%), or both (40.7%). TVR was absent in all patients in the morning but present in over half of them (55.2%) in the evening. All TVR patients complained of leg heaviness *versus* 16.3% of non-TV patients. The great saphenous vein (GSV) diameters of patients with TVR were significantly greater than those without ($P < 0.0001$). After MPFF treatment, TVR was eliminated in most patients (92.5%). The GSV diameter in treated patients was significantly reduced from baseline (5.69-5.14 mm; $P = 0.000001$). The majority of patients (88.6%) no longer experienced leg heaviness, with 11.4% having reduced symptoms. QOL improved.

CONCLUSIONS: More than half of the patients with telangiectasia and reticular varices experience TVR. TVRs can be exposed using the DOL test, which has no impact upon daily life. Daily MPFF (Daflon® 1000 mg) treatment over 90 days eliminated TVR, resolved venous symptoms, and improved QOL.

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In 1890, Friedrich Trendelenburg published his fundamental paper entitled "Ligation of the great saphenous vein in varicose veins of the leg". Since then, the reflux of blood in the venous trunks is traditionally recognized as the major pathophysiological phenomenon leading to the occurrence and progression of varicose veins of the lower extremities.¹ The implementation of the original day or-

thostatic loading test (DOL test) — prolonged vertical loading during the day — has allowed us to identify transient reflux in the great saphenous vein (GSV) of patients classified as C⁰s. This reflux occurs due to the deterioration of the viscoelastic properties of the venous wall.² Such transient refluxes happen in veins without gross morphological changes and only after prolonged vertical

loading.³ With time various theories have evolved, and it is important to highlight that venous valve incompetence is central to venous hypertension, which appears to underpin most or all of the symptoms and signs typically associated with chronic venous disorder (CVD).⁴ Therefore, it is of theoretical and practical interest to describe the peculiarities of the veins of the lower extremities in patients presenting with telangiectasia and reticular varices, after prolonged functional loading during the day (the DOL test).

Telangiectasia and reticular varicose veins (C_sS, En, An, Pn class according to the CEAP classification) are characterized by the dilatation of subpapillary venous plexus and reticular venous plexus. However, it is uncertain whether the area of venous lesions in patients is limited only to aesthetic defect. The subpapillary and reticular veins are known to have elements similar to those in other types of veins.^{5,6} Although this abnormality is often considered as only a cosmetic problem, some patients also complain of discomfort or pain.⁷

Given the potential for the development of varicose tributaries induced by transient reflux,⁸ the detection and treatment of transient venous refluxes in less advanced CVD may help to prevent the subsequent development of varicose forms. Therefore, in all patients diagnosed with transient GSV reflux we prescribed 3 months of treatment with micronized purified flavonoid fraction (MPFF), 1000 mg a day. MPFF has been demonstrated to be beneficial at various stages of venous disease in the different studies including the elimination of transient reflux.^{9,10} In order to identify transient venous refluxes in C_s patient, we used the DOL test in combination with an assessment of the GSV by duplex scanning (DS). We have used the DOL test as a functional assessment of the venous system for many years as we have observed that in all people the veins of the lower limbs are dilated at the end of the day.¹¹ In healthy people such a dilation does not cause any disturbance of the venous outflow. However, in patients with varicose veins or those predisposed to developing varicose veins, the dilated veins become disturbing at the end of the day. It is important that an individual lives a normal life at his/her typical load. Using the DOL test we assessed the individual's venous wall viscoelastic properties.

We aimed to use the DOL test, to expose transient refluxes in the GSV when present, and characterize them using DS. We also evaluated the remedial properties of

MPFF (Daflon® 1000 mg; Servier, Suresnes, France) regarding transient venous refluxes in patients with telangiectasia and reticular vein.

Materials and methods

The trial was performed in accordance with the ethical standards laid down in the 2013 revision of the Helsinki Declaration. This was an open label, descriptive study including women of childbearing age, presenting with C_s veins. Only women with telangiectasia and reticular varicose veins of moderate or severe degree, and who gave their informed consent to participate in the study were included. Non-inclusion criteria included having CVD of class C₂ or higher (CEAP classification), a history of deep or superficial vein thrombosis, lymphedema, grade C3-C4 obesity, a severe physical illness, being pregnant, lactating, or taking the following treatments: anticoagulants, diuretics, or anti-inflammatory agents.

As transient venous refluxes, detectable only in the evening, are not covered by the CEAP classification system, the CEAP classification was carried out on the basis of a leg assessment that was performed in the absence of prolonged orthostatic loading.

All patients were examined using DS (SonoScape S6 system, Sonoscape Co Ltd, Shenzhen, China). A DS examination was carried out, after the DOL-test, on patients in the upright position twice a day, in the morning after a good night's rest (before 10:00 a.m.), and in the evening at the end of the working day (after 6 p.m.).

The responses of veins to daily vertical loading, where subject maintained their usual levels of physical activity or orthostatic gradient, were quantified by measuring the diameter of the GSV in the groin area and in the area of reflux (mm) in the morning and evening. Any change in diameter of the GSV was calculated by subtracting the morning values from the evening values.

A reflux was considered as pathological if its duration exceeded 0.5 s.¹² In order to detect localized refluxes both the thigh and the calf were examined at three different segments.

The clinical examination included the identification of classical venous complaints in the lower extremities.

Patients with an identified transient reflux in the GSV were treated with MPFF (Daflon® 1000 mg) as a monotherapy (in accordance with the instructions for use) for 90 days at a daily dose of 1000 mg. During the course

of the treatment patients were not allowed to use elastic compression.

In the GSV subgroup after 3 months of treatment with MPFF, the DOL test was repeated and veins were assessed using DS. Both the change in the status of veins, evaluated by comparative DS using quantitative indicators, and the change in the rates of complaints, as compared with those present at baseline, were assessed.

The quality of life before and after the treatment was also assessed using the CIVIQ-20 Venous Quality of Life Questionnaire. This tool was designed for use in CVD and was widely validated.¹³

Statistical analysis

The statistical analysis was performed using the nonparametric Mann-Whitney U-test. Mean values of measurement were determined with a 95% confidence interval (CI). For comparing the results in dependent samples, the non-parametric Wilcoxon test was used.

Results

From 2014 to 2015, we included 96 women of child-bearing age (age range 21-47 years; mean age 31 ± 4.4 years), presenting with C,s veins. Skin lesions were bilateral in all patients and the mean duration of cutaneous manifestations was 9.4 ± 3.9 years (ranging from 4 to 24 years). Of the 96 patients, 44 had telangiectasia (45.8%), 13 had reticular varices (13.5%), and 39 had both abnormalities (40.7%). Telangiectasia was localized to the lateral surface of the middle third of thigh in 68 cases (81.9%), on the medial surface of the lower third of thigh in 23 cases (27.7%), in the popliteal area in 83 cases (100.0%), on the anterior and lateral surface of calf in 43 cases (51.8%), and in the ankle area in 32 cases (38.6%).

Telangiectasia was localized in 18 patients (21.7%), multifocal in 52 (62.6%), and generalized in 13 (15.7%) patients. The latter category included cases where the area of skin covered with telangiectasia and reticular veins was greater than the skin area without the dilated vessels. It is noteworthy that the majority of women (71.9%) reported that they had experienced prolonged periods of sitting or standing at work. In 56 women (58.3%), the duration of the working day exceeded 8 hours, and they were working 6 days per week.

Thirty-eight patients (39.6%) were taking combined

oral contraceptives (COC) to prevent pregnancy for more than 1 year, and another 16 patients (16.7%) took COC for the treatment of hormonal disturbances as prescribed by their gynecologist. The duration of hormone treatment ranged from 6 months to 6 years (mean 15 ± 4.8 months).

DOL test

A DS was performed in all patients in the morning after a good night's rest. There was no evidence of reflux in the GSV in any of the 96 patients. In the evening, after the DOL test, another DS was performed and reflux in the GSV was detected in more than half of the patients (55.2%), ranging from 6 to 35 cm. A reflux was observed in 35 patients within the thigh (6 in proximal segment, 14 in middle segment, and 15 in distal segment), 14 patients had reflux with in the calf (10 in the upper third, and 4 in the middle third), and 4 patients had reflux extending for a few segments from the middle third of the thigh to the middle third of the calf. There flux was intercuspatal in 21 patients (39.6%) and commissural in 32 (60.4%).

Interestingly, all 53 women diagnosed with transient GSV reflux had classical venous complaints such as fatigue and leg heaviness by the end of the day. Among patients without transient reflux (N.=43), only 7 women (16.3%) had venous complaints.

We compared the parameters of the GSV in the groin area via a DS examination combined with the DOL test in patients with and without transient reflux. The evening diameters of the GSV in the reflux subgroup (N.=53) were significantly greater ($P=0.000041$) than in subgroup without reflux (N.=43), which was accompanied by a corresponding significant difference in the values of orthostatic gradient (Table I).

TABLE I.—The GSV parameters measured in the groin area in patients with (N. =53) or without (N. =43) the transient reflux in the GSV (N. =43) after the DOL test.

	Evening diameter (mm)	Orthostatic gradient (mm)
With transient reflux in the GSV (N.=53)		
Mean value	5.69	0.89
95% CI	4.00-7.11	0.60-1.30
Without transient reflux in the GSV (N.=43)		
Mean value	4.99	0.61
95% CI	3.50-6.50	0.40-0.80
P value	0.000041	0.000001

TABLE II.—The presence of evening reflux in the GSV after the DOL-test before and after 3-month treatment with MPFF in patients with telangiectases and reticular varices (N. =53).

Extend of the reflux in the GSV	Baseline	After the MPFF treatment
Segmental reflux in the thigh		
Proximal third	6	—
Middle third	14	—
Distal third	15	—
Segmental reflux in the calf		
Proximal third	10	—
Middle third	4	—
Multisegmental reflux in the thigh and calf	4	4*
Total	53	4

*Extent of reflux has reduced to the single segment of the thigh in the middle third.

TABLE III.—The parameters of GSV in the area of transient reflux at baseline and after 3-month treatment with MPFF (Daflon* 1000 mg), according to the results of DS with the DOL test.

	Evening diameter (mm)	Orthostatic gradient (mm)
Baseline		
Mean value	5.69	0.89
95% CI	4.00-7.11	0.60-1.30
3 months of MPFF treatment		
Mean value	5.14	0.64
95% CI	3.50-6.50	0.40-0.80
P value	0.000001	0.000001

TABLE IV.—The results of the quality of life (QOL) assessment using the CIVIQ-20 questionnaire at baseline and after 3 months of treatment with MPFF in patients with telangiectases and reticular varices.

Comparable groups of patients	Baseline	3 months of treatment	P value
QOL score	42.03	30.10	0.00001
95% CI	28.00- 55.00	(15.00- 52.00)	

TABLE V.—The results of baseline and follow-up duplex scanning in patient P.

	Side of lesion	Baseline		3 months of MPFF treatment
		Morning	Morning	Evening
The GSV diameter in the groin area (cm)	Right	1.4	1.45	1.4
	Left	1.3	1.4	1.3
Maximal diameter of the GSV in the groin area (cm)	Right	0.55	0.6	0.6
	Left	0.55	0.6	0.55
Diameter of the popliteal vein at the level of joint gap (cm)	Right	0.7	0.8	0.75
	Left	0.75	0.8	0.75
Presence of reflux in the GSV	Right	No	Extended for 13 cm in the lower third of the thigh	No
	Left	No	No	No
Diameter of the GSV in the reflux zone (cm)	Right	0.55	0.65	0.60

Treatment outcomes

CHANGE IN THE GSV PARAMETERS ASSESSED USING DS

All 53 patients with identified evening reflux received 3 months of treatment with MPFF (Daflon® 1000 mg), in accordance with instructions for use, as a monotherapy. The evening DS performed after 3 months of treatment with MPFF demonstrated the absence or resolution of transient reflux in the GSV in 49 of 53 women (92.5%) who had had reflux diagnosed at baseline. Remarkably, in all these women the reflux was localized with in a single segment of the thigh or calf. In the remaining 4 women with transient GSV multisegmental reflux at baseline, the extent of reflux was reduced to a single segment in the middle third of the thigh (Table II).

The DS performed after 3 months of treatment with MPFF demonstrated a significant reduction in the evening diameter of the GSV in the groin area from 5.69 mm at baseline (95% CI: 4.00-7.11) to 5.14 mm (95% CI: 3.50-6.50) (P=0.000001), with the corresponding significant decrease in the orthostatic gradient, indicating the correction of viscoelastic properties of the vein (P=0.000001) (Table III). The latter explains the elimination of transient reflux as mentioned above.

CHANGES IN THE CLINICAL SYMPTOMS AND QUALITY OF LIFE

At baseline, all women with transient reflux complained of leg heaviness and fatigue, 15 patients (28.3%) reported leg pain by the end of the day, and 21 patients (39.6%) had night cramps. At the end of 3 months of treatment, leg heaviness and fatigue ceased

in 47 patients (88.6%) and was reduced in 6 (11.4%). Leg pain ceased in all patients with this symptom, and night cramps ceased in 50 patients (94.3%) and was substantially reduced in 3 patients (5.6%).

The results of the QOL assessment before and after medical therapy revealed a beneficial effect of treatment with MPFF (Table IV).

To illustrate the successful elimination of transient GSV reflux when medical therapy was used, we present the following clinical case.

A 36-year-old female patient P. presented with complaints of an aesthetic defect in the legs in the form of telangiectasia on both thighs, of leg heaviness, fatigue, and tight pain primarily in the right thigh at the end of working day along with periodic night cramps. She has two pregnancies and one delivery. She had a complicated family history regarding varicose disease among her mother's relatives. Her professional activity (she is a manager at a company) is characterized mainly by sitting at work for 9 hours or more. She visits the fitness club 3 times per week. She has been using the contraceptive agent Jeanine for about 1 year. She is 170 cm tall, weighs 63 kg and has a normosthenic body type. Her legs are normal with no varicosity of superficial veins observed. Telangiectasia is present in the form of a comb with moderate severity on the outer surfaces of her thighs. The GSV diameter (DS scanning) in the lower third of her right thigh after a typical working day at 7:00 p.m. was 6.5 mm. In addition, the intercuspular reflux lasted for 1.8 s (Table V, Figure 1). However, no reflux in the GSV was registered in the morning at 10 a.m. after a good night's rest (Table V, Figure 2). Patient P. was treated with Daflon® 1000 mg (monotherapy) over a 3-month period, and by the end of treatment a comprehensive clinical follow-up and ultrasound examination was carried out. It was noted that at the same level of daily activity the leg heaviness at the end of the day has ceased, and night cramps did not occur anymore. The CIVIQ-20 score improved from 44 to 30. At the follow-up DS at 7:00 p.m., the GSV diameter was 6.5 mm in the groin area, 6.0 mm in the problem area, and no reflux in the GSV was observed (Table V, Figure 3).

Discussion

The DOL test revealed the presence of transient venous reflux, characterized using DS, in patients with telangiectasia and reticular vein in over half of the enrolled

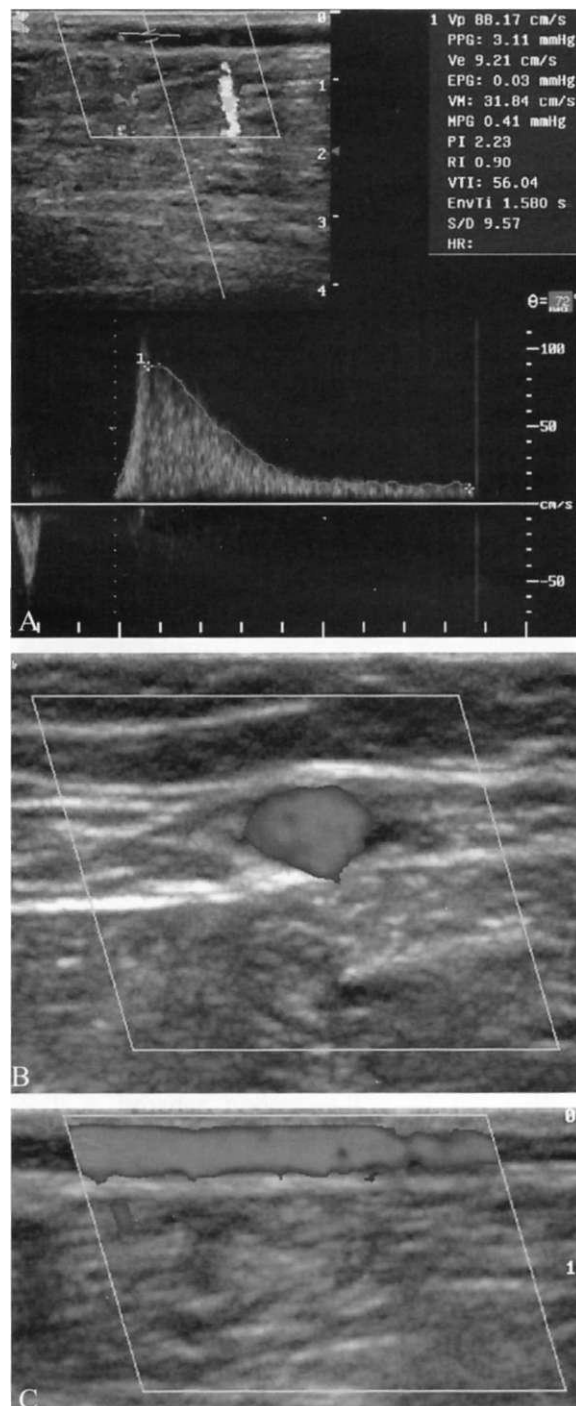


Figure 1.—Doppler ultrasonography (A) and scans in the transverse (B) and longitudinal (C) projections of the right GSV in the lower third of the thigh at the evening after the day orthostatic load in a patient aged 36 years. The intercuspular reflux lasted for 1.8 s and extended by 13 cm. The cross-section diameter of the GSV was 6.0 mm.

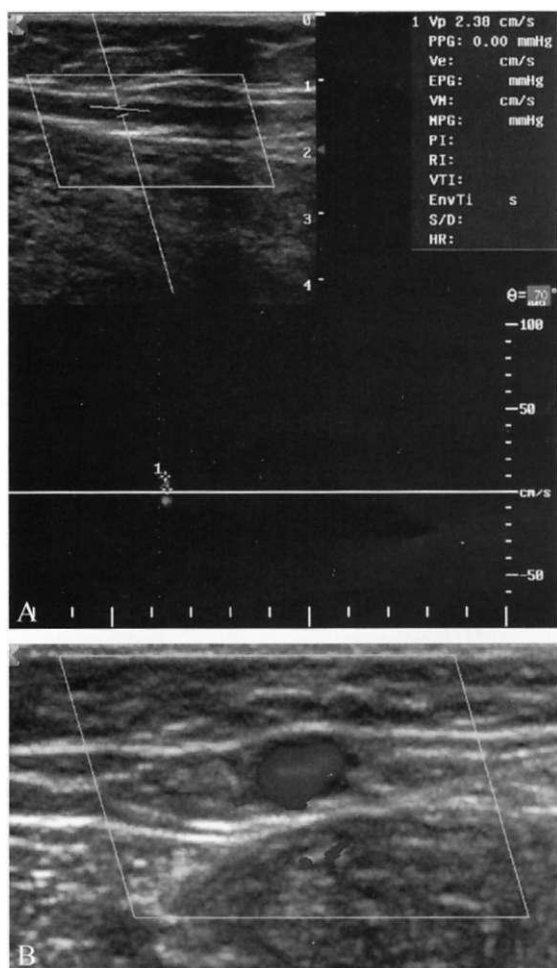


Figure 2.—Doppler ultrasonography (A) and scan in the transverse (B) projection of the right GSV in the lower third of the thigh at 9 a.m. after the proper night's rest. The diameter of GSV in the problem area was 5.5 mm on the right side, and no reflux throughout the GSV was observed.

patients. Our data have shown that telangiectasia and reticular varices, which are undoubtedly linked to minor forms of CVD, are not just localized vascular pathology limited only to the skin. We also demonstrated that deterioration of the viscoelastic properties of the GSV leads to the development of transient venous blood reflux in 55.2% of cases.

A special feature of the registered refluxes is that they are transient by nature, and associated with long-term (daily) orthostatic stress and a sedentary lifestyle. It is important to note that in more than half of the cases a commissural reflux was identified.¹⁴ Transient refluxes in the GSV primarily suggest that there is a functional

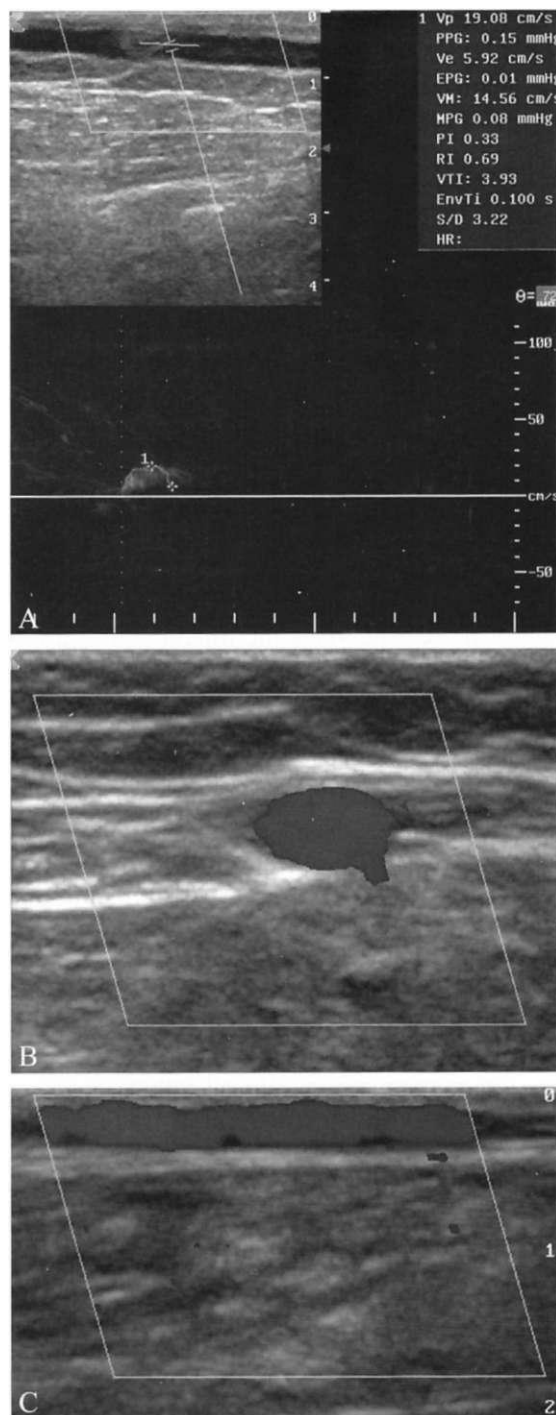


Figure 3.—Dopplerography (A) and scans in the transverse (B) and longitudinal (C) projections of the right GSV in the lower third of the thigh after 3-month treatment with MPPF. The diameter of GSV in the problem area is 5.5 mm on the right side, and no reflux throughout the length of GSV is observed.

proven in a previous study.¹⁹ With MPFF treatment, venous tone is increased due to the modulation of noradrenergic signaling through the reduced norepinephrine metabolism.^{19, 20} Along with the correction of hemodynamic disturbances, treatment with MPFF is associated with a reduction in the intensity of venous complaints and an improvement in the quality of life of patients.

Our study demonstrates an effective means of both revealing and correcting transient refluxes. This is an important finding as refluxes can have devastating consequences on the tributaries (similar to permanent refluxes), in the GSV.⁸ These data also raises the prospect of involving general phlebology practice in the development of an approach to prevent patients transitioning from so called minor classes of CVD (C⁰s and C_s) to the varicose disease (CEAP classes of C² and higher).²¹ However, in order to confirm our findings more studies are needed, and with longer follow-up periods.

Conclusions

In patients with telangiectasia and reticular vein (CEAP class C_s), the pathological changes in the lower extremities include not only the lesions in the affected subpapillary venous and reticular venous plexus but also the deterioration of viscoelastic properties of the GSV. This deterioration can lead to transient evening refluxes in this vein as was observed in over half of the patients in our study. The segmental transient refluxes are most often localized in the middle and proximal segments.

The DOL test is useful for revealing refluxes in the GSV that were subsequently detected using DS. This test is physiological in nature, and consequently does not impact upon the daily life of patients. The DOL test allows us to assess the individual's functional reserve and venous wall viscoelastic properties.

Treatment with MPFF (Daflon* 1000 mg) once a day for 3 months was associated with the complete elimination of transient refluxes in the GSV due to the improvement in viscoelastic properties of superficial veins. This treatment was also associated with the alleviation of venous complaints and an improvement in the quality of life of patients.

References

1. Guias B, Schadeck M, Bressoletier L. [Superficial venous reflux and ultrasound investigations. A review of literature], *Phlebologie* 1994;51:147-54. [Article in French]
2. Tsoukanov YT, Tsoukanov AY, Nikolaychuk A. Great saphenous vein transient reflux in patients with symptoms related to chronic venous disorders, but without visible signs (COs), and its correction with MPFF treatment. *Phlebology* 2015;22:18-24.
3. Van Cleef JF, Hugentobler JP, Desvaux P, Griton P, Cloarec M. [Endoscopic study of reflux of the saphenous valve], *J Mai Vase* 1992;17:1Γ3-6. [Article in French]
4. Bergan JJ, Schmid-Schonbein GW, Smith PD, Nicolaidis AN, Boisseau MR, Eklof B. Chronic venous disease. *N Engl J Med* 2006;355:488-98.
5. Mariani F, Bianchi V, Mancini S. Telangiectases in venous insufficiency: point of reflux and treatment strategy. *Phlebology* 2000;15:38-42.
6. Caggiati A, Phillips M, Lametschwandtner A, Allegra C. Valves in small veins and venules. *Eur J Vase Endovasc Surg* 2006;32:447-52.
7. Weiss RA, Weiss MA. Resolution of pain associated with varicose and telangiectatic leg veins after compression sclerotherapy. *Dermatol Surg Oncol* 1990;16:333-6.
8. Tsukanov YT, Nikolaichuk AI. The Case of GSV Transient (Evening. Orthodependent) Reflux in a Hip Going into the Tributary in Woman with Reticular Varicose Veins (Cl_s). *J Vase Med Surg* 2015;3:219.
9. Nicolaidis A, Kakkos S, Eklof B, Perrin M, Nelzen O, Neglen P, *et al.* Management of chronic venous disorders of the lower limbs. Guidelines according to scientific evidence. *Int Angiol* 2014;33:87-208.
10. Lyseng-Williamson KA, Perry CM. Micronised purified flavonoid fraction. A review of its use in chronic venous insufficiency, venous ulcers and haemorrhoids. *Drugs* 2003;63:71-100.
11. Tsoukanov YT. Local venous hypervolemia as a clinical pathophysiological phenomenon of varicose veins. *Angiol Sosud Khir* 2001;7:53-7.
12. Labropoulos N. Cut point on normal and pathological values of reflux. *Medicographia* 2008;30:157-62.
13. Launois R, Reboul-Marty J, Henry B. Construction and validation of a quality of life questionnaire in chronic lower limb venous insufficiency (CIVIQ). *Qual. Life Res* 1996;5:539-54.
14. Schadeck M. [Duplex scanning study of great saphenous veins in children: diameter, reflux and influence on therapy]. *Phlebologie* 1996;49:413-8. [Article in French]
15. Asbutah AM, Al-Enezi M, Al-Sharifi NM, Almajran A, Cameron JD, McGrath BP, *et al.* Changes in the diameter and valve closure time of leg veins across the menstrual cycle. *J Ultrasound Med* 2014;33:803-9.
16. Tsoukanov YT, Tsoukanov AY, Bagenov VN. The effect of oral contraceptives on the orthostatic diameter of lower limb major veins and its correction. *Angiol Sosud Khir* 2008;14:75-7.
17. Mashiah A, Berman V, Thole HH, Rose SS, Pasik S, Schwarz H, *et al.* Estrogen and progesterone receptors in normal and varicose saphenous veins. *Cardiovasc Surg* 1999;7:327-31.
18. Bogachev VY. Hormone-induced phlebopathy. New problem of modern phlebology. *Angiol Sosud Khir* 2002;8:50-4.
19. Ibegbuna V, Nicolaidis AN, Sowade O, Leon M, Geroulakos G. Venous elasticity after treatment with Daflon 500 mg. *Angiology* 1997;48:45.
20. Gargouil YM, Perdrix L, Chapelain B, Gaborieau R. Effects of Daflon 500 mg on bovine vessels contractility. *Int Angiol* 1989;8:19-22.
21. Eklof B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kistner RL, *et al.* Revision of the CEAP classification for chronic venous disorders: consensus statement. *J Vase Surg* 2004;40:1248-52.

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