Experience of using ultrasound elastography to assess the effectiveness of conservative treatment of varicose veins of lower extremities

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Aims and objectives

To assess a feasibility of ultrasound elastography for monitoring of conservative therapy of the varicose veins of lower extremities with a drug containing micronized purified flavonoid fraction (MPFF).
Methods and materials

A total of 19 patients (38 limbs) with varicose veins (CEAP class C2) were examined. The study group consisted of 4 men (21.1%) and 15 women (78.9%) aged 45 to 85 years; the mean age was 64 years old.

The criteria for inclusion in the group were the following:

- varicose veins of C2 class;
- no history of varicose vein surgery;
- no history of conservative treatment with venoactive drugs;
- no thrombotic changes in the venous system;
- patient's informed consent to participate in the program of examination and treatment.

The first step of evaluation - physical examination and a medical history taking. In women, the number of pregnancies and births was also recorded.

Visual examination of lower extremities was performed in the upright position standing at a couch. The anterior, medial, posterior and lateral surfaces of the femur and tibia were thoroughly examined. The calf volume was measured by measuring tape at the ankle joint level (malleolar volume) and at the border between upper and middle third of tibia.

At the next step of evaluation, the duplex ultrasound evaluation of lower extremity veins was performed under the standard protocol and with ultrasound elastography (USEG) using the expert class ultrasound system «Toshiba» (Japan) with a multi-frequency ultrasound transducer 5-12Hz. All examinations were performed with the patient in supine positions (dorsal and ventral) and upright position, from standard approaches and during afternoon.

Ultrasound elastography of the main trunk of great saphenous vein (GSV) was performed:

- at the border between upper and middle third of femur, and
- at the level of the upper third of lower leg,
- at the place of the most changed varicose tributary of GSV at the lower leg.

Ultrasound elastography of the main trunk of small saphenous vein (SSV) was performed in the upper third of the tibia.
Standard ultrasound examination of the veins of lower extremities implied an assessment of the vessel diameter and its patency, the state of the venous wall, and the presence of spontaneous echo contrast and its parameters. The valvular apparatus and the degree of valvular insufficiency of both surface and deep venous systems of both lower limbs were examined, even in the case of clinically evident unilateral lesion.

If the dilation of tributaries or parts of the main trunk of GSV were found, the diameter and length of dilated part were also calculated. The presence of pathological reflux was determined using the Valsalva maneuver. To identify valvular insufficiency of the muscle-vein sinuses in the calf and of the posterior tibial veins, the maneuver with proximal compression was used.

Ultrasound elastography, as a technique evaluating the elastic properties (stiffness) of tissues, was carried out after standard ultrasound examination. The elasticity of biological tissue describes its ability of reversible deformation, i.e. the property to exert mechanical resistance when the force is applied and to regain the original shape after removal of force. Elastography image is a graphical representation of the displacement of tissue layers under the influence of several cycles of compression/decompression of the investigated vein by sensor. The received echo signal is processed by the device, and the color-coded information on the displaceability of the studied tissue layers is displayed. The dense tissue is indicated in blue, the tissue with moderate elasticity - in green and yellow-green, and softer tissue - in red.

According to our data, the unaltered vein has a soft-elastic structure of the vessel wall/perivasal tissues complex, which is uniformly encoded in green or yellow-green. The width of soft-elastic limbus around the vein is determined by the size of the vessel, as well as the presence of abnormalities. During the USEG of veins and adjacent tissues we evaluated the area of perivasal tissues on the posterior wall of the vessel at the moment of maximal decompression, which has a homogeneous elasticity, as well as the width of perivasal zone of tissue elasticity (Figures 1a, 1b). The vein is coded in red as the softest structure because of the presence of liquid component and formed elements that can move and, therefore, determine a high degree of relative elasticity of the tissue.

Then the patient was prescribed medical therapy with venoactive agent MPFF (Detralex) at a dose of 2 tablets per day (one tablet in the noon and other at evening during the meal) for 3 months. The repeated examination was carried in patients after 3-month course of treatment with Detralex.

The database creation, statistical processing of data and graphical display of the results were performed using computer software MS Excel 97 for Windows 98 and "Biostatistics" (version 4.03). Given the small sample size, the quantitative data were analyzed using non-parametric statistics: the differences between the dependent groups
before and after the treatment were evaluated using the Wilcoxon test. Values are presented as median Me [2 (25%) percentile, and 4 (75%) percentile]. The selected parameters given below in the tables have the following designations: Me - median, n - the size of analyzed subgroup, p - the achieved significance level. The cut-off level of significance was taken at 5%.
Fig. 1: Figure 1. Color elastogram of the intact great saphenous vein (GSV): A (on the left). Color elastogram at the two-dimensional image of GSV. Elastography image of the vessel at the moment of maximal decompression has smooth clear contours with a central (relative to the vessel) location of elastographic color spheres and smooth color transitions. The dashed line indicates the boundaries of the venous wall. B. M-mode in the elastography program. The arrow on the left half of the image indicates the line along which the time-based sweep was performed to get image in the M-mode. The width of perivasal area of homogeneous tissue was defined as the width of the rim on the posterior wall of the vein, which has a uniform green color (curly brace).

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Results

Results of the analyses of complaints identified at baseline, the data of monitoring, recorded in patients' diaries, and data of follow-up examination are summarized in the Table 1.

Table 1. Summary of patients' complaints at baseline and follow-up examinations.

<table>
<thead>
<tr>
<th>Complaints</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduction</td>
<td>Cessation</td>
</tr>
<tr>
<td>Cosmetic defect</td>
<td>17 (89.5%)</td>
<td>no changes</td>
</tr>
<tr>
<td>Feeling of heaviness</td>
<td>12 (63.2%)</td>
<td>5 (26.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (84.2%)</td>
<td>4 (21.1%)</td>
</tr>
<tr>
<td>Night cramps</td>
<td>3 (15.8%)</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Feeling of swelling</td>
<td>14 (73.7%)</td>
<td>5 (26.3%)</td>
</tr>
</tbody>
</table>

The analysis of data has shown that all patients responded well to the treatment with MPFF in terms of reduction in the intensity of symptoms or complaints, or their resolution. Thus, the fatigue was resolved in 63.2% and reduced in 21.1% of patients. The swelling of lower extremities was resolved in 47.4% patients, and 26.3% patients reported periodic occurrence of swelling, but with more rapid resolving at a rest, than prior to the MPFF treatment. In addition, the feeling the heaviness was decreased from 63.2% to 26.3% and completely resolved in 36.9% patients. Night cramps was reduced in 5.3% patients and completely resolved in 10.5% patients.

Further, we analyzed the instrumental data from examinations before and after the treatment with MPFF.

After the 3-month treatment course with standard doses of MPFF (Detralex), the trend was observed to the decrease in the GSV wall thickness, as well as a significant reduction in the diameter of the investigated vein at the fixed level of evaluation.

The color elastogram prior to the treatment showed eccentric location of the elastographic spheres with uneven color transitions. Median width of the perivasal area of homogeneous tissue was 0.35 cm.
Table 2. Parameters of ultrasound elastography of the great saphenous vein (GSV) at the femoral level in patients with varicose veins before and after the treatment with MPFF (Detralex).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before n=17</th>
<th>After n=17</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSV wall thickness (femur), cm</td>
<td>0.54 [0.44; 0.63]</td>
<td>0.49 [0.42; 0.58]</td>
</tr>
<tr>
<td>GSV diameter (femur), cm</td>
<td>3.90 [3.35; 4.08]</td>
<td>3.80 [3.50; 3.960]</td>
</tr>
<tr>
<td>Width of perivasal area of homogeneous tissue, cm</td>
<td>0.35 [0.30; 0.56]</td>
<td>0.54 [0.46; 0.69]</td>
</tr>
<tr>
<td>Strain of perivasal tissue, fraction</td>
<td>0.29 [0.11; 0.32]</td>
<td>0.29 [0.25; 0.38]</td>
</tr>
<tr>
<td>Strain of the posterior wall, fraction</td>
<td>0.26 [0.22; 0.51]</td>
<td>0.34 [0.27; 0.40]</td>
</tr>
</tbody>
</table>

P value NS <0.022 <0.02 <0.05 NS

After the treatment course, the "leveling" of image at color elastogram was observed (Figure 2,3), with the appearance of clear spheres with a gradual transition of colors. Median width of the perivasal area of homogeneous tissue significantly increased from 0.35 to 0.54 cm.

Table 3. Parameters of ultrasound elastography of the great saphenous vein (GSV) at the tibial level in patients with varicose veins before and after the treatment with MPFF (Detralex).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before n=17</th>
<th>After n=17</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSV wall thickness (tibia), cm</td>
<td>0.44 [0.39; 0.4]</td>
<td>0.35 [0.32; 0.40]</td>
</tr>
<tr>
<td>GSV diameter (tibia), cm</td>
<td>3.87 [3.55; 4.25]</td>
<td>3.42 [3.00; 3.93]</td>
</tr>
<tr>
<td>Width of perivasal area of homogeneous tissue, cm</td>
<td>0.29 [0.27; 0.50]</td>
<td>0.39 [0.34; 0.50]</td>
</tr>
<tr>
<td>Strain of perivasal tissue, fraction</td>
<td>0.22 [0.19; 0.45]</td>
<td>0.34 [0.15; 0.66]</td>
</tr>
<tr>
<td>Strain of the posterior wall, fraction</td>
<td>0.31 [0.24; 0.46]</td>
<td>0.30 [0.23; 0.36]</td>
</tr>
</tbody>
</table>

P value <0.020 <0.050 <0.050 NS <0.050

The evaluation of the GSV at the lower leg was performed at 10 cm below the knee bend on the lateral side of tibia. Elastographic images of the studied vessel prior to the treatment mostly did not have a significant distortion of color cartogram. This observed image did not change significantly after the therapy. A significant enlargement of the perivasal area of homogeneous tissue from 0.29 to 0.39 cm was noted, in combination
with a significant reduction in the thickness of the vessel wall (0.44 mm and 0.35 mm before and after the study, respectively) and vessel diameter (3.87 mm and 3.42 mm) (Figure 4,5)

**Table 4.** Parameters of ultrasound elastography of the great saphenous vein (GSV) tributaries at the tibial level in patients with varicose veins before and after the treatment with MPFF (Detralex).

<table>
<thead>
<tr>
<th>GSV tributary wall thickness (tibia), cm</th>
<th>GSV tributary diameter (tibia), cm</th>
<th>Width of perivasal area of homogeneous tissue, cm</th>
<th>Strain of perivasal tissue, fraction</th>
<th>Strain of the posterior wall, fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before n=17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.40 [0.37; 0.44]</td>
<td>3.60 [3.31; 3.81]</td>
<td>0.38 [0.31; 0.43]</td>
<td>0.22 [0.20; 0.25]</td>
<td>0.20 [0.18; 0.21]</td>
</tr>
<tr>
<td>After</td>
<td>0.38 [0.32; 0.41]</td>
<td>3.10 [2.84; 3.35]</td>
<td>0.49 [0.35; 0.52]</td>
<td>0.31 [0.21; 0.25]</td>
</tr>
<tr>
<td>n=17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>NS</td>
<td>&lt;0.020</td>
<td>&lt;0.020</td>
<td>&lt;0.050</td>
</tr>
</tbody>
</table>

The study of the GSV tributaries did not reveal any significant changes in the venous wall thickness. The dilated tributaries of the GSV at the lower legs before administration of the drug were characterized mostly by an eccentric location of color cartogram with irregular contours and absence of smooth transitions of color. The medical treatment was associated with a "normalization" of the displayed colors of elasticity of vessel and perivasal tissues (Figure 6,7). Some increase in the width of perivasal area of homogeneous tissue was observed, as well as a significant increase in the elasticity of perivasal tissues.

**Table 5.** Parameters of ultrasound elastography of the small saphenous vein (SSV) tributaries at the tibial level in patients with varicose veins before and after the treatment with MPFF (Detralex).

<table>
<thead>
<tr>
<th>SSV wall thickness (tibia), cm</th>
<th>SSV diameter (tibia), cm</th>
<th>Width of perivasal area of homogeneous tissue, cm</th>
<th>Strain of perivasal tissue, fraction</th>
<th>Strain of the posterior wall, fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before n=17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.27 [0.22; 0.29]</td>
<td>3.40 [3.13; 3.55]</td>
<td>0.35 [0.28; 0.41]</td>
<td>0.26 [0.22; 0.30]</td>
<td>0.49 [0.37; 0.53]</td>
</tr>
<tr>
<td>After</td>
<td>0.24 [0.21; 0.27]</td>
<td>3.21 [3.10; 3.47]</td>
<td>0.39 [0.32; 0.45]</td>
<td>0.26 [0.23; 0.31]</td>
</tr>
<tr>
<td>n=17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The observed changes in the blood vessels in the GSV and SSV systems were expectedly involved also the small saphenous vein (SSV). At the end of treatment, there was a significant reduction in the SSV wall thickness and its diameter. The width of perivasal area of homogeneous tissue was increased significantly; however, no significant increase in tissue elasticity of perivasal tissue was found (Figure 8,9).
Fig. 1: Figure 1. Color elastogram of the intact great saphenous vein (GSV): A (on the left). Color elastogram at the two-dimensional image of GSV. Elastography image of the vessel at the moment of maximal decompression has smooth clear contours with a central (relative to the vessel) location of elastographic color spheres and smooth color transitions. The dashed line indicates the boundaries of the venous wall. B. M-mode in the elastography program. The arrow on the left half of the image indicates the line along which the time-based sweep was performed to get image in the M-mode. The width of perivasal area of homogeneous tissue was defined as the width of the rim on the posterior wall of the vein, which has a uniform green color (curly brace).

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Fig. 2: Ultrasound elastography of the great saphenous vein (GSV) in patients with varicose veins before the treatment with MPFF.

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Fig. 3: Ultrasound elastography of the great saphenous vein (GSV) in patients with varicose veins after the treatment with MPFF.

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**Fig. 4:** Color elastogram of the great saphenous vein (GSV) before the treatment with Detralex in therapeutic dose.

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**Fig. 5:** Color elastogram of the great saphenous vein (GSV) after the treatment with Detralex in therapeutic dose.

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**Fig. 6:** Color elastogram of the great saphenous vein (GSV) tributary at the lower leg before the treatment with DETRALEX.

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**Fig. 7:** Color elastogram of the great saphenous vein (GSV) tributary at the lower leg after the treatment with DETRALEX.

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Fig. 8: Color elastogram of the small saphenous vein (SSV) before the treatment with DETRALEX.

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Fig. 9: Color elastogram of the small saphenous vein (SSV) after the treatment with DETRALEX.

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Conclusion

The study has shown that the changes identified using the ultrasound elastography are more pronounced in the vessels of large diameter. Intact veins of lower extremities have a homogeneous image of elastogram, suggesting about unaltered histological structure of these tissues. In the presence of varicose transformation, the heterogeneous elastography pattern reflected, probably, the disturbance of histological regularity of tissues surrounding the vessel.

The therapy with MPFF was associated with a trend to normalization of elastographic image of vessel, which relates to the reduction of the severity of aseptic inflammation and normalization of cellular structure, and, therefore, the physical properties of the studied tissue.

The obtained data confirm the feasibility of ultrasound elastography for identification of the objective markers of treatment response to MPFF in varicose disease.