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## **SHEAR WAVE ELASTOGRAPHY AND LIVER PULP ELASTOMETRY (methodical aspects)**

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The clinical significance of fibrosis staging in chronic diffused liver diseases (CDLD) and limitations imposed on biopsy motivated by development of noninvasive methods of assessment of liver fibrosis [13,14]. Transient elastography (TE) became the leading and recognized tool methods for this purpose in Europe.

The pioneer in the elastometry of liver stiffness measurements (LSM) is Fibroscan® Co (Echosence, France) Designers showed for the first time that there is a close correlation of parenchyma stiffness and liver fibrosis stages on the METAVIR scale. This found the confirmation in numerous publications and meta-analyzes [3, 7]. The principle of transient elastometry method is in the LSM measurement as a function of speed distribution in liver of elastic shear wave reproduced by mechanical shock. The transient elastography (TE) key limitation in clinic practice has come to high level of results (20%), that are evaded interpretation. The method makes it impossible to visualize the radiation zone that reduces reliability results for specific patient [17].

Compression (static) elastography integrated as a module into the high level ultrasound equipment uses sensor-induced or natural (i.e. respiratory or cardiac) displacements in a body for producing images of stiffness color mapping (SCM) on the liver slice. As stress force value in this method is not known, it is possible only qualitative relative assessment of tissue stiffness but not a quantitative one [1].

The real-time shear wave elastography (SWE) represents a new noninvasive method for assessment of liver fibrosis based on the LSM quantitative measurement [1, 9,15]. The device family that uses the shear wave (SW) method in the ultrasound elastography and liver parenchyma elastometry are currently presented by three manufacturers: Aixplorer® (Supersonic Imaging S.A., Aix-en-Provence, France), Ultima PA Expert® (Radmir, Ukraine), Acuson S3000® (Siemens, Germany) and manufacturer Epiq® (Philips, Hoolland ) that uses the same method of side wave. Supersonic Imaging Co. proposed to call method as Real-Time Shear Wave Elastography™ (SWE™) Imaging [1, 9, 15].

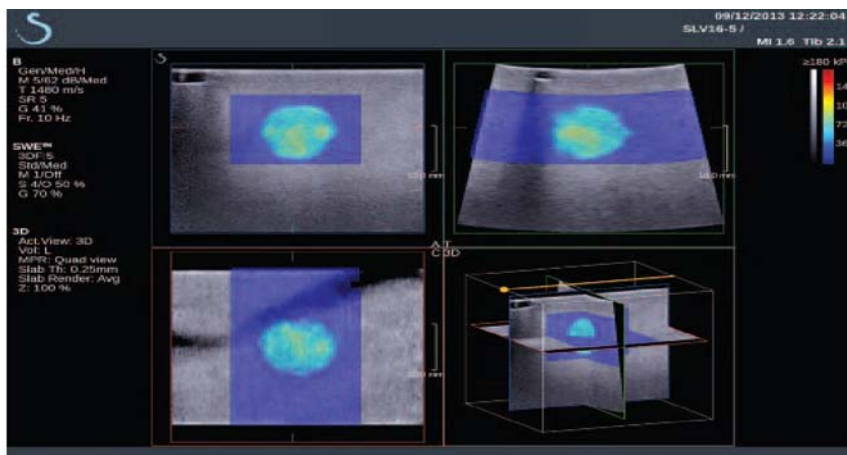
The SWE method is based on the ultrasound beam property to induce mechanical shear waves in the direction lateral to their distribution. Their track speed through the tissue depends on its stiffness or gluey-and-elastic properties. The tissue space covered by probing ultrasound beam depends on Mach cone shaped with the support of the SW several excitation focuses. Besides, the SWE imaging is built up at high image frequency in the B-mode. This method made it possible to evaluate fibrosis stage with greater accuracy as compared to transient elastography (TE) owing to navigation in the B-mode. [9]. Close to the SWE method, but a single-focused method for the LSM assessment is the Acoustic Radiation Force Imaging (ARFI) technology. It is presented by apparatus samples Acuson S2000® (Siemens) and IU 22® (Philips, Holland) [4, 7].

Clinically, detection and staging of liver fibrosis by using the SWE method is of great importance [9, 15], as it allows to make noninvasive the following:

- evaluate liver damage degree at the moment of disease marker detection;
- evaluate disease prediction;
- track the KhDZP dynamics (hepatitis advance and hepatic cirrhosis transition);
- evaluated efficiency of etiotropic and anti-fibrotical treatment;
- avoid liver unwanted biopsy.

Elastography as a term means imaging with 2D and 3D spatial distribution of color pixels in the region of interest (ROI) encoding the required values of tissue stiffness using Young's modulus scale in kilopascals (kPa). This provides the B-mode monochrome representation (picture) of the organ in the real time scale and a quantitative (SCM) data in the region of interest (ROI) (Fig. 1, 2).

Elastometry as a term that means origination from sample volume (SV) of stiffness digital values in kPa. The doctor can volitionally place the sample volume (SV) in the region of interest (ROI) at the most representative areas of the liver. The preliminary stiffness color mapping (SCM) analysis makes it possible to carry out the SV optimal navigation, avoid artifacts and acquire accurate and reliably reproducible quantitative information about organ region stiffness.



**Fig.1.** SWE elastography with 3D spatial distribution of color pixels in the region of interest (homunculus).

## Materials and methods

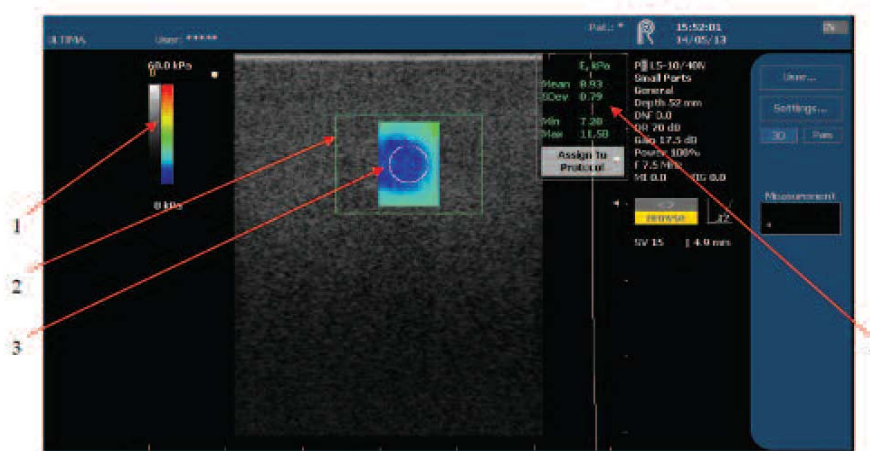
We have studied the SWE opportunities in the LSM assessment for some clinical examinations. In the first work, performed were liver stiffness measurements (LSM) with healthy persons and patients with Wilson-Konovalov disease. There had been examined 25 apparently healthy patients (16 men and 9 women) at the age of 18 years to 49 years (average age is of  $27,21 \pm 0,76$  years) and 28 persons (18 men and 10 women) at the age of 16 years to 47 age (average age is of  $29,67 \pm 0,95$  years) suffering Wilson-Konovalov disease. SWE was performed on the Ultima PA Expert® (Radmir, Ukraine) scanner by convex probe at the frequency range of 1 MHz to 5 MHz.

The LSM elastometry results are represented in Table 1.

It was confirmed that there were sensibly different values of liver stiffness (LS) for healthy persons as compared to patients with Wilson-Konovalov disease according to the SWE data that met information about fibrosis caused by liver biopsy for persons with Wilson-Konovalov disease

and biochemical markers of liver involvement.

The aim of the second work was to find out opportunities and limitation of the SWE application for the LSM assessment in patients with hepatitis C virus (HCV). This examination involved 152 patients (115 men and 37 women, average age was  $43.5 \pm 8,6$  years). The HCV verification was performed according to HCV RNA and anti-HCV LgG and LgM, as well as common clinical examinations took place. Shear wave elastometry (SWE) was performed with the 2-5 MHz convex probe in the right and left lobes of the liver on apparatus Ultima PA Expert® (Radmir, Kharkiv Ukraine). The SWE region of interest (ROI) covering area of  $100 \text{ mm}^2$  ( $10 \times 10 \text{ mm}$ ) using color map scale in kPa allowed the SV navigation for quantitative measurement LSM in kPa of the  $25 \text{ mm}^2$  area ( $5 \text{ mm} \times 5 \text{ mm}$ ) on the ultra-sonogram at the distance in depth of 1 cm to 3 cm from organ capsula. Patient preliminary preparation for ultrasound investigation (USI) included taking foam suppressing medicine-simeticone (espumizan) for 3-5 days by 2 capsules (80 mgr. of simeticone) 3 to 4 times per a day in taking food or following meal as well as there were used enzymatic agents (mezim forte) on the eve according to required procedure before going to bed.



**Fig.2.** View of apparatus screen with the main attributes of shear wave elastography and elastometry (homunculus)

1 - tissue stiffness scale (Young's modulus);

2 - map window in the region of interest (ROI);

3 - sample volume (SV);

4 - indication of tissue stiffness assessments (for Young's modulus in kPa or shear wave distribution velocity in m/s).

Number of the LSM successful measurements in each trial should be of no less than 10 (two series by 5 measurements). We determined median of average measurements in SV that is characterized by LSM in kPa. Besides, it was also calculated the interquartile range (IQR) index. The result was considered to be homogeneous, in case the IQR /median ratio was less than 30%. Comparison of results for the first and second series of measurements included by 5 measurements for each series. They were obtained by one and the same researcher taking into account the intraclass correlation coefficient (ICC) for intraobserver reproducibility analysis.

The LSM median value was calculated for the total organ – 10 measurement of LSM in both lobes and by taking 5 measurements of LSM individually for the right lobe (RL) and the left lobe (LL) respectively. For estimation stage of fibrosis we used threshold values proposed by Ferraioli Get al.

**Liver parenchyma stiffness in healthy persons and Wilson-Konovalov disease persons according th SWE data**

Stiffness value parameter in SV, kPa	Healthy persons (n=25)	Wilson-Konovalov disease (n=28)	p
Average value	4,05±0,29	10,17±0,75	<0,001
Maximum	5,63±0,30	18,00±1,94	<0,001
Minimum	2,59±0,32	5,65±0,69	<0,001

The rate of reliable LSM for total liver (TL) was 76.3%. This is significant lower as compared with the right lobe [(RL) is equal to 92,1%,  $p<0,001$ ] and left lobe [(LL) is equal to 90,8%,  $p=0,001$ ] respectively. Distribution of fibrosis in the liver was heterogeneous which was independently associated with the risk of unreliable total LSM (OR 3,48; 95% CI 1,55-7,81,  $p<0,003$ )

Statistical differences in LSM as to average values between the right and left lobes for the same patient was not detected. The key issue for the SWE referral of most of the patients was the new-onset fibrosis stage. Clear clinical representation of cirrhosis process led to referral quota increase of such patients to be examined for the diagnosis confirmation. Abdominal dropsy suffered by 7 such patients was of no obstacle for the LSM measurements.

As a result the SWE method diagnostic availability was of 97,7%, because increase of IQR/median ratio exceeding 30% was diagnosed in 4 patients (right lobe (RL) and left lobe (LL) in one patient and liver left lobe (LL) only in 3 patients. Measurement problems of the SWE parameters were due to artifacts (signal attenuation, reverberation and aperture poor contact of the Doppler ultrasound probe) and wind.

So, it can be stated that SWE is characterized by an excellent intraobserver repro-ducibility of results as ICC was 0.889 (95% CI 0,778-0,946). The presence of artifacts (especially reverberation) and narrow acoustic window was slightly expressed (2.3%), but it restricted the LSM opportunities to use the SWE method.

At the same day the dual Doppler ultrasound examination of liver was conducted with hepàtitis C virus (HCV) patients in number 2 taken from this group for comparison of visualization conditions and elastometry data on the Aixplorer® (Supersonic Imaging S.A., Aix-en-Provence, France) apparatus with convex probe SC6-1 and frequencies from 1 MHz to 6 MH and on device Ultima PA Expert (Radmir, Kharkiv, Ukraine ) with convex probe at frequencies from 1 MHz to 5 MHz in the liver right and left lobes. Preliminary results show that significant differences in the LSM values were not detected.

As a result of material generalization it made to be possible to share 3 groups of factors rendering a decisive role on quality and validity of data obtained in liver elastography/elastometry method with the SW use as follows:

- 1) patient-dependent factors;
- 2) machine-dependent factors;
- 3) operator-dependent factors.

### Patient-dependent factors.

Apart from fibrosis, many clinical factors can affect the liver tissue stiffness:

- full inspiration and forced respiration (Fig.3)[19];
- factors increasing central venous pressure (CVP)[11];
- intrahepatic and subhepatic cholestasis [17];
- liver steatosis and increase of hepatic necro-phlogistic activity [6,16];
- peliosis (vascular liver involvement );
- Bada-Kiari syndrome (thrombosis of hepatic veins) [10];
- congestivus liver [10];
- major expansive processes in liver;
- increase of intra-abdominal pressure (wind, prelum exertion, close-bodied clothing on the mid section, gastrostasis and plethorical meal, tense ascites) [2, 6, 17];
- cellular infiltration of liver at lymphoproliterative and oncologic processes.

All these factors should be taken into account in interpretation of liver parenchyma stiffness [6,15].

Presence of unstressed abdominal dropsy is not a limitation for liver fibrosis assessment by using the SWE method, as shear waves (SW) are originated in the organ itself and not distributed from the patient body surface resulting from a pressure stamp knock of the Fibroscan device during transient elastography (TE).

### Machine-dependent factors.

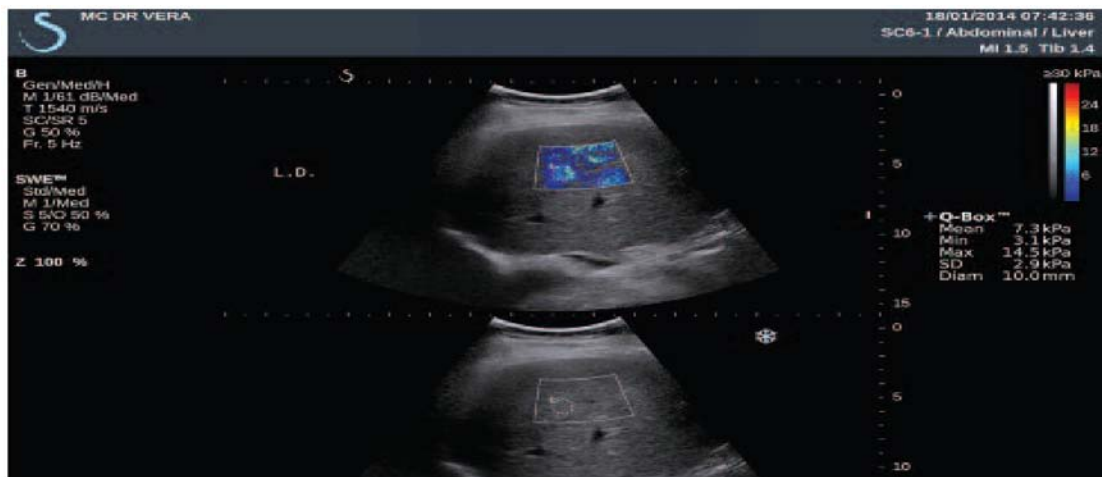
Known limitations and artifacts of the conventional Doppler ultrasound investigation in the B-mode do affect the visualization in the SWE-mode too. These are the problems for selection of the appropriate routes, acoustic windows and artifacts of the ultrasound beam path.

- Narrow intercostal spaces;
- adiposis due to thick layer of the previous subcutis and anteperitoneal fat on the way of ultrasound beam to regions of interest in the liver and reverse direction [6, 17];
- rapid displacements of organ (liver) (closeness of some liver regions to heart, aorta, diaphragm) (Fig.4) [1];



**Fig.3.** Increase of liver parenchyma stiffness values under ultrasound probe compression and full inspiration during subcostal access.

- reverberation, side lobes, reflectors, attenuation (steatosis, bone, gristle, gas, plaster bandages), wind [2, 8];
- deep depth in the region of interest (ROI) (more than 10-17 mm).



**Fig.4.** Artifact of the region of interest (ROI) color non-filling with rapid motion of probe and liver. Overstated stiffness values of normal parenchyma due to difficulties (average value is 7.3 kPa).

#### Operator-dependent factors

- Rapid probe motions relative to the organ (liver) (Fig.4) [1, 2];
- incorrect selection of acoustic window [2];
- region of interest (ROI) sample volume (SV) positioning into artifact zones — reverberation, shades, reflectors, attenuation, wind (Fig.5);
- small depth in region of interest (ROI) (under capsule) and deep depth (attenuation, low frame frequency) [8, 15];
- probe liver additional compression and especially in scanning from hypochondrium [2].

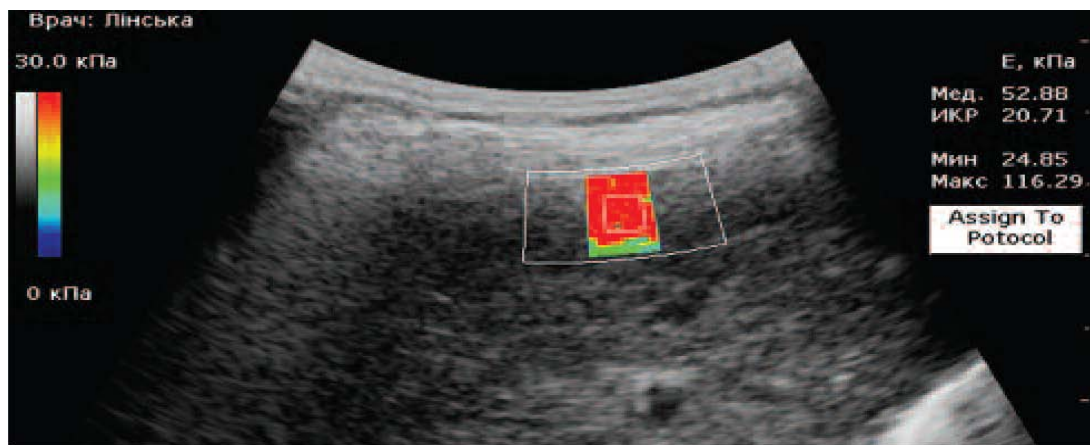
Procedure of successful performance of elastography/elastometry on the SW-based method should take into account all component parts of this process.

1) The patient should be previously informed of the core of procedure, its stages and results.

Patient position: lie on back or the left side being in relaxed, stable and still standby (without inotonia). The right hand is up and takes position behind the head in the manner for getting maximum intercostal spaces. Abstinence from meal takes 5-8 hours. The patient and doctor in charge should do it to the utmost of their power for proximate decrease of wind level ( prior to 2-3 days before investigation the patient meal should follow the zyme and foam suppressor management). There should be a voluntary man's respiration (it is not advised to pay attention of the patient to respiration and modification depth).

2) In the device "Presetting" it is required to select convex format probe (frequency range is from 1 MHz to 6 MHz) and "Trans-abdominal" application. In scanning there are possible two options of acoustical access to the right lobe of the liver. The most preferable is an intercostal access through the VII-IX intercostal spaces to liver segments V,VI, VII. The probe should be positioned in the range of the front and middle axillary lines. Acoustical access to the IV and VIII liver segments is extremely hard (the same as for biopsy) and so it is not used for elastometry in the shear

wave elastometry (SWE) standard situation. The probe should be arranged along ribs with minimum, as possible, skin pressure in contact point. To prevent the shear wave (SW) excitation ultrasound beam power from rib absorption, one should carry out fan-shaped swinging of the probe and control quality of the B-mode on the screen. Only after attaining the qualitative picture in the B-mode, one should stop the probe and switch on the mode of stiffness color mapping (SCM).



**Fig.5.** Artifacts of incorrect selection of acoustic window: positioning of ROI and SW into reverberation zone at the ROI small depth (under capsule) - shown is a significant discontinuity of stiffness values (average value is of 52.88 kPa)!

The second option of the acoustic access to the liver right lobe through hypochondrium is the worst desirable case. However, it makes it possible to exercise visualization of liver segments IV, V, VI, VII. One should take into account the meaningful constraints of this acoustical access. The major constraint is that one can not use the probe compression of the front abdominal wall. The transmissive pressure affecting the hepatic parenchyma leads to artificial raising of measurement for stiffness values. The same overstated stiffness values arise from the attempt to cope with gas difficulties in the large bowel by liver moving-out with diaphragm at the height of full inspiration. This is a blunder that leads to elastometry data overstatement of 3-6 kPa! This artifact is connected, as shown above, with summation of some negative factors: probe enhanced compression and diaphragm prelum of liver parenchyma, pressure increase in the lower cava and difficulty of the dark-red blood outflow from the liver.

For performance of elastography/elastometry of the liver left lobe, the acoustical access to high-riding liver or liver dorsoversion (turn of its front upper surface to the rear in wind, abdominal fullness with gastric contents and gas), postoperative adhesions and stains from the scar of the front abdominal wall is often hard-to-get-at place too. The probe should be arranged in the longitudinal plane (sagittaly) or is less common in lateral plane (frontally) with possibly minimum pressure on the skin at the place of contact as described above. One should move away scanning plane from entry great vessels, hepatportal tracts, a gall bladder and ligaments in the region of interest (ROI) .

### 3) Position of region of interest (ROI) in stiffness color mapping (SCM)

In batching data for color mapping from region of the interest one should move probe in the smooth and slow way (low image frequency in mapping) or even stop any motions of the probe for 3-5 seconds. It makes it possible to avoid motion artifacts and attain mapping stabilization in the region of interest (ROI). This is undeniably that one should provide reliable visualization the B-mode prior to activate the shear mode elastometry (SWE) mode and position the region of interest (ROI). However, for making control over acoustic artifacts impairing the SWE data, one should keep away himself from one important deception! Do not resort to automatic and digital methods

of image optimization in the B-mode that are available in the ultrasound apparatus (harmonics, speckle and reverberation suppression, gamma correction, dynamic range compression, digital filtering and smoothing, persistence, multibeam composite scanning). The B-mode should be optimized as better as possible by exclusive selection of the acoustic window for the ROI navigation in the elastography mode. Planning elastography procedure, it is necessary to leave intact the noises on the B-image (picture) without correction to avoid them in the region of interest (ROI) for stiffness color mapping (SCM) later on and position the sample volume (SV), not counting artifacts common for both modes (reverberations, shades, attenuation and so on). It is important to provide the best and uniform contact between the probe and a skin by applying sufficient gel amount and contact self-control round the whole probe aperture. Probe detachment (especially imperceptible) often leads to B-image saving and a full absence (that discourages the operator) of color map shaping in the ROI elastography. Naturally, any accurate elastography in this situation involved is out of the question.

4) Setting the region of interest (ROI) for color mapping and sample volume (SV) for elastometry.

The shear wave elastography (SWE) settings in the abdominal "Presetting" of the convex probe have been commonly optimized for liver fibrosis assessment by default. Metrology of the shear wave (SW) elastography mode for the ultrasound device is carried out by manufacturer on the special-purpose phantom. Taking this in view, there should be no significant discrepancies in determining stiffness values for various producers that take into account the total contribution of tissue visco-elastic properties in the shear wave elastography (SWE). The examination should start from settings by default.

In positioning the region of interest (ROI) for liver, one should take into account the shaping principle of color mapping in the shear wave elastography (SWE) operation. Ultrasound pulse excites shear waves that are lateral to its propagation axis on the sides of the region of interest. Setting of shear wave excitation to the right or left or both sides simultaneously as to region of interest (ROI) can be selected at your will. Their propagation path is accompanied by tissue deformation, and the second (probing) beam records tissue micron dislocations and makes it possible to calculate Young's module in velocity of the shear wave (SW) propagation and their phases. In accordance with scale values in kPa pixels are color-filled in the region of interest (ROI).

If there are acoustic heterogeneities or artifacts in the region of interest, this will lead to non-homogenous filling or partial dropping out of color mapping pixels in the region of interest ROI. Put the other way round, for color image shaping on the shear way (SW) principle, one should choose the most homogenous areas of liver parenchyma.

The operator can change window size of color mapping in region of interest (Min/Middle/Max). The ROI maximum size in lateral direction is of no more than 25 mm. With the region of interest is decreased in lateral direction up to 10 mm, image frequency will increase i.e. temporal resolution. This makes it easy to solve problem for obtaining homogeneous and representative images in stiffness color mapping (SCM).

Known artifacts of the B-mode are the cause of substantial measurement errors in tissue stiffness. To increase elastometry accuracy it is necessary to avoid visualization aspects at which there are great vessels or other lumps with liquid as well as bony tissues (Fig.6) between the shear wave shaping place and stiffness mapping window in the region of interest (ROI).

More often reverberation takes place on the image in the direction of ultrasound beam orthogonal propagation outgoing from the middle/central part of convex probe on the tissue borders previous to liver (derma, septa between lobules of subcutis, surface band, vaginal opening of intercostal muscles, leaflet of abdominal peritoneum). The region of interest (ROI) should be positioned on each side from central beam reverberations or reverberation region, which is deeply



visible in the B-mode.



**Fig.6.** Artifact of liver parenchyma stiffness increase when region of interest (ROI) is close to lump (cystic lesion) with liquid

The upper border of region of interest (ROI) should be located at a depth of no less 10 mm from liver surface to avoid multiple reflections causing reverberation artifact and overstating stiffness values. Surface layers of the liver parenchyma can also be subjected to excessive mechanical strain due to its pressing to ribs or Glisson's capsule draw because of hepatomegalia (hydrops, amyctic, adipose infiltration).

The ROI lower border is advised to place at a depth of no more than 70 mm from the liver surface. So, one should avoid zones where insufficient penetration power of ultrasound beam leads to image region loss in stiffness color mapping at the ROI lower part.

5) Principles of image selection for analysis of shear wave elastography in the region of interest (ROI SWE) are as follows:

- One should select images from cine-loop corresponding to the moment of color picture stabilization in the region of interest (ROI) (exposure with probe at stop for of 5 seconds). Color should uniformly fill the region of interest (ROI) without empty sections with development of black-and-white background.
- One should not use images including artifacts.
- One should not use the images where the elastogram is non-uniform in the lateral direction. (If the right or left end of the elastogram is painted red or blue it is likely that compression in the lateral direction took place).
- One should not use the images where the elastogram is non-iniform both in the lateral and e axial direction. This is a clear evidence of the elastostogram shaping in noise or artifact conditions.

There should be recorded of no less than 3 cine-loops from each lobe (it is necessary to have a stable elastogram, at least, including 5 images for each cine-loop). After displaying a stable color picture, the probe should be kept unchanged in the region of interest (ROI) for making sure in

stability of the results obtained, viz. there should be stable: stiffness color mapping and taken average value of Young's module from image to image measured. Carrying out remeasurements, one can make sure in reproducibility of measurement results [18].

6) Control parameters of stiffness color mapping in the region of interest (ROI SCM).

- Scale. By analogy with the scale in the Doppler's color mapping (DCM) of streams the scale for stiffness color mapping (SCM) in kPa can be adjusted in the range of 10 kPa to 300 kPa. Adjustment ("Scale") changes stiffness scale (kPa) or for shear wave velocity scale (m/s) by option. The scale blue color corresponds to soft, elastic tissue (low velocity of shear wave (SW) travel) and red color conforms to stiff tissue (shear wave (SW) high velocity). This is taken by all three producer companies of apparatus with the shear wave elastography (SWE) option. Reverse scale inversion is possible. One should be reminded that device color scale of Hitachi Co compression elastography founder and its successors has a reverse meaning: blue color meets stiff tissue and red color corresponds to soft tissue. Naturally, the color perception attributable to specific stiffness values vary as the operator will change the range of scale high limit. For stiffness color mapping (SCM) of liver parenchyma it is recommended to set the scale high limit close to limit of 40kPa to 60 kPa. In this case, the doctor-operator's subjective perception will correlate blue scale values with fibrosis stages F0-F1, green scale values-with stages F2-F3, yellow-red scale values - with fibrosis stages F3-F4. Increase of the upper range more than 100 kPa levels visual differences in fibrosis stages and hinders the sample volume (SV) navigation though it has no impact on measurement values in elastometry.

- Degree adjustment of color and gray-scale picture mixing allows to make the color map in the region of interest (ROI) either more saturated or more clear. Illumination of black-and-white background of the B-picture through the color of region of interest (ROI) makes it possible to control its positioning for keeping out of knowingly stiff or liquid comprising structures

- With unsatisfactory color visualization in the region of interest (ROI), there is an opportunity to change stiffness mapping sensitivity. Decrease of sensitivity threshold value of elastography makes it possible to improve visualization of stiffness value for low signal level in the region of interest (ROI). It is also possible to increase ultrasound beam penetration

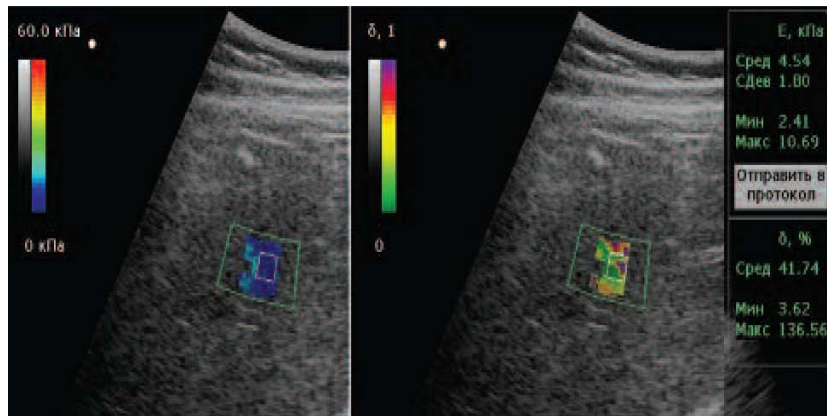
- Selection of position, size and sample volume (SV) number for elastometry. Stiffness color mapping (SCM) makes it possible to navigate the SV position in the space of region of interest (ROI). Sometimes, operator's objective is difficult due to choosing freedom of the SV position. Which of the stiffness values is more representative? The problem is either one should set the sample volume (SV) in the space of the region of interest (ROI) as desired or represent the SV set to cover all region of interest (ROI). According to our reckoning, this is not quiet correct approach. It is advised, where possible, to place the ROI central zones into the sample volume (SV). "Golden" rule of elastometry states the following: stiffness measurement should be taken at that place of region of interest (ROI) where color values are the most homogeneous (solid) and there are no bursts of minimum or maximum stiffness values. Stiffness extreme values both for the stiffness color mapping (SCM) and elastometry are evidence of artifacts, scanning defects or anatomical organizations different from parenchyma in stiffness. It is understandable that ultrasound scanning has spatial resolution in the B-mode of 500  $\mu\text{m}$  and does not allow to obviate all hepatoportal canals in the SV elastography (small triads- porta branches and intrinsic duodenal ampulla and interlobular bile ducts). SV size of 5 mm x 5 mm (round cross-section or squire section) at slice layer of 4-5 mm in thickness  $m$  includes parenchyma volume of 80  $\text{mm}^3$ . It is known that liver acinus changes of 0,5-1,5 mm in size.

- Apparatus of most producer companies provides displaying several elastometry digital parameters on the screen: the major parameter is arithmetic average (AA) of all pixels in the sample volume (SV). However, its isolated use in clinical interpretation is of low significance. It is important that range of values in the sample volume (SV) should be as small as possible. The

additional parameter for measurement evaluation of the AA accuracy and validity is a sigma value (mean-square deviation is designated as  $\sigma$ ). It makes it possible to estimate how much stiffness values in pixel set inside of the sample volume (SV) can differ from average value (AA). The apparatus provide opportunity to change it over the ROI view of stiffness color mapping into the color mapping view of spatial distribution in sigma values. The sample volume (SV) should be placed in most homogeneous fields of distribution for sigma values and avoid extreme values in the shape of bright pink sigma values according to color scale. In scanning the sigma digital value taken from the sample volume (SV) in real time is displayed on the screen even in advance, that makes it possible to leave the parenchyma zone where sigma values exceed 30. More reliable values have to be considered the measurement results having  $\sigma$  - low values. Minimum and maximum stiffness values in the window of results show that measurement result having less difference of these values is more reliable (accurate ). It is not desirable for minimum to exceed sigma value (Fig.7).

It is possible to reduce elastometry and sigma error at the expense of the sample volume (SV) size decrease. However, by analogy with spectroscopic Doppler sonography, decreasing the sample volume (SV) we reduce representativeness of various values of parenchyma stiffness (possibly true) in the ROI range. Naturally, low sample volume (SV) covers minority of liver acinuses and data representativeness is decreased .

In conclusion, it should be required to evaluate average value of liver stiffness from three not related average values. If three information sets taken from one segment of the region of interest (ROI) are greatly disagreed (the difference is more than 1,5-2 kPa), it is recommended this zone to consider to be bad for scanning and it is necessary to change the acoustic window. Making conclusion on the base of scale METAVIR, one should take account the fact that all so called chronic diffuse liver diseases (CDLD), causing fibrosis and cirrhosis, afflict hepaticus parenchyma not in the best uniform manner. Shown is a substantial discontinuity of distribution as to fibrosis stages in the range of liver for a patient by using fan biopsy methods, on autopsies and magnetic resonance (MR) elastography method[5, 12].



**Fig.7.** Identification of artifacts for root-mean-square deviation color mapping (CMS sigma) as to high values of scale

If performances of all stated above scanning techniques and elastometry after obtaining information from the region of interest (ROI), the stiffness values as to average values are different from one segment to another one, it is required to show in conclusion the fibrosis value range as to the METAVIR Fn-Fn+1 scale.

The stiffness numerical data obtained can be saved in the test log both in kPa and in m/s similar to the ARFI method of some manufacturers (Siemens, Philips).

At present, the most fundamental study of the fibrosis staging by the SWE method in

comparison with the TE data and the METAVIR scale are articles of Ferraioli G. et al., 2012 [10, 18]. We advice to use data of these authors in the SWE clinical interpretation of results unless the national scale (Tables 2-4) will be developed.

Table 2

**Data of median, interquartile range (IQR), discharges and values p, received for each fibrosis stage using methods SWE and TE (with changes) [10]**

Parameter	Method	Stage METAVIR			
		F0-F1	F2	F3	F4
Median, kPa	SWE	6,2	7,6	10,0	15,6
	TE	5,6	6,4	9,1	19,8
Диапазон, kPa	SWE	4,5-9,3	5,6-13,0	8,9-12,0	8,0-22,5
	TE	3,5-8,9	3,6-10,2	6,1-20,8	6,4-36,3
IQR	SWE	5,1-6,8	7,2-8,3	9,2-10,1	12,8-18,8
	TE	4,5-6,5	5,4-8,0	8,4-11,6	13,4-23,0
Number of discharges	SWE	1	2	1	0
	TE	0	0	2	0
p	SWE		0,0001*	0,003**	0,09***
	TE		0,02*	0,002**	0,06***

Note. "p" relates to differences between fibrosis consecutive stages (\* -F0-F1 as against F2; \*\* — F2 as against F3; \*\*\* — F3 as against F4).

Table 3

**Analysis of the SWE and TE reproducibility as compared to the METAVIR stages (with changes) [10]**

Method	Stage of METAVIR					Rate of, %
	F0-F1	F2	F3	F4	Total	
F0-F1, kPa						
SWE < 7,1	42	7	0	0	49	85,7
TE < 6,9	43	19	1	1	64	67,2
F2, kPa						
7,1 < SWE < 8,7	4	24	0	1	29	82,8
6,9 < TE < 8,0	3	6	2	0	11	54,5
F3, kPa						
8,7 < SWE < 10,4	2	1	11	2	16	68,8
8,0 < TE < 11,6	2	7	7	1	17	41,2
F4, kPa						
SWE > 10,4	0	1	2	21	24	87,5
TE > 11,6	0	0	3	22	25	88,0
Cumulative reproducibility						
SWE	Weighted ratio K = 0,90				98/118	83,1
TE	Weighted ratio K = 0,83				78/117	66,7

**Results of the SWE and TE clinical response in using threshold values for optimal measurements (with changes) [10]**

Parameter	Method	> F2 (95% CI)	> F3 (95% CI)	= F4 (95% CI)
Threshold, kPa	SWE	7,1	8,7	10,4
	TE	6,9	8,0	11,6
Sensitivity,%	SWE	90,0 (80,5-95,9)	97,3 (85,8-99,9)	87,5 (67,6-97,3)
	TE	69,6 (57,3-80,1 ICC)	89,2 (74,6-97,0)	91,7 (73,0-99,0)
Specificity,%	SWE	87,5 (74,8-95,3)	95,1 (87,8-98,6)	96,8 (91,0-99,3)
	TE	89,6 (77,3-96,5)	88,8 (79,7-94,7)	96,8 (90,9-99,3)
PPV,%	SWE	91,3 (82,0-96,7)	90,0 (76,3-97,2)	87,5 (67,6-97,3)
	TE	90,6 (79,3-96,90)	78,69 (63,2-89,7)	88,0 (68,8-97,5)
NPV,%	SWE	85,7 (72,8-94,1)	98,7 (93,1-100)	96,8 (91,0-99,3)
	TE	67,2 (54,3-78,4)	94,7 (86,9-98,5)	97,8 (92,4-99,7)
LR+	SWE	7,2 (6,3-8,2)	19,7 (18,3-21,2)	27,4 (23,5-32,0)
	TE	6,7 (5,6-8,0)	7,9 (6,9-9,1)	28,4 (25,0-32,2)
LR-	SWE	0,11 (0,04-0,3)	0,03 (0,003-0,2)	0,13 (0,03-0,6)
	TE	0,34(0,1-0,8)	0,12 (0,04-0,4)	0,09 (0,02-0,5)

PPV / NPV is positive and negative predictive value respectively; LR+, LR- is positive and negative likelyhood ratio respectively.

### SUMMARY.

The aim was to identify opportunities and limitations of using shear wave elastography (SWE) for liver stiffness measurements (LSM). We examined 25 healthy individuals, 152 patients with chronic C hepatitis (VHC) and 28 with Wilson-Konovalov disease. SWE was performed on the Ultima PA Expert® (Radmir, Ukraine) scanner with 1-5 MHz convex probe or Aixplorer (Supersonic Imaging SA, Aix-en-Provence, France) and 1-6 MHz convex probe.

In Wilson-Konovalov's disease we stated a significant increase of LS in kPa compared with healthy individuals ( $10.17 \pm 0.75$  vs  $4.05 \pm 0.29$ ;  $p < 0,001$ ), due to the development of liver fibrosis as diagnosed by biopsy.

Reliability of SWE for LSM we studied in patients with chronic hepatitis C. LSM was classified as a failure when no signal was obtained. Reliable LSM were defined when ratio interquartile range/median (IQR/M)  $> 0.30$ . We calculated median value from total liver - TL (10 LSM from both lobes), RL and LL (5 LSM from each) which expressed in kPa. For estimation stage of fibrosis we used cut off values proposed by Ferraioli et al.

The rate of reliable LSM for TL was 76.3% that significant lower as compared with RL (92,1%,  $p < 0,001$ ) and LL (90,8%,  $p = 0,001$ ) respectively Distribution of fibrosis in the liver was heterogeneous which was independently associated with the risk of unreliable total LSM (OR 3,48; 95% CI 1,55-7,81,  $p < 0,003$ ).

## **Conclusions**

1. We stated an excellent intraobserver reproducibility of SWE as ICC was 0.889 (95% CI 0,778-0,946).
2. Artifacts (especially reverberation) and narrow acoustic windows are insignificant in percentage (2.3% patients), but they restrict liver stiffness measurements (LSM) by using shear wave elastography method.
3. The LSM elastometry success achieved by the SWE method depends on strict follow-up of procedure algorithm taking into account patient-, machine- and operator-dependent factors.
4. SWE in combination with B-mode and Doppler sonography in one Doppler ultrasound device should become a routine method for widespread use in determining the fibrosis stage for chronic diffuse liver diseases

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