THREE-DIMENSIONAL ULTRASOUND IN CEREBROVASCULAR EVALUATION

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SUMMARY – Three-dimensional ultrasound has started developing in the fifth decade of the last century using numerous imaging innovations. For the exploration of extracranial circulation, three-dimensional ultrasound is used primarily on carotid arteries that are easy to access due to their anatomical position. In the evaluation of intracranial circulation, three-dimensionality can be achieved only partially due to the size of the bony window that prevents probe movement in all 360°. Three-dimensional ultrasound allows greater spatial resolution than conventional two-dimensional ultrasound. In comparison with magnetic resonance, three-dimensional ultrasound reaches transaxial resolution of 5 mm, longitudinal resolution of up to 10 mm and rotational resolution of up to 40°. Other advantages are noninvasiveness, volumetric tissue analysis instead of planimetric analysis, relatively low cost with high reproduction accuracy, high sensitivity and specificity (r=0.982). The principal shortcomings of three-dimensional ultrasound are the impossibility to distinctly differentiate between periarterial and intra-arterial tissue that will cause problems with tissue segmentation, cost of the ultrasound device that is somewhat more expensive, and the need for a skilled operator. Movement artifacts are most responsible for all artifacts but are easy to diminish with the use of the mechanical arm and ECG synchronization. Three-dimensional ultrasound is best used as a complimentary method of examination along with conventional ultrasound that enables mandatory hemodynamic evaluation. Recently, along with three-dimensional ultrasound, four-dimensional ultrasound is being developed that will allow real time tissue movement analysis and thus atherosclerotic plaque instability assessment.

Key words: *Cerebral arterial diseases – ultrasonography; Carotid stenosis – ultrasonography; Carotid arteries – ultrasonography; Cerebrovascular circulation – physiology; Cerebrovascular circulation – ultrasonography*

The last obstacle in imaging of the human body that separates true tissue pathology from two-dimensional screen or film image is tissue voluminosity. Modern imaging techniques such as computerized tomography (CT) or magnetic resonance (MR) have brought great progress to neurology, especially brain imaging. Still, the "gold standard" and the most popular method of examination in carotid artery imaging is Doppler ultrasound[1].

The idea of three-dimensional ultrasound has been developed since the 1950s when stereoscopy was first introduced[2]. Today's notion of three-dimensional and four-dimensional ultrasound was conceived slightly later and was based on the idea of series of image layers adjacent to one another, which enable the illusion of three-dimensionality. In the next twenty years, substantial progress was made and cerebrovascular exploration was enabled. Currently, three-dimensional ultrasound is widely used in gynecology and obstetrics as well as in cardiology and internal medicine, while the applications in neurology still lack proper precision due to the fine and thin structures that need to be visualized with great accuracy[3-6]. Further development of three-dimensional ultrasound will increase the number of noninvasive methods of examination that will improve the sensitivity and specificity in cerebrovascular diagnostics.

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Three-dimensional ultrasound can be used in the exploration of extracranial circulation, i.e. carotid arteries that are easy to access due to their anatomical position in the neck. Vertebral arteries cannot be examined properly since anatomical obstacles for adequate data sampling remain great (cervical vertebrae). Intracranial visualization of intracranial arteries is only partially allowed since the size and the thickness of bony windows prevent probe motion of 360° that would in turn provide a proper amount of data[7]. Some exception to the aforementioned argument is data acquisition during brain surgery involving trephination[8]. Lastly, three-dimensional analysis has a few prerequisites: known spatial orientation and position to an external reference point in space as well as proper software that allows three-dimensional reconstruction and visualization[9-11].

The main advantage of such analysis is multiangular examination of the desired arterial segment including intravascular approach thus providing greater spatial resolution[12]. Other advantages are noninvasiveness, volumetric instead of planimetric analysis, relatively low cost, and high levels of reproducibility, sensitivity (81.5%-93%) and specificity (82.5%-98.9%)[13,14]. Comparison with MR imaging showed satisfactory results: transaxial resolution of 5 mm, longitudinal resolution of up to 10 mm, and rotational resolution up to 40°[15]. The disadvantages of three-dimensional ultrasound are the impossibility to properly differentiate between periarterial and intra-arterial tissue that causes thresholding problems in tissue segmentation, higher cost compared to conventional ultrasound examination, high operator skill, and various artifacts (cardiac motion, hand movement, swallowing or respiration)[6]. Using probe holders and ECG synchronization could diminish some of the mentioned artifacts[16].

The Principle of Three-Dimensional Image Creation

Ultrasound beam, created by the motion of piezoelectric crystal, from the probe enters the tissue and is reflected back from the tissue, thereby causing mechanical changes in the piezoelectric crystal. That change is used for the interpretation of collected data, the main information being ultrasound beam attenuation and the time needed for ultrasound reflection. Some parts of the emitted ultrasound are absorbed in the tissue while other scatter. From the emitted ultrasound only the central spectral frequencies are used, thereby ensuring greater image quality. Probes differ in emitted frequencies and are used accordingly: lesser precision with greater penetration is gained from lower frequencies of about 2 MHz, and greater precision and lesser penetration from higher frequencies of 7 to 13 MHz. The intensity of ultrasound is usually around a few mW over 1 cm[2,17].

Resolution of the acquired image is defined with impedance, the ratio between the sound pressure and the speed of particle motion induced by this pressure. This primary resolution is the determining factor in three-dimensional interpretation. Moreover, it is the most limiting factor for ultrasound platform resolution because of the difference between the outgoing and the incoming signal between the two periods which allow maximal resolution of about 1 mm. Theoretically, the smallest resolution possible for the ultrasound is 0.2 mm, although in practice such ultrasound platforms are rarely found. In comparison, it can be noted that the resolution of the standard available CT platforms is between 0.3 and 0.5 mm[18].

The size of the pixel (meaning "picture element") is another limiting factor that determines the resolution of three-dimensional image. The glow of specific pixels in B mode is equal to the amplitude of the reflected ultrasound waves that is presented as matrices of specific tissue echoes. The third dimension is achieved by the transformation of pixels into a digital signal and further addition of the slice thickness that is determined from the position of a tissue unit in respect

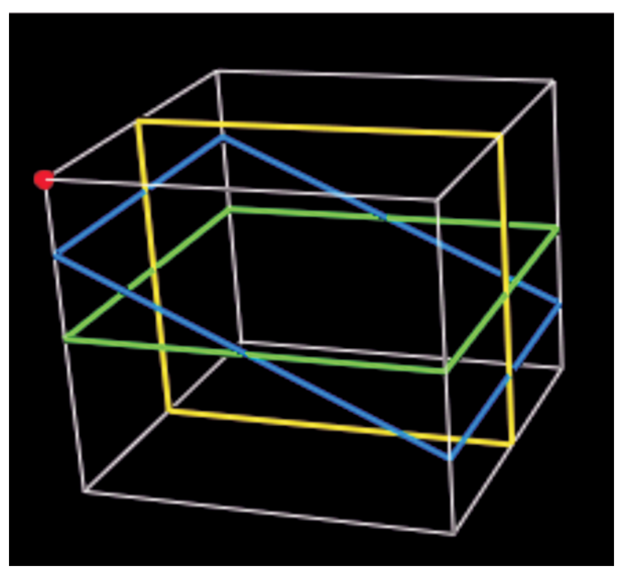

Fig. 1. Three-dimensional wire model representing region of interest (ROI).

to the external, extracorporeal, mark. It is then that the pixel is turned into voxel, a volume unit similar to a cube[15] (Fig. 1). Some platforms allow different slice thickness each time an examination is performed (motor driven units), whereas some have predetermined slice thickness (freehand motion). In case of the "position and orienting measurement" (POM) device, the transducer needs to be placed on the surface of the ultrasound probe and the magnetic coil receiver in proximity of less than 50 cm, which will allow accurate post-processsing creating three-dimensional data sets. The use of the "region of interest" (ROI) focuses the examiner's attention on a particular vascular segment[19]. Gray scale voxels offer information on tissue surface while different planes during examination offer precision. Axial plane is best for intra-arterial surface examination and exact plaque location, whereas coronary and sagittal planes enable detailed evaluation of the possible plaque ulceration. Additionally, oblique planimetry with supplementary interpolation is possible whenever visualization in standard manner does not suffice[11].

Such three-dimensional reconstruction is also used in principal by the CT reconstruction, with additional information derived from recorded voxels on tissue density (Hounsfield units ranging from -1000 to +1000). Such density scale is not yet used in ultrasound. However, conventional B mode is used in plaque histology assessment, therefore similar idea may be applied in the future to three-dimensional reconstruction. Thus, atherosclerotic plaque quantity (diameter, area, circumference, volume) and quality (soft to calcified) could be detected[18].

It is necessary to mention that modern technology of three-dimensional ultrasound also uses some principles borrowed from applied MR technology, specifically the use of radio frequency (RF) signals that enable greater image resolution[20].

Data Acquisition

In order to achieve the highest quality of a three-dimensional image, the quality of the outgoing signal of the ultrasound machine needs to be as high as possible. One of the most important factors is the B mode resolution that has been significantly improved in the last few years with the use of RF signals that have diminished the quantity of the background noise[21]. It should be noted that there is a discrepancy between the frequency of the number of screens shown *per* minute and the frequency of the analogue outgoing ultrasound signal. The greater the difference the greater is the number of images created by interpolation of two adjacent slices. It means that if lower frequencies are used for examination (as for intracranial examination), the error for reconstruction and visualization is great as well as the number of artifacts created in the process. The best solution for this problem is synchronization of the two frequencies.

Data acquisition needs to be incorporated using proper computer software for transformation of analogous data signals into the digital set. Most often, the so-called "framegrabbers" are used. Modern technology allows for internal three-dimensional systems to be incorporated in conventional ultrasound platforms, which then use the raw digital signal. The last solution is the use of video recording from a screen and subsequent three-dimensional analysis. Only the first mentioned approach allows adequate image quality after reconstruction, whereas the last two cannot be used because of the great resolution loss[22].

Sample Collection

Sample collection implies correct spatial organization of the acquired data for three-dimensional reconstruction. Mechanical support is crucial in this step of acquisition; use of "mechanical arms", mechanical pods, motor acquisition or various sweep mechanisms are possible[23]. POM systems that allow for sampling with 6 degrees of freedom, which implies free-hand movement over the ROI, are most often used today[11,24]. Devices such as these are most popular for the use in cerebrovascular exploration.

Motor Acquisition

Devices that use motor driven acquisition are most often attached to the ECG device that enables triggering to a specific part of cardiac movement that in turn diminishes respiratory artifacts[16]. In this way, the resolution of collected data set approaches that of the theoretical value of 0.2 mm. The manner in which reconstruction is performed is closest to that used by the CT or MR reconstruction because the acquired data set is orthogonal. Precision in this case is great and slice thickness is examiner dependent. A disadvantage of this technique is that the patient needs to remain motionless for a longer period of time, which means that the technique is inapplicable as bedside evaluation in critical care situations.

Semi-Quantitative Acquisition

Since this kind of device in not motor driven, it needs to be assumed that the speed of transversing the ROI is a constant as well as the frequency of the incoming data. Considering that the mentioned is, in fact, an assumption, it is not possible to determine with certainty the true size of the voxel. Even though it appears that the collected data would not have the needed precision, the practice has shown, especially in intracranial evaluation, that these images can be successfully correlated to MR angiography. The advantage of this kind of acquisition is short term acquisition (less than a minute) and therefore the technique is applicable in critical care evaluation. It is an assumption that this technique might be applied in early diagnosis of subrachnoid hemorrhage preceding cerebral angiography. Still, this system has the least resolution of all three-dimensional systems[22].

POM Acquisition

A trademark of this kind of acquisition is that the position and orientation are determined through the use of magnetic field. The system was devised on phantom models and *in vivo* exploration of human extremities. Recording can be commenced when a phantom calibrated transducer has been fixed on the ultrasound probe and a magnetic coil receiver has been placed in the vicinity of maximum 50 cm apart. The magnetic coil serves as the extracorporeal reference point that allows for accurate positioning of the living tissue in a Cartesian coordinate system and greater resolution. The maximal possible resolution in this case is less than 1 mm[24].

Recording Technique for POM Acquisition

In our laboratory we use the POM device. The patient needs to be placed in supine position and conventional ultrasound needs to be performed first. Thus, his vascular status and the position of pathological changes can be visualized. Depending on the size of the lesion or the necessary resolution, correct recording time is determined (1 s, 2 s, 5 s, 10 s...). The transducer is then fixed onto the probe and the receiver less than 50 cm apart. We choose the type of application first and then the length of the recording and color scale used. Additionally, prior to each recording the color scale and the measuring scale (quantitative parameters) are set as well as the ROI. A probatory sweep motion is advised. Best is to record the carotid arteries transversally with the probe being placed perpendicularly on the skin surface. If intracranial blood vessels are being monitored, a fan like motion of the probe is preferred[25].

Recorded data sets are postprocessed and are then ready for graphical three-dimensional analysis. The examiner chooses the axis and the plane of his viewpoint that enables different pathology angulation and accurate measurement. Once the best approach has been established the animation option (“steps”) can be used that shows the desired image as a three-dimensional tissue mass which moves in front of our eyes as if held in our hand. That will alleviate the examination and diagnosis.

Additional accuracy can be provided with the use of the ECG gating or triggering. Most often, the R peak is singled out from the cardiac cycle and this diminishes the number of recorded artifacts, increases the reproducibility and shortens the time needed to perform the examination.

Three-Dimensional Reconstruction

Data sample collected from the ROI provides the basis for the construction of the three-dimensional image (Fig. 2). This reconstruction is named rendering and is complicated because of the interpolation of data slices. This argument is the basis of disbelief that free hand probe motion can obtain adequate precision for three-dimensional reconstruction, and furthermore usually the probe sweep is not performed perpendicularly to the insonated blood vessel. The problem with free hand

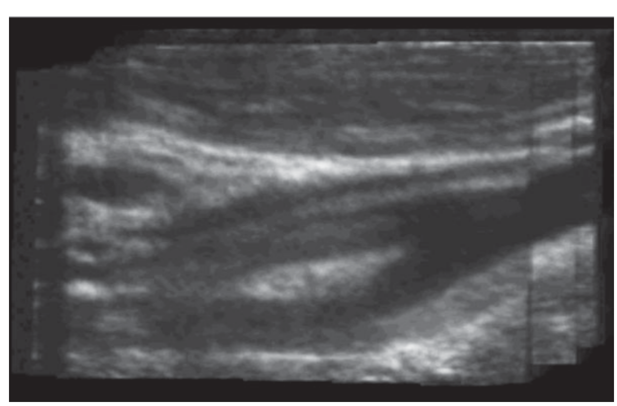

Fig. 2. Longitudinal 3D view of carotid bifurcation.

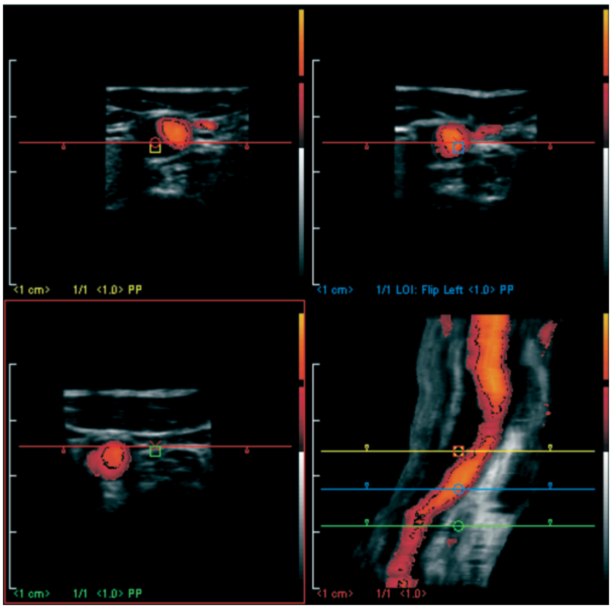

Fig. 3. Parallel slices in transverse view using power Doppler, manual setting on common carotid artery.

motion is oversampling on the one hand and undersampling on the other. In recent years, this has been the focus on technique improvement since free hand motion seems to be the most appropriate way of handling any kind of ultrasound examination. Long lasting solutions are not yet available[26].

Visualization

There are three main modes involved: planar surfacing, structural surfacing and volume[27] (Fig. 3).

Planar surfacing

Three-dimensional object orthogonally analyzed becomes visible in two-dimensional slices in different planes: axial, sagittal or coronary, i.e. the main axes being x, y and z[28]. Axial approach is best for the assessment of plaque area and correct positioning inside a blood vessel as well as for detection of possible irregularity and potential plaque ulceration. Coronary approach can be used for plaque irregularity and the depth of ulceration thus usable in prevention of further cerebrovascular embolization. Lastly, sagittal approach can be used to further enhance the certainty obtained with the coronary approach. This kind of analysis allows greater precision and collection of information about the plaque that are not available with standard ultrasound examination.

Three-dimensional reconstruction offers oblique axes to be used (as proposed by the examiner) and it is important in exploration of the pathology and histopathology of atherosclerosis. This kind of reconstruction offers greater exploitability of the data samples. The quality of oblique planes is directly dependent on resampling and may require further interpolation (the more precise the interpolation, the greater the resolution).

Structural surfacing

Structural surfacing implies that the shades of grey scale represent underlying tissue density. If tissue density is plotted in a coordinate system with three axes, the surface (borders and areas) will be described as calculated polygons. There are two main principles used: use of the same shade of grey color for the whole polygon uniformly or selecting the peak values for each polygon and further interpolation between them (Gouraud's approach)[22] (Fig. 4).

Volume

Volume is shown so that the two-dimensional projections of a semitransparent volume are calculated. For this purpose the technique called maximal intensity projection, the same as for MR angiography, is used by three-dimensional ultrasound. Basically, it means that the value assigned to a pixel implies that it is the maximal value throughout the segment of the ultrasound beam. Further techniques are used as well such as in-

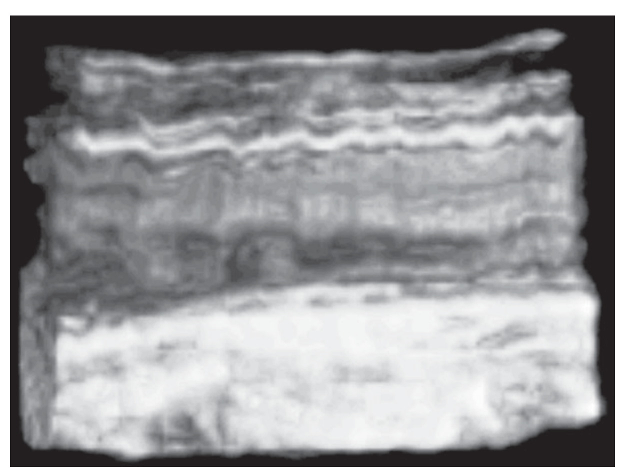

Fig. 4. Three-dimensional appearance due to different shades of gray scale.

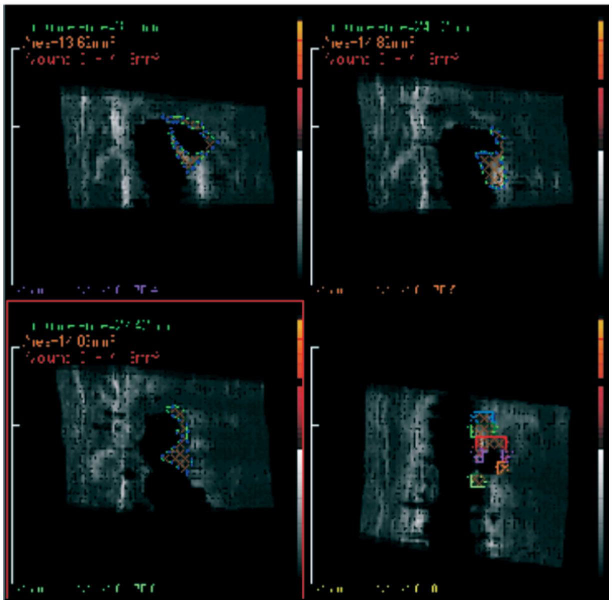

Fig. 5. Volume calculation on ulcerated plaque near the carotid bifurcation.

dentation and darker areas to improve the appearance of three-dimensional image. All the aforementioned points enable volume measurement in a certain tissue, for instance, the carotid plaque volume[29] (Fig. 5).

Segmentation

Segmentation is, in essence, object identification. The most accurate way of this is automated detection of the highest values of grey scale intensities[30,31]. The most common approach to solving this problem is thresholding. It means that the structure of interest that has been three-dimensionally projected is selected on the basis of intensity and thereafter separated from the surrounding tissue, i.e. background echoes. The idea is not, at present, fully implemented and the results of such technique are not final. Additional techniques can be used to correct this situation, such as MCE (minimum cross entropy)[32] thresholding, where the calculated value of grey scale is substituted with the combination of other values or MAP *("maximum a posteriori")*[33] thresholding that allows transformation of grey scale values using Rayleigh's distribution that is, in turn, represented in gaussian mode.

Three-Dimensional Applications

Three-dimensional ultrasound can be used for extracranial and intracranial evaluation[12,34]. Considering that this technique is noninvasive, bedside evaluation and monitoring is possible affecting the mode of treatment and offering better patient care.

Extracranial evaluation

In extracranial evaluation, three-dimensional ultrasound is mostly used for plaque identification, monitoring of the degree of stenosis, plaque surface irregularity analysis and possible ulceration evaluation[35-37]. This might be of particular interest clinically since about 40%-80% of ischemic strokes are caused by proximal embolization[38]. Three-dimensional ultrasound was found useful in volumetric plaque analysis (parallel planimetric analysis) proving interobserver variability of 94% and intraobserver variability of 93.2%, offering the possibility to quantify and monitor plaque progression and regression according to applied therapy that would prevent stroke occurrence (ACE inhibitors, statins)[39]. However, caution is needed when evaluating plaques less than 100 cm^3 and slice thickness should be less than 3 mm. Additionally, interobserver variation of $\pm$20% is not considered relevant[35,40]. More recent publications indicate the possible use in high-precision surgical guiding procedures (cardiac, fetal or vascular), evaluation after carotid endarterectomy and vessel wall stress analysis[41-43]. Examinations can be achieved by the use of gray scale or power Doppler[25].

Beside the observation of carotid plaques, it is possible to investigate other parameters involved in carotid atherosclerosis that are still on a subclinical level. Examples of such investigation may be carotid artery diameter evaluation or direct early pathology of the vessel wall detecting disturbances in blood vessel function. Some parameters can be measured directly (intima-media thickness or carotid artery diameter), while others are mathematically derivable from performed measures (carotid stiffness indexes). So far, this evaluation has been possible with conventional ultrasound using either B-mode or M-mode examination (preferably using RF signals offering greater spatial resolution). Using the third dimension, providing adequate rendering, might enable greater precision in the cerebrovascular status[8,44] (Fig. 6).

Intracranial evaluation

Intracranially, due to volumetric reconstruction, it is possible to simultaneously visualize ipsilateral arteries in the circle of Willis and the vertebrobasilar junction in

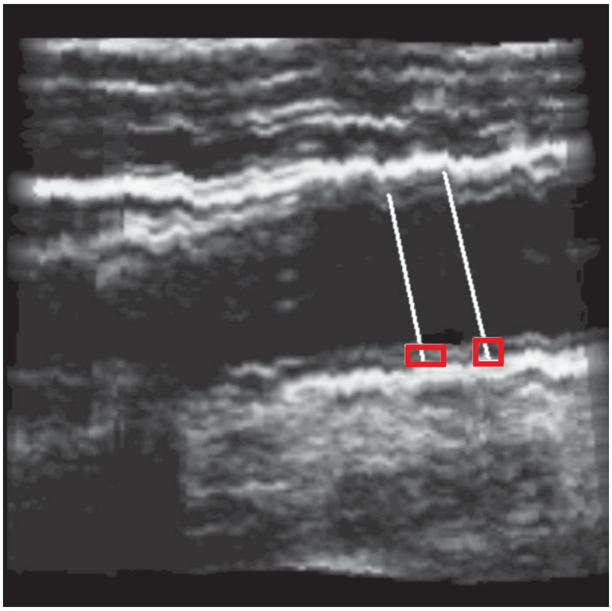

Fig. 6. Systolic and diastolic diameters in common carotid artery.

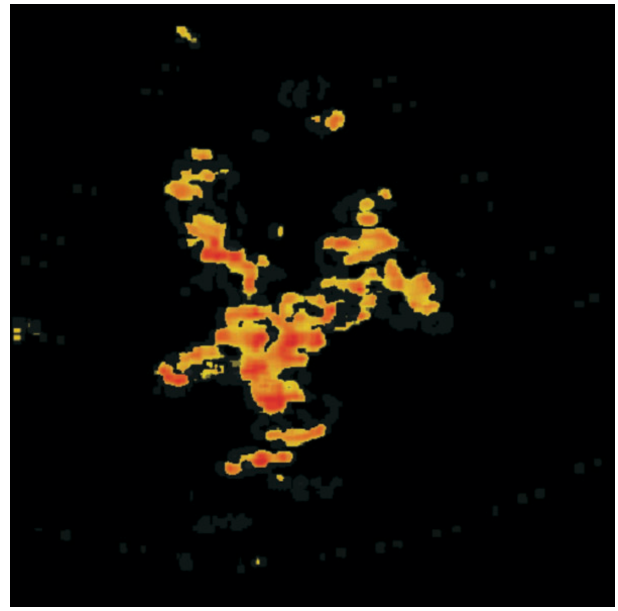

Fig. 7. Transcranial 3D power Doppler, the circle of Willis.

greater number of patients than with conventional transcranial color-coded sonography[8]. Resolution and sensitivity are increased and the amount of background noise is diminished. It is possible to use ultrasound contrast agents and high rate of correlation with DSA brain vessels angiography was proven (r=0.98)[45]. Another study showed that three-dimensional transcranial ultrasound might be used in the evaluation of intracranial hemorrhage monitoring[46].

Intracranial exploration is particularly improved with three-dimensional ultrasound because it enables an insight into an area greater than the circle of Willis and allows rotation in different planes. It is possible to visualize smaller blood vessels originating from the circle of Willis that provide blood supply to the inter-territorial areas (territories bordering ACM and ACA or ACM and ACP). Contrast enhanced ultrasound offers the best image of all[45,47] (Fig. 7). Furthermore, intracranial vertebral artery pathology and angle of insertion into the basilar artery is possible with three-dimensional ultrasound[48] (Fig. 8).

Offering new approaches, ultrasound qualification and monitoring of intracerebral pathology using B-mode ultrasound, larger tumors or ischemic areas can be visualized. Pathological vascularization or the lack of normal vascularization can be detected.

The potential problems in intracranial three-dimensional reconstruction are acquiring accuracy, width of the bony window and adequate three-dimensional rendering.

Four-Dimensional Ultrasound

Carotid plaque motion

Creation of three-dimensional plaque models has revealed that marks set at different positions on the

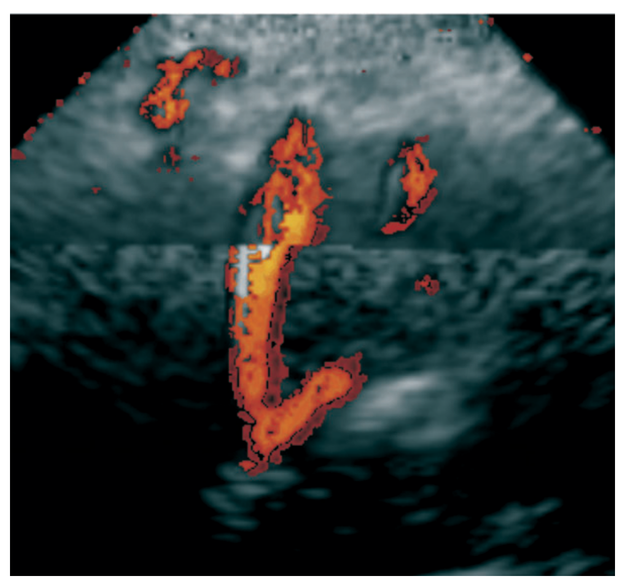

Fig. 8. Transcranial 3D power Doppler, vertebrobasilar circulation.

plaque surface tend to move in different directions, especially if some force is applied. Thus, the theory of internal plaque rupturing under external pressure, such as systolic blood pressure elevation, tends to get deeper eventually causing macroscopic plaque tearing according to specific plaque histology.

Four-dimensional ultrasound implies grabbing of three-dimensional ultrasound images and *post hoc* analysis that allows shear stress investigation through velocity vector analysis of the plaque surface motion. That is the most innocent and timely distinction between asymptomatic and early symptomatic carotid disease. Asymptomatic plaque will show homogeneous vector amplitude and direction, whereas a symptomatic plaque will show discrepancies in the mentioned parameters[49].

Quantitative Experiments

Quantitative measurement implies carotid flow analysis. Shear stress and brain blood flow as well as plaque stability can be assessed mathematically. This kind of development in several dimension ultrasound is highly difficult because it involves changes of flow direction and dependence on the angle of insonation[50]. The most used approach is the use of POM device.

Secondly, the use of RF signals is mandatory instead of low-frequency matrices as in conventional ultrasound. RF signals can be used for velocity representation, and radio wavelength needs to be synchronized with the ultrasound wavelength, high setting for pulse repetitive frequency is advised. If spectral distribution and the shape of the distribution of RF signal is known, it is easy to construct correlation curve with blood velocity, the width of the spectral distribution of the RF signal and noise to signal ratio that is dependent on time. Three-dimensional imaging can be filmed over several cardiac cycles, the shear stress being highest near the vessel wall[51,52].

In conclusion, it is best said that the three-dimensional ultrasound should be used as a complimentary method to conventional ultrasound with compulsory hemodynamic evaluation. Three-dimensional ultrasound can also be used as a basis for creation of four-dimensional ultrasound that will enable real time plaque motion visualization and interpretation.

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Sažetak

TRODIMENZIONALNI ULTRAZVUK U PROCJENI MOŽDANOG KRVOŽILJA

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Trodimenzionalni ultrazvuk se razvija od sredine pedesetih godina prošloga stoljeća uporabom raznih inovacija u slikovnom prikazu. U ispitivanju ekstrakranijske cirkulacije rabi se prvenstveno trodimenzionalni ultrazvuk karotidnih arterija koje su lako dostupne pregledu zbog obilježja njihovog smještaja. U procjeni intrakranijske cirkulacije trodimenzionalnost je moguće samo djelomice postići, jer zbog veličine koštanoga prozora opseg pokreta sondom u svih 360° nije moguće napraviti. Trodimenzionalni ultrazvuk dopušta veću prostornu rezoluciju od konvencionalnog, dvodimenzionalnog ultrazvuka. U usporedbi s magnetnom rezonancijom trodimenzionalni ultrazvuk omogućuje transaksijalnu rezoluciju od 5 mm, longitudinalnu rezoluciju do 10 mm i rotacijsku rezoluciju do 40°. Ostale prednosti su neinvazivnost, volumetrijska analiza tkiva umjesto planimetrijske, relativno niska cijena uz veliku točnost reprodukcije, te visoka osjetljivost i specifičnost (r=0,982). Glavni nedostaci trodimenzionalnog ultrazvuka su nemogućnost jasnog razlikovanja periarterijskog i intraarterijskog tkiva, što uzrokuje probleme u segmentaciji tkiva, trošak nabave ultrazvučnog uređaja koji je nešto veći od troška nabave konvencionalnog uređaja, a uz to je potreban i vrsni operater. Pomaci tkiva također uzrokuju brojne artefakte, no uporabom mehaničke ruke i EKG sinhronizacije moguće je umanjiti navedene poteškoće. Trodimenzionalni ultrazvuk najbolje je rabiti kao dopunsku metodu pregleda uz konvencionalni ultrazvuk koji dopušta nužnu hemodinamsku procjenu. Uz trodimenzionalni ultrazvuk razvija se i četverodimenzionalni ultrazvuk koji omogućava prikaz pomaka tkiva u stvarnom vremenu, čime su dostupne informacije o nestabilnosti aterosklerotskog plaka.

Ključne riječi: *Bolesti moždanih arterija – ultrazvuk; Karotidna stenoza – ultrazvuk; Karotidne arterije – ultrazvuk; Cerebrovaskularna cirkulacija – fiziologija; Cerebrovaskularna cirkulacija – ultrazvuk*