NEUROSONOLOGY IN STROKE

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SUMMARY – This article presents the use of neurosonology in stroke. It is an extended presentation of its use in stroke, as part of the Recommendations for Stroke Management – 2006 Update, published in 2006, endorsed by the Croatian Society for Neurovascular Disorders of Croatian Medical Association; Croatian Stroke Society; and University Department of Neurology, Sestre milosrdnice University Hospital, Reference Center for Neurovascular Disorders of the Croatian Ministry of Health and Welfare. The Recommendations are in concordance with those issued by three European societies represented in the European Stroke Initiative: the European Stroke Council, the European Neurological Society, and the European Federation of Neurological Societies, as well as with the Guidelines of the American Heart Association/American Stroke Association Council on Stroke, affirmed by the American Academy of Neurology.

Key words: *Brain diseases – ultrasonography; Cerebrovascular disorders – ultrasonography; Ultrasonography – Doppler – transcranial*

Introduction

Ultrasound studies are routinely performed in stroke centers. Their greatest advantage is real-time, bedside evaluation of morphology and hemodynamics of brain vessels. The major goal is to identify large obstructive lesions in the extracranial and intracranial basal arteries, and to monitor and facilitate spontaneous or drug-induced thrombolysis in the majority of patients. It also enables differentiation of patients eligible for thrombolysis beyond three hours of stroke onset and identifies lesions amenable for interventional treatment. The detection of rare causes of ischemic stroke such as dissections, intima hyperplasia and other less frequent etiologies is facilitated by the systematic use of ultrasound studies.

The Croatian Society for Neurovascular Disorders of the Croatian Medical Association, Croatian Stroke Society, and University Department of Neurology, Sestre milosrdnice University Hospital as Reference Center for Neurovascular Disorders of the Croatian Ministry of Health and Welfare have published updated guidelines for stroke prevention and management[1-5], in line with the European Stroke Initiative (EUSI) guidelines for ischemic[6-8] or hemorrhagic[9] stroke management, issued by the European Neurological Society, European Federation of Neurological Society and European Stroke Council representing European Stroke Conference, as well as with the North American stroke guidelines[10,11]. Neurosonological investigation of extra- and intracranial vessels should be performed as part of comprehensive stroke treatment for noninvasive bedside evaluation of brain vessel morphology and hemodynamics. Here, expanded data from the usage of neurosonology in stroke are presented, as its possibilities have proved useful in these clinical settings[12,13].

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Management in the Emergency Room

Differentiation of ischemic from hemorrhagic stroke is especially important because of the marked differ-

ence in the management of these conditions. Diagnostic errors based solely on clinical features still occur and the level of accuracy is insufficient to guide treatment decision. Because clinical findings overlap, a brain imaging study is mandatory to distinguish ischemic stroke from hemorrhage or other structural brain lesions that may imitate stroke[1]. In some centers, computed tomography (CT) scan is not available on 24-hour daily basis. Therefore, a useful test in clinicians' hands may help in patient management. Neurosonology has several advantages: it can be performed at bedside and repeated as needed or applied for continuous monitoring; its usage is less expensive, and more readily available. It consists of extracranial color Doppler imaging of carotid and vertebral arteries and transcranial color Doppler sonography (TCCS) for intracranial evaluation, and in experienced clinician may help answer the following questions:

1. Is it an ischemic or hemorrhagic stroke?
2. What is the underlying mechanism: macroangiopathic, cardioembolic, vasculopathy or dissection, or are there signs of vascular malformations?
3. Are there signs of increased intracranial pressure (ICP), or midline shift?
4. What are the advantages of stroke monitoring?
5. Is this patient a candidate for neuroradiological or surgical intervention?
6. What is the expected outcome?

Transcranial Evaluation of Stroke, Vessel Occlusion or Hemorrhage

Detection of arterial stenosis/occlusion and prediction of outcome

One of early CT infarct signs includes the hyperintense middle cerebral artery (MCA) sign (HMCAS), as the result of MCA thrombosis and occlusion. The presence of HMCAS is associated with poor outcome and is a sign of extensive infarction with intracranial midline shifts indicating a high risk of both secondary hemorrhage and large malignant edema formation. Although CT angiography (CTA) and MR angiography (MRA) are reliable tools to obtain information on extracranial and intracranial arterial patency, their accessibility is often lacking.

Transcranial Doppler (TCD) measures local blood flow velocity (BFV) and direction in the proximal portions of large intracranial arteries[12-15]. It is a "blind method", therefore operator dependent, and requires training and expertise to perform and interpret results. Several studies evaluated digital subtraction angiography (DSA), contrast-enhanced CTA, MRA, and ultrasound in the acute stroke setting[16-21]. DSA documented complete arterial occlusion in 76% of acute stroke patients within 6 hours of symptom onset, of which 66% were intracranial[16]. Non-contrast-enhanced TCD has been reported to have a sensitivity of 80% and specificity of 90% compared with DSA in patients presenting within 5 hours of MCA stroke[20,21]. TCD may be used as a screening test to determine the need of further angiographic studies. The bedside availability, convenience to the patient, and continuous monitoring possibility make TCD particularly suitable and practical for emergency evaluations. TCD also allows real-time assessment of the BFV, pulsatility, and microembolization, information that are not available with angiography. Most studies report a good correlation between intracranial ultrasound and angiography[16-21]. TCD and TCCS can detect angiographic occlusions with high (>90%) sensitivity, specificity, positive predictive value, and negative predictive value[16,22,23]. A battery of TCD findings indicating extracranial or intracranial advanced stenosis or occlusion were: reversed ipsilateral ophthalmic artery (OA), reversed ipsilateral anterior cerebral artery (ACA), elevated flow velocity in the contralateral ACA, absence of low signal in the ipsilateral OA or carotid siphon, and diminished pulsatility of flow acceleration in the ipsilateral MCA. Other reported TCD flow findings with the MCA and posterior carotid artery (PCA) occlusions included absent or diminished flow signals and flow diversion to branching vessels, abnormal waveforms, posterior communicating artery (PCoA) flow, compensatory flow increase, or diversion. Such findings had a specificity of 94% with sensitivity of 83% to identify the presence of any proximal extracranial or intracranial arterial occlusion compared with angiography[24]. TCD sensitivity for the anterior circulation occlusions exceeded 90% due to acquisition of more physiological data[24].

Intracranial arterial occlusions detected by TCD are associated with poor neurological recovery, disability, or death after 90 days[25], whereas normal results predict early improvement[26]. In patients with acute ICA territory stroke, TCD findings, stroke severity at 24 hours, and CT lesion size were independent predictors of outcome after 30 days[25]. When combined with carotid duplex sonography, the presence and total number of arteries with suspected steno-occlusive lesions by TCD

in transient ischemic attack (TIA) or stroke patients were associated with poor outcome[27] and an increased risk of further vascular events and death within 6 months[28]. Such combined stroke patient evaluation can identify lesions amendable for interventional treatment (LAIT) in patients with acute cerebral ischemia[29] achieving 100% accuracy.

A recently published article on ultra-early Doppler sonography for stroke in a multicenter trial (Neurosonology for Acute Ischaemic Stroke, NAIS)[30], as part of standard patient assessment, has provided additional functional prognostic information in the hyperacute phase of anterior circulation strokes. The study included 361 patients with moderate to severe clinical deficits (National Institutes of Health Stroke Scale score 5-20). Of these, 34% had normal MCA, 48% had branch occlusion, 2% had severe MCA stenosis, and 16% had main-stem MCA occlusion; 88% of patients with main-stem occlusion were dead or dependent 3 months after stroke. An occlusion of the main-stem of the MCA within 6 h after stroke was an independent predictor of poor outcome (p=0.0006). Good outcome was found in 50% of patients with ultrasonographic diagnosis of branch occlusion and 63% with normal MCA. The authors conclude that neurosonology technique can be used to identify patients at a high risk of poor functional outcome.

TCD-detected M1 MCA occlusions within 6 hours of stroke onset may be an independent predictor of spontaneous hemorrhagic transformation, with a 72% positive predictive value[31], since a delayed (>6-hour) spontaneous recanalization was independently associated (odds ratio [OR] = 8.9, 95% CI = 2.1 to 33.3) with hemorrhagic transformation[32].

TCD is useful for the evaluation of patients with suspected intracranial steno-occlusive disease, particularly in the internal carotid artery (ICA) siphon and MCA.

TCD in monitoring and enhancing recanalization

Applying portable diagnostic ultrasound by detecting residual flow signals around the thrombus, recanalization of the occluded artery can be monitored[33]. An acute arterial occlusion is often partial and incomplete, being a dynamic process of thrombus propagation, reocclusion and infrequent spontaneous recanalization. As previously described, TCD can rapidly identify patients with these lesions regardless of baseline stroke severity. TCD can be performed at bedside simultaneously with neurological examination, vital sign monitoring, blood sampling, causing no delay in t-PA administration. Ultrasound findings for the diagnosis of arterial occlusion amenable for treatment include abnormal waveforms in the vessel supplying a territory affected by ischemia, so-called TIBI waveforms (**T**hrombolysis **I**n **B**rain **I**schemia)[34] and evidence of flow diversion or collateralization[22] to compensate for this lesion.

Ultrasound is believed to have a thrombolytic capacity that can be used for pure mechanical thrombolysis (with high intensities (>2 W/cm^2) or improvement of enzyme-mediated thrombolysis (with lower intensities)[35]. The 300 kHz ultrasound tested in the **TR**anscranial low-frequency **U**ltrasound-**M**ediated thrombolysis in **B**rain **I**schemia (TRUMBI) trial was prematurely stopped because of the high rate (36%) of symptomatic intracranial hemorrhages and no signal of efficacy on early recanalization or clinical outcomes at 3 months.

Poor recovery after systemic tissue plasminogen activator (t-PA) therapy could result from the initial severity of ischemic insult and slow and incomplete thrombolysis. Persisting arterial occlusions can be identified at bedside using portable diagnostic ultrasound by detecting residual flow signals around the thrombus (TIBI flow grades). A narrow pulsed ultrasound beam can be steadily aimed at the thrombus/residual flow interface, exposing more thrombus surface and structures to t-PA, and t-PA activity can be enhanced with 2 MHz TCD. A randomized multicenter, double blind, controlled clinical trial called CLOTBUST (**C**ombined **L**ysis **o**f **T**hrombus in **B**rain ischemia using transcranial **U**ltrasound and **S**ystemic **t**-PA) suggests that continuous 2 MHz, single-element pulsed-wave TCD ultrasonography that is aimed at residual obstructive intracranial blood flow may help expose thrombi to rt-PA and enhance the thrombolytic activity of t-PA[36]. Among 126 patients randomly assigned to receive continuous ultrasonography or placebo (n=63 both), complete recanalization or dramatic clinical recovery within 2 h after the administration of a t-PA bolus occurred in 31 (49%) patients in the treatment group, compared with 19 (30%) patients in the control group (p=0.03). The CLOTBUST trial showed a trend toward sustaining complete recovery at 3 months (41.5% *versus* 28%, modified Rankin scale scores 0 to 1), subject for a pivotal phase III trial. Ultrasound is an inexpensive, noninvasive, real-time monitoring tool to identify nonresponders to systemic t-PA and to select patients with persisting occlusions for intra-arterial interventions. Early brain perfusion augmentation, complete recanalization, and dramatic

clinical recovery are feasible goals for ultrasound-enhanced thrombolysis.

The ultrasound mediated thrombolysis can be further enhanced with the addition of gaseous microbubbles[37]. This approach has just been tested in a controlled multinational clinical trial of perflutren-containing microbubbles, which are not yet commercially available. A diagnostic 2 MHz TCCS 1 hour monitoring may be applied in stroke within 6 hours of stroke onset in patients ineligible for rt-PA[38].

Advantages of TCCS and contrast enhanced TCCS imaging

TCCS monitoring of midline shift (MLS) in patients with space-occupying MCA infarcts has been shown to be of prognostic value and may facilitate detection of patients who are likely to die without hemicraniectomy[39,40]. MLS displacement may predict fatal outcome in patients with malignant MCA infarcts[39]. Thus, close-meshed follow-up of the MLS in large MCA territory infarcts may assist in the detection of patients with rapid progressive edema, and facilitate indication for aggressive treatment and select patients who will benefit from early hemicraniectomy[40].

Several TCCS studies have shown that detection of a homogeneously hyperechogenic area which is sharply demarcated from the surrounding brain tissue is diagnostic for acute intracerebral hemorrhage (ICH)[41-43]. Using this criterion TCCS assessment of acute ICH or stroke complications was investigated in 133 patients with acute hemiparesis and sufficient acoustic bone window, blindly, in agreement with CT scan[44]. Sonography missed 3 atypical bleedings (2 with upper parietal location). In four patients without bleeding, intracerebral hemorrhage was suspected by TCCS because of increased white matter echo density due to macroangiopathy. Stroke complications depicted by CT (disturbance of cerebrospinal fluid circulation, hemorrhagic transformation, midline shift, ventricular bleeding) (n=54) were correctly shown by TCCS in 45 (83%) patients. No complication was missed that would have required further treatment. Such findings in comparison to the "gold standard" of CT showed that TCCS identified stroke complications and differentiated between intracerebral hemorrhage and ischemic stroke with 95% sensitivity and 94% specificity. Thus, if CT scan is not readily available, TCCS may help in identifying patients with primary brain hemorrhage or secondary hemorrhagic complications.

Contrast enhanced TCCS in patients with cerebrovascular disease may be useful in several ways. TCCS can detect the presence and direction of collateral flow in the anterior (ACoA) and posterior (PCoA) communicating arteries in patients with hemodynamically significant (typically >80%) ICA stenosis or occlusion[45], with improvement to as much as 96% diagnostic confidence following the use of echo-contrast agents[46]. The sensitivity and specificity for the detection of ACoA and PCoA collateral flow are good to excellent[41]. Compared with the temporal bone window, the use of the lateral frontal bone window appears to increase the detection of intracranial cross-flow patterns *via* PCoA[47].

Limited data suggest that intracranial steno-occlusive disease including >50% diameter reduction stenosis, or distinction between vessel patency and occlusion with reduced flow velocity, can be detected more reliably with contrast enhanced TCCS than with TCD[48,49]. TCCS can demonstrate areas of parenchymal hypoechogenicity in the MCA distribution suggestive of ischemic cerebral infarction shown on brain CT scan, accompanied by an abnormal blood flow velocity pattern, with fair to good sensitivity and specificity[40]. Spontaneous[40,47] and thrombolytic therapy-induced[50-52] recanalization, as compared with DSA, MRA, or CTA in small numbers of patients[51], can be monitored by serial TCCS examinations, with recanalization being more common in patients treated with thrombolytic therapy[50,52]. Severe neurological deficits and large MCA territory ischemic infarctions have been associated with sonographic signs of MCA occlusion or decreased MCA flow velocities within 12 hours of stroke onset[49], whereas a patent MCA without reduced MCA flow velocities may be predictive of early clinical improvement[41].

(Contrast-enhanced) TCCS is useful in the evaluation and monitoring of patients with ischemic cerebrovascular disease.

TCD in subarachnoid hemorrhage (SAH)

Cerebral vasospasm (VSP) is a delayed narrowing of large capacity arteries at the base of the brain after SAH, often associated with radiographic or cerebral blood flow evidence of diminished perfusion in the distal territory of the affected artery. Angiographic VSP has a typical temporal course, with the onset 3 to 5 days after the hemorrhage; maximal VSP is expected at 5 to 14 days, and gradual resolution over 2 to 4 weeks[53]. In about one half of cases, VSP is manifested by the occurrence of a

delayed neurological ischemic deficit, which may resolve or progress to cerebral infarction with acute or subacute development of focal or generalized symptoms[54]. The incidence of angiographic VSP is over 50%, with symptomatic VSP in 32% of patients[55]. Clinical syndromes believed to be attributable to severe, flow-reducing VSP in each intracranial vessel have been described. Since an inverse relation between cerebral blood flow, cerebral blood flow velocities, and age exists, neurological deterioration may be associated with a number of disorders, and the presence of large-vessel angiographic VSP does not always lead to neurological deterioration.

The findings of TCD flow velocity in the MCA correlate well with clinical grade, CT localization of SAH clot, and time course of angiographic VSP. As mentioned before, these correlations are not always perfect. There is a significant direct correlation between VSP severity after spontaneous SAH and flow velocities in cerebral arteries, although anatomic and technical factors weaken the association for the intracranial ICA and ACA[14,56-59]. For the MCA, flow velocities of >120 or >200 cm/s, a rapid rise in flow velocities, or a higher Lindegaard (*V*MCA/*V*ICA) ratio (6 ± 0.3)[58] reliably predict the absence or presence of clinically significant angiographic MCA VSP, although prediction of neurological deterioration is problematic[57,58]. Similar data for other intracranial vessels are not available. A variety of factors such as technical issues, vessel anatomy, age, intracranial pressure (ICP), mean arterial blood pressure, hematocrit, arterial CO_2 content, collateral flow patterns, and response to therapeutic interventions influence flow velocities and must be taken into account when interpreting TCD results in this setting. The sensitivity and specificity of TCD *vs.* cerebral angiography for the detection of VSP after SAH in the proximal portions of each intracranial artery have been summarized. In a recent meta-analysis[56], only 5 of 26 evaluable TCD studies met at least 7 of 10 criteria for methodologically high-quality studies. In general, data vary by vessel and by diagnostic criteria, disease prevalence, and timing of correlative angiography. Specific causes of false-positive and false-negative TCD examinations have been identified for each intracranial vessel[61] and their impact on the approach to test performance and interpretation has been described. TCD flow velocity criteria appear most reliable for detecting angiographic MCA VSP and BA VSP. The specificity of TCD can be optimized by increasing the flow velocity criteria and sensitivity by the timing of the angiographic correlation for the diagnosis of VSP[59,61].

TCD is useful in monitoring the temporal course of angiographic VSP after SAH. TCD is thought to be valuable in the day-to-day evaluation of SAH patients in VSP and to assess the effect and durability of neuroradiological interventions, but no appropriate prospective study has yet been conducted[62]. In a pilot study[63], TCD was used to detect angiographic VSP following prophylactic transluminal balloon angioplasty in SAH patients at a high risk of developing VSP, as a noninvasive surrogate endpoint. Due to physical principles of Doppler flow velocities[64,65], TCD is not useful for the detection of VSP directly affecting the convexity or vertically oriented branches of the intracranial arteries distal to the basal cisterns, although the presence of VSP at these sites may be suspected in some cases by indirect Doppler waveform observations (e.g., decreased diastolic flow, increased pulsatility, side-to-side differences in pulsatility indexes, etc.).

TCD is useful for the detection and monitoring of angiographic VSP in the basal segments of intracranial arteries, especially the MCA and BA, following SAH.

Monitoring increased ICP and cerebral circulatory arrest

There is a qualitative relationship between progressive increases in ICP and the evolution of abnormal TCD waveforms, assuming a constant arterial CO_2 content and a constant degree of distal vasoconstriction. Pulsatility changes occur when cerebral perfusion pressure is >70 mm Hg. The earliest sign of increased ICP is increased pulsatility, followed by progressive reduction in diastolic flow velocities and reduction in mean flow velocities[66]. As regional or generalized ICP elevation becomes increasingly extreme, diastolic flow reaches zero, followed by an alternating flow pattern with retrograde diastolic flow, disappearance of diastolic flow, appearance of small systolic spikes, and eventually no flow. Once the reverberating flow pattern appears, cerebral blood flow disappears on angiography developing cerebral circulatory arrest.

TCD is useful in monitoring of increased ICP up to the development of cerebral circulatory arrest.

TCCS in subarachnoid hemorrhage

TCCS diagnosis of vasospasm[67] uses TCD criteria[56,60]. In the anterior circulation spasm, the presence of peak mean velocity ratio for MCA/ICA or ACA/ICA >3 is also required[60]. TCCS may detect VSP in major

branches of the circle of Willis following SAH[44]. Limited data suggest that the sensitivity and specificity of TCCS for the detection of intracranial ICA and MCA VSP are excellent.

Large and medium-sized cerebral aneurysms located in the proximal segments of the circle of Willis can sometimes be detected as colored oval structure of a pulsatile nature adjacent to large parent arteries[67-69]. Aneurysms located beyond the field of scanning and those that are thrombosed cannot be detected. TCCS can detect 76% to 91% of non-thrombosed intracranial aneurysms of >6 mm in size[67-69], and the use of echo contrast agents or power Doppler may increase the rate of detection, including aneurysms of >5 mm in size[67-70].

Although arteriovenous malformations (AVMs) can be displayed as areas with a color mosaic, which is related to the focal accumulation of vascular convolutions and spectral hemodynamic abnormalities similar to those in the feeding vessels[72], the accuracy of TCCS in the diagnosis of AVMs remains unknown. There is only one small series of radiologically proven malformations, reporting that TCCS can suggest the presence of all large (>4 cm) and medium-sized (2-4 cm) lesions and two thirds of small (<2 cm) lesions by detecting abnormal increased systolic and especially end diastolic flow velocities and decreased pulsatility in the feeding arteries[73]. TCCS allows incidental suspicion of an AVM, but the diagnostic accuracy of AVM detection is unknown, since most small feeding arterial branches and draining veins as well as the nidus are missed.

(Contrast-enhanced) TCCS is useful in the evaluation and monitoring of patients with aneurysmal SAH or intracranial ICA/MCA VSP following SAH. TCCS is not a screening method of choice for the detection of cerebral aneurysms due to lower sensitivity for smaller aneurysms, and limitation of their detection outside the insonation area. TCCS is useful for incidental suspicion of an AVM in cerebral hemorrhage.

Clinical relevance of embolus detection

The principle of ultrasonic detection of microembolic signals (MES) or "high-intensity transient signals" (HITS) within the intracranial cerebral arteries by TCD is based on different acoustic impedance properties of particulate (solid, fat) and gaseous materials in flowing blood from surrounding red blood cells[75]. The Doppler ultrasound beam is both reflected and scattered at the interface between the embolus and blood, resulting in an increased intensity of the received Doppler signal. The hierarchy of backscatter of the ultrasound, in descending order, is gaseous emboli, solid emboli, and normal-flowing blood. Comparison between studies is difficult because of differences in diagnostic criteria and detection threshold, different instruments, different instrument settings, nature and severity of disease, variability in occurrence of microembolic signals, time between last symptom and detection of microembolic signals, type of treatment, and interobserver variability[75,76]. The physics and technical aspects of ultrasonic detection of microembolic signals or HITS by TCD have been reviewed[74,75], and standards concerning ultrasound device, transducer type and size, insonated artery, insonation depth, algorithms for signal intensity measurement, scale settings, detection threshold, axial extension of sample volume, fast Fourier transform (FFT) size (number of points used), FFT length (time), FFT overlap, transmitted ultrasound frequency, high-pass filter settings, and recording time have been proposed[13,74]. New hardware and software technical capabilities may help in the detection of microembolic signal type and in discrimination from artifacts. However, accurate and reliable characterization of embolus size and composition is not possible with current technology.

Microembolic signals can be detected in wide clinical settings: in patients with asymptomatic and symptomatic high-grade internal carotid stenosis, prosthetic cardiac valves, myocardial infarction, atrial fibrillation, aortic arch atheroma, fat embolization syndrome, and retinal or general cerebral vascular disease. These signals occur in coronary catheterization, coronary angioplasty, direct current cardioversion, cerebral angiography, carotid endarterectomy (CEA), carotid angioplasty, and cardiopulmonary bypass. Although these microembolic signals are clinically silent, they may be clinically important by indicating an increased risk of stroke. In asymptomatic patients, this technique may identify those with an active embolic source, and microembolic detection would therefore preclinically identify a subgroup of patients at a high risk of stroke. In symptomatic patients, after an index event, microembolus detection might be able to select individuals at a high risk of recurrent stroke. Furthermore, this technique could help identify the site of embolizing lesion, particularly in patients with competing sources of embolism. It can also monitor the effects of antithrombotic or fibrinolytic treatment in patients with atherosclerotic or dissecting cerebrovascular disease[76,77]. In patients with high-grade carotid stenosis, sources of asymptomatic microembolic

signals may include ulcerated plaques associated with an increased risk of further cerebral ischemia (OR=8.10, 95% CI=1.58 to 41.57)[78]. The TCD detection of microembolism may serve as a surrogate marker in interventional trials. In patients with a first-ever ischemic event and a high-grade carotid artery stenosis, the prevalence of recurrent stroke is low (approximately 7% *per annum*). However, in symptomatic internal carotid artery stenosis the prevalence of clinically silent embolic signals in recordings of 20 minutes to 4 hours is much higher (approximately 21% to 100%). Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS)[79] was a randomized, double blind trial in symptomatic carotid stenosis, which demonstrated that dual antiplatelet therapy with clopidogrel and aspirin resulted in a rapid reduction in asymptomatic embolization compared with aspirin alone. There were 4 recurrent strokes and 7 TIAs in the monotherapy group *versus* no stroke and 4 TIAs in the dual-therapy group that were treatment emergent and ipsilateral to the qualifying carotid stenosis. MES frequency was greater in 17 patients with recurrent ipsilateral events compared with 90 patients without it (mean±SD 24.4±27.7 *versus* 8.9±11.5 *per* hour; p=0.0003). The results demonstrated the feasibility of using TCD MES detection as a surrogate marker to evaluate the relative efficacy of different combinations of antiplatelet therapy.

TCD is probably useful to detect cerebral microembolic signals in a wide variety of cardiovascular/cerebrovascular disorders/procedures. TCD can be used for diagnosis or monitoring response to antithrombotic therapy in ischemic cerebrovascular disease.

Right-to-left cardiac shunt

Paradoxical embolism *via* a patent foramen ovale (PFO) is a cause of stroke in young adults[80-83]. The presence of an atrial septal aneurysm may increase the stroke risk of a PFO with right-to-left shunting[82,83]. A high correlation between contrast-enhanced TCD and contrast-enhanced transesophageal echocardiography (TEE) was observed, with complete concordance for the "clinically significant" high number of particles shunted. The sensitivity and specificity of contrast TCD for detecting right-to-left cardiac or extra cardiac (pulmonary arteriovenous) shunts may vary by center, protocol, and diagnostic criteria[84]. The routine performance of the Valsalva maneuver during testing can improve sensitivity and specificity. The sensitivity of contrast TCD can also be improved by using a higher volume of agitated saline (10 mL instead of 5 mL), use of echo contrast agents instead of agitated saline, or repeating the Valsalva maneuver if the initial result is negative[84].

Contrast TCD is comparable with contrast TEE for detecting right-to-left shunts due to PFO, with the number of microbubbles for assessment of the shunt size. However, TEE provides direct anatomic information regarding the site and nature of the shunt or presence of an atrial septal aneurysm.

Vasomotor reactivity testing

Large basal conducting vessels remain relatively constant in diameter during moderate pressure fluctuations or changes in microcirculatory function. TCD by measuring BFV can provide an index of relative flow changes in response to small blood pressure changes and physiologic stimuli to assess autoregulation and vasomotor reactivity (VMR) of the distal cerebral arteriolar bed. VMR testing techniques of cerebral autoregulation may be static (at rest) or dynamic (after provocative stimuli). Therefore, VMR testing of cerebral autoregulation includes measuring changes in flow velocities following: 1) hemodynamic stimuli (rapid leg cuff deflation, Valsalva maneuver, deep breathing, ergometric exercise, head-down tilting, orthostatic and lower body negative pressure, beat-to-beat spontaneous transient pressor and depressor changes in mean arterial pressure); 2) CO_2 inhalation (hypercapnia/hyperventilation hypocapnia); 3) breath-holding index (BHI); 4) acetazolamide injection; and 5) transient hyperemia response and its variants[85-92]. VMR testing techniques with TCD have been used to evaluate patients with symptomatic or asymptomatic extracranial ICA stenosis or occlusion[85-92], cerebral small-artery disease and its changes during medical treatment[93]. Although TCD may detect abnormalities of cerebral hemodynamics (increased or decreased pulsatility) in patients with risk factors or symptoms of cerebrovascular disease[86], its value for evaluation of stroke risk is to be investigated in a large prospective study. In patients with asymptomatic 70% extracranial ICA stenosis, the annual ipsilateral ischemic event rate was 4.1% with normal BHI and 13.9% with impaired BHI[93]. In patients with severe (>70%) symptomatic ICA extracranial stenosis, VMR in the ipsilateral MCA is significantly reduced[87], but its improvement can be seen after CEA[88]. Exhausted VMR in the ipsilateral MCA was an independent predictor of the occurrence of ipsilateral

TIA and stroke (OR=14.4, 95% CI=2.63 to 78.74)[86]. In patients with asymptomatic extracranial ICA occlusion, a BHI of <0.69 reliably distinguishes pathologically reduced from normal cerebral VMR and identifies patients at risk of stroke and TIA[93].

TCD vasomotor reactivity testing is considered useful for the detection of impaired cerebral hemodynamics in patients with asymptomatic severe (>70%) stenosis of the extracranial ICA, patients with symptomatic or asymptomatic extracranial ICA occlusion, and patients with cerebral small-artery disease.

Screening of children with sickle cell disease in stroke prevention

In children with sickle cell disease, ischemic cerebral infarction is associated with an occlusive vasculopathy involving distal intracranial ICA, MCA and ACA. One large cohort study[94] with long-term follow-up showed that elevated time-averaged mean maximum blood flow velocity of ≥200 cm/s in the ICA or MCA by TCD is strongly associated with stroke risk. Lowering the hemoglobin S concentration by periodic blood transfusion therapy in children between the ages of 2 and 16 years, with the use of flow velocity criterion monitoring, the Stroke Prevention Trial in Sickle Cell Anemia[95] resulted in a 92% reduction in stroke risk.

TCD screening of children with sickle cell disease between the ages of 2 and 16 years is effective for assessing and lowering stroke risk.

Extracranial Findings in Acute Stroke

Advances in performance and interpretation of extracranial cerebrovascular sonographic studies over the last 20 years[96] have been driven by technological improvements in gray scale and color-coded duplex Doppler sonography (CDDS) examinations, resulting in wide clinical applications and technical performance and interpretation of carotid and vertebral sonographic examinations[97]. On the basis of CDDS, intima-media thickness measurements and plaque location and characterization on gray scale imaging, flow disturbance and areas of stenosis on color Doppler sonography, and flow velocities on spectral Doppler sonography are obtained. The degree of the diameter of a stenosis of the internal carotid artery is the main parameter used for therapeutic approaches. The ultrasonographic characteristics of plaques speak in favor of the plaque stability. Beside atherosclerotic disease, information regarding vasculopathy or dissections as rare causes of stroke can be provided. Such imaging provides morphological and functional information on stroke mechanisms, but also on the risk of stroke recurrence and the possibilities on secondary stroke prevention. It is increasingly becoming the first and often the sole imaging study before endarterectomy, whereas costly and invasive procedures are reserved for special cases.

Carotid imaging

The benefit of carotid endarterectomy in stroke prevention in advanced carotid stenosis was proved in large studies (European Carotid Surgery Trial, ECST, and North American Symptomatic Carotid Endarterectomy Trial, NASCET), using different angiographic methods of estimation of carotid stenosis measurement[98,99]. The Asymptomatic Carotid Surgery Trial (ACST)[100] in primary prevention to reduce the risk of stroke was based on ultrasonographic findings. Although peak systolic velocity (PSV) is the most important component of the carotid Doppler examination[101], the grading of carotid stenosis with ultrasound should not be limited to this parameter only[101-104]. As a screening test, carotid ultrasound should have an optimal tradeoff between sensitivity and specificity with the aim of identifying the highest percentage of patients with the potential of having a severe carotid stenosis. Since ultrasound grading of carotid stenosis is operator dependent and relies on different and individually validated criteria despite the use of similar equipment[105,106], and also depends on plaque characteristics[107], a combination of criteria of ultrasound screening specific to each laboratory should be applied. Such criteria must be accurately defined and tested in prospective studies[108-110]. Between different techniques of noninvasive estimation of carotid stenosis, CCDS showed lowest interobserver variability[104]. Since CCDS also enables visualization of pseudo-occlusion, thus being superior to angiography, comparison is needed[108].

A high correlation between angiography and CCDS in detecting various degrees of carotid stenosis exists. Ultrasound is more sensitive in detecting the category of severe stenosis (near occlusion, pseudo-occlusion).

Plaque analysis

Great interest has surrounded the characterization of plaque morphology, because of the important role in epidemiological studies and for being increasingly used

to evaluate the efficacy of atherosclerosis prevention trials. Moreover, there is evidence that ultrasonographic B-mode characterization of plaque morphology may be useful in assessment of the vulnerability of the atherosclerotic lesion[107.111]. There are some indicia of the classification of unstable or "dangerous" plaques[112,113]. In the Second International Consensus Meeting[111], criteria were determined for the characterization of carotid plaques. Plaque compositions are thus characterized in five steps as follows: 1) uniformly anechogenic plaques, with a high risk of stroke; 2) predominantly hypoechoic plaques with hypoechoic areas of more of 50% of plaque structure; 3) predominantly hyperechoic plaques with hypoechoic areas of less than 50% of plaque structure; 4) calcified plaques, with types 2, 3 and 4 of lower stroke risk; and 5) calcified plaques with the acoustic shadow, making the vessel lumen evaluation impossible, in which the risk of stroke is still under investigation.

While some contend that heterogeneous carotid plaques are more often associated with intraplaque hemorrhage and neurological events[114,115], recent studies have provided good evidence that lipid-rich plaques are more prone to rupture and suggest that an association between intraplaque hemorrhage and a high lipid content as revealed in B-mode ultrasound may support this theory[116]. The presence of hypoechoic ICA plaques has also been reported as an independent risk factor for cerebrovascular events[117,118]. Plaque surfaces can be characterized as regular, irregular (sometimes the disruption of endothelia is visible, or ulcers of 0.4-2 mm) or ulcerated (with the ulcer depth of >2 mm). Plaque ulcers were associated with the appearance of ischemic symptomatology.

The use of CCSD is valuable in plaque characterization.

Intima-media thickness (IMT)

High-resolution ultrasound enables vessel wall evaluation and intima-media thickness (IMT) measurement. It is thought that the thickening of the IMT is an early marker of atherosclerosis. The first description of IMT as "double line" dates from the eighties, the first representing the border of the lumen and vessel far wall, while the second line is generated on the border of the vessel media and adventitia. Ultrasonographic imaging of arterial interfaces is based upon the difference in acoustic impedance between tissues separated by an interface. The spatial location of an interface can only be reliably determined if there is increasing impedance, if an ultrasound beam passes through a structure of lesser density to one of higher density. Otherwise, high impedance structures generate backscattered echoes that shadow the lower impedance structures beyond them. Because of this, the selection of the arterial far wall for making IMT measurements is preferred, since the location reflects the ideal pattern of increasing impedance for ultrasonographic detection of interfaces.

In earlier studies, IMT measurements were performed manually, with the high inter- and intraobserver variability. Nowadays, automated computerized systems are available, simplifying reading and improving both accuracy and variability of IMT measurements. There are numerous protocols for evaluation of IMT. While some protocols include IMT of CCA, others use IMT measurements in the CCA and bifurcation. While physical principles favoring far wall arterial measurement guide some protocols, others include both far and near wall IMT measurements. Epidemiological studies obtained from different investigations have shown variability in CCA-IMT (in 65-year-old males about 0.8-0.73 mm). The results mostly show that males have greater IMT compared to females, and the rate of progression is 0.01 mm *per* year. CCA-IMT represents a marker for subclinical atherosclerosis and an opportunity for early detection of presymptomatic individuals[120-124]. CCA-IMT has been associated with all modifiable (e.g., blood pressure, blood cholesterol, smoking, diabetes, and obesity) and nonmodifiable risk factors (including age, gender, genes, and currently unknown risk factors)[125], with all ischemic stroke subtypes[126], with occurrence of future carotid plaque (CP)[127], and with a high risk of incident myocardial infarction, stroke, and vascular death[128,129]. Therapeutic interventions with blood pressure-lowering agents[130,131], lipid-lowering agents[132,133], as well as multifactor interventions in diabetics[134] can slow the progression of or even reduce carotid IMT. Carotid IMT has been recognized recently as a surrogate marker[135] to evaluate therapeutic interventions in atherosclerotic disease.

Beside IMT, other hemodynamic factors are recently being investigated in order to estimate their possibilities as a surrogate marker of atherosclerosis[136-138].

Vertebral arteries

Although one fourth of ischemic strokes are related to the vertebrobasilar territory, the investigations of the vertebral arteries have not become so popular. The rea-

son is the technical problem due to anatomic position of the vessels, a low rate of vertebral endarterectomies, and a low rate of vertebral stenosis as a cause of vertebrobasilar strokes. Vertebral occlusions may clinically present as a TIA, or a mild stroke.

Besides normal vertebral arteries[139], by means of CCDS, hypoplasia can be displayed[140,141], and the findings may include poor color flow opacification, low flow velocities and increased resistance. The visualization of vertebral artery occlusion depends on the location, diameter and blood flow volume in the artery and collaterals[142]. The hemodynamic spectrum may help in localizing the site of occlusion. In patients with distal occlusion, color Doppler filling may be reduced due to similar hemodynamic changes, as in a hypoplastic vertebral artery. Difficulties in distinguishing the site of occlusion exist, since collateral flow may resemble vertebral artery. Power-enhancement Doppler enables visualization of a vessel with very low flow velocities, as in those vertebral arteries with dampened flow due to distal or proximal occlusive lesions and tortuous course[142-144]. It increases diagnostic confidence of the sonographic examination in patients with suspected vertebral artery disease, like stenosis, occlusion or dissection.

CCDS is useful in evaluation of vertebral artery variations like hypoplasia, and pathology like stenosis, occlusion or dissection.

Vasculitis, vasculopathies, dissections

Vasculitis of the nervous system includes a group of disorders characterized by the histological feature of inflammation of blood vessels. The diagnosis is suspected by the clinical presentation, and confirmed by the signs of inflammation obtained with laboratory analysis or biopsy. The use of CCDS may help in noninvasive visualization of the disease[145], by direct visualization if the location of the disease is present in a segment that is accessible to the ultrasound investigation, i.e. affection of the branches of the aortic arch[146], by indirect signs in hemodynamics of the carotid or vertebral arteries, or by visualizing dark halo around the pin-like color-coded flow in temporal artery[147] or occipital artery[148]. Vasculitis affecting smaller arteries may alter intracranial hemodynamics, which can be measured as impaired vasoreactivity as a marker of smaller vessel involvement.

Of vasculopathies, moyamoya disease[149] and fibromuscular dysplasia[150] may be displayed and may predispose to dissection. Dissections have lately been ever more frequently recognized as relatively common causes of stroke, particularly among young patients. Dissections lead to ischemic strokes through artery-to-artery embolism or by causing significant stenosis and occlusion of the proximal vessel, and in some cases, dissections may lead to formation of a pseudoaneurysm, which can also serve as a source of thrombus formation. Intracranial dissections in the vertebrobasilar territory have a higher risk of rupture, leading to SAH. Dissections may appear as different findings in color-coded Doppler mode[151-155]. When extending from aortic arch, double lumina can be seen. Bifurcation stenosis may dissect leading to the formation of color-coded flow in the plaque base. In younger persons, dissections are usually affecting distal parts of the internal carotid or vertebral arteries. Hypoechoic stenosis of the vessels in distal parts can be seen, or when located intracranially leading to complete occlusion, the indirect signs of distal occlusions are present. Such signs include dampened flow, with a high resistance pattern, and possibly inverse hemodynamics during diastole. The goals of therapy when treating patients with dissections and ischemic stroke are to prevent further ischemic strokes and to promote healing of the dissected vessel, and CCDS may help in monitoring of the vessel healing, in parallel with embolus detection that may show reduction in embolic signals[77,156-158].

The detection of rare causes of ischemic stroke, such as dissections, intimal hyperplasia and other less frequent etiologies, is facilitated by the systematic use of ultrasound studies.

Conclusion

Neurosonology includes both intracranial and extracranial noninvasive cerebrovascular evaluation. Intracranial evaluation enables differentiation between ischemia and hemorrhage, localization of vessel occlusion in ischemic stroke, or identification of vascular abnormalities leading to vessel rupture and hemorrhage. Furthermore, during treatment, TCD has proved to be a method suitable for monitoring the course of stroke, to enhance recanalization, or to recognize complications. Extracranial color and power Doppler enables information of noninvasive carotid and vertebral artery testing. Information on intima-media thickness by means of high-resolution ultrasound are available, as well as on carotid and vertebral artery plaques, echogenicity, plaque surfaces and degree of stenosis. The noninvasiveness and

time resolution of the measurement enable follow up of atherosclerotic, inflammatory vessel wall diseases and of dissections.

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Sažetak

NEUROSONOLOGIJA KOD MOŽDANOG UDARA

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Ovaj članak prikazuje upotrebu neurosonologije u moždanom udaru. Ovo je prošireni prikaz upotrebe u moždanom udaru kao dijela "Preporuka za zbrinjavanje moždanog udara – osuvremenjeno 2006.", koje su objavljene 2006. godine, a odobrilo ih je Hrvatsko društvo za neurovaskularne pormećaje Hrvatskoga liječničkog zbora, Hrvatsko društvo za prevenciju moždanog udara i Klinika za neurologiju KB "Sestre milosrdnice" kao Referalni centar za neurovaskularne poremećaje Ministarstva zdravstva i socijalne skrbi Republike Hrvatske. Preporuke su u skladu s preporukama triju europskih društava uključenih u Europsku inicijativu za moždani udar (*European Stroke Initiative*, EUSI): Europsko vijeće za moždani udar, Europsko neurološko društvo i Europsko udruženje neuroloških društava, kao i s Preporukama Američkoga udruženja za srce/Američkoga društva za moždani udar, što ih je odobrila Američka akademija neurologa.

Ključne riječi: *Bolesti mozga – ultrazvuk; Cerebrovaskularne bolesti – ultrazvuk; Ultrazvuk – Doppler – transkranijski*