NEUROIMAGING TECHNIQUES – IMPROVING DIAGNOSTIC AND THERAPEUTIC OPTIONS IN ACUTE STROKE

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SUMMARY – Transcranial Doppler (TCD) has been in use for over 20 years, mainly as a diagnostic tool to assess intracranial hemodynamics in basal arteries. Recently, TCD has been used as a combined diagnostic and therapeutic tool in the assessment of acute stroke. The combination of TCD and extracranial Doppler may help in the selection of patients that require more aggressive therapeutic approach. Furthermore, neurovascular ultrasound in combination with other imaging techniques such as magnetic resonance imaging (MRI) and computed tomography with specially developed imaging possibilities (DWI and PWI in MRI) may allow for better patient selection for rt-PA treatment, especially in cases where the time window has passed 3 hours, which is one of the criteria for treatment with rt-PA in acute stroke according to the worldwide accepted recommendations based on clinical trials so far. This article presents up-to-date experience with the use of multimodal techniques in acute stroke treatment.

Key words: *Cerebrovascular accident – diagnosis; Cerebrovascular accident – ultrasonography; Brain ischemia – diagnosis; Brain ischemia – physiopathology*

Occlusion of intracranial artery inevitably leads to destruction of the brain tissue, which is very vulnerable if deprived of adequate blood supply. Therefore, prompt reperfusion of ischemic brain tissue is the only effective therapy in acute stroke, and should be initiated as early as possible. Restoration of blood flow in the penumbra region reduces the total infarct size, which is mostly in correlation with final clinical outcome; therefore, it is crucial to quickly identify patients who can receive and benefit from thrombolytic therapy. Although spontaneous lysis occurs and leads to recanalization in stroke patients, this often occurs too late and by the time the recanalization process is finalized, the brain tissue has been irreversibly injured. Clinical observation that spontaneous recanalization occurs relatively often was documented in a study which showed that one week after stroke, the middle cerebral artery (MCA) occlusion spontaneously disappeared in 44%, whereas distal MCA occlusions disappeared in 67% of patients[1]. Since rt-PA has been introduced in clinical practice and its use has been first approved by the National Institutes of Neurological Disorders (NINDS)[2], a number of research and clinical articles have been published which confirm that early reperfusion is the most effective therapy in acute stroke[3]. Until rt-PA has been recognized as the most efficient therapy in acute stroke, antiaggregation therapy, mainly aspirin, has been the only pharmacological agent of proven efficacy in the treatment of ischemic stroke. Anticoagulation therapies in the acute stroke setting have not shown consistent efficacy in clinical trials and therefore have not been recommended as standard therapy. Anticoagulant therapy has a widely accepted place in the secondary prevention of stroke (atrial fibrillation, some other cardiac diseases), and so have other antiaggregation agents such as clopidogrel and less often ticlopidin (because of adverse effects).

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TCD in stroke diagnosis

Urgent detection, localization and assessment of the severity of obstructive arterial lesions by grading systems help triage patients with acute cerebral ischemia and select patients for the most appropriate therapy or invasive angiography. TCD evaluates cerebral blood flow in real time, enables detection of hypoperfusion, stenosis, occlusion and recanalization, may assess the collateral blood flow and vasomotor reactivity, detect emboli passing the circulation, and serves as an excellent method for follow-up of stroke patients[4-7]. TCD is convenient for the patient, as it is noninvasive, may be used at bedside and repeated if necessary in succession. Recent studies have shown that bedside neurovascular ultrasound can play an important role in the diagnostic workup of acute stroke patients. TCD has been found to be especially suitable for the evaluation of intracranial hemodynamics in emergency cases such as stroke. In recent TCD studies, a newly developed grading system of arterial patency has been used to detect the localization and extent of vessel occlusion or stenosis; the previously established TCD patterns of occlusion and recanalization have been redefined into the Thrombolysis in Brain Ischemia (TIBI) system according to the dynamic nature of acute occlusion and recanalization process taking place in acute stroke in patients receiving rt-PA[8]. The TIBI classification consists of 6 grades, which are based on the combination of waveform analysis and flow velocity differences (as compared to normal and flow in the contralateral MCA). Complete MCA occlusion is defined by absent (TIBI 0) or minimal (TIBI 1) flow signals detected at one or more localizations in the range of MCA insonation. The insonation of the MCA is performed through the transtemporal window at a depth of 40-65 mm; the MCA may be further divided into the proximal (M 1) part (46-65 mm depth) and distal (M 2) part (<45 mm). In cases of TIBI 0 or TIBI 1, either terminal internal carotid artery (ICA) or posterior carotid artery (PCA) flow signals must be identified from the ipsilateral window (to exclude inadequate US insonation through the bone). Partial MCA occlusion is diagnosed when blunted (TIBI 2) or dampened (TIBI 3) signals are detected. A blunted flow signal is characterized by delayed (>0.2 seconds) systolic flow acceleration with a pulsatility index (PI) <1.2, which indicates low resistance flow diversion to branching vessels or a residual positive end-diastolic flow at the site of MCA occlusion. A dampened flow signal is identified when normal systolic flow acceleration is present in the pulsatile MCA waveform with mean flow velocities <70% of the contralateral MCA and positive end-diastolic flow with variable PI values. Complete recanalization is diagnosed if low-resistance stenotic (TIBI 4) or normal (TIBI 5) signals are detected through the MCA and with no other signs that would indicate distal persisting occlusion (dampened distal signal or flow diversion).

The TIBI flow grades represent the first systemic classification of residual flow determined by TCD for major intracranial vessels and can be used to quantitate residual flow appearance and assess the vessel patency and its relation to stroke severity. The TIBI grading system has good correlation with angiography, with a sensitivity and specificity of >90% for the MCA territory and >86% for the vertebrobasilar territory[9,10].

The TIBI grading system (Fig. 1) is mostly used in the assessment of MCA occlusion, and proximal and distal vessel occlusion may be diagnosed according to the following criteria:

Proximal MCA occlusion is defined as the presence of minimal flow signal throughout the MCA at an insonation depth from 46 to 65 mm, accompanied by flow diversion in the ipsilateral anterior cerebral artery and posterior cerebral artery.

Distal MCA occlusion is defined as blunted or dampened signals (TIBI 2 or 3) in the symptomatic artery with <30% flow compared with the contralateral MCA and flow diversion signs in ipsilateral neighboring arteries.

Additional studies are needed to test the TIBI grading system for vascular territories other than MCA. Moreover, the TIBI grading system has so far been only used in patients receiving rt-PA and its prognostic value cannot be applied to patients not receiving thrombolytic therapy.

Although rt-PA is recognized as the most effective therapy, only 1%-8.5% of hospitalized stroke patients in daily practice receive rt-PA because of many exclusion criteria (the majority of patients arrive to hospital too late, i.e. not within 3 hours of symptom onset)[11]. However, in patients who do receive rt-PA, less than 50% recanalize, there is a substantial risk of symptomatic hemorrhagic transformation (SICH), and reocclusion occurs in part of the treated patients; these are the major issues that have recently been tackled in clinical studies. During the last few years, mounting evidence from continuous TCD-monitoring studies has confirmed ini-

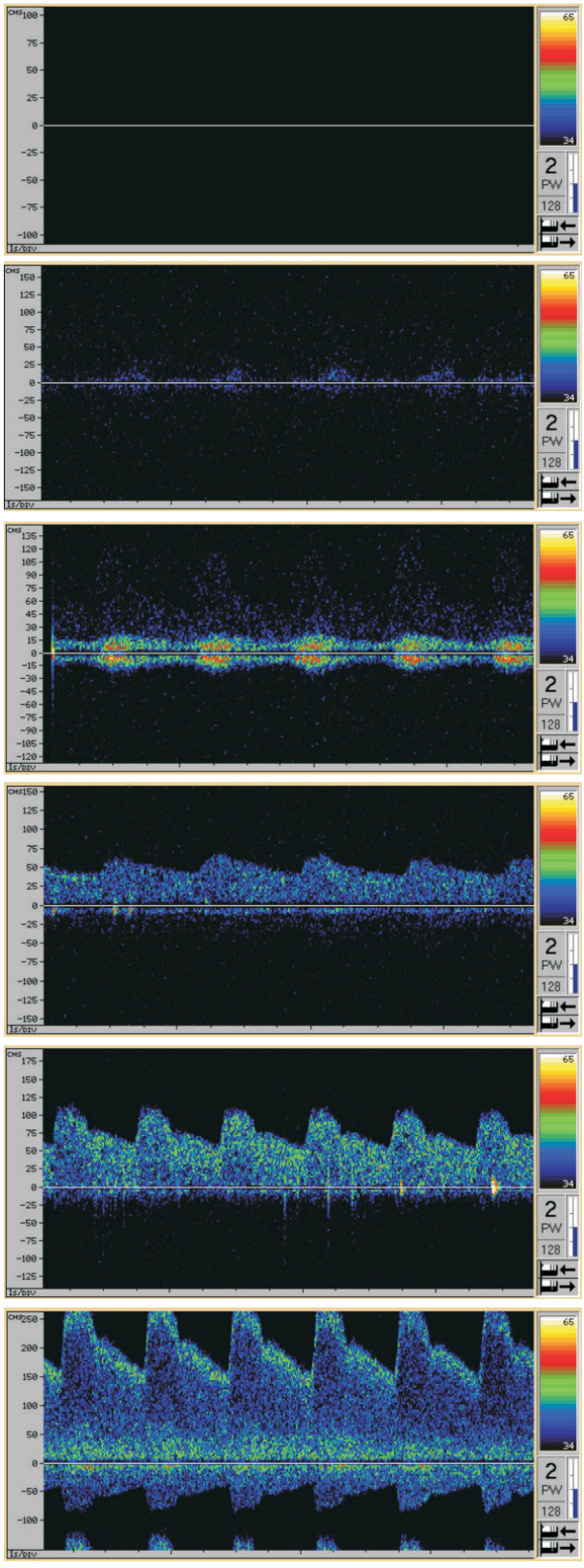

Fig. 1. TIBI grading system control.

TIBI 0: absent – no detectable flow signal despite varying degrees of background noise

TIBI 1: minimal – systolic spikes of variable velocity and duration; absent diastolic flow during all cardiac cycles based on visual interpretation of periods of no flow during end-diastole; in certain cases reverberating flow may be detected which is a type of minimal flow

TIBI 2: blunted – flattened systolic flow accelerations of variable duration compared to control (other MCA); positive end diastolic velocity and pulsatility index <1.2

TIBI 3: dampened – normal systolic flow acceleration; positive diastolic velocity; decreased mean flow velocities (MFV) by >30% compared to control

TIBI 4: stenotic – MFV of >80 cm/s AND velocity differences >30% compared to the control side; or if both affected and comparison sides have MFV <80 cm/s due to low end-diastolic velocities, MFV >30% compared to the control side AND signs of turbulence

TIBI 5: normal – <30% - <30% mean velocity differences compared to control; similar waveform shapes compared to control

tial clinical findings in stroke patients. The dynamic process of thrombus dissolution during thrombolytic therapy has been accurately delineated by continuous TCD monitoring, showing in real time all stages of recanalization and characteristic embolic signals indicating thrombus fragmentation[12]. The speed of clot lysis during continuous TCD monitoring has been categorized into sudden recanalization (abrupt appearance of a normal or low-resistance signal), stepwise (gradual flow improvement over 1-29 minutes) or slow (flow improvement in >30 minutes). Sudden recanalization indicates rapid and complete restoration of flow, stepwise and slow recanalizations reflect proximal clot fragmentation, downstream embolization and continuation of clot migration distally. The pattern of sudden clot lysis has been associated with a higher degree of neurological improvement and better long-term outcome than stepwise and slow recanalization, although sudden recanalization has been observed in only 8%-12% of patients treated with rt-PA[12].

The treatment with rt-PA has been found to be effective in different stroke subtypes[2], however, the response to treatment widely varies, most probably depending on the size, composition and source of the thrombus. Platelet rich, well organized and presumably old thrombi are found to be more resistant to thrombolysis than fresh, fibrin- or red cell-rich clots formed in conditions of stasis[13,14]. In a recent TCD study of stroke patients with proximal MCA occlusion who were treated with rt-PA, early recanalization was shown to be more frequent, faster and more complete in strokes presumably to be cardioembolic (CE) in origin as compared with other stroke subtypes: one-hour recanalization was observed in 59% of CE patients as compared with 8% in large vessel disease group or 50% in patients with stroke of undetermined origin[15]. The rate of complete recanalization was 50% in CE group as compared with 27% in other stroke subtypes. Furthermore, sudden clot lysis during rt-PA administration was identified in 81% of patients with cardiac sources of emboli.

The *in vitro* and clinical studies indicate that faster recanalization occurs in cases of cardioembolic strokes that are more fibrin-rich red clots. Since the rt-PA has a high binding affinity for fibrin, rt-PA penetrates and distributes more homogeneously in fibrin-rich clots, thus enabling more rapid and complete clot dissolution as observed by TCD in the pattern of sudden or stepwise recanalization. Distribution of rt-PA in well organized, platelet-rich clots is limited, which may only result in clot shrinking (since the rt-PA acts mostly on clot surface), movement to more distal parts of the vessel, and prolonging ischemia. In these cases, the presence of distal artery occlusion is correspondent with TIBI 3 grading system (dampened flow signlas, increased resistance to flow in the distal circulation), indicating slow and incomplete recanalization, which is associated with worse long-term outcome[15].

The timing of arterial recanalization after rt-PA therapy evaluated by TCD is in correlation with the observed clinical recovery from stroke. Furthermore, TCD studies have shown that the majority of rt-PA induced recanalizations occur during the first hour after treatment: at 1 hour partial recanalization was observed in 28% and complete in 17% of patients; at 2 hours partial recanalization was observed in 22% and complete in 31% of patients, indicating that only 19% of patients presented with flow improvement at 2 hours[16]. Recanalizations during the following hours occur in a lower percentage, however, clinical improvement if achieved within 6 hours from onset does not significantly differ in early *versus* late recanalization groups.

Early reocclusion has been recognized as a cause of clinical worsening and poor outcome in stroke patients treated with rt-PA, and has been documented on continuous TCD monitoring in ranges from 12% to 34% of patients[17,18]. Reocclusion was more frequent after partial (60%) than after complete recanalization, and after stepwise (53%) and slow (40%) as compared with sudden recanalization patterns. NIHSS ≥16 at baseline and the presence of ipsilateral severe carotid stenosis or occlusion were significantly associated with reocclusion[18].

Furthermore, TCD may be an ideal tool to rapidly identify patients who are targets for additional intra-arterial thrombolytic or mechanical interventions (patients with TIBI grade 0 and 1). The recanalization rate of 25% to 30% observed with proximal large vessel occlusion may explain the limited effect of systemic thrombolysis alone[16,19], and intra-arterial thrombolytic therapy may result in better recanalization rates. TCD may serve as a screening tool to predict outcome and identify a proximal arterial oclussion that requires intra-arterial lysis using the mean flow velocity (MFV) ratio of the MCA bilaterally (the affected MCA-to-contralateral MCA MFV ratio)[20]. In this study, the ratio <0.6 had a sensitivity of 94% and specificity of 100%, positive predictive value of 100% and negative predictive value of 86% for identifying proximal occlusion in the anterior circulation compared with standard cerebral angiography[20].

TCD findings in the setting of acute stroke are used to predict clinical outcome which has been shown to be in the correlation with TIBI grading system and NIHSS score[8]; the 24-hour NIHSS scores were higher in the follow-up of patients with TIBI grade 0 or 1; in this group, 35% of patients improved to grades 4 or 5 in comparison with 52% of patients with initial TIBI 2 or 3.

The follow-up of changes in the TIBI flow grading system enables the physicians to assess the long-term outcome and to facilitate discharge planning in terms of discussing early rehabilitation options and everyday life adjustments for stroke recoveries with family members. Due to many advantages the TCD offers, this technique should be incorporated into the standard acute stroke examination, and serve as a helpful guide for treatment decisions and follow-up of patients.

TCD and Extracranial Doppler

The combined usage of TCD and extracranial Doppler (duplex) further helps in patient selection for best treatment option, as recent studies have shown[21]. The presence of proximal ICA occlusion may warrant other treatment approaches than iv rt-PA since clinical experience has shown that recanalization of the proximal part of ICA almost never occurs with this therapy[22,23]. Carotid and vertebral duplex and TCD examination compared with digital subtraction angiography (DSA) can predict the presence of vascular lesions with 100% sensitivity and 100% specificity, although individual accuracy parameters for TCD and carotid duplex specific to occlusion location ranged from 75% to 96% because of the presence of tandem lesions and 10% rate of no temporal windows[21]. Carotid duplex alone in comparison with DSA has a high sensitivity and specificity if performed in cerebrovascular laboratories with high clinical experience[24]. The combination of intra- and extracranial Doppler examination may point out patients eligible for thrombolysis or exclude patients who would do better with other therapeutic options, as well as indicate patients with TIA who need to be more carefully looked over for stroke prevention.

The so-called tandem ICA/MCA occlusion (severe carotid stenosis or occlusion ipsilaterally to MCA occlusion) due to its specific hemodynamic changes that produces, requires special attention when a stroke patient with a suspected tandem lesion is assessed. The advantage of TCD is that it can detect residual flow in the sub-occluded artery while also detecting the major collateral pathways in the anterior and posterior circulation. Therefore, specific TCD criteria have been established which include 3 major and 3 minor criteria; acute ICA/MCA occlusion is diagnosed if abnormal (or asonic) TIBI waveforms in the MCA are present with one major or two minor findings[25,26]. In acute stroke patients, these TCD criteria have shown sensitivity of 79% and specificity of 86% in comparison with angiography (the "gold" standard) to detect severe ICA stenosis or occlusion[25].

Major criteria include:

1. Collateral flow signals in the anterior or posterior communicating artery or ophthalmic arteries
2. Abnormal ICA siphon or terminal ICA signals (TIBI grading system: absent, minimal, blunted, dampened or stenotic waveforms)
3. Delayed systolic flow accelerations in the MCA or terminal ICA (maximum frequencies arrive late in the systole with normal velocity range)

Minor criteria include:

1. Decreased pulsatility flow index (>0.6 or interhemispheric difference >30%)
2. Flow diversion signs to branching or contralateral vessels (velocity: PCA > MCA; PCA > ICA and contralateral ACA > MCA)
3. Compensatory velocity increase in branching or contralateral vessels (>20% increase in the contralateral hemispheric vessels or vertebrobasilar arteries)

In consecutive ischemic stroke patients, isolated MCA occlusion may be found in 51% and tandem ICA/MCA occlusion in another 17% of patients[26]; in this study, lower NIHSS scores were detected in both groups of patients when associated with positive diastolic flow at the MCA origin assessed with TCD and detectable ≥2 major collaterals, whereas patients with NIHSS scores ≥20 had no diastolic flow at the M1 part of the MCA origin and one or no detectable major collateral indicating occlusion of perforating arteries and probably greater overall thrombus burden[26].

CT and MR Imaging

Current recommendations for stroke treatment with rt-PA allow the administration of thrombolytic therapy within the first 3 hours of symptom onset, at this time window rt-PA is most likely to be effective with less risk for SICH[3]. A substantial number of patients arrive

to emergency departments between 3 and 6 hours after symptom onset, thus late reperfusion therapy might be beneficial in individulas in whom salvageable tissue still persists beyond the first 3 hours, since the duration of ischemic penumbra varies widely among patients. Several factors influence the speed of recruitment of ischemic penumbra into the infarct core, and knowing in exact moment the perfusion status in the individual may select patients who can successfully and safely be treated with rt-PA. No clear benefit of fibrinolytic therapy was demonstrated in patients who were treated between 3 and 6 hours of symptom onset; despite several promising reports, criteria for the treatment in this time period have not yet been established. Up to now, therapeutic window has been defined according to CT scan studies: the disadvantage of CT is that it gives insufficient information regarding the qualitative perfusion changes in the affected cerebral tissue, so penumbra cannot be delineated with this technique; the advantage of CT is good visualization of the presence of intracranial hemorrhage[27].

Multimodal MR and CT imaging protocols are becoming more accessible to the treating physicians and these diagnostic tools (especially MRI) are able to give reliable qualitative information about the perfusion status in the surrounding ischemic region. Multimodal MR and CT imaging protocols have a number of advantages which may help in the selection of patients for reperfusion therapies: they can distinguish hemorrhage from ischemic lesions, delineate infarct core, delineate still reversible salvageable penumbra regions, and even detect parts of brain tissue with only benign oligemia. MRA protocols have the capabilities to detect large vessel stenoses and occlusions; the whole diagnostic process of these imaging protocols (PWI, DWI and MRA) usually takes less than 20 minutes for completion[28,29]. In comparison with CT, DWI is more accurate in identifying acute infarction and more sensitive in the detection of more than 33% of MCA involvement (sensitivity 57%-86% for DWI and 14%-43% for CT), whereas specificity is excellent for both techniques[30]. Furthermore, a positive correlation was found between lesion volume on acute DWI and final infarct volume, whereas no correlation was found between CT volume and final infarct volume[30]. This information is now investigated in order to gain more data on patients who could be selected to benefit from rt-PA therapy beyond 3 hours of symptom onset; the main criterion is the DWI/PWI mismatch. The DWI/PWI mismatch may be used as a surrogate marker of potentially salveagable brain tissue. Using MRI, a mismatch between a larger perfusion-weighted imaging lesion and smaller diffusion-weighted imaging lesion is considered to represent the ischemic penumbra. Perfusion-weighted imaging provides semiquantitative cerebral blood flow imaging and diffusion-weighted imaging is an index of the largely irreversible ischemic core. This definition has been modified with the recognition that the perfusion-weighted imaging lesion includes benign oligemia and that a portion of the diffusion-weighted imaging core is potentially salvageable with rapid reperfusion. DWI/PWI mismatch does not give information on the risk of SICH, since the extent and severity of cerebral ischemia are the major determinants of SICH in stroke patients treated with rt-PA[31]. Studies have shown that both DWI and PWI MRI lesion volumes are highly correlated with the severity of neurological deficit by 24-hour NIHSS score[32], and that among patients who have had an acute stroke with PWI > DWI, who do not have early clinical improvement, the degree of expansion of the initial DWI lesion correlates with the severity of the initial perfusion deficit as measured by the mean transit time and the cerebral blood volume[33].

A recent study has shown that the combination of TCD and MRI (MRI data based on DWI/PWI mismatch) selection criteria for the treatment of patients with rt-PA can be safely and effectively extended to the 3- to 6-hour window[34]. Patients treated in 3-6 hour time window (group B) had a recanalization rate of 55.2% at 2 hours as compared with 49.3% of patients treated in 0-3 hours tome window (group A) (nonsignificant); SICH was 3.8% in group A and 2.4% in group B (nonsignificant). The number of patients who benefited from rt-PA therapy (NIHSS decrease ≥4 points) was slightly higher in group B, and the percentage of patients who worsened in both groups was the same: 11.4% in group A and 7.1% in group B (nonsignificant). Improvement at discharge measured by NIHSS score was similar in both groups and the rate of functional independence was similar in both groups at 3 months: 42% in group A and 38% in group B. Using the combination of TCD and PWI/DWI MR, patients who are not likely to benefit from rt-PA therapy may be selected, and might even improve, avoiding the potential risk of SICH.

The DWI/PWI mismatch concept to select acute stroke patients suitable for reperfusion therapies is currently under investigation with promising results so far. Ongoing trials will try to identify best suitable algorithms

to select patients for late reperfusion therapy: the Diffusion-weighted imaging Evaluation For Understanding Stroke Evolution (DEFUSE) study is investigating whether specific DWI/PWI profiles predict a favorable clinical response to iv rt-PA administered 3-6 hours after stroke onset (NIHSS score >5); Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) aims to determine whether the extent of the ischemic penumbra apparent on PWI/DWI MR identifies patients most likely to benefit from late reperfusion therapy; MR RESCUE trial will try to determine whether patients with a substantial ischemic penumbra on DWI/PWI MR will benefit from Merci Retriever mechanical embolectomy up to 8 hours from symptom onset (Merci Retriever is a mechanical device that captures the clot and withdraws it from the vessel with a balloon positioned proximally for emboli protection; preliminary results seem to be promising)[35]. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS) and Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS) trials are assessing the safety and thrombolytic efficacy of iv desmoteplase in MRI selected patients with acute stroke between 3 and 9 hours of stroke onset; the MRI criteria are the presence of PWI abnormality ≥2 cm in diameter in the grey matter and the presence of still salvageable penumbra (PWI/DWI mismatch >20%); the reperfusion of the penumbra tissue in DIAS trial seems to be dose dependent and the percentage of reperfusion and excellent clinical outcome is significant in treated patients, while the SICH rate has remained low[34]. The ROSIE trial is testing combined reteplase (recombinant peptide) and abciximab (glycoprotein IIb/IIIa antagonist) in patients with NIHSS score ≤16, a perfusion deficit and absence of DWI abnormality more than 1/3 of the MCA territory, results are to be expected. The advantage of ongoing trials is that the majority use similar MRI (PWI/DWI) criteria, so results can be compared; however, some trials (ROSIE) exclude the most severe strokes from the trial, which may influence interpretation of the results.

The PWI MR protocols are not accessible in all hospitals, even DWI is not a routine practice in most hospitals. Due to this lack of diagnostic accessibility, new approaches have been developed that can be used as surrogates to identify persisting penumbra. The PWI abnormality correlates in clinical practice with the extent of ischemic brain tissue that is symptomatic, which is graded by NIHSS scores, this is the so-called "clinical-DWI mismatch" (CDM). CDM is defined as an NIHSS score ≥8 and ischemic volume on DWI ≤25 mL; the cut-off of ≥8 on NIHSS has been associated with cortical perfusion deficits and high rate of neurological deterioration. Within 12 hours of ischemic stroke onset, the CDM may be detected in 52% of patients: with increasing time from stroke onset the frequency of detectable CDM decreases (74% at 3 hours, 48% at 3-6 hours and 46% at 6-12 hours)[36]. The presence of CDM was associated with a higher rate of early neurological deterioration, greater DWI lesion growth at 72 hours, and a larger infarct volume on T2- weighted MRI images at day 30. Prospective studies for the validation of the CDM mismatch concept are needed to determine its reliability to identify patients with potentially salvageable tissue who are candidates for (late) reperfusion therapies (especially because the NIHSS score underestimates infarct volume in the right cerebral hemisphere).

Several CT techniques are now available to image tissue perfusion, of these particular potential has the dynamic perfusion CT (PCT) in which images are acquired during the first pass of a standard iodinated contrast bolus. PCT distinguishes penumbra from benign oligemia, it can delineate collapsed cerebral blood volume (CBV) representing core regions from regions with reduced cerebral blood flow (CBF) but preserved CBV (so-called CBF-CBV mismatch) representing penumbra[28]. Penumbral regions identified by CT CBF-CBV mismatch correlate well with penumbral regions identified by MR DWI-PWI mismatch[37]. However, compared with MR, CT has the disadvantage of less coverage of brain tissue, use of iodinated contrast (a potential risk of allergic reactions) and poor visualization of infratentorial tissues attributable to bone infarct; the advantages are wider hardware availability and more rapid scan acquisition.

TCD in Stroke Therapy

The results of clinical trials exploring new treatment modalities have shown to be promising, particularly the use of continuous TCD monitoring while administering rt-PA and even more recently, the coadministration of microbubbles with rt-PA and TCD monitoring.

The Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic TPA (CLOTBUST) trial (phase II) has recently demonstrated that continuous 2-MHz TCD monitoring of an intracranial artery occlusion enhances systemic thrombolysis in acute stroke patients, may improve outcome and,

what is most important, this enhanced ultrasound (US) monitoring seems to be safe[38]. US enhanced thrombolysis in previous research studies has shown that US has the ability to accelerate the transport and penetration of rt-PA into the clot by creating plasma microstreams within the fibrin-rich thrombus, thus resulting in faster and more successful clot disruption[39]. In the CLOT-BUST trial, complete recanalization or dramatic clinical recovery at 2 hours after rt-PA administration was observed in 49% of patients who were continuously monitored with TCD and in 29% of patients who received only rt-PA; moreover, trends toward better clinical outcomes at 24 hours and at long term were also noted in sonothrombolysed patients. SICH occurred in 4.8% of cases in both treatment groups. Phase II of the CLOT-BUST trial is ongoing.

However, the use of US in acute stroke patients may be potentially harmful, as shown by the results of the Transcranial Low-Frequency Ultrasound Mediated Thrombolysis in Brain Ischemia trial (TRUMBI)[40]. In the TRUMBI trial, low frequency US was used (300 kHz), however, low frequencies may cause mechanical distortion of human brain microvessels leading to vessel disruption, and this was the probable reason for the high rate of SICH of 35% in this study. The high SICH rate (including bleeding in brain areas not affected by ischemia) and no signal of efficacy on early recanalization or clinical outcome at 3 months were the reasons for premature trial cessation.

The administration of microbubbles (MB) further accelerates the US-enhanced thrombolysis in acute stroke, leading to an even more complete recanalization of the artery, as recent studies have shown[41-44]. Microbubbles are small air- or gas-filled microspheres, whose acoustic impedance largely differs from that of the body fluids (blood), thus increasing the reflection of ultrasound – this is the main acoustic property how microbubbles serve as an US contrast agent. In the setting of clot disruption, microbubbles act as cavitation nuclei, and during the application of high-acoustic-pressure US, microbubbles continuously absorb the energy until they explode, releasing the absorbed energy; this is a theoretical presumption that has shown to be effective in a recent study in acute stroke patients[41]. The study combined the standard administration of rt-PA (group rt-PA), plus 2-hour continuous 2-MHz TCD monitoring of the occluded artery (group rt-PA/US) plus iv administration of microbubbles (group rt-PA/US/MB): 3 boluses of 400 mg/dL of the galactose-based microbubbles (Levovist) given at 2, 20 and 40 minutes after rt-PA administration. Two-hour recanalization was seen in 39%, 68% and 71% in the rt-PA, rt-PA/US and rt-PA/US/MB group, respectively. Two-hour complete recanalization rate was significantly higher in the rt-PA/US/MB group (54.5%) as compared with the rt-PA/US group (40.8%) and rt-PA group (23.9%). Symptomatic intracranial hemorrhage was observed in 5.5%, 2.7%, and 2.6% in the rt-PA, rt-PA/US and rt-PA/US/MB group, respectively, indicating that SICH appeared unrelated to US monitoring or microbubble administration, despite the fact that asymptomatic intracranial hemorrhage (in all cases in deep MCA territory) was detected on control CT in 16%, 19% and 23% of patients who recieved rt-PA, rt-PA/US and rt-PA/US/MB, respectively. Moreover, the coadministration of Levovist (3 boluses) during rt-PA infusion was well tolerated in all patients without systemic complications. At 24 hours, 31%, 41% and 55% of rt-PA, rt-PA/US and rt-PA/US/MB treated patients improved by >4 points in the NIHSS score (the median score at admission was 18). Although this study was non-randomized, the sample size was small, and the study was focused on patients with MCA occlusion, the results of the study are encouraging for further trials in this direction.

In conclusion, TCD, extracranial Doppler and MRI (DWI/PWI) can be used in multimodal selection of patients eligible for thrombolysis, especially the combination with PWI MRI allows for decisions to treat patients at an extended time window and to identify patients who will gain more if treated with additional intra-arterial or mechanical interventions. TCD is a helpful tool to detect arterial occlusion and possibly predict arterial reocclusion. The proven usefulness of TCD and carotid duplex in urgent treatment of neurovascular diseases has incorporated these techniques into the recommendations for comprehensive stroke centers[45]. The usefulness of PWI/DWI MRI needs to be further studied before giving recommendations for safe use at an extended time window; studies are currently under way. Ultrasonographic and radiological imaging methods and grading systems combined with clinical presentation help in the establishment of algorithms needed for more appropriate and safer treatment decisions in acute stroke patients as well as in the prediction of short- and long-term outcome.

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Sažetak

TEHNIKE NEUROSLIKOVNOG PRIKAZIVANJA – POBOLJŠANE DIJAGNOSTIČKE I TERAPIJSKE MOGUĆNOSTI KOD MOŽDANOG UDARA

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Transkranijski Doppler (TCD) u upotrebi je preko 20 godina, uglavnom kao dijagnostička metoda za procjenu hemodinamike u intrakranijskim bazalnim arterijama. Odnedavno se TCD rabi kao dijagnostička i terapijska metoda u akutnom moždanom udaru. Kombinacija TCD i ekstrakranijskog Dopplera može pomoći u odabiru bolesnika kojima je potreban terapijski agresivniji pristup. Nadalje, neurovaskularne ultrazvučne metode u kombinaciji s ostalim tehnikama slikovnog prikaza poput magnetske rezonance (MR) i kompjutorske tomografije sa specijalno razvijenim mogućnostima prikaza (DWI i PWI kod MR) omogućuju bolji odabir bolesnika za liječenje pomoću rt-PA, osobito u slučajevima gdje je vremenski prozor prešao 3 sata, što je jedan od kriterija za liječenje pomoću rt-PA u akutnom moždanom udaru prema svjetskim preporukama temeljenim na dosadašnjim kliničkim istraživanjima. U članku se navode najnovije mogućnosti i iskustva multimodalnih tehnika koje se rabe u akutnom moždanom udaru.

Ključne riječi: *Cerebrovaskularni incident – dijagnostika; Cerebrovaskularni incident – ultrazvuk; Moždana ishemija – dijagnostika; Moždana ishemija – fiziopatologija*