Diffusion weighted imaging provides signal proportional to the molecular diffusion of water. With cytotoxic edema, influx of water from the extracellular to intracellular space results in restricted movement of water molecules.

DWI provides highly sensitive detection of acute infarction and it is reliable in differentiating acute stroke form other disease that mimic acute stroke clinically and on conventional MR images.

Becomes positive in animal models within 10 minutes to 2 hours after vascular occlusion. In animals, it normalizes within 2 days. In humans, restricted diffusion has been noted as early as 30 minutes after an acute neurologic deficit; the ADC continues to decrease reaching the nadir at 8-32 hours and remains reduced for 3-5 days. Early reperfusion may alter the time course (some pseudonormalize at 1-2 days); in spite of this the tissue characterized by an initial reduced ADC nearly always undergoes infarction.

DWI with PWI is useful in predicting final infarct size and patient outcome. PWI can give information about the relative cerebral blood volume, relative cerebral blood flow, mean transit time, and time to peak. PWI >DWI = tissue at risk; DWI >PWI = sometimes seen with early reperfusion.

Reversibility and Prediction of outcome: in humans, neither a threshold time nor threshold ADC for reversibility have been established. Nearly all lesions characterized by restricted diffusion progress to infarction. Some case reports of reversible lesions (TIA, hemiplegic migraine, TGA, venous thrombosis, status).

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THE ROLE OF MAGNETIC RESONANCE IMAGING FOR ACUTE ISCHEMIC STROKE

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Background: Although computed tomography (CT) is still considered to be the gold standard of brain imaging before thrombolysis, new reperfusion strategies in acute ischemic stroke lead to more extensive use of magnetic resonance imaging (MRI).

Methods and results: Diffusion- (DWI) and perfusion-weighted (PWI) MRI with MRI angiography are considered the most important examinations in diagnosis of acute ischemic stroke before reperfusion therapy. The effort to extend strict therapeutic time window resulted in the PWI/DWI mismatch concept, established to identify the presence of ischemic penumbra. Nevertheless, a lack of standards for methodology and analysis and existence of different alternative interpretations of such mismatch still present significant limitations of its use in routine clinical practice.

Conclusion: MRI allows accurate diagnosis of the infarct lesion, detection of cerebral arterial occlusion or significant stenosis with evaluation of actual collateral flow and may also display certain reversible ischemic changes. However, the main objective for MRI still remains: improvement of non-invasive rapid and accurate identification of brain tissue at risk for infarction, which may be salvaged by safe and effective reperfusion therapy.

Thrombolysis is presently the only standardized causal therapy for acute ischemic stroke and is considered a safe and effective treatment method[1]. Urgent brain imaging is required to exclude other causes of neurological symptoms before thrombolysis. Computed tomography (CT) of the brain, which was used in most previous clinical trials is largely performed in routine clinical practice and is still recommended as a gold imaging standard before reperfusion therapy[1]. Reliable exclusion of intracerebral (ICH) or subarachnoidal hemorrhage (SAH) as the cause of acute neurological symptoms before rt-PA treatment is the main benefit of CT. On other hand, the role of CT in detection of acute ischemic changes may be at least problematic. At the beginning of the "CT era" in the 1980s, CT findings were considered negative within the first 12 hours from stroke onset regarding presence of early ischemic changes[2, 3]. Thanks to the availability of new CT machines with high spatial resolution in the last decades, a widely respected consensus concerning ability of CT to detect certain (ischemic) changes on brain scans within first 6 hours from stroke onset was created by the neuroradiological community. Nevertheless, the sensitivity of detection of these "early changes" highly varies (between 53 to 92 %) and CT is not able to differentiate the age of these changes[4-6].

Therapeutic strategies for acute ischemic stroke changed dramatically during the last few years and adequate brain imaging has become crucial for optimal patient selection for specific reperfusion treatment. The fact that up to 20 % of diagnoses of ischemic stroke at patient admission are incorrect and that even some of these patients with symptoms mimicking stroke are treated with rt-PA documents very clearly the importance and necessity of accurate stroke diagnosis[7, 8]. This is where magnetic resonance imaging (MRI) became useful. Until the beginning of 1990s, MRI was reserved mainly for the subacute phase of ischemic stroke, because the most widely available conventional sequence – T2-weighted imaging – shows infarct lesions only after 6-8 hours as a hyperintense zone[9, 10] and a T1-weighted sequence even later and as a hypointense lesion[11]. Conventional MRI offered mainly higher resolution capability for detection of relatively smaller infarcts, especially in the brain stem and cerebellum compared to CT[12, 13]. The use of urgent MRI in acute stroke was also limited for generally prevailing pessimism for low sensitivity in the detection of acute ICH or SAH compared to CT. Fortunately, this pessimism disappeared completely when more accurate MRI machines and new echoplanar sequences (T2*) capable of safely detecting brain hemorrhage became established in clinical practice[14-17].

Development of MRI echoplanar techniques facilitated the creation of multiparametric MRI protocols containing several different sequences able to detect accurately not only the infarct lesion, but also significant arterial occlusion or stenosis in the circle of Willis, and permitted evaluation of the actual collateral flow and reversible ischemic changes. These multiparametric protocols were

used in several clinical trials to assess their efficacy and benefits for indication of reperfusion therapy[18-22].

Several MRI sequences, their imaging and technical specifications and mainly their clinical benefit for acute stroke diagnosis will be discussed next.

Diffusion-weighted imaging (DWI)

DWI is crucial for the detection of acute ischemic changes. During ischemic neuronal damage, prompt failure of high-energetic cellular membrane metabolism occurs with membrane pump destruction. This leads to decreased diffusion of H_2O molecules in the context of membrane permeability decrease or to H_2O molecules locked in the cells in the course of developing cytotoxic edema. The decrease of diffusion of H_2O molecules is quantified using apparent diffusion coefficient (ADC) and leads in this case to its decrease represented as a hypointense zone on an ADC map and a hyperintense lesion on DWI scans (Fig. 1). These hyperintense changes represent, according to majority oponion, immediate irreversible ischemic neuronal damage[23-27], namely within several minutes after arterial occlusion[28, 29]. In some cases, if the cerebral blood perfusion is very rapidly restored, these changes could be potentially reversible; e.g., in patients treated with thrombolysis[30-34] or in the case of transient ischemic attack (TIA)[35]. DWI is much more sensitive and accurate in detection of acute ischemic changes compared to conventional CT[36, 37]. Parameter *b-value* determines the sensitivity in measurement of diffusion weighting. *B-value* is calculated from the power and the duration of diffusion gradients and from the time interval between gradient pulses. Higher *b-value* means higher sensitivity for detection of diffusion changes. In addition to diffusion measurement, quantification of ADC and creation of an ADC map are also possible. In the ADC map, single voxels represent quantitative diffusion measurement. The zone of low diffusion appears hypointense and, by contrast, areas of high H_2O molecule diffusion are hyperintense (cerebrospinal fluid) on this map. Significant ADC reduction (about 40-50 %) representing infarct changes correlates very well with histopathological findings[38, 39]. DWI is also useful in patients with acute neurological symptoms and multiinfarct brain lesions of different age; it can identify the acute lesion which corresponds to the present clinical symptoms[40, 41].

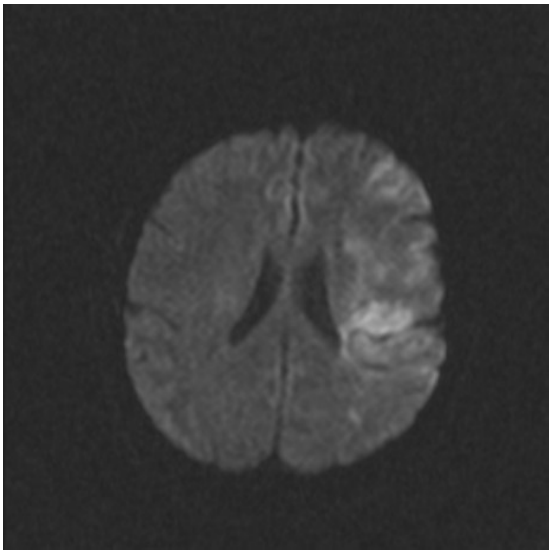

Fig. 1. DWI sequence (b-1000), acute ischemic stroke in territory of left middle cerebral artery; 85 minutes from stroke onset.

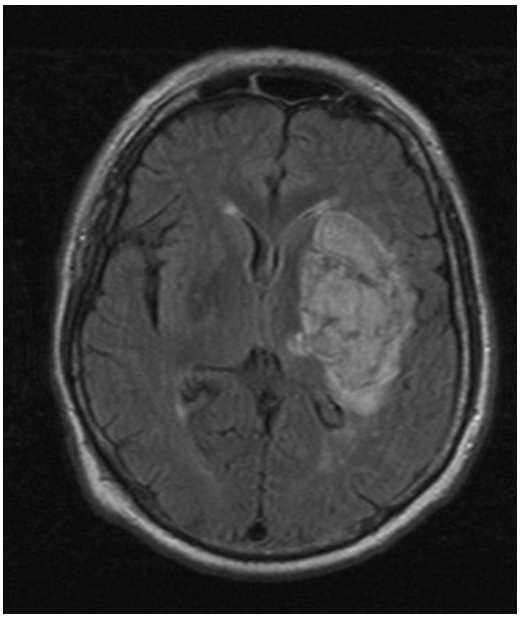

Fig. 2A. FLAIR sequence, acute large hypertonic intracerebral hemorrhage in left basal ganglia and capsula interna; 100 minutes from symptoms onset.

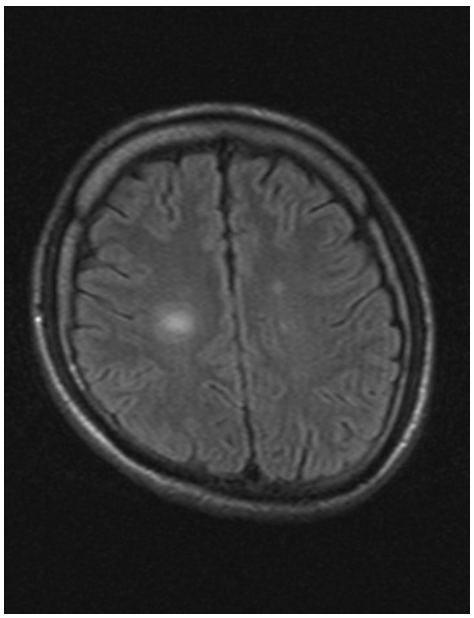

Fig. 2B. FLAIR sequence, small demyelinization lesion in right parietal cortex, clinical symptoms: left-sided moderate central hemiparesis persists 125 minutes.

Quantification of initial infarct volume on DWI may be used for prediction of clinical outcome in patients with stem occlusion of middle cerebral artery (MCA) treated with intravenous/intra-arterial thrombolysis. The results of our retrospective analysis showed that patients with initial infarct volume over 70 ml had significantly higher probability of poor clinical outcome after thrombolysis[42].

Fluid Attenuated Inversion Recovery (FLAIR)

This sequence uses so-called preparation inverse 180° radiofrequency pulse and a long-term inverse time for reduction of cerebrospinal fluid signal. The resulting T2-weighted images with hypointense cerebrospinal fluid allow better detection of hyperintense pathological lesions localized closely to external fluid cisterns or ventricles.

Infarct lesion is visible on FLAIR as a hyperintense zone not earlier than 5 to 6 hours from stroke onset, when vasogenic edema develops and water content increases significantly in the damaged tissue. FLAIR may differentiate subacute and chronic ischemic changes and other types of non-ischemic etiology of neurological symptoms (e.g. tumor, multiple sclerosis etc.)[43-46] (Fig. 2).

T2*

T2* (star) is a very important sequence for detection of hemorrhage. Degradation products of hemoglobin (deoxyhemoglobin and hemosiderin) have paramagnetic properties and cause local inhomogeneity of the magnetic field, which results in signal loss on T2* scans (dark lesion)[47]. T2* may also detects microbleeds and early hemorrhagic transformation of brain infarct[48, 49]. These findings exclude the patients from eventual thrombolytic therapy. Sometimes, for practical reasons of shortening the examination time by about 3 to 4 minutes the "classic" T2* may be replaced by a set of gradient echo EPI images with b = 0, which is part of some EPI-DWI trace sequence protocols[42]. These sequences have lower spatial resolution, but they are highly sensitive for detection of acute hemorrhage (Fig. 3).

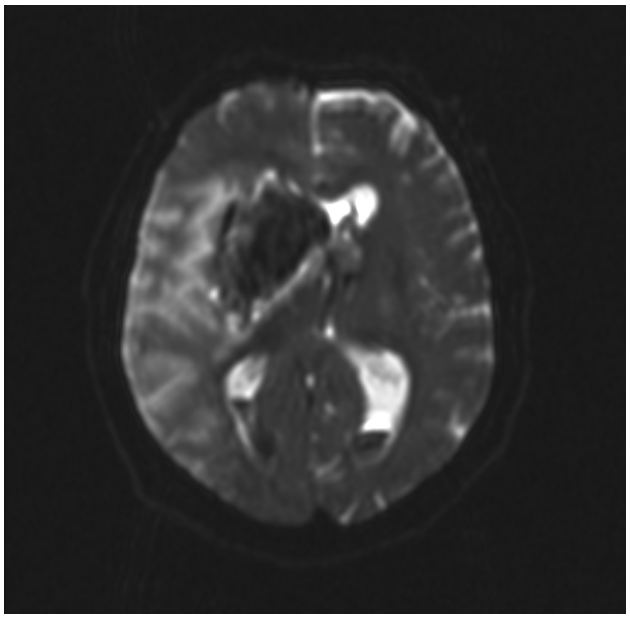

Fig. 3. EPI-DWI sequence (b-0), intracerebral hemorrhage (hypointense) in infarct lesion (hyperintense) in right cortex.

Magnetic Resonance Angiography (MRA)

MRA is used to display the arteries of the circle of Willis using "time of flight" (TOF) technique[50]. The TOF technique detects "new flowing" non-saturated spins in a predefined excited stationary layer during the blood flow. These protons are displayed as a hyperintense zone

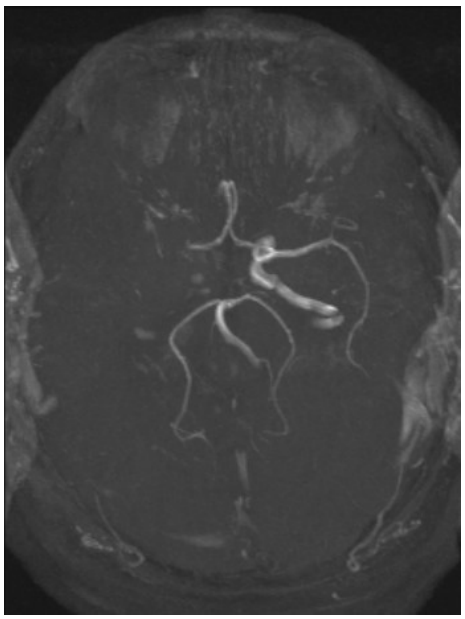

Fig. 4A. 3D TOF MRA sequence, occlusion of intracranial portion of right internal carotid artery.

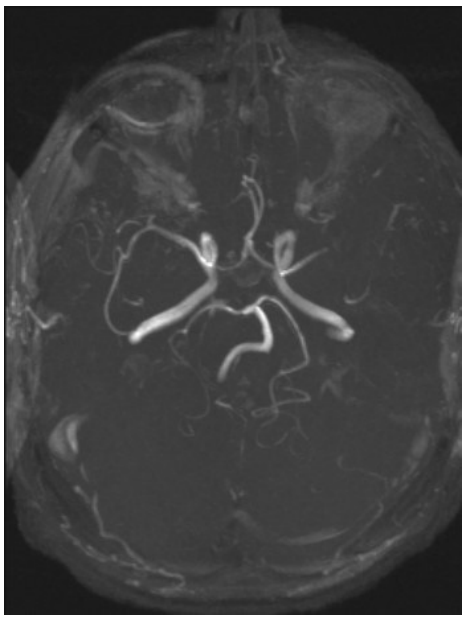

Fig. 4B. 3D TOF MRA sequence, occlusion of left middle cerebral artery (M1).

on a hypointense background. Maximum intensity projection (MIP) results in an angiogram[51]. Obtained basic sublayers may be visualized directly into 2D scans or they may be processed in three-dimensions into high-quality 3D image of the Willis circle, which shows arterial occlusion or significant stenosis[52-55] (Fig. 4).

The reliability of 3D TOF MRA was repeatedly confirmed by comparison with digital subtraction angiography (DSA), CT angiography (CTA) and duplex sonography in past[56-57].

3D TOF MRA may also display the collateral flow in occlusion of MCA stem or internal carotid artery (ICA)[58, 59]. A possible limitation is the less accurate imaging of smaller and more peripheral branches of cerebral arteries compared to DSA and CTA[55], although MRA provides enough information about cerebral arteries for accurate diagnosis of ischemic stroke[60, 61].

Ischemic stroke may also be caused by pathology in the extra-cranial portion of carotid and vertebral arteries, most commonly by occlusion or significant stenosis of the internal carotid artery (ICA). For this reason, MRA of extra-cranial portion of cerebral arteries is added to the examination protocol in some stroke units. 3D TOF MRA is used on a standard basis and its accuracy was also evaluated using of comparison DSA and CTA[62]. A disadvantage of non-contrast MRA is the long duration of the examination, which is typically about 10 minutes. Therefore a different MRA technique using intravenous administration of contrast paramagnetic agent (contrast-enhanced magnetic resonance angiography, CE-MRA) began to be used in the last decade. CE-MRA significantly reduces the examination time and moreover, is capable of very accurate quantification of the degree of stenosis, which is comparable to invasive DSA thanks to using special techniques with high spatial resolution and special post-processing software[63-67].

Perfusion-weighted imaging (PWI)

PWI represents a set of techniques, which can detect hemodynamic changes in brain tissue on a microvascular level. A paramagnetic contrast agent (gadolinium) is applied as an intravenously administrated bolus. Subsequent signal changes, which are caused by contrast agent passage through brain tissue, are detected by ultra-fast MR sequences[68]. The most visible signal changes are caused by difference of contrast agent concentration in extra/intravascular space. Gradient echo-planar imaging (EPI) is mostly used in PWI.

The passage of contrast agent through brain causes signal decrease. In ischemic tissue perfusion is decreasing and therefore the contrast agent has minimal or no concentration in this ischemic zone and signal is relatively increased[69]. Although the dynamics of signal changes provide some information about cerebral microcirculation, the relative signal loss does not correlate directly with any physiological parameter. The derivation of a "signal – time" curve and "concentration of contrast agent – time" curve acquired during first passage of contrast agent are needed to calculate (semi-) quantitative parameters of cerebrovascular hemodynamics[69]. The results of these complicated derivations are several hemodynamic parameters: cerebral blood flow (CBF), cerebral blood volume (CBV). Two other parameters are derived from the "concentration of contrast agent – time" curve. First is the "mean transit time" (MTT); time interval when signal returns to baseline after passage of the contrast agent. Second is the "time to peak" (TTP); time when the concentration of gadolinium becomes maximal in the region of interest[70]. These parameters are mostly used in clinical practice only as qualitative indices of cerebral perfusion in the form of color maps because of highly time-consuming post-processing calculations of parameter values[71].

Ischemic penumbra and the mismatch concept

Time is one of the most important limitations for more extensive use of intravenous thrombolysis in acute stroke patients. Recently updated guidelines published on the internet[72] allow the administration of IVT within first 4.5 hours from stroke onset based on results from ECASS III trial[73], however such rt-PA administration is off the current European labeling. Nevertheless, imaging technologies provide information about the presence of the potentially salvageable ischemic brain tissue until several hours from stroke onset[74-76]. This zone is called ischemic penumbra and represents brain tissue, which is at risk for infarct growth and which is potentially salvageable by early recanalization therapy[77]. Biochemically, penumbra is defined as a zone of suppressed protein synthesis caused by blood hypoperfusion, but without irreversible energetic damage with ATP depletion. Tissue which is only hypoperfused without suppression of protein synthesis is not at risk for infarct growth. Logically, brain tissue should be salvaged before the onset of decrease in protein synthesis and of ATP depletion. However, there is no routinely available technology, which is capable to display these biochemical changes. Presently, only positron emission tomography (PET) can detect accurately the real ischemic penumbra using radioactive oxygen (^{15}O) with short half-time[78-80]. PET penumbra is defined as zone of critical decrease of blood flow, but with preserved O_2 consumption with evidence of high value of O_2 tissue extraction[81].

The development of new MRI techniques encouraged also the identification of ischemic penumbra using MRI. The concept of PWI/DWI mismatch appeared as a result of MRI technical improvement. Mismatch was defined as a difference between PWI lesion surface area and hyperintense DWI zone surface area on respective MRI scans and this surface area difference should represent tissue at risk for infarct growth[82-85]. Patients with ischemic penumbra presented on MRI may have higher profit from thrombolytic therapy several hours after stroke onset compared to patients without detected penumbra[86-88].

The frequent use of this mismatch concept may indicate its great reliability and accuracy for decision to perform thrombolysis beyond standard 3-hour therapeutic window. However, several facts should be discussed because they may challenge this concept.

Although hyperintense changes displayed on DWI are still considered to be a marker of irreversible damage of brain tissue[23-27] present immediately after arterial

occlusion[28, 29], cases of significant DWI lesion regression are repeatedly reported in patients with rapidly restored cerebral perfusion after thrombolysis[30-34] or in the case of TIA[35].

Furthermore, several aspects of PWI are still being discussed: choice of the most accurate and optimal („cost-effective") MRI technique for PWI, assessing a reliable post-processing method for quantification of hemodynamic parameters, which better characterize tissue at risk of infarction – penumbra[89-91]; PWI cannot differentiate benign oligemia and real penumbra reliably[92]. Non-standardized design of the corresponding MRI sequences still limits objective interpretation of the achieved results. Not only several doses of contrast agent, but also different sequence techniques and different methods of parameter measurements are used during PWI examination and it is still not clear which of them should be used in routine clinical practice[93]. Analogously, the concept of PWI/DWI mismatch is still largely being discussed. Some authors consider it as an approximation of the real penumbra[77], different definitions and methods of mismatch quantification are problematic for other authors[93]. At present, several definitions are established; some authors defined mismatch as the absolute difference between PWI and DWI lesion[82, 83, 94], others as the difference between 50 % of PWI lesion and DWI lesion[95]. The mismatch volume was measured in most trials directly on MRI scanner monitor and some evaluated the volume only visually[84, 85]. These facts which limit routine use of mismatch lead to creation of other new concepts. One of them is the mismatch between the degree of neurological deficit in NIHSS and the initial infarct volume on DWI – clinical-diffusion mismatch (CDM). CDM was defined as presence of NIHSS ≥ 8 and infarct volume on DWI ≤ 25 ml[95]. CDM was compared to PWI/DWI mismatch and a significant agreement with high specificity and predictive value was found[96]. Contrariwise, Lansberg et al. reported that clinical improvement after IVT performed in patients between 3 and 6 hours from stroke was significantly correlated to the presence of PWI/DWI mismatch, but not to presence of CDM[97]. Our retrospective analysis of 79 patients treated with IVT within 3 hours showed better clinical results in patients with present CDM before thrombolysis[98].

CONCLUSION

At present, MRI allows accurate diagnostics of acute brain infarct lesion (actual size, localization), detection of occlusion or significant arterial stenosis and evaluation of actual collateral flow. MRI can also detect some reversible ischemic changes. This information may help better identify the patients with probably higher benefit from thrombolysis, especially beyond the standard therapeutic time window[74-77, 86-88, 98].

However, the main objective for MRI still remains: the improvement of non-invasive rapid and accurate identification of brain tissue at risk for infarction, which may be salvaged by safe and effective reperfusion therapy.

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