REVIEW

Comparison of PET and DW / PW-MRI in Acute Ischemic Stroke

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Abstract: The penumbra - tissue perfused below the flow threshold for functional disturbance but above that for maintenance of morphological integrity - is the target for therapy in acute ischemic stroke. Irreversible tissue damage and penumbra can be reliably identified by multitracer positron emission tomography (PET) which has severe limitations due to complexity, invasiveness and radiation exposure. Therefore other modalities served as surrogate markers, with diffusion / perfusion-weighted magnetic resonance imaging (DW / PW - MRI) and perfusion computed tomography (PCT) being applied widely in clinical routine.

In order to evaluate the limitations of DW / PW - MRI a comparative study was performed in acute stroke patients in whom cerebral perfusion was assessed by perfusion-weighted magnetic resonance imaging (PW-MRI) and $H_2{}^{15}O$-PET, tissue damage was estimated by diffusion-weighted magnetic resonance imaging (DW-MRI) and 11C-flumazenil (FMZ) PET and DW / PW - MRI mismatch was related to the tissue with increased oxygen extraction fraction (OEF) as an indicator of penumbra. The lesions in DW - MRI and in FMZ-PET were reliable predictors of final infarct on late MRI, but DW - MRI showed a high false positive rate. PW - MRI was limited in estimating flow and yielded values comparable to $H_2{}^{15}O$-PET only in the range between 20 and 30 ml/100g/min. The DW / PW - MRI mismatch overestimated the penumbra as determined by increased OEF. These limitations of DW / PW - MRI have to be considered if used for selection of patients for treatment and might have an impact on the outcome of clinical trials based on this surrogate marker. (Keio J Med 57 (3) : 125 –131, september 2008)

Key words: brain ischemia, ischemic stroke, positron emission tomography, diffusion / perfusion weighted magnetic resonance imaging, oxygen extraction fraction, mismatch, stroke therapy, thrombolysis, reperfusion

Introduction

Therapy in acute ischemic stroke can only be effective as long as potentially salvageable tissue is present within the brain area affected by the perfusional disturbance. Therefore, the identification of the penumbra - tissue perfused at a level which impairs function but preserves morphology[1–3] - and the distinction of this potentially reversible condition from irreversibly damaged tissue is of utmost importance for the initiation of treatment strategies targeted at reperfusion and protection of ischemically compromised but viable brain areas. Whereas the model of regional ischemic damage with a core of fast developing necrosis and a surrounding area with delayed damage and a potential for recovery, i.e. the penumbra, was developed from animal experiments, the transfer of this concept into clinical application in patients with acute ischemic stroke is limited by the inaccuracy in differentiating functional impairment from morphological destruction in early stroke. Various imaging modalities have been applied for this task: PET of regional cerebral blood flow and energy metabolism was the first imaging technique employed for penumbra detection, which was defined as the region with increased oxygen extraction fraction and termed “misery perfusion” for this purpose.[4] PET is still considered the gold standard for detection of penumbra and irreversibly damaged tissue,[5,6] but its availability is limited to a few centres and restricted by

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the complex logistics involved. DW / PW - MRI is widely available and has become the routine method for the acute evaluation of stroke patients. The area of diffusion / perfusion mismatch has been used as a surrogate marker of the penumbra and promising results were achieved in identifying patients with a chance to respond to therapy.[7–9] Recently also determination of perfusion by x-ray computed tomography(CT) was successfully applied to detection of potentially salvageable ischemically compromised tissue.[10]

Detection of Penumbra

Severity and extent of the ischemic compromise can be clearly assessed in experimental models for which flow thresholds for preservation of function and morphology were defined.[2,3] Ischemic tissue is only amenable to therapy as long as the lack of blood supply did not lead to morphological destruction and only caused functional impairment. This tissue, termed the penumbra,[1] is perfused at a level within the thresholds of functional impairment and morphological integrity and has the capacity to recover if perfusion is improved. The extent of this tissue compartment is dependent on residual flow and duration of flow disturbance: It can be clearly demonstrated in animal experiments with permanent and transient occlusion of cerebral vessels[11] that the volume of functionally impaired but morphologically intact tissue is large and involves even the centre of the vascular territory with impaired blood supply immediately after the onset of the perfusional disturbance, and it becomes progressively smaller with time elapsed since the vascular attack.[5] This concept as developed in animal experiments defines the penumbra as a dynamic process depending on residual perfusion and duration, with conversion into irreversible neuronal damage over time, progressing from the centre of dense ischemia to the surrounding tissue with less severe but still critically hypoperfused adjacent areas.

In the clinical setting of acute stroke management the assessment of the condition of the ischemically affected tissue is extremely difficult and necessitates logistically complex and expensive investigative procedures, which cannot be performed routinely. Studies performed in selected cases with determination of regional cerebral blood flow (rCBF), regional cerebral consumption of oxygen ($rCMO_2$), regional oxygen extraction fraction (rOEF), and regional cerebral metabolic rate for glucose ($rCMR_{glc}$) by PET have broadened the knowledge of pathophysiological mechanisms leading to ischemic infarction and in some instances could explain the success or failure of therapeutic interventions. In individual cases, disturbances of flow and energy metabolism in the acute stage could be related to the final fate of the tissue: synchronous decreases of flow and oxygen consumption below threshold values predicted infarction, whereas uncoupled decreases of flow with oxygen consumption preserved at a higher value termed "misery perfusion" by Baron *et al*. (1981)[12] indicated tissue with uncertain prognosis, i.e. the potential for recovery or necrosis. The determination of absolute values of thresholds in patients, however, is difficult since the necessary calculation requires arterial blood sampling. Additionally, measurements of tracer concentrations are affected by considerable variability causing especially high statistical errors at low count rates. As a consequence, the reported values for the threshold of morphological damage and of the upper limit of penumbra given by different authors vary considerably (review in Heiss *et al*, 2000).[13] These values are also affected by the time of determination after the vascular attack since the variability of flow in the course after the attack which has a considerable effect on outcome cannot be assessed. For preservation of morphology the necessary oxygen consumption was determined to be around 65µmol/100g/min, the flow thresholds ranged between 5 and 12 ml/100g/min. For the upper limit of the penumbra flow values between 14 and 22 ml/100g/min were reported. These values corresponded to those assessed by other methods as PW-MRI, single photon emission computed tomography (SPECT), and Xe-enhanced computed tomography (Xe-CT).

Using flow values measured in the first hours after a stroke various compartments of tissue and their contribution to the final infarct on CT/MRI can be determined. If the threshold for probable infarction was arbitrarily set to the conventional value of 12 ml/100g/min and that for the upper limit of penumbra to 18 ml/100g/min[14] a large compartment of the final infarct (70%) was critically perfused, i.e. at a level predicting necrosis; a smaller compartment (18%) had flow values in the penumbra range and a fairly small compartment (12%) was sufficiently perfused.[15] This result carries important implications for treatment of acute stroke: a significant effect can only be achieved if perfusion is improved before irreversible damage has occurred.

Detection of Irreversibly Damaged Tissue

The determination of rCBF is an unreliable predictor for the assessment of irreversible damage. For that purpose quantitative measurement of $CMRO_2$ and CBF is necessary requiring arterial blood sampling which is prohibited when invasive strategies, e.g. thrombolysis, are planned. Therefore, a marker of neuronal integrity is needed which can noninvasively distinguish between viable and irreversibly damaged neurons. As such tracers labelled ligands of central benzodiazepine receptors can be applied which reliably differentiated infarcted from non-infarcted cortex in animal experiments and in stroke patients.[16] Using ^{11}C-flumazenil(FMZ) as a marker of

neuronal integrity and $H_2{}^{15}O$ for flow determinations, the pathophysiological changes early after ischemic stroke could be more accurately specified: 55% of the volume of the final infarct had FMZ uptake decreased below the limit of 95% probability for infarction at the study in the first hours after stroke; 21% of the final infarct had flow below 14 ml/100g/min, the 95% probability threshold for survival, but FMZ above the critical value, thereby indicating penumbra tissue. Only 13% of the final infarct exhibited neuronal integrity and CBF values above the penumbral range. These results stress again the crucial role of early reperfusion in the treatment of ischemic stroke. Only a rather small compartment is initially viable and sufficiently perfused, but eventually becomes necrotic mainly owing to delayed mechanisms; only this tissue volume may benefit from neuroprotective or other measures exclusively targeted to secondary damage.

Limitations of DW / PW - MRI

Without doubt DW / PW - MRI is the most widely available and most utilised method to detect tissue amenable for therapy in patients with acute stroke and it is therefore the preferred method for selection of patients and for evaluation of treatment effects in stroke trials.[17–19] However, the assumption that the diffusion / perfusion mismatch represents the penumbra as challenged by several limitations of DW / PW - MRI[20]:

1 The initial diffusion lesion does not only consist of irreversibly infarcted tissue; diffusion lesions may be reversed if blood flow is restored at an early time point.[7–9]
2 True penumbra cannot be clearly differentiated from tissue experiencing oligemia; the perfusion-weighted imaging abnormality often overestimates the final infarct volume and thereby the amount of tissue at risk.[21]

These facts are further accentuated by methodological limitations, especially perfusion techniques and data evaluation are not truly quantitative and vary among centres.[22] In order to account for these inaccuracies Kidwell *et al*[20] proposed a modified model of ischemic compromised tissue as observed by DW / PW - MRI in which the penumbra includes the diffusion / perfusion mismatch region, minus the region of benign oligemia as well as a portion of the initial diffusion abnormality itself. The definition of this tissue compartment, however, remains to be controversial and several attempts have been made to identify perfusion or apparent diffusion coefficient thresholds for better differentiation of these regions,[21,23–27] but a consensus on the best method is still hampered by the lack of standardisation of methodological approaches to image post processing and analysis which restricts pooling of data and cross-comparison of results across studies. More sophisticated analytical procedures may help to improve accuracy in distinguishing core from penumbral tissue.[28]

Comparison of MRI and PET

Absolute or relative thresholds derived from DW / PW - MRI are still not reliable in predicting the fate of ischemic tissue.[28] Therefore, a validation of MR signatures on results from PET measurements might help in the interpretation of the respective finding and in the assessment of the accuracy of the various measures for predicting tissue outcome. Comparative studies with PET and MRI were performed in 3 groups of patients with respect to assessment of cortical damage, measurement of perfusion and delineation of penumbra tissue.

Irreversible Cortical Damage

For the prediction of irreversible cortical damage results from DW - MRI (median 6.5 hours after symptoms onset) and FMZ PET (median 85 min between DW - MRI and PET) were compared with infarct extension 24 to 48 h later on T2-weighted MRI in 12 acute stroke patients.[29] Cortical areas were categorised as infarction or normal according to their appearance on follow-up MRI and volumes of interest (VOIs) of 6-mm diameter were fitted into the cortical rim of the coregistered DW - MRI, apparent diffusion coefficient (ADC), and FMZ images. Across all patients' volumes of interest, the threshold probability integrals of final infarction or noninfarction were interactively computed, and positive prediction curves were obtained on which 95% prediction limits could be defined.[16] These values - FMZ binding 3.2 times the mean of the contralateral white matter, DW - MRI intensity 1.18 times the contralateral area, ADC 0.83 times the contralateral region - represent the 95% probability threshold of final infarction. When the volumes of tissue beyond these thresholds were compared, close correlations between volumes with FMZ and DW - MRI beyond threshold as well as between predicted and final infarct volumes were obtained, but the volumes did not completely overlap. Overall, 83.5% of the final infarct (median, 14.9 cm^3) was predicted by decreased FMZ binding, 84.7% by increased DW - MRI signal, and 70.9% by reduced ADC value. However, because of the incongruities, only a small part of the final infarct was not predicted by FMZ or DW - MRI value beyond the critical limit (median, 1.1 cm^3). The false-positive rates showed significant differences: only a small part (median, 0; mean, 0.9 cm^3) of the finally noninfarcted tissue had initially decreased FMZ binding, whereas 5.1 cm^3 of finally normal tissue showed an increased DW - MRI signal (25.9% of the total volume of DW - MRI increase) and 3.6 cm^3 showed a decreased ADC value (22.3% of

total volume). These differences were significant ($P<0.01$, Wilcoxon test). The volumes of infarcted tissue not predicted by decreased FMZ or changed DW - MRI signal were comparable. In single cases, areas with markedly increased DW - MRI signal did not show either impaired FMZ binding or a lesion on late MRI, as reported previously,[30] but in most cases the differences with respect to FMZ binding and DW - MRI signals were at the borderline of the ischemic territory.

Perfusion in and around the Ischemic Territory

For the assessment of perfusion within the oligemic and ischemic territory results from PW - MRI (median 8 hours after symptoms onset) were compared with cerebral blood flow measurements obtained with $H_2{}^{15}O$-PET (interval 60 min between PW - MRI and PET) in 11 acute stroke patients.[31] After coregistration of the MR and PET images, an individual brain atlas was created for each patient. Then the volume of hypoperfusion of <20 ml/100 g per minute (PET CBF) was created with the use of a voxel-based threshold function. Within the same brain atlas, the time to peak (TTP) images were analyzed with stepwise increasing thresholds, i.e. with increasing relative TTP delays (2, 4, 6, 8, 10 seconds with respect to the unaffected hemisphere). The volume of CBF hypoperfusion ranged from 1.2 to 362 cm^3 (median, 34.5 cm^3). The voxelbased 3-dimensional fusion of each patient's hypoperfusion volume (CBF) and the respective set of TTP volumes were used to create subcompartments to calculate sensitivity and specificity values for each TTP threshold. The TTP threshold of 4 seconds reliably identified hypoperfused tissue (sensitivity, 0.827) and excluded normoperfused tissue (specificity, 0.768). Increasing the TTP threshold to 6 seconds impaired the ability to detect hypoperfusion (sensitivity, 0.765) but improved the rate of correctly identified normoperfused tissue (specificity, 0.875). From this small sample size, it can be concluded that a TTP delay between 4 and 6 seconds is useful to differentiate cerebral hypoperfusion of <20ml/100 g/ min.

Delineation of Penumbra Tissue

For the demarcation of the volume of tissue at risk (penumbra) the areas of mismatch from DW / PW - MRI were compared to those of increased oxygen extraction fraction (OEF) as determined from PET of cerebral blood flow (CBF) and cerebral metabolic rate of oxygen ($CMRO_2$) in 5 patients with acute and 5 patients with subacute state after stroke due to vascular stenosis.[32] As surrogate markers of the penumbra, DW / PW - MRI revealed a mismatch between the volumes of TTP prolonged beyond 4 sec and the volume of increased DW - MRI signal, and volumes of increased OEF (>150%) were calculated from CBF and $CMRO_2$ maps measured by PET. The comparison of the volumes identified by these modalities demonstrated a high variability: all 10 patients showed areas of TTP prolongation on PW images (median volume, 162 cm^3; range, 8 to 450 cm^3). However, in only 6 of 10 patients was an elevated OEF identified on PET images (median volume, 65 cm^3; range, 12 to 240 cm^3). The areas of OEF elevation were always located within the areas of TTP prolongation but were significantly smaller and covered only 8% to 58% (median, 33%) of the TTP area. These preliminary data demonstrate a high sensitivity but a low specificity of the chosen threshold to identify penumbral tissue as defined by PET: in 40% of the patients with TTP > 4, no OEF elevation was found. In the remaining 60% with OEF elevation and TTP > 4, only a third of the TTP volume corresponded to elevated OEF. These findings may explain the poor relation between increased OEF and TTP values in a correlation analysis based on volumes of interest. The results of our small patient sample indicate that TTP threshold > 4 seconds does not sufficiently discriminate between normal and increased OEF in ischemic tissue.

These preliminary data on the comparison of PET and DW / PW - MRI for assessment of perfusion, identification of irreversible tissue damage, and distinction of penumbra indicate that imaging with these different modalities yields complementary information on the dynamics of pathophysiological events in ischemic brain tissue. The findings of DW - MRI/ADC imaging correlate well with those of FMZ PET and predict the final infarct extension.[26,33] However, the increased DW - MRI signal carries a considerable false-positive rate, a clinically important restriction of DW - MRI that was demonstrated in previous studies of patients with transient ischemic attack and those treated with thrombolysis.[7,34,35] PW - MRI-derived TTP maps are only indirect surrogates of CBF because they are based on a different pathophysiological approach.[36] Hence, a TTP prolongation of > 4 seconds allows only a vague estimate of hypoperfusion of 20ml/100 g/ min.[37] Because of this indirect assessment of perfusion from TTP prolongation, which therefore inconsistently corresponds to elevated OEF,[38] the mismatch volume in DW / PW - MRI does not reliably reflect misery perfusion as defined by PET. Despite the importance of MRI in clinical practice for the selection of patients who might benefit from revascularization procedures, the differences between the imaging methods and their specific methodological restrictions should be taken into account when results are compared and definitions of various tissue conditions are transferred between the modalities.

Effects of Treatment on the Penumbra

The efficacy of treatment in ischemic stroke can only

be proven by controlled randomized double blind clinical trials, as successfully performed for thrombolysis within the 3-hour-window[39,40] (The NINDS rtPA Stroke Study Group 1995, The Atlantis 2004). Since such controlled trials require large patients' populations collected in many stroke centres and therefore usually take long time and considerable funds, surrogate markers are applied to predict potential therapeutic effects in small groups of patients. It has to be kept in mind that proven effects on surrogate markers always must be confirmed in controlled trials based on sufficient patients' populations. Based on experimental results in stroke models[41] neuroimaging has been used as a surrogate marker to indicate therapeutic effects of various treatment strategies.

Non-enhanced x-ray CT which is still the first line diagnostic procedure in management of acute ischemic stroke[42] does not reliably predict response to thrombolysis.[43] Some studies demonstrated an increased risk of intracerebral hemorrhage after tPA if early ischemic signs involved more than 1/3 of the mci-territory, but this finding was not replicated in other studies.[44] Clinical CT mismatch was not related to response to tPA treatment[45] and the semi-quantitative analysis of early ischemic signs by ASPECTS[46] did not predict effect of tPA.[47,48]

Thrombolysis is still the only approved therapy for acute ischemic stroke, and its effect was demonstrated recently in several imaging studies, in which reperfusion to penumbral tissue was associated with improvement in neurological deficits. In a small cohort selected from the NINDS study, Grotta *et al*. (1998)[49] found a significantly greater reperfusion in the rtPA treated patients than in the placebo group. The volume of tissue salvaged by reperfusion was established in a study in which CBF, as determined by $H_2{}^{15}O$-PET within 3 hours of stroke onset, was compared with the volume of infarction determined on MRI 3 weeks after the ictus.[50] The percentage of initially critically ischemic voxels (i.e. with a flow below the threshold of 12 ml/100g/min) that became reperfused at almost normal levels clearly predicted the degree of clinical improvement achieved within 3 weeks. Overall, only 22.7% of the grey matter that was initially perfused at rates below the conventional threshold of critical ischemia became necrotic after thrombolytic therapy in this small sample of 12 patients. That means, that a considerable portion of the critically hypoperfused tissue was probably salvaged by the reperfusion therapy. Another PET study in 11 patients[13] indicated that hypoperfused tissue could benefit from reperfusion only as long as cortical flumazenil binding was not reduced to or below 3.4 times the mean uptake in white matter. This marker of neuronal integrity can therefore serve as an indicator for irreversibly damaged tissue that is not amenable to treatment.

Some investigators applied dynamic perfusion-CT[10,51] for the selection of patients for thrombolysis and reported favourable outcome if a mismatch between the core of ischemia (significant reduction of regional cerebral blood volume, i.e. below 2.0 ml/100g/min) and the area with decreased perfusion (regional mean transit time above 145% of contralateral area) but maintained blood volume (> 2 ml/100g/min) was found. Dynamic CT was used in patients treated with intra-arterial revascularization procedures and could distinguish ischemic tissue likely to infarct from that likely to survive.[52] Further studies are needed to confirm the value of this surrogate marker for prediction of clinical outcome after treatment.

The difference in the volumes of abnormality in DW / PW - MRI - as an approximation to the zone of the penumbra - has also been used as a surrogate marker of efficacy in stroke trials.[53] Several groups reported results of serial DW and PW imaging in patients undergoing intravenous or intra-arterial thrombolysis. The main finding proved inhibition of lesion growth in patients experiencing reperfusion compared with patients with persistent perfusion deficit.[54] Normalization of PW - MRI and increases in ADC were closely associated with the reperfusion seen after thrombolytic therapy[7,55] and the DW / PW - MRI mismatch could be used as an effective selection criterion even in patients admitted more than 3 hours after onset of symptoms.[18] However, in some cases perfusion deficits can be resolved and DW - MRI signatures of early ischemic injury can be reversed by prompt vessel recanalization.[7] This means that the ischemic penumbra includes not only a region of diffusion / perfusion mismatch, but also portions of the volume of initial diffusion abnormality.

The DW / PW - MRI mismatch was used for selection of patients in several clinical trials. In patients with mismatch the outcome was more favourable after tPA treatment, especially if thrombolysis was initiated 3 - 6 hours after stroke onset.[56,57] The diffusion / perfusion mismatch could identify subgroups of patients which might benefit from thrombolysis 3 - 6 hours after stroke onset[58] and DW / PW - MRI mismatch was more accurate than the clinical-diffusion-mismatch for selecting patients for reperfusion treatment.[59] However, if only patients with DW / PW - MRI mismatch were included into controlled clinical trials, the outcome in the treated groups was not improved: despite preliminary studies indicated a favourable effect for desmoteplase,[60,61] citicholine[17] and NXY-059[62] the large confirmatory clinical trials did not prove the efficacy of these therapeutic regimens.[63–65] In conclusion, the various techniques that permit the identification of potentially salvageable tissue (i.e. a surrogate measure of penumbra) have considerable limitations and can only be applied with caution for the definition or even extension of the window of therapeutic opportunity in patients with acute ischemic stroke.

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