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Validation of MRI Determination on PET Measurements in Ischemic Stroke

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Abstract

The concept of the ischemic penumbra was formulated based on animal experiments showing functional impairment and electrophysiological disturbances with decreasing flow to the brain below defined values (the threshold for function) and irreversible tissue damage with blood supply further decreased (the threshold for infarction). The perfusion range between these thresholds was termed “penumbra”, and restitution of flow above the functional threshold was able to reverse the deficits without permanent damage. In further experiments the dependency of the development of irreversible lesions on the interaction of severity and duration of critically reduced blood flow was established, proofing that the lower the flow the shorter the time for efficient reperfusion. As a consequence infarction develops from the core of ischemia to the areas of less severe hypoperfusion.

The translation of this experimental concept as the basis for efficient treatment of stroke requires non-invasive methods by which regional flow and energy metabolism can be repeatedly investigated to demonstrate penumbra tissue, which can benefit from therapeutic interventions. Positron emission tomography (PET) allows the quantification of regional cerebral blood flow, the regional oxygen extraction fraction and the regional metabolic rate for oxygen. By these variables a clear definition of irreversible tissue damage and of critically perfused but potentially salvageable tissue (i.e. the penumbra) can be achieved in stroke patients. However, PET is a research tool and its complex logistics limit clinical routine applications. As a widely applicable clinical tool perfusion/diffusion weighted magnetic resonance imaging (PW/DW-MRI) is used, and the “mismatch” between the PW- and the DW-abnormalities served as an indicator of the penumbra. However, comparative studies of PW/DW-MRI and PET pointed to an overestimation of the core of irreversible infarction as well as of the penumbra by MRI modalities. Some of these discrepancies can be explained by unselective application of relative perfusion thresholds, which might be improved by more complex analytical procedures. Heterogeneity of the MRI signatures used for the definition of the mismatch are also responsible for disappointing results in the application of PW/DW-MRI for the selection of patients for clinical trials. As long as a validation of the mismatch selection paradigm is lacking its use as a surrogate marker of outcome is limited.

Energy requirements of brain tissue

The energy demand of the nervous tissue is very high and therefore sufficient blood supply to the brain must be maintained consistently. The brain's oxygen consumption is almost entirely for the oxidative metabolism of glucose, which in normal physiological conditions is the almost exclusive substrate for the brain's energy metabolism (*1*). It must be kept in mind that the glucose metabolized in neuronal cell bodies is mainly to support cellular vegetative and house-keeping functions.
Increases in glucose consumption (and regional blood flow) evoked by functional activation are confined to synapse-rich regions and is rather high compared to the demand of neuronal cell bodies (*2*).
Overall, 87 % of the total energy consumed is required by signalling, mainly action potential propagation and postsynaptic ion fluxes, and only 13 % is expended in maintaining membrane resting potential (*3*).

Flow thresholds for preservation of function and morphological integrity

The different energy requirements for maintenance of membrane function and for propagation of information (signals) lead to different thresholds of energy consumption and consequently blood flow required for supply of sufficient biochemical substrates as well as for preservation of neuronal function and morphological integrity.
Experimental work on the ischemic flow thresholds of brain tissue demonstrated the existence of two critical levels of decreased perfusion: first, a level representing the flow threshold for reversible functional failure (functional threshold); second, a lower threshold below which irreversible membrane failure and morphological damage occur. The range of perfusion values between those limits was called the "ischemic penumbra," (*4*) which was characterized by the potential for functional recovery without morphological damage, provided that local blood flow can be re-established at a sufficient level and within a certain time window.
Whereas neuronal function is impaired immediately when blood flow drops below the threshold, the development of irreversible morphological damage is time dependent. The interaction of severity and duration of ischemia in the development of irreversible cell damage was studied by simultaneous recordings of cortical neuronal activity and

local blood flow (*5*). On the basis of a large number of neurons assessed during and after ischemia of varying degree and duration, it was possible to construct a discriminant curve representing the worst possible constellations of residual blood flow and duration of ischemia still permitting neuronal recovery. Typical points on this curve are blood flow rates of almost 0, 10, or 15 ml/100 g per minute maintained for periods of 25, 40, and 80 minutes, respectively. Between 17 and 18 ml/100 g per minute, the duration of ischemia tends to infinity, thus indicating that this low flow state can lead to morphological damage when maintained for very long, as yet undefined periods of time. These results broaden the concept of ischemic penumbra: the potential for postischemic recovery of functionally impaired cells is determined not only by the level of residual flow in the ischemic phase but also by the duration of the flow disturbance.

Progression of ischemic tissue damage

Infarct progression can be differentiated into 3 phases:
During the acute phase at flows below the threshold of energy metabolism required for maintenance of basic housekeeping (~20 % of pre-occlusion values) in the core tissue, injury is a direct consequence of the ischemia-induced energy failure and the resulting terminal depolarization of cell membranes is established within a few minutes after the onset of ischemia. During the subsequent subacute phase the irreversible damage expands into the areas around the core where flow ranges between 25 – 50 % of pre-occlusion values (i.e. below the value required for function due to axonal and synaptic activity, defined as the penumbra) until after several hours (usually approx. 6 h) the lesion has extended over all the area with critically reduced blood supply. Finally, a delayed phase of tissue injury evolves, which may last for several days or even weeks, in which secondary phenomena – vasogenic edema, inflammation, programmed cell death – may contribute to further progression of tissue damage.
In the early phases of ischemia reperfusion is a successful treatment, which can prevent infarction if initiated in a phase when nerve cells are not irreversibly damaged. If residual flow is low or close to zero, the time for effectful reperfusion is short and often treatment cannot be initiated early enough. In the subacute phase efficient reperfusion can be attained in many cases, and this is the basis of the up to

now only successful treatment of stroke by thrombolysis (*6*) or interventional thrombectomy (review in (*7*).

A multitude of electrical and biological disturbances interact in the progression of irreversible cell damage in ischemia. Peri-infarct spreading depression like depolarizations play a central role in the cascade of molecular mechanisms involved in the propagation of ischemic damage; they include release of excitatory and inhibitory neurotransmitters, activation of receptors and receptor-operated ion channels, influx of calcium, free radicals formation, nitric oxide generation, dysfunction of endoplasmatic reticulum, mitochondrial disturbances, and others (review in (*8*).

Identification of the penumbra by imaging

It must be stressed that the concept of the penumbra is based on neurophysiological and functional studies in experimental modals of focal ischemia. The transfer of this concept into imaging modalities is difficult as most markers used in experimental studies necessitate invasive procedures. In order to follow these pathophysiologic changes in humans non-invasive imaging modalities are required, which provide quantitative maps of several important physiologic variables, including regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV), regional cerebral metabolic rate of oxygen ($rCMRO_2$) and of glucose (rCMRGlc), and up to now only positron emission tomography (PET) is able to measure these variables repeatedly.

Early PET studies in stroke have identified various tissue compartments within a brain territory compromised by ischemia (*9-12*). Tissue with rCBF < 12 ml/100 g/min or $rCMRO_2$ < 65 µmol/100 g/min at the time of measurement (usually several hours after stroke) was found to be infarcted on late CTs. Relatively preserved $CMRO_2$ was an indicator of maintained neuronal integrity in regions with severely reduced CBF. This pattern, coined misery perfusion (*13*) served as a definition of the penumbra that is characterised as the area of an increased oxygen extraction fraction (up to >80 % from the normal value of approximately 40 %) (Fig. 1). Regions with CBF between 12 and 22 ml/100 g/min have an unstable metabolic situation; infarction might develop if low flow values persist. These PET studies allow the classification of three regions within the disturbed vascular territory: the core of ischemia with a flow <12 ml/100

g/min usually showing a transition into necrosis; a penumbra region with a flow between 12 and 22 ml/100 g/min of still viable tissue but with uncertain chances for infarction or recovery; and a oligaemic area (>22 ml/100 g/min) not primarily damaged by the lack of blood supply. It has to be kept in mind that the condition of the tissue is changing with time; the extent of the penumbra and its conversion into infarction is a dynamic process, and irreversible damage spreads from the core of ischemia to its border. This can be followed directly with advanced PET equipment, by which changes in the physiologic variables were studied after occlusion of the middle cerebral artery (MCA) in baboons and cats. These experimental findings from sequential studies and anecdotal clinical investigations at different time-points after the attack (*14*), imply that the extent of the penumbra, i.e. of morphologically intact but functionally impaired tissue, depends on the time of measurement, relative to the onset of ischemia. The volume is large and the flow values are low if the penumbra is defined in the first hours of ischemia; at this point of time reperfusion strategies are most effective. The volume is small if defined later, limiting the efficacy of treatment.

Measurement of blood flow values and determination of oxygen extraction fraction require arterial blood sampling and the clinical applicability is further limited by the complex logistics and instrumentation involved; isolated flow determinations at a single time-point might be confusing as long as the pattern over time is not known. A marker of neuronal integrity is needed that can identify irreversibly damaged tissue irrespective of the time elapsed since the vascular attack and irrespective of the variations in the blood flow over time, which also does not require arterial blood sampling. The central benzodiazepine receptor ligand flumazenil (FMZ) binds to the GABA receptor abundant in the cerebral cortex. These receptors are sensitive to ischemic damage and can therefore identify early neuronal loss. (*15*).

MR-mismatch as a surrogate for the penumbra

Due to the complexity of the methodology, the limited access, the invasive and complicated procedures and the exposure to radioactivity, PET cannot be applied in clinical routine. MR studies using diffusion and perfusion imaging might provide a differentiation between the core and the penumbra: the early diffusion weighted

imaging (DWI) lesion might define the ischemic core and adjacent critically hypoperfused tissue might be identified with perfusion-weighted imaging (PWI) (*16, 17*). Therefore, brain regions with hypoperfusion assessed by PWI but without or limited restricted diffusion (PWI / DWI mismatch) were assumed to represent the penumbra. This surrogate definition of the penumbra has several uncertainties (*18*): 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. However reversal of the acute diffusion lesions beyond 3-4,5 hours is infrequent (*19*). Critical perfused tissue (i.e. penumbra) cannot be clearly differentiated from tissue experiencing oligaemia without the application of well defined perfusion maps and thresholds (*20*); the PWI abnormality often overestimated the amount of tissue at risk. These facts are further accentuated by methodological limitation, because perfusion techniques and data evaluation vary among centres (*21, 22*). Absolute or relative thresholds derived from PW-/DW-MRI are still not reliable in predicting the fate of ischemic tissue, and this is especially due to the difficulty to quantify perfusion by MRI (*23*). With the applied tracer bolus tracking it is difficult to measure accurately the delay of tracer arrival, dispersion and transit in pathologically perfused tissue and to determine the arterial input function. These uncertainties are accentuated when collateral perfusion to areas beyond occluded arteries should be assessed. The differences in PET and MR based CBF measures might also be due to the contrast agent which in DSC-Perfusion MR is non-diffusible intravascular (Gadolinium DTPA) and diffusible (15O-Water) in PET (*24*).

Validation of MRI signatures on PET measurements

A comparison of PW-DW imaging results on quantitative measurements of flow values and oxygen consumption or FMZ uptake in the same patients early after stroke is necessary for the assessment of the accuracy of the applied signatures for predicting tissue outcome. Several studies were performed in order to validate mismatch as a surrogate of penumbra on PET-derived discrimination of irreversibly damaged, critically perfused “at risk” and oligemic “not at risk” tissue.

DWI - Ischemic Core

The studies demonstrated that the DWI lesion compared to FMZ PET predicts more or less the finally infarcted tissue, but contains up to 25 % false positive, i.e. surviving tissue (*25*). Other comparative studies of fully quantitative 15O-PET (CBF, OEF and CMRO2) in stroke showed that part of the DWI lesion had preserved normal CMRO2 and OEF as measured with PET (*26-28*). One study comparing PET derived MTT with PW MTT suggested that this flow surrogate could improve infarct prediction within the DWI lesion (*29*). These studies along with other studies indicate that parts of the DWI lesion indicated impairment of energy metabolism, which might contain penumbral tissue and therefore could be reversible. The high sensitivity but low specificity of diffusion weighted MR to infarct core detection might be improved if a threshold is applied to delineate the DWI lesion, e.g. a relative intensity of 120% of the DWI lesion (*25*).

PWI - Normoperfusion

Perfusion values determined by MR bolus tracking were comparable to flow rates measured by $H_2{}^{15}O$ PET in normal volunteers, but tracer delay caused errors in CBF estimates even in healthy persons and should be corrected (*30*).

PWI - Penumbra

The difficulty in defining the penumbra with PW/DWI mismatch is thought to be mainly related to PW data acquisition, which is a complex process, and the surrogate parameters used to estimate perfusion are variable and somewhat arbitrary (*31*). Overall, PWI is unable to provide a reliable quantitative estimation of cerebal perfusion when compared to gold-standards such as PET, SPECT or Xe-CT in stroke (*32-34*).

Dynamic susceptibility Contrast (DSC) PW-MRI relies on surrogates of perfusion parameters calculated from the non-deconvolved or deconvolved tissue residue function (time contrast curve) of the intravascular MR contrast bolus. The non-deconvolved parameters e.g. time-to-peak (TTP) or first moment (FM) are calculated without deconvolution and the need of an AIF. The deconvolved parameters e.g. CBF, CBV, MTT and Tmax (Fig. 2), which are thought to be more quantitative, rely on an arterial input function (AIF) from large vessels (e.g. proximal MCA) (*31*).

Several comparative PET MRI studies have tried to validate the performance of perfusion maps from PW-MR in stroke patients. The goal of these comparative studies was the detection of (i) the best parameter maps and (ii) the optimal thresholds to detect the tissue at risk of infarction (Fig. 3):
One study compared the non-deconvolved parameter time to peak (TTP) with PET CBF. They found delays of 4 and 6 sec reliably identified hypoperfused and excluded normoperfused tissue (threshold arbitrarily set to 20 ml/100 g/min), but still overestimated the size of the critically perfused tissue (*35*) and therefore overestimated the volume of critically perfused but salvageable tissue, i.e. the penumbra. Another study (*28*): Of 13 patients showing considerable PW-DWI mismatch only 8 had areas with elevated OEF typical for penumbra tissue, and these areas were bigger on PW / DWI than on PET. This overestimation of the CBF by distribution maps was confirmed in another comparative PET MR study of 5 patients (*32*). They detected a moderate correlation between PET and MRI derived CBF with even weaker correlations if the data were pooled due to individual variations. However the relative distribution of the perfusion maps was similar in PET and PWI. A comparative simultaneous 15O-H2O PET/MRI study in a clinical acute stroke setting (*36*) observed limited correspondence between PET-CBF and PWI-CBF, -TTP and -Tmax. Also a higher variability of PWI-CBF was detected as compared to PET-CBF measures. This study showed, in line with previous studies (*32, 37*) an overestimation of PW based cerebral blood flow measures. Overall, the mismatch volume in PW / DWI as conventionally calculated does not reliably reflect misery perfusion, i.e. the penumbra as defined by PET.

Recently, several methods have been proposed to improve the reliability of assessment of perfusion using MR methods (*38-40*) but they all need to be validated by quantitative measures. Therefore PET validated and calibrated thresholds of the most predictive MR perfusion maps have to be implemented for optimal mismatch detection. More advanced analytical procedures may help to identify more reliably the threshold between critical and non-critical hypoperfusion and to reduce variance of determined values.
A comparative PET MR study detected the best threshold independent PW maps as well as their optimal critical flow thresholds by comparative receiver operating characteristic (ROC) curve analysis. They established the deconvolved maps CBF

(<21.7 ml/100g/min) and the time driven maps Tmax (>5.5 seconds) along with the non-deconvolved map rTTP (>4.2 seconds) to be the most predictive to discriminate the penumbral flow threshold as defined by PET-CBF <20 ml/100g/min (*20, 41*). These results were in line with the above mentioned study of 5 patients which described an optimal penumbra threshold of Tmax >5.4 seconds and rTTP >4.8 seconds (*32*).

Another study proposed a simple MR-based and PET-validated calibration which reduced the variability of individual critical flow thresholds and consequently improved the detection of the mismatch, i.e. the penumbra in the acute stroke setting (*42*). A series of recent comparative PET-MR studies improved mismatch quantification and prediciton of PW maps by (i) standardisation of the placement of the arterial input function (AIF) used for deconvolution (*43*) and (ii) establishing the influence of the deconvolution techniques, i.e. standard singular value deconvolution (sSVD) versus block circulant oSVD (*44*). These studies recommended an AIF placement within the proximal MCA contralateral to the ischemic tissue and the standard SVD method adequate to calculate the best maps for mismatch detection (CBF and Tmax).

In summary the improvement of mismatch detection achieved by these studies are important, since current clinical studies, e.g. EXTEND and ESCASS-4:ExTEND (*45, 46*) use PW imaging for treatment stratification and standardisation of post-processing is crucial.

<u>The penumbra as a surrogate marker for treatment efficiency</u>

The efficacy of treatment in ischemic stroke can only be proven by controlled randomized double blind clinical trials. 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. In recent years identification of salvageable tissue by neuroimaging has gained much interest as a surrogate marker for treatment efficiency in stroke.

The effect of the only approved conservative therapy for acute ischemic stroke was established also in imaging studies, in which reperfusion to penumbral tissue was followed by improvement in neurological deficits: Reperfusion was significantly increased in rtPA treated patients compared to controls. 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. This study demonstrated that a considerable portion of the critically hypoperfused tissue was probably salvaged by the reperfusion therapy.
The PW / DWI mismatch as the estimated zone of the penumbra has been proposed as a surrogate marker of efficacy of stroke treatment (*47*). Several groups reported results of serial PW / DWI in patients after intravenous or intra-arterial thrombolysis. Inhibition of lesion growth and even normalization of PWI (*48*) were seen with reperfusion after thrombolytic therapy and PW / DWI mismatch was proposed as an effective selection criterion for rTPA treatment of patients admitted more than 3 hours after onset of symptoms (*49*). In some cases perfusion deficits can be resolved (*50*) and DWI signatures of early ischemic injury can be reversed by prompt vessel recanalization (*51*). If mismatch was still present 3 – 6 hours after stroke onset thrombolysis started beyond the accepted therapeutic window was followed by favourable outcome (*52, 53*). As a consequence of the beneficial effect of thrombolysis observed in patients with PW / DWI mismatch this signature was used for selections of patients in several clinical trials (reviews in (*47*)).

Several studies have included selection of patients for i.v. thrombolysis with PW / DWI mismatch: In DEFUSE and EPITHET DWI and PWI volumes were calculated after patient enrolment and outcomes were based on MRI profiles. The Desmoteplase in Acute Stroke (DIAS 2) study included only patients with visually assessed mismatch.

In DEFUSE (Albers et al 2006, 508) with open label use of tPA 3 – 6 hours after symptoms onset (n=74), 40 patients had a mismatch (defined as a Tmax delay of more than 2 sec) 1.2 times larger than the DWI lesion. Reperfusion and recanalization were associated with favourable outcome in mismatch patients, and this effect was more apparent in the subgroup of patients who did not have a

malignant profile. However, this study was not designed to show clinical benefit since there was no placebo control group.

EPITHET (*54*) was a randomized double-blind placebo-controlled trial of tPA within 3 – 6 hours after symptoms onset (n=101). With the same mismatch definition as in DEFUSE the study failed to demonstrate a statistically significant attenuation of infarct growth in the tPA group. However, reperfusion was strongly associated with good clinical outcome. Unfortunately this study failed to prove mismatch imaging selection due to an insufficient number of non-mismatch (nonpenumbral) patients.

Desmoteplase, a newer thrombolytic agent, was administered 3 – 9 hours after symptom onset in a multicenter placebo controlled double blind dose ranging study (DIAS-2, n=186, (*55*)) of patients selected by PW / DWI mismatch (20 %) or CT perfusion based mismatch. This study did not show a benefit of desmoteplase. However, the results might be affected by (i) the selection criterion visual assessment of mismatch which might be inadequate for patient selection, (*56*) and (ii) the low rate of patients with vessel occlusion.

A meta analysis of several mismatch based thrombolytic studies from the DIAS, DIAS-2, DEDAS, EPITHET and DEFUSE trials for delayed treatment showed an increased recanalization. However this analysis did not confirm improvement of clinical outcome in delayed thrombolysis (*57*).

Even though these trials did not show an improvement of clinical outcome, they support the pathophysiological basis of mismatch based treatment selection. The missing confirmation of a clinical benefit in the selection of patients for treatment by MRI profiles might be related to inappropriate definition of critically perfused and salvageable tissue. A more complex analysis of data might be required including baseline DWI and PWI lesion volumes (*58*) and coregistration of mismatch and infarct location (*59*). Therefore the EXTEND Trial and its European counterpart ECASS-4 :ExTEND Trial, both pase III trials to validate mismatch based delayed treatment of ischemic strokes with rt-PA were set up (*45, 46*). These phase III, multicenter, randomized, double-blind, placebo controlled trials include 400 patients, testing rtPA versus placebo within the 4,5-9 hour time window and in wake-up

strokes. Patient selection is based on a rigorous and standardised MRI and CT mismatch definition. However, as long as a validation of the mismatch selection paradigm in this phase III trial is lacking selection of patients for delayed treatment based on mismatch cannot be recommended in routine care (*57*), and this surrogate marker of outcome must be used with caution (*60*)

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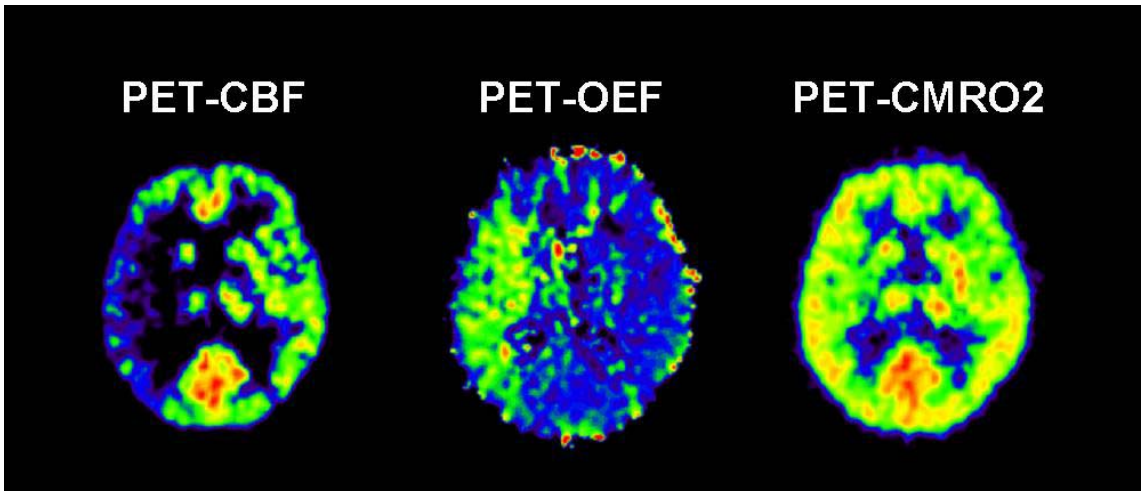
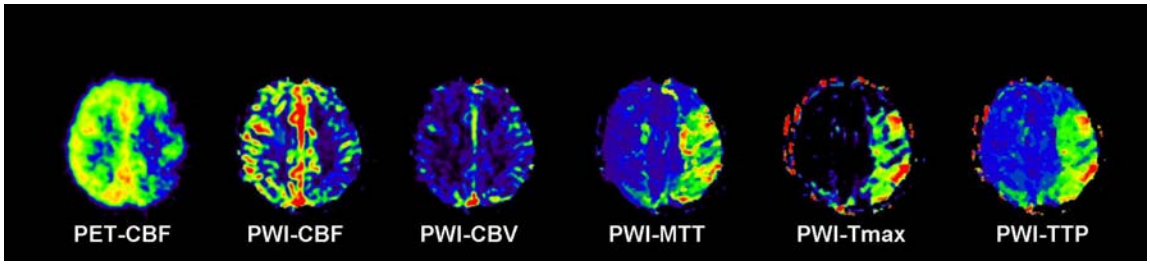
Legends

Figure 1:



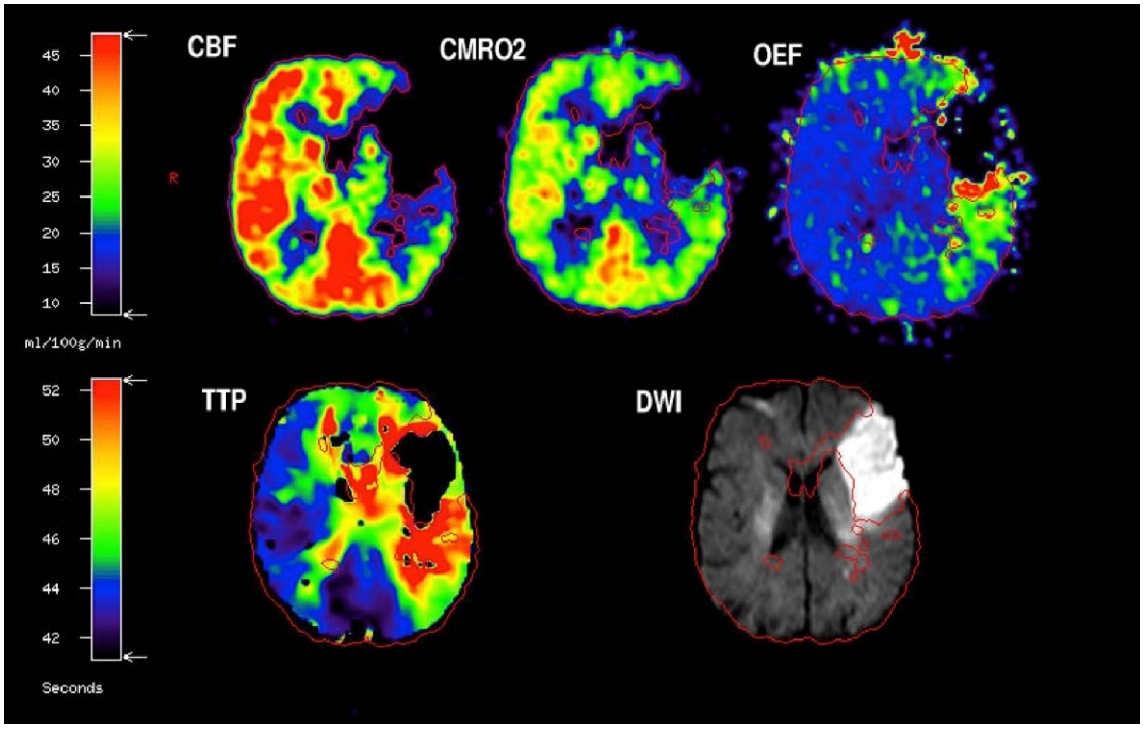
Acute stroke Patient measured with 15O-PET (cerebral blood flow, CBF; oxygen extraction fraction, OEF and cerebral metabolic rate of oxygen, CMRO2). Penumbral tissue is represented by reduced CBF, compensatory increased OEF but normal CMRO2.

Figure 2:



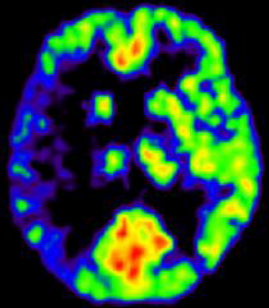
Acute stroke Patient measured with 15O-water-PET (cerebral blood flow, CBF) and perfusion weighted (PW)-MR (cerebral blood flow, CBF; cerebral blood volume, CBV; mean transit time, MTT; time to maximum, Tmax and time to peak, TTP). Areas of “tissue at risk” (<20 ml/100g/min) are well depicted by PW-maps.

Figure 3:

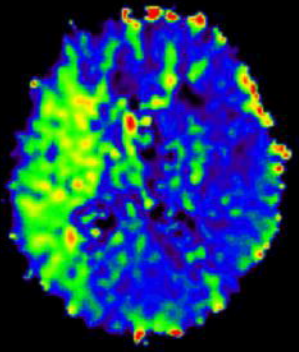


Hypoperfusion with preserved CMRO2 and elevated OEF 5 h after stroke identifying the penumbra (upper row). Corresponding mismatch in TTP and DWI (lower row).

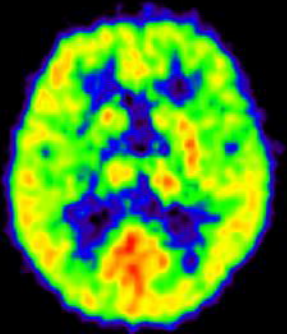
PET-CBF

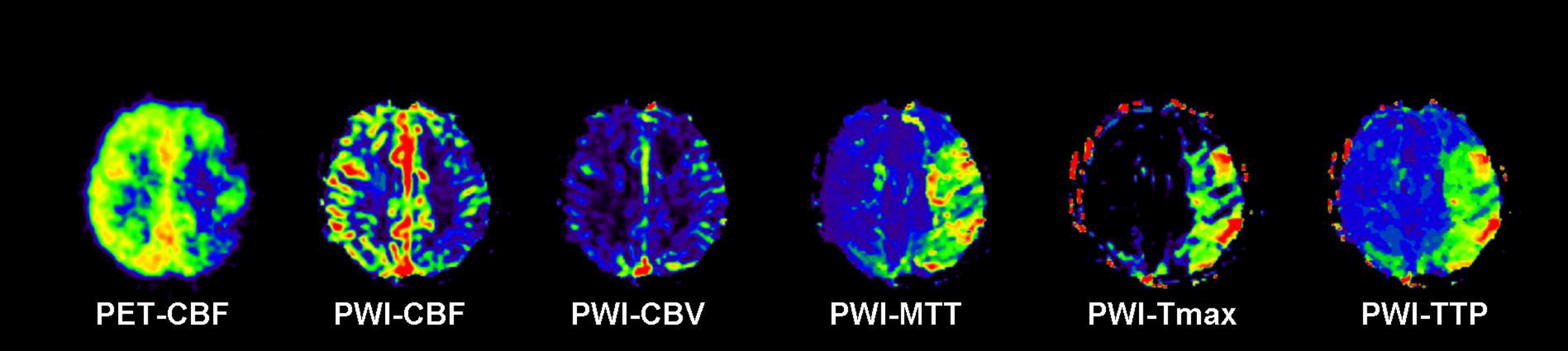


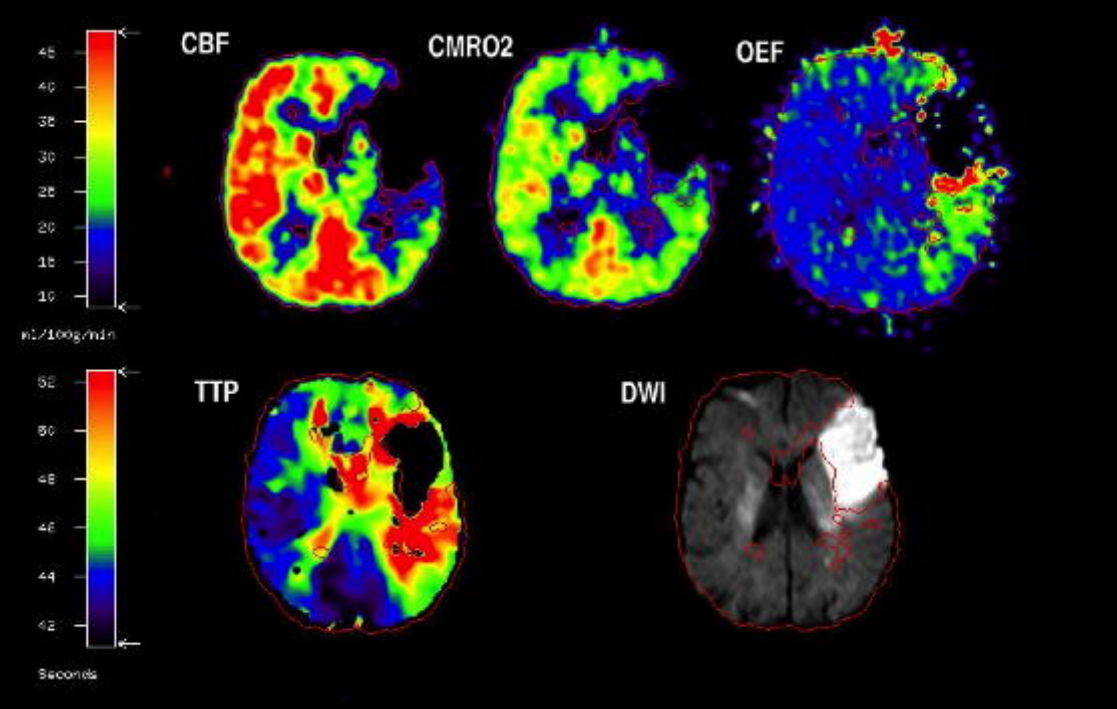
PET-OEF



PET-CMRO2




PET-CBF
PWI-CBF
PWI-CBV
PWI-MTT
PWI-Tmax
PWI-TTP


CBF
CMRO2
OEF
TTP
DWI
Seconds