The Concept of Ischemic Penumbra in Acute Stroke and Therapeutic Opportunities

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Key Words

Penumbra • Acute ischemic stroke • Ischemic penumbra • Acute stroke • Acute stroke therapy

Abstract

Ischemic penumbra was first defined by Astrup in 1981 as perfused brain tissue at a level within the thresholds of functional impairment and morphological integrity, which has the capacity to recover if perfusion is improved. It exists, even for a short period of time in the center of ischemia, from which irreversible necrosis propagates to the neighboring tissues over time. Penumbra has become the focus of intense imaging research to differentiate it from infarction. Accurate detection of this 'tissue at risk' could be used to identify patients who would benefit most from acute treatment. Currently, recombinant tissue plasminogen activator (rtPA) is the only approved drug that has shown significant benefits in acute stroke patients when administered intravenously less than 4.5 h after stroke. However, its use is limited. Discrimination between infarct core and the surrounding potentially salvageable tissue is useful to better identify patients suitable for treatment. This can be achieved by positron emission tomography, single-photon-emission computed tomography, computed tomography perfusion scan and perfusion-weighted and diffusion-weighted magnetic resonance imaging. Identification of the penumbra might enable selective rtPA use in patients with large penumbras and small infarct cores, even beyond the 4.5-hour time window, where the penumbra may persist for more than 12 h. The purpose of this review was to describe neuroimaging mo-

dalities capable of identifying penumbra tissue so as to provide surrogate markers for new trials in acute ischemic stroke patients.

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Introduction

There are a variety of definitions for ischemic penumbra [1–4]. However, the concept of 'penumbra' during focal cerebral ischemia was introduced by Astrup in 1981 [5] and refers to the regions of brain tissue, usually peripheral in location, where blood flow is sufficiently reduced to cause hypoxia, severe enough to arrest physiological function, but not so complete as to cause irreversible failure of energy metabolism and cellular necrosis [6]. As tissue tolerance to ischemic damage is dependent on residual flow and duration of flow disturbance [7], ischemic penumbra is a dynamic process. It exists for a short period of time even in the center of ischemia, where irreversible necrosis propagates to the neighboring tissue over time. This renders the time window of therapeutic opportunity variable and ill-defined; it is very short for

Search strategy and selection criteria: references for this review were identified by searches of PubMed from 1975 until October 2008 with the terms 'ischemic penumbra', 'acute stroke', 'acute stroke therapy', 'PWI/DWI RMI', 'positron emission tomography', 'single photon emission computed tomography', 'magnetic resonance imaging', 'perfusion computed tomography'.

the core of ischemia and may extend to several hours in the moderately ischemic surrounding tissue [8].

Reperfusion of this ischemic brain region is the most effective therapy for acute ischemic stroke [9]. Currently, recombinant tissue plasminogen activator (rtPA) is the only approved drug for acute stroke and shows significant benefits when administered intravenously less than 4.5 h after stroke [10, 11]. However, its use is limited because a large proportion of patients are admitted more than 4.5 h after symptom onset [12]. In addition to a number of contraindications, uncertainties regarding selection criteria for patients who might benefit from thrombolysis contribute to the low rate of stroke patients treated with rtPA. Discrimination between infarct core and surrounding, potentially salvageable, tissue is useful for better identification of patients suitable for treatment. This can be achieved by positron emission tomography (PET), single-photon-emission computed tomography (SPECT), computed tomography (CT) perfusion scan and perfusion-weighted (PW) and diffusion-weighted (DW) magnetic resonance imaging (MRI). Identification of the penumbra might allow for selective rtPA use in those patients with a large penumbra and a small infarct core even beyond the 4.5-hour time window, where it has been shown that the penumbra may persist for more than 12 h.

Experimental Basis of the Ischemic Penumbra

The idea that there exist two ischemic thresholds in the pathogenesis of cerebral infarction, one for functional impairment and the other for morphological damage, the perfused penumbra tissue ranging between these two values, came from seminal microelectrode studies on the baboon cortex in the late 1970s, which measured the effects of progressive reductions in cerebral blood flow (CBF) [13, 14]. These studies described a level of CBF reduction that led to cessation of cortical evoked responses in the absence of terminal increases in extracellular potassium or reductions in pH and an even greater decrease in CBF, where large increases in extracellular potassium and reductions in pH indicative of failure of membrane ion homeostasis and cell death occurred [15]. The interaction between severity and duration of ischemia in the development of irreversible cell damage was also studied by simultaneous recordings of cortical neuronal activity and local blood flow in cats [7]. Blood flow rates of approximately 0, 10, and 15 ml·100 g⁻¹·min⁻¹ maintained for periods of 25, 40, and 80 min, respectively, are the

worst possible constellation of residual blood flow and duration of ischemia that still permits neuronal recovery [8]. Differences among species must be taken into consideration when experimental results are compared. In monkeys and cats, large infarcts develop with residual flow rates of 12 ml·100 g⁻¹·min⁻¹ lasting for up to 2–3 h [16, 17], and individual cells may become necrotic at lower flow values after shorter periods of time [1]. However, middle cerebral artery (MCA) occlusion in rats induces selective neuronal necrosis in the caudate-putamen after only 15 min, localized infarcts in the caudate-putamen and selective neuronal necrosis in the neocortex after 30 min, and cortical infarcts after 60 min. With an occlusion time of 120–180 min, infarct sizes increase and reach those found after permanent MCA occlusion [8, 19].

Though the ischemic penumbra has been described on the basis of blood flow and physiological parameters, ischemic cell damage involves a cascade of biochemical and molecular mechanisms. The influx of Ca²⁺ into cells, the release of excitatory amino acids, and the activation of receptors and receptor-operated ion channels are key mechanisms in the biochemical cascade leading to tissue damage [20]. Protein synthesis reduction/arrest is the earliest and most sensitive metabolic response to ischemia that may be reversible in the penumbra but not in the core [21]. This occurs after CBF reductions of only 50% and is not caused by failure of energy metabolism because adenosine triphosphate (ATP) depletion is not observed until CBF decreases to 20% [22]. In addition, apoptosis-related genes induced after focal ischemia may contribute to cell death in the core and selective cell death adjacent to an infarct [23]. More recently, DNA microarray studies have identified large numbers of genes that are either upregulated or downregulated after temporary MCA occlusion in rats [24–27]. Gene-regulated responses to focal cerebral ischemia, thought to affect outcome and have therapeutic implications, have been investigated and include adhesion molecules, cytokines, chemokines, matrix metalloproteinases, apoptosis-inducing genes, DNA repair genes, nitric oxide synthase, tumor necrosis factor, NF-κB, interleukins, COX-2 and growth factors [23, 28].

Concerning neuronal recovery in the penumbra around a focal infarction, recent findings have revealed that synapses and their networks express a high degree of functional and structural plasticity [29]. Synapses, synaptic vesicles, axon terminals, and spines were reported to degenerate with a reduction in their numbers and sizes, until after 4 days and then recover from 1 to 12 weeks after the ischemic insult [30].

These results document the complexity of the molecular events that characterize brain tissue response to incomplete focal ischemia [31].

Methods for Imaging the Penumbra in Humans

CT selects stroke patients for thrombolysis on the basis of the absence of hemorrhage and the presence of early CT ischemic changes. Since patients with an ischemic penumbra are more likely than those without to respond to therapy, identification of the former is fundamental [32]. From the mid 1970s, PET, SPECT, and MRI have enabled investigators to assess brain function. Recently, the development of ultrafast CT equipment has led to increased availability of CT perfusion that evaluates CBF and cerebral blood volume (CBV) qualitatively [33]. Furthermore, these neuroimaging techniques permit to distinguish stroke patients from those with stroke-mimicking conditions.

Positron Emission Tomography

Early pathophysiological changes occurring after focal ischemia can be followed by PET, which provides quantitative maps of several important physiological variables, including regional CBF, regional CBV (rCBV), regional cerebral metabolic rate of oxygen (rCMRO₂), and regional cerebral metabolic rate of glucose as well as neurotransmitters and neuroreceptors such as benzodiazepine receptors (BZRs) with flumazenil, an accurate marker of neuronal loss [8, 34]. As PET is considered the gold standard for these measurements, it is also used to evaluate the degree of ischemic brain damage. Multitracer studies have defined the penumbra as reduced CBF tissue with preserved CMRO₂ and increased oxygen extraction fraction (OEF) [2, 8]. Regarding irreversible tissue damage at the time of investigation (usually several hours after the ischemic event), CMRO₂ is the most reliable parameter with about 65 $\mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ as its threshold. Studies examining early CBF and CMRO₂ measurements in infarcts identified on late CT scans and a flow threshold of 12 $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ were described, which also predicted irreversible damage [35]. Relatively preserved CMRO₂ was accepted as an indicator of maintained neuronal function in regions with severely reduced CBF. Regions with CBF between 12 and 22 $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ display an unstable metabolic situation. In these areas, infarction will develop if low flow values per-

sist, and thus are considered to be in the penumbra zone [36]. However, this method is complex, invasive (it needs arterial blood sampling) and costly, and requires multi-tracer application. Central BZR ligands are thought to be markers of neuronal integrity [37]. Labeled BZR ligands have been successfully used to distinguish between infarcted and deactivated tissues after stroke [38, 39]. Labeled flumazenil was administered 3–16 h from symptom onset to 10 patients with acute ischemic stroke [40]. The early changes in flow, oxygen consumption, and flumazenil binding were compared with permanent disturbances of glucose metabolism while the final infarct sizes were determined using MRI or CT, 12–22 days after stroke. Cortical regions with reduced flumazenil binding, usually within the larger areas of disturbed blood flow, predicted the final infarcts while, in 1 case, areas with severely depressed glucose metabolism were indicative of marked neuronal loss. The predictive value of reduced flumazenil binding was comparable to that of rCMRO₂ reduction ($<60 \mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$). In these areas, OEF could still be increased, limiting the usefulness of this variable as an indicator of viability. Unlike studies with oxygen tracers, the use of BZR ligand does not require arterial puncture and patient cooperation; in addition, it produces superior image quality and has the potential of SPECT application [8]. Moreover, perfusion can be assessed by following the early distribution of the same tracer. This makes BZR radioligands useful in acute ischemic stroke.

In a study in which the final infarcts were analyzed with respect to flow values and flumazenil uptake in the first hours after stroke, probability thresholds of flumazenil binding and blood flow could be calculated in order to predict the final state of the tissue and define the range of the penumbra [41]. As the 95% prediction limit for infarction, a flumazenil uptake of 3.4 times the average uptake in the white matter was found; as the flow range in the penumbra, 4.8–14.1 $\mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ were obtained.

The fact that BZR radioligands can actually be used to select patients was shown in another study of 11 patients with hemispheric stroke in whom thrombolysis had been started within 3 h of symptom onset [42]. At the beginning of thrombolysis, cortical CBF and flumazenil binding were assessed by PET. Those early PET findings were related to a change in neurological deficit and to the extent of cortical damage on MRI or CT 3 weeks after stroke. Hypoperfusion was observed in all cases, and in 8 patients the values were below the critical thresholds estimated at 12 $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, comprising 1–174 ml of cortical tissue. Substantial reperfusion was seen in

most of these regions 24 h after thrombolysis. In 4 cases, distinct areas of decreased flumazenil binding were detected. These patients suffered from permanent lesions in cortical areas corresponding to their flumazenil defects (112 vs. 146, 3 vs. 3, 2 vs. 1, and 128 vs. 136 ml). In the other patients, no morphological defects were detected on MRI or CT, although blood flow was critically decreased in areas with volumes of up to 78 ml before thrombolysis. These findings suggest that in BZR imaging with flumazenil, PET distinguishes between irreversibly damaged and viable penumbra tissue early after stroke and can be used to identify patients who can benefit from reperfusion therapy.

Due to the low concentrations of BZRs in the white matter and basal ganglia, these values apply only to the cortex but still permit a reliable measure of irreversibly damaged and potentially salvageable portions of an ischemic area.

As a tracer of hypoxic viable tissue, ^{18}F -fluoromisonidazole (FMISO) could also be used to detect an ischemic penumbra [35, 43]. Areas exhibiting increased FMISO uptake have been detected 6.25–42.5 h after stroke and reported to be maximal in the first hours after symptom onset. They declined with time and disappeared after several days. The areas were usually distributed over the periphery of the infarct identified on late CT, but extended into normal tissue adjacent to the infarct in a few cases [44]. These findings suggest that FMISO binding is increased in tissue at risk and mirrors the temporal and spatial distribution of penumbras. However, these results need direct calibration by conventional PET measurements. Since reliable detection of FMISO uptake is delayed (>2 h between tracer injection and imaging), the value of this tracer is limited for therapeutic decisions in the acute phase of ischemic stroke [35].

PET is the oldest imaging technique employed for penumbra detection and is currently considered the gold standard. However, the use of PET is limited due to its cost, the complex logistics involving a multidisciplinary team, and patient access is quite limited during the acute phase of stroke [33]. Therefore, multisequence procedures have greatly evolved over time, making these modalities a reliable tool in the study of acute ischemic stroke.

Single-Photon-Emission Computed Tomography

In the stroke setting, SPECT has been used for the evaluation of cerebral perfusion [45, 46]. However, only when ^{133}Xe is used and the clearance of this inert gas is followed can rCBF be quantified [47]. Handling of the

radioactive gas, the complexity of data analysis, and the rather coarse spatial resolution obtained with this tracer limit the routine application of this technique [8]. The tracer most often used in acute ischemic stroke is $^{99\text{m}}\text{Tc}$ -hexamethylpropylene-amino-oxime, which replaced ^{123}I -N-isopropyl-*p*-iodoamphetamine for perfusion studies. The newer tracer $^{99\text{m}}\text{Tc}$ -ethyl-cysteinate-dimer (ECD) reflects both perfusion and the metabolic status of the tissues as the retention of ECD requires the presence of cytosolic esterase and therefore depends on the presence of viable cells [8]. In addition to the radiotracers designed to measure perfusion, there are also a number of agents used to measure various aspects of neurochemistry. These radiotracers enable the quantification of presynaptic and postsynaptic neuroreceptors and neurotransmitter synthesis. Such neurochemical studies show promise for assessing diseases in which abnormalities of a single neurotransmitter play a prominent pathophysiological role.

In acute ischemic stroke, detection of a penumbra based on SPECT studies alone is difficult because the obtained values are relative perfusion measures standardized against contralateral or cerebellar regions and the functional and morphologic states of the tissue are assessed only indirectly. Earlier SPECT studies failed to show any advantage of SPECT over a structured clinical evaluation in predicting the evolution of acute stroke [48]. However, using ECD in the first 6 h after stroke, Barthel et al. [49] were able to predict which patients would develop massive necrosis of the MCA territory. Other studies have suggested that patients with a normal SPECT scan, performed within 3–6 h from stroke onset, will most likely recover spontaneously and therefore may not benefit from thrombolysis [50–52]. Furthermore, studies performed at a later time after the onset of symptoms could also identify different tissue compartments and SPECT results could help predict neurological development in addition to neurological scores [53, 54].

It can be concluded that severely reduced tracer uptake over a large area is associated with poor outcome whereas normal or increased uptake is predictive of a good clinical outcome. The level of flow decrease that predicts extended infarction or hemorrhagic complications was estimated at different values and varied between complete lack of ECD uptake and a relative decrease in perfusion to 35–60% of the contralateral value [55–57]. The threshold for a moderately ischemic area with a good chance of recovery was set at 70% of contralateral tracer uptake in several studies [58, 59].

SPECT is beneficial in the evaluation of acute stroke but, unfortunately, the need to perform either CT or MRI

in the acute phase makes it difficult to perform SPECT within the time frame allotted for the evaluation of these patients [46].

Magnetic Resonance Imaging

Today, several centers use MRI, including PW/DWI imaging (PWI/DWI), as a diagnostic tool for hyperacute stroke before deciding on therapy. Hyperintense areas on DWI are generally believed to represent irreversible ischemic changes [60], and the apparent diffusion coefficient of water (ADC) can be calculated from DWI as a comparative measure. PWI requires the intravenous administration of gadolinium and provides information about brain tissue perfusion at a given time.

DWI shows the area of reduced diffusion as a hyperintense region, which follows the redistribution of water from the extracellular to intracellular space as a consequence of reduced ATPase activity [61]. In the core of this area, ATP remains depleted, indicating necrotic transformation because of severely reduced perfusion [62]. As disturbances of the water-ionic homeostasis occur immediately with the disruption of perfusion, DWI is able to detect the initial ischemic disturbance within 2.5 min after arterial occlusion [63, 64]. ADC values gradually normalize in 5–10 days and then increase in chronic lesions [65]. This gradual increase may indicate the development of vasogenic edema and cellular necrosis [66]. However, the DWI lesion persists for another week or so because DWI also detects prolonged T_2 signals. The changes in DWI signals correlate with histological defects and metabolic abnormalities as assessed by autoradiographic and chemical imaging procedures at follow-up [67]. Diffusion lesions may be heterogeneous in the early stages of ischemia in humans. Within 6 h of stroke onset, DWI has a reported sensitivity of 95% and a specificity of nearly 100% [68]. Multiple experimental and human studies have demonstrated that in the first few hours after ischemia onset, some DWI changes are reversible, generally those associated with less severe ADC changes [69–71].

PWI by bolus tracking demonstrates regions of hemodynamic abnormality [72]. The most widely used indicator of brain perfusion is the 'time-to-peak', i.e. the time until the greatest concentration of gadolinium is achieved in each voxel. PWI can be converted into maps of relative CBV, qualitative mean transit time (MTT), and relative CBF [73]. The regions defined as the ischemic penumbra were characterized by a mean 73% increase in MTT of the gadolinium bolus and a 29% increase in relative CBV.

This model-independent measure allows an estimation of the severity of ischemia in comparison with the nonaffected hemisphere [74]. The most widespread technique used in current studies is deconvolution of the arterial input function, which yields quasi-absolute measures and does not involve comparison with the uninvolved site. The PWI parameter used is $T_{\max}$, which is the deconvoluted time to peak [75, 76]. $T_{\max}$ is the maximum of the tissue residue function characteristics to each voxel and reflects how much the tissue response lags behind the stimulus by an arterial input into the voxel and inherently corrects for the length of the gadolinium bolus. $T_{\max}$ has been shown to be a sensitive parameter to detect perfusion deficits and tissues condemned to infarction [77].

The PWI/DWI mismatch region, defined as the difference in volume of tissue between the smaller diffusion lesion and the larger perfusion deficit, is thought to approximately correspond to the ischemic penumbra [78]. However, there are several observations to make.

First, several authors have demonstrated that diffusion lesions may be partially or even fully reversible when reperfusion occurs within 2–3 h [61, 64, 79–81] and in as many as 20% of patients in the 6-hour time window [69–71, 80]. DWI changes seem to reflect much more complex pathophysiological changes than was originally thought, and more experimental and observational data are needed to clarify this issue. However, for practical purposes, the majority of the DWI seems to reflect the infarct core and can be used as a useful index for its extent within the first hours of ischemic stroke [32].

The second observation applies to the results of Schlaug et al. [78], who analyzed the extension of the diffusion lesion into the impaired reperfusion area on the first day after stroke and 24–72 h later. Decreases in rCBF to 37% and decreases of rCBV to 47% in the contralateral region were used to identify penumbral tissue, whereas the ischemic core showed a more severe reduction in rCBF (12% of the contralateral region) and rCBV (19% of the contralateral region). The operationally defined values for penumbra and core (37 and 12% of the contralateral region, respectively) may be translated into CBF values (18.5 and 6 $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$, respectively) and correspond to the values obtained in quantitative PET studies. The diffusion abnormality enlarged to 376.6% into the region of hypoperfusion within 48 h in all the patients, but did not reach the full volume of the initial perfusion abnormality (59.2 vs. 96.6 ml, on average). An explanation for this anomaly could be that with semi-quantitative perfusion measures such as seen with PWI, the distinction between benign oligoemia and true pen-

umbral tissue is unclear. As blood flow within the brain falls, there is a substantial oligoemic reserve where brain tissue remains functionally unaffected [8]. PWI does definitely show benign oligoemia. Hence, the mismatch between PWI and DWI could be much larger than the true penumbra [32]. The probability of infarction increases with the severity of the transit time delay. $T_{\max}$ of 4–6 s has been most closely correlated with the final infarct volume. This has led to the conclusion that transit time delays <4–6 s are likely benign [82]. Other authors have shown that identification of absolute PWI thresholds for infarction is not possible because they are time dependent and concluded that there is no single threshold and, therefore, no mismatch definition that can predict tissue fate for all patients. For the time being, it is reasonable to use $T_{\max}$, recognizing that this is only an estimate of the tissue at risk [83, 84]. A recent study that directly compared MRI perfusion with PET data in acute stroke indicated that a $T_{\max}$ of more than 5.5 s best indicated the penumbra [85].

Despite these imaging uncertainties, MRI mismatch is reasonably robust in representing the at-risk tissue and it remains the most practical tool for identifying at-risk cerebral tissue during the early phase of acute stroke [32]. Kidwell et al. [86] performed an analysis on a subset of patients treated with mechanical embolectomy up to 8 h from symptom onset and subjected them to MRI before and after embolectomy. Approximately half of the patients had a penumbra pattern before treatment and recanalization was achieved in 70% of them. At day 90, 89% of patients with a penumbral pattern and recanalization had a good outcome compared with only 14% of patients without a penumbral pattern but with recanalization. These data suggest that only patients with an MRI-defined penumbra pattern are likely to benefit from therapy [86]. Clinical trials [75, 88–90] support that it is safe and effective to expand the time window for rtPA to up to 6 h in patients with tissue at risk as defined by MRI. In fact, in stroke patients treated 3–6 h after symptom onset, early reperfusion was associated with significantly increased odds of achieving a favorable clinical response in patients with a perfusion/diffusion mismatch and a lower rate of symptomatic intracerebral hemorrhage. Patients without mismatch did not appear to benefit from early reperfusion [91, 92]. Recently, EPI-THET, a placebo-controlled randomized study [76], found that alteplase was nonsignificantly associated with lower infarct growth and significantly associated with increased reperfusion in patients who had a mismatch on MRI. However, a phase III trial (DIAS-II), that had a pri-

mary clinical outcome, was negative [93]. Despite these uncertainties, other trials are using the penumbra paradigm [94].

Perfusion Computed Tomography

Brain CT scan is the examination most frequently used for the emergent evaluation of patients with acute stroke because of its wide availability and proven benefit. It has been utilized as a screening tool in most of the major therapeutic trials conducted to date [10]. Conventional CT scans are useful for distinguishing between ischemic stroke and intracerebral or subarachnoid hemorrhage, and can also rule out other conditions that could mimic stroke such as brain tumors. More recently, CT has been used to detect very early ischemic changes within the first few hours of ischemic stroke [46, 95]. Scanning time has been shortened with the advent of helical CT scanners. This enables tracking of an intravenously infused contrast bolus in the vascular bed and the identification of major-artery occlusions by CT angiography [96]. By continuous scanning of the entire brain after CT angiography, tissue perfusion can be assessed and regions distal to a vascular occlusion can be identified because they appear hypodense or hypoperfused relative to the rest of the brain [8]. Perfusion CT techniques, such as slow-infusion/whole brain perfusion CT and dynamic perfusion CT, may help distinguish irreversible infarction from other tissues. Slow-infusion perfusion CT is useful for evaluating the perfusion of the entire brain, but provides only qualitative information related to CBV and therefore cannot be used to differentiate reversible from nonreversible ischemia [96, 97]. Dynamic perfusion CT involves dynamic acquisition of sequential CT slices during the intravenous administration of iodinated contrast media [98] and enables estimation of CBF, CBV and MTT. Areas with prolonged MTT are hemodynamically compromised. In these areas, the regions with increased CBV resulting from vasodilatation and collateral recruitment are considered to have preserved autoregulation and to represent 'tissue at risk' whereas regions with decreased CBV correspond to the infarct core [99, 100]. Relative CBV thresholds (compared with the contralateral hemisphere) in hypoperfused tissue destined to infarct or to survive, are similar to those described for SPECT or PET and therefore might enable definition of the penumbra [101]. However, most CTs performed after processing analyses defining infarct cores do not use relative CBV for this purpose: they use quasi-absolute CBV obtained by

deconvolution either with venous output or arterial input. In a study, 42 stroke patients successively underwent perfusion CT/CT angiography and MRI examinations within 3–9 h following symptom onset; 14 would have been suitable candidates for reperfusion treatment based on MRI findings. The correlation between perfusion CT/CT angiography and MRI was excellent for infarct size, cortical involvement, and internal cerebral artery occlusion and substantial for penumbra/infarct ratio. Relying on MRI or perfusion CT/CT angiography would have led to the same treatment decisions in all cases but 1 [102].

Therapeutic Opportunities

Within 3 h of symptom onset, all randomized controlled trials of patients treated with rtPA are examined with simple CTs and this remains the typical method of decision-making in acute MCA strokes in most centers. Screening for eligibility for intravenous thrombolysis within 3 h of stroke with MRI was feasible at an experienced center, but at the expense of delay of about 20 min in treatment [103]. Using penumbral imaging permits to exclude patients within the 4.5-hour window who will not benefit from recanalization therapy. This is because they have either already completed their infarct or because they have already spontaneously recanalized/reperfused. While such patients are very infrequent in the 0- to 3-hour window, they are not uncommon in the 3- to 4.5-hour window. In the 4.5- to 6-hour period after stroke onset, treatment by revascularization is supported by more limited evidence even if there is support showing the value of reperfusion in the 3- to 6-hour window based

on appropriate patient selection. For the time being, the body of evidence for MRI variables, particularly DWI/PWI mismatch, is greater than for CT perfusion maps [103]. Because CT is not as sensitive as DWI for the detection of lacunar or posterior fossa strokes, MRI has clear advantages over CT perfusion – unless time is a constraint. Furthermore, almost all current CT perfusion techniques lack whole-brain coverage. CT perfusion can be used instead if patients are unsuitable for MRI, and may be preferred in the future if the penumbra is validated in larger series [104]. MRI and CT perfusion as well as PET and SPECT can also be valuable in patients with stroke presenting more than 6 h after symptom onset, in patients with unknown time of onset (e.g. ‘awakening stroke’) [105, 106], in patients with stroke in progression [107], and in patients with malignant MCA stroke, who may benefit from other treatments (e.g. decompressive craniectomy). Currently, PET and SPECT have a more limited role in the evaluation of acute stroke due to their costs and current lack of availability.

Conclusions

Discrimination between infarct core and surrounding potentially salvageable tissue is important so as to better identify patients suitable for treatment. This can be achieved by PET, SPECT, CT perfusion scan and PWI/DWI. Identification of the penumbra could enable a better selection for rtPA use among patients with large penumbras and small infarct cores even beyond the 4.5-hour time window as it has been shown that the penumbra may persist for more than 12 h.

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