Measurements of cerebral perfusion have become an important part of diagnostic imaging and therapy monitoring in a variety of brain diseases. Magnetic resonance perfusion imaging provides high-resolution images of various perfusion parameters in addition to the important morphological information acquired during the same imaging session. In conjunction with magnetic resonance imaging (MRI) diffusion-weighted imaging MR perfusion imaging has developed to a mainstay in early stroke imaging. The delineation of the so-called “tissue at risk” of ischemic damage characterized as a mismatch between alterations in diffusion-weighted and perfusion images is a key information if thrombolysis is a treatment option. Current ongoing clinical trials will show whether this information may allow to further extend the time window for thrombolytic therapy in stroke.

MR perfusion imaging allows the investigation of the well-established relationship between cerebral activity, metabolism, and regional hemodynamics. Under a wide range of physiological conditions the cerebral blood flow (CBF) is maintained at a constant level to provide a sufficient oxygen and glucose supply to the brain. This autoregulatory control is affected by the small cerebral arterioles, which are able to reduce the vascular resistance by widening of arterial sphincters and consecutive dilatation of small veins to maintain normal cerebral flow even under conditions where the systemic arterial blood pressure is as low as 70 mm Hg. A further drop of the perfusion pressure results in a CBF decrease, which is partly compensated with a higher oxygen extraction fraction and a reduction of cellular metabolism and energy demand. Irreversible tissue damage occurs if CBF drops below 10–12 mL/100 g of brain tissue per minute.

The complexity of these CBF patterns and autoregulatory control in various cerebrovascular diseases require the assessment of different parameters of cerebral perfusion, including the CBF, the cerebral blood volume, and the mean transit time (MTT). Considering these various parameters of cerebral perfusion, different stages of impaired brain perfusion can be identified. The dilatation of small arterioles, as the initial reaction to compensate for a reduced perfusion pressure, would increase the cerebral blood volume and to a certain extent the MTT while maintaining CBF at a constant level. This pattern is known as stage-one cerebral ischemia. With a decreasing perfusion pressure, the cerebral blood volume and the MTT will further increase; however, the CBF can no longer be kept at a constant level and will progressively decrease. This latter perfusion pattern is described as stage-two cerebral ischemia. If CBF falls beneath the critical level (stage three), irreversible damage to brain parenchyma will occur. Positron emission tomography (PET) and 133-xenon computed tomography (CT) can visualize and absolutely quantify these changes. However, both methods remain largely impractical for routine and emergency clinical use. Single photon emission tomography based on the detection of the distribution of 99m-technetium labeled hexamethylpropyleneamine oxime is a widely used method, although provided data are only relative indicators, and model-based calculation of CBF, cerebral blood volume, and MTT is imprecise. The potential of MRI to delineate the different perfusion parameters has been extensively evaluated in the recent years and the advantages of a multimodal MRI approach to various cerebrovascular disorders and cerebral tumors have been underlined.

In general, MRI offers two generic approaches to determine cerebral perfusion parameters. First, the blood flowing into an imaging slice can be marked either by magnetically tagging the selected slice or by the blood flowing into it. These techniques of arterial spin labeling are time-consuming, and measurable signal changes in states of reduced flow are usually small. However, if time is not a constraint, these techniques are promising especially if hemodynamic responses to various stimuli are studied during the same MRI study or breakdown of the blood-brain barrier compromises contrast-agent-based methods.
The second approach uses fast dynamic acquisition to monitor signal changes during the passage of a bolus of contrast agent through the brain parenchyma. Presuming an intact blood-brain barrier and fast contrast injection signal changes during the first passage through the brain allow the quantification of the various perfusion parameters. In principle, T1- as well as T2*-dependent properties of the applied contrast agent can be used. T1-weighted images require small quantities of contrast but images are greatly affected by a breakdown of the blood-brain barrier and produce only relatively poor signal-to-noise ratios. Therefore, susceptibility-based brain perfusion imaging has become a widespread tool for the assessment of cerebral perfusion. During the passage through the brain the contrast agent cannot pass the intact blood-brain barrier and T2*-weighted sequences provide a good means of contrast because the compartmentalized susceptibility differences in the blood pool create microscopic field gradients that extend into the tissue and enhance T2*-dephasing, rendering the tissue dark. Relative regional cerebral blood volume (rCBV), time of bolus arrival, and bolus peak can be derived in a straightforward manner based on tracer kinetics theory; assuming that the change in relaxivity (ΔR2* = 1/ΔT2*) is proportional to the time-dependent contrast agent concentration: ΔR2*(t) = k(contrast agent), where k is a field strength and pulse sequence specific constant. Presuming a monoexponential behavior, the signal intensity changes can be converted into concentration time curves (C(t) = −ln(S(t)/S0)/(kTE)), where S0 is the baseline signal before injection, and S(t) the tissue signal present at time t. These concentration time curves need to be subsequently fitted to a gamma-variate function to correct for recirculation. From the fit parameters, the different perfusion parameters can be computed on a voxel-by-voxel basis and graphically represented in perfusion parameter maps. These include the relative rCBV map calculated by simple integration of the concentration versus time curve; the MTT map—a flow-dependent measure—which is calculated by dividing the integral of concentration-time curve by its height; the regional cerebral blood flow index as the ratio of volume and transit time; the time of bolus arrival (T0) map; and the time to bolus peak (TTP). Like single photon emission tomography, this technique does not provide absolute measures for CBV and CBF, which means that no comparison to normal values can be made. However, intraindividual perfusion changes can be readily and quickly visualized and the derived data closely correlate to data acquired by other imaging modalities (Figure 1).

Besides this straightforward calculation of relative perfusion data, MRI data can also be used for absolute quantification. However, absolute quantification requires the simultaneous registration of an arterial input function and modeling the vascular architecture, which is mathematically expressed through the residue function R(t). The residue function describes how an impulse is retained in the vasculature as a function of time. The concentration of a tracer in a given volume of interest can then be expressed as a function of flow, arterial input, and the residue function. Although this approach has various inherent difficulties as there is no a priori knowledge of the diseased vessel architecture, numerical approaches (such as fast Fourier transform and singular value decomposition) to calculate the deconvolution of concentration-time curves with the arterial input function have shown similar results compared to quantified PET measurements. However, these very promising numerical approaches to derive quantitative MRI perfusion data still have limitations in the diseased vasculature. Deconvolution techniques are still sensitive to dispersion and, in some cases, to delays of the arterial input downstream of where it is measured. In such cases in which the blood reaches the tissue through collaterals, the chosen arterial input is not truly representative and may cause underestimation of the MTT. Unlike the determination of relative perfusion measurements, the calculation of quantitative data requires a more extensive computation that is not readily available at all clinical scanners for the emergency setting of stroke.
imaging. Furthermore, an appropriate imaging technique has to be selected to correctly image the arterial input function.

The requirement for high temporal resolution has led to widespread use of echo planar imaging techniques (EPI). Single-shot and segmented EPI techniques are the most commonly used. T2*-sensitive 3D whole brain perfusion imaging has also become available. With the more widespread use of higher field MRI scanners, the increment of susceptibility at higher magnetic field strength has led to a further improvement of these imaging techniques by either increasing the temporal resolution to subsecond imaging or reducing the amount of contrast agent required.

To date, the choice of the best imaging technique, i.e., T1-EPI, T2*-EPI, T2*-Presto, remains a fundamental question as it affects the sensitivity of the imaging experiment to blood vessel size, i.e., small capillaries or larger arteries.

Clinical application of MR perfusion imaging

Modern approaches to patients with acute ischemic stroke have emphasized early diagnosis and management since the recognition that early cerebral infarction may be in part reversible. Roughly 80% of ischemic infarcts are caused by thromboembolic occlusions of intracranial arteries of one of the major cerebral vessels; however, the extent of brain damage as a result of inadequate perfusion is usually smaller than the affected vessel territory. Collateral circulation may provide sufficient energy and oxygen supply to parts of the affected vessel territory, which allows it to maintain basic functional cellular activity. With their high sensitivity to acute cerebral infarction, the combined use of echo planar diffusion-weighted and perfusion imaging has gained a major role. Diffusion imaging detects early diffusion changes associated with cytotoxic edema following energy metabolism failure and disrupture of ion homeostasis. Perfusion has the potential to characterize the degree of regional hyperperfusion, which seems to be an important prognostic factor to determine final infarct extension (Figure 2).

In our series of patients with acute stroke, the areas of a significantly reduced rCBV in conjunction with a prolonged MTT were good predictors for final infarct size and clinical outcome in spontaneously developing stroke. However, if thrombolysis is a treatment option, MRI alone may refine selection of candidates. Identification of vessel obstruction and exclusion of hemorrhage, the most important differential diagnosis of acute stroke, can be readily performed within minutes in the MR scanner. A perfusion–diffusion mismatch, which indicates tissue with decreased perfusion extending beyond that of diffusion abnormalities, is thought to represent tissue at risk of infarction, which is potentially salvageable with successful systemic or local thrombolysis. Such mismatches can be present even if vascular occlusion cannot be demonstrated. The effect of thrombolysis with regards to penumbral salvage has been found to be more pronounced if a mismatch is present. The degree of hypoperfusion in the mismatch area as defined by MRI perfusion parameter maps, first of all the MTT maps, seems to provide a more important information in clinical decision making than the time of treatment after stroke onset. Therefore the identification of thresholds for various perfusion parameters has been proposed, but it is still a matter of controversy. MTT prolongations of more than 22% compared to salvaged regions as well as TTP prolongation of more than 6 seconds were found in areas of later infarction and thus considered as critical levels. Nevertheless, absolute thresholds should still be considered cautiously as even a less severe hypoperfusion may lead to ischemic damage if the duration of hypoperfusion is long enough. Thus, reperfusion either spontaneous or post treatment has a great impact on tissue fate. Ongoing studies will show whether information derived from MRI perfusion and diffusion imaging may allow to further extend the time window for thrombolytic therapy in stroke. To date, thrombolytic treatment without the visualization of a perfusion deficit can only be used within the time constraints of early stroke studies.

MRI perfusion imaging has also been used with increasing interest to assess patients with extracranial vascular disease, especially patients with carotid vessel disease. Platelet formation within the vessel lumen is the origin of thromboemboli in a large group of patients. Although there is evidence that the severity of stenosis correlates with the incidence of thromboembolism, the degree of stenosis does not correlate to the amount of hypoperfusion downstream to the occlusion and to the risk of hypoperfusional infarcts. The risk of hypoperfusional infarcts is determined by the amount of collateral circulation available, which varies among patients according to the individual anatomy of the circle of Willis and further leptomeningeal collateralization. However, the risk of hypoperfusional infarcts can be assessed by imaging the regional cerebral perfusion. MRI has the ability to delineate these changes and to depict perfusion abnormalities. However, if relative values are provided, results may be misleading in the presence of bilateral carotid vessel disease. Intra-individual comparison of perfusion parameters
CHAPTER 6

Figure 2 Parts (a) and (b) show the perfusion parameter maps of a patient with acute middle cerebral artery (MCA) occlusion imaged within the time window for intraarterial thrombolysis. On the rCBV map (a) there is only a small perfusion deficit within the right basal ganglia corresponding to an early diffusion-weighted imaging abnormality (c). The cortex of the right MCA territory demonstrates no differences on rCBV maps compared to the contralateral side. However, TTP maps (b) show a large area of hypoperfusion in the right MCA territory. This mismatch area between diffusion-weighted imaging and perfusion imaging is large enough to justify thrombolysis. The corresponding angiogram (d) clearly shows the occlusion of the MCA (arrow).

Before and after therapy or in combination with vascular dilatory challenge, such as acetazolamide, to characterize the individual cerebral perfusion reserve capacities is a reliable method.

MR perfusion imaging can further be applied in any brain disease where regional abnormalities of CBF are suspected (Figure 3). Small vessel diseases, arteriovenous malformations, the various types of dementia, and tumor vascularization are under ongoing investigation. It is likely that the shortcomings of relative MRI perfusion data will be overcome in the near future when postprocessing programs will be implemented on routine clinical scanners, and absolute quantification of perfusion data may add information to the differential diagnosis of these various diseases. In addition, the use of blood pool agents that do not suffer from diffusion across the vascular endothelium and concomitant contrast changes, once they will be available for clinical first-pass imaging, will further increase the accuracy of MRI rCBV and CBF measurements.

MR perfusion imaging has yet evolved to a mainstay of neuroimaging.
Figure 3. A time-to-peak map of a patient with acute symptomatic migraine demonstrates a delayed bolus arrival in the posterior middle cerebral and the posterior cerebral artery territory. Regions of interest and the corresponding concentration–time curves are displayed. The hypoperfusion of the affected side can be clearly seen. The effect of gamma-variate fitting to correct for recirculation is shown.

Bibliography

Original publications


CHAPTER 6


Thomaalla G, Schwark C, Sobesky J, et al. Outcome and symptomatic bleeding complications of intravenous thrombolysis within 6 hours in MRI-selected stroke patients. Comparison of a German Multicenter Study with the Pooled Data of ATLANTIS,
MR perfusion imaging of the brain

ECASS and NINDS tPA Trials. Stroke March 2006; 37(3): 852–858.