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DIFFUSION AND DYNAMIC SUSCEPTIBILITY CONTRAST PERFUSION WEIGHTED MAGNETIC RESONANCE IMAGING IN HUMAN ACUTE ISCHEMIC STROKE

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ACADEMIC DISSERTATION

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SUMMARY

Ischemic stroke is the third leading cause of death and the leading cause for permanent adult neurological disability in the developed countries. Its acute treatment is possible for a subgroup of patients only within three to six hours after symptom onset. As the early therapeutic decision is essential, identifying individual patients of this subgroup has been a diagnostic challenge. Recently, functional magnetic resonance imaging (fMRI) techniques, diffusion weighted imaging (DWI) and dynamic susceptibility contrast (DSC) perfusion imaging, have shown promise in being capable of characterizing the ischemic tissue, in the form of apparent diffusion coefficient (ADC), and the abnormal hemodynamics associated with it in the form of cerebral blood volume (CBV), cerebral blood flow (CBF), contrast agent mean transit time (MTT), and cerebral blood flow heterogeneity (FH). This study aimed to assess the variation of these commonly used indices in a normal aging population, and to characterize the behaviour of these indices in ischemic stroke patients. The study consists of five publications; the first two reporting the behaviour of DWI and DSC MRI –based indices, respectively, in a normal aging population, and the last three reporting the four different DSC MRI based indices in untreated ischemic stroke patients. The study showed that, in general, the indices are not affected by aging. Further, it was shown that the method of determining CBV and MTT does not affect the visual interpretation of tissue at risk, but has to be taken into account for quantitative analysis and automated interpretation algorithms. Finally, it was shown that the hemodynamical abnormality caused by ischemic stroke reduces in size during the first week whereas the ischemic core itself enlarges in naturally evolving stroke. The study enhances the basis of applying DWI and DSC MRI in ischemic stroke patients by reporting the effect of normal aging and normal brain subregional differences in the indices as well as the evolution of the hemodynamically abnormal tissue volumes in an untreated ischemic stroke during the first week. Further, by reporting the failure of traditional and the success of more novel methods to accurately determine CBV and MTT, the study lays ground for quantitative measures of DSC MRI indices.

CONTENTS

LIST OF ORIGINAL PUBLICATIONS

I Helenius J, Soinne L, **Perkiö J**, Salonen O, Kangasmäki A, Kaste M, Carano RAD, Aronen HJ, Tatlisumak T. Diffusion-weighted MR imaging in normal human brains in various age groups. AJNR Am J Neuroradiol 2002;23:194-199

II Helenius J, **Perkiö J**, Soinne L, Østergaard L, Carano RAD, Salonen O, Savolainen S, Kaste M, Aronen HJ, Tatlisumak T. Cerebral hemodynamics in a healthy population measured by dynamic susceptibility contrast magnetic resonance imaging. Acta Radiol 2003;44:538-546

III **Perkiö J**, Aronen HJ, Kangasmäki A, Liu Y, Karonen J, Savolainen S, Østergaard L. Evaluation of four postprocessing methods for determination of cerebral blood volume and mean transit time by dynamic susceptibility contrast imaging. Magn Reson Med 2002;47:973-981

IV Aronen HJ, **Perkiö J**, Karonen JO, Vanninen RL, Østergaard L, Liu Y, Könönen M, Vanninen EJ, Soimakallio S, Kuikka JT. Perfusion-weighted MRI in human acute ischemic stroke: A comparison with the progression of the infarct on diffusion-weighted images. Acad Radiol 2002;9(suppl 1):S160-164

V **Perkiö J**, Soinne L, Østergaard L, Helenius J, Kangasmäki A, Martinkauppi S, Salonen O, Savolainen S, Kaste M, Tatlisumak T, Aronen HJ. Abnormal intravoxel cerebral blood flow heterogeneity in human ischemic stroke determined by dynamic susceptibility contrast magnetic resonance imaging. Accepted for publication in Stroke. In press.

STATEMENT OF INVOLVEMENT

The author has made the following contributions to the original publications forming the thesis: substantial contributions to conception and design, data-analysis and interpretation of data, acquisition of data (Paper V), drafting the article and revising the article critically for important intellectual content, and final approval of the version to be published.

ABBREVIATIONS AND SYMBOLS

α	Shape parameter of the gamma-variate functioṇ
β	Shape parameter of the gamma-variate function
ADC	Apparent diffusion coefficient
AIF	Arterial input function
BBB	Blood bran barrier
c	Concentration
c_a	Arterial concentration
c_t	Tissue concentration
CBV	Cerebral blood volume
CBF	Cerebral blood flow
$CMRO_2$	Cerebral metabolic rate of oxygen
CPP	Cerebral perfusion pressure
ΔR2	Change in T2 relaxation rate
ΔR2*	Change in T2* relaxation rate
DSC	Dynamic susceptibility contrast
DTPA	Diethylenetriaminepentaacetic acid
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
ε	Singularity threshold
EPI	Echo planar imaging
f	Relative flow
FH	Flow heterogeneity
$\Gamma(x)$	Gamma function
$h(t)$	Probability density function of transit times
I	Identity matrix
κ	Scale factor
k	Proportionality constant
K	Constant scale factor in gamma-variate function
MRI	Magnetic resonance imaging
MTT	Mean transit time
NMR	Nuclear magnetic resonance
OEF	Oxygen extraction fraction
R2	T2 relaxation rate
R2*	T2* relaxation rate
$R(t)$	Residue function
ROI	Region of interest
σ	Singular value
S	Nonnegative diagonal matrix consisting of singular values
$S(t)$	Signal intensity
$S(t_0)$	Initial signal intensity
SNR	Signal-to-noise ratio
SVD	Singular value decomposition
t_0	Tracer arrival delay
T1	Longitudinal relaxation
T2	Transversal relaxation
TE	Echo time
TR	Repetition time
V	Base matrix of a singular value decomposition

U	Base matrix of a singular value decomposition
W	Nonnegative diagonal matrix consisting of the inverses of singular values
w(f)	Probability density function of relative flow rates

1 INTRODUCTION

Cerebral functions rely on adequate oxygen delivery to meet the metabolic demands of the functioning neurons. Oxygen, and other nutrients, are delivered to cerebral tissue through the cerebrovascular system and the endothelial lining of the cerebral capillaries. Within certain functional limits, cerebral autoregulation ensures sufficient transport of metabolites during the varying requirements posed by local neuronal tissue. However, outside these functional limits, cerebral autoregulation breaks down and insufficient amounts of oxygen and other nutrients reach the tissue for it to function normally. Severe lack of oxygen causes neuronal tissue to cease functioning in a matter of minutes with the damage becoming irreversible within a few hours. The acute reduction of blood supply, acute stroke, is one of the major causes of adult neurological disability and one of the leading causes of death in the developed countries (Beauchamp and Bryan, 1998). In four of five strokes, the abrupt decline in oxygen delivery is due to a local blockage of blood flow and referred to as ischemic stroke (Schellinger *et al.*, 2004). Luckily, the progression of ischemic stroke can many times be inhibited by thrombolytic therapy targeted at dissolving the clot, which blocks the blood flow, provided the therapy can be administered within 3 or 6 hours after the onset of symptoms (Group, 1995; Hacke *et al.*, 1998). However, the thrombolytic therapy can lead to complications and is contraindicated by hemorrhage posing the need to assess the risks involved with the therapy separately in each individual case.

Magnetic resonance imaging (MRI) is an increasingly available radiological tool, which allows the rapid assessment of cerebrovascular disease. The physical principles forming the basis of MRI were discovered in the 1940's (Bloch *et al.*, 1946; Purcell *et al.*, 1946) and awarded the Nobel Prize in physics in 1952. However, the methodology evolved into a clinical tool only after several decades and further discoveries (Lauterbur, 1973; Mansfield, 1977), which were awarded the Nobel Prize in medicine in 2003. In the advent of MRI's clinical era, in the late 1970's and early 1980's, its use was confined to anatomical imaging mainly based on soft tissue contrast, which was far superior to its diagnostic competitors, computed tomography, ultrasound, and the methods based on nuclear medicine. In addition to its strengths in forming different tissue contrasts, the growth of MRI as a clinical tool was supported by the freely selectable slice orientation and the complete lack of ionizing radiation. As the signal detection concepts and the power of hardware evolved, the spatial and temporal resolutions of MRI increased creating an opportunity to detect tissue functionality with MRI. In the late 1980's, magnetic resonance angiography (Wedeen *et al.*, 1985), diffusion weighted imaging (DWI) (Le Bihan *et al.*, 1986; Le Bihan *et al.*, 1988) and dynamic susceptibility contrast (DSC) –based perfusion imaging (Villringer *et al.*, 1988) were introduced. Due to the wide range of contrast formation and imaging techniques, MRI has a high diagnostic capability and applications in a versatility of pathologies. One major group of these pathologies is neurological disorders.

The present study focuses on the use of DWI and DSC MRI in describing human ischemic stroke. The study is composed of 5 publications and a summary. The first two publications describe DWI and DSC MRI findings in normal population laying the foundation for applying these methods in the diseased brain. The third publication compares four different approaches for determining cerebral blood volume (CBV) and contrast agent mean transit time (MTT). The fourth publication investigates the possibility of predicting the evolution of the infarct based only on knowledge of tissue perfusion in the form of cerebral blood flow (CBF) at 24hrs after symptom onset. The fifth publication follows the course of the sizes of CBV, CBF, MTT, and cerebral blood flow heterogeneity (FH) abnormalities during the first week of developing infarct. Thus the first two publications describe the methods in normal material, and the last three publications focus on the application of CBV,

CBF, MTT and FH in ischemic stroke. The summary section provides background of the theory utilized in the publications and puts the results into perspective with present advances in the field.

2 CEREBRAL HEMODYNAMICS AND ITS AUTOREGULATION

Tissue regulates and meets its needs for metabolic substrates through cerebral hemodynamics. The exchange of substances, e.g. oxygen and carbon dioxide, between blood and tissue operates at the microvascular level, where the diameter of the capillaries is only around 5μm. Blood-brain-barrier (BBB), the tight junctions between capillary endothelial cells, restricts the exchange preventing proteins and polypeptides from entering the brain whereas allowing the passive transport of water, carbon dioxide and oxygen (Ganong, 2001).

Cerebral autoregulation seeks to maintain CBF relatively constant despite variations in cerebral perfusion pressure (CPP). Changes in CPP over a wide range have only a small effect on CBF (Powers, 1991). This autoregulation is mediated through cerebrovascular resistance so that when CPP is reduced, the ratio CBV:CBF is increased. Another part of tissue oxygen metabolism regulation mechanism is considered to be the distribution of CBF (Kuschinsky and Paulson, 1992), which in normal capillaries is wide around a mean flow (Kuschinsky and Paulson, 1992; Hudetz *et al.*, 1996). In cases of lowered local CPP there is a significant reduction in the high flow components leading to a less dispersed flow velocity distribution (Hudetz*, et al.*, 1996; Vogel and Kuschinsky, 1996), which improves oxygen delivery to the tissue (Kuschinsky and Paulson, 1992; Østergaard *et al.*, 2000). However, when the capacity for compensatory vasodilation has been exceeded, autoregulation fails (Powers, 1991). Any further reduction in CPP produces a decrease in CBF. With decreasing CBF, oxygen extraction fraction (OEF) increases to maintain the cerebral metabolic rate of oxygen ($CMRO_2$) to drive neuronal function. Should the CPP continue to fall, the increase in OEF at some point is no longer adequate to supply the energy needs of the brain (Sette *et al.*, 1989) and brain dysfunction results. If circulation is rapidly restored, the dysfunction may be reversible, otherwise the damage is irreversible resulting in an infarct.

Infarction is caused by a severely reduced blood flow in a vessel due to e.g. thrombus of artherosclerotic plaque. The reduced blood flow leads to hypoxia, or even anoxia, but in any case to an interruption of the oxygen supply of the tissue perfused by the clotted vessel and subsequently to ischemic stroke. Consequently, the primary goal of acute stroke treatment is to restore normal blood flow as soon as possible. This is performed primarily by the use of clot-lysing drugs, which have to be applied as soon as possible after the clot formation to ensure the restoration of the function of the damaged neurons. As the application of clot-lysing drugs is contraindicated in hemorrhagic stroke, the diagnosis of the quality and extent of stroke is extremely important in making the therapeutic decision in the early phase of stroke. MRI provides a possibility to assess these aspects of stroke with DWI and DSC MRI.

3 MEASUREMENT OF TISSUE WATER DIFFUSION BY MAGNETIC RESONANCE IMAGING

3.1 Water diffusion in tissue

In human tissue, the water molecules are constantly in random Brownian motion due to their thermal energy. The surroundings of the tissue water molecules contain obstacles, such as membranes, which the molecules cannot readily penetrate. The path of a single water molecule therefore reflects the structure of its microscopic environment. As the intracellular space contains far more obstacles than the extracellular space, the diffusion is more restricted in the intracellular space. Although, this Brownian motion is based on the intermingling of the water molecules and is thus a microscopic phenomenon, as large amounts of molecules are involved it gives rise to a macroscopically observable and measurable phenomenon known as diffusion.

3.2 Diffusion weighted magnetic resonance imaging

The phenomenon of nuclear magnetic resonance (NMR) was initially discovered by Bloch (Bloch, 1946; Bloch, *et al.*, 1946) and Purcell (Purcell, *et al.*, 1946) followed by the introduction of the principle of spin echo by Hahn (Hahn, 1950), which included the notion that the random thermal incoherent motion of the spins would reduce the amplitude of the observed spin echo signal in the presence of a magnetic field inhomogeneity. In essence, it stated that any spin echo –based pulse sequence is sensitive to incoherent motion of water molecules due to the facts that the molecules have time to diffuse between the excitation pulse and the reversing π-pulse as well as between the π-pulse and the time of the echo and that the motions at these two time windows are not correlated. In conventional pulse sequences, however, the time is too short for any significant diffusion weighting to be present and for the effect of diffusion to be measurable. Consequently, the measurement time has to be prolonged or the effect of diffusion amplified during the short measurement time. Founding on the work of Carr and Purcell (Carr and Purcell, 1954) and Torrey (Torrey, 1956), Stejskal and Tanner (Stejskal and Tanner, 1965) developed the methodology and theory of the pulsed gradient spin echo experiment, which made possible the direct measurement of the diffusion and opened the window for quantitative measurements of molecular diffusion coefficients. The method is based on amplifying the effect of the inherent diffusion on the MR signal by additional diffusion gradients set symmetrically on either side of the reversing π-pulse. The measurement of water diffusion by MRI was made possible by the pioneering work by Lauterbur (Lauterbur, 1973) introducing imaging gradients and by Mansfield (Mansfield, 1977; Mansfield, 1984) introducing ultrafast echo planar imaging (EPI) technique. Imaging gradients allowed spatial localization of measured signal in the imaging volume and were thus a prerequisite for imaging in general. EPI technique shortens considerably the time required to form an image due to the filling of the k-space after only one single excitation pulse. The drawback of EPI is lower signal-to-noise ratio (SNR) than in conventional imaging, but the benefits of rapid data collection are indispensable in imaging water diffusion.

DWI is based on introducing diffusion gradients in a basic spin echo experiment. Any phase shift due to the motion of a spin during the diffusion gradient is amplified by the gradients. By positioning the diffusion gradients symmetrically around the π-pulse, the amplification is effectively eliminated for stationary spins, but for incoherently moving spins the amplified phase shift leads to a temporally distorted echo and subsequently decreases the echo signal of the whole spin ensemble of the voxel. The first diffusion images on a whole-body system were obtained by Le Bihan (Le Bihan, *et al.*, 1986; Le Bihan, *et al.*,

1988) and the clinical importance of diffusion imaging as being capable of detecting ischemic tissue within minutes after stroke in an experimental animal model was demonstrated by Moseley et al (Moseley *et al.*, 1990) and in human ischemia by Warach et al (Warach *et al.*, 1992).

3.3 Diffusion weighted magnetic resonance imaging in acute stroke

The detection of ischemia with DWI is based on the alteration of water diffusion due to the pathology. The MR signal from an imaging voxel includes components from both intra- and extracellular water. As the diffusion of intracellular water is more restricted than the diffusion of extracellular water due to limiting structures such as microparticles and membranes, the fraction of intracellular water to extracellular water is directly reflected in the measured diffusion from a particular voxel. In acute stroke, the breakdown of sodium-potassium pumps leads to cytotoxic edema and to the growth of the fraction of intracellular space within an imaging voxel. This effectively results in a net decrease of the measured diffusion in the voxel.

4 MEASUREMENT OF TISSUE PERFUSION WITH DYNAMIC SUSCEPTIBILITY CONTRAST MAGNETIC RESONANCE IMAGING

Dynamic susceptibility contrast magnetic resonance imaging (DSC MRI) provides the means for non-invasive *in vivo* assessment of normal and diseased microvascular system, which has earlier been impossible due to the lack of appropriate techniques sensitive at the capillary level. DSC MRI is based on the use of single shot EPI techniques (Mansfield, 1977) and susceptibility contrast (Villringer*, et al.*, 1988) induced by gadolinium –based contrast agents, which have allowed the measurement of the first pass circulation of contrast agents through the brain (Rosen *et al.*, 1990; Belliveau *et al.*, 1991; Rosen *et al.*, 1991a; Rosen *et al.*, 1991b). The dynamic data sets collected during the first pass circulation through the brain can be used to generate different functional maps of the *in vivo* hemodynamics of the normal and pathological brain (Belliveau *et al.*, 1990). These maps can be used to characterize and measure various aspects of structure and hemodynamics of normal and diseased microvascular system. The first reported functional MRI study demonstrating increased local CBV in response to neuronal activation was based on DSC MRI (Belliveau*, et al.*, 1991).

4.1 Susceptibility contrast

Paramagnetic substances distort the magnetic field through short-range interactions due to their large magnetic moments and dipole-dipole interactions. They affect both the observed T1 and T2 relaxation times due to the interactions between the unpaired electrons of the paramagnetic ion and the hydrogen nuclei of water molecules (Bloembergen *et al.*, 1948; Solomon, 1955; Bloembergen, 1957). The modification of tissue contrast due to T2 relaxation enhancement is referred to as susceptibility contrast. The effect of the paramagnetic substance to both T1 and T2 is dependent on a dipole-dipole term and a scalar component. The dipole-dipole term describes the ability of tissue water protons to approach the paramagnetic center of the contrast agent. Thus the relaxivity increases with the amount of water protons capable of moving into close proximity of the agent. Further, as the magnetic moment of an unpaired electron spin is 657 times greater than that of a proton, the relaxation efficiency of an electron is very high. Subsequently, metal ions that have several unpaired electrons are efficient agents in enhancing relaxivity. The scalar component describes the probability of contact interaction between the unpaired electron of the paramagnetic substance and water proton nucleus in the form of correlation time including rotation, electron spin relaxation, and chemical exchange components. Thus, the longer it takes for the paramagnetic ions to rotate, or the longer the electron spin relaxation time is, the more efficient is the relaxivity effect of the contrast agent. Most popular contrast agents in the clinical setting are gadolinium and dysprosium, which both have a large net molecular magnetic moment due to large number of unpaired electron spins coupled with relatively long electron spin relaxation times. Due to their inherent toxicity, gadolinium and dysprosium are typically applied in the vasculature chelated to a ligand molecule, such as diethylenetriaminepentaacetic acid (DTPA).

Susceptibility contrast was introduced into human MRI studies by Villringer *et al* (Villringer*, et al.*, 1988), showing that, in addition to the T1-effect, the paramagnetic contrast agent has the ability to alter T2 relaxation rates if present in high enough concentrations and compartmentalized into intravascular space. The high concentration of an intravascular paramagnetic contrast agent produces a magnetic susceptibility difference between the capillaries filled with the contrast agent and the surrounding tissue. The susceptibility difference in turn produces local magnetic field gradients extending to a distance outside the vessel roughly equal to the vessel diameter. As water molecules diffuse

through these field gradients they rapidly lose their phase coherence leading to an increase in T2 (and T2*) relaxation rates. The magnetic susceptibility effect thus results from local magnetic field gradients induced by intravascular compartmentalization of the contrast agent and it dominates over the T1 relaxation enhancement in high concentrations (Villringer, *et al.*, 1988).

4.2 Relation of signal and concentration

As DSC imaging is based on nuclear magnetic resonance, it detects primarily tissue water protons, not the contrast agent molecules. Thus, in DSC imaging, the measured signal is not directly a measure of the contrast agent concentration. Rather, the signal arises from the changes in the characteristics of tissue water protons due to the susceptibility effect induced by the external contrast agent and is a measure of T2 (or T2*) relaxation rate, denoted as R2 (or R2*) (Villringer, *et al.*, 1988). The signal intensity, *S(t)*, measured in the DSC MRI experiment can be expressed as

$$S(t) = S(t_0)(1 - e^{-TR \cdot \Delta R1})e^{-TE \cdot \Delta R2}, \qquad [1]$$

where $S(t_0)$ is the initial signal intensity, *TR* is repetition time, and *TE* echo time. According to both empirical measurements (Villringer, *et al.*, 1988; Rosen, *et al.*, 1990; Lev *et al.*, 1997) and theoretical simulations (Fisel *et al.*, 1991; Kennan *et al.*, 1994; Weisskoff *et al.*, 1994b; Boxerman *et al.*, 1995), in the clinically applicable range, there is an approximately linear relationship between the change in the R2 (or R2*), relaxation rate and the concentration

$$c(t) \propto \Delta \mathrm{R2} \qquad [2]$$

Substituting Eq. [2] to Eq [1] and assuming T1 to remain unchanged during the measurement, the concentration can be expressed

$$c(t) = k \cdot \Delta R2 = -\frac{k}{TE} \ln\left(\frac{S(t)}{S(t_0)}\right), \qquad [3]$$

where *k* is a proportionality constant, which depends on the properties of the contrast agent and tissue.

4.3 Principles of tracer kinetics – Indicator dilution theory

The kinetics of a non-diffusible contrast agent can be described by indicator dilution theory (Meier and Zierler, 1954; Lassen and Perl, 1979). An indicator is defined as an identifiable substance, which is introduced into blood circulation, either as an instantaneous bolus injection or by continuous intravascular infusion, and which is subsequently diluted in the circulation. Indicator dilution theory describes the behaviour of such a substance in the vasculature. Indicator dilution theory requires the indicator to remain in the vasculature,

which in cerebral microvasculature translates into a requirement of an intact blood-brain-barrier. In the case of a disrupted BBB, the contrast agent is able to leak into the tissue and distort the contrast by acting as a diffusible contrast agent. Thus an intact BBB is a prerequisite for using the indicator dilution methodology for assessing tissue perfusion.

The indicator dilution methodology can be used to measure blood volume and blood flow as the volume of solution necessary to dilute the injected indicator to equal the observed concentration is exactly the volume of blood that had diluted the injectate over the time interval in which indicator was recovered (Stewart, 1894). The output concentration, *c(t)*, is a convolution of the input function, $c_a(t)$, and the probability density function of transit times *h(t)* (Meier and Zierler, 1954)

$$c(t) = \int_0^t c_a(\tau)h(t-\tau)d\tau \,. \qquad [4]$$

According to Eq. [4] the output (or venous) concentration is a convolution between the input function and the probability density function of transit times. In DSC MRI, the frequency function of transit times is not measured directly. Rather, the residue function, which describes the amount of contrast agent present in the vasculature is measured. The residue function is defined as (Østergaard *et al.*, 1996c)

$$R(t) = 1 - \int_0^t h(\tau)d\tau \,, \qquad [5]$$

with *R(0)=1*, *R(∞)=0* and *R(t)* being a monotonically decreasing function of time. The observed tissue concentration, $c_t(t)$, becomes (Østergaard, *et al.*, 1996c)

$$c_t(t) = CBF \cdot \int_0^t c_a(\tau)R(t-\tau)d\tau \,. \qquad [6]$$

According to Eq. [6], the impulse response function, $CBF \cdot R(t)$, can be determined through deconvolution, assuming $c_t(t)$ and $c_a(t)$ are known. As CBF is a scalar, the impulse response function is shaped by the residue function and as the residue function is normalized to unity, the impulse response function is scaled by CBF. This essentially suggests that as *R(0)=1*, the height of the impulse response at that point corresponds to CBF.

4.4 Tissue impulse response

Tissue impulse response holds information on tissue blood flow characteristics on several aspects. As the underlying distribution, the residue function, is a probability density function, the height of the impulse response is directly scaled by CBF (Østergaard *et al.*, 1996b; Østergaard, *et al.*, 1996c). Thus, the impulse response holds information of the mean CBF in the voxel. Further, the integral over the impulse response function equals to the CBV in the

voxel whereas, as indicated by the central volume theorem, the integral over the residue function equals to the MTT (Paper III). However, in addition to CBV, CBF, and MTT, the impulse response function can be utilized to extract additional information of the capillary blood flow characteristics of the voxel, although it requires modeling the vasculature to some degree (Østergaard *et al.*, 1999).

Tissue impulse response is obtained by deconvolving Eq. [6] usually by a model-independent method, such as singular value decomposition (SVD) (Østergaard*, et al.*, 1996b; Østergaard*, et al.*, 1996c). SVD was developed by several mathematicians during the 19th and 20th century (Stewart, 1993) and is based on the fact that every m x n ($m \geq n$) matrix can be deconstructed into the product of three matrixes $\mathbf{U} \cdot \mathbf{S} \cdot \mathbf{V}^{\mathbf{T}}$, where **U** and **V** are orthogonal matrices, such that $\mathbf{U}^{\mathbf{T}} \cdot \mathbf{U} = \mathbf{V}^{\mathbf{T}} \cdot \mathbf{V} = \mathbf{I}$, and **S** is a nonnegative diagonal matrix constituting of the singular values of matrix, i.e. $\mathbf{S} = \mathrm{diag}(\sigma_1,\sigma_2,\ldots,\sigma_n)$, where σ are the singular values. The utilization of SVD in the context of DSC MRI requires discretization of Eq. [6] so that

$$c_t(t) = \Delta t \cdot CBF \cdot \sum_{i=0}^{j} c_a(t_i) \cdot R(t_j - t_i), \qquad [7]$$

where Δt is the sampling interval of the DSC MRI experiment. Eq. [7] can further be expanded into matrix notation $\mathbf{c} = \mathbf{A} \cdot \mathbf{b}$, where **b** includes the elements of the impulse response function, **A** the elements of the arterial input function, and **c** the elements of output concentration. Tissue impulse response, **b**, can be solved using SVD as $\mathbf{b} = \mathbf{V} \cdot \mathbf{W} \cdot \mathbf{U}^{\mathbf{T}} \cdot \mathbf{c}$, where $\mathbf{V} \cdot \mathbf{W} \cdot \mathbf{U}^{\mathbf{T}} = \mathbf{A}^{-1}$ and $\mathbf{W} = \mathrm{diag}(\sigma_1^{-1},\sigma_2^{-1},\ldots,\sigma_n^{-1})$. Further, the elements of the diagonal matrix **W** are set to

$$W_{i,j} = \begin{cases} \dfrac{1}{\sigma} & j = i, S \geq \varepsilon \\ 0 & j = i, S < \varepsilon \end{cases}, \qquad [8]$$

where ε is a singularity threshold usually set to some fixed percentage of σ_{max}.

Whereas SVD represents a model-independent technique to solve tissue impulse response, it can be supplemented with a vascular model to enhance the information content obtained from the tissue impulse response. Based on the vascular model developed by Kroll *et al* (Kroll *et al.*, 1996) and King *et al* (King *et al.*, 1993; King *et al.*, 1996), Østergaard *et al* (Østergaard*, et al.*, 1999) introduced methodology to assess intravoxel flow heterogeneity by DSC MRI. The model is based on a major feeding artery in series with 20 small parallel vessels of equal length (Østergaard*, et al.*, 1999). The distribution of transit times is included by setting appropriate flows and weights to the parallel vascular paths (King*, et al.*, 1996; Østergaard*, et al.*, 1999). Consequently, the flow heterogeneity is described by a probability density function assigning a probability, *w(f)*, to a given relative flow, *f*, i.e. flow relative to the mean flow in the vascular path (Østergaard*, et al.*, 1999). The distribution of transit times is extracted directly from the tissue impulse response, as Eq. [5] leads to

$$h(t) = -\frac{dR}{dt}. \qquad [9]$$

The distribution of transit times is thus given by the slope of the residue function (or the impulse response function) and is associated with the distribution of relative flow rates by the central volume theorem (Stewart, 1894)

$$f \cdot F = \frac{V}{t} \qquad [10]$$

and by requiring

$$w(f)df = h(t)dt. \qquad [11]$$

With the assumption of all the vascular paths having equal volume, the distribution of flow rates follows from Eqs [10] and [11]:

$$w(f) = -\frac{t}{f} \cdot h(t), \qquad [12]$$

with the normalization condition

$$\int_0^\infty f \cdot w(f)df = \int_0^\infty w(f)df = 1. \qquad [13]$$

4.5 Dynamic susceptibility contrast magnetic resonance imaging in describing tissue microcirculation

4.5.1 Cerebral blood volume

At the advent of DSC MRI, CBV was the parameter of interest (Rosen *et al.*, 1989) being applied to cerebral neoplasms (Aronen *et al.*, 1992b; Aronen *et al.*, 1994; Aronen *et al.*, 2000). It describes tissue perfusion from the point of view of capillary density and is fairly straightforward to determine. Assuming, the whole amount of contrast agent passes through the region of interest during the time of measurement and each molecule is observed only once, the measured concentration time curve is an indication of the amount of contrast agent particles that have passed through the region. By calculating the area under the concentration time curve, or rather integrating the concentration time curve with respect to time, the whole amount of contrast agent that has passed through the region can be determined. This measure is an indication of the capability of the region to pass contrast agent, and thus also blood, through it. In other words, it is a measure of capillary density or microvascular blood volume.

The limits for the integration of the concentration time curve can be selected in several ways and should be optimized with respect to postprocessing time, computing requirements and depending on whether relative or absolute values are required (Paper III). In general, for tracer kinetic principles to hold only the area under the tissue first pass should be calculated excluding second and further pass effects.

CBV is determined as (Stewart, 1894; Meier and Zierler, 1954; Zierler, 1962; Zierler, 1965)

$$CBV = \kappa \frac{\int_{firstpass} C_t(\tau) d\tau}{\int_{firstpass} C_a(\tau) d\tau}, \qquad [14]$$

where κ is a scale factor accounting for the density of brain tissue and the differences in hematocrit and proportionality constant between capillaries and large vessels (Rempp *et al.*, 1994). Commonly, κ is set to 1 (Axel, 1980). As the transit of the contrast agent through the body is often rapid compared to cerebral vascular transit times, first and subsequent transits often overlap, complicating first pass area determination (Sorensen and Reimer, 2000).

4.5.2 Cerebral blood flow

Tissue perfusion is often identified with CBF. The determination of CBF is not straightforward, but requires knowledge of the arterial input function (AIF), which is inherently difficult to determine with DSC MRI. In 1996, Østergaard *et al* (Østergaard*, et al.*, 1996b; Østergaard*, et al.*, 1996c) showed that CBF could be estimated without the need for knowledge about absolute arterial concentration levels. The methodology builds on the premise that only the shape of the AIF is required and knowledge of the absolute concentration levels and the underlying vascular structure can be neglected. The studies of Østergaard *et al* (Østergaard*, et al.*, 1996b; Østergaard*, et al.*, 1996c) showed, that CBF and the tissue impulse response can be determined simultaneously and fairly independently from the underlying vascular structure by nonparametric deconvolution of a tissue concentration time curve with a non-invasively determined AIF. Although this methodology as such does not enable the determination of the absolute CBF values it has been shown to yield gray matter to white matter CBF ratios in excellent agreement with PET studies (Østergaard*, et al.*, 1996b; Østergaard*, et al.*, 1996c).

4.5.3 Contrast agent mean transit time

The time that it takes from blood to move from artery side to venous side, i.e. the time blood spends in the capillary bed, is characterized by the MTT of the contrast agent. Due to the inherent differences of MRI and nuclear medicine imaging techniques, the methodology for determining MTT as the normalized first moment of the contrast agent efflux curve can not be utilized with DSC MRI (Weisskoff *et al.*, 1993). However, utilizing the methodology to determine CBF (Østergaard*, et al.*, 1996b; Østergaard*, et al.*, 1996c), MTT can be determined by the central volume theorem as the ratio CBV:CBF (Stewart, 1894).

4.5.4 Intravoxel flow distribution and oxygen metabolism

In normal human cerebral capillaries, CBF is markedly heterogeneous (Gaehtgens, 1991; Kuschinsky and Paulson, 1992; Hudetz *et al.*, 1994). This heterogeneity of CBF is believed to be linked to tissue oxygen metabolism regulation mechanism (Kuschinsky and Paulson, 1992; Gjedde *et al.*, 1999). In states of altered cerebral hemodynamics, such as functional activation or lowered perfusion pressure due to a pathology, the flow velocities show a more homogeneous distribution (Hudetz*, et al.*, 1996; Vogel and Kuschinsky, 1996), which is believed to improve oxygen delivery (Kuschinsky and Paulson, 1992; Østergaard*, et al.*, 2000) thus providing a regulatory mechanism for the tissue to adapt to an altered hemodynamical situation. This heterogeneity of cerebral blood flow, FH, has been shown to be assessable by DSC MRI (Østergaard*, et al.*, 1999). The method is based on observing the distribution of transit times by DSC MRI and converting that to distribution of flow values (Østergaard*, et al.*, 1999) utilizing tools originally developed for describing major vessel transport and microvascular tracer retention (King*, et al.*, 1993; King*, et al.*, 1996). The FH determined by DSC MRI has been shown to confirm the heterogeneous flow distribution in normal cerebrovascular circulation (Østergaard*, et al.*, 1999) and homogenization of the flow distribution in the setting of compromised circulation in acute stroke (Østergaard*, et al.*, 2000).

5 AIMS OF THE STUDY

The study aimed to investigate the use of DWI and DSC MRI in describing human ischemic stroke. The specific aims were:

1. to determine the apparent diffusion coefficient (ADC) for normal brain structures in healthy volunteers using spin echo echo planar MRI and to determine whether the ADC varies with age, gender, or between brain hemispheres. (Paper I)

2. to determine, whether CBV, CBF, and MTT obtained using spin echo echo planar DSC MRI for normal brain structures in healthy volunteers vary with age, gender, or between brain hemispheres. (Paper II)

3. to test the robustness and specificity of four commonly used post processing methods to determine CBV and MTT by Monte Carlo simulations, with special emphasis on the discrimination between normal and hypoperfused tissue and by clinical DSC MRI studies of patients with acute ischemic stroke. (Paper III)

4. to determine whether a substantial mismatch (>50%) between reduced cerebral blood flow and DWI-based ischemic lesion, within 24 hours of the onset of symptoms predicts a substantial (>50%) growth of the infarct during the first week. (Paper IV)

5. to investigate the course of abnormal cerebral blood flow heterogeneity and compare it with the corresponding courses of CBV, CBF, and MTT during the first week on an ischemic stroke, and to investigate the ability of the perfusion indices to predict clinical scale. (Paper V)

6 MATERIALS AND METHODS

6.1 Patient and volunteer material

The patient and volunteer material utilized in the Papers are described briefly in Table 1. The study protocol was approved by the ethical committee of the Departments of Neurology and Radiology at Helsinki University Central Hospital, or the Department of Clinical Radiology at Kuopio University Hospital. The study was carried out according to the Declaration of Helsinki and the institutional guidelines. In all cases, an informed consent was obtained from the volunteer, the patient or the patient's relative prior to the study. None of the patients was treated with thrombolytic therapy nor did any of the patients receive experimental neuroprotective agents.

Table 1. Overview of patient and volunteer material.

Paper	N	Description
I	80	Volunteers, age range 22-85
II	80	Volunteers, age range 22-85
III	13	Acute stroke patients, less than 24 hours from the onset of symptoms
IV	57	Acute stroke patients, less than 24 hours from the onset of symptoms
V	10	Hypercute stroke patients, less than 6 hours from the onset of symptoms

6.2 Imaging hardware and sequences

DWI and DSC MRI were performed with clinical 1.5T MR scanners (Magnetom Vision, Siemens Medical Systems, Erlangen, Germany) at Helsinki University Central Hospital (Papers I, II, V) and at Kuopio University Hospital (Papers III and IV). DSC MRI was performed with a spin echo EPI sequence (TR 1500ms, TE 78ms, FOV 260mm, matrix 116×256). Seven slices were imaged repeatedly 40 times at 1.5 second intervals. Before the injection of contrast agent, four (Kuopio material) or seven (Helsinki material) sets of baseline images were collected. Gadopentetate dimeglumine (Magnevist, Schering AG, Berlin, Germany; 0.2 mmol/kg of body weight) was injected during the dynamic imaging into an antecubital vein at a constant speed of 5 ml/s using an MR compatible power injector (Spectris, Medrad, Pittsburgh, PA). After the injection of the contrast agent, i.v. lines were immediately flushed with a bolus of saline at the same injection rate. DWI was performed to locate the ischemic core by a spin echo EPI sequence (TR 4000ms, TE 103ms, FOV 260mm, matrix 96×128 interpolated to 256×256) obtaining 19 slices, each with a reference T2-weighted image (b value, 0s/mm2) and three diffusion weighted images with orthogonally applied diffusion gradients (b value, 1000s/mm2).

6.3 Simulation studies

In order to assess the accuracy and precision of the four integration methods in Paper III, a series of Monte Carlo simulations was performed, using realistic synthetic signal time curves with known values for CBV, MTT, CBF, residue characteristics and covering a range of SNRs typical of clinical DSC MRI patient studies.

6.4 Determination of apparent diffusion coefficient

The diffusion weighted images obtained in the three orthogonal directions were coregistered and the natural logarithms of the images were averaged to form a rotationally invariant resultant image. Linear least-squares regression was used to determine the line connecting the resultant image and the natural logarithm of the reference T2-weighted image (b=0) on a pixel-by-pixel basis. The slope of the line was identified with ADC. The calculations were performed with a commercially available software program (MatLab, Mathsoft, Natick, MA).

6.5 Determination of perfusion parameters

CBV was determined by integrating the first pass of tissue concentration time curve within each voxel with respect to time. The first pass was set to begin and end at the same time for all the pixels, i.e. the lower and upper limits of the integration of the tissue concentration time curve were set based on inspection of the whole brain concentration time curve. The lower limit was set as the point, which visually determined was the last point before the first pass of the bolus, and the upper limit as the point where concentration visually determined had the lowest value after the first pass of the bolus, but before the appearance of recirculation. In Paper III, three additional methods to determine CBV were investigated. First, the upper integration limit was extended over the whole dynamic perfusion time series. Second, a gamma-variate function (Thompson Jr and Starmer, 1964; Gobbel and Fike, 1994; Boxerman *et al.*, 1997)

$$c(t) = K(t - t_0)^{\alpha} e^{-(t-t_0)/\beta}, \quad t>t0 \qquad [15]$$

where t_0 corresponds to the tracer arrival delay, K is a constant scale factor, and α and β are arbitrary parameters describing the shape of the distribution, was fitted to the concentration time curve on a pixel-by-pixel basis and the CBV was determined as area under the fitted function (Boxerman*, et al.*, 1997)

$$CBV = K\beta^{(1+\alpha)}\Gamma(1+\alpha), \qquad [16]$$

where $\Gamma(x)$ denotes the gamma function. Third, CBV was determined as the area under the tissue impulse response function (Vonken *et al.*, 1999).

CBF was determined as the maximum value of the deconvolved tissue impulse response (Østergaard*, et al.*, 1996c).

MTT was determined through the central volume theorem (Stewart, 1894; Meier and Zierler, 1954) utilizing knowledge of CBV and CBF

$$MTT = \frac{CBV}{CBF}. \qquad [17]$$

FH was determined from the slope of the residue function as described in section 4.4. The FH in each voxel was then compared, with Kolmogorov-Smirnov test, to a reference FH describing normal flow distribution (Østergaard, *et al.*, 1999). The FH was judged abnormal in two distinct ways; if it deviated from the normal FH statistically significantly ($P<0.05$), denoted FH(05), and if it deviated from the normal FH statistically very significantly ($P<0.01$), denoted FH(01).

6.6 Region of interest analyses

In the analysis the diffusion images of the volunteer material (Paper I), 18 distinct neuroanatomic structures were selected for the analysis in each hemisphere. These structures were the frontal, parietal, temporal, occipital, and cerebellar gray matter and white matter, the caudate nucleus, the putamen, the thalamus, the internal capsule, the pons, and the CSF in the lateral ventricles (frontal horn, middle part, posterior horn). The regions of interest (ROIs) were manually drawn on the T2-weighted (b=0) images on which the structures could easily be identified. The ROIs were subsequently transferred to the corresponding ADC maps.

In the analysis of the perfusion images of the volunteer material (Paper II), 10 distinct neuroanatomic structures were selected for analysis in each hemisphere. These structures were frontal, parietal, temporal, and occipital gray and white matter, caudate nucleus and thalamus. First, T2-weighted images were used to identify the anatomic the equivalent CBV and MTT maps. Special care was taken to avoid the contamination of the white matter ROIs with the regions of leukoaraiosis. For each ROI, the surface area and the mean, SD, and range of the given values were obtained.

In the analysis of patient data (Papers III, IV, and V), the infarcted tissue was determined as the region of visually judged decreased diffusion in the average diffusion image and, to eliminate the effect of T2-shine-through, by reviewing the area in the ADC image. The hypoperfused tissue was determined in CBV, CBF, MTT, and FH maps as the region that appeared visually abnormal compared with the corresponding contralateral region. The size of the ischemic lesion and the perfusion abnormality were determined by multiplying the corresponding area by the slice thickness and assuming the interslice gap to contain a lesion or an abnormality of the same surface area as the slice above it. All the ROIs were manually drawn and the analysis was performed with commercially available image analysis software (Alice, Perceptive Systems, Inc., Boulder, CO).

7 RESULTS

7.1 Volunteer material

The mean ADC values for the main brain structures are presented in Table 2. With the exception of the lateral ventricles, the ADC values were not affected by aging. The left and right hemispheres had similar ADC values, and no sex difference was found. In normal brain, the ADC values in both gray and white matter were within a relatively narrow range. (Paper I)

No difference between the hemispheres was found, whereas significant differences between the cerebral lobes were identified in CBV, CBF, and MTT. With the exception of frontal and parietal cortical gray matter MTT, the perfusion parameters were not affected by age. Males had higher MTT and CBV than females. (Paper II)

Table 2. ADC-values for the main brain structures from 80 volunteers (Paper I). The mean ± SD are presented with the range of values.

	Cortical GM	WM	Basal ganglia	Thalamus
ADC ($x10^{-3}$ mm^2/s)	0.89 ± 0.04 (0.78–1.09)	0.70 ± 0.03 (0.62–0.79)	0.75 ± 0.03 (0.64–0.83)	0.73 ± 0.03 (0.67–0.82)

7.2 Ischemic stroke patients

Clear differences in precision and accuracy between four different methods for determination of relative as well as absolute CBV and MTT values were found. The method of determining CBV (and MTT) did not affect the visual interpretations of tissue at risk. For relative CBV and MTT measurements, typical for clinical assessment of focal pathologies, numerical integration over the whole image range was found to be optimal in terms of computational efficacy, SNR, and accuracy of relative values. However, for absolute CBV and MTT measurements, the CBV and MTT obtained as the area under the deconvolved tissue curve by SVD was found to provide the most accurate estimates. (Paper III)

In Papers IV and V, the cerebral infarct was shown to have a potential to enlarge after the first day. The size of initial CBF-DWI mismatch (within 24 hours of symptom onset) was found to roughly predict infarct growth during the first week after stroke. (Paper IV)

The sizes of the initial perfusion abnormalities (within 6 hours of symptom onset) were found to decrease in size during the first week. In the hyperacute phase and at 24hrs, the FH abnormality was shown to be larger than CBV and CBF abnormalities whereas no difference was observed at one week. In all three imaging sessions MTT was the largest perfusion abnormality. FH was shown to outperform CBV, CBF, and MTT in predicting clinical condition. In accordance with previous studies, the sizes of hyperacute FH, CBV, CBF, and MTT abnormalities were found to correlate with ischemic lesion size at 24hrs and at one week. (Paper V)

8 DISCUSSION

8.1 Diffusion weighted imaging in acute stroke

DWI is highly sensitive and specific to detect acute cerebral ischemia (Warach *et al.*, 1995; Gonzalez *et al.*, 1999) being more sensitive than computed tomography (Barber *et al.*, 1999; Gonzalez*, et al.*, 1999) and T2-weighted MRI (Lutsep *et al.*, 1997; Gonzalez*, et al.*, 1999). The ADC decreases rapidly in acute ischemia (Warach*, et al.*, 1992; Weber *et al.*, 2000; Ahlhelm *et al.*, 2002) followed by a reversal in ADC in 5 to 10 days, first returning to healthy level (Warach*, et al.*, 1995; Schwamm *et al.*, 1998; Ahlhelm*, et al.*, 2002) and subsequently rising above normal in chronic phase (Warach*, et al.*, 1992; Weber*, et al.*, 2000; Ahlhelm*, et al.*, 2002) due to cavitation and replacement of brain tissue with water in necrotic tissue. Due to the temporal evolution of the ADC values from the initially reduced values to pseudonormalization and further elevation above normal levels, DWI is especially useful in estimating the lesion age and in differentiating acute ischemic lesions from chronic ones (Marks *et al.*, 1996; Singer *et al.*, 1998; Oliveira-Filho *et al.*, 2000). Typically, an untreated ischemic infarct increases in size during the first week after the insult (Sorensen *et al.*, 1996; Baird *et al.*, 1997; Barber *et al.*, 1998; Karonen *et al.*, 1999). Further, the increase in the volume of the lesion is more pronounced between the first two days of the developing infarct than between the second day and a week (Karonen*, et al.*, 1999; Karonen *et al.*, 2000a). DWI is already a part of clinical stroke imaging in many centers (Mullins *et al.*, 2002).

Whereas the lesion visible on the acute DWI generally predicts the irreversibly damaged ischemic core, this is not always the case; reversal of the DWI lesion back to normal without any intervention has been reported (Grant *et al.*, 2001; Fiehler *et al.*, 2002a; Fiehler *et al.*, 2002b). Based on animal studies, this does not mean that the ischemic tissue would have fully recovered (Li *et al.*, 1999). The results of previous studies therefore indicate that tissue with elevated signal intensity on DWI is not necessarily infarcted, and early normalization of high signal intensity lesions does not mean that the tissue will eventually survive.

The determination of ADC requires determining at least two different diffusion weighted images with differing b-values. As there is no significant difference in the ADC estimates between using two or several b-values (Burdette *et al.*, 1998) and as in clinical imaging, the imaging time is seeked to be minimized, only two different b-values are commonly used with the other being zero to minimize the need for sampling different diffusion orientations. Utilizing EPI in DWI results in an intrinsic sensitivity to magnetic field inhomogeneities in the form of susceptibility artefact. Although, the higher field strength provides higher SNR, the rise in susceptibility artefact counteracts the benefits. However, parallel acquisition techniques, such as sensitivity encoding (Pruessmann *et al.*, 1999), reduce the sensitivity to susceptibility effects by shortening the EPI readout train and will become more important in higher field strengths.

DWI captures only an isotropic approximation of the diffusion in a voxel. Albeit, diffusion weighted images are collected in the three orthogonal main gradient directions enabling the determination of the diagonal elements and the trace of the tensor, DWI is unable to assess true diffusion anisotropy. However, water diffusion in human tissue is anisotropic and a diffusion tensor is required to describe the direction-dependency of the diffusion (Basser *et al.*, 1994). Building on the concept of DWI, diffusion tensor imaging (DTI) is a technique to map the whole diffusion tensor, including the off-diagonal elements, and thus determining the rotationally invariant description of the diffusion in a voxel. DTI is effectively able to pinpoint the directions of the highest and lowest diffusion in a voxel and can be used to map tissue structures with highly aligned microstructure such as white matter fiber tracts (Conturo *et al.*, 1999). For a more detailed investigation of tissue microstructure, e.g. fiber crossing, more advanced data collection and analysis techniques are required. Some

that have been suggested include multitensor imaging (Tuch *et al.*, 2002) and diffusion spectrum imaging and q-ball imaging (Tuch *et al.*, 2003), both of which are based on q-space methodology (Callaghan, 1993). However, the drawback of these more advanced methods is the significantly longer imaging time required to sample the data and relatively demanding analysis methodology, which have delayed the incorporation of these techniques into clinical stroke imaging.

8.2 Limitations of dynamic susceptibility contrast magnetic resonance imaging

8.2.1 Utilization of the susceptibility effect

Compartmentalization. In normal brain, the BBB keeps the contrast agent compartmentalized in the intravascular space. Especially neoplastic growth and in rare occasions also cerebrovascular disease, may affect the permeability of BBB and consequently blood and the contrast agent are able to leak into the tissue. This leakage prevents the utilization of susceptibility contrast as it is masked by the T1-effects arising from extravascular contrast agent concentration. As the blood volume in a voxel is typically very small (around 2-4%) (Fisel*, et al.*, 1991), even a small amount of leaked contrast agent is enough to effectively cancel the susceptibility effect. In practice, the leakage results in a severe miscalculation of CBV, as the signal in the tissue concentration time curve rises well above baseline and subsequently reduces the temporal integral over the curve. There are several methods to account for the increased T1 enhancement. One such method is to use a contrast agent that produces minimal T1 enhancement such as dysprosium. However, in clinical use this is an undesirable property as post-contrast T1-weighted images are routinely required. Another method to account for the T1 enhancement is to apply a predose of contrast agent saturating the interstitial space before the execution of DSC imaging. The most novel method is to simultaneously model both T1 and T2 enhancements and thus acquire the maximum amount of information from the first pass passage of the contrast agent (Weisskoff *et al.*, 1994a; Østergaard *et al.*, 1996a). The methodology is based on dividing the observed concentration into intra- and extravascular components. The intravascular component is assumed to be proportional to the vascular signal in a nonleaky reference region, which is considered as an input function for the extravascular component. This method allows the determination of the leakage-corrected CBV and additionally the permeability of vascular endothelium.

Concentration of the contrast agent. As the contrast agent concentration and T2 relaxation rate are approximately linearly dependent (Villringer*, et al.*, 1988; Rosen*, et al.*, 1990; Fisel*, et al.*, 1991; Kennan*, et al.*, 1994; Weisskoff*, et al.*, 1994b; Boxerman*, et al.*, 1995; Lev*, et al.*, 1997), the higher the contrast agent concentration the higher the signal drop during the first pass of the agent and consequently the better quality of the post processed perfusion maps (Boxerman *et al.*, 1992). The quality can be enhanced by increasing injection speed tightening the contrast agent bolus or by using a contrast agent with higher susceptibility effect, e.g. dysprosium, reducing the amount of required contrast agent (Sorensen and Reimer, 2000). It has been demonstrated that perfusion maps (CBV) produced by higher doses of contrast have better SNRs and are able to depict more detailed anatomical and pathological structures than the lower dose maps (Aronen *et al.*, 1992a; Aronen *et al.*, 1992c). The utility of CBV maps depends strongly on the on the SNR of the maps (Boxerman*, et al.*, 1997) indicating that the perfusion raw data should be collected with as high an SNR as possible. The injected dose as such does not affect gray:white CBV ratios (Lev*, et al.*, 1997). Most of the clinical studies have been performed using 0.5 molar gadolinium chelates (gadopentetate dimeglumine, gadodiamide, gadoteridol, gadolinium-DO3A, gadobenate dimeglumine, gadoversetamide) with doses of 0.1-0.2 mmol/kg body weight (Sorensen and Reimer, 2000). A 1.0 molar gadolinium chelate (gadobutrol) has been evaluated for cerebral

perfusion in a multicenter study reporting the dose 0.3 mmol/kg being optimal with gradient echo sequences at 1.0 Tesla field strength (Benner *et al.*, 2000).

Injection speed. Although, the indicator dilution theory is valid for both instantaneous and continuous injections, to obtain the concentration levels necessary for the susceptibility contrast in DSC MRI, the injection of the contrast agent has to be concise. If the injection of the tracer is slow (infusion) the T1-effects of the tracer dominate over the susceptibility effects (Villringer*, et al.*, 1988). Consequently, in DSC imaging the tracer has to be injected as a bolus. Ideally, the bolus would be infinitely short allowing the straightforward utilization of the tracer kinetic principles. However, practical constraints limit the injection speed distributing the contrast agent to a finite bolus. In practice, an automated power injection is required to maintain constant injection speed and to produce constant bolus shape (Sorensen and Reimer, 2000). The injection of a saline bolus right after the contrast agent bolus helps the passage of the contrast agent bolus to the heart and reduces the dispersion, which the bolus experiences on its passage through the vasculature. The injection rate into a peripheral vein is typically 5ml/second. The contrast-to-noise ratio of CBV maps is dependent on the contrast agent dose but not on the injection rate (Lev*, et al.*, 1997). However, when extracting information about CBF, MTT, and the characteristics of the residue function, where the identification of the arterial input function is needed, the faster injection rate may be beneficial.

Field strength. The sensitivity to susceptibility effect increases with the field strength (Villringer*, et al.*, 1988). This has direct consequences for the quality of perfusion images. First, it enables increasing the temporal sampling frequency in higher field strength by maintaining contrast agent dose. Alternatively, the contrast agent dose can be reduced to maintain the level of perfusion image quality of lower field strength. Maintaining both temporal sampling frequency and contrast agent dose, the higher field allows to decrease the noise content in the tissue concentration time curve and thus improve the accuracy of the perfusion parameter estimates.

Deconvolution technique. As DSC MRI data is inherently noisy, the method of performing the deconvolution is crucial for obtaining reliable and repeatable results. There are broadly two kinds of methods available; those that assume a function for the tissue tracer retention, the model-dependent methods, and those that do not, the model-independent methods. Østergaard et al. (Østergaard*, et al.*, 1996b; Østergaard*, et al.*, 1996c) showed that model-independent techniques yield better estimates of the underlying CBF values independent of the vascular structure with the optimal method being SVD. However, SVD has the tendency of underestimating CBF in the case of delayed tissue tracer input compared to the arterial input function as it cannot distinguish between delayed input and increased transit time (Calamante *et al.*, 2000). Even though a straight delay of tracer arrival can, in theory, be accounted for, modelless approaches cannot distinguish tracer dispersion in feeding vessels from tracer retention in capillary bed: large vessel dispersion will be interpreted as a low flow (Østergaard*, et al.*, 1996b; Østergaard*, et al.*, 1996c; Calamante*, et al.*, 2000). The use of model-independent techniques to assess tissue tracer retention eliminate the requirement of models describing vascular structure and function. Whereas the use of these kind of models allows distinguishing major vessel dispersion and microvascular retention as well as the identification of tracer arrival delays, they have to be used very carefully not to lose generality and thereby bias the determined indicators of tissue perfusion.

8.2.2 Signal acquisition

As both T2 and T2* are sensitive to susceptibility contrast, both spin and gradient echo – based pulse sequences can be used to detect it. Gradient echo sequences do not employ full

refocusing of the magnetic field inhomogeneities, and the signal loss subsequently arises directly from the microscopic susceptibility gradients that cause local changes in the resonance frequency of water protons. Spin echo sequences, however, do employ full refocusing of the magnetic field inhomogeneites, which accounts for these changes and hence appreciable signal loss is not registered but instead the signal loss in spin echo sequences is caused by the diffusion of water into areas of different local magnetic fields and is observed with long echo times. It has been demonstrated by theoretical modeling and by Monte Carlo simulations that spin echo measurements are mainly sensitive to vessels of a size similar to the water diffusion length (<20μm), whereas gradient echo measurements are less dependent on the vessel size (Fisel*, et al.*, 1991; Weisskoff*, et al.*, 1994b; Boxerman*, et al.*, 1995). Similar results have been found in human brain (Speck *et al.*, 2000). In other words, spin echo sequences are more sensitive to microvasculature than gradient echo sequences and thus provide information more closely linked with the properties of capillaries than gradient echo sequences. The drawback in spin echo sequences is their lower SNR compared with gradient echo sequences: gradient echo sequences with a dose of 0.1 mmol/kg of gadolinium-DTPA contrast agent produce a susceptibility effect (signal loss in the brain) of a magnitude approximately similar to spin echo sequences with with a dose of 0.2 mmol/kg (Aronen*, et al.*, 1992a). The inherent difference between spin and gradient echo techniques enables the determination of an index describing the difference of the two techniques. The index can be determined by a hybrid pulse sequence including alternating gradient and spin echo –based data collection during the same first pass circulation through human brain and expressed in the form of the ratio $\Delta R2^*/\Delta R2$, which serves as an indicator of vessel size (Dennie *et al.*, 1998; Donahue *et al.*, 2000).

8.2.3 Determination of the arterial input function

The AIF is a prerequisite to utilize the indicator dilution theory for determining CBF and subsequently MTT and FH. Due to inter alia the fact that microvascular and major vessel hematocrit differ in the brain due to rheologic effects (Lammertsma *et al.*, 1984), the proportionality constant relating signal and concentration is not equal for tissue and major vessels. The conversion of signal into concentration by Eq. [3] does therefore not apply for the AIF as it does for the brain parenchyma. Subsequently, the area under the curve for AIF and tissue concentration time curve cannot be directly compared. Whereas the shape of the AIF can be determined with rather good accuracy (Porkka *et al.*, 1991), the height of the function remains arbitrary and thus the size of the AIF has to be normalized to the injected dose to produce quantitative results (Axel, 1980; Rosen*, et al.*, 1990). Further, sensitivity to signal change is a function of vessel size so that the amount of signal change is not the same in large and small vessels for a given amount of gadolinium. The methodology is thus highly sensitive to the individual details of microvascular architecture (Kiselev, 2001).

The signal loss in the vicinity of a major artery arises due to dephasing of spins near a single vessel. The field gradients due to the artery, which cause spin dephasing, depend on the orientation of the vessel relative to the magnetic field and the size of the vessel, which are very difficult to measure from DSC images. The signal loss in the tissue, however, is due to dephasing of spins in field gradients produced by an essentially random distribution of blood vessels with random sizes and orientations (Boxerman*, et al.*, 1995). Consequently, in tissue voxel the orientation of a single capillary does not bias the signal from the whole voxel and a reasonable approximation for the quantitative relationship between the tissue signal and contrast agent concentration is conceivable. However, it is not possible to measure absolute concentrations of contrast agent within an artery. The long echo times optimized for tissue signal loss may cause complete signal loss at major vessels (Ellinger *et al.*, 2000). For this

reason, smaller arterial branches with partial volume effects with surrounding tissue are used to determine the shape of the arterial input function (Østergaard, *et al.*, 1996b; Østergaard, *et al.*, 1996c).

Ideally, AIF should be unique for each imaging voxel, but that is in practice not plausible. Commonly, a single AIF is selected for the whole brain (Østergaard, *et al.*, 1996b) or brain hemisphere (Thijis *et al.*, 2004). Typically, the AIF is estimated from a branch of the middle cerebral artery with the assumption, that the AIF for each individual voxel has the same characteristics and that the contrast agent reaches all parts of the brain at the same time and without significant dispersion during its passage from the major artery to the brain parenchyma. However, even in normal brain there is delay and dispersion, which in patients with cerebrovascular disease is pronounced, introducing inaccuracy in the perfusion estimates (Calamante, *et al.*, 2000). The occluded vessels themselves can contribute to a delay in the arrival time of the contrast agent and dispersion of the shape of the bolus at the imaging voxel. The CBF estimates are therefore be dependent on the site of AIF measurement (Wu *et al.*, 2003b; Thijis, *et al.*, 2004). It has been shown that when the AIF leads the tissue, CBF is underestimated independent of extent of delay, but dependent on MTT (Wu *et al.*, 2003a). Further, when the AIF lags the tissue, flow may be over- or underestimated depending on MTT and extent of timing differences (Wu, *et al.*, 2003a). There are a number of methods being developed to overcome these obstacles. A method to obtain arrival timing-insensitive flow estimates and hence a more specific indicator of ischemic injury have been introduced (Wu, *et al.*, 2003b). One possible solution to more accurately estimate the AIF is determining AIF locally for a group of voxels (Alsop *et al.*, 2002), in seeking to approximate the true input to a voxel.

8.2.4 Quantification issues

Due to problems described above, quantification of perfusion indices is not straightforward. The problems have been circumvented by assuming uniform values for hematocrite in the capillaries and large vessels (H_{artery} / $H_{capillaries}$ = 0.45/0.25), and assuming the same proportionality constant for both tissue and the arteries (Rempp, *et al.*, 1994). However, tissue hematocrite is in fact a complex function of, e.g. vessel size and physiological conditions and thus likely to be subject dependent. Alternatively, absolute values can be estimated by cross-calibration with another technique (Østergaard *et al.*, 1998a; Østergaard *et al.*, 1998b). This methodology utilizes the same technique for determining relative CBF as described above regarding only information of the shape of the AIF and neglecting the estimate for absolute arterial concentration. The area of the AIF is assumed to be proportional to the injected contrast dose and an estimate for the 'true' CBF is subsequently obtained from the measured CBF with a conversion factor. The conversion factor has been determined by comparing a sample set of DSC MRI flow values with those obtained by positron emission tomography (Østergaard, *et al.*, 1998a; Østergaard, *et al.*, 1998b). However, cross-calibration has been investigated only within young healthy subjects and the assumption that the same fraction of cardiac output reaches the brain may not hold true with aging or in pathological microcirculation. In pathophysiological condition, a correction factor based on the area of the venous output function, measured from the superior sagittal sinus has been demonstrated to provide enhanced the accuracy of the CBF estimates (Lin *et al.*, 2001). Cross-calibration thus suggests to be one of the most promising methods to quantify perfusion values by DSC MRI. Whereas the actual predictive value of DWI and DSC MRI of stroke evolution remains at the group level, these techniques already are a vital part of clinical decision making and are actively being developed to allow forming risk profiles on an individual basis.

8.3 Imaging stroke with diffusion and dynamic susceptibility contrast perfusion weighted imaging

Typically in acute stroke, a perfusion abnormality in the DSC–based images exceeds the DWI–based ischemic lesion (Sorensen*, et al.*, 1996; Barber*, et al.*, 1998; Rordorf *et al.*, 1998; Karonen*, et al.*, 1999; Sorensen *et al.*, 1999; Parsons *et al.*, 2001). The difference in size between the perfusion abnormality and the DWI –based lesion is referred to as diffusion-perfusion mismatch and is considered to be an estimate of the ischemic penumbra, tissue where the neurons are functionally silent but structurally intact and thereby potentially salvageable with recanalization (Sorensen*, et al.*, 1996; Karonen*, et al.*, 1999; Schlaug *et al.*, 1999; Karonen *et al.*, 2000b)

Combined diffusion– and perfusion–weighted imaging has been shown to be able to detect hemodynamically different subregions inside the initial perfusion abnormality (Liu *et al.*, 2000). Further it has been shown, that tissue survival may be different in these subregions and may be predicted (Liu*, et al.*, 2000). Also the detection of T1 contrast enhancement has been shown to assist in determining the age of infarct (Karonen *et al.*, 2001). Liu *et al*. have found genetic bias in the eplison 4 carriers to show enhanced infarct growth during the first week supporting the increased general vulnerability of the brain in the epsilon 4 carriers (Liu *et al.*, 2002).

Recently, the use of DSC imaging has been extended to address oxygen delivery to tissue. The methodology is based on oxygen delivery being limited by the capillary surface area and the affinity of oxygen to hemoglobin even for modest CBF values (Gjedde*, et al.*, 1999). By measuring the capillary surface area, which is determined indirectly from microvascular blood volumes, flow, and the intravoxel flow distribution, the net flow of oxygen into tissue can be predicted and estimates for oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen ($CMRO_2$) determined (Østergaard *et al.*, 2001).

Measurement of ADC combined with perfusion MRI may help distinguish different subregions in acutely hypoperfused brain (Liu *et al.*, 2003). Further, it has been shown, that the assessment of the risk of infarction is obtained with higher specificity and sensitivity with algorithms that combine acute DWI and PWI than with algorithms that use DWI or PWI individually (Wu *et al.*, 2001). This underlines the importance of utilizing both methods in the acute stroke imaging protocol. Additionally, phase-contrast MR angiography has been shown to provide complementary information to that with diffusion- and perfusion-weighted imaging in predicting the outcome of patients with acute stroke (Liu *et al.*, 2004), it is important to include angiography in the imaging protocol.

9 CONCLUSIONS

In the present study, the application of combined DWI and DSC MRI in normal aging and in ischemic stroke was evaluated. The effect of normal aging and normal brain subregional differences on the normal variation of ADC and perfusion indices were reported as well as the behavior of the sizes of DWI, CBV, CBF, MTT, and FH –based abnormalities in an untreated ischemic stroke during the first week. Further, by reporting the failure of traditional and the success of more novel methods to accurately determine CBV and MTT, the study lays ground for quantitative measures of DSC MRI indices. The main conclusions are:

1. the ADC values, determined using spin echo EPI, for normal brain structures in healthy volunteers (age range 22-85 years) are unaffected by age in normal gray and white matter, and the ADC values are not biased according to brain hemisphere or gender. (Paper I)

2. in healthy volunteers (age range 22-85 years), there is no difference between the hemispheres, whereas there are significant differences between the cerebral lobes in CBV, CBF, and MTT determined by spin echo EPI. With the exception of frontal and parietal cortical gray matter MTT, the perfusion parameters are not significantly dependent on age. Males have higher MTT and CBV than females. (Paper II)

3. the method of determining CBV (and MTT) does not affect the visual interpretations of tissue at risk. However, a method taking into account the recirculation effects of the contrast agent have to be utilized for assessing perfusion on a quantitative level. (Paper III)

4. a substantial mismatch (>50%) between initial CBF-DWI mismatch (obtained within 24 hours of symptom onset) is associated with substantial (>50%) infarct growth during the first week after stroke. (Paper IV)

5. the sizes of the initial perfusion abnormalities (within 6 hours of symptom onset) decrease in size during the first week of ischemic stroke. The mean FH abnormality is larger in size than the mean CBV and CBF abnormalities, but smaller than the mean MTT, in the hyperacute phase and at 24hrs, whereas there is no difference at one week. FH may be superior to CBV, CBF, and MTT in predicting clinical condition. (Paper V)

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REFERENCES

1. Ahlhelm F, Schneider G, Backens M, Reith W, Hagen T. Time course of the apparent diffusion coefficient after cerebral infarction. Eur Radiol 2002;12:2322-2329
2. Alsop D, C,, Wedmid A, Schlaug G. Defining a local input function for perfusion quantification with bolus contrast MRI. Tenth Scientific Meeting of the International Society of Magnetic Resonance in Medicine. Honolulu, Hawaii, 2002
3. Aronen HJ, Boxerman JL, Goldberg IE, Weisskoff RM, Belliveau JW, Provenzale JM, Vevea JM, Calder CM, Campbell TA, Brady TJ, Rosen BR. CBV mapping: Optimization of contrast dose and imaging sequences. Eleventh Annual Meeting of Society of Magnetic Resonance in Medicine. Berlin, Federal Republic of Germany, 1992a
4. Aronen HJ, Goldberg IE, Pardo F, Hochberg FH, Kennedy DN, Buchbinder BR, Belliveau JW, Weisskoff R, Cohen MS, Fischman AJ, Campbell TA, Calder CM, Brady TJ, Rosen BR. Susceptibility-contrast CBV imaging: Clinical experiences in brain tumor patients. Eleventh Annual Scientific Meeting of the Society of Magnetic Resonance in Medicine. Berlin, Federal Republic of Germany, 1992b
5. Aronen HJ, Provenzale JM, Goldberg IE, Thulborn KR, Gonzalez RG, Hochberg FH, Pardo FS, Calder CM, Campbell TA, Brady TJ, Rosen BR. Comparison of low and high dose (0.1 and 0.3 mmol/kg) gadodiamide in central nervous system lesions. Eleventh Annual Scientific Meeting and Exhibition of the Society of Magnetic Resonance in Medicine. Berlin, Federal Republic of Germany, 1992c
6. Aronen HJ, Gazit IE, Louis DN, Buchbinder BR, Pardo FS, Weisskoff RM, Harsh GR, Cosgrove GR, Halpern EF, Hochberg FH, Rosen BR. Cerebral blood volume maps of gliomas: comparison with tumor grade and histologic findings. Radiology 1994;191:41-51
7. Aronen HJ, Pardo FS, Kennedy DN, Belliveau JW, Packard SD, Hsu DW, Hochberg FH, Fishman AJ, Rosen BR. High microvascular blood volume is associated with high glucose uptake and tumor angiogenesis in human gliomas. Clin Cancer Res 2000;6:2189-2200
8. Axel L. Cerebral blood flow determination by rapid-sequence computed tomography: A theoretical analysis. Radiology 1980;137:679-686
9. Baird AE, Benfield A, Schlaug G, Siewert B, Lovblad KO, Edelman RR, Warach S. Enlargement of human cerebral ischemic lesion volumes measured by diffusion-weighted magnetic resonance imaging. Ann Neurol 1997;41:581-589
10. Barber PA, Darby DG, Desmond PM, Yang Q, Gerraty RP, Jolley D, Donnan GA, Tress BM, Davis SM. Prediction of stroke outcome with echo planar perfusion- and diffusion-weighted MRI. Neurology 1998;1998:418-426
11. Barber PA, Darby DG, Desmond PM, Gerraty RP, Yang Q, Li T, Jolley D, Donnan GA, Tress BM, Davis SM. Identification of major ischemic change. Diffusion-weighted imaging versus computed tomography. Stroke 1999;30:2059-2065
12. Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. Biophys J 1994;66:259-267
13. Beauchamp NJ Jr., Bryan RN. Acute cerebral ischemic infarction: a pathophysiologic review and radiologic perspective. AJR 1998;171:73-84
14. Belliveau JW, Rosen BR, Kantor HL, Rzedzian RR, Kennedy DN, McKinstry RC, Vevea JM, Cohen MS, Pykett IL, Brady TJ. Functional cerebral imaging by susceptibility-contrast NMR. Magn Reson Med 1990;14:538-546

15. Belliveau JW, Kennedy DN, McKinstry RC, Buchbinder BR, Weisskoff RM, Vevea JM, Cohen MS, Brady TJ, Rosen BR. Functional mapping of the human visual cortex using magnetic resonance imaging. Science 1991;254:716-719
16. Benner T, Reimer P, Erb G, Schuierer G, Heiland S, Fischer C, Geens V, Sartor K, Forsting M. Cerebral MR perfusion imaging: first clinical application of a 1 M gadolinium chelate (Gadovist 1.0) in a double-blinded randomized dose-finding study. J Magn Reson Imaging 2000;12:371-380
17. Bloch F. Nuclear induction. Phys Rev 1946;70:460-474
18. Bloch F, Hansen WW, Packard M. Nuclear induction. Phys Rev 1946;69:127
19. Bloembergen N, Purcell EM, Pound RV. Relaxation effects in nuclear magnetic resonance absorption. Phys Rev 1948;73:679-712
20. Bloembergen N. Proton relaxation times in paramagnetic solutions. J Chem Phys 1957;27:572-573
21. Boxerman JL, Weisskoff RM, Aronen HJ, Rosen BR. Signal-to-noise and tissue blood volume maps from dynamic NMR imaging studies. Eleventh Annual Scientific Meeting of the Society of Magnetic Resonance in Medicine. Berlin, Federal Republic of Germany, 1992
22. Boxerman JL, Hamberg LM, Rosen BR, Weisskoff RM. MR contrast due to intravascular magnetic susceptibility perturbations. Magn Reson Med 1995;1995:555-566
23. Boxerman JL, Rosen BR, Weisskoff RM. Signal-to-noise analysis of cerebral blood volume maps from dynamic NMR imaging studies. J Magn Reson Imaging 1997;7:528-537
24. Burdette JH, Elster AD, Ricci PE. Calculation of apparent diffusion coefficients (ADCs) in brain using two-point and six-point methods. J Comput Assist Tomogr 1998;22:792-794
25. Calamante F, Gadian DG, Connelly A. Delay and dispersion effects in dynamic susceptibility contrast MRI: simulations using singular value decomposition. Magn Reson Med 2000;44:466-473
26. Callaghan PT. Principles of nuclear magnetic resonance microscopy. Oxford University Press, Oxford, Great Britain, 1993. 516 p.
27. Carr HY, Purcell EM. Effects of diffusion on free precession in nuclear magnetic resonance experiments. Phys Rev 1954;94:630-638
28. Conturo TE, Lori NF, Cull TS, Akbudak E, Snyder AZ, Shimony JS, McKinstry RC, Burton H, Raichle ME. Tracking neuronal fiber pathways in the living human brain. Proc Natl Acad Sci U S A 1999;96:10422-10427
29. Dennie J, Mandeville JB, Boxerman JL, Packard SD, Rosen BR, Weisskoff RM. NMR imaging of changes in vascular morphology due to tumor angiogenesis. Magn Reson Med 1998;40:793-799
30. Donahue KM, Krouwer HG, Rand SD, Pathak AP, Marszalkowski CS, Censky SC, Prost RW. Utility of simultaneously acquired gradient-echo and spin-echo cerebral blood volume and morphology maps in brain tumor patients. Magn Reson Med 2000;43:845-853
31. Ellinger R, Kremser C, Schocke MFH, Kolbitsch C, Griebel J, Felber SR, Aichner FT. The impact of peak saturation of the arterial input function on quantitative evaluation of dynamic susceptibility contrast-enhanced MR studies. JCAT 2000;24:942-948
32. Fiehler J, Fiebach JB, Gass A, Hoehn M, Kucinski T, Neumann-Haefelin T, Schellinger PD, Siebler M, Villringer A, Rother J. Diffusion-weighted imaging in acute stroke--a tool of uncertain value? Cerebrovasc Dis 2002a;14:187-196

33. Fiehler J, Foth M, Kucinski T, Knab R, von Bezold M, Weiller C, Zeumer H, Rother J. Severe ADC decreases do not predict irreversible tissue damage in humans. Stroke 2002b;33:79-86
34. Fisel CR, Ackerman JL, Buxton RB, Garrido L, Belliveau JW, Rosen BR, Brady TJ. MR contrast due to microscopically heterogeneous magnetic susceptibility: Numerical simulations and applications to cerebral physiology. Magn Reson Med 1991;17:336-347
35. Gaehtgens P. Heterogeneity of capillary perfusion. Blood Vessels 1991;28:197-200
36. Ganong WF. Review of Medical Physiology. McGraw-Hill, New York, New York, 2001. 870 p.
37. Gjedde A, Høst Poulsen P, Østergaard L. On the oxygenation of hemoglobin in the human brain. Adv Exp Med Biol 1999;471:67-81
38. Gobbel GT, Fike JR. A deconvolution method for evaluating indicator-dilution curves. Phys Med Biol 1994;39:1833-1854
39. Gonzalez RG, Schaefer PW, Buonanno FS, Schwamm LH, Budzik RF, Rordorf G, Wang B, Sorensen AG, Koroshetz WJ. Diffusion-weighted MR imaging: Diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. Radiology 1999;210:155-162
40. Grant PE, He J, Halpern EF, Wu O, Schaefer PW, Schwamm LH, Budzik RF, Sorensen AG, Koroshetz WJ, Gonzalez RG. Frequency and clinical context of decreased apparent diffusion coefficient reversal in the human brain. Radiology 2001;221:43-50
41. Group TNIoNDaSr-PSS. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-1587
42. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, Schneider D, Diez-Tejedor E, Trouillas P. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. Lancet 1998;352:1245-1251
43. Hahn EL. Spin Echoes. Phys Rev 1950;80:580-594
44. Hudetz AG, Feher G, Knuese DE, Kampine JP. Erythrocyte flow heterogeneity in the cerebrocortical capillary network. Adv Exp Med Biol 1994;345:633-642
45. Hudetz AG, Feher G, Kampine JP. Heterogeneous autoregulation of cerebrocortical capillary flow: evidence for functional thoroughfare channels? Microvasc Res 1996;51:131-136
46. Karonen JO, Vanninen RL, Liu Y, Østergaard L, Kuikka JT, Nuutinen J, Vanninen EJ, Partanen PLK, Vainio PA, Korhonen K, Perkiö J, Roivainen R, Sivenius J, Aronen HJ. Combined diffusion and perfusion MRI with correlation to single-photon emission CT in acute ischemic stroke: ischemic penumbra predicts infarct growth. Stroke 1999;30:1583-1590
47. Karonen JO, Liu Y, Vanninen RL, Østergaard L, Partanen PLK, Vainio PA, Vanninen EJ, Nuutinen J, Roivainen R, Soimakallio S, Kuikka JT, Aronen HJ. Combined perfusion- and diffusion-weighted MR imaging in acute ischemic stroke during the 1st week: a longitudinal study. Radiology 2000a;217:886-894
48. Karonen JO, Nuutinen J, Kuikka JT, Vanninen EJ, Vanninen RL, Partanen PL, Vainio PA, Roivainen R, Sivenius J, Aronen HJ. Combined SPECT and diffusion-weighted MRI as a predictor of infarct growth in acute ischemic stroke. J Nucl Med 2000b;41:788-794
49. Karonen JO, Partanen PL, Vanninen RL, Vainio PA, Aronen HJ. Evolution of MR contrast enhancement patterns during the first week after acute ischemic stroke. AJNR Am J Neuroradiol 2001;22:103-111

50. Kennan RP, Zhong J, Gore JC. Intravascular susceptibility contrast mechanisms in tissues. Magn Reson Med 1994;31:9-21
51. King RB, Deussen A, Raymond GM, Bassingthwaighte JB. A vascular transport operator. Am J Physiol 1993;265:H2196-H2208
52. King RB, Raymond GM, Bassingthwaighte JB. Modeling blood flow heterogeneity. Ann Biomed Eng 1996;24:352-372
53. Kiselev VG. On the theoretical basis of perfusion measurements by dynamic susceptibility contrast MRI. Magn Reson Med 2001;46:1113-1122
54. Kroll K, Wilke N, Jerosch HM, Wang Y, Zhang Y, Bache RJ, Bassingthwaighte JB. Modeling regional myocardial flows from residue functions of an intravascular indicator. Am J Physiol 1996;271:H1643-H1655
55. Kuschinsky W, Paulson OB. Capillary circulation in the brain. Cerebrovasc Brain Metab Rev 1992;4:261-286
56. Lammertsma AA, Brooks DJ, Beaney RP, Turton DR, Kensett MJ, Heather JD, Marshall J, Jones T. In vivo measurement of regional cerebral haematocrit using positron emission tomography. J Cereb Blood Flow Metab 1984;4:317-322
57. Lassen NA, Perl W. Tracer kinetic methods in medical physiology. Raven Press, New York, New York, 1979. 189 p.
58. Lauterbur PC. Image formation by induced local interactions: Examples employing nuclear magnetic resonance. Nature 1973;242:190-191
59. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. Radiology 1986;161:401-407
60. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. Separation of diffusion and perfusion in intravoxel incoherent motion MR imaging. Radiology 1988;168:497-505
61. Lev MH, Kulke SF, Sorensen AG, Boxerman JL, Brady TJ, Rosen BR, Buchbinder BR, Weisskoff RM. Contrast-to-noise ratio in functional MRI of relative cerebral blood volume with sprodiamide injection. J Magn Reson Imaging 1997;7:523-527
62. Li F, Han SS, Tatlisumak T, Liu KF, Garcia JH, Sotak CH, Fisher M. Reversal of acute apparent diffusion coefficient abnormalities and delayed neuronal death following transient focal cerebral ischemia in rats. Ann Neurol 1999;46:333-342
63. Lin W, Celik A, Derdeyn C, An H, Lee Y, Videen T, Østergaard L, Powers WJ. Quantitative measurements of cerebral blood flow in patients with unilateral carotid artery occlusion: a PET and MR study. JMRI 2001;14:659-667
64. Liu Y, Karonen JO, Vanninen RL, Østergaard L, Roivainen R, Nuutinen J, Perkiö J, Könönen M, Hämäläinen A, Vanninen EJ, Soimakallio S, Kuikka JT, Aronen HJ. Cerebral hemodynamics in human acute ischemic stroke: a study with diffusion- and perfusion-weighted magnetic resonance imaging and SPECT. J Cereb Blood Flow Metab 2000;20:910-920
65. Liu Y, Laakso MP, Karonen JO, Vanninen RL, Nuutinen J, Soimakallio S, Aronen HJ. Apolipoprotein E polymorphism and acute ischemic stroke: a diffusion- and perfusion-weighted magnetic resonance imaging study. J Cereb Blood Flow Metab 2002;22:1336-1342
66. Liu Y, Karonen JO, Vanninen RL, Nuutinen J, Perkiö J, Vainio PA, Soimakallio S, Aronen HJ. Detecting the subregion proceeding to infarction in hypoperfused cerebral tissue: a study with diffusion and perfusion weighted MRI. Neuroradiology 2003;45:345-351
67. Liu Y, Karonen JO, Vanninen RL, Nuutinen J, Koskela A, Soimakallio S, Aronen HJ. Acute ischemic stroke: predictive value of 2D phase-contrast MR angiography - serial

study with combined diffusion and perfusion MR imaging. Radiology 2004;231:517-527
68. Lutsep H, Albers G, De Crespigny A, Kamat GN, Marks MP, Moseley M. Clinical utility of diffusion-weighted magnetic resonance imaging in the assessment of ischemic stroke. Ann Neurol 1997;41:574-580
69. Mansfield P. Multi-planar image formation using NMR spin echos. J Phys 1977;C10:L55-L58
70. Mansfield P. Real-time echo-planar imaging by NMR. Br Med Bull 1984;40:187-190
71. Marks MP, de Crespigny A, Lentz D, Enzmann DR, Albers GW, Moseley ME. Acute and chronic stroke: navigated spin-echo diffusion-weighted MR imaging. Radiology 1996;199:403-408
72. Meier P, Zierler KL. On the theory of the indicator-dilution method for measurement of blood flow and volume. J Appl Physiol 1954;6:731-744
73. Moseley ME, Cohen Y, Mintorovitch J, Chileuitt L, Shimizu H, Kucharczyk J, Wendland MF, Weinstein PR. Early detection of regional cerebral ischemia in cats: comparison of diffusion- and T2-weighted MRI and spectroscopy. Magn Reson Med 1990;14:330-346
74. Mullins ME, Schaefer PW, Sorensen AG, Halpern EF, Ay H, He J, Koroshetz WJ, Gonzalez RG. CT and conventional and diffusion-weighted MR imaging in acute stroke: study in 691 patients at presentation to the emergency department. Radiology 2002;224:353-360
75. Oliveira-Filho J, Ay H, Schaefer PW, Buonanno FS, Chang Y, Gonzalez RG, Koroshetz WJ. Diffusion-weighted magnetic resonance imaging identifies the "clinically relevant" small-penetrator infarcts. Arch Neurol 2000;57:1009-1014
76. Parsons MW, Yang Q, Barber PA, Darby DG, Desmond PM, Gerraty RP, Tress BM, Davis SM. Perfusion magnetic resonance imaging maps in hyperacute stroke. Relative cerebral blood flow most accurately identifies tissue destined to infarct. Stroke 2001;32:1581-1587
77. Porkka L, Neuder MS, Hunter G, Weisskoff RM, Belliveau JW, Rosen BR. Arterial input function measurement with MRI. Tenth Annual Meeting of the Society of Magnetic Resonance in Medicine. San Francisco, California, 1991
78. Powers WJ. Cerebral hemodynamics in ischemic cerebrovascular disease. Ann Neurol 1991;29:231-240
79. Pruessmann KP, Weiger M, Scheidegger MB, Boesiger P. SENSE: sensitivity encoding for fast MRI. Magn Reson Med 1999;42:952-962
80. Purcell EM, Torrey HC, Pound RV. Resonance absorption by nuclear magnetic moments in a solid. Phys Rev 1946;69:37-38
81. Rempp KA, Brix G, Wenz F, Becker CR, Guckel F, Lorenz WJ. Quantification of regional cerebral blood flow and volume with dynamic susceptibility contrast-enhanced MR imaging. Radiology 1994;193:637-641
82. Rordorf G, Koroshetz WJ, Copen WA, Cramer SC, Schaefer PW, Budzik RF Jr., Schwamm LH, Buonanno F, Sorensen AG, Gonzalez G. Regional ischemia and ischemic injury in patients with acute middle cerebral artery stroke as defined by early diffusion-weighted and perfusion-weighted MRI. Stroke 1998;29:939-943
83. Rosen BR, Belliveau JW, Chien D. Perfusion imaging by nuclear magnetic resonance. Magn Reson Q 1989;5:263-281
84. Rosen BR, Belliveau JW, Vevea JM, Brady TJ. Perfusion Imaging with NMR contrast agents. Magn Reson Med 1990;14:249-265
85. Rosen BR, Belliveau JW, Aronen HJ, Kennedy D, Buchbinder BR, Fischman AJ, Gruber M, Glas J, Weisskoff RM, Cohen MS, Hochberg FH, Brady TJ. Susceptibility contrast

imaging of cerebral blood volume: human experience. Magn Reson Med 1991a;22:293-299
86. Rosen BR, Belliveau JW, Buchbinder BR, McKinstry RC, Porkka LM, Kennedy DN, Neuder MS, Fisel CR, Aronen HJ, Kwong KK, Weisskoff RM, Cohen MS, Hopkins A, Brady TJ. Contrast agents and cerebral hemodynamics. Magn Reson Med 1991b;19:285-292
87. Schellinger PD, Kaste M, Hacke W. An update on thrombolytic therapy for acute stroke. Curr Opin Neurol 2004;17:69-77
88. Schlaug G, Benfield A, Baird AE, Siewert B, Lövblad KO, Parker RA, Edelman RR, Warach S. The ischemic penumbra: operationally defined by diffusion and perfusion MRI. Neurology 1999;53:1528-1537
89. Schwamm LH, Koroshetz WJ, Sorensen AG, Wang B, Copen WA, Budzik R, Rordorf G, Buonanno FS, Schaefer PW, Gonzalez RG. Time course of lesion development in patients with acute stroke: serial diffusion- and hemodynamic-weighted magnetic resonance imaging. Stroke 1998;29:2268-2276
90. Sette G, Baron JC, Mazoyer B, Levasseur M, Pappata S, Crouzel C. Local brain haemodynamics and oxygen metabolism in cerebrovascular disease. Positron emission tomography. Brain 1989;112:931-951
91. Singer MB, Chong J, Lu D, Schonewille WJ, Tuhrim S, Atlas SW. Diffusion-weighted MRI in acute subcortical infarction. Stroke 1998;29:133-136
92. Solomon I. Relaxation processes in a system of two spins. Phys Rev 1955;99:559-565
93. Sorensen AG, Buonanno FS, Gonzalez RG, Schwamm LH, Lev MH, Huang-Hellinger FR, Reese TG, Weisskoff, RM, Davis TL, Suwanwela N, Can U, Moreira JA, Copen WA, Look RB, Finklestein SP, Rosen BR, Koroshetz WJ. Hyperacute stroke: evaluation with combined multisection diffusion-weighted and hemodynamically weighted echo-planar MR imaging. Radiology 1996;199:391-401
94. Sorensen AG, Copen WA, Østergaard L, Buonanno FS, Gonzalez RG, Rordorf G, Rosen BR, Schwamm LH, Weisskoff RM, Koroshetz WJ. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow and mean transit time. Radiology 1999;210:519-527
95. Sorensen AG, Reimer P. Cerebral MR perfusion imaging: principles and current applications. Georg Thieme Verlag, Stuttgart, 2000. 152 p.
96. Speck O, Chang L, DeSilva NM, Ernst T. Perfusion MRI of the human brain with dynamic susceptibility contrast: Gradient-echo versus spin-echo techniques. J Magn Reson Imaging 2000;12:381-387
97. Stejskal EO, Tanner JE. Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient. J Chem Phys 1965;42:288-292
98. Stewart GN. Researches on the circulation time in organs and on the influences which affect it. Parts I-III. J Physiol (London) 1894;15:1-89
99. Stewart GW. On the early history of the singular value decomposition. SIAM Rev 1993;35:551-566
100. Thijis VN, Somford DM, Bammer R, Robberecht W, Moseley ME, Albers GW. Influence of arterial input function on hypoperfusion volumes measured with perfusion-weighted imaging. Stroke 2004;35:94-98
101. Thompson HK Jr., Starmer CF. Indicator transit time considered as a gamma variate. Circ Res 1964;XIV:502-515
102. Torrey HC. Bloch equations with diffusion terms. Phys Rev 1956;104:563-565
103. Tuch DS, Reese TG, Wiegell MR, Makris N, Belliveau JW, Wedeen VJ. High angular resolution diffusion imaging reveals intravoxel white matter fiber heterogeneity. Magn Reson Med 2002;48:577-582

104. Tuch DS, Reese TG, Wiegell MR, Wedeen VJ. Diffusion MRI of complex neural architecture. Neuron 2003;40:885-895
105. Warach S, Chien D, Li W, Ronthal M, Edelman RR. Fast magnetic resonance diffusion-weighted imaging of acute human stroke. Neurology 1992;42:1717-1723
106. Warach S, Gaa J, Siewert B, Wielopolski P, Edelman RR. Acute human stroke studied by whole brain echo planar diffusion-weighted magnetic resonance imaging. Ann Neurol 1995;37:231-241
107. Weber J, Mattle HP, Heid O, Remonda L, Schroth G. Diffusion-weighted imaging in ischaemic stroke: a follow-up study. Neuroradiology 2000;42:184-191
108. Wedeen VJ, Meuli RA, Edelman RR, Geller SC, Frank LR, Brady TJ, Rosen BR. Projective imaging of pulsatile flow with magnetic resonance. Science 1985;230:946-948
109. Weisskoff RM, Chesler D, Boxerman JL, Rosen BR. Pitfalls in MR measurement of tissue blood flow with intravascular tracers: Which mean transit time? Magn Reson Med 1993;29:553-558
110. Weisskoff RM, Boxerman JL, Sorensen AG, Kulke SM, Campbell TA, Rosen BR. Simultaneous blood volume and permeability mapping using a single Gd-based contrast injection. Second Meeting of the International Society of Magnetic Resonance in Medicine. San Francisco, California, 1994a
111. Weisskoff RM, Zuo CS, Boxerman JL, Rosen BR. Microscopic susceptibility variation and transverse relaxation: Theory and experiment. Magn Reson Med 1994b;31:601-610
112. Villringer A, Rosen BR, Belliveau JW, Ackerman JL, Lauffer RB, Buxton RB, Chao YS, Wedeen VJ, Brady TJ. Dynamic imaging with lanthanide chelates in normal brain: contrast due to magnetic susceptibility effects. Magn Reson Med 1988;6:164-174
113. Vogel J, Kuschinsky W. Decreased heterogeneity of capillary plasma flow in the rat whisker-barrel cortex during functional hyperemia. J Cereb Blood Flow Metab 1996;16:1300-1306
114. Vonken EPA, van Osch MJP, Bakker CJG, Viergever MA. Measurement of cerebral perfusion with dual-echo multi-slice quantitative dynamic susceptibility contrast MRI. J Magn Reson Imaging 1999;10:109-117
115. Wu O, Koroshetz WJ, Østergaard L, Buonanno FS, Copen WA, Gonzalez RG, Rordorf G, Rosen BR, Schwamm LH, Weisskoff RM, Sorensen AG. Predicting tissue outcome in acute human cerebral ischemia using combined diffusion- and perfusion-weighted MR imaging. Stroke 2001;32:933-942
116. Wu O, Østergaard L, Koroshetz WJ, Schwamm LH, O'Donnell J, Schaefer PW, Rosen BR, Weisskoff RM, Sorensen AG. Effects of tracer arrival time on flow estimates in MR perfusion-weighted imaging. Magn Reson Med 2003a;50:856-864
117. Wu O, Østergaard L, Weisskoff RM, Benner T, Rosen BR, Sorensen AG. Tracer arrival timing-insensitive technique for estimating flow in MR perfusion-weighted imaging using singular value decomposition with a block-circulant deconvolution matrix. Magn Reson Med 2003b;50:164-174
118. Zierler KL. Theoretical basis of indicator-dilution methods for measuring flow and volume. Circ Res 1962;10:393-407
119. Zierler KL. Equations for measuring blood flow by external monitoring of radioisotopes. Circ Res 1965;16:309-321
120. Østergaard L, Rabinov J, Rosen BR, Gyldensted C. Simultaneous blood flow, blood volume and blood brain barrier permeability mapping using Gd-based contrast agents.

Fourth Scientific Meeting of the International Society for Magnetic Resonance in Medicine. New York, New York, 1996a
121. Østergaard L, Sorensen AG, Kwong KK, Weisskoff RM, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part II: Experimental comparison and preliminary results. Magn Reson Med 1996b;36:726-736
122. Østergaard L, Weisskoff RM, Chesler DA, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part I: Mathematical approach and statistical analysis. Magn Reson Med 1996c;36:715-725
123. Østergaard L, Johannsen P, Høst-Poulsen P, Vestergaard-Poulsen P, Asboe H, Gee AD, Hansen SB, Cold GE, Gjedde A, Gyldensted C. Cerebral blood flow measurements by magnetic resonance imaging bolus tracking: Comparison with [15O]H20 positron emission tomography in humans. J Cereb Blood Flow Metab 1998a;18:935-940
124. Østergaard L, Smith DF, Vestergaard-Poulsen P, Hansen SB, Gee AD, Gjedde A, Gyldensted C. Absolute cerebral blood flow and blood volume measured by magnetic resonance imaging bolus tracking: Comparison with positron emission tomography values. J Cereb Blood Flow Metab 1998b;18:425-432
125. Østergaard L, Chesler DA, Weisskoff RM, Sorensen AG, Rosen BR. Modeling cerebral blood flow and flow heterogeneity from magnetic resonance residue data. J Cereb Blood Flow Metab 1999;19:690-699
126. Østergaard L, Sorensen AG, Chesler DA, Weisskoff RM, Koroshetz WJ, Wu O, Gyldensted C, Rosen BR. Combined diffusion-weighted and perfusion-weighted flow heterogeneity magnetic resonance imaging in acute stroke. Stroke 2000;31:1097-1103
127. Østergaard L, Chesler DA, Gjedde A, Wu O, Gyldensted C, Rosen BR, Sorensen A. Microscopic flow heterogeneity: Its determination by PWI and role in cerebral oxygen metabolism. Ninth Scientific Meeting of the International Society of Magnetic Resonance in Medicine. Glasgow, Scotland, 2001

APPENDIX: ORIGINAL ARTICLES