Clinical Perfusion MRI

Techniques and Applications
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PBB To Angela, Blake, Bob, and Ian, gone but not forgotten
XG To Sélène and Lou, for keeping me always on my toes
GZ To Mimi, Kenji, and Noah, with love and appreciation
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Diseases of the brain remain the largest single cause of human suffering worldwide [1], and an extraordinarily wide range of symptoms can be observed with brain ischemia, including both acute and chronic neurological and/or psychological deficits. These two facts have prompted a very long quest to better understand, observe, and quantify blood flow in the living human brain – more than a century-long quest, in fact [2]. The advent of in vivo advanced imaging techniques in humans has therefore perhaps naturally been put to use to study blood flow to the brain, and indeed all organs.

While routine imaging of the larger vessels has become relatively straightforward, with a variety of imaging methods ranging from ultrasound to X-rays and beyond to magnetic resonance imaging (MRI), the measurement of tissue-level blood flow has been more challenging. The ability to measure capillary-level blood flow, or tissue perfusion, is of perhaps greater medical importance since the cell is the critical functional entity of human biology. However, methods to measure the various parameters that characterize tissue perfusion have been frankly more challenging than the imaging of the larger vessels in living humans. A variety of methods were initially developed using radioactive tracers, including planar imaging as well as tomographic methods such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT). The fundamental principles of these methods have since been adapted for use with the currently far more widely available modalities of X-ray computed tomography (CT) and MRI.

In 1991, Belliveau and colleagues [3] at the Massachusetts General Hospital demonstrated that brain perfusion could be measured in humans with MRI using bolus injection of MR contrast agent, a technique which has become known as dynamic susceptibility contrast (DSC) MRI. This technique is a use of contrast agents that has regulatory approval at the time of this writing. Initial applications were in the brain, most notably for studying functional brain activation and the evaluation of patients with cerebrovascular disease, and this methodology is now widely used in clinical practice. The related technique of dynamic contrast-enhanced (DCE)-MRI also looks at contrast agent kinetics following bolus injection, but over a slightly slower time scale, and has found application in oncological imaging applications, perhaps most frequently in the clinical evaluation of lesions of the breast. In the early 1990s, landmark papers by Detre et al. [4, 5] demonstrated the ability to image cerebral blood flow entirely non-invasively, without the injection of an exogenous tracer, a technique now known as arterial spin labeling (ASL)-MRI. Although the utilization of this method in routine clinical neuroimaging has been somewhat less compared to DSC, perhaps because of some of the technical difficulties (now mostly overcome), the method is beginning to be used with increasing frequency. For all of these methods, the greatest volume of studies to date have been performed in the brain, with applications to other organ systems mostly still at an earlier stage of development.

In 2000, when Peter Reimer and I wrote the book Cerebral MR Perfusion Imaging: Principles and Current Applications [6], only DSC was in routine clinical use. Since then, the use of ASL, DCE, and DSC has steadily progressed, both for neuro- and non-neuro imaging applications. The current book covers these more recent advances, and gives the reader an excellent understanding of the theoretical and experimental aspects of perfusion MRI. For the clinician or researcher, in addition to a knowledge of data acquisition methods, it is of particular importance to understand the algorithms and analysis methods used to generate perfusion maps from the raw MR image data. Careful consideration of many factors is required in order to generate reproducible.
quantitative perfusion images. This book not only describes recommended acquisition and analysis procedures, but also discusses limitations and potential pitfalls that may be encountered. While not every clinical case may require quantitative measurement, without a firm grasp of the techniques and their associated strengths and weaknesses, the interpreter will ultimately be limited in their ability to draw conclusions, and hence the need for this book. Case reports at the end of the clinical chapters describe how such methods can be applied in real-life situations.

With the popularity of perfusion MRI and its ability to aid in sorting through clinical questions has come greater support from equipment manufacturers. All major equipment vendors now provide substantial support for clinical perfusion MRI, and the role of microvascular flow continues to be of critical importance, indeed increasingly appreciated importance, in many diseases. One recent example is the advent of anti-angiogenic therapy, where the need to understand tumor- and organ-level microvascular flow has taken on tremendous importance. I expect that many additional areas will emerge as we gain greater insight into human physiology, and I also expect perfusion MRI to continue to develop and mature technically. This book, therefore, is timely and needed, as it provides both clinicians and researchers with a comprehensive and state-of-the-art evaluation of perfusion MRI.

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2012

References
Blood flow is one of the most fundamental physiological parameters. Maintenance of adequate blood flow is vital for the health of biological tissue. The growth and function of many organ systems are linked tightly to their blood supply. In addition, many disease processes are associated with either increases or decreases in flow compared with normal values. The development and validation of non-invasive tools for the measurement of flow have been longstanding goals, both in biomedical research and in clinical practice.

Traditionally, the imaging of flow, or perfusion, has been accomplished using either nuclear medicine-based techniques involving radioactive isotopes, or X-ray computed tomography (CT) methods using radio-opaque contrast agents. However, soon after the introduction of magnetic resonance imaging (MRI) for anatomical imaging, research began on techniques for depicting flow. Since then, progress has been rapid, not least because MR methods have the advantage of not involving radiation, and in the case of arterial spin labeling-based techniques, are completely non-invasive. This makes them particularly appealing for use in a wide range of populations, including children and normal subjects. In addition, MR perfusion can be combined with the armamentarium of other structural, vascular, physiological, metabolic, and functional techniques available with MR to provide a comprehensive, “one-stop” examination for the patient.

Perfusion MRI is now a part of clinical practice, most notably for evaluating neurological disease. In particular, these techniques have been most developed for studying cerebrovascular disease and tumors of the central nervous system (CNS). However, perfusion MRI also has had a major impact in certain organ systems outside the CNS, including the breast, heart, and prostate. Techniques and applications continue to be developed, and over time perfusion MRI is likely to become widely used in organ systems throughout the body.

This book is divided into two major parts, the first section covering the theoretical background of the measurement of perfusion, technical aspects of dynamic susceptibility contrast (DSC) and dynamic contrast enhancement (DCE), and arterial spin labeling (ASL). Chapters are also included on its use in neuroscience (including functional MRI), and MRI methods for measuring blood volume and oxygenation. The second section contains a comprehensive review of clinical applications of perfusion MRI, in neurological diseases including stroke and brain tumors, neurodegeneration, as well as applications throughout the body (breast, heart, prostate, and other organ systems). Finally, there is a chapter dedicated to perfusion MRI in pediatrics.

This book is mainly focused on perfusion MRI in humans; however, on occasion, reference is made to preclinical studies when appropriate. However, it is not intended to be a reference work for researchers using preclinical MRI in animal models, even if many of the principles and techniques for clinical and preclinical perfusion MRI are similar. Other areas that this book does not specifically cover include vascular imaging (i.e., MR, CT, or X-ray angiography), MR perfusion using unconventional or unapproved tracers, or other non-MR methods of measuring perfusion, such as X-ray CT perfusion (CTP) or positron emission tomography (PET). These topics are beyond the scope of the current volume.

Despite the popularity of perfusion MRI in clinical use, there is currently a need for a book that covers this topic in detail. Clinical Perfusion MRI: Techniques and Applications aims to fill this gap, and to provide the reader with a comprehensive, yet readable, treatment of this topic. In a single volume, it provides clinicians with the basic knowledge needed to use this technique in their clinical practice. The widespread adoption of high-quality, clinical perfusion MRI will result in improved diagnoses and management decisions, resulting in better clinical outcomes in individual patients worldwide.
Abbreviations

AAT  arterial arrival time
aBV  arterial blood volume
ACA  anterior cerebral artery
ACE-I angiotensin-converting enzyme inhibitor
ACS  acute coronary syndrome
ACZ  acetazolamide
AD   Alzheimer’s disease
ADC  apparent diffusion coefficient
AIF  arterial input function
AMI  acute myocardial infarction
ASE  asymmetric spin echo
ASL  arterial spin labeling
ASPECTS Alberta Stroke Program Early CT Score
ATA  arterial transit artifact
ATT  arterial transit time (ms)
AUC  area under the curve (for ROC analysis)
AV   atrioventricular
BAT  bolus arrival time (ms)
BOLD blood oxygenation level-dependent contrast
BV   blood volume
CA   Contrast agent
CAD  computer-assisted diagnosis; or coronary artery disease
CAS  carotid artery stenting
CBF  cerebral blood flow (ml/100 g/min)
CBV  cerebral blood volume (ml/100 g)
cCBV  corrected cerebral blood volume (usually corrected for leakage of contrast)
CFR  cardiac flow reserve
CHD  congenital heart disease
CMRO2  Cerebral metabolic rate of oxygen consumption (mmol O2/100 g/min)
CNR  contrast-to-noise ratio
CNS  central nervous system
COMI  cerebral oxygen metabolic index
CPP  cerebral perfusion pressure (mmHg)
CS   coronary sinus
CT   computed tomography
CTA  CT angiography
CTA  Computed tomography angiography
CTC  contrast concentration versus time curve
CTP  CT perfusion
CXA  coronary X-ray angiography
DCE  dynamic contrast enhancement
dHb  deoxyhemoglobin
DMN  Default mode network
DNP  Dynamic nuclear polarization
DSA  digital subtraction angiography
DSC  dynamic susceptibility contrast
DWI  diffusion-weighted imaging
EBCT  electron beam CT
EBRT  external beam radiation therapy
ECG  electrocardiogram
EES  extravascular extracellular space
EPI  echo-planar imaging
EPSTAR EPI-based signal targeting by alternating radiofrequency pulses, an early pulsed ASL sequence
FA   flip angle
FAIR  flow alternating inversion recovery, one of the early pulsed ASL sequences
fMRI  functional MRI
FSE  fast spin echo
FSL  Functional magnetic resonance imaging of the brain Software Library, a freeware post-processing imaging toolkit from the University of Oxford
FTD  frontotemporal dementia
FTLD  Frontotemporal lobar degeneration
GABA gamma-aminobutyric acid, an inhibitory neurotransmitter
GE   gradient echo
GESSE gradient echo sampling under the spin echo
GFR  glomerular filtration rate
GM   gray matter
GRASE gradient and spin echo
GRE  gradient echo
HbO2  oxyhemoglobin
Hct  hematocrit
HHT  hereditary hemorrhagic telangiectasia
HII  hypoxic-ischemic insult
ICA  internal carotid artery
ICDs  implanted cardioverter-defibrillators
ICV  intracranial volume (cm³)
IVD  ischemic vascular dementia
JPA  juvenile pilocytic astrocytoma
Ktrans  Forward rate constant for transfer of a contrast agent between the vascular and extravascular space
LGE  late gadolinium enhancement, a marker of dead tissue on cardiac MR
LV   left ventricular
MACE major adverse cardiac events
MAGIC multiple acquisitions with global inversion cycling
MCA  middle cerebral artery
MCI  mild cognitive impairment
MDCT  multi-detector CT
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>MEG</td>
<td>magnetoencephalography</td>
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<tr>
<td>MEGESE</td>
<td>multi-echo gradient echo/spin echo</td>
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<tr>
<td>MION</td>
<td>monocristalline iron oxide nanoparticles, a type of USPIO</td>
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<tr>
<td>MTR</td>
<td>maximum intensity change per unit time interval ratio</td>
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<td>MRA</td>
<td>magnetic resonance angiogram</td>
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<tr>
<td>mRS</td>
<td>modified Rankin score</td>
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<td>MRS</td>
<td>magnetic resonance spectroscopy</td>
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<tr>
<td>MRV</td>
<td>magnetic resonance venography</td>
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<tr>
<td>MT</td>
<td>magnetization transfer</td>
</tr>
<tr>
<td>MTT</td>
<td>mean transit time (in seconds)</td>
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<tr>
<td>NAC</td>
<td>neo adjuvant chemotherapy</td>
</tr>
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<td>NASCET</td>
<td>North American Symptomatic Carotid Endarterectomy Trial, from which a standard grading system for arterial stenosis has been derived</td>
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<tr>
<td>NPV</td>
<td>negative predictive value</td>
</tr>
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<td>NSF</td>
<td>nephrogenic systemic fibrosis</td>
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<tr>
<td>PASL</td>
<td>pulsed arterial spin labeling</td>
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<tr>
<td>PC</td>
<td>phase contrast</td>
</tr>
<tr>
<td>PCA</td>
<td>posterior cerebral artery</td>
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<tr>
<td>pCASL</td>
<td>pseudo-continuous ASL, sometimes also called pulsed-continuous ASL</td>
</tr>
<tr>
<td>PCI</td>
<td>percutaneous coronary intervention (angioplasty and stent placement)</td>
</tr>
<tr>
<td>pCT</td>
<td>perfusion CT</td>
</tr>
<tr>
<td>PE</td>
<td>pulmonary embolism</td>
</tr>
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<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PFS</td>
<td>progression-free survival</td>
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<tr>
<td>PH</td>
<td>peak height</td>
</tr>
<tr>
<td>PIVORE</td>
<td>Proximal inversion with a control for off-resonance effect</td>
</tr>
<tr>
<td>PK</td>
<td>pharmacokinetic</td>
</tr>
<tr>
<td>PLD</td>
<td>post-label delay (in seconds), used primarily for continuous or pseudo-continuous ASL sequences</td>
</tr>
<tr>
<td>PNET</td>
<td>primitive neuroectodermal tumor</td>
</tr>
<tr>
<td>PPV</td>
<td>positive predictive value</td>
</tr>
<tr>
<td>PS</td>
<td>permeability surface area product</td>
</tr>
<tr>
<td>PSR</td>
<td>percentage of signal recovery (in bolus DSC)</td>
</tr>
<tr>
<td>PVL</td>
<td>periventricular leukomalacia</td>
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<tr>
<td>PWI</td>
<td>perfusion-weighted imaging</td>
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<tr>
<td>Q2TIPS</td>
<td>Second version of quantitative imaging of perfusion by using single subtraction with addition of thin-section periodic saturation after inversion and time delay</td>
</tr>
<tr>
<td>qBOLD</td>
<td>quantitative blood oxygenation level-dependent contrast</td>
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<td>QSM</td>
<td>quantitative susceptibility mapping</td>
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<tr>
<td>QUASAR</td>
<td>Quantitative signal targeting by alternating radiofrequency labeling of arterial regions, a multi-delay ASL sequence</td>
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<td>QUIPSS I</td>
<td>Quantitative Imaging of Perfusion using a Single Subtraction method I</td>
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<td>QUIPSS II</td>
<td>Quantitative Imaging of Perfusion using a Single Subtraction method II</td>
</tr>
<tr>
<td>QUIXOTIC</td>
<td>Quantitative Imaging of Extraction of Oxygen and Tissue Consumption</td>
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<tr>
<td>R(t)</td>
<td>Residue function, or fraction of tracer remaining in the voxel following an infinitely sharp bolus</td>
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<tr>
<td>R2</td>
<td>1/T2, Relaxivity rate for spin echo experiments</td>
</tr>
<tr>
<td>R2*</td>
<td>1/T2*, Relaxivity rate for gradient echo experiments</td>
</tr>
<tr>
<td>RAS</td>
<td>renal artery stenosis</td>
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<tr>
<td>RCC</td>
<td>renal cell carcinoma</td>
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<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumors</td>
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<tr>
<td>ROC</td>
<td>receiver operator characteristic</td>
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<tr>
<td>ROI</td>
<td>region of interest</td>
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<tr>
<td>rs-MRI</td>
<td>resting state functional MRI</td>
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<tr>
<td>RVD</td>
<td>renovascular disease</td>
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<tr>
<td>SAGE</td>
<td>Spin and gradient echo</td>
</tr>
<tr>
<td>SAR</td>
<td>specific absorption rate</td>
</tr>
<tr>
<td>SE</td>
<td>spin echo</td>
</tr>
<tr>
<td>SI</td>
<td>signal intensity</td>
</tr>
<tr>
<td>SNR</td>
<td>signal-to-noise ratio</td>
</tr>
<tr>
<td>SPECT</td>
<td>single photon emission computed tomography</td>
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<tr>
<td>SPM</td>
<td>Statistical Parameter Mapping, a freeware software program that runs within Matlab, from the University College of London</td>
</tr>
<tr>
<td>SSFP</td>
<td>steady-state free precession, a method of image readout</td>
</tr>
<tr>
<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
</tr>
<tr>
<td>SVD</td>
<td>singular value decomposition, a popular method of performing deconvolution</td>
</tr>
<tr>
<td>SWI</td>
<td>susceptibility-weighted imaging</td>
</tr>
<tr>
<td>TDL</td>
<td>tumefactive demyelinating lesion</td>
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<tr>
<td>TE</td>
<td>echo time</td>
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<tr>
<td>TEE</td>
<td>transthoracic echocardiogram</td>
</tr>
<tr>
<td>THM</td>
<td>tissue homogeneity model</td>
</tr>
<tr>
<td>TI</td>
<td>inversion time or delay (in pulsed ASL)</td>
</tr>
<tr>
<td>Tmax</td>
<td>normalized bolus delay (in seconds)</td>
</tr>
<tr>
<td>TR</td>
<td>repetition time</td>
</tr>
<tr>
<td>TRUST</td>
<td>T2 relaxation under spin tagging</td>
</tr>
<tr>
<td>TTE</td>
<td>transthoracic echocardiogram</td>
</tr>
<tr>
<td>USPIO</td>
<td>ultrasmall superparamagnetic iron oxide</td>
</tr>
<tr>
<td>V/Q scan</td>
<td>ventilation perfusion scan, used in the lung to diagnose pulmonary emboli</td>
</tr>
<tr>
<td>VASO</td>
<td>vascular space occupancy</td>
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<tr>
<td>vCBV</td>
<td>venous CBV</td>
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<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>Venc</td>
<td>velocity-encoding level, used for phase contrast angiography</td>
</tr>
<tr>
<td>VOI</td>
<td>venous output function</td>
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<tr>
<td>VS-ASL</td>
<td>velocity-selective ASL</td>
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<tr>
<td>WHO</td>
<td>World Health Organization, a grading system for brain tumors</td>
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<tr>
<td>WM</td>
<td>White matter</td>
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<td>WML</td>
<td>White matter lesions</td>
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<td>Xe-CT</td>
<td>Xenon-enhanced CT</td>
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<tr>
<td>Y0</td>
<td>tissue oxygen saturation (%)</td>
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