Imaging the Kidney using Magnetic Resonance Techniques: Structure to Function

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Abstract

Purpose of review

Magnetic resonance imaging (MRI) offers the possibility to non-invasively assess both the structure and function of the kidney in a single MR scan session. This review summarises recent advancements in functional renal MRI techniques, with a particular focus on their clinical relevance.

Recent findings

A number of MRI techniques have been developed that provide non-invasive measures of relevance to the pathophysiology of kidney disease. Diffusion-weighted imaging (DWI) has been used in chronic kidney disease (CKD) and renal transplantation, and appears promising as a measure of renal impairment and fibrosis. Longitudinal relaxation time (T_1) mapping has been utilised in cardiac MRI to measure fibrosis and oedema; recent work suggests its potential for assessment of the kidney. Blood oxygen level dependent (BOLD) MRI to measure renal oxygenation has been extensively studied, but a number of other factors affect results making it hard to draw definite conclusions as to its utility as an independent measure. Phase contrast and arterial spin labelling (ASL) can measure renal artery blood flow and renal perfusion respectively without exogenous contrast, in contrast to dynamic contrast enhanced (DCE) studies. Current data on clinical use of such functional renal MR measures is largely restricted to cross-sectional studies.

Summary

Renal MRI has seen significant recent interest and advances. Current evidence demonstrates its potential, and next steps include wider evaluation of its clinical application.

Keywords: Magnetic resonance imaging, diffusion-weighted imaging, diffusion-tensor imaging, blood oxygen level dependent MRI, arterial spin labelling, dynamic contrast enhanced MRI, chronic kidney disease, acute kidney injury, transplantation

Introduction

In comparison to other specialities, advances in imaging techniques have been slow to translate in clinical nephrology. The potential of computerised tomography and magnetic resonance imaging (MRI) to provide improved structural characterisation of the kidneys has long been appreciated. However, these modalities are used relatively infrequently outside of specific indications such as renovascular disease. Renal MRI in particular is an area of immense promise and there have been considerable recent advances, as previously summarised [1]; the combination of highly detailed structural images combined with functional assessment of the kidney is particularly compelling (illustrated in Figure 1). In this review, we aim to summarise important recent developments in functional renal MRI, with a particular focus on potential clinical applications.

Detection of fibrosis

Renal fibrosis can result from acute or chronic renal injury, and it is the degree of interstitial fibrosis and tubular atrophy that is often the most important determinant of long-term renal outcome [2]. Non-invasive characterisation of fibrosis on a whole kidney basis would have significant utility in characterising severity of disease, assessing recovery and informing prognosis. A number of MR techniques show promise in this area.

Diffusion-weighted MRI

Diffusion-weighted MRI (DWI) assesses Brownian motion of water within tissues, quantified by the apparent diffusion coefficient (ADC). Microstructural barriers, which differ depending on tissue composition, determine ADC. ADC may also be affected by factors such as tubular flow and capillary perfusion, which can be better distinguished using the intravoxel incoherent motion (IVIM) model to quantify pure diffusion (ADC_D). Diffusion tensor imaging (DTI) can assess the directionality of movement of water molecules, which provides information regarding the structural homogeneity of

tissues and is quantified by fractional anisotropy (FA). As an example, greater structural homogeneity arises from the linear arrangement of medullary tubules.

A number of studies have used these techniques in patients with chronic kidney disease (CKD), and compared MRI measurements with renal function and renal biopsy. Li *et al* studied 12 healthy volunteers and 71 patients with CKD (all with chronic glomerulonephritis, GN) who had renal DWI within 10 days of renal biopsy [3]. Patients had glomerular filtration rate (GFR) measured using isotope renography. More severe histological changes on renal biopsy correlated with lower ADC values. However ADC values did not significantly correlate with GFR or serum creatinine concentration, and the usefulness of ADC values in differentiating renal pathology types was limited. Similar findings were reported by Zhao *et al*, but in their study of 35 patients with CKD (25 who had renal biopsies showing chronic GN), GFR and renal biopsy fibrosis scores did correlate with ADC [4]. Using DTI, a lower FA has been shown to be associated with the magnitude of GFR reduction and degree of fibrosis on renal biopsy in patients with GN (CKD stage 1-3), although there was less clear separation of FA values between CKD stages as compared to ADC values [5]. It should be noted that the varying methods and grading systems to describe histological changes, as well as the choice of DWI b-values and directions, raise some concerns about comparisons across studies.

A recent patient study applied DWI and DTI in 64 patients within two weeks of renal transplantation (33 with immediate graft function, 31 with delayed graft function, DGF) [6]. 26 of these patients had transplant biopsies that were carefully analysed to quantify fibrosis, inflammation and oedema. In those patients with DGF, ADC in the transplant was significantly lower in the cortex and medulla, and FA lower in the medulla only (it was suggested that the ability of DTI to detect changes in the medulla but not the cortex reflected the greater structural homogeneity of the medulla). In those who had biopsies, both ADC and FA correlated positively with estimated GFR (eGFR) and inversely with degree of fibrosis, but interestingly a number of histological changes (inflammation, tubular injury score, capillary density, amount of oedema) had no relationship to ADC or FA. This suggests that not only may ADC and FA be good non-invasive measures for fibrosis, but that these measures cannot

differentiate between acute tubular injury and acute rejection. These data go some way to informing the mechanisms by which ADC and FA are reduced, implying increased cellular density and collagen as a direct effect of fibrosis may be more important than changes in tubular function/flow or capillary perfusion.

Although there remain some knowledge gaps, particularly as to whether ADC or FA can inform long term prognosis and whether findings of current studies are applicable to aetiologies of CKD other than GN, taken together these studies suggest that DWI has a potential role in assessing degree of renal fibrosis.

T_1-mapping

The assessment of the longitudinal (T_1) relaxation time of tissue may provide an assessment of either fibrosis (due to association of collagen with supersaturated hydrogel) or inflammation (interstitial oedema, cellular swelling) [7]. T_1 values have been shown to correlate well with fibrosis and oedema in cardiac [8] and liver imaging [9]. In an animal model of acute kidney injury (AKI) induced by 30min or 45min of ischaemia followed by reperfusion, Hueper *et al* demonstrated that the T_1 relaxation time of renal tissue increased significantly at days 1 and 7, and was associated with renal inflammation [10]. At day 28, medullary and cortical tissue T_1 returned towards baseline values in milder AKI, but remained abnormal in the more severely affected animals, correlating with persistent inflammation and tubular injury scores. Changes in tissue T_1 at day 7 appeared to predict subsequent loss of kidney volume (as a marker of chronic damage) whereas histological changes did not. Whilst these results suggest the promise of early characterisation of AKI severity and prognosis, the method of inducing AKI in animal models is far removed from clinical AKI, and human studies are now needed. In a study of cardiorenal syndrome, Breidthardt *et al* showed that chronic parenchymal damage, as indicated by prolonged T_1 relaxation, appears to underlie chronic cardiorenal syndrome rather than decreased perfusion [11].

Renal oxygenation

Blood oxygen level dependent (BOLD) MRI

Hypoxia has been implicated as a key process in the progression and failed recovery of many forms of acute and chronic kidney disease [12, 13]. The emergence of BOLD-MRI, which can provide an indication of tissue oxygenation, has therefore stimulated much interest. BOLD-MRI is relatively simple to implement, utilising the paramagnetic affect that deoxyhaemoglobin exerts to shorten the transverse relaxation time constant (T_2*), which is also expressed as R_2* (1/T2*). Higher R_2* (or lower T_2*) is an indicator of lower tissue oxygenation (pO_2). Due to their relative positions on the oxygen dissociation curve, BOLD-MRI is more sensitive at detecting changes in medullary as compared to cortical pO_2.

Despite the sometimes-demonstrated sensitivity of BOLD-MRI in animal models and healthy volunteers, clinical studies have produced inconsistent results. The large number of studies in CKD, diabetic nephropathy and kidney transplantation, with some animal studies of AKI, are summarised in a comprehensive review by Neugarten and Golestaneh [14]. Whereas some investigators have reported a reduction in oxygenation in CKD, a more recent study by Pruijm *et al* which compared healthy controls (n=45), CKD patients (n=95) and treated hypertensives (n=58) found no differences in cortical or medullary R_2* between groups [15]. On giving a furosemide injection, medullary oxygenation increased in the healthy volunteers (a reduction in oxygen consumption results from inhibition of sodium transport in the ascending limb of the loop of Henlé) with a slight and significant attenuation in this response in the hypertensive and CKD groups respectively. Whilst these results may point away from hypoxia playing an important role in CKD, other explanations exist including BOLD-MRI being too insensitive (particularly as it is an indirect qualitative method which may be inaccurate if there is heterogeneity in blood flow, oxygen delivery and consumption across the cortex and medulla) or that it is an attenuated response to increased oxygen demand as opposed to differences in baseline oxygenation that are important. Overall, the striking differences in results from studies make it difficult to draw firm conclusions. In part these differences may reflect issues related to both

the origin and analysis of BOLD-MRI data, combined with a number of clinical factors that may affect BOLD-MRI image intensity other than oxygenation, such as hydration status, age, haematocrit, dietary sodium, pH or even body temperature [1, 14]. Pohlmann *et al* demonstrated that T_2* qualitatively mirrors changes in renal tissue pO_2 but is also associated with confounding factors including vascular volume fraction and tubular volume fraction [16]. At present, additional technical advances to unravel these links are required before the quantitative capabilities of BOLD-MRI can be integrated to clinical practice, as evidenced by the failure of BOLD-MRI to discriminate between different stages of chronic kidney disease in 280 undifferentiated CKD patients [17]. For example, quantitative susceptibility mapping (QSM) is very sensitive to microstructure and chemical composition and can spatially resolve the source of the signal change in BOLD MRI [18].

T_2-Relaxation Under Spin Tagging (TRUST)

The relationship between the R_2 tissue relaxation rate and oxygen saturation can be used to quantify the oxygen dependence of an organ or tissue. Using a method of T_2–relaxation-under-spin-tagging (TRUST) MRI it is possible to enhance separation of the blood and tissue signal. In the brain, combining this with measures of blood flow allows the global metabolic rate of oxygen to be calculated [19]. Theoretically, it should be possible to apply the same methods to assess renal oxygen metabolism ($RMRO_2$), providing an alternative to BOLD-MRI. Alternatively, recent studies have described the use of 2D multi-echo gradient and spin echo (MEGSE) or triple echo asymmetric spin echo (ASE), combined with Arterial Spin Labeling (ASL) to form spatial maps of $RMRO_2$ [20]. To our knowledge, there are no clinical studies in this area at present.

Measuring blood flow and perfusion

Changes in large vessel flow as well as changes in tissue perfusion at the capillary level have relevance to a number of different renal diseases, but importantly may also provide insights into efficacy of therapies. Measurement of renal perfusion can be separated into those techniques that require

exogenous contrast agents (dynamic contrast enhanced (DCE) MRI) and those that do not (arterial spin labelling (ASL)).

Phase contrast MRI

Phase contrast (PC-MRI) is the current standard for the measurement of renal blood flow (RBF) in the renal artery and veins. PC-MRI uses the velocity-induced phase changes of moving blood to quantify blood flow. Apart from in patients with significant anatomical variations, this technique has been shown to correlate well with a number of alternative measures of renal blood flow [21]. In 11 patients with CKD (mean creatinine 215±78μmol/l) PC-MRI was used to measure RBF, and showed good reproducibility (coefficient of variation (CoV) of 12.9%), with RBF being significantly lower in CKD patients as compared with healthy volunteers [22]. Interestingly, the reproducibility of BOLD-MRI was better in the same cohort of patients (CoV of 8.0 %). Prowle *et al* demonstrated that it was possible to use PC-MRI to measure renal blood flow in 10 critically ill patients with AKI and sepsis. As compared to healthy volunteers, blood flow was reduced [23]. These pilot studies pave the way for additional research to understand changes in RBF across the evolution of acute and chronic kidney diseases and how this contributes to different pathologies, as well as assessing changes in RBF in response to therapy. Importantly, PC-MRI can also be applied in the aorta to provide a contemporaneous measurement of cardiac output, allowing assessment of RBF alongside systemic haemodynamics and cardiac function.

Arterial spin labelling

Arterial Spin Labelling (ASL) uses magnetically labelled water protons in blood that act as a diffusible tracer, providing an alternative to exogenous intravenous contrast. Tissue perfusion is determined by subtracting control images (no labelling applied to arterial blood) from the labelled image (radiofrequency magnetic labelling). Animal studies have shown that ASL can detect changes in renal perfusion commensurate with the degree of induced ischaemia, which correlate with histological

damage and change in renal function [24]. A number of recent studies have employed ASL in the assessment of kidney disease. In two separate studies, Rossi and Tan both used ASL to compare CKD patients (n=9 and n=5 respectively) with healthy volunteers and found that cortical perfusion levels were lower in CKD [25, 26]. ASL has also been used in AKI; Dong *et al* reported a reduction in both cortical and medullary perfusion in a group of 11 patients with AKI mostly due to intrinsic renal disease [27]. Although the first human study in AKI, the clinical description of the AKI episodes was limited with lack of clarity around timing of MRI with respect to onset or peak of AKI, severity of AKI and baseline CKD status. Furthermore the cross-sectional nature of the study obscured the relationship between ASL measurements and renal recovery. In renal transplant patients, Heusch *et al* employed ASL in a heterogeneous group of 98 renal transplant patients who underwent MRI-ASL between 3 days to 11 years after renal transplantation [28]. Despite the wide variation in patient selection, the results demonstrated that renal perfusion was lower in those patients with lower eGFR values. Importantly, this is one of the few studies with prospective follow up of at least six months. 12 patients, all of whom had reduced eGFR at baseline, subsequently had graft loss (due to a variety of reasons) and these patients had significantly lower baseline ASL measurements as compared to those patients with a baseline eGFR <30ml/min/1.73m^2 who had stable transplant function. Despite this, it was difficult to assess how much ASL-MRI contributed to individual risk stratification because it wasn't clear if there were other differences in clinical parameters or baseline eGFR levels between the patients with and without graft loss. Similar associations between a reduction in perfusion and GFR have been shown in a cross-sectional study of 62 renal transplant patients [29]. Finally, a study from our centre demonstrated the potential of MRI to assess response to treatment. Multiphase ASL was used to measure changes in renal perfusion in healthy volunteers in response to two different colloid fluid regimens [30].

It is promising that the clinical studies employing ASL have so far produced relatively consistent results and the technique has great potential. However, there are still technical considerations that need to be addressed before ASL can become more widely utilised, including the variation in ASL acquisition

schemes that may prevent comparison between different techniques and between different MRI platforms, differences in post processing and complex analysis requirements.

Dynamic contrast enhanced MRI

Dynamic contrast enhanced (DCE) MRI can be used to determine renal perfusion and provide a direct measure of GFR but requires administration of an exogenous contrast agent. Zollner *et al* investigated the results of different pharmacokinetic models in a quantitative analysis of renal blood flow (RBF) and GFR in an animal model of AKI using deconvolution analysis and a two-compartment renal filtration model [31]. Significant differences between control and AKI animals were detected by functional parameters (GFR and RBF), suggesting this technique is useful to determine renal damage as evidenced by spatially resolved abnormal changes in renal tissue.

Opinion is still divided as to the extent to which these techniques should be utilised in patients with impaired renal function in view of the association of gadolinium and nephrogenic systemic fibrosis. Recent studies are therefore limited to those patients with less severe reductions in eGFR and are less numerous as compared to those employing ASL techniques. Woodard *et al* used a DCE-MRI method that they had previously developed to automatically estimate the volume of cortex, medulla, collecting system, fat, and fibrosis based on the patterns of tissue enhancement following gadolinium administration [32]. From a larger population study of the elderly in Iceland, 493 patients with an eGFR >30ml/min/1.73m^2 were randomly selected of whom 40% had CKD. Total and segmental (cortical and medullary) volumes correlated with eGFR and albuminuria, and after adjustment for these factors DCE-MRI measurements associated with a number of risk factors for CKD progression. Although prospective data are still required, the authors concluded that this automated methodology could add to the assessment of patients with CKD and would be easily translated onto clinical scanners. However, the reluctance to use DCE-MRI in patients with more advanced CKD may limit generalisability.

Challenges and next steps

A number of challenges remain prior to functional renal MRI techniques becoming commonplace in the clinical environment. Some are technical barriers to their development and translation. Many of the newer MRI techniques (such as ASL and T_1 mapping) are currently performed only in dedicated research centres due to the need for specialized scan sequences, intensive post-processing, or highly specialised support and in-house development. Some of the methodologies are not standardised and it is difficult to compare results from different centres. Solutions to this require a degree of unification in acquisition and processing across centres and across different MR platforms. Alongside this, collaborative infrastructure development for multicentre studies is needed around scan capabilities, data handling, quality assurance, processing and analysis. Collaboration with manufacturers will also be key for the development of improved technology, such as the use of higher field strength MR scanners to move renal imaging from 3 Tesla to 7 Tesla to obtain significant improvements in signal-to-noise ratio and spatial resolution [33], or in vivo sodium (^{23}Na) MRI of the kidneys [34].

Secondly, there is a clear need to design and deliver clinically led studies that incorporate prospective follow up, so we can build on the existing evidence base that mostly comprises cross-sectional studies with relatively small patient numbers. There is a challenge to demonstrate how renal MRI can used to improve diagnosis, assist prognosis and assess response to therapies in patients with different forms of kidney disease.

Finally, we propose that the strength of renal MRI lies in the potential to deliver multi-parametric image acquisition, to simultaneously assess structure, function, blood flow perfusion and fibrosis. By doing so, not only is an inclusive assessment of the kidney made but different functional techniques may provide complementary information to address some of the technical issues when performed in isolation. To illustrate this, one of our current studies evaluating MRI in patients with CKD is utilising structural images, angiography, phase contrast, arterial spin labelling, BOLD-MRI, DWI and DTI within a one hour scan protocol, relating MR results to histology, measured GFR and progression of CKD over the subsequent one year (Figure 2).

Conclusion

The recent, exciting advances in renal MRI illustrate that complimentary measures of kidney structure and function are now possible within a single MR scan session that may provide unparalleled insights into the pathophysiology of renal disease in man. The techniques must now be tested in clinically led studies that demonstrate the value of this approach to clinicians; this will be essential prior to translation to clinical practice.

Key points

- A number of functional MRI techniques have been developed for the kidney
- It is possible to measure renal artery blood flow, renal perfusion, oxygenation and surrogates of fibrosis/inflammation non-invasively and without contrast agents
- Current data show potential value of these measurements in cross-sectional studies in CKD, AKI and renal transplantation
- Next steps include studies to demonstrate clinical application and utility of these techniques

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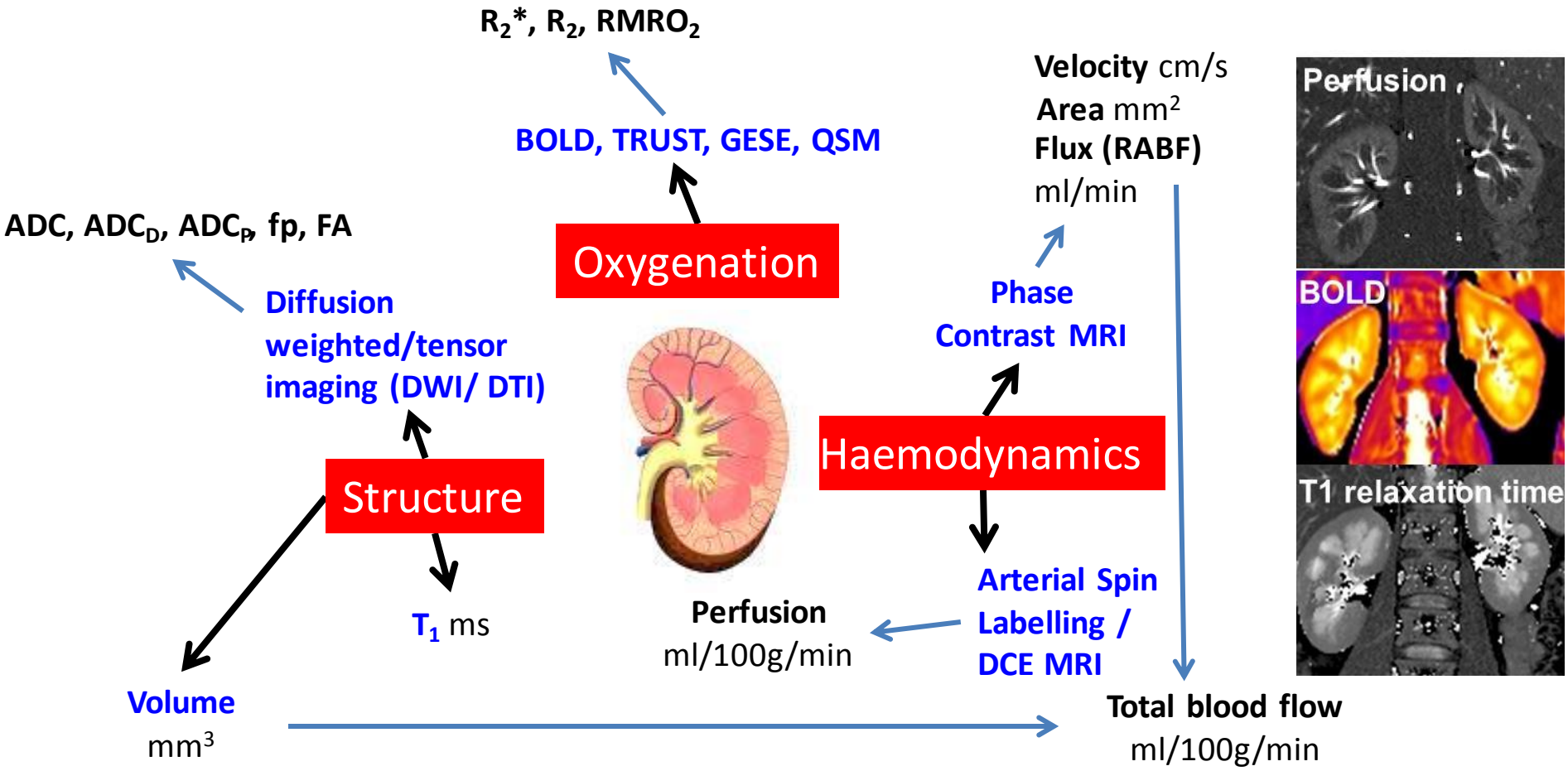
R_2*, R_2, $RMRO_2$
BOLD, TRUST, GESE, QSM
Oxygenation
ADC, ADC_D, ADC_P, fp, FA
Diffusion weighted/tensor imaging (DWI/ DTI)
Structure
T_1 ms
Volume mm^3
Velocity cm/s
Area mm^2
Flux (RABF) ml/min
Phase Contrast MRI
Haemodynamics
Arterial Spin Labelling / DCE MRI
Perfusion ml/100g/min
Total blood flow ml/100g/min
Perfusion
BOLD
T1 relaxation time