Perfusion Imaging

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Introduction

Perfusion is generally characterized by the blood flow (in the capillary bed) in milliliter per minute per gram tissue. Perfusion is commonly used as a surrogate metric to measure the rate at which oxygen and glucose is transported to the tissue of interest so that its metabolism and function can be obtained. Different tissues demonstrate a different degree of sensitivity to changes in blood supply, of which neuronal tissue, the bowel, and the myocardium are the tissues reacting most sensitively to a sudden drop in blood flow, even if it persists just for a short period of time.

For example, changes in the hemodynamic properties of brain tissue are used as metrics for tissue status and patient outcome despite a well-known discrepancy between blood flow and neuronal function/electrical activity. Typically, when perfusion pressure and blood flow drops the vascular system automatically tries to maintain the supply of nutrients by means of vasodilation. However, this increase in blood volume can only be kept to a certain level. If blood flow continues to drop, autoregulation fails and tissue becomes ischemic. If not reperfused in time, the tissue will continue on to infarction, which indicates the state of irreversible cell death. However, if perfusion can be reestablished in a timely manner tissue can be salvaged, and is therefore the focus of intense research in clot lysis and mechanical thrombectomy studies. Due to the increased concentration of metabolic products, reactive hyperemia and increased perfusion is often observed after ischemic conditions can be removed. Moreover, as ischemia also perturbs the integrity of oligodendrocytes and endothelial cells reestablishing blood flow can also lead to harmful effects, such as secondary hemorrhages. The better blood flow conditions and other markers of tissue state are known the better are the outcome prediction for a patient.

For MRI two disciplines to quantify hemodynamic parameters have evolved over the years: 1) Dynamic susceptibility weighted (DSC) MRI and 2) Arterial spin labeling (ASL). Their principle mechanism as well as their strengths and weaknesses will be reviewed briefly in this overview.

Dynamic Susceptibility Weighted (DSC) MRI:

In DSC the signal change induced by the administration of a bolus of *intravascular* tracer material is measured dynamically with a rapid pulse sequence, such as gradient-echo or spin-echo single-shot spiral or EPI. Typically, the tracer (Gd-DTPA) is injected into the right antecubital vein using a dual-piston power injector at a high flow rate (~6ml/sec) and followed by a saline chaser of similar volume and flow rate. On modern systems the sampling resolution for DSC is usually between one and two seconds. Shorter sampling resolutions would be generally

preferred, but are usually limited because a reasonable number of slices is needed to cover the entire brain (or at least the region of interest) and to reduce the confounding effects from increased T_1-weighting with shorter TRs.

The major difference between spin-echo and gradient-echo sequences is their different sensitivity to the presence of the intravascular tracer. GRE sequences are generally more sensitive (~x2) to gadolinium than SE sequences. This is mainly because GRE sequences utilize both static and dynamic dephasing principles, whilst SE sequences are only based on dynamic dephasing principle. However, while GRE demonstrates an increasing sensitivity to the tracer with increasing vessel size, SE is sensitive only to vessels at the capillary level. Using (double-dose) SE is often more appealing because it reduces the 'vascular blooming effect' from larger vessels otherwise seen on GREs. That said, SE affords fewer slices per TR, thus limiting the volume that can be covered for a given temporal resolution. Here, the *static dephasing* regime describes the additional ΔR_2^* ($1/\Delta T_2^*$) shortening within and adjacent to vessels due to the additional quasi-static magnetic inhomogeneous environment produced by magnetic susceptibility differences induced in the vasculature. The *dynamic dephasing* regime describes the MR signal drop and apparent T_2 reduction from protons diffusing within the magnetically inhomogenous area surrounding the capillaries, which is exaggerated by the presence of the contrast material. Do note, that the latter is technically a diffusion attenuation process rather than a spin-spin relaxation process.

Quantifying hemodynamic parameters from bolus perfusion MRI is based on the central volume principle, which states that the response to an instantaneous arterial input at the pre-capillary level can be characterized by *h(t)* on the venous post-capillary level. Here, *h(t)* characterizes the distribution of all the transit times the tracer needs to travel through the capillary vessel tree within one voxel. From a system theory perspective *h(t)* can be also seen as the impulse response function. The first moment of this distribution function provides information about the mean time the tracer needs to transit through the capillary bed (MTT). What we measure in MRI is usually not the venous outflow, but the amount of contrast agent that remains in the capillary bed, i.e. $r(t)=1-h(t)$, which is called the residue function. In practice, the arterial input is normally more remote from the capillary bed and typically several seconds long. The response one observes in the tissue *c(t)* is therefore modulated by the shape of the arterial input function (AIF) and deviates from *r(t)*. In fact, the measured tissue response *c(t)* is characterized by a convolution of both functions, that is: $c(t)=\text{CBF}\bullet aif(t)\otimes r(t)$. Under the assumption that for *t=0* all the tracer is still in the capillaries, i.e. $r(0)=1$, the cerebral blood flow (CBF) can be computed by deconvolving *aif(t)* from *c(t)*: $\text{CBF}\bullet r(t)=c(t)\otimes^{-1} aif(t)$. The deconvolution can be performed either in the Fourier domain or the time domain. One major challenge is however the stability of the estimated *r(t)*. Without any precautions, the solution is very unstable, especially in the presence of noise. Typically, regularization is used, which is a mathematical procedure to stabilize the solution.

The cerebral blood volume is usually determined by the area under the first pass uptake curve and is normalized by the arterial blood volume (which is ideally

100%). However, one needs to consider that the contrast agent distributes only in the plasma space (i.e. 1-hematocrit) and, in addition, that this distribution volume is different between large and small vessels. Because even larger vessels often suffer from partial volume effects, larger veins such as the sagittal sinus are often used instead. Based on the central volume principle the MTT can then be computed as MTT=CBV/CBF or alternatively from the first moment of the residue function.

Because the AIF is usually sampled remote from the voxels of interest, there is some delay and dispersion happening between the site where the AIF was measured and the true arterial input into the voxel. While delay effects between regions of interest and the AIF measurement site can be corrected for (e.g. by means of Fourier deconvolution or circular deconvolution) and the delay information can be used as another diagnostic metric (T_{max}), dispersion is more problematic as it changes the shape of the AIF. One potential approach to overcome dispersion is to use local instead of global AIFs. Rather than CBF, a number of clinical trials have used now T_{max}, which has been demonstrated to be a sensitive marker for tracer delivery, maybe less so for perfusion abnormalities. Here, T_{max} is the time difference between the start of a bolus of infinitesimally small width and its arrival in the voxel of interest. In other words, T_{max} is the bolus arrival time corrected for the variability by the bolus broadening of the AIF. Time-based hemodynamic parameters, such as MTT or T_{max}, have thus far been preferred by clinician over CBF and CBV since they are easier to read. That is, they usually have a very 'flat' image contrast in normal regions, which makes abnormalities much easier to delineate. In contrast, CBF and CBV abnormalities are more difficult to outline as one sees a pronounced gray/white difference even in normal tissue. At this point is important to realize that MTT describes more the effects the tracer experiences during its travel through the capillary bed, whilst T_{max} describes more the tracers' experience of effects as it was *en route* to the capillary system regardless where the event (of delay) happened somewhere between the AIF pickup site and the voxel of interest. Thus, T_{max} is clearly not a marker describing perfusion abnormalities in one voxel alone, but it is nevertheless an established metric in stroke trials and provides complimentary information to MTT.

It should be stressed that much of what has been said about deconvolution and the quantitfication of hemodynamic parameters applies also to CTP, the only difference to MRI is that quantitative CBF and CBV measurements need to be corrected for the non-linearity between MR signal and tracer concentration. For arterial blood in GREs this is typically a quadratic behavior. In addition, it is also important that the tracer concentration is not picked too high or otherwise the arterial signal time course reaches the noise floor and becomes highly non-linear. Therefore, a very early echo with little T_2^*-weighting is often used to avoid this 'plateau effect'. The orientation of the vessel relative to the main magnetic field needs to be considered as well. Ignoring partial volume effects for a moment there would be substantial differences in CBF and CBV when the same amount of contrast agent is on board but when the AIF is measured in the ICA or the transverse M1 segment of the MCA because of the different vessel orientation. Finally, there is also a difference in relaxivities between arteries and tissue, which has to be correct when the MR signal is converted into concentration values.

In summary, DSC has been demonstrated to be a very powerful tool to interrogate the perfusion status. It has found utility in stroke as it can be performed relatively quickly and provides not only blood flow maps but also maps with temporal hemodynamic information (MTT, T_{max}) as well as blood volume. Currently, it is still common practice (except for MTT and T_{max}) to review maps mostly on a quantitative level and taking benefits of the usual hemispheric differences in stroke. A few studies, however, are now focusing on more quantitative aspects. This is especially important when there are no clear hemispheric differences in blood flow abnormalities, such as seen in Moya-Moya patients or patients with chronic bilateral carotid artery disease. Very often, one is interested an assessment of the residual vascular reserve following diamox administration, which of course requires a small test-retest variability.

Arterial Spin Labeling (ASL):

The second method that is used by the MR community to measure perfusion is ASL. The concept of ASL is also very elegant. It uses the water protons themselves. Here, the arterial water is labeled by RF pulses and used as a tracer. Since it is water, the tracer is considered diffusible (similar to $H_2{}^{15}O$-PET, xenon or NO) although an increasing number of researchers include now permeability in their ASL models. In contrast to radioactive tracers, such as $H_2{}^{15}O$, the decay rate of the RF labeled water is even faster than that of the already short-lived ^{15}O PET tracer.

The basic idea of ASL is to perform two experiments. One, in which arterial blood is labeled (by inversion or saturation), and another one, the *control experiment*, which is usually identical but carried out without arterial labeling. The difference between those two measurements is proportional to the blood flow. Originally, the blood flow related changes in the signal were modeled as changes in the apparent T_1 relaxation time. However, a more comprehensive model is Buxton's generalized kinetic model, which very much resembles the convolution approach discussed above adapted to diffusible tracers. ASL can be largely categorized into two groups: 1) Continuous ASL (CASL) and 2) Pulsed ASL (PASL). Overall, the approach for all methods is pretty simple. Instead of a bolus of contrast agent, the magnetization of flowing spins is altered from its normal state in a way that it generates a box-car function of modulated spins (saturated or inverted) flowing into the region of interest.

In CASL a constant RF waveform is played out at a thin slice proximal to the imaging slice, thus impressing the box-car function on the blood that flows through the slice while the labeling RF waveform was on. When this bolus arrives at the imaging plane it slightly alters the signal depending on the blood flow. Most commonly a scheme is used where the flowing arterial blood together with the slice selection gradient and the RF pulse achieve an adiabatic inversion. The control experiment is usually an acquisition without labeling. Early on, it was recognized that the slice-selective labeling pulse introduces considerable magnetization transfer effects in the imaging slice, which of course differed from the control experiment and confounded blood flow measurements. Therefore, David Alsop designed an AM pulse for the control experiment (with an MT effect comparable to that of the label pulse) in which he re-inverted the label in an adjacent slice distal to

the labeling slice. Alternatively, Alfonso Silva used small labeling coils, which allowed him to label vessels in the neck. Since the transmit field of these coils tapered off enough, it wouldn't affect the imaging plane. These localized labeling coils can be also used to selectively label different vessels (e.g. left or right carotid or vertebral arteries to map vascular territories).

After the blood has been labeled, the label dies off with T_1, which means that the blood should reach the imaging slice quickly (i.e. short bolus arrival times) but also that the capillary transit times should be short (i.e. short mean transit times). Using higher field strengths where T_1 of blood gets longer is certainly very helpful. While T_1 loss is probably still acceptable in subjects with normal perfusion, caution has to be exercised in stroke patients or patients with chronic cerebrovascular abnormalities where one sees delayed bolus arrival and/or passage times. Another issue that needs to be carefully looked at is the timing of the acquisition. If one starts image acquisition to early after the labeling RF pulse has ended, one will first see predominantly a low-resolution angiogram as no label has yet reached the parenchyma. Therefore, introducing a considerable post-label delay is crucial for ASL studies. However, this must be chosen deliberately as it might vary with age and pathology. Typically, in stroke regions where perfusion pressure is lower or because of collateral blood supply, longer post-label delays need to be added. Otherwise, one will end up seeing the label being still trapped in the larger vessels.

The second variant of ASL is PASL. Here, the box-car label is generated by playing out a short RF pulse to saturate or invert spins in a thick slab proximal to the imaging region. The control experiment with is MT-balanced would be achieved by labeling a slab distal to the imaging region as was suggested by Edelman in his EPISTAR methods. As an alternative to these thin slice (CASL) or thick slab (PASL) approaches FAIR was introduced as another variant of PASL. Here, the labeling is achieved by performing a selective inversion of the imaging region, which allows the influx of fresh unlabeled blood from regions outside the inverted slice. As a control experiment, a non-selective inversion of the entire volume was used. What the postlabel was for CASL to avoid imaging when the arterial label is still trapped in larger vessels, is here the inversion time for PASL. Another smart approach to better characterize the tail end of the label is the QUIPPS II mechanism. Over the last few years many other variants of PASL have been introduced (too many to be covered in this review) and the corresponding acronyms are occasionally overwhelming. The great variety of different labeling approaches might have been also counter-productive for gaining broader use in the public as it is difficult to decide which method is the most suitable for a certain application. The variety of methods is also difficult to handle when it comes to comparability between different centers/vendors which makes it more difficult for multi-center trials and general clinical use.

Since the subtraction of two noisy images where difference is on the order of a few percent requires smart acquisition and post-processing schemes. It advisable to interleave the acquisition of label and control data rather than to acquire all the 'label' data first and then continue on to acquire the 'control' data. That is, between each TR one should switch between label and control. This approach works generally fine, unless there is still some residual label when the control experiment

is performed. One should also keep the physiological noise at a minimum. Physiological noise contributions increase with SNR and thus with slice thickness or field strength. In this context, it is also advisable to use sampling trajectories that excessively oversample the origin of k-space, such as spiral for example. Spirals have also the advantage that they a gradient moment nulled around the center of k-space. Ultimately, a major key to a good ASL study is probably background suppression. David Alsop has introduced a very nice approach with a train of inversion pulses to suppress static tissue over a wide range of T_1 values. Using background suppression eliminates a large portion of the noise from static tissue.

Two more recent developments in ASL that are very interesting are velocity-selective ASL and region-selective ASL. In velocity selective ASL, a diffusion-weighted preparation is used during labeling and acquisition to label only spins in a certain velocity range independent from their location. This should make ASL also less sensitive to delay effects. Region-selective ASL allows one to tag individual arteries either by small selective labeling coils or regionally selective labeling pulses, and thus to map out normal and pathologic flow territories, collateral flow, etc.

In summary, ASL elegantly tags protons in blood and uses it as an instrinsic diffusible tracer. No contrast agent is required which makes the method particularly attractive for patients with considerable renal insufficiency or children. Clearly, ASL has matured over the last several years. Keys to for successful implentation of ASL involve background suppression, 3D scanning, and a sequence that is less sensitive to physiological noise. The majority of ASL methods are useful in studies with short-to-normal bolus arrival times and MTTs. Except for velocity-selective ASL most other ASL are more or less sensitive to prolonged label delays.

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