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Non-invasive functional imaging of Cerebral Blood Volume with Vascular-Space-Occupancy (VASO) MRI

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Abstract

Functional MRI (fMRI) based on changes in cerebral blood volume (CBV) can directly probe vasodilatation and vasoconstriction during brain activation or physiologic challenges, and can provide important insights into the mechanism of Blood-Oxygenation-Level-Dependent (BOLD) signal changes. At present, the most widely used CBV fMRI technique in humans is called Vascular-Space-Occupancy (VASO) MRI and this article provides a technical review of this method. VASO MRI utilizes T1 differences between blood and tissue to distinguish these two compartments within a voxel and uses blood-nulling inversion recovery sequence to yield an MR signal proportional to 1-CBV. As such, vasodilatation will result in a VASO signal decrease and vasoconstriction will have the reverse effect. The VASO technique can be performed dynamically with a temporal resolution comparable to several other fMRI methods such as BOLD or Arterial-Spin-Labeling (ASL), and is particularly powerful when conducted in conjunction with these complementary techniques. The pulse sequence and imaging parameters of VASO can be optimized such that the signal change is predominantly of CBV origin, but careful considerations should be taken to minimize other contributions, such as those from the BOLD effect, CBF, and CSF. Sensitivity of the VASO technique remains to be the primary disadvantage when compared to BOLD, but this technique is increasingly demonstrating utility in neuroscientific and clinical applications.

Keywords

CBV; VASO; fMRI; BOLD; vasodilatation; vasoconstriction; hypercapnia; breath-hold

1. Introduction

Functional imaging of Cerebral Blood Volume (CBV) in humans requires a way to specifically modulate the blood magnetization inside a voxel in an effort to separate its signal from that of surrounding tissue. This has to be done with high temporal resolution (i.e. allowing for dynamic imaging), independent of flow velocity (i.e. sensitive to CBV, not CBF), and ideally non-invasively (i.e. without the need for exogenous contrast agent).

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Fortunately, MRI is a versatile approach and several aspects of the blood MR properties may allow us to achieve this goal. A first example of this is the use of hemoglobin as an endogenous paramagnetic vascular contrast agent, and to employ sophisticated experimental and theoretical approaches to separate the effects of venous blood volume and oxygenation (1–4). One limitation of this (venous) CBV method is the complexity of the model involving simultaneously measurements of T2 and T2* and that the measurement needs to be conducted at relatively high spatial resolution to reduce the influence of macroscopic field inhomogeneity due to, for example, shimming imperfection. Therefore, isolation of pure blood volume effect at a temporal resolution sufficient for functional brain mapping is not trivial with this method.

Another way of distinguishing blood signal from the tissue would be the use of strong magnetic field gradients to remove blood signal (5), but in this case the efficiency of signal separation depends on vascular flow and thus on vascular size. Even at very high gradient strengths, it may not be possible to null the smallest arterioles and capillaries (6) and the results are likely difficult to quantify.

While working on methods to simplify the interpretation of the BOLD effect by removing the intravascular contribution, we serendipitously discovered a new way to monitor blood volume, namely by using T1 differences between blood and tissue to null the intravascular signal (7,8). The details of this pulse sequence are described in later sections, but the basic principle of this approach is illustrated in Figure 1. If the blood signal can be specifically removed (nulled), a measurement of the MRI magnetization will yield signal approximately proportional to 1-CBV, under the assumption of a constant water volume in the voxel. Thus an increase in blood volume through relaxation of the smooth muscle and pericytes will lead to a reduction in MRI signal (Figure 1). A reduction in CBV should show the opposite. Basically, the signal change depends on the space occupied by the vasculature, which led us to name the approach “Vascular Space Occupancy” or “VASO” MRI. The present article provides a current review on this still developing technique.

2. Theory and pulse sequence

2.1 VASO

The VASO sequence and its variations utilize the T1 differences between blood and brain tissue to determine relative volume fractions of these compartments in a voxel, thereby obtaining a CBV-sensitive MR signal. In the original VASO technique, a spatially non-selective (i.e. global) inversion RF pulse is applied to invert the spins of both blood and tissue, after which the longitudinal magnetization will recover at the spin-specific T1 relaxation rate (Figure 2). Because blood T1 is longer than T1 of tissue (of both gray and white matter), the time it takes for the blood magnetization to cross zero will be greater than that of tissue. The zero-crossing inversion time (TI) for a spin species can be determined by solving the following equation:

$$1 - 2 \cdot e^{-TI/T_1} + e^{-TR/T_1} = 0 \quad [1]$$

where TR is the repetition time, TI is the inversion time, and T1 is the longitudinal relaxation time of the spin. Let us consider a gray matter voxel (without CSF). The voxel contains blood at a partial volume fraction of V and tissue at a partial volume fraction 1-V. When an excitation RF pulse is applied at the “blood-nulling” TI, the signal is expected to be inversely related to the space occupied by vasculature:

$$S = S_{tissue} + S_{blood} = M_0 \cdot [C_{tissue} \cdot (1-V) \cdot (1 - 2 \cdot e^{-TI/T_{1,t}} + e^{-TR/T_{1,t}}) + 0] \quad [2]$$

where M_0 is a constant giving the MR signal per unit volume of water protons at equilibrium; C_{tissue} is the water proton density of tissue (ml of water per ml of tissue); V is the CBV in ml of blood per ml of brain; $T_{1,t}$ is the tissue T_1 value, which is 920ms at 1.5T and 1086ms at 3T based on whole blood T_1 values of 1350ms (7) and 1624ms (9), respectively.

From Equation 2, it can be readily derived that a signal reduction is expected when CBV increases due to brain activation or physiologic challenges:

$$\frac{\Delta S}{S} = \frac{S_{\text{activated}} - S_{\text{baseline}}}{S_{\text{baseline}}} = \frac{V_{\text{baseline}} - V_{\text{activated}}}{1 - V_{\text{baseline}}} = -\frac{\Delta V}{1 - V_{\text{baseline}}} \quad [3]$$

Therefore, this technique can provide an approach for functional brain mapping based on CBV. This effect may be easier to appreciate in the context of a realistic example. Let us consider a voxel containing 0.05 fractions of blood and 0.95 fractions of tissue at baseline. Upon neural activation, a 20% increase in CBV takes place and the CBV value becomes 0.06. The tissue space then becomes 0.94. Comparing the signals between the two states, a decrease on the order of 1% is expected.

These hypothesized outcomes were confirmed by the experimental findings. Using checkerboard visual stimulation, the VASO signal indeed showed a decrease during the activated state (Figure 3a) (7). The technique also showed expected responses to physiologic challenges such as breath-hold (Figure 3b) and hyperventilation (Figure 3c) (7).

Several points should be noted on the choice of this sequence. One reason that the VASO pulse sequence is sensitive to total CBV is because it takes advantage of the fact that T_1 difference between arterial and venous blood is relatively small (Table 1) (compared to tissue-blood difference), thus arterial and venous blood signals can be nulled simultaneously.

In VASO, an inversion time TI that results in nulling of blood signal is used for two reasons. First, BOLD-related T_2^* and T_2 changes are more pronounced in blood than in tissue (10). Therefore, by nulling the blood signal, the intravascular BOLD contributions to the VASO fMRI signal can be minimized (notice that by using the shortest possible TE, the extravascular BOLD signals are minimized too). Second, by removing the blood signal term in the model, the relationship between VASO signal change, i.e. $\Delta S/S$, and CBV are relatively simple (see Equation [3]), which is useful in quantitative assessment of physiologic effects.

The spatially non-selective inversion RF pulse is usually performed with a body coil, which ensures that the signal model described above is applicable for static spins as well as the majority of blood spins in motion that can contribute within TR, thereby minimizing the sensitivity of VASO signal to flow velocity or its change during brain activation.

Another observation that can be made from Equation [3] is that, since CBV in the brain parenchyma is relatively small (ranging from 0.014 in the white matter to 0.055 in the gray matter (11)), $1 - \text{CBV}_{\text{baseline}}$ is close to unity. Thus, the VASO signal in Equation [3] is insensitive to the exact value of $\text{CBV}_{\text{baseline}}$. In fact, under the approximation that $1 - \text{CBV}_{\text{baseline}}$ is close to 1, the VASO fMRI signal change ($\Delta S/S$) reflects primarily absolute blood volume change, ΔCBV . This feature may present an advantage of VASO fMRI in terms of signal stability, as several previous studies have suggested that the amount of absolute change during activation is more stable across physiologic states (of the same individual) and participants whereas the relative change is more variable (12–14) because it

depends on the baseline physiology. There is indeed some evidence that VASO fMRI signal manifests less variation among subjects compared to BOLD (15).

2.2 Variants of VASO using TI-values not corresponding to blood-nulling

Given the known T1 differences between blood and tissue, the TI at which maximum magnetization difference can be achieved is actually not the blood-nulling time. Simple numerical simulation of longitudinal magnetization suggests that the maximum difference is obtained at a TI of 1400 ms at 3T (assuming signal recovering from $-M_0$), which is approximately the mid point between tissue (16) and blood T1 (9). Based on this notion, Wu and colleagues devised a modified VASO approach to image CBV changes during brain activation (17). The modified sequence provided activation maps and temporal responses similar to the original VASO, but was found to provide a 1.6-fold higher CNR. One limitation of this modified VASO approach is that the relationship between VASO signal and CBV becomes considerably more complicated and the quantification of CBV changes requires the knowledge of exact value of tissue T1, which could be slightly different for different tissue types, brain regions, and age ranges (17). Another confounding factor is the BOLD effect, which, in the modified approach, contributes a larger intravascular component, which again adds complexity to the model and quantification (17).

Another variant of VASO employs a TI at which gray matter signal is nulled, so that the observed MR signal is based only on blood magnetization (18,19) and is thus intrinsically negative in sign, while appearing positive in magnitude images. When CBV increases, a signal increase is expected and the signal change, $\Delta S/S$, is in principle directly related to $\Delta CBV/CBV$. This approach was proposed by two groups of investigators, which both demonstrated improved CNR of the method in comparison with the original VASO (18,19). This improvement in sensitivity was attributed to an increase in percentage signal change despite a lower SNR, considering that $CNR = SNR \times \% \text{ signal change}$. A limitation of this method is that the observed signal change seems to significantly underestimate the CBV change. When using an 8Hz black-white checkerboard, Wu et al. reported a signal increase of 12.3% (18), while Shen et al. noted a 7.2% increase (19), both considerably lower than the expected CBV changes of around 30% from results of contrast agent based CBV experiments (20). A possible reason for this underestimation is the residual BOLD effect present in the gray-matter nulled (suppressed) technique. Unlike the original VASO, the gray matter nulled VASO signal is counteracted by the intravascular BOLD signal, which can be much greater than extravascular BOLD (especially at 1.5T and 3T) and, moreover, does not diminish with spin-echo acquisition (21–23).

An interesting approach is the use of multiple values of TI (with fixed TR) in the same scan session (24). Such data includes all information provided by the above mentioned single-TI methods: TI to null blood, TI to null tissue, and TI that gives maximum blood-tissue magnetization difference. Figure 4 shows an example of signal change as a function of TI for visual stimulation fMRI using 13 TI values (24). The rich information provided by this dataset can be used to fit the experimental results to a biophysical model that includes both CBV and BOLD effects and obtain an estimation of multiple physiologic parameters. Gu and colleagues, who were the first group to test this approach, estimated baseline CBV of 4.5 ± 0.4 ml/100ml brain (mean $\pm$ SD), activated CBV of 5.9 ± 0.6 ml/100ml brain, and venous oxygenation of $78.7 \pm 5.9\%$ under activated state (24), all of which are in good agreement with expected physiology. This technique was further improved by Glielmi et al. (25) and Ciris et al. (26) to improve spatial coverage. One limitation of multi-TI approaches is longer total scan duration (>30 minutes). A second limitation is that the estimation of physiologic parameters uses nonlinear fitting of multiple data points and, at present, the data quality only permits reliable fitting at the level of region of interest, but not on a voxel-by-voxel level.

2.3 Inflow-based VASO (iVASO) MRI

VASO fMRI is sensitive to changes in total CBV, but does not differentiate blood volume changes in arterial or venous compartments. An iVASO approach (27,28) was recently devised to provide sensitivity specifically to CBV changes in arteries and arterioles (CBV_a). This is physiologically important because it is known that arterial and venous vessels have drastically different responses during brain activation (29,30). Instead of inverting all blood in the brain, iVASO inverts only the blood in the upstream feeding arteries by a spatially selective inversion. Several inversion schemes can be employed, among which the flip-back iVASO (a non-selective inversion followed by a slab-selective inversion of the imaging slice and superior brain) is commonly used because of its maximum inversion volume towards the major arteries, and optimal inversion efficiency and profile (Figure 5a). MR images are acquired when inverted blood water protons flowing into the slice are nulled. As the time for inverted blood water protons to reach and perfuse the arterioles (400–1400 ms in human GM) (31–33) is in the range of the TI values (300–1150 ms at 3T) used in VASO MRI (34), the iVASO approach can achieve predominantly arterial and arteriolar blood nulling. Figure 5b shows typical iVASO results from human fMRI experiments with visual stimulation. Similar to VASO, the negative iVASO signal change is attributed to vasodilation. An arterial volume (CBV_a) increase of about 58% in the visual cortex was observed. This value is greater than total CBV changes (usually reported to be around 30%), but is expected considering that arterial compartment has the most pronounced vasodilatory responses. This value is also consistent with the range of values reported in the literature, including MRI in animals (29,35–37) and humans (33,38), and optical imaging studies (39–41). Although the inversion schemes in iVASO are similar to some of those in pulsed Arterial Spin Labeling (ASL) methods (42–45), the contrast mechanisms are fundamentally different (Figure 5c). ASL measures tissue perfusion (i.e. CBF) based on the exchange between labeled blood water and tissue water protons in the capillary bed by using a long TI and/or crusher gradients to suppress arterial signal (46–48), while iVASO is designed to highlight the vascular contribution from the arterial compartment with images acquired at the blood nulling TI at which the inflowing blood has barely reached the post-arterial compartments.

The initial iVASO method (27,28) could only detect relative CBV_a changes, but not giving absolute CBV_a values. It was later expanded to include a control scan without blood nulling in order to quantify absolute CBV_a without exogenous contrast agent. This approach was developed by two independent groups at the same time (49,50). The control scan, which intends to provide identical information for the static tissue, uses two consecutive non-selective inversions. Other imaging parameters of the “nulling” and “control” scans are kept identical. The difference signal between the two scans reflects the amount of inflowing blood (with tissue signal subtracted out). Absolute CBV_a can be quantified from the difference signal (S_{diff}) using the iVASO theory derived in (50). Another critical requirement in iVASO is that one needs to separate the effect of CBV_a from that of transit time. In general, the iVASO difference signal at a single TI is approximately proportional to $(CBV_a/\delta_a) \cdot (TI - \Delta)$ (δ_a and Δ are the vascular transit times, Figure 5c). Therefore, absolute CBV_a can only be obtained if vascular transit times are known or measured. Note that transit times may vary in different cortical regions, and may alter during brain stimulation. To account for heterogeneity in these times, interleaved nulling and control images can be acquired at multiple TIs, from which three unknowns (CBV_a , Δ and δ_a) can be fitted independently (50). In addition, velocity encoding bipolar gradients can be incorporated in both nulling and control scans to suppress the larger vessel (artery) signals, thereby sensitizing iVASO signals predominantly to the arterioles (50,51). Figure 6 shows typical data for absolute CBV_a quantification with iVASO. Eight TIs were used and S_{diff} in GM was displayed as a function of TI. The effect of inflowing blood can be seen clearly in the S_{diff} signals. Figure 6b also shows a typical fitting of S_{diff} with multiple TIs using the

iVASO theory. The fitted CBV_a , Δ , and δ_a maps for this subject are shown in Figure 6c. The average GM CBV_a from 11 subjects was measured to be 1.27 ± 0.13 ml/100 ml, in line with previous reports in the literature (3,38,52–54).

3. Signal mechanism and confounding factors in VASO

3.1 BOLD contributions

In order to obtain true CBV weighted signal, the BOLD effect needs to be minimized. The BOLD effect typically has two components, intravascular and extravascular (21,22). Let us first consider the T_2^* BOLD effect, which is relevant when a gradient-echo sequence is used for signal acquisition. At 1.5T, the intravascular and extravascular components, based on contributions to total R_2^* changes, are about 53% and 47%, respectively (55). At 3T, these values become about 33% and 67%, respectively (55). That is, the relative contribution from extravascular tissue increases with field strength (56). These observations of field dependence are consistent with biophysical model simulations (21). In VASO, the intravascular BOLD contribution is eliminated because of the blood nulling, but the extravascular contribution remains in a manner proportional to TE. Thus an increase in TE value can gradually negate the VASO effect, causing an under-estimation of CBV changes. When conducting visual VASO fMRI as a function of TE, it was observed that the VASO effect at 3T is completely offset by BOLD at a TE of approximately 70 ms (55). For these reasons, the shortest TE possible is desirable in VASO experiments.

Similar principles can be applied to T_2 BOLD effects relevant for spin-echo (SE) acquisition schemes. SE VASO fMRI has been studied under various TE values and it was found that the percent signal change is minimally dependent on the TE used (34), suggesting that the extravascular T_2 effect (at 3T where the experiments were conducted) is relatively small. Therefore, it seems that the estimated ΔCBV will be minimally dependent on TE when SE acquisition is used, making SE EPI a preferred acquisition scheme for 3T (and presumably lower field strength). However, note that CNR is the product of percent signal change and SNR. Given that SNR still decays exponentially with time in SE, a shortest TE remains desirable for sensitivity reasons.

It should also be noted that, although extravascular SE BOLD effect seems to be negligible at 3T, this may not be the case at higher field strength (e.g. at 7T). This is because SE BOLD is attributed to the spin diffusion in heterogeneous magnetic fields and, since the field heterogeneity is proportional to field, the BOLD effect is expected to be greater even with the same diffusion parameters (21,22).

3.2 Inflow effects

The VASO theory described above is based on the assumption that all blood spins are in a steady state by the time they reach the imaging volume. This assumption is only valid when the coverage of RF transmission includes the entire body of the subject. However, even when using a body coil for transmission, the effective inversion volume produced usually can cover only the lower neck and upper chest region. As a consequence, some fast flowing blood spins may not have seen sufficient number of inversion pulses to reach a steady state at the time of signal reception (34). The non-steady-state inflowing blood spins can be categorized into three types based on the time when they enter the transmit coil: I) spins entering before the end of readout of the previous TR; II) spins entering between the readout of previous TR and the inversion pulse of current TR; III) spins entering after the inversion pulse of current TR. The three types of non-steady-state spins have experienced at least one, only one and zero inversion pulses before image acquisition, respectively. Theoretical simulations and experimental results have demonstrated that type I and II non-steady-state blood spins would yield a larger (more negative) VASO signal change during vasodilation,

while type III spins have the opposite effect (17,34,57,58). Lu et al developed a “magnetization reset” technique (58) to eliminate type I non-steady-state blood spins. This technique applies a spatially nonselective saturation module (90° RF pulse followed by spoiler gradients) immediately after each readout (17,58), which establishes the steady state for all spins within the transmit coil for the next scan. More recently, Hua et al proposed to use motion-sensitized crushing gradients to suppress type II and III non-steady-state spins (59). As these spins enter the transmit coil at a relatively late time, they tend to be located in relatively large arterial vessels inside the voxel and usually have a relatively high flow velocity at the time of the motion-sensitized gradients. Thus, the gradients are expected to be highly effective in crushing out these signals. This crusher scheme can be implemented with bipolar gradients in sequences such as echo-planar-imaging (EPI), or more generally, as a spatially nonselective Carr–Purcell–Meiboom–Gill (CPMG) based T_2 preparation module with inserted motion-sensitized crushing gradients applied immediately before the readout (motion-sensitized driven equilibrium, MSDE) (60–62). One drawback of this approach is that it increases the effective TE which introduces some unwanted signal loss from T_2/T_2^* decay and additional BOLD effect during functional activation. Minimal TE is always recommended and one can use multi-echo extrapolation method to alleviate the BOLD contamination. Interestingly, experimental results in Hua et al. (2012) show little BOLD effect resulting from the T_2 preparation module with an effective TE of 15 ms at 7T, which may be explained by the fact that T_2 -weighted BOLD effect at short TE is mainly in the intravascular compartment (63,64), which is nulled in VASO MRI. In summary, the inflow effects in VASO MRI can be minimized by combining the magnetization reset and crushing gradient techniques (59). When these additional sequence components are not available, a TR of 5 s or longer at 3T (to minimize type I and II effects) and a large-volume inversion (to minimize type III effect) are recommended for predominant CBV contrast.

3.3 Perfusion (CBF) contributions

The VASO contrast is also affected by CBF, especially when short TR is used (34). Similar to ASL, the inverted blood spins bring down the residual extra-vascular tissue signal through water exchange. CBF typically increases during neuronal activation, which further reduces tissue signal and results in a larger (more negative) VASO signal change than what is expected for CBV alone. Donahue et al. (34) extended the original VASO theory with the perfusion (CBF) contributions using a single-compartment model established in the ASL literature (65,66). The results revealed that the perfusion contributions can be considerably reduced using a TR of 5s or longer, when compared to shorter TR (34,67,68). Note that the single-compartment model assumes fast (instant) exchange between blood and tissue water. However, the average water exchange time in the capillary compartment has been reported to be 0.5–1 s (69–71), which should make the actual effect smaller within the time scale of VASO experiments. Indeed, a theoretical work by Wu et al (72), which proposed a two-compartment model with finite capillary permeability for VASO, demonstrated smaller perfusion effects (< 10% of the CBV effect) in VASO signals.

The other potential perfusion contribution in the VASO contrast arises from water exchange from tissue to blood, which would alter blood T_1 and thus lead to imperfect blood nulling in capillaries and venules. A parenchymal model consisting of four pools (spins in blood and in tissue, spins exchanging from blood to tissue and from tissue to blood) was constructed to investigate such effects (7). The model also takes into account the fact that the spins exchanging from tissue to blood may flow out of the imaging slice before acquisition and the probability of that is assumed to decrease linearly with the time of exchange (TI). Simulations using this model with and without the water exchange effects showed negligible (about 0.02%) influence on the overall VASO signal. Another study (72) used a two-compartment model with a slightly different assumption on the potential outflow of spins

exchanging from tissue to blood. In this model, it was assumed that the spins that were originally in the tissue but were later exchanged into the capillary (blood) compartment stayed in the imaging voxel by the time of image acquisition. Thus one has a scenario that, although the tissue signal was lower than expected (due to incoming “black” blood spins), the blood signal was higher than expected (due to the incoming “bright” tissue spins). The net effects on the total signal were actually small because these two effects partially cancel out. With this model, Wu et al. estimated the effect to be 0.15% at 3T (72).

The perfusion contributions in iVASO are negligible. Depending on the TI used, iVASO can be sensitized predominantly to arterial and arteriolar blood effects, where negligible exchange between blood and tissue occurs due to limited permeability of the vessel wall. For longer TI values, the labeled blood water can reach capillary bed and exchange with tissue water. Notice that the TI for blood nulling can never be more than 1.2 s ($TR = \infty$ in Eq. [1]) at 3T and 1.7 s at 7T. In human GM, the mean transit times (MTT) for arterial and capillary are in the range of 800–1000 ms (31,33,54,73) and 500–1000 ms (74,75), respectively. Therefore, even at the longest TI, capillary contribution is small, which can be accounted for in the iVASO theory (50) by introducing an “extraction fraction” (E) for water (76). Simulations assuming complete exchange ($E = 1$) and no exchange ($E = 0$) in capillaries showed less than 0.03% difference in the iVASO signal, which is well within experimental error (50). Furthermore, when the measured iVASO difference signals (S_{diff}) were fitted with the iVASO theory, it was shown that the perfusion rate (CBF) parameter in the model is not sensitive to the fitting, indicating again that such perfusion effects are negligible in iVASO.

3.4 CSF effects

In gray matter, CSF occupies about 10–15% of the voxel volume. Since CSF contains few macromolecules, its T1 value is long (~4300 ms at 3T) and relatively insensitive to magnetic field strength (77) with respect to the difference with blood and tissue. Consequently, CSF magnetization is negative at the blood-nulling TI, which is opposite in sign compared to the gray/white matter magnetization (34,57,78,79). CSF partial volume effects can affect VASO fMRI by altering the baseline VASO signal, and thus CBV quantification. Some investigators have also suggested that CSF volume fraction may change during brain activation, which could have further implications in VASO fMRI (78,79).

Let us first discuss the effect of CSF partial voluming under the assumption that CSF volume fraction does not change between baseline and activated states. Since CSF magnetization is negative, it will offset part of the positive tissue magnetization and result in a lower baseline signal, S_{withCSF} . Upon brain activation, the signal change, ΔS , is not affected by CSF, thus the sensitivity (or CNR) is unchanged. However, the percent signal signal, $\Delta S/S_{\text{withCSF}}$, will be greater with CSF partial voluming. Figure 7 shows simulation results of VASO percent signal change as a function of CSF partial volume (at fixed CBV change). The problem is exacerbated when the CSF volume fraction so large that it outweighs the tissue signal and reverses the sign of the net magnetization of the voxel, an issue similar to those occurring in certain ASL implementations such as the Flow-Alternating-Inversion-Recovery (FAIR) (80). This could take place when CSF occupies >50% of the voxel. Under this circumstance, a tissue volume reduction would actually result in a VASO signal increase (Figure 7) as far as the magnitude images are concerned (which is typically used in fMRI analysis). Therefore, the quantification of CBV change from VASO fMRI signal (e.g. Equation [3]) is no longer valid unless CSF partial volume fraction is known or assumed. The CSF effect can be alleviated by the use of double-inversion, termed FLAIR-VASO, so that both blood and CSF are nulled at the time of image acquisition (34). Under these schemes, the sign of the magnetization is always positive and the quantification of ΔCBV from the VASO fMRI signal becomes simpler again. A

drawback of the double-inversion scheme, however, is that the TR needs to be longer and the remaining tissue signal is lower compared to the original VASO sequence (34).

The discussion above has assumed that CSF partial volume does not change upon activation. Some investigators have suggested that this may not be the case and that CSF volume may in fact reduce with activation (78,79,81). They based this on the hypothesis that, during brain activation, both tissue and CSF space decreases (rather than tissue only) to some extent to maintain a constant intracranial space, which is not distensible (79,82). Then, according to the signal contribution model described above, positive tissue magnetization will decrease upon activation but, in the meanwhile, negative CSF magnetization will also decrease. The combined effects results in a minimal change in the net VASO signal, thus a lack of activation. Scouten and Constable first noted this during brain activation in certain brain regions (e.g. auditory cortex) where CSF partial volume is high (78). They reported similar effects during vasodilatory challenges such as hypercapnia (79). Other investigators, however, noted that this effect is only <0.2% in amplitude and is within the range of experimental error (34). Further studies from independent research groups are needed to better understand whether or not CSF volume fraction alters with activation.

3.5. Human validation of VASO with contrast agent based method

Validation of VASO fMRI was recently performed by comparing the VASO results to a more traditional CBV method, bolus-tracking of Gd-DTPA (83). A small bolus (0.1 mmol/kg) of Gd-DTPA was injected intravenously while gradient-echo EPI images were continuous acquired to sample the dynamic curve reflecting the regional concentration of the bolus. The area under the curve is known to be proportional to CBV. This experiment was performed three times on each subject under resting, 4 Hz flashing-checkerboard, 8 Hz flashing-checkerboard, respectively. In the same individuals, VASO fMRI was performed. Figure 8a shows the comparison of activation maps using the two methods. Figure 8b further showed quantitative results of percent CBV changes, demonstrating excellent agreement between the techniques (83).

4. Practical Considerations

4.1 Gradient-echo and spin-echo acquisition schemes

Most VASO studies so far have used single-shot GE EPI with a shortest TE possible (7,34,55,84–86). A short TE is important because the CNR of VASO has been shown to decay exponentially with TE (55), part of which is due to the counteracting BOLD effects as described earlier. Half scan (partial Fourier) and parallel imaging are often needed in order to achieve a desirable TE of less than 10 ms at 3T. Further reduction in TE can be achieved by using a single-shot in-out spiral acquisition (center k-line acquired at TE=3ms), which has been shown to have excellent sensitivity (17).

Single-shot SE EPI has also been evaluated (34). Although SE acquisition tends to have a longer TE compared to GE EPI, an advantage is that the extravascular BOLD effect is expected to be negligible (at 3T) (34). Thus, SE EPI and GE EPI (both at shortest TE possible) may provide similar sensitivity, although a direct comparison between these two methods has not been reported. Additionally, for both GE and SE EPI, one can use signal extrapolation of multiple echoes to further reduce the effect TE (34,55), thereby minimizing the residual BOLD effect in VASO.

Fast-spin-echo (also known as HASTE) based acquisition has also been used in VASO. It was reported that FSE approach produced less image distortion and provided a 46% increase in CNR compared to GE EPI (87).

4.2 Sequence components to suppress flow contributions

It is also recommended that one (or a series of) non-slice-selective saturation pulse be applied immediately following the acquisition to reset the spin history of the entire brain (17,58,59). This scheme was shown to reduce the inflow effects. The addition of bipolar (in GE EPI) or unipolar (in SE EPI) gradients may further reduce the flow contributions (17). Although not yet thoroughly examined, the combination of these two schemes, i.e. magnetization reset RF pulse and crusher gradients, may provide an optimal approach for VASO fMRI at short TR (e.g. 2 seconds) (59).

4.3 Combining VASO sequence with ASL and BOLD sequences

Two-dimensional VASO acquisition has been combined with ASL acquisition in the same sequence by interleaving a slab-selective inversion (spin-inverting from the VASO point-of-view but non-inverting from ASL point-of-view) with a non-selective inversion (spin-inverting from both VASO and ASL point-of-view) (88). The BOLD data can also be obtained in the same sequence by using a dual-echo acquisition following the ASL excitation pulse (88).

4.4 Multi-slice and 3D VASO acquisitions

The extension of VASO from 2D to 3D is not trivial because there is only one zero crossing point on the magnetization recovery curve. That is, if one slice is excited at the blood nulling time, by the time the next slice is ready to be excited, the blood inside that slice would already have non-zero signal. In the past several years, a number of techniques have been devised to overcome this limitation. One approach, Multiple-Acquisition-with-Global-Inversion-Cycling (MAGIC) (89), applies a global inversion following the acquisition of the first slice, which inverts the blood magnetization to (slightly) negative again. Then after a short recovery time, the blood signal will cross the zero point for a second time, at which point slice #2 can be excited and acquired. This strategy can be repeated multiple times to provide a multi-slice version of VASO (89). A limitation of the MAGIC approach is that the tissue signal is gradually attenuated as increasing number of global inversion pulses are applied. Thus the signal intensity is by definition inhomogeneous across slices, resulting in slice-dependent activation sensitivity and also making it difficult to conduct image realignment. Additionally, the MAGIC pulse sequence at high field (e.g. 7T) may be limited by SAR constraints, depending on the type of inversion pulses used.

Another more practical technique that is increasingly used in VASO fMRI is the 3D Gradient-and-spin-echo (GRASE) acquisition scheme (90–92). In this scheme, two fast imaging methods, EPI and FSE, are combined which can provide 3D volume coverage. In single-shot GRASE, EPI is often applied in the y direction and FSE is applied in the z direction. Combined with aggressive parallel imaging factors, this scheme can usually provide 20 slices with an in-plane matrix of 64×64 and a total echo train length of 200–300 ms. This method was previously used in ASL acquisition (93) and, more recently, applied to VASO (90–92). With this advanced scheme, VASO fMRI has been used in cognitive tasks, where it yielded reliable activation (91). The advantage of this method is that all slices are acquired simultaneously, thus there is no issue of slice intensity differences and all slices can be acquired when the blood is nulled. One limitation of single-shot 3D GRASE is that spatial smoothing is usually seen in the z-direction due to the very long echo train length, which may not be ideal for high resolution fMRI studies. Another minor pitfall is that it would be difficult to add crusher gradients in the GRASE sequence. Thus, alternative strategies such as velocity-sensitive T2 preparation (59) need to be used if the inflow effect is to be suppressed.

Another possible approach to conduct 3D acquisition is to use the FLASH sequence in which all k lines of the volume are sequentially acquired with short TR, short TE and small flip angle shots following a single inversion (59), to some extent similar to the MPRAGE sequence (94). Advantages of this acquisition include the absence of image distortion and minimal BOLD effect, thus ideally suited for high field (e.g. 7T) VASO. A potential confounding factor is that the blood signal is no longer nulled in later k lines and the signal contrast mechanism may be affected (59).

It should be noted that there has also been rapid advances in the field of fast imaging techniques in recent years. These methods, although not yet applied to the application of VASO, may provide new opportunities in the near future. One such technique is called MR inverse imaging (95), which applies frequency and phase encoding in two spatial directions similar to conventional EPI, while spatial discrimination in the third direction is achieved by solving the inverse problem utilizing information from all array channels. With this technique, whole-brain acquisition can be achieved following a single RF excitation within about 100 ms (95). Another interesting acquisition technique is called multiplexed-EPI (M-EPI) (96,97), which combines two forms of fast imaging approaches, namely temporal multiplexing (m) utilizing simultaneous echo refocused EPI and spatial multiplexing (n) with multi-banded RF pulses. Therefore, $m \times n$ images can be acquired with a single-shot acquisition. Additionally, there exist other high speed imaging technologies such as compressed sensing (98) and MR-encephalography (99) that use k-space undersampling to achieve high temporal resolution. These cutting-edge technologies may offer great potentials for expanding the utility of VASO imaging.

4.5 SNR, percent signal change, and CNR of VASO fMRI

The inversion pulse applied in VASO also suppresses tissue signal to approximately 20% of the equilibrium magnetization, which is the primary reason for the relatively low sensitivity of this technique. The SNR of VASO is thus about 1/5 of that of BOLD (assuming long TR) (7). The percent signal change of VASO is determined by ΔCBV as stated earlier. For example, typical brain activation results in a CBV increase from 5% (of voxel volume) to 6.5% (20), therefore VASO fMRI signal is often on the order of 1.5%, which is similar to the percent signal change of BOLD (7). Consequently, the CNR of VASO fMRI is about 1/5 of that of BOLD, which has been confirmed by experimental data (7). This ratio was found to be dependent on spatial resolution. For example, at a voxel size of $2 \times 2 \times 5 \text{ mm}^3$, the CNR of VASO was 1/3 of that of BOLD (7). This finding can be attributed to the notion that task-based VASO signal changes are spatially more localized (see detailed discussion below) to parenchyma, thus smaller voxel allows the identification of true activated tissue with minimal partial voluming effect from tissue that is not active and draining vein areas. Finally, the sensitivity of VASO fMRI is better than that of ASL (7,84).

Sensitivity of VASO MRI can be improved by additional considerations in the pulse sequence. Hua et al. (86) designed the magnetization transfer (MT) enhanced VASO (MT-VASO) approach, which employs semi-solid based MT effects to augment the residual tissue signal at blood nulling TI, thereby boosting SNR and CNR for VASO MRI (86). While there are large MT effects in many brain tissues such as GM and especially WM, these are smaller in blood where they are based on low concentration macromolecules with exchangeable protons (100,101). Such effects can be kept small when using low-to-medium irradiation power ($< 3 \mu\text{T}$) and duration ($< 500 \text{ ms}$), and especially when using a frequency offset far away from water resonance ($> 40 \text{ ppm}$) (86). Application of an MT (off-resonance RF irradiation) pulse before or after the VASO inversion pulse can be used to accelerate the recovery process for tissue magnetization, thereby obtaining a higher residual tissue signal at TI (86). As an off-resonance frequency can be chosen at which MT effects in blood are negligible, the blood nulling TI is not affected. It has been shown that the MT-VASO

approach can improve SNR and CNR for VASO fMRI by approximately 40% at 3T, while preserving the CBV sensitivity (86).

4.6 VASO MRI at ultra-high field

VASO MRI was originally developed on 1.5T (7). To date, most human VASO studies have been performed on 3T scanners (24,28,34,49,55,84,85,87,88,90–92,102). While ultra-high field (7T and above) has the advantage of enhanced intrinsic SNR of MR images, VASO MRI faces several technical challenges at higher field. First, the convergence of tissue and blood T_1 values reduces the residual tissue signal at the blood nulling TI, which negates the SNR gain at higher field. Second, the BOLD effect is much greater at higher field, which counteracts the small negative VASO signal change and results in an underestimate of CBV changes in the brain. Third, the imaging sequences commonly used for VASO MRI at 3T, such as EPI, TSE (87) and GRASE (90,92), suffer from increased geometrical distortion (EPI and GRASE) and higher power deposition (TSE and GRASE) at ultra-high field. Finally, body coils on human scanners are not yet available for ultra-high field, leading to more substantial inflow effects. Many of the techniques discussed earlier can be used to improve SNR for VASO MRI on ultra-high field. Hua et al. showed that the MT-VASO approach yields greater SNR enhancement at 7T than 3T, furnishing an improvement of 149% compared to conventional VASO (59). They also employed a 3D fast gradient echo (fast GRE, also known as turbo field echo, TFE, or TurboFLASH) sequence to minimize the BOLD contamination (short TE, 1.8 ms) and to reduce image distortion and power deposition (low flip-angle, 7°). As discussed earlier, the inflow effects can be minimized by incorporating the magnetization reset module and crushing gradients. With these technical improvements, initial results (simulations and experiments) with the 3D fast GRE MT-VASO sequence in normal human brains at 7T demonstrated better SNR than at 3T (59). Huber et al. have recently also applied a slab-selective VASO at 7T and yielded excellent SNR (15).

5. Localization of the VASO effect

5.1 Which vessels dilate during brain activation?

VASO fMRI is based on changes in CBV. Thus, the localization of VASO signal is primarily dependent on the relationship between the dilating vessels and the active neural tissue. A large body of literature in neurovascular coupling suggests that the vessels that are capable of dilating consist of smaller arteries and arterioles that are 100–200 microns in diameters (103). These vessels are equipped with smooth muscle cells that can dilate or constrict vessel lumen based on microenvironment changes (104). While it is not entirely clear how these vessels are controlled by neuronal tissue, recent evidence suggested that astrocytes plays an important role in sensing the neural activation and transmitting the signal to vasculature via its end-feet which are attached to the outer wall of the vessel (105,106). It is also known that calcium concentration change and nitric oxide release are critical steps in mediating these processes. There is also some evidence that pericytes may play a role in controlling the diameters of capillaries by wrapping around the vessel, since capillaries do not have smooth muscle themselves (107).

Since astrocytes and pericytes are small cells, the vessels they interact with tend to be within a few hundred microns of the active neural tissue, making CBV change a marker that is spatially very close to the true activation. This presents an advantage over BOLD. In BOLD, it is well known that, although the blood oxygenation increase originates in capillaries, the oxygenated blood will travel through venous structure and the effect can be observed along its path, even in large veins several centimeters away (108).

It is also important to point out that the vessels that are capable of actively dilating are primarily arterial and arteriolar vessels (103). More discussion on its implications for VASO MRI is provided in the later section.

5.2 Evidence from animal imaging literature

Consistent with predictions from vascular physiology, several pieces of imaging evidence also suggest a high spatial specificity of CBV based brain mapping techniques. Using superparamagnetic nanoparticles (MION) as an MRI CBV agent (which are approved for animal use but not in humans), Jin and Kim showed that across cortical layers the CBV fMRI signal was most prominent in layer IV (Figure 9a), the afferent layer where synapses (and presumably synaptic potentials) are most abundant (109). In contrast, the BOLD signal did not manifest a layer specificity (Figure 9b). The investigators further implemented the non-contrast VASO (Figure 9c) method, showing a signal profile (Figure 9d) comparable to the MION CBV method but distinctive from that of BOLD.

Optical imaging results also suggested highly specific localization of CBV based activation. Sheth and colleagues studied neural activation in rat barrel cortex using optical intrinsic signal imaging and spectroscopy, which allowed simultaneous evaluations of CBV and oxygenation changes (110). The investigators found non-specific activation using the (late phase) oxygenation signal. In contrast, the CBV changes were localized to single whisker column in the cortex with a vascular spread function of ~600 microns, which was similar to the spread function of early phase oxygenation response (i.e. initial dip). This spread function was shown to be able to distinguish cortical regions 400 micron apart.

5.3 Evidence from human imaging data

In human studies, the question of whether the VASO activated voxels are predominantly located in brain parenchyma or large vessels can be probed by examining the T1 properties of the voxels, because parenchyma tissue has a shorter T1 compared to blood (7,18). It was found that the T1 of VASO activated voxels was 1031 ± 20 ms (at 1.5T) (7), which is close to the tissue T1 (16). On the other hand, the T1 of BOLD activated voxels was significantly ($p < 0.03$) longer (1103 ± 23 ms), suggesting an increased partial volume effect from blood (or CSF) (7).

When VASO fMRI is performed at higher spatial resolution, the localization of the activated voxels became more apparent. Donahue et al. performed VASO fMRI at 0.8×0.8 mm² in-plane resolution and demonstrated that the activated voxels are selectively located in cortical gray matter with few voxels in sulci between cortical banks (where the vessels are located) (34).

5.4 Localization of iVASO signal

The arterial origin of the iVASO signal has been validated by measuring its T₂ values, which are highly oxygenation level dependent (64). Figure 10a shows the T₂ values of the inflowing blood (S_{diff}) between two consecutive TIs measured at 3T (50). As expected, they were within the arterial range between TI = 600–750 ms, started to drop around TI = 800ms, and came down towards the capillary range at longer TIs. Although the standard deviations are big, largely due to the low SNR, the general trend is quite clear. Another evidence that the iVASO signal is primarily originated from the arterial compartment is shown in Figure 10b. The hemodynamic response during visual stimulation detected by iVASO (CBV_a) uniformly preceded the VASO (total CBV) time course by approximately 1s ($P < 0.01$) (27,28). This observation agrees with optical studies in animals that reported earlier response in arterioles upon neuronal activation (39,111).

6. Application to brain physiology and BOLD mechanism

As the first non-invasive CBV technique in humans, VASO fMRI has been performed in conjunction with BOLD and ASL fMRI to separately evaluate various contributing factors in the BOLD phenomenon, including CBV and CBF. Furthermore, using a theoretical framework developed by Lu et al. (84) and later adopted by Lin et al. (112,113) and Hua et al. (85), oxygenation extraction fraction (OEF) and cerebral metabolic rate of oxygen (CMRO₂) can also be estimated. One important outcome of this work is that it provided new insights on the physiological origins of the BOLD post-stimulus undershoot (114–116), which has important implications for neurovascular coupling mechanisms in the brain. Lu et al. (84) conducted BOLD, ASL (CBF) and VASO (CBV) fMRI experiments in human brains during visual stimulation, and found that both CBF and CBV returned to baseline shortly after stimulus cessation, whereas CMRO₂ remained elevated during the BOLD undershoot, which implies a predominant metabolic origin for the BOLD undershoot. Donahue et al. (117) provided further evidence for this notion by showing that, in contrast to visual stimulation, BOLD signals following a short-term breathhold task did not show significant undershoot, while the vascular changes (CBF and CBV) persisted for a longer period before returning to baseline. Hua et al. (85) further investigated this phenomenon by separately examining arterial and post-arterial CBV effects with iVASO and VASO. The results suggested that both delayed post-arterial CBV recovery and enduring increased CMRO₂ may have contributed to the BOLD post-stimulus undershoot, with relative contributions of approximately 20% and 80%, respectively. In the same study, it was also shown that the estimated CMRO₂ during breathhold dropped below baseline, which echoes with several recent reports showing decreased brain activity during 5% CO₂ inhalation in humans (118) and suppressed neuronal activity during moderate hypercapnia in animals (119). It is generally believed that hypercapnia induces exclusively vascular response and no metabolic or neuronal activity. However, these findings (85,118,119) suggests that this assumption may not hold under certain conditions and care must be taken when using hypercapnia as a calibration method in fMRI (120).

Another important application of VASO MRI is to experimentally measure the intra- and extra-vascular fractions of the BOLD effect in order to understand the compartmental contributions of the BOLD signal (55). In fact, the original inversion recovery blood nulling concept was designed to eliminate intravascular signal and isolate the extravascular tissue compartment in BOLD experiments (8). With multi-echo VASO fMRI, Lu and colleagues were able to measure parenchymal extravascular R_2^* and its change during activation (55). The extravascular BOLD contribution, which can be estimated by comparing extravascular R_2^* changes with total parenchymal R_2^* changes in BOLD fMRI, were found to be 47% and 67% at 1.5T and 3T, respectively. A similar study was recently performed on a 7T human scanner, which reported a 90% extravascular contribution to the overall BOLD effect (121,122). As expected, the BOLD effect is increasingly shifted to the extravascular tissue compartment at higher field (56).

7. Application of VASO in neuroscience

So far most work on VASO has been technical or physiologic studies which used simple sensory or motor fMRI paradigms. Application of VASO fMRI in neuroscience paradigm is still in its early stage, mainly due to technical limitations associated with spatial coverage and sensitivity. While the impact of VASO in neuroscience is not yet clear, there have been two studies that showed initial feasibility. Lu et al. used VASO fMRI to study retinotopic mapping in early visual areas and were able to identify multiple retinotopic representations of the visual field in the early visual areas: ventral maps include V1, V2, VP and V4v; dorsal maps include V1, V2, V3 and V3A (Figure 11) (102).

In another study, Poser and Norris used a 3D GRASE VASO technique to study brain activation during a Stroop task, which is a color-word interference test (91). The authors observed CBV increase in lateral occipitotemporal gyri, intraparietal sulci, posterior and anterior inferior frontal sulci, and occipital and motor areas. A CBV decrease was noted in cingulate cortices, the lateral parietal sulci, the frontal cortices, and the right lateral superior parietal lobe. These findings were consistent with a previous report using BOLD. Notably, Poser and Norris observed that, while BOLD is more sensitive than VASO in most of the brain regions, VASO appeared to provide a superior detection power in inferior frontal lobe for activations and in superior frontal for deactivations (91). This can be attributed to the fact that BOLD sequence is more susceptible to field inhomogeneity at the tissue-air interface. Therefore, VASO fMRI may have utility in understanding cognitive processes involving (inferior) frontal lobe function.

8. Applications of VASO to clinical conditions

VASO fMRI is particularly useful in clinical conditions where blood volume, flow and oxygenation may be decoupled, thus examination of individual parameters is important. Donahue and colleagues studied VASO responses to breath-hold challenge in patients with internal carotid artery (ICA) stenosis, and compared them to a group of healthy volunteers (123). In control subjects, breath-hold induced a VASO signal change of $-1.9 \pm 0.6\%$, consistent with expected effect of vasodilatation. Interestingly, the VASO reactivity was more negative ($-3.6 \pm 1.5\%$) in the patients compared to the controls, suggesting an autoregulatory response that the blood vessels were dilated even before the hypercapnia challenge. Furthermore, the VASO reactivity was found to normalize after interventions such as carotid endarterectomy or stent placement (123). Additionally, a postbreath-hold overshoot was observed in patients, which is consistent with compensatory microvascular vasoconstriction and may be a marker of hemodynamic impairment (123).

Hsu and colleagues examined VASO response to breathhold in patients with meningiomas (124). It was observed that blood vessels in non-tumoral tissues were still able to dilate with breathhold challenge, but the vessels in the tumor regions showed minimal responses, suggesting that the blood vessels in tumors have lost their autoregulatory capacity (125).

9. Summary

At present, VASO MRI is the choice of method for CBV-based fMRI in humans. With careful selection of sequence components and imaging parameters, fMRI signals in VASO are expected to predominantly reflect total parenchymal CBV (i.e. microvascular) changes during brain activation. Physiology of brain vasculature further predicts that these changes originate mainly from arteries and capillaries with small, if any, contribution from the venous side. VASO MRI is particularly useful in situations where a pure contrast mechanism is desirable, since the more widely used BOLD signal reflects a combinations of multiple variables, including CBV, CBF, CMRO₂, and baseline venous oxygenation. VASO MRI can also play an important role in physiologic or clinical conditions in which the normal coupling of blood oxygenation, flow, and volume is altered or disrupted.

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Abbreviations used

fMRI functional MRI

CBV	Cerebral Blood Volume
BOLD	Blood-Oxygenation-Level-Dependent
VASO	Vascular-Space-Occupancy
ASL	Arterial-Spin-Labeling
TI	Inversion Time
MAGIC	Multiple-Acquisition-with-Global-Inversion-Cycling
MT	magnetization transfer
GRASE	Gradient-and-spin-echo

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Figure 1.

Illustration of how CBV changes could result in VASO signal changes (Modified from Peppiatt et al. 2006 (107) with permission). The blood magnetization is nulled in VASO, thus the MR signal of the vascular component is zero. Upon vasodilatation, a greater fraction of the voxel is nulled, therefore a signal decrease is expected.

Figure 2. VASO pulse sequence (a) and corresponding magnetizations (b) of blood and tissue.

Figure 3.

VASO responses to (a) flashing checkerboard visual stimulation, (b) breathhold, and (c) hyperventilation. Red voxels indicate regions with a significant response. The plots indicate time courses of the red voxels. Note that a VASO signal decrease indicates vasodilatation (CBV increase), whereas a VASO signal increase indicates vasoconstriction (CBV decrease). The black bars in the plots indicate the periods during which the stimulus/challenge was applied. (Modified from Lu et al. 2003 (7) with permission).

Figure 4.

Signal change of VASO fMRI as a function of TI. The symbols indicate experimental data and the black curve indicates model prediction. The experiment employed visual stimulation and the occipital cortex was used for signal averaging. The blood-nulling TI is 889 ms. (Adapted from Gu et al. 2006 (24) with permission).

Figure 5. Inflow-based VASO (iVASO) MRI. (a) Schematic illustration of the flip-back iVASO pulse sequence. RF and GR represent radiofrequency and gradient pulses, respectively. The numbers 1 and 2 indicate the non-selective and selective inversion, respectively. Adapted from Hua et al. 2011a (28) with permission. (b) Representative iVASO fMRI results (4 blocks of flashing checkerboard visual stimulation). The voxels with significant CBVa increases are highlighted with their z-scores (color scale). Time course averaged over all activated voxels is shown on the right. The horizontal bars at the bottom indicate the duration of stimulation. The red (stimulus) and blue (baseline) points were used in activation detection. Adapted from Hua et al. 2011a (28) with permission. (c) Illustration of the different principles employed between iVASO and pulsed ASL. Δ is the time needed for inverted blood to traverse the gap between the inversion (dashed box) and image plane (solid box) and δa the time needed for blood to traverse the arterial compartment before reaching the capillaries. The sum, $\Delta + \delta a$, is defined as the arterial transit time. In view of the impermeability of arterial vessels, it is assumed that blood water predominantly exchanges with tissue water in the capillary bed. The major difference between the contrast mechanisms is that iVASO is designed to highlight the vascular signal in the arterial and arteriolar compartments by nulling arterial blood while keeping a full signal in others, whereas ASL is sensitized to perfusion by monitoring labeled spins that have exchanged from the capillary compartment to extravascular tissue. In fact, a proper ASL acquisition

eliminates unwanted arterial blood effects by applying crusher gradients or a long post-labeling delay. Adapted from Hua et al. 2011b (50) with permission.

Figure 6.

Absolute CBVa quantification with iVASO MRI. Representative results from one subject at 3T: (a) Difference images for each TI in arbitrary units (a.u.). (b) Average S_{diff} (a.u.) in GM and WM as a function of TI. The error bars represent the standard deviations across the slice, which may have substantial variations in view of the vessel heterogeneity in different cortical regions. The mean GM curve was fitted with the iVASO theory. The two vertical dotted lines depict the fitted Δ and $\Delta + \delta_a$. (c) Fitted maps of CBV_a , Δ and δ_a in units of ml/100 ml, ms, and ms, respectively. For this data set, the gap between inversion and slice was 7 mm, and crusher gradients of $b = 0.3 \text{ s/mm}^2$ were applied. Adapted from Hua et al. 2011b (50) with permission.

Figure 7.

Simulation results of VASO signal change as a function of CSF volume fraction in the voxel. No CSF volume changes were considered. That is, it was assumed that CSF occupies a certain fraction of the voxel but this fraction does not change comparing activated state to resting state. Other assumptions used in the simulation were: baseline CBV fraction 0.047, activation-induced CBV change 30%, TR=3000 ms, TI=889 ms, CSF T1=4300 ms, Tissue T1=1166 ms.

Figure 8.

Comparison of VASO fMRI with bolus-tracking CBV fMRI. (a) Activation maps of these two CBV fMRI methods under visual stimulations using 4Hz and 8Hz flashing checkerboard. (b) Scatter plot of percent CBV changes estimated with the two methods. Modified from Lin et al. 2011 with permission (83).

Figure 9. Spatial specificity of CBV-based fMRI signal in comparison to BOLD-based signal. Panels (a), (b) and (c) show activation maps using MION-based CBV, spin-echo BOLD, and VASO, respectively, in cat visual cortex. Panel (d) shows signal amplitude as a function of distance to the cortical surface. Both VASO and MION-based fMRI show activation signals peaked around layer IV of the cortex whereas the BOLD signal was widespread across all layers. (Adapted from Jin and Kim, 2008 (109) with permission).

Figure 10.

Arterial origin of the iVASO signal. (a) T_2 values in GM for blood representing the difference between adjacent TIs (e.g. T_2 at TI = 629 ms is from the blood that flows in between TI = 523 and 629 ms, i.e. $S_{\text{diff}}(\text{TI}=629) - S_{\text{diff}}(\text{TI}=523)$) measured by a T_2 -preparation based ($\tau=10\text{ms}$, $\text{TE}=0/40/80/160\text{ms}$) sequence. Note that only TIs longer than 600 ms were included to allow sufficient inflowing blood in GM. The two horizontal dash-dot lines indicate the T_2 values for arterial (98% O_2 , 138.8 ms) and capillary (77% O_2 at baseline when assuming exponential O_2 decay, 96.6 ms) blood with normal hematocrit level (0.44) reported from *ex vivo* measurements using CPMG sequence ($\tau_{\text{CPMG}} = 10$ ms). The vertical dotted line depicts the average arterial transit time ($\Delta + \delta_a$). Mean values in GM were calculated per subject and then averaged across subjects ($n = 5$; error bars represent inter-subject SDs). For these experiments, the gap between inversion and imaging slice was 7 mm and crusher gradients of $b = 1.8 \text{ s/mm}^2$ were applied. Adapted from Hua et al. 2011b (50) with permission. (b) Hemodynamic responses for visual activation detected by iVASO and VASO. Time courses were scaled by the ratio of mean $\Delta S/S$ between VASO and iVASO to have coinciding maximal effects. True amplitudes of VASO and iVASO $\Delta S/S$ are on the left and right vertical legends, respectively. The vertical dotted lines mark the start and cessation of the stimulus. The points during the transition periods show error bars describing the inter-subject standard deviation ($n = 7$). Adapted from Hua et al. 2011a (28) with permission.

Figure 11.

Retinotopic maps obtained with VASO fMRI. The 3D maps are shown from two different views. Imaging parameters were: MAGIC-VASO sequence, gradient-echo EPI, TR=3 s, TI=822 ms, TE=8.7 ms, flip angle =90°, matrix 80×80, SENSE factor 2, FOV=240 mm, nine slices (3mm thickness, no gap). Modified from Lu et al. 2005 (102) with permission.

Table 1Blood T_1 values in the literature.

Oxygenation Level (%)	Species	Arterial (> 90%)	Capillary (70 – 90%)	Venous (< 70%)
Field Strength (T)				
1.5	Bovine	1355±38 (7)		1390±44 (7)
	Human			1540±23 (77)
3.0	Bovine	1664±14 (9)		1584±5 (9)
	Human			1852±104 (126) 1717±39 (127) 1748±117 (128)
7.0	Bovine		2212±53 (129)	
	Human			2587±283 (77)
11.7	Rat	2813±56 (130)		2768±69 (130)

Note: All T_1 values summarized were measured at body temperature (37°C) and typical hematocrit level (0.41–0.43).