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Time-Resolved MRI Oximetry for Quantifying $CMRO_2$ and Vascular Reactivity

Felix W Wehrli, Zachary B Rodgers, Varsha Jain, Michael C Langham, Cheng Li, Daniel J Licht, and Jeremy Magland

Laboratory for Structural NMR Imaging, Department of Radiology, Perelman School of Medicine, University of Pennsylvania

Abstract

This brief review of magnetic resonance susceptometry summarizes the methods conceived in the authors' laboratory during the past several years. It is shown how venous oxygen saturation is quantified in large draining veins by field mapping and how this information, in concert with simultaneous measurement of cerebral blood flow, yields $CMRO_2$, the brain's rate of oxygen consumption. The accuracy of this model-based approach in which the blood vessel is approximated as a long, straight cylinder, for which an analytical solution for the induced field exists, is discussed. It is shown that the approach is remarkably robust, allowing for time-resolved quantification of whole-brain metabolism at rest and in response to stimuli, thereby providing detailed information on cerebral physiology in health and disease not previously amenable by noninvasive methods.

Brain Oxygen Metabolism

The human brain accounts for only 2% of the body's weight but 20% of the body's total energy requirement (see, for example, [1]). This enormous energy demand, necessary to maintain the default mode of brain activity, is incompletely understood. Oxygen consumption, typically quantified as the cerebral metabolic rate of oxygen ($CMRO_2$), has been measured in various ways, most typically by positron emission tomography (PET), which yielded values on the order of 130 $\mu\text{mol}/\text{min}/100\text{g}$ [2] in the resting awake state. Even during light sleep $CMRO_2$ is only insignificantly lower [3], and only in deep sleep [4], and more so during anesthesia [5], is energy demand substantially lower. Further, incremental $CMRO_2$ increases in response to mental tasks have been found to be minor relative to the brain's baseline demand. The brain's default-mode energy demand is satisfied by oxidation of glucose to water and carbon dioxide. The resulting free energy generates ATP, the body's universal currency of energy. In contrast, incremental demand during task activation is supplied via the glycolytic pathway of glucose oxidation.

The ratio of the oxygen consumed over the oxygen supplied by blood flow (oxygen extraction fraction, OEF) has been found to be largely independent of the region of the brain in which it is measured [2]. Even though oxygen consumption of gray matter is four to five times greater than that of white matter, the greater oxygen demand is offset by a commensurate increase in the rate of delivery in the form of cerebral blood flow. Once OEF

is known, $CMRO_2$ can be quantified from a measurement of blood flow by invoking Fick's principle, typically expressed as:

$$CMRO_2 = C_a \cdot CBF \cdot (SaO_2 - SvO_2) \quad [1]$$

Here, C_a is the blood's oxygen carrying capacity, CBF is the cerebral blood flow, and SaO_2 and SvO_2 are the arterial and venous oxygen saturations, respectively. The difference between arterial and venous oxygen saturation, $SaO_2 - SvO_2$, is also referred to as AVO_2D arterio-venous oxygen saturation difference, AVO_2D . It is related to oxygen extraction

fraction as $OEF = \frac{AVO_2}{SaO_2}$ and, as long as arterial blood is fully saturated, $OEF = AVO_2$.

A recent review by Yablonskiy et al examined the various MRI based approaches for quantifying OEF , the key parameter that yields $CMRO_2$ via Eq. 1, along with the underlying theoretical models [6]. In this brief review we show how whole-brain OEF can be obtained by a quantitative MRI technique that relies on the measurement of the magnetic susceptibility of venous blood in one of the major cerebral veins, which together with simultaneous measurement of CBF by phase-contrast blood-flow velocimetry yields $CMRO_2$.

An increase in oxygen demand, for whatever reason, is enabled by neurovascular control mechanisms involving a cascade of signaling steps that lead to vasodilation, and thus enhance arterial blood flow. This physiologic mechanism linking increased blood flow to neurometabolic demand is known as neurovascular coupling, and is well preserved in normal physiology. However, neurovascular coupling becomes disrupted in many common pathologies including hypertension, ischemic stroke [7], traumatic brain injury [8], obstructive sleep apnea [9] and Alzheimer's disease [10]. The cerebrovascular dysregulation in many of these disorders is believed to be mediated by the deleterious action of reactive oxygen species on cerebral blood vessels [11].

Principle of MRI Susceptometry and Alternative Approaches to Measure Venous Oxygen Saturation

Magnetic Properties of Whole Blood

All magnetic resonance based methods for estimating SvO_2 rely on the blood's magnetic properties, specifically the paramagnetism of deoxyhemoglobin, first elucidated by Linus Pauling in the 1930s [12]. In oxyhemoglobin the six 3d electrons of Fe^{2+} at the center of the molecule's porphyrin moiety occupy the three lower energy orbitals, resulting in spin $S=0$. On the other hand, the slightly reduced ligand field splitting separating the two sets of orbitals in deoxyhemoglobin makes the configuration with single orbital occupancy and parallel electron spins more energetically favorable, resulting in a spin $S=2$.

While venous blood is not in itself paramagnetic, because of deoxyhemoglobin's paramagnetism, it is less diamagnetic than arterial blood or surrounding tissue, both of which have susceptibility near -9×10^{-6} (SI units), similar to that of water. In other words, venous blood displays *relative* paramagnetism in MR images. We will return to the exact value of the susceptibility of fully desaturated blood, or rather its difference relative to diamagnetic tissues, in the following section. Measurement of the induced magnetic field inside a blood vessel can, along with geometric information (which determines the so-called demagnetizing field, see for example, [13]), yield intravascular magnetic susceptibility, and thus SvO_2 [14] [15].

Lastly, we note that magnetic susceptibility is scale dependent. This is evident when we consider individual erythrocytes embedded in plasma. In venous blood, intracellular susceptibility is far less diamagnetic than that of its surroundings, i.e. plasma. Thus, the net susceptibility of whole-blood is a volume-weighted sum of its constituent values. This is an important distinction as the intra- to extracellular susceptibility difference gives rise to local gradients to which plasma and intracellular water molecules are exposed. Thulborn et al [16] first showed that water molecular diffusion in these local gradients is the dominant transverse relaxation mechanism in deoxygenated blood and measurement of blood water T_2 has since given rise to an important method for quantifying blood oxygen saturation noninvasively in vivo [17,18,19].

Model-Based Approaches for Quantifying Blood Magnetic Susceptibility: Accuracy and Reproducibility

In 1997, Haacke et al estimated oxygen saturation in a pial vein by modeling the vessel as a long, pseudo-infinite, cylinder [14]. Subsequently, Fernandez et al extended this idea to quantify OEF of the entire brain by measuring SvO_2 in the internal jugular vein, the major outflow conduit draining the blood from the brain [15].

To understand the underlying physical principle of the method we need to recall that the induced magnetic field resulting from compartmental differences in magnetic susceptibility depends on the compartments' physical shape (see, for example, [13]). While in general the induced internal field has to be computed numerically, analytical solutions exist for ellipsoids. Of particular interest in this context is the rotational ellipsoid with an aspect ratio (short axis/long axis) $\rightarrow \infty$ based on the notion that a blood vessel resembles a long cylinder.

Though the absolute field cannot be measured, only the field inside the cylinder relative to its surroundings is relevant, for which the following simple relationship holds:

$$\Delta B_{int} = \frac{\Delta\chi}{2} \left(\cos^2\theta - \frac{1}{3} \right) B_0 \quad (2)$$

Here, ΔB_{int} is the z-component of the induced field relative to the field far removed from the cylinder, $\Delta\chi$ is the difference in susceptibility between the two compartments and θ is the angle of the cylinder axis with respect to the applied field B_0 . The relative field outside the vessel is unperturbed as long as the vessel is parallel to B_0 but in general, obeys the following relationship (see, for example, [20]):

$$\Delta B_{ext} = \left(\frac{\Delta\chi}{2} \sin^2\theta \cdot \frac{a^2}{r^2} \cdot \cos 2\varphi \right) B_0 \quad (3)$$

Here, a is the vessel radius, r the distance perpendicular to the vessel axis, and φ is the angle between the direction of r and the plane defined by B_0 and the vessel axis. The relationships expressed by Eqs. 2 and 3 are illustrated in Figure 1.

The internal field ΔB_{int} inside the vessel can be computed by phase difference mapping, i.e. by measuring the phase difference between the intra- and extravascular signal. This is relatively straightforward as long as the inhomogeneity outside the vessel can be ignored, i.e. if $\Delta B_{ext} \approx 0$ can be assumed. Inspection of Eq. 2 shows that for small angles, in practice for $\theta < 20^\circ$ ($\sin^2\theta \sim 0.1$), ΔB_{int} falls off quickly with a/r , decreasing to <5% five cylinder (i.e. vessel) radii away from the vessel axis. Further, we note that because of the sinusoidal

relationship with the azimuthal angle ϕ , ΔB_{ext} averages to zero within a circular tissue reference region.

The blood magnetic susceptibility χ scales with hematocrit, Hct , and the fraction of deoxygenated hemoglobin ($1 - SvO_2$) as

$$\Delta\chi = \Delta\chi_{do} \cdot Hct \cdot (1 - SvO_2) \quad (4)$$

The constant $\Delta\chi_{do}$ represents the susceptibility difference between fully oxygenated and fully deoxygenated blood. The accuracy of the method critically hinges on the value of this constant. While some prior work used a value of 0.18 ppm cgs (see, for example, [20] and references cited), this value is based on early work by Weisskoff et al [21] (who, incidentally, coined the term “susceptometry”). Later, Spees et al remeasured $\Delta\chi_{do}$, finding a value of 0.27 ppm by MR as well as SQUID experiments [22]. More recently, Jain et al measured the phase difference in an array of sample tubes oriented parallel to the external field relative to water for human blood at 37°C covering the entire range of oxygen saturation values, in comparison to blood gas analysis as the ground truth [23]. They obtained a value of 0.273 ± 0.006 ppm in excellent agreement with [22].

Measurement of ΔB is obtained from the difference in the phase between two successive echoes:

$$\Delta\phi(x, y) = \gamma \cdot \Delta B \cdot \Delta TE \quad (5)$$

where $\Delta\phi(x, y)$ is the relative phase at pixel location (x, y) , γ is the gyromagnetic ratio, and ΔTE is the inter-echo time.

Combining Eqs. 2, 4 and 5 yields for the venous blood oxygen saturation SvO_2 :

$$SvO_2 = 1 - \frac{2\Delta\phi_{ie}}{\gamma B_0 \cdot \Delta TE \cdot \Delta\chi_{do} \cdot Hct \left(\cos^2\left[\theta - \frac{1}{3}\right] \right)} \quad (6)$$

Eq. 6 assumes that $\Delta B_{ext} \approx 0$. Here, $\Delta\phi_{is} = \Delta\phi_{intra} - \Delta\phi_{extra}$ represents the intra- to extravascular phase difference. Further, SvO_2 is expressed as a fraction ranging from 0 to 1, therefore requiring multiplication by 100 to obtain the more familiar percent units.

Figure 2 shows a magnitude and phase-difference image at the level of the internal jugular vein. We note the small increase in phase for the jugular vein while all arteries appear with tissue background phase. The angle θ between vessel axis and static magnetic field orientation required in Eq. 6 is computed from the tangent of the vessel relative to B_0 . Note that errors from flow-induced phase in the case of vessel obliquity are eliminated if the phase difference is computed from two successive equal-polarity echoes [24].

Among the potential sources of error in MR susceptometry is the static field inhomogeneity caused by interfaces between air and tissue, given the large susceptibility difference between these two compartments (~ 9 ppm). One approach practiced in the past is high-pass filtering as a means to mitigate the effects of these low spatial-frequency modulations of the phase resulting from large-scale induced magnetic fields. Langham et al conceived an alternative method that acquires data by fitting the static field inhomogeneity to a second-order polynomial, after appropriate weighting and masking of the vessels of interest [25]. This method has been applied systematically in the authors' susceptometry work, including for obtaining the phase maps of Figure 2.

Given that blood vessels – in particular veins – usually do not have circular cross-section, and exhibiting curvature, branching and tapering, one may wonder how these deviations from the long circular cylinder model affect the accuracy of the method. This problem has recently been addressed by Li et al [26] via simulation of the internal magnetic field arising from common veins (superior sagittal sinus (SSS), jugular and femoral veins) using a voxel-based perturbation method [27], which has been shown to be accurate in situations where $\Delta\chi \ll 1$ (see also subsequent section). At a typical venous oxygen saturation of 65%, the absolute error in %HbO₂ estimated via a closed-form cylinder approximation was <3 %HbO₂ averaged over three locations in the three veins studied (superior sagittal sinus (SSS), jugular and femoral vein) and did not exceed 5% for vessel tilt angles <30° at any one location. In the SSS (which has essentially triangular cross-section), the error at the three locations indicated in the 3D venogram of Figure 3 was 0.7, 2.8 and 4 %HbO₂. Similarly, the error was evaluated in phantoms mimicking the quasi-triangular cross-section of the SSS, and compared with the results in sample tubes of circular cross-section, both containing gadolinium-doped water yielding magnetic susceptibility consistent with venous blood [28]. The entire assembly was immersed in water representing surrounding tissue. The relative mean difference between the susceptibility values derived from the phase measurements in the circular and triangular vessel phantoms was 2.6%, which would correspond to an average absolute difference in SvO₂ of 0.8% at a Hct of 0.42. These data, along with those of the studies described below, suggest the infinite cylinder model to be remarkably accurate for SvO₂ quantification.

Numerical Approaches to Obtain Spatially Resolved Susceptibility from Induced Field Maps

Rather than relying on a model for deriving susceptibility from a measurement of the internal field, there has been growing interest in numerically evaluating $\Delta\chi(x, y, z)$ from field maps. The induced field, $\Delta B_z(x, y, z)$ can be thought of as arising from the magnetic dipoles represented by $\Delta\chi(x, y, z)$. Symbolically, the relationship between ΔB and $\Delta\chi$ can be written

as a convolution of the source, $\Delta\chi$, with a dipole kernel d , as $\frac{\Delta B_z}{B_0} = \Delta\chi \otimes d$ (see, for example, [29]). Unfortunately, computation of $\Delta\chi$ is an ill-posed inverse mathematical problem whose solution is fraught with difficulties even though recent progress has been encouraging (see, for example, [30]). The source, in our case of measuring SvO₂, would be the spatial distribution of magnetic susceptibility arising from deoxyhemoglobin in the venous tree. In preliminary work, Fan et al showed that inversion of the field map to yield intravenous susceptibility, and thus oxygen saturation in cerebral veins, may be feasible [31].

T₂-Based Approaches

An alternative MR-method for quantifying SvO₂ exploits the modulation of the transverse relaxation time caused by diffusion of the water in the intrinsic field gradients within and surrounding erythrocytes that contain partially deoxygenated blood [17]. The transverse relaxation time T₂, which decreases with decreasing SvO₂, is typically derived as the time constant of a Carr-Purcell spin-echo decay. Since the irreversible dephasing (the underlying T₂ mechanism) is a function of both field strength and inter-echo spacing, the method requires calibration curves. Lu et al perfected the original method to yield images free of stationary tissue signals thereby minimizing partial volume errors. The method, termed T₂ Relaxation Under Spin Tagging (*TRUST*) [19] has since been shown to allow robust measurement of SvO₂ and, along with flow, to yield CMRO₂, both at baseline and in response to various stimuli [32,33]. Nevertheless, compared to susceptometric techniques *TRUST* requires longer scan time even though more recent embodiments have improved

temporal resolution to a little over one minute [34]. Further, by collecting projections rather than full images, Jain et al succeeded in shortening scan time to about 15 seconds [35].

Time-Resolved Quantification of Whole-Brain CMRO₂ at Rest and In Response to Stimuli

Simultaneous Measurement of Flow and SvO₂

Resting-State CMRO₂ and Response to Isometabolic Stimuli—Jain et al designed a pulse sequence consisting of four interleaved axial gradient-echoes toggling between a location superior to the carotid bifurcation, for measurement of total cerebral blood flow (*tCBF*), and a location at the level of the SSS for quantifying SvO₂, together enabling CMRO₂ quantification with a temporal resolution of 30 s [28]. Global SvO₂ was inferred from SvO₂ in the SSS, which is the main cerebral draining vein accounting for approximately 50% of cerebral venous drainage, and in which oxygen saturation values have been shown to match global SvO₂ [19]. Flow velocity was measured from transverse images at the level of the internal carotid arteries and vertebral arteries (the major inflow conduits) using conventional phase-contrast techniques. Temporally averaging over the cardiac cycle and spatially across each of the four vessels yielded *tCBF* in mL/100 g/min tissue, normalized to brain mass derived from a 3D set of anatomic images. Average SvO₂, *tCBF*, and global CMRO₂ values in eight healthy subjects were 64±4%, 45.2±3.2 mL/100 g/min, and 127±7 μMol/100g/minute, respectively. These data agree well with literature values [19,36]. Short-term reproducibility was excellent, allowing systematic differences between study subjects to be evaluated. As expected, AVO₂D was negatively correlated with blood flow (R=0.74, p<0.01) consistent with the principle that subjects with greater flow extract less oxygen as a means of keeping CMRO₂ constant (Figure 4a). In spite of the narrow distribution in CMRO₂ in the eight subjects there were small but statistically significant differences between subjects (Figure 4b).

Lastly, it has been shown that the method can be regionalized by selecting, for example, a cortical vein in lieu of a large draining vein for susceptometry [37,38], as originally suggested by Haacke et al [14]. Jain et al [37] demonstrated the feasibility of determining regional CMRO₂ (*rCMRO₂*) corresponding to the middle cerebral artery (*MCA*) territory by measuring regional CBF (*rCBF*) in the *MCA* and *rSvO₂* in the great vein of Galen, the largest superficial cortical vein pertaining to that vascular territory. From this they quantified *rCMRO₂* to a visual stimulus, finding that during task-based stimulation *rCBF* and *rSvO₂* increased in parallel. Fan et al, using similar approaches, reported *rSvO₂*, *rCBF* and *rCMRO₂* data in the cerebral cortex of healthy subjects [38]. However, the difficulty in defining corresponding blood flow supply and drainage regions imposes significant limitations on these techniques.

The methodology described above was subsequently evaluated to study the effect of an isometabolic stimulus, in this case hypercapnia [39]. While significant increases in SvO₂ and *tCBF* were observed during hypercapnia (p<0.005), no change in CMRO₂ was noted (p>0.05). Figure 5 shows images at baseline, during stimulus and during recovery for both *tCBF* and SvO₂ illustrating the dynamic hypercapnic response. Figure 6 displays the time-course of the two functional measures. The data are in good agreement with those by Chen and Pike [40], who reported a conservation of CMRO₂ during mild hypercapnia but are at variance with those by Xu et al. [33], who observed a small decrease in CMRO₂ during hypercapnia with the effect being dose dependent. Further, the fractional changes in *tCBF* and end-tidal carbon dioxide were correlated (R²=0.72, p<0.005), as were baseline SvO₂ and *tCBF* (R²=0.72, p<0.005). The data also implied a correlation between CVR and baseline *tCBF* (R²=0.44, p=0.052), with CVR=6.1±1.6%/mm Hg CO₂. Additionally, an average

undershoot of $6.7 \pm 4\%$ and $17.1 \pm 7\%$ was observed in SvO_2 and $tCBF$ upon recovery from hypercapnia in six subjects. The data thus suggest that the method allows detailed information to be obtained on whole-brain neurometabolism at rest and in response to a stimulus, thereby opening the potential to study neurovascular reactivity in a host of disorders where neurometabolic coupling is dysregulated [10,41,42].

Clinical Applications to the Brain in Neonates with Congenital Heart Disease

—More recently, some of the authors of the current review article applied the above approach to a cohort of neonates with congenital heart disease. The anatomic abnormalities in these patients are known to alter cerebral hemodynamics and are implicated as a major risk factor for the brain injuries seen in this population. Here, $tCBF$ and oxygen metabolism were studied in 26 pre-operative neonates with congenital heart disease, at rest and during hypercapnia, the latter as a means to determine whether neurovascular reactivity was affected. Unlike in the previously reviewed work in adults, flow measurements in the carotid and vertebral circulation is not feasible due to the extremely small size of these vessels. Therefore, both flow and SvO_2 were measured in the SSS, accounting for the fact that the latter drains only about 50% of cerebral blood flow. During hypercapnia, $tCBF$ was found to increase by 115% and AVO_2D decrease by 52% (both $p < 0.001$) without a change in $CMRO_2$ ($p = 0.65$), demonstrating a neurovascular response in these infants very similar to that found earlier in adults. In a subset of patients ($N = 8$), postoperative data were also available, showing a substantial increase in $CMRO_2$ postoperatively. Lastly, the data suggest that preoperative $CMRO_2$ is predictive of outcome in terms of periventricular leukomalacia, a known consequence of brain hypoxia, in that low $CMRO_2$ in patients was found to be associated with greater white matter damage. Full details of this study are being published elsewhere.

High-Speed $CMRO_2$ Measurement in Response to Non-Steady-State Stimuli

Although a temporal resolution of 30 seconds for $CMRO_2$ quantification represents a significant improvement over previous techniques, it is not adequate to allow measurement of quasi real-time changes, such as in response to neurologic stimuli or during dynamic physiologic challenges as in apnea. In recent work by some of the authors, $CMRO_2$ quantification was achieved with a temporal resolution of 3 seconds by a combination of view sharing in which the central portion of k-space is sampled more often than the periphery and SSS-based estimation of total cerebral blood flow [43]. The technique was applied in 10 healthy adults during a volitional apnea paradigm of three repeated 30 s breath-holds.

Figure 7a displays the cohort-averaged time-course for venous and arterial oxygen saturation (the latter obtained by pulse oximetry), as well as $tCBF$. We note some desaturation during breath-hold period along with the expected increase in SvO_2 and blood flow. The corresponding computed parameters (AVO_2 and $CMRO_2$) are shown in Figure 7b. Subject-averaged maximum changes in $tCBF$ and AVO_2D were $43.5 \pm 9.4\%$ and $-32.1 \pm 5.7\%$, respectively, resulting in a small ($6.0 \pm 3.5\%$) but statistically significant ($p = 0.00044$, two-tailed t-test) increase in average end-apneic $CMRO_2$.

Apnea has in the past often been assumed to be an isometabolic stimulus in BOLD fMRI studies, for calibrating the BOLD signal to quantify relative $CMRO_2$ changes (see, for example, [44]). The above results suggest that apnea may in fact be slightly pro-metabolic. The authors of [43] conjectured that increased $CMRO_2$ could represent a mechanism for buffering brain energy in anticipation of prolonged apnea, which eventually would lead to exhaustion of energy stores.

The high temporal-resolution paradigm in this work provides a simple tool for assessing neurovascular reactivity and neurovascular coupling in response to apnea in diseases in which this response may be blunted, such as obstructive sleep apnea [9,45,46]. Finally, application of the technique to regional drainage veins, as discussed previously, such as those draining the visual cortex, could be applied to neural activation tasks toward a better understanding of the biophysical origins of the BOLD signal and BOLD post-stimulus undershoot [47] [48].

Conclusions and Future Directions

We have described MRI susceptometry, a method for quantifying blood oxygen saturation in veins from the susceptibility-induced MR signal phase. Combined with blood flow measurement, the technique has been shown to enable quantification of brain oxygen consumption at baseline as well as in response to physiologic challenges. Outside the intended scope of the present review the method also has demonstrated its potential to evaluate vascular reactivity in the extremities and applications in other organ systems should be feasible.

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Figure 1. Schematic showing relationship between applied field, B_0 , vessel orientation and angles θ and ϕ in Eqs 2 and 3.

Figure 2. Measurement of venous oxygen saturation: a) magnitude gradient-echo image at the level of the common carotid arteries; phase-difference image showing increased phase for jugular veins (arrows) but not arteries. From the intra- to extravascular phase difference SvO_2 in the jugular vein was computed from Eq. 6 as 65%.

Figure 3.

a) Axial gradient-echo image showing the superior sagittal sinus (SSS); (b) 3D rendition of SSS and orientation relative to the applied field; (c) analytically computed field map at location 2 (panel B); (d) model-based field map for the infinite cylinder approximation and the same tilt angle of 20.1° , yielding very similar field pattern, with an average intravascular field difference of 0.010 ppm, corresponding to 2.6% HbO_2 (from Li et al [26], with permission).

Figure 4.

a) Correlation between AVO_2D and total cerebral blood flow in eight subjects ($R^2=0.74$, $P<0.006$). Note that subjects with higher CBF values tend to have lower AVO_2D ; b) Scatter plot of the cerebral metabolic rate of oxygen ($CMRO_2$) for each subject over three scanning sessions illustrating reproducibility. The vertical span of each diamond represents the 95% confidence interval for each group (from Jain et al [28], with permission).

Figure 5.

Images from which venous oxygen saturation (SvO_2) and total cerebral blood ($tCBF$) flow during baseline, hypercapnia and recovery were derived: **a)** Axial magnitude image distal to the carotid bifurcation, used for quantification of tCBF; **b)** velocity images during baseline, hypercapnia and recovery showing increased velocity during the stimulus phase; **c)** axial magnitude image showing SSS; **d)** phase difference images during baseline, hypercapnia and recovery showing reduced intravascular phase during hypercapnia, commensurate with decreased oxygen extraction during hypercapnia (modified, from [39], with permission).

Figure 6.

Time-course of $tCBF$ and S_vO_2 during normocapnia (purple) and hypercapnia (pink) in a representative subject showing how the two parameters change in concert with each other. Note undershoot during recovery from hypercapnia (from [39], with permission).

Figure 7.

a) Time-course plot of cohort-averaged S_aO_2 , S_vO_2 , and $tCBF$ absolute parameter values; b) $tCBF$, AVO_2D , and $CMRO_2$ absolute parameter values. Error bars indicate ± 1 SD, shaded areas the apnea period. All values in time-course plots represent averages across the three repeated blocks of the paradigm. The bracketed sections 'Base' and 'EA' indicate the data used for computing average baseline values and end-apnea values (from Rodgers et al [43], with permission).