Sources of Systematic Bias in Hypercapnia-Based CMR_{O2} Estimation using Functional MRI

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Introduction

An ability to measure neurovascular coupling using MRI may have significant impact as a tool in clinical diagnosis. This will require appropriate physiological interpretation of BOLD fMRI studies, which involve simultaneous changes in cerebral blood flow (CBF), cerebral blood volume (CBV), and the rate of aerobic metabolism (CMR_{O2}). Here, we present a thorough re-examination of systematic bias in the widely used hypercapnia-normalized method for CMR_{O2} estimation [1,2], specifically highlighting an unexamined dependence on the value of the hypercapnia calibration constant (M). This re-examination of the model is of broad applicability to the fMRI community, especially given the difficulty of measuring M—due to the low magnitude of CBF changes during hypercapnia (~30 %), the large extrapolation required from measurable values, and the relatively small number of repeat measurements typically used to determine M.

Experimental

CMR_{O2} during neural activation may be estimated from BOLD and CBF measurements by the relationship [1]

$$\frac{\Delta BOLD}{BOLD_0} = M\left[1-\left(\frac{CMR_{O_2}}{(CMR_{O_2})_0}\right)^{\beta}\left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\right]$$

where α is the Grubb coefficient (0.38), and β is a constant describing the oxygenation and field strength dependence of the BOLD effect (β=1.5 commonly used). M represents the hypothetical maximum BOLD signal change resulting from a CBF increase sufficiently large to result in 100% oxy-Hb saturation in the venous vessels. This method relies on an epoch of iso-metabolic CBF increase, induced by CO_2-breathing, to calibrate the BOLD signal at resting CMR_{O2}.

We use simulated data to illustrate trends in the neurovascular coupling model. We also investigate the theoretical transformation between BOLD vs. CBF and CMR_{O2} vs. CBF spaces using a grid to illustrate how the choice of model parameters will influence the outcome of a neurovascular coupling study.

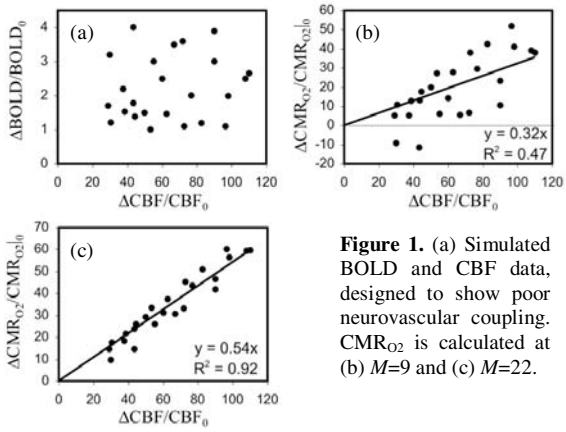

Figure 1. (a) Simulated BOLD and CBF data, designed to show poor neurovascular coupling. CMR_{O2} is calculated at (b) M=9 and (c) M=22.

Results

A simulated set of BOLD–CBF neural activation data is shown in Figure 1, intended to reflect *poor* neurovascular coupling. Using these data to estimate CMR_{O2}, we see that using an M value of 9 (Figure 1b) yields CMR_{O2}:CBF estimates that exhibit some overall linearity (R^2=0.47 and slope 0.32). When the assumed value of M is changed to 22, we observe a dramatically improved apparent linearity (R^2=0.92), as well as a greater slope (0.54). Figure 2 illustrates the relationship between BOLD vs. CBF space and CMR_{O2} vs. CBF space, by performing the transformation on a grid with sensible upper and lower ranges for BOLD–CBF data. The grid is color coded, with the quadrant that typically contains neural activation data in black and the quadrant typically containing deactivation data in blue.

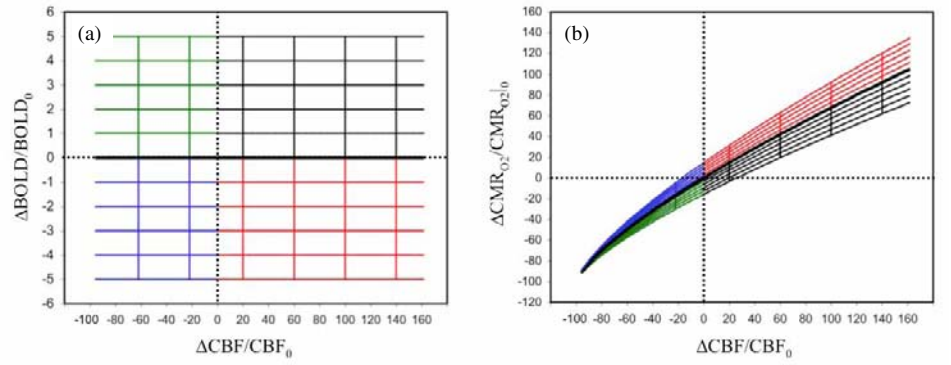

Figure 2. (a) Grid constructed on BOLD vs. CBF coordinate frame, with BOLD increments of 1 % and CBF increments of 20 %. (b) Change in CMR_{O2} calculated at each point on the grid, plotted as CMR_{O2} vs. CBF at M=22. Colored regions of the grid are provided to show correspondence between (a) and (b). The line $\Delta BOLD/BOLD|_0=0$ in (a) is shown as a thick curve in (b)

Discussion and Conclusions

The CBF:CMR_{O2} coupling ratio of 3.1:1, as obtained from the fitted slope in Figure 1b, is well within the range of an estimate provided by Kastrup *et al* (3.3:1), who also uses an M value of 9 [3]. The CBF:CMR_{O2} coupling ratio of 1.85:1 for the simulated data in Figure 1c, is similar to that observed by Hoge *et al* (2:1), who also uses an M value of 22 [2]. It is surprising to observe that the major results pointing to strongly linear cerebrovascular coupling in the literature may be replicated using a simulated set of "poor" data, with M chosen to match the respective M for a given study. This behavior is generalized in Figure 2. BOLD vs. CBF space is seen to be mapped onto a weakly nonlinear sliver of CMR_{O2} vs. CBF space. Figure 2 shows the remarkable covariance between CBF and CMR_{O2} — data anywhere within the activation region (black) will appear roughly linear at M=22. CMR_{O2} estimates from *de*activation data (blue region) are expected to display far greater tightness of coupling, regardless of their actual BOLD and CBF values—a conjecture that is supported by data in the literature [4,5]. We explore the compression of the BOLD vs. CBF grid, towards the central curve $\Delta BOLD/BOLD|_0=0$ (thick line) as M is increased, and investigate the implications of covariance between the coupling slope and the "tightness" of coupling. In summary, our results demonstrate the extent to which the tightness of CMR_{O2}–CBF coupling and the slope can be predicted from the value of M alone. This argues for a much more careful measurement of M to minimise this potential bias.

[1] Davis TL, *et al*. Proc Natl Acad Sci USA 1998;95:1834-9. [2] Hoge RD, *et al*. Proc Natl Acad Sci USA 1999;96:9403-8. [3] Kastrup *et al*. Neuroimage 2002;15:74-82. [4] Uludag et al. Neuroimage 2004;23:148-55. [5] Stevanovic *et al*. Neuroimage 2004;22:771-8.