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Comment on ‘Estimating a modified Grubb’s exponent in healthy human brains with near infrared spectroscopy and transcranial Doppler’

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Abstract

The relationship between cerebral blood volume (CBV) and blood flow (CBF) has gained widespread interest because of its utility in using functional magnetic resonance imaging and optical imaging methods to estimate the cerebral metabolic rate of oxygen (CMRO₂). A recent paper by Leung *et al* (2009 *Physiol. Meas.* **30** 1–12) nicely presents measurements relating CBV to cerebral blood flow velocity (CBFV) as measured by near infrared spectroscopy and transcranial Doppler, respectively. They suggest that this relationship cannot be inverted to estimate CBF (or CBFV) from CBV, and that doing so to estimate CMRO₂ is inappropriate. We argue that these data, and other related published data, do permit the estimation of CBF from CBV and thus enable CMRO₂ to be estimated when only measures of CBV and deoxygenated hemoglobin are available.

Keywords

Grubb’s exponent; cerebral metabolic rate of oxygen; near infrared spectroscopy; functional magnetic resonance imaging; cerebral blood flow; cerebral blood volume

Comment

The estimation of CMRO₂ by functional magnetic resonance imaging (fMRI) and optical imaging requires measures of CBF and oxygen extraction fraction, the latter of which is typically determined from CBV and deoxygenated hemoglobin (HbR). The changes in CMRO₂ can be expressed as (Mayhew *et al* 2001)

$$1 + \frac{\Delta \text{CMRO}_2}{\text{CMRO}_{2,0}} = \left(1 + \frac{\Delta \text{CBF}}{\text{CBF}_0} \right) \left(1 + \frac{\Delta \text{HbR}}{\text{HbR}_0} \right) \left(1 + \frac{\Delta \text{CBV}}{\text{CBV}_0} \right)^{-1}$$

where the subscript ‘0’ indicates a baseline value and indicates an absolute change.

With fMRI, changes in CBF and HbR are typically measured using arterial spin label imaging and blood oxygen level-dependent imaging respectively; changes in CBV are estimated from the measured changes in CBF to calculate changes in CMRO₂ (Davis *et al* 1998). Optical imaging, through the spectroscopically varying absorption of oxygenated (HbO) and deoxygenated hemoglobin, provides a different measure of CBV, which is assumed to be proportionally related to the total hemoglobin concentration HbT = HbO + HbR; CMRO₂ changes are then calculated by estimating the CBF change from the measured CBV change (Boas *et al* 2003).

The assumed relationship between changes in CBF and changes in CBV is thus central to the estimation of CMRO₂ changes. This relationship is commonly expressed in terms of a Grubb's exponent, G , as (following Leung *et al* (2009))

$$\left(\frac{CBV}{CBV_o}\right) = \left(\frac{CBF}{CBF_o}\right)^G$$

or

$$G = \frac{\log(CBV/CBV_o)}{\log(CBF/CBF_o)}.$$

Leung *et al* (2009) measured this exponent with transcranial Doppler (TCD) and near infrared spectroscopy and compared their value with that obtained from a number of other studies, reproduced in table 1 with some additional information for each study. As stated by Leung *et al* (2009), one cannot simply invert Grubb's exponent to get the dependence of CBF on CBV but must instead perform the linear regression with CBF as the dependent variable and CBV as the independent variable. We have thus performed the analysis for all the studies presented in table 1 using their data as given in the relevant papers, both for CBV as the dependent variable and CBF as the independent variable and vice versa. As expected, the inverted Grubb's exponent estimated in this manner is different from the inverse of Grubb's exponent.

However, we note that both of these calculations assume that the dependent variable is functionally dependent on the independent variable and that the variance in the linear regression comes only from the variance in the dependent variable. These conditions do not hold as both CBV and CBF are functions of other physiological stimuli (for example arterial blood pressure or arterial CO₂ partial pressure), and thus neither is directly dependent on the other. Furthermore, all the experimental studies presented in table 1 have noise in the measures of both CBV and CBF. A more appropriate analysis of these data must consider the variance in both parameters, as is done by the total least-squares (TLS) method; Grubb's exponent estimated by TLS is thus also presented in table 1. All the values obtained fall between the two different linear regression analyses, although they all are closer to the values obtained when assuming that CBF is error-free. This is due to the fact that equal variances on the two measurements equate to a larger proportional error in CBV. If the actual

values of the errors were known, the most likely estimate of Grubb's exponent could be calculated rigorously, using an approach proposed by Krystek and Anton (2007).

The values given in table 1 have values of G in the range 0.28–0.56, which is consistent with the values found in other studies (Sheth 2004, Huppert *et al* 2007). This is a large range of values for Grubb's exponent. Variations are likely to arise due to the differences in the form of stimulus, species and anesthesia used. Uncertainty in the exact value of Grubb's exponent will reduce confidence in the prediction of CBV from CBF or vice versa, and thus any estimates of the change in CMRO₂; however, without knowledge of the likely errors in both measurements, this cannot be quantified here.

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Table 1.

Grubb's exponent as reported by various studies and re-estimated from the data contained within the related papers. Note that we did not constrain the data fits to have a 0 intercept.

Studies	Methods	State	Grubb's exponent CBV versus CBF	Inverse Grubb's exponent CBF versus CBV	Grubb's exponent TLS
Jones <i>et al</i> 2001	Optical and laser Doppler	Dynamic	0.29 (1/3.40)	2.90 (1/0.34)	0.30 (1/3.36)
Grubb <i>et al</i> 1974	PET	Steady	0.38 (1/2.62)	2.14 (1/0.47)	0.39 (1/2.55)
Lee <i>et al</i> 2001	MRI	Steady	0.36 (1/2.81)	2.81 (1/0.36)	0.36 (1/2.82)
Jones <i>et al</i> 2001	Optical and laser Doppler	Steady	0.30 (1/3.32)	3.01 (1/0.33)	0.30 (1/3.29)
Ito <i>et al</i> 2003	PET	Steady	0.28 (1/3.53)	2.39 (1/0.42)	0.29 (1/3.41)
Leung <i>et al</i> 2009	Optical and TCD	Steady	0.30 (1/3.33)	1.80 (1/0.56)	0.32 (1/3.10)