Cortical Cerebral Blood Flow in Aging: Effects of Haematocrit, Sex and Ethnicity.

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Synopsis

Cerebral blood flow (CBF) estimates using arterial spin labelling (ASL) show unexplained variability in older populations. We studied the impact of haematocrit (Hct) on CBF quantification in a tri-ethnic elderly population cohort. Hct was measured from blood samples and pseudo-continuous ASL performed on 3T MR. CBF was estimated using a fixed value of 43.5% (model 1) and individually measured Hct (model 2) to calculate the longitudinal relaxation time of blood in simplified Buxton equations. CBF estimates using individual Hct were lower than CBF estimates using a mean Hct in all ethnic and sex categories except white European men.

Purpose

Cerebral blood flow (CBF) measured using arterial spin labelling(ASL) has been recognised as an early biomarker for dementia, cognitive decline and small vessel disease [1-4]. However, CBF estimates show unexplained variability in older populations. We studied the impact of haematocrit (Hct) on CBF quantification in a tri-ethnic elderly population.

Background

Deriving quantitative perfusion values from the raw MRI signal requires application of a model containing several assumptions relating to physiological properties of the blood and tissues. The ISMRM white paper recommendations include the application of a simplified Buxton equation for quantification of single post-labelling delay ASL using 1650ms as the longitudinal relaxation time of blood (T1$_{blood}$) at 3T [5]. This value has been derived from experiments under appropriate physiological conditions and assuming an average adult Hct of 43.5%[6]. Hct varies by sex with females typically having lower Hct than males [7] and there is evidence regarding Hct differences between some ethnic groups [8, 9]. The purpose of this study was to investigate the influence of Hct on the estimation of CBF and to determine how this impacts on the associations of CBF with sex and ethnicity.

Methods

Study subjects (n = 493, 40% female, age mean (SD) 71.6 ±5.9 years) were an elderly community-dwelling London based population cohort from three ethnic backgrounds (White European, South Asian and African Caribbean) drawn from the SABRE Study (SABREstudy.org). Hct was measured using an impedance based, direct current sheath flow method (Sysmex XE2100) from a venous blood sample. 3T cerebral MR (Achieva, Philips, Best, The Netherlands) included a sagittal T1-weighted 3D-TFE (TR/TE/TI 7/ 3.2/836ms, flip-angle 18°, voxel size 1mm^3), and a transversal 2D pseudo-continuous arterial spin labelling (PCASL), (EPI, TR/TE 4615/15ms, flip-angle 90°, voxel size 3.75mm x 3.75mm x 5mm, 1mm slice gap, 20 slices), labelling duration 1800ms, post labelling delay 2000ms. Tissue segmentation was obtained using the Geodesic Information Flows framework [10]. T1$_{blood}$ was calculated based on the formula: T1=(0.52*Hct+0.38)$^{-1}$ [6] either with fixed value of 43.5% (corresponding to the standard value of T1=1650ms), used in model 1 (CBF_fixed), or calculated based on the Hct values measured from each participant and used in model 2 (CBF_Hct). Partial volume correction was applied based upon the method used in [11]. Differences in perfusion between CBF models stratified by sex and ethnicity were calculated. Statistical significance (p<0.05) between the CBF models was tested with paired Student's t-tests.

Results

Results are shown in *Table 1*. The mean (SD) Hct level in men was 43.0% (±3.5), and in women was 39.6% (±3.0). CBF modelling with individual Hct adjustment decreased CBF estimates in all ethnic and sex categories except white European men. The decrease for women was - 2.7 mL/100g/min (p<0.001, 95% confidence interval (CI) -3.0, - 2.4 mL/100g/min). The size of this effect differed by ethnicity with estimated perfusion in South Asian women found to be lower by – 3.0 mL/100g/min (p<0.001, 95% CI -3.6, - 2.5 mL/100g/min), and African Caribbean women by -3.1 mL/100g/min (p<0.001, CI -3.6, -2.5 mL/100g/min). Example CBF_fixed and CBF_Hct maps are shown in *Figure 1* for a woman with Hct of 37.5%. Correction for individual Hct altered sample frequency distributions of CBF values, especially in non-European ethnicity women (*Figure 2*). *Figure 3* demonstrates the inverse linear relationship of Hct with CBF_fixed and CBF_HCT models. This relationship is reduced with use of the CBF_Hct model although some association of Hct with CBF in men remained (r = - 0.18, P = .002). Further adjustment for potential confounders of mean arterial blood pressure, Body Mass Index, diabetes and dyslipidemia did not affect this relationship when entered in a regression model (β= -0.3, P = .020, CI -0.6, -.05 mL/100g/min).

Discussion

This study has shown that Hct levels differ according to sex and ethnicity and this influences CBF estimated from ASL. Our findings suggest that research studies using ASL to measure CBF should routinely measure Hct and adjust T1$_{blood}$ accordingly. Further research is warranted into whether adjustment of the Hct value in CBF models to accommodate demographic differences provides stronger associations with cerebrovascular disease, dementia and cognitive decline than previous models using a fixed mean Hct value. Such an approach may improve early risk assessment in ethnic groups

Conclusion

Studies of elderly populations using ASL to estimate CBF, uncorrected for the influence of an inappropriate fixed Hct mean to set the value of T1 blood, may lead to systematic underestimation of risk of the neurodegenerative diseases of old age when CBF is used as a biomarker. Whenever possible, individualised measures of Hct should be included in ASL derived estimates of CBF.

Acknowledgements

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Figures

		Cortical CBF_fixed (ml/100g/min)	Cortical CBF_Hct (ml/100g/min)	Mean Difference (ml/100g/min)	95% CI (ml/100g/min)	Mean Difference (%)	p-value
	All	50.1 ±7.9	48.8 ±7.3	-1.3	(-1.5 -1.1)	-2.6	<0.001
	Men	50.0 ±8.3	49.6 ±7.6	-0.4	(-0.7 -0.1)	-0.8	0.005
	Women	50.2 ±7.2	47.5 ±6.8	-2.7	(-3.0 -2.4)	-5.4	<0.001
White European	All	51.8 ±8.3	51.1 ±7.5	-0.7	(-1.0 -0.4)	-1.4	<0.001
	Men	51.1 ±8.6	51.1 ±7.7	0.0	(-0.5 0.4)	0.0	0.9
	Women	53.2 ±7.6	51.1 ±7.0	-2.1	(-2.6 -1.6)	-4.0	<0.001
South Asian	All	49.1 ±7.3	47.3 ±6.7	-1.8	(-2.2 -1.4)	-3.7	<0.001
	Men	49.4 ±8.1	48.4 ±7.3	-1.0	(-1.5 -0.6)	-2.0	<0.001
	Women	48.7 ±5.8	45.7 ±5.0	-3.0	(-3.6 -2.5)	-6.2	<0.001
African Caribbean	All	47.6 ±6.7	45.8 ±6.3	-1.8	(-2.3 -1.3)	-3.8	<0.001
	Men	47.7 ±7.0	47.4 ±6.4	-0.3	(-0.9 0.3)	-0.6	0.3
	Women	47.6 ±6.6	44.5 ±6.0	-3.1	(-3.6 -2.5)	-6.5	<0.001

Data are mean ±standard deviation, except mean difference (%). P- values were calculated using a paired Student's t-test, 95% confidence interval (CI)

Table 1: Comparison of cerebral blood flow estimated using a fixed haematocrit value (43.5%) (CBF_fixed),and using correction for individual haemtocrit (CBF_Hct) by sex and ethnicity.
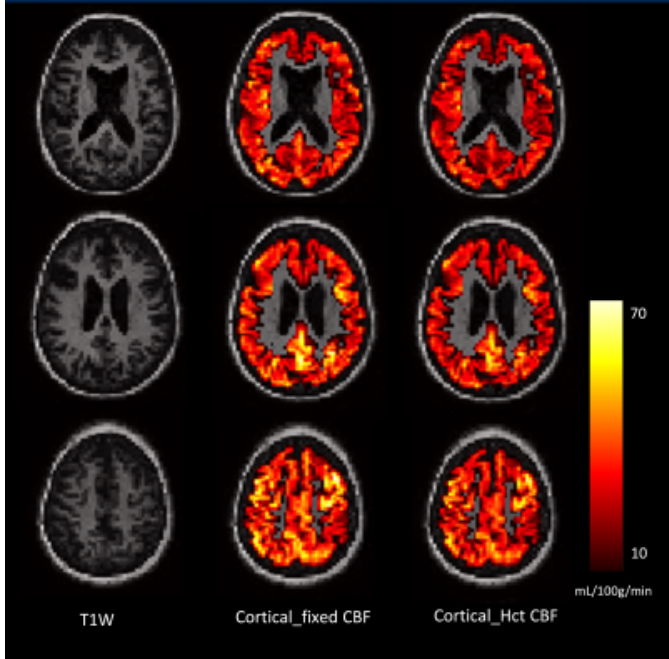
Figure 1: 3 slices of CBF maps overlaid on T1w image without and with adjustment for measured haematocrit. The CBF_Hct model shows lower CBF values in the cortex than the CBF_fixed model. The subject was a white European woman with an haematocrit of 37.3%.
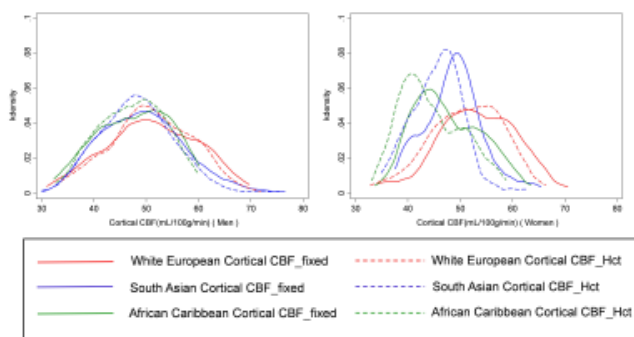

Figure 2: Kernel density (kdensity) plots of CBF without correction for individual haematocrit (CBF_fixed) and with correction for individual haematocrit (CBF_Hct) by sex and ethnicity.
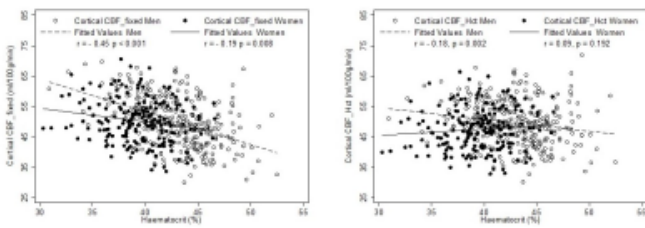

Figure 3: Scatterplots showing the effect of correction for individual haematocrit on the correlation between haematocrit and cortical cerebral blood flow in men and women.