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Normal Reference Range Values of Arterial Spin Labeling of Magnetic Resonance Imaging Brain Perfusion during Normal Maturation from Childhood through Adolescence to Adulthood

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ABSTRACT

OBJECTIVE The aim of this study was to evaluate cerebral blood flow using arterial spin labeling magnetic resonance imaging in normal healthy subjects from childhood through adolescence to adulthood.

METHODS A total of 38 normal, healthy subjects age between 8 and 32 were evaluated during the years 2018-2021 using arterial spin labeling magnetic resonance imaging.

RESULTS The average region of interest (ROI) of all brain regions combined in all subjects was 37.05 ± 11.94/100 g per minute. The difference in average ROI in all regions in males and females was not statistically significant. The differences in average ROI in each of the brain regions by age group was not statistically significant. The average ROI of all brain regions combined and in each of the regions were not statistically significantly correlated with age.

CONCLUSIONS During the transition from childhood through adolescence to adulthood, there is no correlation between age or gender and overall cerebral blood flow in all regions as measured by the arterial spin labeling (ASL) method.

KEYWORDS arterial spin labeling (ASL), cerebral blood flow, normal maturation

INTRODUCTION

Growth and development of brain parenchyma during the period from childhood through to adulthood is important for both for the structure and function of the human brain (1). One prior study reported that brain perfusion is related to normal development of the human brain, especially during from age 10 to 20 years (2).

Two advantages of using magnetic resonance imaging (MRI) rather than other imaging methods, e.g., computed tomography, x-ray scans, and ultrasound, are that with MRI there is no radiation and that it provides high image resolution. MRI is helpful for studying the structure of brain parenchyma. Metabolism cannot be measured directly by MRI, but cerebral perfusion and cerebral blood flow can be quantified and coupled to levels of cerebral oxygen and glucose consumption (3) which reflected brain's metabolism and neuronal function.

Generally, MRI-based perfusion techniques are usually involve imaging after administration of a paramagnetic contrast agent to dynamically track passage of a labeled bolus through the vasculature. However, the use of exogenous contrast injection is limited in patients with renal failure due to the associated risk of nephrogenic systemic fibrosis (4), as well as in children due to technical difficulties and ethical problems related to contrast agents.

Measurement of cerebral perfusion has become important tool in clinical evaluation of the brain. There are many methodologies available for cerebral perfusion evaluation. For example, dynamic susceptibility contrast (DSC)-MRI

measures perfusion by dynamic imaging of the passage of a contrast agent while arterial spin labeling (ASL) generates an image by magnetically labeling water molecules and using them as an endogenous tracer as they travel to an organ of interest.

ASL is a quantitative method for cerebral perfusion measurement which is used to evaluate cerebral blood flow (CBF) non-invasively by magnetically labeling inflowing blood without requiring a gadolinium-based tracer (5,6). A limitation of ASL is a very low signal-to-noise ratio (SNR) due to the fact that the inflowing labeled molecules comprise only about 1% of the static tissue signal which requires an increase in total scan time, making the technique sensitive to motion artifacts. ASL does, however, have the advantage of using an endogenous tracer by magnetically labeling water in arterial blood supply. ASL is a completely non-invasive and non-ionizing technique, making it safe for repeated measurements and providing increased patient comfort during measurement. The parameter measured with ASL is CBF, the delivery rate of oxygen and nutrients to the capillary bed. CBF is expressed as the volume of blood per volume of tissue per minute (mL/100 g/min). ASL is suitable for use in longitudinal and multicenter studies (7,8).

In recent years, the ASL technique has been more popular in clinically relevant research such as cerebrovascular disease, neurodegenerative disease and brain tumors. However, alteration in cerebral blood flow during human maturation could potentially affect disease interpretation. There have been few studies of ASL in Thailand. In this study, we investigated the ASL signal in terms of cerebral blood flow in healthy subjects aged between 8 and 32 years. In very young patients, a limitation of MRI is that it cannot be performed without use of sedation. However, sedation can interfere with cerebral blood flow interpretation. For example, previous studies have shown a significant increase in cerebral blood flow in halogen-sedated children compared with awake children. Other factors can also affect interpretation such as patient movement (9) that was not an issue in this study, however, as no sedation was used. Additionally, females have been found to have greater cerebral blood flow than males (10). In this study, the authors provided normal reference values of ASL using the MRI technique in healthy subjects of both genders aged between 8 and 32 years, for which reference values will be benefit for further clinical application.

METHODS

The study was approved by the ethics committee and informed consent was waived. Retrospective analysis of normal healthy subjects in Vajira Hospital between year 2018 to 2021 was conducted. The gender and age of subjects were recorded. Patients undergoing MRI study due to non-specific symptoms such as abnormal movement, precocious puberty or hormonal disturbance with no gross MRI abnormality, e.g., brain infarction, hemorrhage or abnormal mass lesion were included. Only non-sedated brain MRI subjects were included in this study.

MRI data acquisition

Cerebral blood flow was measured using arterial spin labeling, scanned by a 3.0 tesla MR system (Ingenia, Philips Medical System, Best, the Netherlands) with a 20-channel head coil. Pulse sequences used for analysis were 3D pCASL (pseudocontinuous arterial spin labeling) acquired with GRASE read-out, providing normalized images with a 4-pulse background suppression scheme with the following parameters: repetition time 4200 ms; echo time 12 ms; NEX 1; field of view 240 mm; matrix size 64x60; thickness 6 mm. Scanning time was 4.56 minutes. The label duration of this sequence was 2000 ms.

Postprocessing

The ASL images, which included mainly gray matter plus some included white matter, was segmented into major vascular territories. The four regions of interest (ROIs) were defined as the left and the right cortical vascular territories of the anterior cerebral artery (ACA), the middle cerebral artery (MCA) and the posterior cerebral artery (PCA). Vascular territory ROIs were manually drawn by neuroradiologist based on anatomic landmarks on a signal ASL image using a standard Montreal Neurological Institute template.

Statistical analysis

Subject characteristics are reported as descriptive statistics. Continuous data is presented as mean ± standard deviation (SD). Categorical data are presented as number and percentage. All ROI reference values are reported as mean and standard deviation. The correlation between age and ROI values was analyzed using Pearson correlation coefficients. The unpaired t-test was used to evaluate the differences in ROI between males and females. One-way analysis of variance (ANOVA) was performed to assess the effect of age on ROI values. A *p*-value less than 0.05 was considered statistically significant. All analyses were conducted using PASW Statistics (SPSS) 18.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of the subjects are presented in Table 1. A total of 38 healthy subjects (15 males and 23 females) were studied, age between 8 and 32 years (mean ± standard deviation: 15.68 ± 7.16 years). The largest group of subjects were in age the group 8-16 years (60.5%).

The average ROI of all regions combined and all subjects was 37.05 ± 11.94/100 g per minute. The values for males was 36.51 ± 13.70/100 g per minute and for females was 37.40 ± 10.95/100 g per. The differences in average ROI of all regions combined between males and females was not statistically significant (p = 0.826) and there were no statistically significant differences between male and females in the ROI for any of the regions (Table 2).

The average ROI of all regions studied combined was 35.47 ± 11.85/100 g per minute in the age group 8-16 years, 38.30 ± 10.66/100 g per minute in the age group 17-24 years, and 41.19 ± 14.81/100 g per minute in the age group 25-32 years. There was no statistically significant difference in the average ROI of all regions combined among the age groups (p = 0.556).

Table 1. Demographic data

Variable	n = 38
Age (years): mean ± SD	15.68 ± 7.16
Age (years): n (%)	
8-16	23 (60.5%)
17-24	9 (23.7%)
25-32	6 (15.8%)
Sex: n (%)	
Male	15 (39.5%)
Female	23 (60.5%)

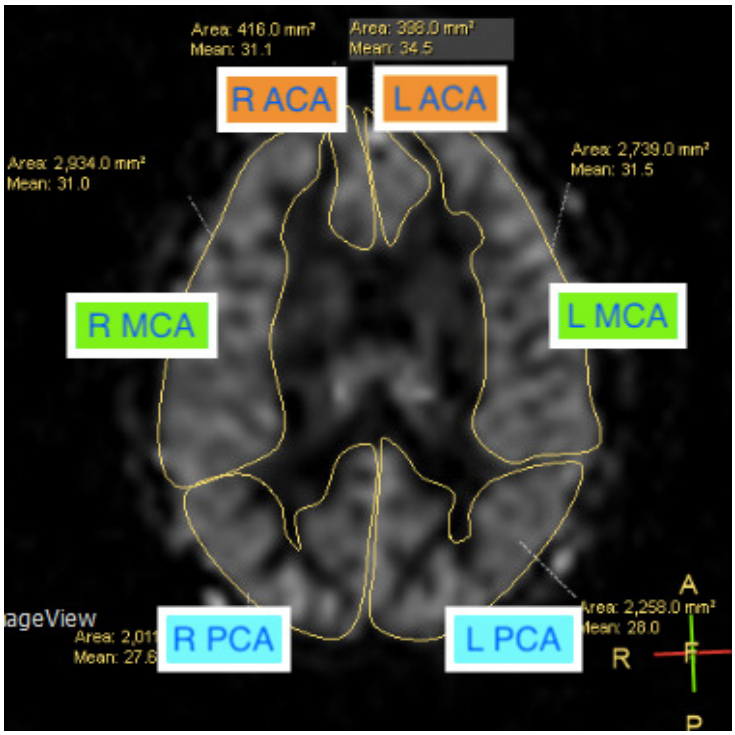

Figure 1. Example of an arterial spin labeling image segmentation based on the vascular flow territories for six vascular territories: anterior cerebral arteries, middle cerebral arteries, and posterior cerebral arteries on both the right and left sides

Table 2. Mean and standard deviation of ROI in males and females

Parameter	Total (n=38)	Male (n=15)	Female (n=23)	*p*-value[#]
All average ROI	37.05 ± 11.94	36.51 ± 13.70	37.40 ± 10.95	0.826
Average ROI ACA	40.31 ± 13.05	38.84 ± 14.97	41.28 ± 11.89	0.580
Average ROI MCA	36.00 ± 11.46	35.94 ± 13.08	36.04 ± 10.57	0.979
Average ROI PCA	34.83 ± 12.61	34.75 ± 14.49	34.88 ± 11.56	0.977

[#]Independent t-test

Table 3. Mean and standard deviation of ROI by age group

	Age 8-16 (n=23)	Age 17-24 (n=9)	Age 25-32 (n=6)	*p*-value
All average ROI	35.47 ± 11.85	38.30 ± 10.66	41.19 ± 14.81	0.556
Average ROI ACA	39.25 ± 14.37	40.94 ± 8.23	43.44 ± 14.99	0.781
Average ROI MCA	35.03 ± 12.02	36.68 ± 9.86	38.68 ± 12.90	0.779
Average ROI PCA	32.14 ± 10.00	37.29 ± 14.42	41.44 ± 17.50	0.223

Table 4. Correlation between age and ROI parameters

	Pearson correlation coefficients (r)	*p*-value
Average ROI ACA	0.042	0.801
Average ROI MCA	0.061	0.717
Average ROI PCA	0.257	0.119

The difference in average ROI in each of the regions between age groups was also not statistically significant (Table 3).

The average ROI of all regions combined and of each of the regions were not statistically significantly correlated with age (All: r = 0.125, ACA: r = 0.042, MCA: r = 0.061, PCA: r = 0.257) (Table 4).

DISCUSSION

Our study excluded elderly subjects because the aging process may affect cerebral blood flow. This study also excluded very young subjects because the necessary sedation would interfere with cerebral blood flow interpretation. The authors aimed to analyze specifically healthy adolescent subjects during the transition from childhood into adulthood.

Our CBF measurement of subjects with a mean age of 15.68 ± 7.16 years showed a mean CBF value of 37.05 ± 11.94 mL/100 g per minute, a lower CBF value than prior studies as described in Table 5. For instance, in a previous study with a mean age of 11 years, Hales et al. (11) reported a mean CBF value of 62 ± 4 mL/100 g per minute. A study with a mean age of 11 ± 3 years by Jane et al. (12) reported a mean CBF value of 65 ± 10 mL/100 g per minute. Another study with a mean age of 32 years by Wang et al. (13) measured a mean CBF value of 58 ± 12 mL/100 g per minute. Studies by Pollock et al. (14) showed a cerebral perfusion plateau between 4-11 years with rates of CBF greater than 90 mL/100 g per minute which then rapidly decreased after age 11, with rates of CSF in adolescents less than 90 mL/100 g per minute. Assessment of CBF is affected by the partial volume effect which is related to the voxel size of ASL and is several times that of 3D T1-weighted acquisitions. Different types of tissues have different perfusion characteristics, e.g., perfusion in white matter is less than in grey matter. A study by Vavilala et al. (15) found the normal average CBF in adult humans to be about 50 mL/100 g per minute, with lower values in white matter (about 20 mL/100 g per minute) and higher values in gray matter (about 80 mL/100 g per minute). Our study included both gray and white matter which may have resulted in lower CBF values than the

Table 5. Comparison of mean age and mean CBF of this study and prior studies

	Mean age (years)	Mean CBF ± SD (mL/100 g per min)
This study	15.68 ± 7.16	37.05 ± 11.94
Hales et al. (11)	11	62 ± 4
Jane et al. (12)	11 ± 3	65 ± 10
Wang et al. (13)	32	58 ± 12
Pollock et al. (14)	4-11 years - mean CBF > 90 >11 years - mean CBF < 90	

average CBF values reported in prior studies.

Variation of cerebral blood flow values can be influenced by factors such as differences in label duration time which can impact the CBF perfusion map. Another potential factor that may affected for data processing is that baseline hematocrit levels may different in different populations.

The authors evaluated CBF values in different age groups, 8-16, 17-24 and 25-32 years, and found negative correlation with age in all three. As well as CBF values in regional vascular territories, our results showed negative correlation with age in all regions of vascular territories combined which agrees with previous a study by Hales et al. (11). A previous study by Zhang et al. (16) showed age to be negatively correlated with CBF, but, after adjusting by global value, CBF was found to decrease with age in certain regions but to increase in others, suggesting that different analysis methods can affect the age-related CBF pattern.

The propose of this study is to provide a reference range of cerebral blood flow in normal healthy subjects which can be further used for comparison with pathologies that cause abnormal cerebral blood flow, e.g., cerebrovascular disease, dementia and cognitive disorder, tumor, vascular malformation, infections such as encephalitis and migraine-associated hyperperfusion.

There are several limitations to our study including the small sample size and that it was a single time period study. Future investigation is needed with larger sample sizes in both longitudinal and multicenter studies.

CONCLUSION

This study provides normal reference values of cerebral blood flow using arterial spin labeling magnetic resonance imaging in normal healthy subjects age from 8 to 32 years. During the transition from childhood through adolescence to adulthood, there is no correlation with age, gender or brain region in cerebral blood flow as measured using the ASL method. In the future, these data will aid evaluation of clinical conditions of patients with disorders affecting cerebral blood flow such as cerebrovascular disease, brain tumor or neurodegenerative disease. However, due to the small sample size in this study, the use of these results in clinical evaluations should be done with caution.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

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