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Utility of Pseudocontinuous Arterial Spin Labeling Perfusion Imaging to Evaluate the Age and Gender Related Changes in Normal Cerebral Blood Flow

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Abstract

Aim: *To assess the usefulness of ASL perfusion imaging in evaluation of age and gender related changes in normal cerebral blood flow.*

Materials and methods: *Eighty normal individuals (43 females and 37 males; age range 20–79 years; mean age = 50.12±16.87 years) were scanned at 3.0 T MR Station. The subjects were divided intotwo separate age groups that included adults (n_1 = 40; 21 females and 19 males; age 20-49 years; mean age 35.2±7.45) and elderly (n_2 = 40; 22 females and 18 males; age 50-79 years, mean age 65.05±8.00) respectively. The individuals with possible risks of artifacts that may degrade ASL imaging were excluded. The gray-white CBF ratios of all four lobes were extracted and statistically analyzed.*

Results: *No significant difference of gray-white CBF ratios were found among the four different lobes (p>0.05) within same age group whereas, a significant difference in each lobes was noticed between two age groups (p=0.00). On bivariate analysis using Pearson's correlation, a significant negative correlation was observed between an increasing age, and gray-white CBF ratios of all four lobes in both age groups (frontal: r = −0.24,* ***temporal:*** *r = - 0.26, parietal: r= - 0.25; occipital: r= -0.29, p = 00) in young and (frontal: r = −0.95;* ***temporal:*** *r = -0.94; parietal: r = - 0.9; occipital: r = -0.91, p = 00) in elderly, respectively.No significant effect of gender was found in any age group (P > 0.05).*

Conclusion: *Among various MR techniques, arterial spin labeling is comparatively reliable way to quantify the perfusion variance in different age groups.*

Keywords: *Magnetic resonance imaging; Arterial spin labeling perfusion imaging; Cerebral blood flow.*

I. INTRODUCTION

Perfusion refers to the delivery of oxygen and nutrients to the tissues by means of blood flow. Continuous and sufficient cerebral blood flow (CBF) is vital to neural function and an important measure in the understanding of brain pathophysiology. CBF reflects the amount of blood perfusion in the brain, measured in ml of blood per 100 g of brain tissue per minute. Its value decreases with age in both sexes. A higher CBF value has been reported in women than in men probably due to the effect of estrogen.[1, 2, 3]Kety and Schmidt were the first to measure mean CBF, using nitrous oxide (Fick's formula) and reported a global mean CBF level of 54 ± 12 ml/100 g/min, in healthy young men, which is still regarded as a reasonable value.[4]Many pathological conditions such as acute stroke, brain tumors, neurodegenerative diseases, and epilepsy are associated with abnormal CBF values. CBF is also important in the monitoring of treatment of many brain diseases and also in the functional brain imaging.[5, 6]

Various methods for the quantitative measurement of CBF have been developed such as single photon emission computerized tomography, positron emission tomography (PET), computed tomography, and magnetic resonance imaging (MRI). Almost all of these methods employ a model of tracer kinetics which requires the contrast agent to quantify the CBF. These techniques are expensive and most require radiation exposure. The authors of these studies have shown a significant negative correlation between age and gray and white matter CBF ratio in both adult and elderly age groups and have given possible explanations for the changing CBF based on development and also regional variation.[7, 8, 9, 10, 11, 12]Thus, it is important to establish a robust noninvasive method, suitable for longitudinal and cross-sectional studies of various neurovascular and neurodegenerative diseases.

Arterial spin labeling (ASL) is a noninvasive MR perfusion technique reported first by Detre*et al*.,[13] in 1992, based on the use of magnetically labeled blood-water protons as an endogenous tracer. Due to the

noninvasiveness and easy availability of the ASL technique, there is revival of interest in reinvestigating the effects of age and gender on CBF in the normal population. In the past, a number of studies have evaluated the age- and gender-related effect on CBF using the ASL technique.[14, 15, 16, 17]In the current study, we have used the fast three-dimensional pseudocontinuous ASL (3D $_{P}$CASL) technique to quantify age-related changes in CBF of all the four lobes of the brain. A Study with larger subjects that use the $_{P}$CASL technique for determining the normal mean CBF values of gray and white matter of whole brain in the different age groups (adult and elderly) is highly warranted.

This study was approved by Yangzhou University Health System Institutional Review Board.

II. Materials And Methods

Subjects And Imaging: Between January 2014 and January 2016, eighty normal individuals of varying age (20-79 years, mean age = 50.12±16.87 years, 43 females and 37 males) were scanned. The subjects were divided into two separate age groups that included adults (n_1=40; 21 females and 19 males: age range 20-49years; mean age 35.2±7.45 years) and elderly (n_2= 40, 22 females and 18 males; age range 50-79 years, mean age 65.05±8.00 years) respectively.

Conventional MR images were acquired using a 3.0T MR imaging system (Discovery MR750; GE Healthcare, Fairfield, CT, USA) with a 16-channel coil specifically for imaging the head. Conventional sequences included axial, sagittal and coronal T2-weighted, axial T1-weighted, fluid-attenuated inversion recovery sequence and DW imaging.

ASL imaging used a 3-dimensional (3D) pseudocontinuous ASL method and was performed as follows: Repetition time (TR), 4,632 msec; echo time (TE), 1.5 msec; acquisition matrix, 96x61; field of view (FOV), 24 cm; slice thickness, 4 mm; interslice gap, 0 mm and post label delay, 1,535 msec with spiral acquisition along with 3D proton density-weighted fast spin echo (FSE) EPI sequence as follows: TR, 3.9 msec, TE, 1.9 msec, parallel imaging factor, 2; acquisition matrix, 96x61; FOV, 24 cm; slice thickness, 4 mm and interslice gap, 0 mm.. The total acquisition time for perfusion measurement was 1:20 min. Patients with underlying cardiac disease, hypertension, or vasculopathy that could alter ASL perfusion, as well as patients with motion artifacts or dental braces or hardware that degrade ASL imaging were excluded.

Image evaluation

Qualitative Assessment: All images were reviewed by two neuroradiologists who were blinded to the clinical and histopathological history of the cases. The images were evaluated using Funtool software package with the Advantage 4.5 Workstation (GE Healthcare).

Three bilateral maximally perfusion regions of the gray and white matter ineach lobe were located by drawing regions of interest (ROIs) of area 5-15 mm2 and their average values were extracted. Gray-white CBF ratios of each lobe were calculated based on the values obtained from both sides.

Statistical analysis: All statistical analyses were performed using SPSS 16.0 (Version 18, SPSS Inc. Chicago, IL, USA). The ANOVA and unpaired Student's t-test were used for the comparison of CBF ratios of different lobes within each group followed by the comparison between two age groups. $P<0.05$ was considered to indicate a statistically significant difference.

III. Results

The gray-white CBF ratios of different lobes in adults individuals were measured in a lowest to highest range as frontal: 1.44 -1.59 (mean 1.49 ± 0.04), temporal: 1.4-1.52 (mean 1.44 ± 0.04), parietal: 1.37-1.55 (mean 1.46 ± 0.04) and occipital: 1.46-1.58 (mean 1.42 ± 0.04), respectively. Similarly, in elderly group, the measurements were 1.25-1.44 (mean 1.35 ± 0.005), 1.18-1.38 (mean 1.28 ± 0.06), 1.2-1.4 (mean 1.30 ± 0.06) and 1.16-1.36 (mean 1.25 ± 0.06) in frontal, temporal, parietal and occipital lobes, respectively. No significant difference of gray-white CBF ratios was noticed among different lobes ($p>0.05$), whereas, a significant difference ($p =0.00$) was found in each lobes when the values of both groups were compared with each-others[Table 1].

On bivariate analysis using Pearson's correlation, a significant negative correlation was observed between an increasing age, and gray-white CBF ratios in all four lobes within both the groups [(frontal: $r = -0.24$, temporal: r = - 0.26, parietal: r= - 0.25; occipital: r= -0.29) [Fig.1A, B, C and D] and (frontal: $r = -0.95$; temporal: r = -0.94; parietal: r = - 0.9; occipital: r = -0.91) in adults and elderly, respectively [Fig.2A, B, C and D].

IV. Discussion

The determination of the changing perfusion patterns accompanying normal brain development, and the creation of a reference set of normal values of CBF in different age groups is a necessary prelude to the use of CBF measurement in the diagnosis and management of brain disorders. This study reports the age-related

changes in cerebral perfusion on 80 normal subjects of varying age (20-79 years) measured by the $_{P}$CASL technique at 3T MRI scanner. Xu*et al*.,[18]compared the reliability and accuracy of $_{P}$CASL with 15-O-water PET in normal children as well as young and elderly subjects. The recently published studies also showed that compared to the previous ASL and PET perfusion studies, $_{P}$CASL provides better reliability in repeated measurements for the entire age group from children to elderly subjects (Fig. 3A,B and C).

In adults (20-49 years), our whole gray-white CBF ratios valuesare consistent with the values obtained by other authors in their studies. However, in most of the previous studies, the measurements were expressed in the form of separate gray and white matter CBF mean values, unlikely to this study where the values are expressed in gray-white CBF ration of an entire lobe. A significant difference (*P*= 0.00) was found in the gray-white CBF ratios between both age groups. These findings were similar to that reported in previous studies conducted using ASL, PET, and Xenon 133 (Table2).There are a number of possible explanations for the high values of CBF during the development phase. During its growth and development, the brain produces a vast excess of neurons, synapses, and dendritic spines and achieves its maximum volume by the middle of the second decade of life (for both males and female subjects). [19] Several factors have been proposed to account for the reduction in CBF in the older age groups. Firstly, there is a loss of brain substance and hence decreased cerebral metabolism. It has been reported that populations of cerebral cortical neurons progressively decrease in number with age, especially in the superior temporal and precentral regions.[20]A gradual increase in the ventricular size with advancing age also correlates well with reduction in the CBF and metabolism. [21] Chen*et al*., demonstrated that reduction in the CBF in the older age is independent of cortical thinning and atrophy .[22]

Significant age-associated CBF reduction was widely observed throughout the cortex, and the current findings may indicate a distinct pattern characteristic of the normal aging process. Our measurements of the CBF-age relationship in the frontal and parietal regions were in excellent agreement with the observations made by Biagi*et al*;[16]. According to the modern neurophysiologic concepts, developed in particular by Luria,[23]the frontal lobes play a fundamental role in programming behavior, whereas the parietal, temporal, and occipital regions are involved in analyzing and memorizing information. It, therefore, seems logical that during the state of rest, while the subject is receiving a low level of sensory stimulation, only the regions involved in thought process and behavioral programming remain active. This explains the finding of hyperperfusion in the frontal region.

Application Of ASL In Brain Tumors

Absolute measures of CBF in brain tumor populations may not be as critical as in assessment of cerebrovascular disease given heterogeneity in populations because of age and histopathology, and relative measures comparing to global CBF or white matter will likely be more practically useful [24,25].Gaaet al.[26] first reported the use of ASL in brain tumors, applying EPISTAR. Warmuth et al. [25] reported the first comparison of ASL CBF measures with perfusion parameters generated from DSC perfusion MRI for the evaluation of both primary and secondary brain neoplasms before and after treatment. They used a PASL approach implemented at 1.5T. Coverage was limited to 3 imaging sections, but they were able to show that both ASL and DSC perfusion MRI approaches allowed a distinction between high grade gliomas (HGG) and low grade gliomas (LGG), with higher tumor blood flow (TBF) and blood volume in HGG (and metastases).

V. Conclusion

Quantitative assessment of normal cerebral blood flow maps can be clinically useful for the comparative evaluation with several types of brain disorders. While dynamic susceptibility contrast (DSC)-magnetic resonance imaging (MRI) and H2[15O] positron emission tomography (PET) are well-established methods for investigating normal cerebral blood flow in almost all age groups, arterial spin labeling (ASL) MRI has emerged as a versatile complement that warrants regular consideration in the clinical setting.We report a reference dataset of normal values of CBF in different age groups using $_{P}$CASL. Our results demonstrate a significant age-related decline in CBF values with increasing age. Knowledge of the patterns of age-associated CBF decline is invaluable for distinguishing normal changes from the more detrimental disease-related degeneration. Regional variability of CBF helps in the assessment of local cerebral disease.

Acknowledgements

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Table 1: Comparison of gray-white CBF ratios with mean and standard deviation and p value
Data reported as mean ± SD; *student t test, level of significance 0.05

Locations	Gray-White CBF ratios		P value*
	Adults (age 20-49yrs) (n_1=40)	Elderly (age 50-79yrs) (n_2=40)	
Frontal lobe	1.49 ± 0.04	1.35 ± 0.05	0.00
Temporal lobe	1.44 ± 0.04	1.28 ± 0.06	0.00
Parietal lobe	1.46 ± 0.04	1.30 ± 0.06	0.00
Occipital lobe	1.42 ± 0.04	1.25 ± 0.06	0.00

Table 2: Various grey matter cerebral blood flow, white matter cerebral blood flow and regional cerebral blood flow values from the previous studies

Author	Modality	Regions	Age group	CBF
Chen et al. 2011	PASL	Frontal CBF	< 40 years	62 ± 12
			40-60 years	56 ± 15
			> 60 years	49 ± 15
		Temporal CBF	< 40 years	60 ± 12
			40-60 years	64 ± 14
			> 60 years	55 ± 17
		Occipital CBF	< 40 years	55 ± 12
			40-60 years	57 ± 19
			> 60 years	46 ± 13

Guofan et al 2010	$_{P}$CASL	GM CBF	24-40 years 50-73 years	48 ± 7 43 ± 2
		WM CBF	24-40 years 50-73 years	21 ± 3 24 ± 4
Boneka et al 2011	DSC MRI	GM CBF WM CBF	29-50 years	54 ± 21 23 ± 10
Neetu et al 2016	$_{P}$CASL	GM CBF WM CBF	18-60 years > 60 years 18-60 years >60 years	58.78±6 48.26±4 19.08±1.4 18.56±1.2

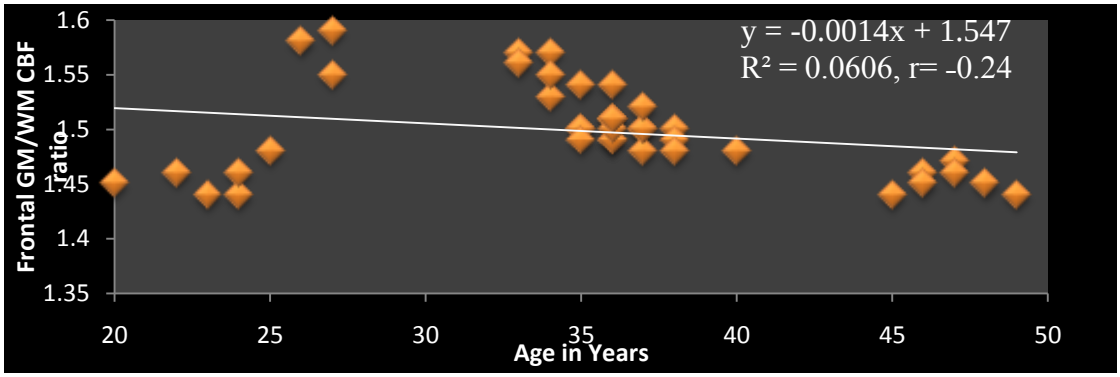


Fig.1A: Scatter plot of gray and white matter cerebral blood flow (CBF) ratio of frontal lobe in adults.

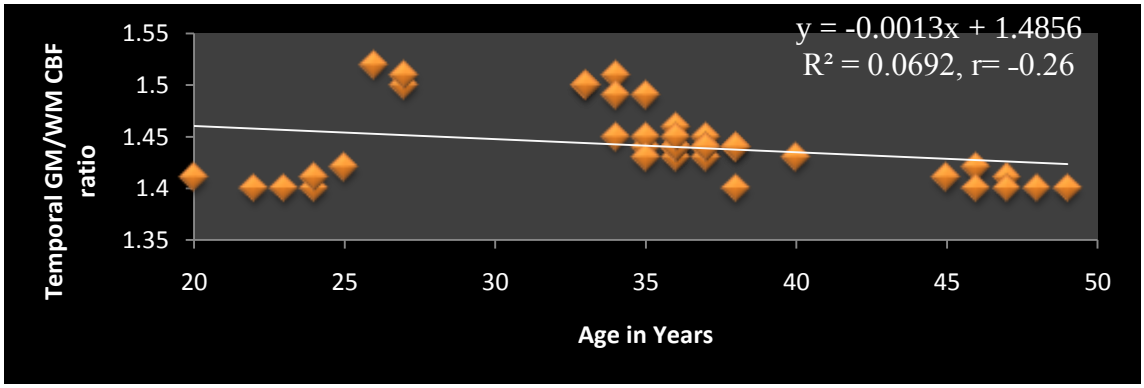


Fig.1B: Scatter plot of gray and white matter cerebral blood flow (CBF) ratio of temporal lobe in adults.

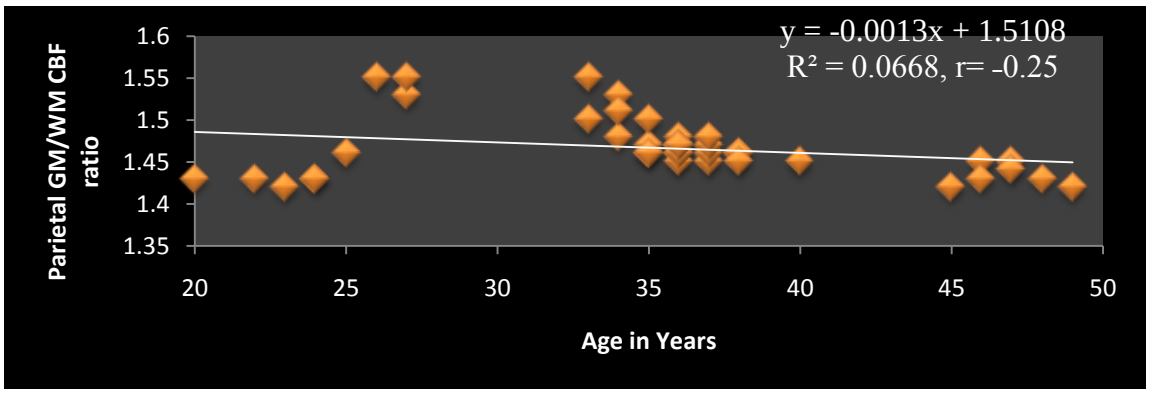


Fig.1C: Scatter plot of gray and white matter cerebral blood flow (CBF) ratio on parietal lobe in adults.

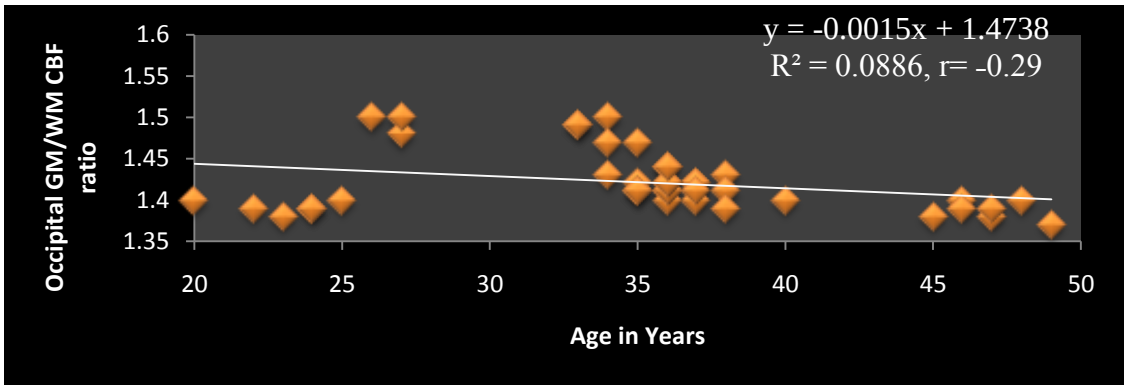


Fig.1D: Scatter plot of gray and white matter cerebral blood flow (CBF) ratio of occipital lobe in adults.

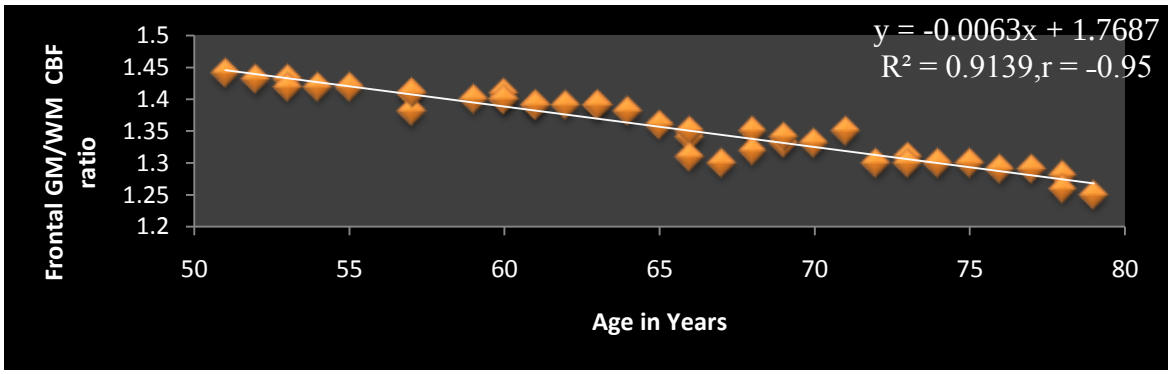


Fig.2A: Scatter plot of gray and white matter cerebral blood flow (CBF) ratio of frontal lobe in elderly.

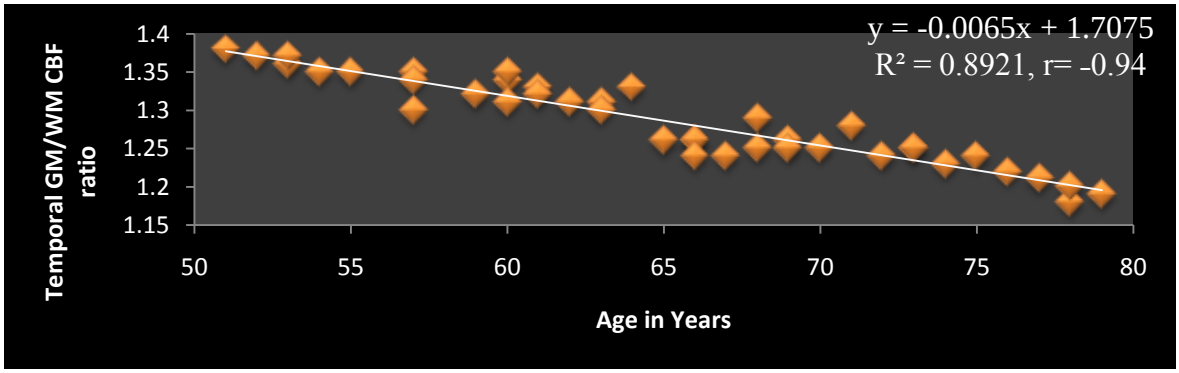
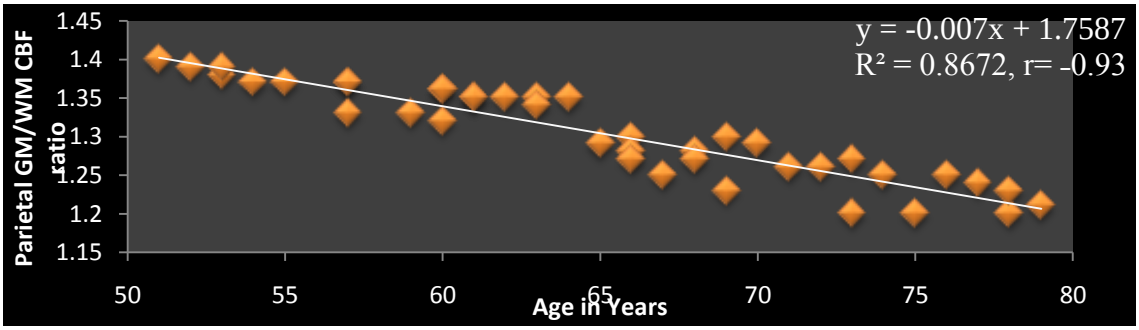


Fig.2B: Scatter plot of gray and white matter cerebral blood flow (CBF) ratio of temporal lobe in elderly.



ig.2C: Scatter plot of gray and white matter cerebral blood flow (CBF) ratio of parietal lobe in elderly

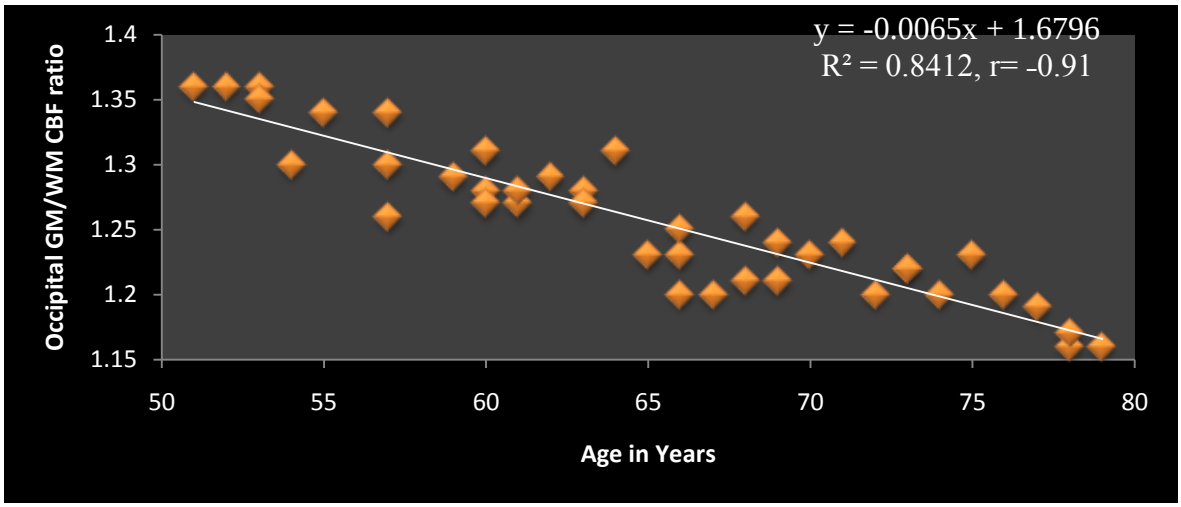


Fig.2D: Scatter plot of gray and white matter cerebral blood flow (CBF) ratio of occipital lobe in elderly.

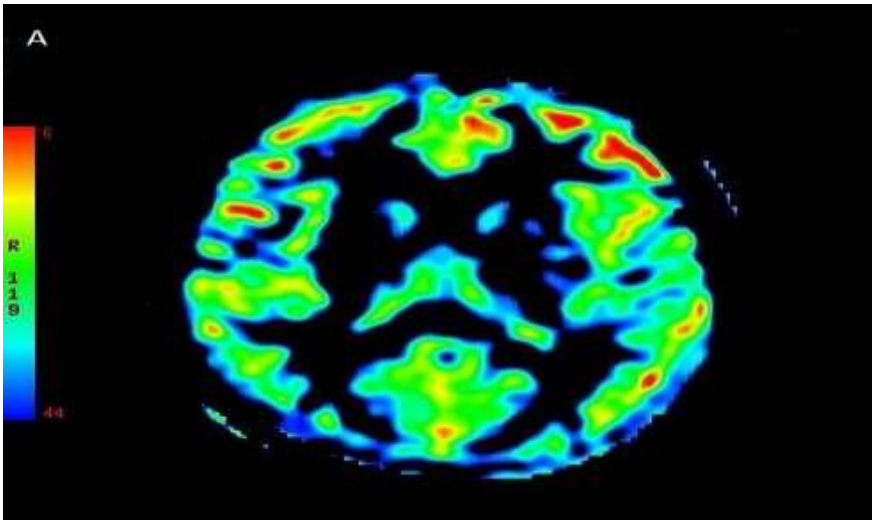


Fig.3A: The cerebral color flow map of a 26-year-old female

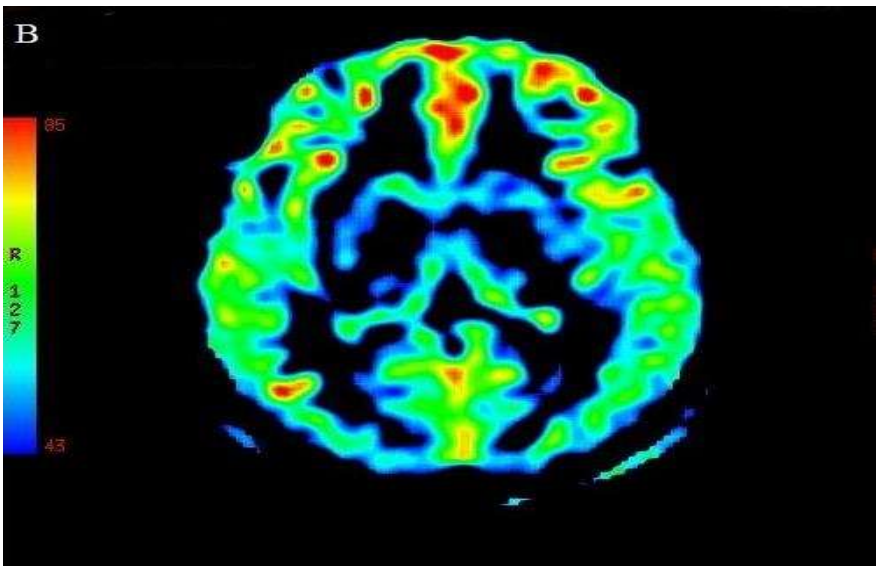


Fig.3B: The cerebral color flow map of a 32-year-old female

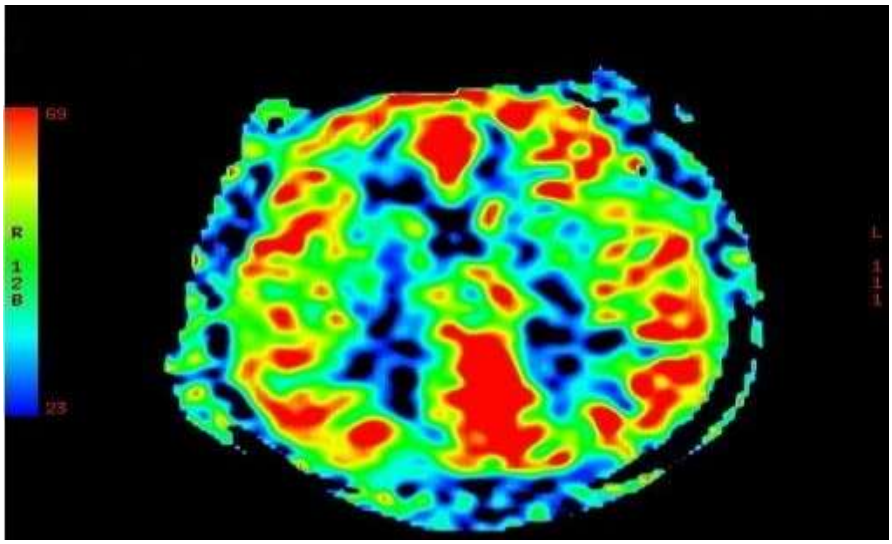


Fig.3C: The cerebral color flow map of a 60-year-old female