Original Article

Diagnostic Accuracy of Differentiation between Primary Central Nervous System Lymphoma and High-Grade Glioma Using Dynamic Susceptibility Contrast Perfusion Curve Analysis

Theeraphol Panyaping, MD[1], Nat Wimolsiri, MD[1], Tiparom Sananmuang, MD[1]

[1] Department of Diagnostic and Therapeutic Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Objective: To determine diagnostic accuracy of visualized dynamic susceptibility contrast (DSC) perfusion curve pattern in differentiation between primary central nervous system lymphoma (PCNSL) and high-grade glioma (HGG).

Materials and Methods: Forty-one patients (nineteen cases of PCNSL and twenty-two cases of HGG) acquired between January 2010 and November 2017 were included in the present study. The DSC perfusion curve patterns were retrospectively reviewed by two neuroradiologists, divided into two patterns as 1) return of time-intensity curve above the baseline after initial drop, and 2) return of time-intensity curve below or equal to baseline. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy were analyzed.

Results: Return of time-intensity curve above the baseline on DSC perfusion was found in 15 of 19 (78.9%) PCNSL cases, and only two of 22 (9.1%) HGG cases, p-value<0.001; whereas return of time-intensity curve below or equal to baseline was found in only four of 19 (21.1%) PCNSL cases and 20 of 22 (90.9%) HGG cases, p-value<0.001. Return of time-intensity signal curve above the baseline pattern had sensitivity of 78.9%, specificity of 90.9%, PPV of 88.2%, NPV of 88.3%, and accuracy of 85.4% for diagnosis of PCNSL, respectively.

Conclusion: Visualized DSC curve pattern has a role in differentiation between PCNSL and HGG. Presence of return of time-signal intensity curve above the baseline could suggest the diagnosis of PCNSL.

Keywords: PCNSL, HGG, DSC perfusion, Curve analysis, Return curve above baseline

Received 12 December 2019 | Revised 21 February 2020 | Accepted 24 February 2020

J Med Assoc Thai 2020;103(9):920-5
Website: http://www.jmatonline.com

Primary central nervous system lymphoma (PCNSL) and high-grade glioma (HGG) have imaging characteristic different from each other. However, in many circumstances, these two types of neoplasm may appear with similar findings on conventional magnetic resonance (MR) imaging, causing difficulty in making a certain diagnosis[1-3]. Therapeutic decision of PCNSL and HGG are also different, hence, it would be crucial to know if the diagnostic imaging tool could give further information for more accurate diagnosis between these two entities.

Perfusion MR imaging has been playing an important role in tumor imaging during the past decade. The clinically available technique of dynamic susceptibility contrast (DSC) perfusion has been used the most. Principle of DSC perfusion contributes to first-pass effect of gadolinium-base contrast agent injection through capillary bed induced T2*-weighted signal loss in extravascular space and measured change of transverse relaxivity resulting in relative cerebral blood volume (rCBV) estimation[4-7].

Many studies have shown that both PCNSL and HGG had increased rCBV, which was found to be higher in HGG rather than those of PCNSL[8-11].

Correspondence to:

Sananmuang T.

Department of Diagnostic and Therapeutic Radiology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, 270 Rama VI Road, Ratchathewi, Bangkok 10400, Thailand.

Phone: +66-2-2011000, **Fax**: +66-2-2011297

Email: poriferax@hotmail.com

How to cite this article:

Panyaping T, Wimolsiri N, Sananmuang T. Diagnostic Accuracy of Differentiation between Primary Central Nervous System Lymphoma and High-Grade Glioma Using Dynamic Susceptibility Contrast Perfusion Curve Analysis. J Med Assoc Thai 2020;103:920-5.

doi.org/10.35755/jmedassocthai.2020.09.10913

Distinct patterns of DSC perfusion time-intensity curve were also described, with typical patterns of HGG as rapid signal intensity fall followed by returning curve below or equal to the baseline; while the majority of PCNSL showed overshoot of the signal intensity above the baseline(11-13). There are few studies reporting the diagnostic accuracy of visualization method of the DSC time-intensity curve analysis(14), as well as its reproducibility in routine clinical practice for differentiation between PCNSL and HGG. The purpose of the present study was to evaluate diagnostic accuracy of visualized DSC curve pattern in differentiation between PCNSL and HGG.

Materials and Methods

Patients

The present study retrospectively recruited all patients with histopathological diagnosis of PCNSL or HGG who underwent conventional MR imaging and DSC perfusion acquired between January 2010 and November 2017. Patient data gathering was done using electronic medical record and picture archiving and communication system (PACS), including patient's age, gender, immune status, and steroid use. Patients who had surgical tumor removal, radiation, or chemotherapy prior to DSC perfusion acquisition, as well as degraded image quality were excluded. From the 54 patients enrolled, after excluding the cases with degraded image quality and uncertain treatment history, 41 patients were included in this study, comprising 19 PCNSL and 22 HGG cases.

Image acquisition

Images were acquired in the routine conventional MR imaging by using 3T MR scanner (Philips Intera®, Philips Medical Systems, Best, Netherland) and 1.5T (Signa®, GE Medical Systems, Milwaukee, Wisconsin) equipped with standard head coil. DSC perfusion was performed using gradient-echo EPI sequences (TR=1,300 ms, TE=35 ms, FA=60°, FOV 24×38 cm for 3T scanner; and TR=2,000 ms, TE=80 ms, FA=90°, FOV 28×28 cm for 1.5T scanner). First, 0.1 mmol per kg of gadobutrol was injected as a preload for the subsequent DSC perfusion to correct T1-weighted effect of vascular leakage on rCBV. After that, 0.1 mmol per kg of contrast material at rate of 5 ml per second was injected via injector at least five minutes after the preload injection. Perfusion images were analyzed using vendor provided software (In44telliSpace Portal®, Philips Medical Systems, Best, Netherland, and FuncTool® Performance, GE Medical Systems, Milwaukee, Wisconsin). The gamma-variate fitting of perfusion curves was used for brain tumor DSC-MR imaging data analysis. The CBV was relative measurement without using software modeling for rCBV correction.

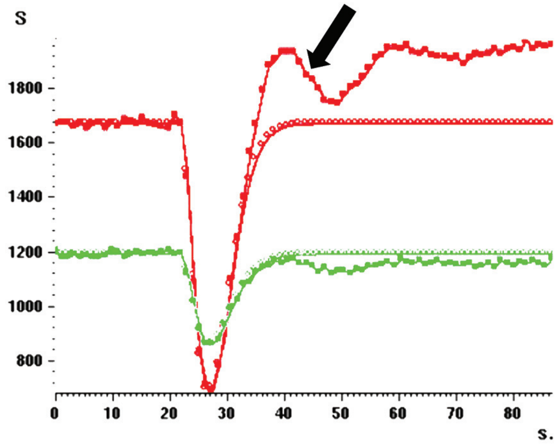

Figure 1. Return of time-signal intensity curve above the baseline after initial drop (arrow).

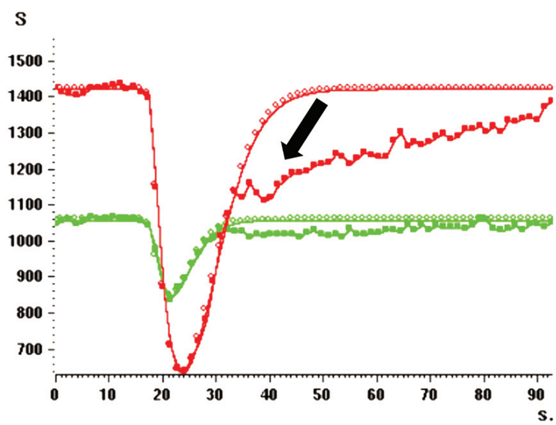

Figure 2. Return of time-signal intensity curve under the baseline after initial drop (arrow).

Image analysis

Circular regions of interest (ROIs) were drawn in solid enhancing portion of the tumor, carefully avoiding the cystic parts, hemorrhage, or calcification. ROIs at contralateral normal appearing white matter were also routinely placed. ROI areas were ranging between 20 to 35 mm³ (5 to 7 pixels). DSC curve analysis was determined as two categories by visual inspection as 1) presence of returning curve above the baseline after initial signal intensity drop (Figure 1), and 2) returning curve below or equal to the baseline after initial signal intensity drop (Figure 2).

Two neuroradiologists (one with seven and one with two years of experience in neuroradiology) were assigned as interpreters for interobserver reproducibility. Both interpreters were blinded to patient's clinical information, pathological results, and conventional MR imaging. All cases interpreted in disagreement were reevaluated in consensus. Intraobserver reproducibility was done by the reevaluation of DSC curve analysis after at least 1-month interval.

Statistical analysis

Analysis was performed using Stata, version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College station, TX: StataCorp LP). The standard diagnostic accuracy parameters included sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy. Comparison of mean variables was analyzed by independent t-test. Differences in categorical variables between the groups were analyzed by using the chi-square test and Fisher's exact test according to expected data frequency. The significance level was set at p-value less than or equal to 0.05. Intraclass correlation coefficient (ICC) was used for evaluation of reproducibility.

Results

Forty-one patients were enrolled in the present study, comprising of 22 men and 19 women. There were 19 cases of PCNSL and 22 cases of HGG. Of the 19 PCNSL cases, 15 cases were diffuse large B-cell lymphoma, while the other cases were defined as unspecified non-Hodgkin lymphoma. Of the 22 HGG cases, there were 18 glioblastomas, three anaplastic astrocytomas, and one anaplastic oligoastrocytoma.

The mean age in patients with PCNSL was 56.32±15.43 years, while that of HGG was 51.64±20.04 years (p=0.413). Gender distribution was significantly different between the two groups (p=0.045), as there were seven (36.8%) males and 12 (63.2%) females with PCNSL, and 15 (68.2%) males and seven (31.8%) females with HGG. For the steroid usage, there were only 34 cases with available data. None of 15 PCNSL cases had steroid administration prior to DSC MR imaging, while 15 (78.9%) out of 19 HGG cases received steroid (p<0.001). No significant differences in types of MRI machine usage between the two types of the tumor was found (p=0.599) (Table 1).

For PCNSL, 15 (78.9%) cases showed returning curve above the baseline after initial drop (Figure 3), while the other four (21.1%) cases revealed returning curve below or equal to the baseline. For HGG, only two (9.1%) cases (two glioblastomas) showed returning curve above the baseline, while the other 20 (90.9%) cases revealed returning curve below or equal to the baseline (Figure 4, Table 2). The use of DSC curve pattern as presence of returning curve above the baseline had sensitivity of 78.9%, specificity of 90.9%, PPV of 88.2%, NPV of 83.3%, and accuracy of 85.4% for the diagnosis of PCNSL. ICC was 0.825 for reader 1, 0.907 for reader 2, and 0.872 between

Table 1. Demographic data between PCNSL and HGG

	PCNSL (n=19) n (%)	HGG (n=22) n (%)	p-value
Age (year); mean±SD	56.32±15.43	51.64±20.04	0.413
Sex			0.045
Male	7 (36.8)	15 (68.2)	
Female	12 (63.2)	7 (31.8)	
Steroid use	0 (0.0)	15 (78.9)	<0.001*
MRI machine			0.599
1.5T	4 (21.1)	5 (22.7)	
3T	15 (78.9)	17 (77.3)	

PCNSL=primary central nervous system lymphoma; HGG=high-grade glioma; SD=standard deviation

* p<0.05 is statistically significant

Table 2. Time-intensity curve pattern

	Lymphoma n (%)	Glioma n (%)	p-value
Reader 1/1			
Above baseline	14 (73.7)	0 (0.0)	<0.001*
Below or equal to baseline	5 (26.3)	22 (100)	
Reader 1/2			
Above baseline	13 (68.4)	1 (4.5)	<0.001*
Below or equal to baseline	6 (31.6)	21 (95.5)	
Reader 2/1			
Above baseline	13 (68.4)	2 (9.1)	<0.001*
Below or equal to baseline	6 (31.6)	20 (90.9)	
Reader 2/2			
Above baseline	14 (73.7)	2 (9.1)	<0.001*
Below or equal to baseline	5 (26.3)	20 (90.9)	
Consensus			
Above baseline	15 (78.9)	2 (9.1)	<0.001*
Below or equal to baseline	4 (21.1)	20 (90.9)	

* p<0.05 is statistically significant

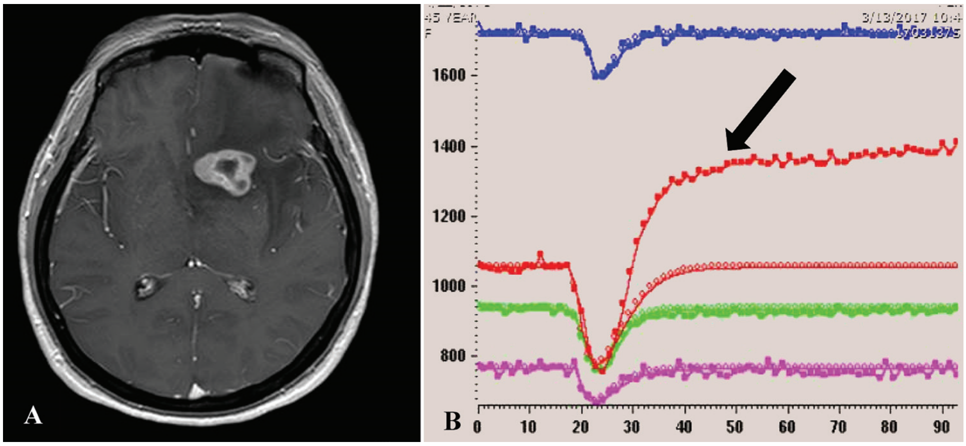

Figure 3. Primary CNS lymphoma in a 45-year-old woman. (A) Axial contrast-enhanced T1 weighted image shows a thick irregular rim enhancing mass at the left basal ganglion. (B) DSC perfusion reveals mild hyperperfusion with return of time-signal intensity curve above the baseline after initial drop (arrow).

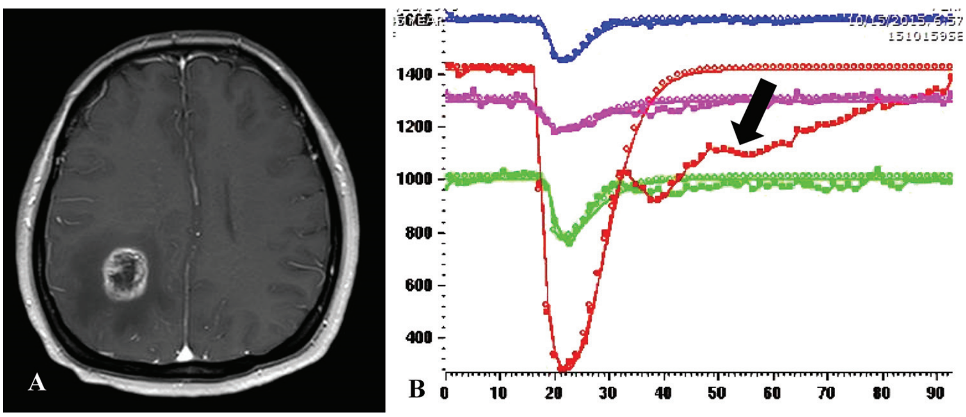

Figure 4. Glioblastoma in a 50-year-old man. (A) Axial contrast-enhanced T1 weighted image shows a thick irregular rim enhancing mass at the right parietal lobe. (B) DSC perfusion reveals marked hyperperfusion with return of time-signal intensity curve under the baseline after initial drop (arrow).

Table 3. Inter- and intraobserver variability

	ICC (95% CI)
Interobserver	0.872 (0.801 to 0.917)
Intraobserver variability for reader 1	0.825 (0.671 to 0.906)
Intraobserver variability for reader 2	0.907 (0.826 to 0.951)

ICC=intraclass correlation coefficient; CI=confidence interval

the two readers (Table 3).

Discussion

In the present study, 15 cases (78.9%) of patients with PCNSL demonstrated return of time-intensity curve above the baseline on DSC perfusion, which had relatively high sensitivity of 78.9% for the diagnosis of PCNSL. This perfusion curve pattern also had high specificity of 90.9%, with PPV of 88.2%, NPV of 83.3%, and accuracy of 85.4% for the diagnosis of PCNSL. Good reproducibility between different observers and the same observer over time was also noted.

The authors' result is consistent with previous studies, which have proved difference of time-intensity curve pattern between PCNSL and HGG. Hartman et al in 2003 showed that the characteristic signal overshoot above the baseline with relatively low maximum rCBV in six cases of PCNSL compared with six cases of GBM, and suggested that these two parameters were helpful in differentiating between the two entities(11). Another review of Chinchure et al in 2011 also gathered four typical perfusion curve patterns of HGG, including 1) rapid steep fall in signal intensity (SI) with rapid return to baseline, 2) rapid steep fall in SI with a tendency to return to baseline but not reaching it, 3) rapid steep fall in SI with little tendency to return to baseline, and 4) rapid steep fall in SI with rapid return to baseline, followed by a second smaller dip, as well as, reported same characteristic signal overshoot of PCNSL[12].

This characteristic DSC perfusion curve pattern was thought to be the results of greater degree of blood-brain barrier (BBB) disruption and higher vascular permeability in PCNSL. On the other hand, relatively intact vascular integrity for HGG was found[11]. On histopathology, PCNSL showed two distinctive populations of endothelial cells as 1) electron-dense cells, indicative of apoptosis, which this cell death resulted in complete disintegration of the endothelium with frank discontinuities of the endothelial cell component of the blood-tumor barrier in capillaries and postcapillary venules, 2) and electron-lucent cells, which had increased cell volume, indicated of cellular regeneration. Neither type of endothelial cells change was observed in gliomas, which also lacked perivascular neoplastic lymphocytic cuffing[15]. Gadolinium based contrast agent extravasated into the extravascular extracellular space had effect in reducing the T2* signal-intensity loss by overwhelming T1 effects in the interstitium[11].

The quantitative analysis from studies of Mangla et al[16] in 2011 and Xing et al[14] in 2013 showed quantitative results for percentage signal intensity recovery, which was higher in PCNSL than in HGG. Threshold value at 89% gave 100% sensitivity, 88.5% specificity, 87% PPV, 100% NPV, and 93.5% accuracy. The current study was focusing on visual inspection of curve pattern with evaluation of its value in routine clinical practice.

For steroid usage, the authors' available data revealed significant steroid administration in HGG rather than PCNSL. The authors believe that these steroids can result in decreased degree of vasogenic edema but would not affect the tumor perfusion. A previous study about effect of dexamethasone on cerebral perfusion in HGG patients also agreed with this concept[17]. The present study also showed different gender predilection between these two neoplasms. Previous study reported that there may be higher global cerebral perfusion in women than in men[18], but there has not been published data of gender relationship with CNS tumor perfusion pattern. However, the authors believe that this minor difference would not alter the present study result.

The present study had some limitations. It was retrospective study with relatively small sample size. Larger number of enrolled patients with highly delicate prospective control may give more accurate result.

Conclusion

PCNSL can be differentiated from HGG by presence of signal recovery above the baseline on DSC perfusion curve. This pattern can be used as a potentially specific marker for diagnosis of PCNSL with good reproducibility and can be easily applied in routine clinical practice.

What is already known on this topic?

There have been a few previous studies comparing DSC perfusion curve between PCNSL and HGG. Many cases of PCNSL showed characteristic signal recovery above the baseline, likely related to greater degree of BBB disruption.

What this study adds?

This study was focusing on visual inspection of DSC perfusion curve pattern comparing between PCNSL and HGG. Return of time-intensity curve above the baseline pattern was found in high percentage of PCNSL cases. However, this perfusion curve pattern could be found in some HGG cases. In addition, return of time-intensity curve above the baseline pattern had high sensitivity, specificity, and accuracy for the diagnosis of PCNSL.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Stadnik TW, Demaerel P, Luypaert RR, Chaskis C, Van Rompaey KL, Michotte A, et al. Imaging tutorial: differential diagnosis of bright lesions on diffusion-weighted MR images. Radiographics 2003;23:e7.
2. Haldorsen IS, Espeland A, Larsson EM. Central nervous system lymphoma: characteristic findings on traditional and advanced imaging. AJNR Am J Neuroradiol 2011;32:984-92.
3. Toh CH, Castillo M, Wong AM, Wei KC, Wong HF, Ng SH, et al. Primary cerebral lymphoma and glioblastoma multiforme: differences in diffusion characteristics evaluated with diffusion tensor imaging. AJNR Am J Neuroradiol 2008;29:471-5.
4. Welker K, Boxerman J, Kalnin A, Kaufmann T, Shiroishi M, Wintermark M. ASFNR recommendations for clinical performance of MR dynamic susceptibility contrast perfusion imaging of the brain. AJNR Am J Neuroradiol 2015;36:E41-51.

5. Chavhan GB, Babyn PS, Thomas B, Shroff MM, Haacke EM. Principles, techniques, and applications of T2*-based MR imaging and its special applications. Radiographics 2009;29:1433-49.
6. Zaharchuk G. Theoretical basis of hemodynamic MR imaging techniques to measure cerebral blood volume, cerebral blood flow, and permeability. AJNR Am J Neuroradiol 2007;28:1850-8.
7. Paulson ES, Schmainda KM. Comparison of dynamic susceptibility-weighted contrast-enhanced MR methods: recommendations for measuring relative cerebral blood volume in brain tumors. Radiology 2008;249:601-13.
8. Liao W, Liu Y, Wang X, Jiang X, Tang B, Fang J, et al. Differentiation of primary central nervous system lymphoma and high-grade glioma with dynamic susceptibility contrast-enhanced perfusion magnetic resonance imaging. Acta Radiol 2009;50:217-25.
9. Toh CH, Wei KC, Chang CN, Ng SH, Wong HF. Differentiation of primary central nervous system lymphomas and glioblastomas: comparisons of diagnostic performance of dynamic susceptibility contrast-enhanced perfusion MR imaging without and with contrast-leakage correction. AJNR Am J Neuroradiol 2013;34:1145-9.
10. Kickingereder P, Wiestler B, Sahm F, Heiland S, Roethke M, Schlemmer HP, et al. Primary central nervous system lymphoma and atypical glioblastoma: multiparametric differentiation by using diffusion-, perfusion-, and susceptibility-weighted MR imaging. Radiology 2014;272:843-50.
11. Hartmann M, Heiland S, Harting I, Tronnier VM, Sommer C, Ludwig R, et al. Distinguishing of primary cerebral lymphoma from high-grade glioma with perfusion-weighted magnetic resonance imaging. Neurosci Lett 2003;338:119-22.
12. Chinchure S, Thomas B, Wangju S, Jolappara M, Kesavadas C, Kapilamoorthy TR, et al. Mean intensity curve on dynamic contrast-enhanced susceptibility-weighted perfusion MR imaging--review of a new parameter to differentiate intracranial tumors. J Neuroradiol 2011;38:199-206.
13. Thomas B, Krishnamoorthy T, Gupta AK, Kesavadas C, Radhakrishnan VV, Kapilamoorthy TR. MR perfusion imaging and intensity-time curve analysis in cerebral tumors. Proc Intl Soc Mag Reson Med 2007;15:3510.
14. Xing Z, You RX, Li J, Liu Y, Cao DR. Differentiation of primary central nervous system lymphomas from high-grade gliomas by rCBV and percentage of signal intensity recovery derived from dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. Clin Neuroradiol 2014;24:329-36.
15. Molnár PP, O'Neill BP, Scheithauer BW, Groothuis DR. The blood-brain barrier in primary CNS lymphomas: ultrastructural evidence of endothelial cell death. Neuro Oncol 1999;1:89-100.
16. Mangla R, Kolar B, Zhu T, Zhong J, Almast J, Ekholm S. Percentage signal recovery derived from MR dynamic susceptibility contrast imaging is useful to differentiate common enhancing malignant lesions of the brain. AJNR Am J Neuroradiol 2011;32:1004-10.
17. Bastin ME, Carpenter TK, Armitage PA, Sinha S, Wardlaw JM, Whittle IR. Effects of dexamethasone on cerebral perfusion and water diffusion in patients with high-grade glioma. AJNR Am J Neuroradiol 2006;27:402-8.
18. Ghisleni C, Bollmann S, Biason-Lauber A, Poil SS, Brandeis D, Martin E, et al. Effects of Steroid Hormones on Sex Differences in Cerebral Perfusion. PLoS One 2015;10:e0135827.