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ROLE OF 3D ASL TO STUDY PERFUSION CHANGES IN WHITE MATTER IN PATIENTS OF MILD TO MODERATE HYPERTENSION.

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ABSTRACT

Background: There is a global decrease in cerebral blood flow (CBF) in grey as well as normal appearing white matter in patients of hypertension. This hypoperfusion leads to development of leuko-ariosis over time in normal appearing white matter. The decreased perfusion in white matter (WM) in early stages of hypertension can be assessed by 3D pseudo-continuous Arterial Spin Labeling (pCASL) even when it appears normal on conventional MRI sequences. **Methods** :It was as a hospital based analytic cross sectional study based on 60 patients divided into two groups, 30 patients in each (hypertensive and non-hypertensive) to study perfusion changes by 3D ASL MRI, in patients of hypertension and whether Perfusion parameters correlate better with Systolic blood pressure(SBP) or Diastolic blood pressure(DBP). **Results*:*** ASL parameters decreased with increasing SBP across the spectrum of normal and high BP. In subjects with hypertension, there appeared to be a window of optimal mid-range SBP where brain perfusion was the highest. Statistically significant negative association was observed between SBP and Right centrum semiovale (-0.423) and Left centrum semiovale (-0.423) while statistically significant positive association was seen between DBP and Left posterior horn of periventricular white matter. Positive correlation was seen between SBP and Right posterior horn of periventricular grey matter, Left posterior horn of periventricular white matter only. **Conclusion:**.3D ASL is a non invasive technique and has the ability to detect subtle White Matter hemodynamic abnormalities even at the early stage of hypertension, even when these white Matter regions appear normal in conventional MR images. Hence with ASL, early management can be initiated to prevent the catastrophic events occurring in late stages of hypertension.

KEYWORDS: 3D ASL, Perfusion Changes, White Matter, Mild to moderate Hypertension.

INTRODUCTION

Hypertension is a progressive cardiovascular syndrome arising from complex and interrelated aetiologies. Early markers of the syndrome are often present before Blood Pressure (BP) elevation is sustained; therefore, hypertension cannot be classified solely by discrete BP thresholds. Essential hypertension is a rise in blood pressure of unknown cause that increases risk for cerebral, cardiac, and renal events.

Hypertension has been described above 140/90 mm Hg for individuals <60 years old and above 150/90 mm Hg for individuals >60 years old.[1] Hypertension affects the small vessels in the brain. Unlike large vessels, small vessels cannot be visualized in vivo; therefore, the parenchymal lesions are taken as the markers of cerebral small vessel disease.[2]

On conventional MRI sequences various markers of cerebral small vessel disease secondary to hypertension are lacunar infarcts, cerebral microbleeds, white matter lesions and enlarged perivascular spaces.[3,4] It has been found that there is no clear order in which the MRI markers appear however enlarged perivascular spaces are the most prevalent. Cerebral micro-bleeds associated with hypertension are already present at middle age & prevalence rises strongly with age. It was also found that Diastolic BP was associated with lobar microbleeds whereas systolic BP with infra-tentorial microbleeds.[5]

White matter (WM) diseases including WM hyperintensities, lacunars infarcts, cerebral microbleeds, and dilation of perivascular spaces, are commonly observed in cerebral small vessel disease (CSVD) secondary to hypertension. Recent evidence suggests that high blood pressure (BP) can aggravate the cardiovascular burden and result in small vessel structural modifications and impaired blood–brain barrier. Such a loss of vascular integrity may be associated with a decrease in cerebral blood flow (CBF).

In patients of hypertension there is a global decrease in cerebral blood flow (CBF) in grey as well as normal appearing white matter. This hypoperfusion leads to development of leukoariosis over time in normal appearing white matter.

Several methods can be used to detect changes in CBF in vivo; for instance, transcranial Doppler technique (TCD), computed tomography (CT) perfusion imaging, positron emission tomography (PET), and magnetic resonance imaging (MRI) including dynamic susceptibility contrast (DSC), and arterial spin labeling (ASL) perfusion imaging. More recently, 3D pseudo-continuous arterial spin labeling (pCASL) using fast spin-echo (FSE) spiral acquisition has been developed to allow higher signal-to-noise ratio (SNR) and better immunity to the arterial transit effect.

Perfusion computed tomography (CT) is a technique that allows rapid qualitative and quantitative evaluation of cerebral perfusion by generating maps of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT). The technique is based on the central volume principle (CBF =CBV/MTT). It is a fast technique with which quantitative values of perfusion parameters can be acquired, however the accuracy of the flow values obtained has not been fully validated. In addition, there is an added hazard of ionizing radiation exposure.

MRI perfusion techniques used include Diffusion susceptibility contrast (DSC) MRI, dynamic contrast enhanced (DCE) MRI and arterial spin labelling (ASL).DCE & DSC have the shortcoming that they use an external contrast agent so there is risk of toxicity at high doses. Secondly absolute quantification of CBF cannot be done by any of these above methods.

Arterial spin labeling (ASL) is a magnetic resonance (MR) imaging technique that can be used for the measurement of brain perfusion noninvasively at the tissue level. Benefiting from the contrast of inflowing magnetically labelled blood, it omits the need of an external contrast agent.[6,7] The non invasive character of ASL with its freely diffusible tracer, blood water, makes it highly desirable for studying brain function.[8]

The decreased perfusion in WM in early stages of hypertension can be assessed by 3D pCASL even when it appears normal on conventional sequences.[9]

It has been shown that majority of voxels in WM perfusion signal can be detected by ASL scan in clinically feasible scan time (3- 4min).[8] It has been recently showed that pCASL was able to measure perfusion in majority of the cerebral WM with adequate SNR level by using appropriate tagging duration and post labeling delay (PLD).[10]

To the best of our knowledge, very few previous studies have investigated differences in the patients with hypertension with an ASL technique and no study was there on the population of northern India.

In our study we found out that hypertensive patients exhibit reduced CBF compared to non-hypertensive and that reduced CBF in certain brain regions correlates with deficits in specific cognitive domains; blood pressure is inversely related with CBF in hypertensive patients such that lower blood pressure is linked with better perfusion condition. Our aim was to study the perfusion changes by 3D ASL in white matter in cases of mild to moderate hypertension on MRI. Our observation revealed that the perfusion changes are detected much earlier in hypertensive cases by ASL than the white matter hyperintensities.

MATERIAL AND METHODS

The study was aimed to see perfusion changes by 3D ASL in white matter in cases of mild to moderate hypertension on MRI. Changes in normal appearing white matter with pseudo continuous ASL (pCASL) sequence was studied. The findings were compared with non-hypertensive control group matched for age &sex.

The research procedure was in accordance with the approved ethical standards of Indira Gandhi Medical Collage and Hospital ,Shimla, Ethics Committee.

Study design: Hospital based cross sectional study.

Study location: Department of Radio-diagnosis, IGMC, Shimla.

Study duration: July 2018 to June 2019.

Sample Size: 30 controls and 30 patients.

Methodology: An informed written consent was taken from whosoever met the inclusion criteria.

Detailed history of hypertension & duration of symptoms were taken from patients coming for MRI brain due to various pathologies. Before starting MRI exam, measurement of BP of all the patients was performed. Auscultator method of BP measurement was used. Based on the BP measurements patients were classified in normotensive and hypertensive group. The patients underwent MRI and pseudo-continuous 3D ASL perfusion parameters were studied.

Inclusion Criteria

- Patients irrespective of gender.
- Patients presenting with history of hypertension.
- Patients aged more than 10 years.

Exclusion criteria

- Patients with cochlear implant, cardiac pacemaker, aneurismal clip.

- Claustrophobic patients unable to lie in gantry.
- Patients with pathologies which may lead to white matter changes confounding the study purpose.

MR Imaging Acquisition

MR images were obtained on 1.5T Magnetom Avanto system (Siemens, Erlangen, Germany) by using 18-channel head coil.

MR imaging sequences were included in the following order

- T1weightedSpinEcho(TR=500ms,TE=8.6ms,slicethickness=5 mm, Flip Angle = 150 ,bandwidth = 190 Hz)
- T2 (TR = 3500 ms, TE = 111 ms, slice thickness = 5.0 mm, number of averages = 2, FOV = 230 mm^2, bandwidth = 203 Hz, time of acquisition = 1.56 minutes, matrix size = 208 ×230).
- 2D FLAIR (TR = 9000 ms, TE = 93 ms, slice thickness = 5mm, number of averages = 1, FOV = 230 mm^2, bandwidth = 179 Hz, time of acquisition = 2.06 minutes, matrix size = 230 ×230).
- Diffusion weighted imaging (DWI) and Apparent Diffusion Coefficient (ADC) [TR = 3400 ms, TE = 100 ms, Bandwidth = 1042 Hz , FOV 230 mm2 , matrix size = 154 x 192 , axial section thickness = 5mm , acquisition time = 0.07 millisecond, b value = 1000]
- 3D pCASL (TR=4000ms, TE=38ms, slice thickness= 3mm, FOV=192, bandwidth= 75 2Hz , time of acquisition= 3.16 minutes, PLD= 0.5s, matrix size=63X64).

STATISTICAL ANALYSIS

We stratified the study participants based on their BP measurement as normotensive and hypertensive (cut off SBP 140/ DBP 90).We compared the perfusion parameters by each stratum using one way analysis of variants (ANOVA).We also calculated correlation coefficient (r) between BP measurements (systolic as well as diastolic) with values of perfusion parameters. Graphical comparison was performed by BOX & WISKEL graphs and correlation was evaluated between the perfusion parameters and systolic and diastolic BPs separately. Data was cleaned and entered in MS excel worksheet and there upon transferred to EPI-INFO version 7.2 software. Descriptive statistics were used to summarize the demographic data. Proportions and percentages were used to describe categorical variables. For continuous variables in which data was normally distributed mean and standard distributions were calculated and for non-normal distribution, median and inter quartile range was calculated. This data was analyzed using appropriate statistical test techniques.

OBSERVATIONS AND RESULTS

Presenting Hospital based analytic cross sectional study on perfusion changes by 3D ASL in white matter using MRI, in consecutive patients of hypertension was conducted in the Department of Radio-diagnosis, IGMC, Shimla.

Total 60 patients were studied among which 30 were cases (Hypertensive) and 30 were Controls (Without hypertension). The means age of the studied patients was 41.68±18.67 ranging from 12-82 years. The majority of the studied patients were male (61.67%).

The association of systolic and diastolic blood pressure in the cases and the controls and the association was found to be statistically significant ($p<0.05$).

The distribution of patients on the basis of their age with respect to case and control shows that the majority of patients were between 21-40 years range while in cases the majority of patients were above 40 years and in controls they were below 40 years and the association was significant ($p<0.05$).

3D ASL has the ability to detect subtle WM hemodynamic abnormalities even at the early stage of hypertension , even when these WM regions appear normal in conventional MR images.

CBF decreased with increasing SBP across the spectrum of normal and high BP. In subjects with hypertension, there appeared to be a window of optimal mid-range SBP where brain perfusion was the highest.

Table No. 1 Demographic profile of the studied patients.

Parameters		No. of Patients (n=60)	Percentage (%)
Age in years	≤20	6	10.0
	21-40	27	45.0
	41-60	15	25.0
	>60	12	20.0
Mean age		41.68±18.67 (12-82)	
Gender	Male	37	61.67
	Female	23	38.33

The table number one shows the demographic profile of the studied patients with mean age 41.68±18.67 years and the majority of patients were males (61.67%) followed by females(38.33%)

Table No. 2 Distribution of patients in cases and controls on the basis of SBP and DBP.

Blood pressure (mmHg)	Cases (n=30)	Controls (n=30)
Systolic BP	149.0±7.66	126.2±9.04
Diastolic BP	86.73±8.08	79.46±7.39

The table no. 2 shows the systolic and diastolic blood pressure in the cases and the controls.

The average SBP in the cases was 149.0±7.66 & DBP was 86.73±8.08.The average SBP in the controls was 126.2±9.04 & DBP was 79.46±7.39

Table No. 3 Distribution of patients on the basis of their age with respect to cases.

Age in years	Cases (n=30)	Percentage
≤20	1	3.33
21-40	11	36.67
41-60	8	26.67
>60	10	33.33

The table no.3 shows the distribution of cases on the basis of their age.

Table No. 4 Distribution of patients on the basis of their gender with respect to case and control.

Gender	Cases (n=30)	Controls (n=30)	Total (n=60)	p-value
Male	21 (70.0)	16 (53.33)	37 (61.67)	0.184
Female	9 (30.0)	14 (46.67)	23 (38.33)	

The Table No.4 shows the distribution of patients on the basis of their gender with respect to case and control and the association was found to be statistically insignificant (p>0.05).

Table No. 5 WMHs on MRI conventional sequences.

WMHs on MRI	Cases (n=30)	Controls (n=30)	p-value
Right centrum semiovale	6 (20.0)	6 (20.0)	>0.05
Left centrum semiovale	6 (20.0)	5 (16.67)	0.739
Right anterior horn of periventricular white matter	9 (30.0)	3 (10.0)	0.053
Left anterior horn of periventricular white matter	9 (30.0)	2 (6.7)	**0.019**
Right posterior horn of periventricular white matter	5 (16.67)	4 (13.33)	0.717
Left posterior horn of periventricular white matter	8 (26.67)	1 (3.33)	**0.011**
Genu of corpus callosum	6 (20.0)	4 (13.33)	0.488
Splenium of corpus callosum	4 (13.33)	1 (3.33)	0.161

The Table No.5 shows the WMHs on MRI conventional sequences on the basis of cases and the controls and the association of Left anterior horn of periventricular white matter, Left posterior horn of periventricular white matter was found to be statistically significant among the cases and the controls (p<0.05) while the other parameters were showing insignificant association (p>0.05).

Table No. 6 ASL Parameters of the studied patients.

ASL	Cases (n=30)	Controls (n=30)	p-value
Right centrum semiovale	78.5±21.18	94.53±19.14	**0.018**
Left centrum semiovale	72.9±18.01	84.17±19.56	**0.024**
Right anterior horn of periventricular white matter	65.03±17.52	73.87±17.06	0.053
Left anterior horn of periventricular white matter	64.43±19.27	73.27±14.45	**0.049**
Right posterior horn of periventricular white matter	63.5±17.73	69.77±13.22	0.126
Left posterior horn of periventricular white matter	61.83±14.8	70.23±18.05	0.054
Genu of corpus callosum	82.9±17.14	97.03±27.41	**0.019**
Splenium of corpus callosum	88.1±17.37	100.57±22.68	**0.020**

The Table No.6 shows the ASL values among hypertensive and non hypertensive group and the association of Right centrum semiovale, Left centrum semiovale, Genu of corpus callosum and Splenium of corpus callosum was found to be significantly associated among the groups(p<0.05)

Table No.7 Pearson correlation between blood pressure and grey matter.

		SBP	DBP
Right centrum semiovale	Pearson Correlation	-0.464**	-0.199
	P value	0.001	0.127
Left centrum semiovale	Pearson Correlation	-0.413**	-0.215
	P value	0.001	0.099
Right anterior horn of periventricular white matter	Pearson Correlation	-0.248	0.065
	P value	0.056	0.619
Left anterior horn of periventricular white matter	Pearson Correlation	-0.294*	0.018
	P value	0.023	0.891
Right posterior horn of periventricular white matter	Pearson Correlation	0.183	0.030
	P value	0.161	0.817
Left posterior horn of periventricular white matter	Pearson Correlation	0.180	-0.052
	P value	0.168	0.692
Genu of corpus callosum	Pearson Correlation	-0.142	-0.175
	P value	0.279	0.181
Splenium of corpus callosum	Pearson Correlation	-0.153	-0.120
	P value	0.242	0.363
**. Correlation is significant at the 0.01 level (2-tailed).			
*. Correlation is significant at the 0.05 level (2-tailed).			

The Table No.7 shows the vicariate analysis of Systolic and diastolic BP with ASL parameters and statistically significant negative association was observed between SBP and Right centrum semiovale(- 0.464) and Left centrum semiovale (-0.413)and Left anterior horn of periventricular white matter(-294)while statistically significant positive association was seen between DBP and Left posterior horn of periventricular white matter. Positive correlation was seen between SBP and Right posterior horn of periventricular white matter, Left posterior horn of periventricular white matter only. DBP was associated negatively with Right centrum semiovale, Left centrum semiovale, Genu of corpus callosum and Splenium of corpus callosum.

DISCUSSION

The white matter (WM) in the brain is a particularly relevant and potentially indicative area of cerebral small vessel disease (CSVD) in hypertensive patients. However, based on the hypothesis we raised in this study that, at the early stage of hypertension, most of the white matter (WM) regions can be normal-appearing despite their potentially reduced perfusion level. Recent progress in MRI perfusion techniques open the possibility to noninvasively study the cerebro-spinal fluid (CBF), which could shed light on the potential effect of hypertension on perfusion in the WM, and in turn provide an early imaging biomarker to assess the risk of cerebral small vessel disease.

Recent studies have demonstrated that WM diseases tend to cluster in several specific locations: the deep WM of the centrum semiovale, the anterior and posterior horns of the periventricular region, and the genu and splenium of the CC.[11,12,13]

Very few studies have been performed previously in the patients on whom the perfusion parameters were studied based on increased or decreased SBP and DBP. **Wang T et al.[6]** did a study on Reduced Perfusion in Normal-Appearing White Matter in Mild to Moderate Hypertension as Revealed by 3D Pseudo-continuous Arterial Spin Labeling, **Tryambake Det al[14]** studied the intensive blood pressure lowering Increases cerebral blood flow in older subjects with hypertension and **Glodzik L et al[15]** also performed a study on different Relationship Between Systolic Blood Pressure and Cerebral Perfusion in Subjects With and Without Hypertension.

Findings in comparison to other studies-

Mean Age

In our study, the majority of patients were of age between 21- 40 years (45.0%) followed by 41-60 years (25.0%) and the mean age was reported as 41.68±18.67 years in the total (60) studied patients and if we talk about only the cases; (36.67%) patients were in between age 21-40 years while 8 (26.67%) were between 41-60 years. Similar finding were reported by **Wang T et al[6]** who depicted the mean age of the cases as 47.9±8.3 years and that of the controls as 46±8.4 years. **Glodzik L et al[15]** and **Tryambake D et al[14]** also reported the mean age of the hypertensive patients above 40 years. This shows that the problem of hypertension usually occurs in the elderly patients that to above 40 years that are in their 5th and above decades of life.

Gender

In our study, majority of patients were males (61.67%) as compared to the females (38.33%) and the association of males and females in the cases and the controls group was found to be statistically insignificant (p>0.05). Our study was in accordance with **Virhammar J et al[16]** who reported insignificant association of gender in the

studied groups (p>0.05). **Wang T et al[6]** also stated the males in the majority in their study.

SBP and DBP in the cases and the controls

In the present study, the means SBP in Cases and controls was 149.0±7.66 mmHg and 126.2±9.04 mmHg respectively while DBP was 86.73±8.08 mmHg and 79.46±7.39 mmHg in cases and controls respectively. Our findings were similar to the study performed by **Wang T et al,[6] Glodzik L et al[15]**and **Elmstahl S et al.[17]**

WMHs on MRI conventional sequences

In the present study, association of WMHs in different regions of interest (ROI) on MRI conventional sequences in cases and the controls was calculated and the association of right anterior horn of periventricular white matter, left anterior horn of periventricular white matter, left posterior horn of periventricular white matter was found to be statistically significant among the cases and the controls (p<0.05) while the other parameters were showing insignificant association (p>0.05).In a study done by **Gunstad J et al[18]**it was observed that no relationship emerged between average pressure and WMH for either systolic or diastolic BP.

ASL Parameters in cases and controls

The ASL values among hypertensive and non-hypertensive group were studied and the association of Right centrum semiovale, Left centrum semiovale, Genu of corpus callosum and Splenium of corpus callosum was found to be significantly associated among the groups (p<0.05). **Fisher CM et al[19]** found in their study prolonged hypertension can lead to alterations in small vessels, including atherosclerosis of smaller (100–500 lm) perforating arteries and the arteriolosclerosis of the smaller (<100 lm) vessels. These small arteries and arterioles undergo medial thickening associated with hyaline deposition and intimal proliferation, which accounts for the reduction in luminal diameter and an increased resistance to the flow.[20] As arterial narrowing increases, it results in a reduction in capillary perfusion, which can further lead to ischemia and lacunar infarction.[21] Furthermore, attributable to the inability of sclerotic vessels to dilate, occasional drops in BP can lead to a significant decrease in blood flow into the WM among patients with arteriolosclerotic vessels.[22] Study done by **Strandgaard S et al[23]** has demonstrated that auto-regulatory limits were shifted upwards among hypertensive subjects. Moreover, CBF values in the pre-hypertension group were closer to hypertension, while their brain volumes were closer to volumes of subjects with normal BP. Our results strongly support the premise that CBF impairments precede structural changes because balanced steady- state free precession ASL method is minimally affected by partial volume effects. Our observations are in line with earlier studies showing that hypertension confers higher risk of stroke as compared with lower BP and suggest early treatment of elevated BP.[24]

Our results are in agreement with some but not all previous observational studies in midlife hypertensive patients, where lower BP was associated with higher CBF.[25][26] **Kimura Y et al.[27]** in an interventional study which have shown BP lowering increases CBF. However, this has not been a finding in all studies, which may reflect methodological or small sample sizes in some studies.[28][29] Our study has specific features which add to understanding of the effects of BP on CBF.

Consistent with the previous study done by **Wang T et al,[6]** the findings indicated that the CBF in genu of the Corpus Callosum was relatively stable; resulting in that there was no significant difference between the control and hypertensive groups. In addition, the splenium of CC was susceptible of being injured by declined CBF in hypertension and exhibited declining of CBF in cases.

Study Limitations

Our sample size was relatively small, which may account for the inability to reach statistical significance in the genu of corpus callosum. We did not have reliable information about the duration of hypertension.

The study was conducted in healthy people with hypertension and the results might not apply to frail older people or individuals with autonomic dysfunction.

Strengths

One of a kind study that uses MRI and 3D ASL techniques.

Recommendations

Although more studies with larger sample size are warranted to replicate these findings and confirm the generaliability of the BP levels found in our group, our results have the potential to inform treatment goals for general and hypertensive populations.

Further work is necessary to determine whether similar changes are seen in white matter CBF with intensive BP lowering as the increase in gray matter CBF.

CONCLUSION

Our study showed that 3D ASL has the ability to detect subtle changes in cerebral blood flow parameters in white matter regions at relatively early stages of hypertension. The observed decrease in cerebral blood flow in these regions may suggest an increased risk of cerebral small vessel diseases. ASL is a non-invasive technique which can be used in clinically feasible scan time (~ 3– 4 minutes) to assess the early changes in brain parenchyma caused by hypertension and early management can be initiated to prevent the catastrophic events occurring in late stages of hypertension. As it is a non-invasive technique with no need of intravenous (i/v) contrast agents therefore can be used repeatedly without any harm to the patients. Furthermore it can be used safely in patients with renal impairment without the risk of contrast nephropathy. We also conclude that perfusion

changes are detected much earlier in hypertensive cases by ASL than the white matter hyperintensities.

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