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FULL PAPER

Altered cerebral blood flow in patients with unilateral venous pulsatile tinnitus: an arterial spin labeling study

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Objectives: Abnormal neuronal activity and functional connectivity have been reported in patients with venous pulsatile tinnitus (PT). As neuronal activity is closely coupled to regional brain perfusion, the purpose of this study was to investigate the cerebral blood flow (CBF) alterations in patients with unilateral venous PT using arterial spin labeling (ASL).
Methods: This study included patients with right-sided PT between January 2018 and July 2019. A healthy control (HC) group matched 1:1 for gender and age was also recruited. All subjects underwent ASL scanning using 3.0T MRI. The correlation between altered CBF and Tinnitus Handicap Inventory (THI) score as well as PT duration was analyzed.
Results Twenty-one patients with right-sided PT and 21 HCs were included. The mean PT duration of the patients was 35.9 ± 32.2 months, and the mean THI score was 64.1 ± 20.3. Compared with the HCs, the PT patients exhibited increased CBF in the left inferior parietal gyrus and decreased CBF in the bilateral lingual gyrus (family-wise error corrected, $p < 0.05$). The increased CBF in the left inferior parietal gyrus showed a positive correlation with the THI score in PT patients ($r = 0.501$, $p = 0.021$).
Conclusions PT patients exhibit regional CBF alterations. The increased CBF in the left inferior parietal gyrus may reflect the severity of PT.
Advances in knowledge: This study not only presents evidence for the potential neuropathology of PT from the perspective of CBF alterations but also offers a new method for investigating the neuropathological mechanism of PT.

INTRODUCTION

Pulsatile tinnitus (PT) is characterized by the noise perception synchronized with the heart rate.[1] It can be classified as arterial, venous and arteriovenous,[2] and venous PT accounts for 84% of all PT patients.[3] Sigmoid sinus wall dehiscence with or without diverticulum has been reported as a primary etiology of venous PT.[4–6] The sound caused by abnormal blood flow in the venous sinus is transmitted to the inner ear through the dehiscent area. After sigmoid sinus wall reconstruction, the sound can disappear completely or is significantly relieved.[7,8] Long-term PT seriously interferes with patients' quality of life, and sometimes even leads to depression and suicide.[9]

More attention has been paid to the central nervous mechanism of tinnitus. Previous studies using resting-state fMRI found abnormal neuronal activity[10,11] and functional connectivity in unilateral PT patients.[12,13] These findings indicate that pathophysiological changes exist in the brains of PT patients. As neuronal activity and regional brain perfusion are closely coupled, increased neuronal activity may cause an increase in regional cerebral blood flow (CBF).[14,15] Thus, we speculate that CBF alterations may be presented in PT patients, a hypothesis that has not been tested by other researchers.

Arterial spin labeling (ASL) is a perfusion imaging technique that uses magnetically labeled arterial blood protons as an endogenous contrast medium.[16] Due to its ease of implementation and high signal-to-noise ratio, 3D pseudo-continuous ASL has been considered an important method for clinical imaging research in recent years.[17] Compared with traditional perfusion imaging techniques such as positron emission tomography (PET), dynamic contrast-enhanced and dynamic susceptibility contrast MRI, ASL has the advantages of non-invasiveness, simplicity, and low cost. Because CBF and neuronal activity are closely linked,[15] ASL may be an alternative functional marker.[17] Moreover, since the ASL signal originates from capillaries, it provides increased spatial specificity for neuronal activity.[18,19] Therefore, ASL has been increasingly used in neurological and psychiatric disorders.[20–22]

In this study, we used the 3D pseudo-continuous ASL technique to investigate the CBF alterations in patients with unilateral venous PT. In addition, the correlation between altered CBF and tinnitus severity as well as tinnitus duration was analyzed.

METHODS AND MATERIALS

Subjects

All PT patients for this study were recruited from the ear, nose, and throat department between January 2018 and July 2019. Patients meeting the following criteria were included: 1. persistent pulse-synchronous tinnitus in the right ear; 2. significant improvement in symptoms with compression of the right internal jugular vein[8]; 3. normal otoscopic, audiometric and tympanometric evaluations; 4. sigmoid sinus wall dehiscence with or without diverticulum found on CT arteriography and venography (CTA/V) examination and diagnosed as the main etiology[23,24]; 5. ASL performed before the operation and 6. the complete disappearance of the sound after sigmoid sinus wall reconstruction.

A 1:1 gender-, age-, handedness- and education level-matched healthy control (HC) group was also enrolled. The exclusion criteria for all PT patients and HCs were as follows: non-PT, hearing loss (hearing thresholds > 25 dB hearing level for 0.250, 0.500, 1, 2, 3, 4, 6, and 8 kHz frequencies),[25] hyperacusis, neurological diseases, tumor, stroke, systemic diseases (such as diabetes, hypertension, and hyperlipidemia), a history of drug and alcohol abuse within the past 3 months or contraindication to MRI examination. The severity of tinnitus in PT patients was evaluated by the Tinnitus Handicap Inventory (THI) score.

The Medical Research Ethics Committee of our institution approved this study protocol. In accordance with the Helsinki Declaration, every participant in this study provided written informed consent.

Image acquisition

Brain imaging was obtained on a GE Discovery MR750W 3.0-Tesla scanner (Milwaukee, WI, USA) and eight-channel phased array coil. ASL data were obtained by a 3D pseudo-continuous fast spin echo sequence with background suppression (36 slices; echo time [TE], 10.7 ms; repetition time [TR], 4854 ms; post-label delay [PLD], 2025 ms; slice thickness, 4 mm without gap; number of excitations, 3; in-plane resolution, 3.37×3.37 mm; field of view [FOV], 240×240 mm; flip angle [FA], 111°). The scanning time of the ASL sequence was 4 min and 42 s. We used foam padding to prevent head movement and earplugs to reduce noise. During the ASL data acquisition, all HCs and patients with PT were asked to stay awake, keep their eyes closed, and avoid thinking of anything.

Image processing

We obtained the maps of CBF by pairwise subtraction of the ASL control and label images. The CBF images of 21 HCs were co-registered to a PET-perfusion template in the standard space of Montreal Neurological Institute (MNI) by Statistical Parametric Mapping (SPM8). Subsequently, the standard CBF template of the MNI specific to this study was obtained by averaging the co-registered CBF images for the 21 HCs. We co-registered all the CBF images to the standard CBF template with resampling to $2\times2\times2\ mm^3$. The CBF of each voxel was normalized by dividing the average CBF of the whole brain to detect smaller CBF differences between groups.[26] Finally, the CBF images were smoothed with an 8 mm full-width at half maximum (FWHM) Gaussian kernel.

Statistical analysis

SPSS v.22.0 was used for the statistical analysis. Fisher's exact test and two-sample t-test were performed to calculate the group differences in baseline data. Significant difference was set as $p < 0.05$.

Two-sample t-test was used to explore the group difference in CBF, with gender and age as covariates. The significance threshold of cluster-level family-wise error (FWE) correction was set to $p<0.05$. A correlation analysis was performed between altered CBF and the clinic data.

RESULTS

Demographic characterization

In this study, 21 patients with right-sided PT and 21 HCs were included. No subjects were excluded during the pretreatment phase. Baseline information on the participants is shown in Table 1. The mean PT duration of the patients was 35.9 ± 32.2 months, and the mean THI score was 64.1 ± 20.3. The two groups were well-matched in terms of gender (fisher's exact test, p = 1.000), age (two-sample t-test, p = 0.951), education level (two-sample t-test, p = 0.480), and handedness (two-sample t-test, p = 1.000).

CBF differences between groups

The group differences in CBF are exhibited in Table 2 and Figure 1. Compared with the HCs, the PT patients demonstrated significantly increased CBF in the left inferior parietal gyrus (FWE corrected, $p < 0.05$). In contrast, the bilateral lingual gyrus demonstrated decreased CBF in PT patients compared with HCs (FWE corrected, $p < 0.05$). The CBF values of analyzed brain regions in PT patients and HCs are shown in Table 3.

Correlation between CBF and the duration as well as severity of PT

In PT patients, the increased CBF in the left inferior parietal gyrus showed a positive correlation with the THI score (r = 0.501, p = 0.021) (Figure 2). There were no significant correlations between the CBF in the bilateral lingual gyrus and the THI score as well as the duration in PT patients.

Table 1. Demographic and clinical data for PT patients and HCs

	PT (*n* = 21)	HC (*n* = 21)	*P* value
Age (years)	39.3 ± 10.2	39.1 ± 9.7	0.951[b]
Gender (male/female)	2/19	2/19	1.000[a]
Education (years)	11.3 ± 3.7	12.1 ± 3.2	0.480[b]
Handedness	21 right-handed	21 right-handed	1.000[b]
PT duration (months)	35.9 ± 32.2	NA	NA
THI score	64.1 ± 20.3	NA	NA

Data are presented as the mean ± standard deviation. PT: pulsatile tinnitus; HC: healthy control; THI: Tinnitus Handicap Inventory; NA: not applicable
[a] Fisher's exact test; [b] Two-sample t-test.

DISCUSSION

In this study, we used 3D pseudo-continuous ASL to investigate CBF alterations in patients with unilateral venous PT. These patients revealed increased CBF in the left inferior parietal gyrus and decreased CBF in the bilateral lingual gyrus. Moreover, the increased CBF in the left inferior parietal gyrus showed a positive correlation with the THI score.

PT patients revealed increased CBF in the left inferior parietal gyrus, the core of the tinnitus network.[27] This network, confirmed by several studies,[28–30] comprises the ventrolateral prefrontal cortex, inferior parietal area, parahippocampal cortex and auditory cortex.[27] It constitutes a basic framework for understanding the pathophysiology of tinnitus. De Ridder asserted that the inferior parietal gyrus was involved in auditory memory, auditory memory retrieval and auditory perception in this tinnitus network.[27] This region was even considered to represent the minimum brain activity required for effective sound retrieval from auditory memory.[27] The inferior parietal gyrus is also a key component of the dorsal visual stream,[31] which is responsible for processing acoustic information.[32,33] A magnetoencephalography study found that the inferior parietal gyrus can regulate the activity of auditory-related cortex in tinnitus patients.[34] Transcranial magnetic stimulation in this region can significantly relieve tinnitus symptoms.[29,30] These findings suggest that the inferior parietal gyrus may play a causal role in tinnitus perception. Notably, the abovementioned studies mainly focused on non-PT patients. An fMRI study of PT found increased amplitude of low-frequency fluctuation (ALFF) and regional homogeneity (ReHo) in the inferior parietal gyrus, suggesting that the neuronal activity was increased in this brain region.[11] As neuronal activity and brain perfusion are closely coupled, increased neuronal activity in the left inferior parietal gyrus may lead to an increase in CBF in this region, which is consistent with our finding. Moreover, this region, as a component of the cognitive control network (CCN),[35] is involved in abnormal functional connectivity in PT patients.[12] Thus, the inferior parietal gyrus plays a key role in PT. In this study, we also found that increased CBF in the left inferior parietal gyrus was positively correlated with the THI score. This finding suggests that increased CBF in the left inferior parietal gyrus is more likely a reflection of the severity of PT. Based on these findings, we will investigate the CBF changes in patients with different treatment outcomes after surgery, and further explore whether the changed CBF in the left inferior parietal gyrus can be used as a non-invasive biomarker for PT diagnosis and treatment evaluation.

Table 2. Brain regions with significant CBF differences between PT patients and HCs

Brain region	Peak MNI (mm) x y z	Peak T value	Cluster size (mm^3)
PT >HC			
L inferior parietal gyrus	−42−44 46	4.58	344
PT <HC			
R lingual gyrus	32−64 −8	−4.80	273
L lingual gyrus	−14−82 −2	−4.86	296

PT: pulsatile tinnitus; HC: healthy control; CBF: cerebral blood flow; MNI: Montreal Neurological Institute; L: left; R: right.

Figure 1. CBF differences between patients with unilateral PT and HCs. Compared with HCs, the patients with unilateral PT showed increased CBF in the left inferior parietal gyrus as well as decreased CBF in the bilateral lingual gyrus (FWE-corrected $p < 0.05$). PT: pulsatile tinnitus; HC: healthy control; CBF: cerebral blood flow; FWE: family-wise error

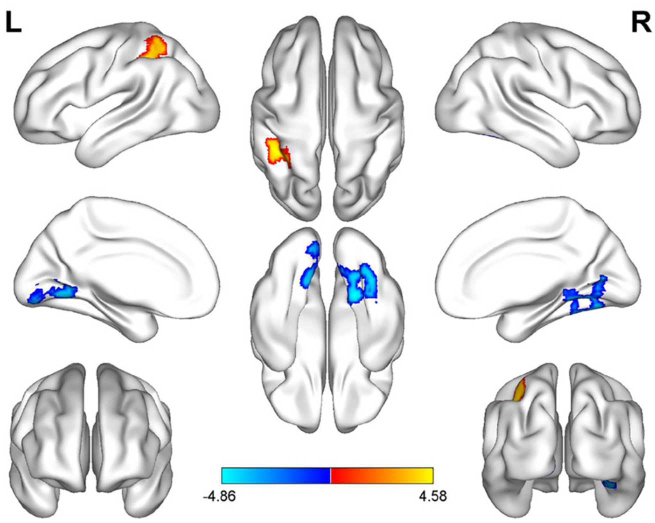

Table 3. The CBF values of analyzed brain regions in PT patients and HCs

	PT	HC
L inferior parietal gyrus	52.83 ± 11.25	48.31 ± 7.92
R lingual gyrus	47.08 ± 9.93	55.74 ± 8.88
L lingual gyrus	48.01 ± 10.10	57.32 ± 9.20

Data are presented as the mean ± standard deviation. Values are in units of mL / 100 g / min. PT: pulsatile tinnitus; HC: healthy control; L: left; R: right.

The lingual gyrus is an essential part of the visual-related cortex.[36] In this study, PT patients showed decreased CBF in the bilateral lingual gyrus, raising the question of whether PT can lead to CBF alterations in the visual-related cortex. A previous fMRI study showed decreased ALFF values in the lingual gyrus in PT patients, indicating decreased neuronal activity in this region.[37] This result is line with the decrease in CBF in our finding. The auditory cortex is closely related to the visual cortex in anatomy and functional connectivity.[36,38] Increased functional connectivity in the visual-auditory network was also observed in PT patients in an fMRI study.[12] Furthermore, neuronal activity of the visual cortex may be directly modulated by the auditory cortex.[39] In this study, we also found increased CBF in the left inferior temporal gyrus and middle temporal gyrus (overlapped with the auditory cortex) in PT patients, but the CBF in these regions was not significantly different. This may be related to the relatively small sample size of this study. In addition, a direct network connection exists between the left inferior parietal cortex and the visual association areas, as reported in a magnetoencephalography study.[34] Therefore, increased CBF in the left inferior parietal gyrus, as observed in this study, may be involved in altering the CBF of the bilateral lingual gyrus.

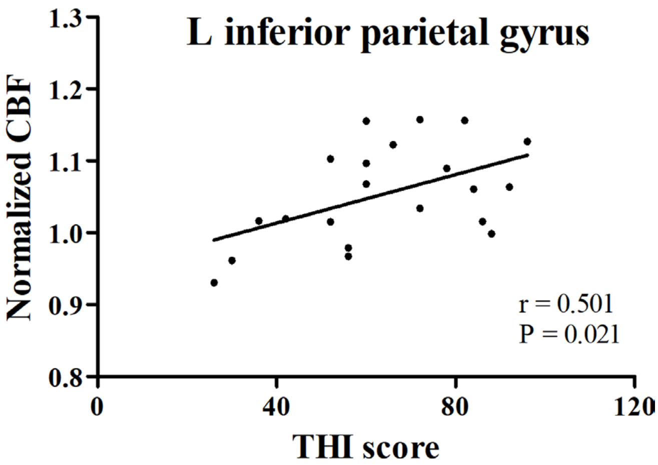

Figure 2. Correlation between the normalized CBF and THI score in patients with unilateral PT (r = 0.501, p = 0.021). PT: pulsatile tinnitus; CBF: cerebral blood flow; THI: Tinnitus Handicap Inventory

Our study has several shortcomings. First, this was a preliminary study with a small sample size. PT accounts for approximately 4% of all tinnitus cases.[23] Therefore, it is a relatively uncommon disease. As we enroll more PT patients in future studies, we will study CBF alterations in PT patients with different durations of PT. Second, only right-sided PT patients were included in this study. Right-sided PT is the most common type in clinical practice,[40] which possibly represents the disease status of most patients. Moreover, a previous fMRI study found the difference in functional connectivity characteristics between left-sided and right-sided PT.[25] In the future, we will include more left-sided PT patients to explore the effect of the laterality of PT on brain perfusion. Third, previous studies have reported differences in brain structure and function between left- and right-handed individuals.[41–43] In order to exclude the effect of handedness, all the subjects in this study are right-handed. Fourth, considering the radiation exposure and low incidence of sigmoid sinus wall abnormalities in asymptomatic individuals,[5] CTA/V was not performed on HCs to evaluate sigmoid sinus wall abnormalities in this study. Fifth, morphological changes may affect the measurement of CBF. Previous studies have confirmed no significant difference in brain volume between the PT patients and HCs.[10,12,13,37] Hence, we did not conduct a morphological study in this work. In addition, we will further explore the CBF changes in patients after successful surgery to reveal the effect of PT on brain perfusion.

CONCLUSION

In conclusion, we identified altered CBF in the left inferior parietal gyrus and bilateral lingual gyrus, which may be involved in the neuropathological process of patients with PT. In this study, we also found that the increased CBF in the left inferior parietal gyrus may reflect the severity of PT. These findings not only present evidence for the potential neuropathology of PT from the perspective of CBF changes but also offer a new method for investigating the neuropathological mechanism of PT.

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