Evaluating the morphological changes of intracranial arteries and whole-brain perfusion in undetermined isolated vertigo

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ABSTRACT

Purpose: To determine the morphological changes of intracranial arteries and whole-brain perfusion in undetermined isolated vertigo (UIV) patients using 320-detector row computed tomography (CT).

Methods: A total of 150 patients who underwent CT angiography (CTA) and CT perfusion (CTP) imaging were divided into UIV group and benign paroxysmal positional vertigo (BPPV) group. Sixty individuals with sex- and age-matched without vertigo and cerebral diseases served as the control. The morphological changes of intracranial arteries, perfusion parameters and vascular risk factors (VRFs) were analyzed, calculated and compared.

Results: In UIV patients, hypertension (HT), hyperlipidemia and number of VRFs ≥3 occurred more commonly (P < 0.0125, respectively). The incidence of vertebral artery dominance (VAD), vertebral artery stenosis (VAS) and basilar artery curvature (BAC) were significantly higher (P < 0.0125, respectively). HT was an independent risk predictor of non-VAD (OR: 5.411, 95%CI: 1.401; 20.900, P = 0.014). HT and VAD associated with BAC served as risk predictors (OR: 4.081, 95%CI: 1.056; 15.775, P = 0.041 and OR: 6.284, 95%CI: 1.848; 21.365, P = 0.003, respectively). The absolute difference in relative values of CTP parameters from cerebellum and brainstem were significantly different (P < 0.05), and hypoperfusion was found in the territories of the non-VAD side and the BAC cohort (P < 0.05, respectively).

Conclusions: On the basis of multiple VRFs, morphological changes of vertebrobasilar artery (VBA) and the unilateral hypoperfusion of the cerebellum and brainstem, that acts as a herald for IV occurrence, which should be paid cautious attention to UIV patients.

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1. Introduction

Vertigo is a common public health care issue with a broad differential diagnostic challenge to the clinicians. It often results from peripheral vestibular diseases such as benign paroxysmal positional vertigo (BPPV) [1,2]. Isolated vertigo (IV), a clinical symptomatology conception, invests vestibular diseases such as benign paroxysmal positional vertigo (BPPV) and cerebellar/brainstem ischemic events [1,5–7]. The abnormal morphological changes of intracranial arteries did not refer to stenosis or occlusion simply. Retrospective data posited that impaired perfusion through abnormal vertebrobasilar artery (VBA) remained an important factor in recurrent IV when the etiology was unclear especially combined with vascular risk factors (VRFs) [5–10].

320-detector row CT system is a new, non-invasive technique for evaluating the abnormalities of blood flow. Perfusion imaging with this CT system could provide simultaneous CT angiography (CTA) and CT perfusion (CTP) imaging by only one scan with isotropic and isophasic anatomical and functional information of the whole brain. Vascular information and perfusion regions, especially posterior circulation ischemic changes, could be detected according to this system [11–13].

The aim of the present study is to elucidate the relationship among VRFs, the morphological changes of intracranial arteries and whole-brain perfusion in patients with IV by one-stop imaging using 320-detector row CT.

Previous studies [3,4] emphasized that recurrent episodes of IV was rarely attributable to vascular events, while several small series studies revealed contradictory findings [1,5–7]. The abnormal morphological changes of intracranial arteries did not refer to stenosis or occlusion simply.
2. Materials and methods

2.1. Ethical considerations

This study was approved by the Medical Ethics Committee, the First Affiliated Hospital of Jinan University, China. And registered in the WHO clinical trial registry (registration number: ChiCTR-DCD-15006540). Written informed consent was obtained from all the patients.

2.2. Experimental design and patient population

This was a prospective study. A total of 150 patients from the Department of Neurology, First Affiliated Hospital of Jinan University were enrolled from December 2012 to July 2015. Their ages were >40 years old and divided into two groups: The UV group including 76 patients (39 males and 37 females; mean age, 61.59 ± 11.07 years; range, 40–82 years) and BPPV group composed of 74 patients (28 males and 46 females; mean age, 59.04 ± 11.78 years; range, 40–81 years). All UV patients included those following criteria: the unidentified recurrent IV (excluding Meniere’s disease, vestibular neuritis, vestibular paroxysmia and other inner ear deficient symptoms such as sudden deafness, tinnitus, hearing loss); no focal neurological signs; normal head impulse test; no head trauma; no history of migraine; no acute infarction and hemorrhage or tumor on head CT or MR image; no orthostatic hypotension or subclavian steal syndrome; excluding anemia, renal insufficiency, congenital heart disorders, emotional disease; no history of poisoning; no related drugs taken that could induce vertigo. Vertigo can be accompanied with nausea or vomiting, unsteady gait, nystagmus, more than one vertigo attack and intolerance to head motion, and persists indeterminately. BPPV patients were diagnosed according to the clinical guidelines [14]. All patients underwent 320-detector CT row imaging examinations and standard blood tests in 2 days of the onset of symptoms. Subjects merged with VRFs received investigation and primary prevention. All BPPV patients received repositioning treatment.

A group of 60 sex- and age-matched individuals (28 males and 32 females; mean age, 58.75 ± 14.36 years; range, 40–87 years) who had received whole-brain perfusion imaging using 320-detector dynamic volume CT at our hospital were retrospectively chosen as control subjects. All control cases were devoid of vertigo symptoms, central neurological deficits, other inner ear deficient symptoms, and cerebral diseases on CT or MR examination.

2.3. Baseline evaluation

Data gathered including demographic information and VRFs were identified. Details on VRFs including age ≥ 60 years, hypertension (HT), diabetes mellitus (DM), hyperlipidemia, coronary artery disease (CHD), smoking have been previously published [1,15].

2.4. CT protocol

All the patients underwent whole-brain perfusion imaging with a 320-detector row system (Aquilion ONE; Toshiba Medical Systems, Tokyo, Japan). The scan parameters were: 80 kV tube voltage, 112–187 mA tube current, 512 × 512 matrices, 320 mm field of view (FOV), 0.35 s rotation time, and 0.5 mm × 320 collimator. The whole brain of each patient were covered by a single scan as a result of z-direction coverage of 160 mm.

A total of 50 ml of anion-ionic contrast material (CM) with an iodine content of 370 mg/ml (Ultradent 370®; Bayer-Schering, Berlin, Germany) were administered at a flow rate of 6 ml/s using a dual-shot injector (Dual Shot Alpha; Nemoto-Kyorindo, Tokyo, Japan) through a 20-gauge intravenous injection catheter inserted into an antecubital vein. A 60 ml 0.9% saline chaser was followed with the same flow rate after the injection of CM. The whole-brain perfusion imaging was started at the 7th second after the injection to obtain a mask, and acquisition was continued at every 2 second intervals from the 12th second to the 36th second. Then, after a 3-second pause, 5-second intervals were used from the 40th second to the 60th second. Thus, the 19 whole-brain volume data were acquired for every patient and the total acquisition time was 60 s.

The acquired perfusion volume data was loaded into Vitrea Fx 6.3 workstation (Vital images, Minnetonka, MN, USA). CTP was reconstructed by the Brain Analysis software package. Perfusion maps included relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV), mean transit time (MTT), time to peak (TTP) were generated using a delay-invariant single-value decomposition algorithm (SVD +, Vital Image, and Toshiba Medical System). The observers manually drew regions of interest (ROIs), which contain 5–150 pixels, while attempting to exclude areas with necrosis, vessels or calcifications. The observers measured each ROI of the CTP parameters and recorded them.

The digital subtraction of the whole-brain volume data was performed on display workstation (Toshiba Medical System, Japan), which allowed for subtraction of 3D reconstructions and CTA images. Vascular diameter was measured using dedicated open-source imaging software (OsiriX64-bit) on the transverse images.

2.5. Data analysis

Two experienced neuroradiologists, blinded to all clinical information and the final diagnosis, independently interpreted and measured the CTA images and perfusion maps of all patients. The image interpretation results were unified as follows: (1) the same results between the two readers (agreement) and (2) the final results after discussion between the two readers in the disagreement.

2.6. Measurements and analysis of CTA images

The morphology of intracranial arteries from both anterior and posterior circulation were analyzed and evaluated comprehensively. Cerebral anterior circulation arteries included bilateral anterior cerebral artery (ACA) and middle cerebral artery (MCA). Posterior circulation arteries included bilateral posterior cerebral artery (PCA), vertebral artery (VA) and basilar artery (BA).

The average measurement of intracranial VBA system, starting from the vertebrobasilar junction (both VAs and the BA), was made at three consecutive points with 3 mm distance [16]. Intracranial arterial stenosis was calculated and analyzed according to Samuels method [17]. Stenosis rate = 1 – Ds / Dn × 100% (Ds represents the intracranial artery stenosis diameter, Dn as normal diameter). Definition: (1) 0% for normal, (2) <50% for mild stenosis, (3) 50–69% for moderate stenosis, (4) 70–99% for severe stenosis, (5)100% for occlusion. (3) and (4) have been considered as stenosis in the current study.

The diagnosis of ACA hypoplasia was based on the diameter < 1 mm or the absence of A1 segments [18]. A nonvisualized P1 segment with a fetal type PCA was interpreted as aplasia [19].

VAD was defined as (1) side-to-side diameter difference ≥ 0.3 mm or (2) the VA connected to the BA in a more straight manner if both VAs were visually similar to an angle criterion on CTA [16]. VA hypoplasia (VAH) was defined as a V4 diameter of ≤ 2.0 mm [20,21]. In this study, VAH was considered as a synonym of contralateral VAD. Non-VAD side was defined as the opposite side of VAD, unilateral VAH and VA stenosis (VAS).

BA hypoplasia (BAH) was defined as a diameter < 2 mm [22]. The BA curvature (BC) was classified into C type (toward either the right or the left sides), S type (multiple bends), and J type according to a course of BA navigation at the vertebrobasilar junction [23]. The degree of BAC was based on the lateral-most position of the BA throughout its course and classified into left (L) side or right (R) side (0, midline; 1, medial to lateral margin of the clivus or dorsum sellae; 2, lateral to the lateral margin of the clivus or dorsum sellae; and 3, in the cerebellopontine
angle cistern). Moderate to severe BAC was defined as degree ≥ 2 of the above criteria [16].

2.7. Measurement and analysis of perfusion maps

The drop target of ROIs were similar to a symmetrical mirror, seven regions were located in the bilateral frontal cortex and parietal cortex, frontal lobe, internal capsule and striatum and thalamus, superior side of temporal lobe, occipitotemporal lobe, cerebellum and brainstem in the level of the vestibular nucleus, which placed the analogous circular area as the symmetrical ROIs respectively (Fig. 1). Each ROI was measured three times and the average was determined.

Considering the physiological differences in each individual and allowing convenient comparisons among three groups, a relative mean value of the two mirror ROI values of each parameter was calculated (=The absolute difference of parameter value between left to right ROI) that could reflect the differences between the two regional perfusion values including absolute rCBV (arCBV), absolute rCBF (arCBF), absolute MTT (aMTT), absolute TTP (aTTP) on which later statistical analysis was performed.

2.8. Morphological changes of intracranial arteries and corresponding region perfusion changes

The correlation in the corresponding territory of intracranial morphological arteries changes with perfusion situation was analyzed when the patterns of intracranial arteries yielded statistically significant differences.

Fig. 1. Outlines of ROIs (indicated by red circles) consisting of diffusion-weighted MR, CT scans and corresponding perfusion maps including relative cerebral blood volume (rCBV), time to peak (TTP), relative cerebral blood flow (rCBF), and mean transit time (MTT). (A. Frontal cortex and parietal cortex. B. Frontal lobe. C. Internal capsule, striatum and thalamus. D. Superior side of temporal lobe. E. Occipitotemporal lobe. F. Cerebellum. G. Brainstem.)
For ACA territories, the definition of the frontal lobe parenchyma and part of the parietal lobe cortex were used. The main territories of MCA were the internal capsule, the striatum, parietal lobe. In addition, our ROIs of frontal cortex and parietal cortex have to be considered as territories of both MCA and ACA. The territories of PCA were the occipitotemporal lobe and the thalamus. The definition of VA blood flow distribution was the cerebellum derives from branches arising from posterior inferior cerebellar artery (PICA), and the main territory of BA was the brainstem [16,21]. Hypoperfusion would be considered based on a previously published algorithm if low CBF, low CBV, delayed MTT, and delayed TTP were found in the corresponding regions of the blood flow distribution of intracranial arteries [21].

Considering that CTP parameter thresholds for infarct core, penumbra or hypoperfusion are not universally accepted because the scan protocols or the postprocessing methods widely varied among the manufacturers, using rigid quantitative thresholds for the definition of infarct core and hypoperfusion area was avoided in this study [21,24].

If statistically significant morphological changes of intracranial arteries (including VAD, VAS and BAC) were observed in UIV patients, then the corresponding perfusion features in the blood flow territory of abnormal arteries were analyzed. For the VA and its corresponding cerebellum perfusion, the perfusion in non-VAD and normal VA were evaluated first, followed by the perfusion situations of non-VAD side and the VAD side exploration. For the BA and its corresponding brainstem perfusion, the perfusion of BAC and normal BA were evaluated first, followed by the perfusion situations in BAC side and the opposite side to BAC exploration. Indistinct BAC direction and “S” type BAC were excluded from this cohort due to its bending direction ambiguity.

Hypoperfusion finding is not surprising since this is a well observed finding in patients with long standing artery stenosis [25]. So when we investigated the presence of a relative cerebellar and brainstem hypoperfusion in the non-VAD and BAC cohort with UIV patients, the exclusion and inclusion of VAS, VA occlusion (VAO), BA stenosis (BAS) would be discussed respectively.

2.9. Statistical analysis

Statistical analysis was performed using SPSS version 16.0A (IBM, Armonk, NY, USA). For comparison among the groups, Chi-square test (or Fisher exact test when any expected cell count was < 5 for a 2 × 2 table) was used for categorical variables, while independent-samples t-test was used for continuous variables. In view of this study was divided into three groups, statistical analysis were also performed between every two groups (P < 0.0125 were considered statistically significant between two groups). One-way analysis of variance (ANOVA) method was performed to compare continuous variables and relative CTP parameters values among three groups. If a significant difference was found for a parameter, LSD or Tamhane’s T2 test was performed. Parametric results were presented as mean ± standard deviation (SD) after passing a normal distribution test. All P < 0.05 were considered statistically significant.

To determine the risk predictors for morphological changes of arteries, the correlation between the vascular factors with the shapes were assessed using non-conditioned logistic regression analysis. The statistical positive morphological changes of intracranial arteries (non-VAD and BAC, the degree of BAC) were regarded as dependent variables, and VRFs were regarded as the potential predictors at first. Then VAD was regarded as a potential predictor, along with other VRFs and BAC or the degree of BAC was regarded as dependent variables respectively. Odds ratio (OR) and 95% confidence interval (CI) were calculated for each variable. Variables with OR > 1 and P < 0.05 at univariate test statistics were included in the regression model as positive risk predictors.

3. Results

3.1. General subject demographics

The distribution of relevant demographic and selected radiological characteristics for the three groups were shown in the Table 1. The age and gender ratio were comparably matched in the three groups (P > 0.05, respectively).

Several VRFs were more common in the UIV group than the other two groups [HT, hyperlipidemia, number of VRFs ≥ 3 (P < 0.0125, respectively), and those VRFs were no statistically significant differences between BPPV and control groups (P > 0.05, respectively). Even though DM was significantly different among the three groups (P = 0.027), further analyses were carried out between any two groups. Statistically significant differences were observed between UIV and BPPV groups.

Table 1: Baseline and radiological characteristics among three groups.

| Characteristics | UIV group (n = 76) | BPPV group (n = 74) | Control group (n = 60) | P |
|-----------------|-------------------|---------------------|------------------------|---|
| General demographic data |                |                     |                        |   |
| Age, y, mean ± SD | 61.59 ± 59.04 ± 58.75 ± 59.04 ± 58.75 ± | >0.05 | |
| Sex, M/F | 37/39 | 46/28 | 32/28 | >0.05 |
| VRFs [n(%)] |                |                     |                        |   |
| Age ≥ 60 years | 40 (52.63) | 37 (50.00) | 26 (43.33) | >0.05 |
| HT | 60 (78.95) | 32 (43.24) | 22 (36.67) | <0.0125* |
| DM | 20 (26.32) | 7 (9.46) | 11 (18.33) | 0.027 |
| Dystipidemia | 40 (52.63) | 23 (31.01) | 16 (26.67) | <0.0125* |
| CHD | 11 (14.47) | 6 (8.11) | 6 (10.00) | >0.05 |
| Smoking | 18 (23.68) | 10 (13.51) | 8 (13.33) | >0.05 |
| Number of VRFs ≥ 3 | 47 (61.84) | 14 (19.82) | 21 (35.00) | <0.0125* |
| Intracranial vascular morphology changes [n(%)] |                |                     |                        |   |
| ACA | 2 (2.63)/2 | 1 (1.35)/4 | 1 (1.67)/0 | >0.05 |
| stenosis/hypoplasia | (2.63) | (5.41) | (0.00) | |
| MCA stenosis | 9 (11.84) | 3 (4.05) | 6 (10.00) | >0.05 |
| PCA | 5 (6.58)/3 | 0 (0.00)/1 | 2 (3.33)/2 | >0.05 |
| stenosis/hypoplasia | (3.95) | (1.35) | (3.33) | |
| VAS | 8 (10.53) | 0 (0.00) | 0 (0.00) | <0.0125* |
| VAO | 2 (2.63) | 1 (1.35) | 3 (5.00) | >0.05 |
| VAD(VAH) | 53 (69.74) | 29 (39.19) | 14 (23.33) | <0.0125* |
| Direction of VAD(VAH) |                |                     |                        |   |
| L side | 33 (43.42) | 19 (25.68) | 12 (20.00) | >0.05 |
| R side | 20 (26.32) | 10 (13.51) | 2 (3.33) | >0.05 |
| BAS | 4 (5.26) | 0 (0.00) | 2 (3.33) | >0.05 |
| BAH | 7 (9.21) | 1 (1.35) | 2 (3.33) | >0.05 |
| BAC | 49 (64.47) | 32 (43.24) | 19 (31.67) | <0.0125* |
| Direction of BAC |                |                     |                        |   |
| L side | 6 (7.89) | 10 (13.51) | 5 (8.33) | >0.05 |
| R side | 38 (50.00) | 16 (21.62) | 13 (21.67) | >0.05 |
| Unclassification side |                |                     |                        |   |
| Type of BAC |                |                     |                        |   |
| C-type | 27 (35.53) | 9 (12.16) | 7 (11.67) | >0.05 |
| J-type | 19 (25.00) | 17 (22.97) | 10 (16.67) | >0.05 |
| S-type | 3 (3.95) | 6 (8.11) | 2 (3.33) | >0.05 |
| Degree of BAC |                |                     |                        |   |
| Grade 0 | 27 (35.53) | 42 (56.76) | 41 (68.33) | >0.0125* |
| Grade 1 | 23 (30.26) | 24 (32.43) | 12 (20.00) | >0.05 |
| Grade 2 | 21 (27.63) | 7 (9.46) | 4 (6.67) | >0.0125* |
| Grade 3 | 5 (6.58) | 1 (1.35) | 3 (5.00) | >0.05 |
| Moderate to severe | 26 (34.21) | 8 (10.81) | 7 (11.67) | >0.0125* |

UIV indicates undetermined isolated vertigo; BPPV, benign paroxysmal positional vertigo; VRFs, vascular risk factors; HT, hypertension; DM, diabetes mellitus; CHD, coronary heart disease; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; VAS, vertebral artery stenosis; VAO, vertebral artery occlusion; VAD, vertebral artery dominance; VAH, vertebral artery hypoplasia; L, left; R, right; BAS, basilar artery stenosis; BAH, basilar artery hypoplasia; BAC, basilar artery curvature.

★ Statistical significance was observed in UIV vs. BPPV ([P = 0.0125, respectively], and no statistical significance was observed in BPPV vs. Control ([P > 0.05, respectively]. P > 0.05 means there were no statistically significant differences among the three groups, or between any two groups.
(P < 0.0125), but no significant difference was observed between UIV and control patients (P > 0.0125). Thus, DM being more common in the UIV group than the other two groups could not be concluded (Table 1).

3.2. CTA of intracranial vascular changes

No statistical significance was observed in the ratio of ACA, MCA and PCA stenosis, ACA and PCA hypoplasia among the three groups (P > 0.05, respectively). Compared with the other two groups, the higher prevalence of VBA morphological changes were found in UIV group [VAD (VAH), VAS, BAC, moderate to severe BAC (P < 0.0125), respectively]. Interestingly, the curvature of BA was usually orientated to the smaller VA diameter side and the opposite direction side of VAD. Most UIV patients existed with moderate to severe BAC in 34.21% (26/76) (P = 0.000), but there were no statistical significances between the BPPV and control groups (P > 0.05, respectively) (Table 1).

3.3. Relationship between VRFs and the morphological changes of intracranial arteries

In UIV patients, HT was an independent positive risk predictor of non-VAD (OR: 5.411, 95% CI: 1.401; 20.900, P = 0.014). HT and VAD were the risk predictors of BAC (OR: 4.081, 95% CI: 1.056; 15.775, P = 0.041 and OR: 6.284, 95% CI: 1.848; 21.365, P = 0.003, respectively). However, in the BPPV or control patients, there were no positive risk predictors for VAD and BAC (P > 0.05, respectively).

It has been found that VAS or VAO was frequently seen on the smaller VA diameter side (P = 0.000). BAS was associated with BAH in UIV patients (P = 0.000) (Table 2).

3.4. CTP parameter analysis results

In UIV patients, statistically significant differences were found in arCBV, arCBF, aMTT, aTTP of brainstem ROIs (P < 0.05, respectively). Similar results were shown in arCBV, arCBF, amTT of cerebellum ROIs (P < 0.05, respectively) (Fig. 2). No significant differences were found in the CTP parameters of any other regional ROIs in UIV patients, or BPPV and the control patients (P > 0.05, respectively).

3.5. The correlation in the corresponding territory of abnormal arteries with regional perfusion

In UIV patients, hypoperfusion was observed on non-VAD side or BAC cohort. The cohort of non-VAD side showed a regional cerebellum hypoperfusion compared with normal VA of about 83.02% (44/53) (P = 0.002). Non-VAD side showed a regional cerebellum hypoperfusion compared with the VAD side in 66.04% (35/53) (P = 0.000). BAC cohort showed a regional brainstem hypoperfusion compared with the normal BA in 79.59% (39/49) (P = 0.012). Further analysis addressed in BAC cohort, a regional brainstem hypoperfusion were on the opposite side of BAC compared with BAC in 77.2% (34/44) (P = 0.000) (Table 3).

When VAS, VAO and BAS were excluded, the cohort of non-VAD side showed a regional cerebellum hypoperfusion compared with normal VA of about 81.40% (35/43) (P = 0.005). Non-VAD side showed a regional cerebellum hypoperfusion compared with the VAD side in 60.47% (26/43) (P = 0.000). BAC cohort showed a regional brainstem hypoperfusion compared with the normal BA in 76.92% (30/39) (P = 0.034). Further analysis addressed in BAC cohort, a regional brainstem hypoperfusion were on the opposite side of BAC compared with BAC in 69.44% (25/36) (P = 0.000) (Table 4).

Figs. 3 and 4 show two UIV examples of a hypoperfusion of cerebellum or brainstem related to VAH and the opposite side of BAC. More blue area depicts prompt and deeper degree of hypoperfusion.

4. Discussion

To our knowledge, this is the first prospective research that adds several newonic viewpoints to the existing knowledge in UIV patients. Our preliminary study demonstrated that a high prevalence of abnormal posterior circulation, including VBA anatomical structure changes, unequaliﬁquilibrium cerebellum and brainstem hemodynamic co-existed with VRFs including HT, hyperlipidemia, number of VRFs ≥ 3 in UIV patients. The presence of relative hypoperfusion of cerebellum on non-VAD side and relative hypoperfusion of brainstem in BAC cohorts were positive in patients with UIV. Our results suggested that BPPV might be a peripheral benign disease and less associated with central vascular origin. In addition, UIV might originate from posterior circulation system and variety of detecting methods of vascular factors were imperative. However, some UIV cases remain normal in terms of vascular morphology or perfusion. Patients with a reversible remission state still need further exploration.

4.1. VRFs and the morphological changes of intracranial arteries

In the current study, morphological changes of anterior circulation arteries did not yield statistically significant results, suggesting that there is no obvious relationship with central anterior circulation and vertigo. A possible explanation is that the posterior circulation arteries have a vertical course while the anterior circulation arteries have a horizontal course. Some well-known VRFs such as HT, hypercholesterolemia, DM might lead to abnormal morphological changes of posterior circulation vessels [26].

Consistent with previous research [27], our study showed that HT, hyperlipidemia, number of VRFs ≥ 3 were more commonly in UIV patients. A possible explanation was that systemic VRFs were associated with atherosclerosis, which resulted in the chronic process of abnormal vascular remodeling such as bending or extend, especially in posterior circulation ultimately [26]. A hypoplastic or small intracranial VA calibre and BAH due to its decreased flow volume and velocities, are more prone to stenosis or occlusion by nature, especially in the presence of VRFs [16,22,27]. Haemodynamic changes from vertebrobasilar junction

| Table 2 |
| Presence of a relative stenosis/occlusion on the smaller VA or BAH side in UIV patients. |

|          | VAS/VAO (n = 10) | Non-VAS/VAO (n = 56) | P      | BAH side (n = 71) | Normal BA (n = 69) | P      |
|----------|------------------|----------------------|--------|------------------|--------------------|--------|
| Smaller VA | 9 (90.00)        | 3 (4.55)             | 0.000  | BAS              | 4 (57.14)          | 0 (0.00) | 0.000  |
| Normal VA | 1 (10.00)        | 63 (95.45)           |        | Non-BAS          | 3 (42.86)          | 69 (100.00) |        |
| VRFs ≥ 3 | 7 (70.00)        | 46 (69.70)           | >0.05  |                  | 4 (57.14)          | 42 (60.87) | >0.05  |
| VRFs < 3 | 3 (30.00)        | 20 (30.30)           |        |                  | 3 (42.86)          | 27 (39.13) |        |

All values given as absolute numbers (%). VAS, vertebral artery stenosis; VAO, vertebral artery occlusion; BAH, basilar artery hypoplasia; BAS, basilar artery stenosis; VRFs, vascular risk factors.

a Defined by the smaller VA diameter side including the opposite side to the vertebral artery dominance and vertebral artery hypoplasia side.

b Defined by the as a basilar artery diameter < 2 mm.
makes the BA curve to the side of the weaker VA, so BAC are usually directed to the smaller VA diameter side [16]. VRFs were not the direct etiological factors of vertigo while they could threaten the morphological changes of arteries for its long-term effect. VAD combined with BAC might play an important role in vertigo attack of vascular origin. However, perfusion of corresponding regions were not evaluated in this research [28].

4.2. Morphological changes of intracranial arteries and whole-brain perfusion

In UIV patients, hypoperfusion was found commonly on the non-VAD side and the opposite side of BAC, no matter VAS, VAO and BAS were included or excluded. Such causal relationships might be explained by some following hemodynamic mechanisms. Firstly, slow blood flow on non-VAD side might increase the susceptibility to thrombosis or poor clearance of thrombi, affecting the distal perforating arteries such as PICAs which irrigates the ipsilateral cerebellum [21]. Secondly, the inner wall of BAC might be more thrombogenic because of a low wall shear stress and slower bloodflow. Thirdly, high resistance to bloodflow in a curved BA can cause low blood pressure on the opposite side of BAC. Moreover, BAC compresses and stretches the pontine perforating artery [23]. These above factors can be associated with microvascular obstruction, which lead to hypoperfusion finally.

Compared with anterior circulation arteries, VBA system lack adequately growing collateral arteries, which could cause or exacerbate the posterior circulation in cerebellum and brainstem leading to hypoperfusion. It is also a possible reason that there was no obvious statistical difference of CTP parameters in some anterior circulation arteries, so the stenosis or hypoplasia artery of corresponding perfusion area might be due to the simultaneous collateral circulation.

However, there was also no obvious hypoperfusion in non-VAD or BAC cohort with some UIV patients. A possible explanation is the compensatory hemodynamic function of VBA during interictal period in attack of vertigo.

Table 3
Presence of a relative cerebellar and brainstem hypoperfusion in the non-VAD and BAC cohort with UIV patients.

| Indicators (n) | Hypoperfusion | No hypoperfusion | P   |
|---------------|---------------|------------------|-----|
| Non-VAD side (n = 53) | 44 (83.02) | 9 (16.98) | 0.002 |
| Normal VA (n = 23) | 11 (47.83) | 12 (52.17) |     |
| Non-VAD side (n = 53) | 35 (66.04) | 18 (33.96) | 0.000 |
| VAD side (n = 53) | 10 (18.87) | 43 (81.13) |     |
| BAC (n = 49) | 39 (79.59) | 10 (20.41) | 0.012 |
| Normal BA (n = 27) | 14 (51.85) | 13 (48.15) |     |
| Opposite of BACb (n = 44) | 34 (77.27) | 10 (22.73) | 0.000 |
| BAC side (n = 44) | 7 (15.91) | 37 (84.09) |     |

All values given as absolute numbers (%). VAD, vertebral artery dominance; BA, basilar artery; BAC, basilar artery curvature.

Table 4
Presence of a relative cerebellar and brainstem hypoperfusion in the non-VAD and BAC cohort with UIV patients.

| Indicators (n) | Hypoperfusion | No hypoperfusion | P   |
|---------------|---------------|------------------|-----|
| Non-VAD cohort (n = 43) | 35 (81.40) | 8 (18.60) | 0.005 |
| Normal VA cohort (n = 23) | 11 (47.83) | 12 (52.17) |     |
| Non-VAD side (n = 43) | 26 (60.47) | 17 (39.53) | 0.000 |
| VAD side (n = 43) | 9 (20.93) | 34 (79.07) |     |
| BAC cohort (n = 39) | 30 (76.92) | 9 (23.08) | 0.034 |
| Normal BA cohort (n = 27) | 14 (51.85) | 13 (48.15) |     |
| Opposite of BACc (n = 36) | 25 (69.44) | 11 (30.56) | 0.000 |
| BAC side (n = 36) | 5 (13.89) | 31 (86.11) |     |

All values given as absolute numbers (%). VAD, vertebral artery dominance; BA, basilar artery; BAC, basilar artery curvature.

Fig. 2. The absolute difference in relative values of CTP parameters from cerebellum and brainstem ROIs among the three groups. (A. Absolute relative cerebral blood volume (arCBV). B. Absolute relative cerebral blood flow (arCBF). C. Absolute mean transit time (aMTT). D. Absolute time to peak (aTTP.). *Significant statistical difference compared with the other two groups.

a Defined by the opposite side to the vertebral artery dominance and vertebral artery hypoplasia, stenosis or occlusion.

b Defined by the opposite direction side to BAC, and clear "C" or "J" type curvature toward either the left or the right sides.

c Defined by the opposite direction side to BAC, and clear "C" or "J" type curvature toward either the left or the right sides. And exclude VAS or VAO, BAS.
4.3. The possible mechanism and prognosis of UIV

A previous study has showed the pathogenesis of metabolic syndrome such as some VRFs were involved in males with vertigo of unknown etiology [27]. However, the relationship between VBA changes and IV symptoms is not completely understood so far. Certain studies have tried to explain its etiology and mechanism [6-9,28]. Our current research showed there were hypoperfusion in non-VAD and BAC cohort. Thus, we postulate that the asymmetrical VA flow and the morphological curvature flow pattern of BA might influence the haemodynamic changes in the VBA system, impairing the pathway between the cerebellum, brainstem and vestibular cortices, and finally leading to vestibular dysfunction and vertigo [16,29]. However, whether the direct etiology of central posterior circulation vertigo is ischemic lesions themselves or the disequilibrium induced in the bilateral vestibular pathway is the cause, needs more accurate fundamental researches for confirmation.

Disequilibrium perfusion of the mirrored posterior circulation ROIs was a risk predisposing factor of recurrent isolated vascular vertigo. The risk of stroke is greater for vertigo patients with ≥3 risk factors than for patients with 1 to 2 risk factors or general population without any risk factors [1]. A regional hypoperfusion is a hidden sign for the risk of stroke in vertebrobasilar disease [15]. However, whether this state may be reversible or be on behalf of potential subsequent signals for posterior ischemic stroke is still not clear. Whether isolated vascular vertigo can occasionally confer a risk prodromal sign of an impending pontocerebellar ischemic event is worthy of further exploration.

Our study had some limitations. Firstly, this study focused on the phenomenon and the overall number of patients was small. A larger
number of patients may provide more precise values. Secondly, in case of ROIs, manual measurement errors might exist and minor parts of the focal hypoperfusion may be ignored due to technical limitations of CTP. Thirdly, considering the variabilities of anatomic form, the definition of territories about cerebral arteries are too general. Finally, the case group was based on subjective feelings of patients and thus, cannot discriminate the severity classification of the vertigo.

5. Conclusion

This study demonstrated that unusual morphology of intracranial VBA and hypoperfusion should raise suspicion of a more likely etiology in UV patients with multiple VRFs, which should pay more cautious attention. It is still unclear whether recurrent IV with pre-existing hyponxia in UIV patients with multiple VRFs, which should pay more cautious attention. VBA and hypoperfusion should raise suspicion of a more likely etiology.

Conflicts of interest

There are no conflicts of interest.

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