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Cerebral Blood Flow in the Visual and Parieto-insular Vestibular Corticies in the Patients after Cerebral Ischemia with or Without Dizziness

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Abstract

Background: Post stroke dizziness may be unexpectedly severe. Observations in patients with chronic cerebral ischemia suggested that dizziness episodes are attributable to a decrease in the regional cerebral blood flow (CBF) in the visual cortex due to remote effects from the parieto-insular-vestibular cortex (PIVC).
Methods: We studied cerebral blood flow in 15 patients who did- (group 1) and 15 who did not (group 2) experience dizziness since the onset of cerebral infarction.
Results: Comparison of the 2 groups at rest showed a significant decrease in CBF in the visual cortices (right and left, $p < 0.001$), the PIVC (right, $p = 0.026$; left, $p = 0.040$), and the left temporal lobe ($p = 0.042$) in group 1. After acetazolamide (ACZ) loading, CBF was decreased significantly only in both visual cortices (right, $p = 0.044$; left, $p = 0.004$) of group 1.
Conclusion: Our findings indicate that the visual cortex and PIVC were strongly implicated in dizziness after cerebral ischemia.

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Dizziness, Cerebral blood flow, Cerebral ischemia, Acetazolamide, Xenon enhanced tomography, Visual cortex, Parietoinsular vestibular cortex

Introduction

Although the percentage of patients in whom stroke is unequivocally identified as the reason for their dizziness is low, considering the large number of patients reporting this symptom, the number of patients with a stroke etiology may be much higher than is currently acknowledged [1,2]. Ibudilast (CAS 50847-11-5) acts as a phosphodiesterase (PDE)-4 inhibitor by modulating the cyclic adenosine monophosphate (cAMP) second messenger system [3,4]. It has been shown to increase the cerebral blood flow (CBF) in patients with chronic ischemic cerebrovascular lesions [5,6] and to ameliorate dizziness in the chronic stage of cerebral infarction [7]. Elsewhere [8,9] we reported that patients with a cerebral infarct who suffered episodes of dizziness but no depression manifested a significant CBF increase in the visual cortex and resolution of their dizziness after the administration of ibudilast.

In another study we documented that after acetazolamide (ACZ) loading, CBF was significantly increased in the bilateral visual cortices and the bilateral PIVC and dizziness was ameliorated in patients with chronic cerebral ischemia who received ibudilast therapy [10]. Those findings indicated that the visual cortex and PIVC are implicated in dizziness after cerebral ischemia. In the current study we investigated the state of the CBF both at rest and after ACZ loading in the visual cortex and PIVC of stroke patients with and without dizziness before ibudilast therapy.

Materials and Methods

Patients

This study was approved by the Ethics Committee of our institution; prior written informed consent was obtained from all patients. All 30 patients manifested cerebral ischemia without depression. As shown in Table 1, we divided them into 2 equal groups; group 1 did, and group 2 did not suffer dizziness. Group 1 patients reported vertigo, lightheadedness, presyncope, anxiety, and general malaise at the start of and during this study. CBF measurements were taken at least one month after the onset of ischemic stroke.

Depression scoring

There is a strong correlation between the Japan Stroke Society Depression (JSS-D) score and the Hamilton Depression scale ($HAM\text{-}D_{17}$); the threshold for post-stroke depression on the JSS-D score is 2.40 [11]. We recorded the JSS-D score approximately one month after stroke onset.

CBF measurements

We adapted the standard Xe-CT CBF system to a Philips scanner (120 kV, 200 mA, Brilliance CT 6, Amsterdam, The Netherlands) [12,13]. The patient's head was immobilized and secured using a vacuum-activated cranial mold and aligned along the orbitomeatal plane with a laser light. A scout film was obtained to select the CT slices; two 10-mm-thick slices, separated by 15 mm, were used for the CBF study. After selecting the scan level, the patients were connected to a 30% xenon gas inhalation system (AZ-726, Anzai Medical Corp., Tokyo, Japan). They inhaled stable xenon for 3 min (wash-in); this was followed by 4-min desaturation (wash-out). An AZ-7000 instrument (Anzai Medical Corp.) was used to obtain the CBF values. The airway was tightly sealed with a facemask that covered the mouth and nose.

ACZ loading

In animal studies [14], ACZ (Diamox®, Lederle, Pearl River, NY, USA) delivered at very large doses did not increase CBF any more than smaller doses. On the other hand, depending on the condition of human brain tissues, at 500 - 2000 mg it may increase CBF [15]. For ACZ loading, 1 g (15 mg/kg) of ACZ was administered by rapid intravenous infusion; the CBF response to the vasodilatory challenge was determined approximately 15 min later [16]. CBF was measured at rest and after ACZ loading. Changes in CBF were recorded for each region of interest (ROI) on 2 slices from cortical and subcortical areas (Figure 1). CBF (mL/100 g/min) was calculated on corresponding ROI on the CT slices using Kety's autoradiographic equation [17].

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		Dizziness (-) n=15	Dizziness (+) n=15
Age (mean ± sd)		64.3±8.9	61.8±15.7
Gender (n of F / M)		8/7	8/7
JSSD (mean ± sd)		1.42±0.69	1.65±0.64
Past history	Diabetus mellitus	4	5
	Hypertension	13	12
	Dyslipidemia	6	5
	Gout	1	1
	Atrial fibrillation	1	1
Site of lesion Supra-tentorial (cerebrum)	Left MCA terminal zone	3	1
	Right MCA terminal zone	1	
	Left thalamus		1
	Right thalamus	1	1
	Right internal capsule		
	Left putamen	1	1
	Right putamen	1	
	Left centrum semiovale	1	
	Left corona radiata		
	Right corona radiata	1	3
	Left caudate		
	Right parieto-insular- vestibular cortex		1
	Left frontal subcortex	1	
	Right parietal subcortex	1	1
	Right occipital lobe		1
Infra-tentorial (cerebellar, brainstem)	Left cerebellar hemisphere		2
	Right pons	1	
	Left pons	2	2
	Left medulla oblongata		1

Table 1: Case Profile.

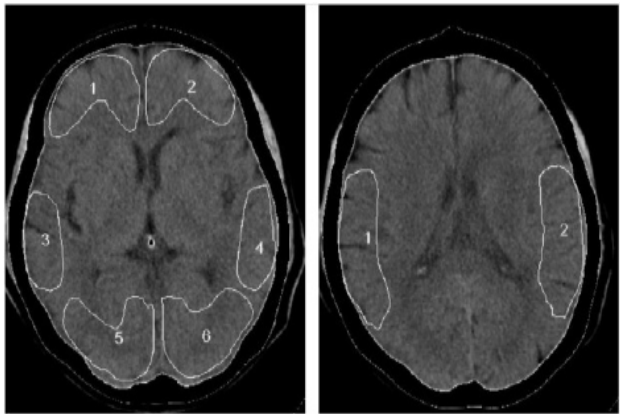

Figure 1: Sections analyzed on CT images. Slices 1 and 2 are axial images that include the basal ganglia and the temporo-parietal cortex, respectively. ROIs were selected on each image. Slice 1: The level of the analyzed slice passed through the basal ganglia and included the midsection of the anterior horns of the lateral ventricles, the caudate putamen, thalamus, and pineal body posteriorly. Three pairs of cortices corresponding to the frontal cortex (1 and 2), the temporal cortex (3 and 4), and the occipital cortex (5 and 6) were assessed. Slice 2: 1 and 2 represent the temporo-parietal cortex including the parieto-insular vestibular cortex (PIVC).

Statistical analysis

Statistical analysis was with the paired t-test. We compared CBF in each group at rest and after ACZ loading. Differences of $p < 0.05$ were considered statistically significant.

Results

All 30 patients presented with cerebral ischemia without depression (JSS-D score < 2.4). As shown in Table 1, their age, gender, and JSS-D score were not significantly different. The distribution of factors in their past medical history, e.g. diabetes mellitus, hypertension, and dyslipidemia was similar as was the distribution of the lesion site (supratentorial, group 1, n = 10, group 2, n = 12; infratentorial, group 1, n = 5, group 2, n = 3). While only one group 1 patient presented with a PIVC lesion, there were 5 group 1- and 3 group 2 patients with lesions in the cerebellar hemisphere and brainstem. Comparative CBF data are shown in Table 2. Comparison of the CBF at rest showed that in group 1 it was significantly lower in both visual cortices (right and left, $p < 0.001$), both PIVC (right, $p = 0.026$; left, $p = 0.040$), and in the left temporal lobe ($p = 0.042$) (Figure 2). After ACZ loading, CBF was significantly decreased only in both visual cortices (right and left, p=0.044) of group 1 (Figure 3).

		R O I	Dizziness (+) n=15	Dizziness (-) n=15	*p*-value
Slice-1	1	Rest	34.4±7.1	31.1±6.9	0.201
		ACZ	46.8±10.4	41.0±9.9	0.129
	2	Rest	33.1±8.0	29.7±5.7	0.184
		ACZ	49.9±13.3	41.5±13.0	0.093
	3	Rest	38.5±9.5	33.3±6.1	0.085
		ACZ	53.7±11.8	47.3±9.7	0.119
	4	Rest	36.5±8.8	30.7±5.8	0.042*
		ACZ	48.9±14.6	44.7±10.7	0.385
	5	Rest	30.5±3.6	23.4±3.2	<0.001*
		ACZ	42.0±8.6	35.5±8.3	0.044*
	6	Rest	30.8±3.3	22.4±2.8	<0.001*
		ACZ	44.4±9.5	34.2±7.9	0.004*
Slice-2	1	Rest	39.2±10.3	32.2±5.2	0.26*
		ACZ	56.1±16.5	45.3±13.2	0.056
	2	Rest	38.5±11.0	31.3±6.8	0.040*
		ACZ	51.9±14.8	46.6±11.6	0.290

Table 2: Comparison of the cerebral blood flow.
Data are mean ± S.D. Statistical analysis was with the paired t test. * p<0.05.
Cerebral blood flow measured in ml / 100g / min.
ACZ: cerebral blood flow after acetazolamide (ACZ) loading.

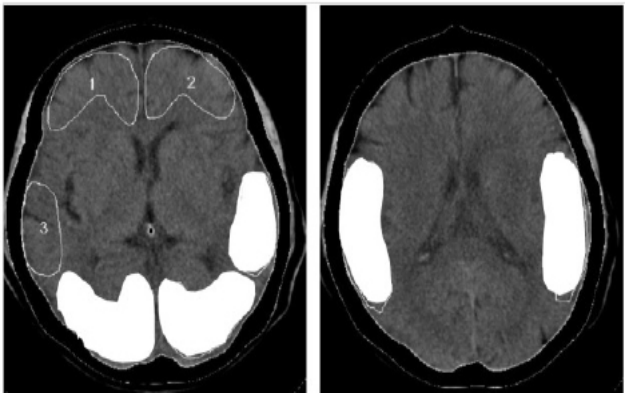

Figure 2: CBF at rest was significantly decreased in both visual cortices (right and left, p < 0.001), both PIVC (right, p = 0.026; left, p = 0.040), and in the left temporal lobe (p = 0.042) of patients with dizziness.

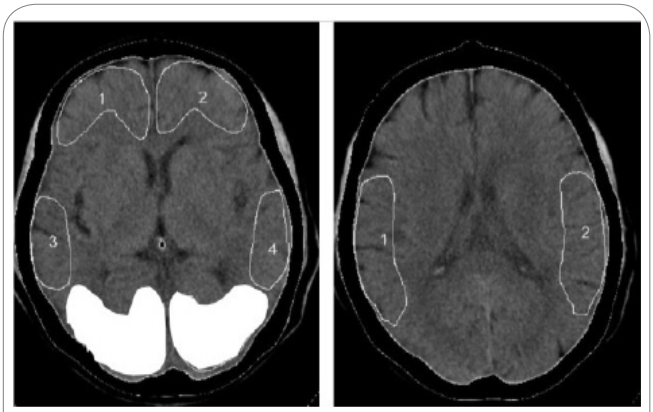

Figure 3: After ACZ loading CBF was decreased significantly only in both visual cortices (right, p = 0.044; left, p = 0.004) of patients with depression (blank areas in the ROI).

Discussion

Our comparison of CBF at rest in patients with and without post-stroke dizziness (group 1 and 2, respectively) showed a significant decrease in both visual cortices, both PIVC, and the left temporal lobe in group 1. The left temporal lobe can be considered as part of the PIVC. However, after ACZ loading, CBF in group 1 was significantly decreased only in both visual cortices.

Ours is the first demonstration of a significant decrease in the at-rest CBF in the visual cortex of patients with post-stroke dizziness. This finding confirms again that deactivation of the visual cortex during vestibular stimulation suppresses visual motion inputs thereby protecting the vestibular system from conflicting visual motion inputs [18-21]. The observed decrease in CBF in the visual cortex may be explicable by the selective inhibition of remote excitatory pathways leading to a decrease in the neuronal firing rate below the resting level. We posit the presence of flow inhibition from the PIVC to the visual cortex (Figure 4). After ACZ loading the results for the visual cortices were the same as they were at rest, indicating a severe functional reduction in the visual cortex where cerebral vasoreactivity is absent (Figure 3 and Figure 5).

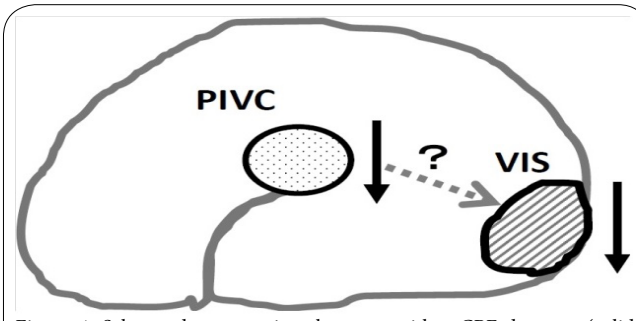

Figure 4: Scheme demonstrating the areas with a CBF decrease (solid arrows). PIVC: parieto-insular vestibular cortex (dotted area), VIS: visual cortex (slashed area).The gray arrow and question mark indicate flow inhibition from the PIVC to the VIS.

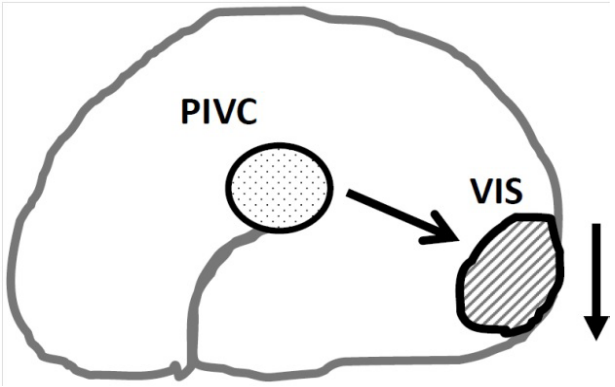

Figure 5: Scheme demonstrating the areas with a CBF decrease (external arrow). PIVC: parieto-insular vestibular cortex (dotted area), VIS: visual cortex (slashed area). The internal arrow indicates flow inhibition from the PIVC to the VIS.

This is also the first documentation of a significant CBF decrease in the PIVC at rest in patients with post-stroke dizziness (Figure 2 and Figure 4). The PIVC has been identified as a vestibular area [22-24] and infarcts [25] and hemorrhage [26] in this region may produce transient rotational vertigo. In fact, in one of our group 1 patients the lesion site was the right PIVC. Based on earlier and our findings we suggest that stroke in the PIVC results in the concomitant elicitation of a CBF decrease and dizziness. Despite the decrease in the CBF in the PIVC at rest, it may retain its ability to inhibit the visual cortex (Figure 4). After ACZ loading, the PIVC recovered cerebral vasomotor reactivity and inhibited the visual cortex (Figure 5). The at-rest CBF in the visual cortex and PIVC were significantly decreased in patients with dizziness who were sensitized to the experience of dizziness. Furthermore, after ACZ loading, only CBF in the visual cortex of patients with dizziness was significantly decreased.

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