Annals of Nuclear Medicine Vol. 18, No. 5, 369–374, 2004

Clinical significance of cerebrovascular reserve in acetazolamide challenge —Comparison with acetazolamide challenge H_2O-PET and Gas-PET—

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Objective: The response of cerebral blood flow (CBF) to acetazolamide (ACZ) challenge is frequently determined in clinical settings to evaluate cerebrovascular reserve (CVR). A reduced CVR can indicate patients with occlusive cerebrovascular disease and compromised hemodynamics who may be at increased risk of cerebral ischemia. However, how precisely ACZ reflects cerebral hemodynamic impairment remains obscure. The present study aims to clarify the pathological significance of CVR in patients with occluded carotid arteries. ***Methods:*** We recruited seventeen patients with occlusive lesions in the internal carotid artery (ICA) or middle cerebral artery (MCA). We assessed these patients in terms of resting cerebral blood flow (CBF) and the CVR response to ACZ challenge using H_2O positron emission tomography (PET). In addition, we evaluated hemodynamic parameters including oxygen extraction fraction (OEF) using Gas-PET. ***Results:*** We identified a significant negative correlation between the CVR and OEF or the cerebral blood volume (CBV)/CBF ratio, as a potential index of cerebral perfusion pressure. Although the CVR values were reduced in all regions with elevated OEF (Stage II), these values were highly variable regardless of the CBV/CBF ratios. The cut-off value of CVR alone could not detect Stage II, but when combined with resting CBF, misery perfusion accompanied by increased OEF was detected with high sensitivity (6/7) and specificity (61/62). ***Conclusion:*** CVR could be applied as an index reflecting both autoregulatory capacity and OEF. The present study also supported the notion that SPECT with ACZ challenge can be clinically applied to detect misery perfusion.

Key words: acetazolamide, hemodynamics, positron emission tomography

INTRODUCTION

DETERMINING THE DEGREE of hemodynamic compromise in chronic cerebrovascular disease is clinically important to predict subsequent ischemic stroke.[1–3] According to Powers' classification of chronic hemodynamics compromised with occlusive cerebrovascular disease,[4,5] hemodynamic impairment can be categorized into two stages. Stage I (autoregulatory vasodilatation) is defined as an increase in cerebral blood volume (CBV) in the hemisphere distal to the occlusive lesion, with normal cerebral blood flow (CBF), oxygen extraction fraction (OEF), and cerebral metabolism rate for oxygen ($CMRO_2$). Stage II (autoregulatory failure) is characterized by reduced CBF and increased OEF with normal $CMRO_2$ and is termed "misery perfusion."[6] These stages were originally defined using ^{15}O gas steady state positron emission tomography (Gas-PET) and have been widely applied to assess patients with severe atherosclerotic carotid artery stenosis or occlusion. Although PET is a very reliable quantitative tool with which to evaluate cerebral hemodynamic status, the procedure is expensive and is not routinely available.

Received December 2, 2003, revision accepted March 2, 2004.

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Cerebral blood flow can be measured quantitatively or qualitatively using several methods, including single photon emission computed tomography (SPECT). However, since individual measurements of CBF alone do not adequately assess cerebral hemodynamic status, paired blood flow measurements are taken with resting values being established, followed by measurements after stimulation of cerebral vasodilation. The CBF response to acetazolamide (ACZ) challenge determined as cerebrovascular reserve (CVR) in SPECT, transcranial Doppler (TCD), and magnetic resonance angiography (MRA), is frequently used as an index of autoregulatory vasodilation in clinical settings to evaluate hemodynamic impairment. However, relationships between CVR measured by PET and other hemodynamic parameters must be clarified before CVR can be widely used as an index of cerebral hemodynamic impairment. The present study attempts to establish the CVR to ACZ as a reliable index of Stage I and Stage II hemodynamic compromise in patients with chronic occlusive cerebrovascular disease using both Gas-PET and H_2O-PET.

MATERIALS AND METHODS

Patients

We used simultaneous Gas-PET and ACZ challenge H_2O-PET to examine 25 consecutive patients with cerebrovascular disease at Osaka University Medical School Hospital. Immediately before the PET study, each patient underwent neurological and neuro-radiological evaluations, including an evaluation for occlusive cerebrovascular disease by Doppler ultrasonography, MRI, magnetic resonance angiography (MRA), and cerebral angiography. MRI was performed in the orbito-meatal plane with 5-mm-thick sections using a 1.5-T unit (1.5-T Sigma Horizon; GE Medical System; 1.5-T Magnetome Vision; Siemens). Infarction was defined as a focal area with prolonged T1 and T2 relaxation times. The maximal interval between the MRI and PET studies was 30 days. Patients underwent the PET study at least 4 weeks after their most recent clinical episode, when their neurological condition had stabilized. Cerebral angiography was performed in all patients. The maximum percentage stenosis and the presence of ulceration, which can cause artery-to-artery embolism, were evaluated according to the recommendations of the North American Symptomatic Carotid Endarterectomy Trial (NACET).[7] We studied severe stenosis (70%–99%) and cerebrovascular artery occlusion. And, the mechanism of stroke in each patient was clinically diagnosed and classified according to the National Institute of Neurological Disorders and Stroke (NINDS) Classification of cerebrovascular disease III.[8] Patients with embolic infarction (large infarction) who had cardioembolic risk factors such as atrial fibrillation, valvular heart disease, or myocardial infarction and with acute phase were excluded from this study. We finally studied 17 consecutive patients [8 men, 9 women; mean age 56.5 ± 16.7 yr (mean ± SD)]. Five patients had cerebral infarction (lacuna infarction and/or minimal infarction in the territory of the affected arteries), eight had transient ischemic attacks, and four had asymptomatic carotid artery disease. Table 1 summarizes the clinical features and the angiographic and MRI findings.

Table 1 Patient characteristics

Patient No.	Age/Sex	Neurological Deficits	Disease	Angiographic Findings	MRI Findings
1	31/F	Rt hemiparesis	TIA	Bil ICAO	Rt BG*
2	71/M	Lt hemiparesis	TIA	Rt ICAO	Bil BG*
3	59/M	Headache	TIA	Rt MCAS	Bil BG & CR*
4	66/M	Rt hemiparesis & Dysarthria	CI	Lt MCAO	Lt MCA territory**
5	29/F	Lt hemiparesis & Visual field defect	CI	Bil ICAO	Rt parieto-occipital lobe**
6	62/M	Rt sensory disturbance	CI	Lt ICAS	Bil BG*
7	69/F	Lt hemiparesis	TIA	Rt MCAO	None
8	19/M	None	Asymptomatic	Bil MCAO	Lt parietal lobe**
9	39/F	Lt hemiparesis & Dysarthria	TIA	Rt MCAO	None
10	67/M	Dizziness	Asymptomatic	Lt ICAO	Lt BG*
11	74/M	Lt ischemic retinopathy	Asymptomatic	Lt ICAO	None
12	72/M	None	Asymptomatic	Lt ICAS	Lt CR*
13	63/F	None	TIA	Lt ICAS	None
14	56/F	Lt hemiparesis	TIA	Rt MCAO	Rt MCA territory**
15	59/F	Dysarthria	CI	Bil ICAO	Lt CR*
16	69/F	Lt sensory disturbance	CI	Rt MCAO	Rt CR*
17	56/F	Lt hemiparesis	TIA	Rt ICAS	None

Rt, right; Lt, left; Bil, bilateral; TIA, transient ischemic attack; CI, cerebral infarction; Asymptomatic; asymptomatic carotid artery disease; MCA, middle cerebral artery; MCAS, middle cerebral artery stenosis; MCAO, middle cerebral artery occlusion; ICAS, internal carotid artery stenosis; ICAO, internal carotid artery occlusion; BG, basal ganglia; CR, corona radiata: *lacuna infarction; **small infarction (<15 mm)

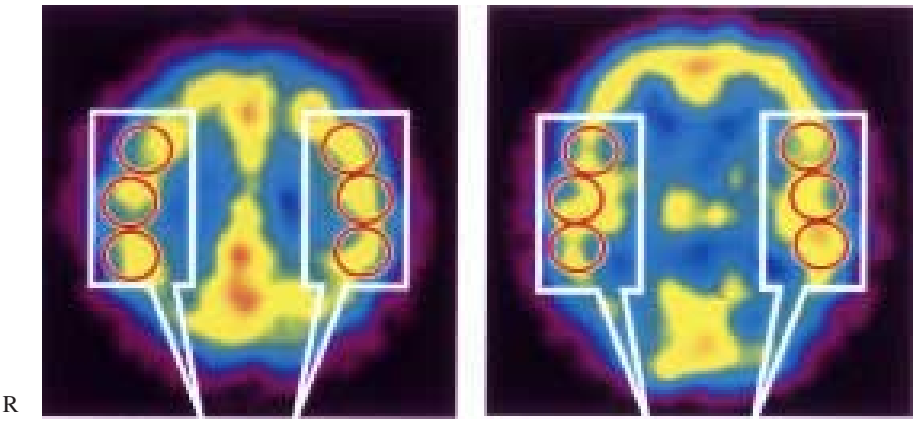

Fig. 1 Comparison of CVR and gas-PET parameters. A comparison of CVR and gas-PET parameters in 68 ROI in all MCA territories revealed significant negative correlations between CVR and OEF ($r = -0.559$; $p < 0.0001$) and between CVR and CBV/CBF ($r = -0.331$; $p < 0.0095$). Values of CBF and $CMRO_2$ were not correlated with CVR.

PET Imaging

All patients were scanned with a Headtome V/SET 2400W system (Shimadzu Co., Ltd., Kyoto, Japan), which acquires 63 slices with an interslice distance of 3.1 mm. All scans were performed at a resolution of 3.7 mm FWHM in the transaxial direction and at 5 mm in the axial direction. The patient's head was immobilized in a holder and positioned using light beams to obtain transaxial slices parallel to the orbito-meatal line. Before the PET study, we performed germanium 68-gallium 68 transmission scanning over 10 minutes for attenuation correction. Images were reconstructed using an ordered-subset expectation maximization (OS-EM) algorithm (12 iterations with 4 ordered subsets). The [^{15}O]gas steady state method required the patients to inhale a mixture of $C^{15}O_2$ (550 MBq/min) and $^{15}O_2$ (1,300 MBq/min) through a mask. The scan time was nine minutes, and four samples of blood were manually obtained from the radial artery during each scan. We measured the concentration of the radiotracer activity in whole blood and plasma using a well counter, as well as the arterial blood hematocrit, hemoglobin concentration, PaO_2 and $PaCO_2$ values. The CBV was measured after inhalation of 2,000 MBq of $C^{15}O$ and a 9-minute scanning period. We manually sampled arterial blood three times during the scan and measured radiotracer activity in whole blood. The values for CBF, $CMRO_2$, and OEF were calculated based on the steady state method, and $CMRO_2$ and OEF were corrected according to the CBV.

After the Gas-PET examination, patients received a 36-sec intravenous bolus of 1,110 MBq $H_2{}^{15}O$ at a flow rate of 30 m*l*/min through a cannula placed in the antecubital vein to initiate ACZ challenge [^{15}O]H_2O PET. Data were acquired over a scanning period of 160 s using a 128 × 128 matrix. Regional CBF was determined from the $H_2{}^{15}O$ bolus injection and autoradiographic methods while the participants were in a resting state and 10 minutes after the injection of ACZ. Input function was evaluated for 4 minutes at a rate of 5 m*l*/min by continuous arterial blood sampling via a catheter needle inserted in the radial artery, and ^{15}O radioactivity was concurrently measured using a beta-detector (Shimadzu Corp., Kyoto, Japan). The study protocol complied with the standard ethical guidelines of Osaka University Medical School, and written informed consent was obtained from all participants.

Data Analysis

All PET data were analyzed using the "Dr. View pro5.0" image analysis software system (Asahi Kasei Joho System Co., Ltd., Tokyo, Japan) running on a UNIX system and an Indigo 2 station (Silicon Graphics, Mountain View, CA, USA). Circular regions-of-interest (ROI), 20 mm in diameter, were placed over the cortex at the levels of the basal ganglia (lower MCA territory) and parietal lobe (upper MCA territory) on PET images from each patient (Fig. 1). All ROI generated on the resting CBF and ACZ-challenge CBF images measured using H_2O-PET were transferred to the CBF, OEF, $CMRO_2$, and CBV images measured using Gas-PET. All ROI on PET images can be made to exactly coincide using this system. Sixty-eight regions were finally investigated in images from 17 patients (four regions per patient: right, left, upper and lower MCA). The following equation estimated the percentage increase in rCBF induced by the ACZ challenge in the form of the CVR: CVR = (ACZ challenge CBF – Resting CBF)/Resting CBF.

Seven age-matched normal volunteers with non-focal neurological symptoms and without evidence of ischemic lesions after MRI or stenotic lesions in the major cerebral arteries after MRA, underwent H_2O-PET to determine

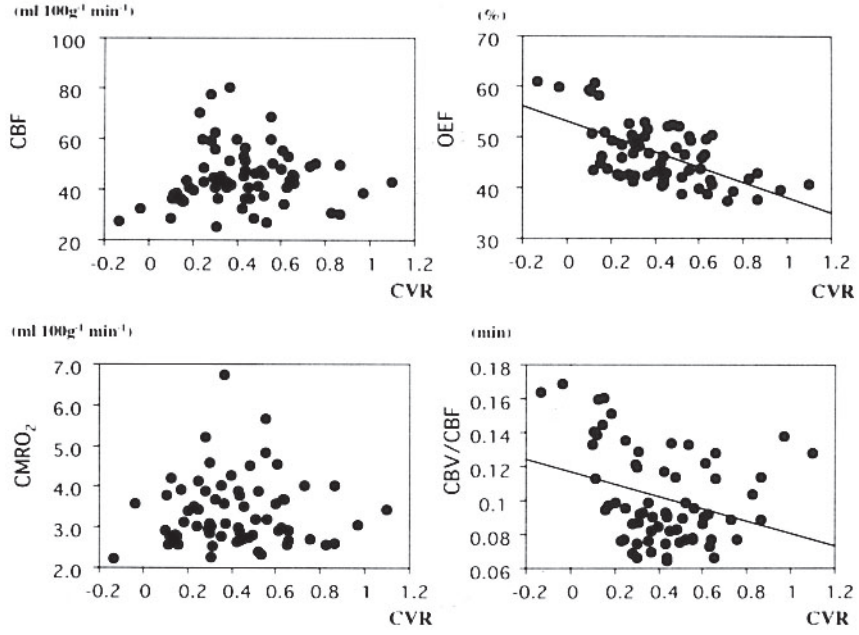

Fig. 2 ROI setting. Circular regions-of-interest (ROIs), 20 mm in diameter, were placed on cerebral cortices of middle cerebral artery territories on the levels of basal ganglia and parietal lobe in PET images of each patient.

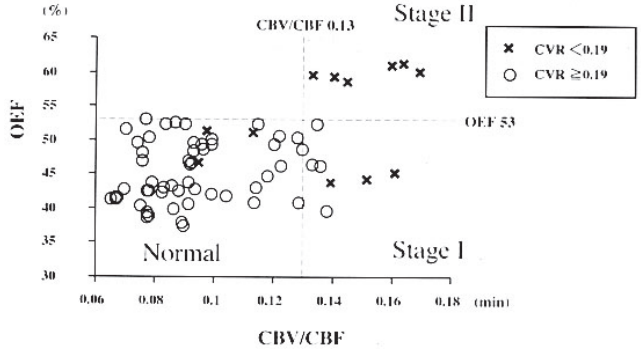

Fig. 3 CVR measured by ACZ challenge H_2O-PET in normal, Stage I and Stage II regions. Plot of values of OEF versus CBV/CBF ratio for all 68 ROI with complete quantitative PET studies. Abnormal values (mean + 2SD) for OEF and CBV/CBF ratio are indicated by dotted lines. All six regions diagnosed as Stage II by Gas-PET (*upper right quadrant*) corresponded perfectly with reduced CVR (CVR < 0.19). CVR values were decreased in three of 54 regions diagnosed as normal (*lower left quadrant*) and in three of eight regions diagnosed as Stage I (*lower right quadrant*).

normal control values. Normal Gas-PET values from healthy controls were not available. We therefore utilized Gas-PET parameter values from seven patients with no infarction and no severe stenosis or occlusion (<50%) who had non-specific brain symptoms without focal signs (pre-operation for cerebral aneurysm, headache, dizziness and syncope) as the normal values. We assessed the relationship between the CVR measured by H_2O PET and the Gas-PET parameters in the MCA territories using linear-regression analysis and Pearson's correlation coefficient. All data are expressed as means ± SD. Differences in data between groups were statistically evaluated using an unpaired t-test. Differences with p values of <0.05 were considered statistically significant.

RESULTS

The normal control values for the CBF and CVR measured by H_2O PET for the MCA territories were 45.5 ± 8.5 m*l* 100 g^{-1} min^{-1} and 0.49 ± 0.15 (mean ± SD). The CVR values were judged abnormal when beyond the mean – 2SD of the normal controls. All 68 regions were classified into two groups according to the CVR values measured by H_2O PET: reduced group (N = 12) with a CVR value of <0.19 (mean – 2SD) and a normal group (N = 56) with a CVR of 0.19 or higher. We used normal Gas-PET parameter values as follows: CBF, 46.9 ± 11.3 m*l* 100 g^{-1} min^{-1}; OEF, 44.1 ± 4.62%; $CMRO_2$, 3.39 ± 0.82 m*l* 100 g^{-1} min^{-1}; CBV, 4.22 ± 0.75 m*l* 100 g^{-1}; and CBV/CBF ratio, 0.09 ± 0.02 min. All regions were classified into three groups based on their OEF values: normal, OEF < 48.7% (mean + 1SD of the mean OEF value); slightly increased, 48.7% ≤ OEF < 53.3% (mean + 2SD of the mean OEF value) and increased, OEF ≥ 53.3%. We classified 68 regions into three groups compared with the base of our normal ranges of CBV/CBF and OEF. The three groups were normal [CBV/CBF < 0.13 min (mean + 2SD of the mean CBV/CBF ratio); OEF < 53.3%; N = 54], Stage I [CBV/CBF ≥ 0.13 min and OEF < 53.3%; N

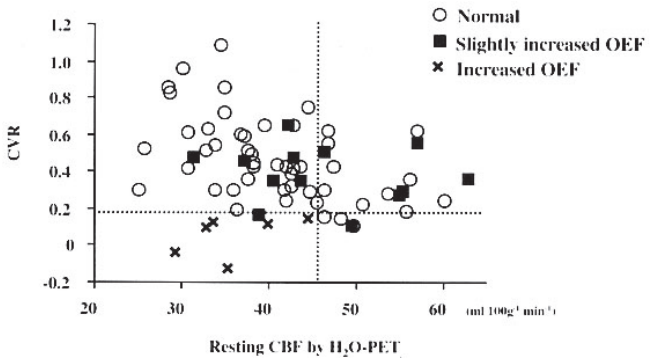

Fig. 4 Detection of Stage II cerebral hemodynamic failure using ACZ challenge H_2O-PET. Plot of CVR versus resting CBF values for all 68 ROI with quantitative ACZ challenge H_2O-PET studies. Cut-off values for CVR and CBF of 0.19 (mean – 2SD) and 46.9 m*l* 100 g^{-1} min^{-1} (normal value) respectively (*lower left quadrant*), led to sensitivity and specificity values of 86% (6/7) and 98% (61/62), respectively, for detecting misery perfusion (OEF ≥ 53.3%).

= 8] and Stage II [OEF ≥ 53.3%; N = 6].

Comparison of CVR with other PET parameters

We compared the CVR and PET parameters in the 68 ROI of all MCA territories and found a significant negative correlation between CVR and OEF ($r = -0.559$; $p < 0.0001$; Fig. 2) and between CVR and CBV/CBF ($r = -0.331$; $p < 0.0095$; Fig. 2). The CBF and $CMRO_2$ did not correlate with the CVR (Fig. 2).

CVR in normal, Stage I and Stage II regions

The CVR was reduced in all six regions diagnosed as Stage II by Gas-PET (Fig. 3). However, CVR values were decreased in three of the 54 regions diagnosed as normal and in 3 of the 8 regions diagnosed Stage I (Fig. 3). Therefore, CVR was actually variable in the Stage I and normal groups.

Detection of Stage II cerebral hemodynamic failure using resting CBF and CVR

The three groups classified based on their OEF values were plotted according to CBF at rest and the CVR values obtained from the ACZ challenge H_2O-PET study (Fig. 4). A CVR cut-off value of 0.19 (mean – 2SD) combined with a CBF cut-off value of 46.9 m*l* 100 g^{-1} min^{-1} (normal value) resulted in sensitivity and specificity for detecting misery perfusion of 86% (6/7) and 98% (61/62), respectively (OEF ≥ 53.3%). Therefore, the combination of the CVR and CBF appears to be a reliable index with which to accurately detect Stage II hemodynamic compromise in occlusive carotid diseases.

DISCUSSION

The present study revealed a significant negative correlation between the CVR and the OEF and between the CVR and the CBV/CBF ratio in the MCA territories of patients with occlusive cerebrovascular disease. The CVR value of all regions with an elevated OEF was below 0.19. Additionally, the combination of CVR and CBF was highly sensitive and specific for detecting misery perfusion (OEF ≥ 53.3%). However, when the CBV/CBF ratio was elevated and OEF was normal (Stage I), the CVR was highly variable. These results support the notion that [^{123}I]*N*-isopropyl-*p*-iodoamphetamine SPECT (^{123}I-IMP SPECT) with ACZ challenge is clinically useful.[9,10]

Gibbs et al. applied the CBF/CBV ratio instead of vasodilative capacity as an indicator of autoregulatory vasodilation in brain tissue with decreased cerebral perfusion pressure.[11] The CBF/CBV ratio (or its inverse, the CBV/CBF ratio) is mathematically equivalent to the vascular mean transit time (MTT)[5] and could be more accurate than CBV alone as an index of cerebral perfusion pressure.[12] Although correlated with the CBV/CBF ratio, the CVR value was quite variable in the Stage I and normal groups. Some investigators have reported that CBV increases within the autoregulatory range,[13–15] while others have found minimal or no increases in CBV until autoregulatory capacity is exceeded.[12,16] CBV may be a complex physiological parameter, since it is composed of arterial, capillary and venous compartments.[17]

Based upon Powers' previous theory,[4,5] we originally surmised that CVR to ACZ would gradually decrease in the Stage I and would fall below zero in Stage II. However, the correlation between CVR and OEF in the present study was negative, suggesting that OEF may increase even at the stage when CVR in response to ACZ is still maintained. The correlation between CVR and OEF ($r = -0.559$) was closer than that between CVR and CBV/CBF ($r = -0.331$), suggesting that CVR can be an index reflecting both reduced perfusion pressure and increased OEF. In the modified model of hemodynamic and metabolic responses to a reduction in cerebral perfusion pressure after Powers et al.,[4] OEF can increase with reductions in CBF through autoregulatory ranges while CBV may not change.[18,19] The risk of ischemic stroke with increased OEF and increased CBV being higher than that with increased OEF and normal CBV suggests that OEF together with CBV can reflect hemodynamic compromise more precisely than OEF alone.[19] Recent studies have demonstrated the usefulness of the CVR to ACZ for predicting ischemic stroke.[20] Therefore, the CVR to ACZ challenge in H_2O-PET combined with OEF in Gas-PET may be a better index with which to predict future stroke than OEF alone since more information about cerebral perfusion pressure is added.

In conclusion, the CVR to ACZ challenge could be influenced by both autoregulatory capacity and OEF.

Whether the combination of CVR with OEF may indeed add more predictive information about future ischemic stroke should be examined in a prospective study. The present results supported the notion that SPECT with ACZ challenge can be applied in clinical practice to detect patients with misery perfusion.

ACKNOWLEDGMENTS

The authors would like to thank the staff of the Department of Nuclear Medicine and the Cyclotron staff of Osaka University Medical School Hospital for technical support.

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