Abstract. A decrease in the cerebral blood flow (CBF) response to acetazolamide may indicate an increase in cerebral blood volume (CBV) caused by reduced perfusion pressure in patients with major cerebral artery steno-occlusive lesions. However, a decrease in cerebral metabolic rate of oxygen (CMRO₂) caused by ischemic changes may also decrease the CBF response to acetazolamide by decreasing the production of carbon dioxide. The purpose of this study was to determine whether the values of CBV and CMRO₂ are independent predictors of the CBF response to acetazolamide in major cerebral arterial occlusive disease. We used positron emission tomography to study 30 patients with major cerebral artery steno-occlusive lesions. The CBF response to acetazolamide was assessed by measuring baseline CBF and CBF 10 min after an intravenous injection of 1 g of acetazolamide. Multivariate analysis was used to test the independent predictive value of the CBV and CMRO₂ at baseline with respect to the percent change in CBF during acetazolamide administration. Both increased CBV and decreased CMRO₂ were significant and independent predictors of the reduced CBF response to acetazolamide. CBV accounted for 25% of the variance in the absolute change in CBF during acetazolamide administration and 42% of the variance in the percent change in CBF, whereas CMRO₂ accounted for 19% and 4% of the variance, respectively. In patients with major cerebral arterial occlusive disease, a decrease in CMRO₂ may contribute to the reduced CBF response to acetazolamide, although an increase in CBV appears to be the major contributing factor.

Keywords: Cerebral blood flow – Cerebral oxygen metabolism – Carotid artery disease – Positron emission tomography – Acetazolamide

Introduction

Evaluation of the cerebral blood flow (CBF) response to acetazolamide is widely used to estimate the degree of cerebral autoregulatory vasodilation in response to reduced perfusion pressure in patients with major cerebral arterial occlusive diseases, because acetazolamide is safe and easily administered during the assessment of vasodilatory capacity [1, 2, 3]. The CBF response to acetazolamide assessed by quantitative CBF may be predictive of increased risk of stroke [4, 5, 6], suggesting that evaluation of the CBF response to acetazolamide may be important for the management of patients with steno-occlusive lesions of the major cerebral arteries [2, 3]. However, it is a matter of controversy whether the evaluation of CBF response to acetazolamide is valid for quantitative assessment of cerebral autoregulatory vasodilation [7, 8]. At present, the relationship between the CBF response to acetazolamide and the baseline hemodynamic and metabolic status in patients with major cerebral arterial occlusive diseases is not well understood [7].

If the CBF response to acetazolamide reflects the degree of cerebral vasodilation, it should be correlated with the value of cerebral blood volume (CBV) at baseline. However, only a few studies have shown a negative correlation of the CBF response to acetazolamide with the baseline CBV value in patients with major cerebral arterial occlusive diseases, and the correlation coefficients were low [9]. This may be because not only CBV but also the cerebral metabolic rate of oxygen (CMRO₂) may affect the CBF response to acetazolamide. The vasodila-
tery effect of acetazolamide probably occurs through inhibition of carbonic anhydrase in circulating red blood cells, which interferes with CO₂ clearance from the brain via conversion to circulating bicarbonate [2, 10]. Consequently, increased levels of CO₂ around cerebral vessels will cause cerebral vasodilation. If this is the case, the vasodilatory effect of acetazolamide may be dependent on the level of the production of CO₂, which may be correlated with baseline CMRO₂; decreased CMRO₂ may cause a reduction of the CBF response to acetazolamide. However, the negative effect of the decrease in CMRO₂ may be partly counterbalanced by the positive effect of the decreased CBV which may be accompanied by the decrease in CMRO₂ [11, 12]. Thus, the true effects of CBV and CMRO₂ on the CBF response to acetazolamide may be clear only after adjustment for each other’s effects. Clarification of the contribution of CMRO₂ to the CBF response to acetazolamide is important to determine whether evaluation of the CBF response to acetazolamide is valid for quantitative assessment of cerebral autoregulatory vasodilation.

In this study, we analysed the relationships among the CBF response to acetazolamide and other hemodynamic and metabolic parameters determined using positron emission tomography (PET), including CBV and CMRO₂, by performing multivariate analysis in patients with major cerebral arterial occlusive disease. The purpose of the study was to determine whether increased CBV and decreased CMRO₂ are independent predictors of the reduced CBF response to acetazolamide.

Materials and methods

Patients. We studied 30 consecutive patients, aged 64±8 (mean±SD) years, including 22 men, with atherothrombotic occlusion or stenosis (>70% diameter reduction) of the internal carotid artery (ICA) or middle cerebral artery (MCA). In all patients, the latest ischemic event had not occurred within the previous month. None had heart failure or had undergone superficial temporal artery–MCA anastomosis. Nine patients had no symptoms, two had a transient ischemic attack (TIA), and 19 had a minor hemispheric stroke with mild disability. All symptoms were related to the affected carotid distribution. In the 21 symptomatic patients, the interval between the latest ischemic event and the evaluation by PET was 6±15 months.

Asymptomatic patients underwent magnetic resonance (MR) angiography because of headache, dizziness, syncope, vertigo, or tinnitus, and were thereby diagnosed as having major cerebral arterial disease. In all patients, MR imaging disclosed only minor abnormalities in the MCA territory or watershed areas of the hemisphere with major arterial disease. In three asymptomatic patients and one patient with TIA, MR imaging was normal. Among 26 patients with infarcts, six had unilateral cortico-subcortical watershed infarcts and 14 had unilateral subcortical infarcts, and six had bilateral subcortical infarcts. Vascular lesions were documented by using conventional angiography in 23 cases and MR angiography in seven. Conventional or MR angiography revealed unilateral ICA occlusion in six cases, unilateral extracranial ICA stenosis in 15, unilateral MCA occlusion in one, unilateral MCA stenosis in four, bilateral extracranial ICA stenosis in one, and ICA occlusion with contralateral extracranial ICA stenosis in three. In three symptomatic patients with bilateral disease, only the side with more severe vascular lesions (ICA occlusion) was symptomatic. No significant disease of the posterior cerebral artery was seen in any patient. The vertebrobasilar system was angiographically normal in all but two patients. The interval between the conventional or MR angiography and PET study was 1.6±1.8 months.

PET measurements. All the subjects underwent PET scans with a whole-body Advance (General Electric Medical System, Milwau-kee, Wis) PET scanner, which permits simultaneous acquisition of 35 image slices in a two- or three-dimensional acquisition mode with inter-slice spacing of 4.25 mm [13, 14]. Written informed consent was obtained from each subject under the guidance of the Ethics Committee of the Shiga Medical Center. Performance tests showed the intrinsic resolution of the scanner to be 4.6–5.7 mm in the transaxial direction and 4.0–5.3 mm in the axial direction. As part of the scanning procedure but before the tracer administration, ⁶⁸Ge/⁶⁸Ga transmission scanning was performed for 10 min for attenuation correction. For reconstruction of the PET data, images were blurred to 6.0 mm full-width at half-maximum in the transaxial direction using a Hanning filter. Functional images were reconstructed as 128×128 pixels, with each pixel representing an area of 2.0 mm × 2.0 mm.

The subjects were positioned in the scanner with their heads immobilized with a head-holder and positioned with light beams to obtain transaxial slices parallel to the orbitomeatal line. A small cannula was placed in the left brachial artery for blood sampling. Firstly, a baseline H₂¹⁵O study was performed. After intravenous bolus injection of 555 MBq of H₂¹⁵O into the right antecubital vein, a 3-min dynamic PET scan was started at the time of tracer administration with frame durations of 5 s × 12, 10 s × 6 and 20 s × 3. Arterial blood was continuously drawn from a catheter in the radial artery by using a mini-pump (AC-2120, Atto Co., Tokyo, Japan), and the concentration of radioactivity was monitored with a coincidental flow-through radioactivity detector, Pico-Count (Bioscan Inc., Washington, DC, USA) [15], and used as an input function for data analysis.

After the baseline H₂¹⁵O study, a series of ¹⁵O-gas studies was performed. C¹⁵O₂ and ¹³O₂ were inhaled continuously through a mask [14]. At least 10 min after beginning inhalation of the tracer, and after the brain radioactivity count had reached a plateau, a 5-min PET scan was started. Arterial blood was sampled manually from the brachial artery three times during each scan. Each sample was collected for 10–20 s to average the fluctuation due to the respiratory cycle, and the activity of the radiotracer concentration of whole blood and plasma was measured with a well counter. Inhalation of C¹⁵O with 3-min scanning was used to measure CBV. Arterial samples were obtained manually twice during the scanning, and the activity of the radiotracer concentration of whole blood was measured.

After the ¹⁵O-gas study, 1 g of acetazolamide was administered intravenously [16]. Ten minutes after the administration, a second H₁⁵O study was done: an intravenous bolus injection of 555 MBq of H₁⁵O and a 3-min dynamic PET scan were performed in the same way as in the baseline study.

Arterial hematocrit, hemoglobin concentration, PaO₂, and PaCO₂ were also measured. The mean physiological data for the patients acquired during the PET study before and after acetazolamide administration are presented in Table 1.