Acetazolamide Stress Brain-Perfusion SPECT Predicts the Need for Carotid Shunting During Carotid Endarterectomy

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Although carotid shunting is occasionally necessary to prevent cerebral ischemia during carotid endarterectomy, there is no reliable indication for this procedure. The purpose of this study was to evaluate whether acetazolamide stress brain-perfusion SPECT can predict the need for carotid shunting during carotid endarterectomy. **Methods:** Basal and acetazolamide stress brain-perfusion SPECT imaging was performed using a 1-d protocol and ^{99m}Tc-ethylcysteinate dimer (ECD) in 75 patients (12 women, 63 men; mean age, 64.8 y) before carotid endarterectomy. The need for carotid shunting during carotid endarterectomy was determined by the development of neurologic deterioration after carotid clamping under regional anesthesia. Regional cerebral blood flow, cerebrovascular reserve, the presence of contralateral carotid stenosis (≥70%), and clinical risk factors, including age, sex, history of minor stroke or transient ischemic attack, diabetes mellitus, hypertension, and smoking, were assessed with regard to whether they could predict the need for shunting. **Results:** Carotid endarterectomy was performed safely without carotid shunting in 61 of 75 patients (81.3%). Carotid shunting was required in 14 patients (18.7%). Seven of 21 patients with a contralateral carotid stenosis, 9 of 41 with a reduced regional cerebral blood flow, and 11 of 30 with a reduced regional cerebrovascular reserve underwent carotid shunting. Patients with a reduced cerebrovascular reserve had a significantly higher number of carotid shunts performed ($P < 0.01$) than did those with a normal reserve, whereas contralateral carotid stenosis ($P = 0.054$) showed borderline significance. Reduced cerebral blood flow and clinical risk factors did not predict the need for carotid shunting ($P > 0.1$). Multiple logistic regression analysis showed that reduced cerebrovascular reserve was the only reliable predictor of the need for carotid shunting ($P < 0.01$). When a severely reduced cerebrovascular reserve (8/8) or reduced cerebral blood flow and cerebrovascular reserve with contralateral carotid stenosis (6/7) were present, carotid shunting was necessary, with positive and negative predictive values of 91% (10/11) and 94% (60/64), respectively. **Conclusion:** A reduced cerebrovascular reserve can predict the development of cerebral ischemia during carotid clamping. Acetazolamide stress brain-perfusion SPECT may be useful as a complementary method in determining selective carotid shunting during carotid endarterectomy.

Received Oct. 29, 1999; revision accepted Mar. 8, 2000.

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Key Words: ^{99m}Tc-ECD; acetazolamide; SPECT; carotid shunt; endarterectomy

J Nucl Med 2000; 41:1836–1841

Carotid endarterectomy (CEA) is known to be effective in prevention of stroke or transient ischemic attack (TIA) associated with high-grade internal carotid artery (ICA) stenosis (*1–3*). However, perioperative stroke occasionally complicates CEA. The benefit of CEA largely depends on minimizing the risk of perioperative stroke. The pathogenic mechanisms of perioperative stroke are thromboembolism from the operative site, acute ICA thrombosis, intracranial hemorrhage, and hypoperfusion during carotid clamping (*4–6*).

Carotid shunting has been advocated to prevent ischemic stroke from hypoperfusion during carotid clamping. However, the routine use of a shunt during CEA is associated with clots within the shunt, embolization of air or atheromatous debris, or intimal injury, which may cause neurologic complications or recurrent stenosis (*6,7*). A shunt may also limit the exposure of the distal portion of the plaque. Thus, selective carotid shunting is advocated in patients who otherwise develop cerebral ischemia during CEA (*6*).

Neurologic deterioration of the awake patient under regional anesthesia (*8,9*), electrocardiographic (EEG) abnormality under general anesthesia (*10–12*), or the presence of contralateral ICA occlusion has been considered as the indication for carotid shunting (*13*). However, neurologic deterioration of the conscious patient can be a distressing experience for both patient and surgeon. In addition, regional anesthesia is not appropriate for all patients, and most surgeons prefer general anesthesia. EEG monitoring under general anesthesia is limited by a lower sensitivity in predicting the requirement for shunting, errors caused by inadequate interpretation, the effect of anesthetics, or the availability of an expert neurologist (*9,14*). The presence of stenosis or occlusion of the contralateral ICA does not always indicate the need for carotid shunting because most patients undergoing CEA do not exhibit cerebral ischemia (*8–10,15–17*).

Findings of a reduced perfusion reserve or lack of a perfusion reserve on acetazolamide (ACZ) stress brain-perfusion SPECT (ACZ-SPECT) have been shown to be useful for the selection of patients most likely to benefit from CEA or bypass surgery (*18–21*). Although previous studies have shown the correlation between ACZ-SPECT and carotid stump pressure or somatosensory evoked potentials, the results of ACZ-SPECT were not compared with neurologic examination under regional anesthesia or EEG monitoring under general anesthesia (*20,21*). The usefulness of ACZ-SPECT in detecting subgroups of patients at high risk for cerebral ischemia who require carotid shunting has not been established. The purpose of this study was to evaluate the value of ACZ-SPECT in predicting the need for carotid shunting during CEA and to identify the subgroups of patients at higher risk for the development of cerebral ischemia during carotid clamping.

MATERIALS AND METHODS

Subjects

Between January 1996 and March 1999, preoperative ACZ-SPECT was performed on 77 patients for CEA associated with ICA stenosis. Two patients were excluded because the stroke in evolution occurred before CEA and underwent CEA with elective carotid shunting under general anesthesia. Therefore, the final study population consisted of 75 patients (63 men, 12 women) who were between 37 and 81 y old (mean age, 64.8 ± 9.2 y). All subjects signed an informed consent form based on the guidelines of the hospital's human clinical study committee before participating in the study.

Diagnosis of carotid stenosis was based on carotid Doppler sonography (75 cases), MR angiography (52 cases), or conventional angiography (35 cases), which was performed within 2 wk before CEA. The severity of ipsilateral and contralateral ICA stenosis is listed in Table 1. The indications for CEA included high-grade (≥70%) ICA stenosis. There were 42 minor strokes, 21 TIAs, and 12 asymptomatic high-grade (≥70%) ICA stenoses but with positive lesions on CT or MRI.

ACZ-SPECT

All patients underwent preoperative ACZ-SPECT using ^{99m}Tc-ethylcysteinate dimer ([ECD] Neurolite; DuPont-Merck Pharmaceutical Co., Billerica, MA) for the evaluation of cerebrovascular hemodynamics. We used a 1-d protocol of basal SPECT and ACZ-SPECT (Fig. 1). Initially (n = 12), we used a protocol of 555 MBq ^{99m}Tc-ECD and 20 min of imaging time for basal SPECT and 1110 MBq ^{99m}Tc-ECD and 10 min for ACZ-SPECT. The lag time between the administration of ACZ and the second dose of ^{99m}Tc-ECD for ACZ-SPECT was 20 min, which was the same as the imaging time of basal SPECT. This protocol was modified later, as shown in Figure 1 (n = 63), with an increased dose of ^{99m}Tc-ECD to reduce the imaging time. SPECT imaging was acquired using a triple-detector gamma camera (Triad XLT 20; Trionix, Twinsburg, OH) equipped with a low-energy, ultra-high–resolution, parallel-hole collimator in a 128 × 128 matrix.

The raw SPECT projection images were reconstructed by filtered backprojection after postprocessing with a Hamming filter with a cutoff frequency of 0.80–0.85 cycle/cm. To obtain ACZ stress projection data, the basal (first) projection image was subtracted from the second projection image multiplied by 2.0, which was the correction factor for the differences in acquisition time between the basal and the second scan. The basal and ACZ stress projection data were then reformatted to construct transaxial images parallel to the orbitomeatal line using Sunviews in a Sun Sparc 10 workstation (Sun Microsystems, Mountain View, CA).

Two nuclear physicians, who were unaware of the patient data and endarterectomy results, performed visual assessment of the SPECT images. A "10-bend" color palette was used in displaying the SPECT images. The cerebellum was assigned a value of >90% perfusion (white color). Cerebral perfusion was considered to be abnormal if a region of any gray matter area had <60% (green, dark green, and blue) of normal deep ipsilateral cerebellar activity (*22*). Regions with cerebral infarction on CT and MRI were not included in the analysis. Reduced regional cerebral blood flow (reduced rCBF) was defined as abnormal cerebral perfusion over at least a third of the territory of the middle cerebral artery on the basal SPECT image. Reduced regional cerebrovascular reserve (reduced rCVR) was defined as abnormal cerebral perfusion that fell into an even lower color range from basal SPECT after ACZ administration (*23,24*) over at least a third of the territory of the middle cerebral artery. The severity of reduced rCVR was also classified into mild and severe grades (Fig. 2).

The SPECT findings were classified into 4 types as described by Kuroda et al. (*25*) with modification: type N/N, normal rCBF and normal rCVR; type R/N, reduced rCBF and normal rCVR; type N/R, normal rCBF and reduced rCVR; and type R/R, reduced rCBF and reduced rCVR.

TABLE 1
Distributions of 75 Patients Who Underwent Carotid Endarterectomy According to ICA Stenosis

ICA stenosis (%)	Ipsilateral (n = 75)	Contralateral (n = 75)
Occlusion	1	14
70–99	74	7
50–69	0	15
<50	0	39

CEA and Carotid Shunting

Carotid clamping and CEA were performed under regional anesthesia. We assessed the neurologic status of conscious (awake) patients for 1 min after clamping. Carotid shunting was performed selectively before CEA when symptoms or signs of cerebral ischemia such as change of consciousness or paralysis of extremity developed. In patients who did not need the carotid shunting initially, we assessed the neurologic status continuously during CEA and performed carotid shunting when neurologic deterioration occurred.

Reduced rCBF, reduced rCVR, and the presence of contralateral carotid stenosis (≥70%) were assessed to see whether they could predict the need for carotid shunting. The scintigraphic criteria of ACZ-SPECT for selective carotid shunting were derived after the endarterectomy results were compared with scintigraphic findings.

Statistical Analysis

The incidence of carotid shunting during CEA was analyzed according to the degree of contralateral ICA stenosis, rCBF, rCVR,

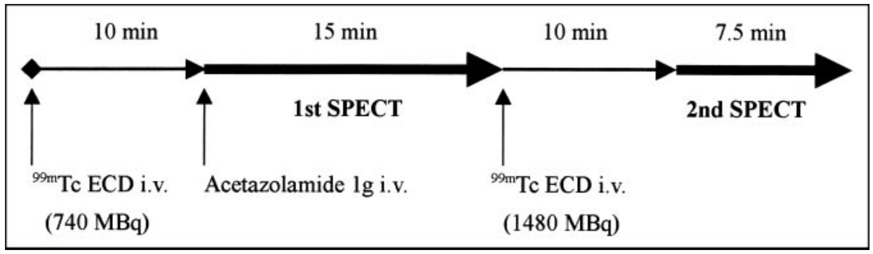

FIGURE 1. One-day protocol of basal and ACZ-SPECT. i.v. = intravenously.

and clinical risk factors, including age, sex, history of minor stroke or TIA, diabetes mellitus, hypertension, and smoking, using the Fisher's exact test. With the presence or absence of carotid shunting as a dependent variable, multiple logistic regression analysis was also performed to identify the independent association of the preoperative predictors. $P < 0.05$ was considered to be statistically significant.

RESULTS

CEAs were performed safely without carotid shunting in 61 of 75 patients (81.3%). Carotid shunting was required in the remaining 14 patients (18.7%) because of a change of consciousness (12 patients) or development of motor weakness (2 patients) after carotid clamping. Of these, 12 patients experienced neurologic deficit within 1 min after carotid clamping. A change of consciousness developed during CEA in 2 additional patients, who underwent carotid shunting. No postoperative neurologic complications occurred in any patient.

Of the 14 patients who underwent carotid shunting, 7 had a significant stenosis (≥70%) or occlusion of the contralateral ICA, 9 had a reduced rCBF, and 11 had a reduced rCVR on preoperative ACZ-SPECT. Seven of 21 patients (33.3%) with a significant contralateral stenosis, 9 of 41 patients (22.0%) with a reduced rCBF, and 11 of 30 patients (36.7%) with a reduced rCVR underwent carotid shunting (Table 2). Univariate analysis showed that the patients with a reduced rCVR had a significantly higher number of carotid shunts performed ($P < 0.01$) than did those with a preserved rCVR. The need for carotid shunting was also related to the severity of reduced rCVR. All 8 patients with a severely reduced rCVR underwent carotid shunting, whereas only 3 of 22 with a mildly reduced rCVR did (Table 2).

The presence of significant contralateral ICA stenosis or occlusion showed borderline significance ($P = 0.054$). No significant difference was found in predicting the carotid shunting procedure in relation to rCBF, age, sex, history of minor stroke or TIA, diabetes mellitus, hypertension, and smoking ($P > 0.1$). When all of these predictors of carotid shunting during CEA were considered together, a reduced rCVR was the only significant predictor of the need for carotid shunting (multiple logistic regression analysis, $P < 0.01$) (Table 2).

Table 3 shows the incidence of carotid shunting according to the types of SPECT findings and severity of the contralateral ICA stenosis. Six of 7 patients (85.7%) who had reduced rCBF and rCVR on ACZ-SPECT (type R/R) with significant contralateral ICA stenosis needed carotid shunting during CEA (Table 3). When severely reduced rCVR (8/8) or reduced rCBF and rCVR with significant contralateral ICA stenosis (6/7) were applied as the criteria to predict the need

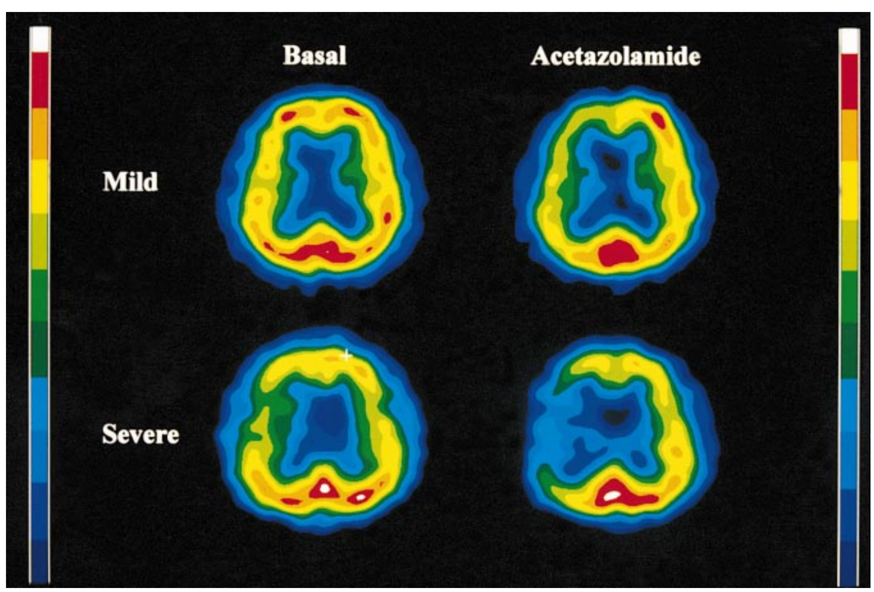

FIGURE 2. Severity of reduced rCVR on ^{99m}Tc-ECD ACZ-SPECT. Mild grade indicates reduced rCVR with abnormal distributions that fell into 1 color range from basal SPECT after ACZ administration (10%–20% change). Severe grade indicates reduced rCVR with drop of at least 2 color ranges from basal SPECT after ACZ administration (>20% change).

TABLE 2
Prediction of Need for Carotid Shunting During Carotid Endarterectomy by Clinical Risk Factors, rCBF, and rCVR on ACZ-SPECT

Predictor of carotid shunting	No. of carotid shunts (%)	Fisher's exact test	Crude odds ratio	Logistic regression	
				Odds ratio	*P*
Age (y)					
<59 (n = 21)	2 (9.5)	NS	2.7	4.3	NS
≥60 (n = 54)	12 (22.2)				
Sex					
Female (n = 12)	1 (8.3)	NS	2.9	0.9	NS
Male (n = 63)	13 (20.6)				
Minor stroke or TIA					
No (n = 12)	2 (16.7)	NS	1.2	0.4	NS
Yes (n = 63)	12 (19.0)				
Diabetes mellitus					
No (n = 42)	6 (14.3)	NS	1.9	2.3	NS
Yes (n = 33)	8 (24.2)				
Hypertension					
No (n = 17)	3 (17.6)	NS	1.1	0.5	NS
Yes (n = 58)	11 (20.0)				
Smoking					
No (n = 30)	4 (13.3)	NS	1.9	1.7	NS
Yes (n = 45)	10 (22.2)				
Contralateral ICA stenosis (%)					
<70 (n = 54)	7 (13.0)	$P = 0.054$	3.4	2.2	NS
≥70 (n = 21)	7 (33.3)				
rCBF					
Normal (n = 34)	5 (14.7)	NS	1.6	1.5	NS
Reduced* (n = 41)	9 (22.0)				
rCVR					
Normal (n = 45)	3 (6.7)	$P < 0.01$	8.1	13.5	<0.01
Reduced† (n = 30)	11 (36.7)				
Mild‡ (n = 22)	3 (13.6)				
Severe§ (n = 8)	8 (100)				

*<60% of normal deep ipsilateral cerebellar activity over one third of territory of middle cerebral artery on basal SPECT image.

†Abnormal cerebral perfusion that fell into even lower color range from basal SPECT after ACZ administration over at least one third of territory of middle cerebral artery.

‡One color range from basal SPECT after ACZ administration (10%–20% change).

§At least 2 color ranges after ACZ administration (>20% change).

NS = not significant ($P > 0.1$).

for carotid shunting, the positive and negative predictabilities of ACZ-SPECT were 90.9% (10/11) and 93.8% (60/64), respectively.

DISCUSSION

Our results show that reduced rCVR was the most reliable preoperative predictor of the need for carotid shunting. The subgroups of patients at high risk for cerebral ischemia who required carotid shunting during CEA were patients with severely reduced rCVR or reduced rCBF and rCVR with significant contralateral ICA stenosis. When severely reduced rCVR or reduced rCBF and rCVR (type IV) with significant contralateral ICA stenosis were applied as the criteria for carotid shunting, the positive and negative predictabilities were 91% and 94%, respectively. They are significantly higher than those of other reported preoperative anatomic or clinical predictors, including contralateral ICA stenosis or occlusion or history of recent infarction (*15–17*). Our findings indicate that ACZ-SPECT is a noninvasive and reliable preoperative method to identify patients at risk of developing cerebral ischemia during CEA, and this procedure is useful to the surgeon who would prefer to be selective in using carotid shunting.

The incidence of selective carotid shunting on the basis of EEG monitoring or monitoring of the awake patient during CEA has been reported to be 4%–20% (*9,10,12,14–17*), which is similar to our result of 18.7%. In our study, carotid shunting was needed in 11 of 30 patients (36.7%) with a reduced rCVR. Two previous studies showed that reduced rCVR was highly predictive of the development of cerebral ischemia during CEA (*20,21*). Tawes et al. (*20*) reported that a reduced rCVR was highly correlated with low stump pressure during CEA. In their study, 48 of 68 patients had a decreased vascular reserve on the preoperative ACZ-SPECT using ^{99m}Tc-hexamethylpropyleneamine oxime (HMPAO). All of these patients had a carotid shunt placed during CEA, and the other 20 patients who had normal ACZ-SPECT did not receive shunts. However, the incidence (71%) of selective shunting in their study was higher than that of other previous studies, and their indication for carotid shunting was low carotid stump pressure instead of the development of neurologic deterioration or abnormal EEG findings after carotid clamping.

Palombo et al. (*21*) also observed 4 of 43 patients who required shunting, all of whom had a poor cerebrovascular reserve in the preoperative ACZ-SPECT using ^{99m}Tc-HMPAO. In their study, however, the indication for carotid shunting was abnormal somatosensory evoked potentials. The number of carotid shunts performed in their study was relatively small to draw a definite conclusion.

TABLE 3
Incidence of Carotid Shunting During CEA According to Types of ^{99m}Tc-ECD ACZ-SPECT Findings and Severity of Contralateral ICA Stenosis

SPECT findings	Contralateral ICA stenosis		Total
	<69%	70%–100%	
Type N/N	1/17 (5.9)	0/4	1/21 (4.8)
Type R/N	2/20 (10.0)	0/4	2/24 (8.3)
Type N/R	3/7 (42.9)	1/6 (16.7)	4/13 (30.8)
Type R/R	1/10 (10.0)	6/7 (85.7)	7/17 (41.2)
Total	7/54 (13.0)	7/21 (33.3)	14/75 (18.7)

Values in parentheses are percentages.

A reduced rCVR reflects an inadequate collateral blood flow and decreased vasodilatory capacity to maintain the cerebral blood flow against a further decrease in perfusion pressure (*20,21,23,24*). Because carotid clamping may cause a critical reduction of cerebral perfusion in the area of the reduced rCVR, it is not surprising that cerebral ischemia developed more frequently during carotid clamping in patients with a reduced rCVR than in those with a normal rCVR. Many studies have indicated that ACZ-SPECT allows an objective assessment of regional vasoreactivity to ACZ and is a feasible method to detect the cerebrovascular compromise (*18,23–25*). Hirano et al. (*26*) observed that a reduced rCVR corresponded perfectly to an elevated oxygen extraction fraction and suggested that a significantly reduced rCVR represents the stage II hemodynamic failure (misery perfusion) determined with PET studies. Although our study did not include the quantitative analysis of the rCBF and oxygen extraction fraction, most patients with a severely reduced rCVR or reduced rCBF and rCVR with severe contralateral ICA stenosis might have misery perfusion or intracerebral steal by ACZ stress (*27*).

In our study, not only rCVR but also rCBF was assessed to identify the preoperative predictors for the development of cerebral ischemia during CEA. In contrast to a rCVR, a reduced rCBF did not predict the need for carotid shunting. Although a reduced rCBF indicates severe cerebrovascular compromise in patients with carotid or cerebral artery stenosis, localized or global cerebral atrophy, selective neuronal loss, or cerebral diaschisis can cause reduced cerebral blood flow despite adequate collateral flow (*23,24*). In addition, cerebral blood flow can be normal in spite of a decreased cerebral perfusion pressure because of vasodilatation of the cerebral resistance arteries. Therefore, it does not often reflect the true cerebrovascular compromise.

Patients with a contralateral ICA occlusion or high-grade stenosis are generally thought to be at great risk for cerebral ischemia during carotid clamping (*13*) because the contralateral ICA might be the main collateral route of the cerebral blood supply during carotid clamping. However, the incidence of cerebral ischemia that required carotid shunting during CEA has been variable in patients with a contralateral ICA occlusion or severe stenosis. With general anesthesia, Green et al. (*17*) and Phillips et al. (*13*) reported ischemic EEG changes after carotid clamping in 37% and 43% of cases with a contralateral ICA occlusion, respectively. These incidences were significantly higher than those without a contralateral ICA occlusion. With awake patient monitoring, Hafner and Evans (*15*) observed the need for a shunt in 30% of cases with a severe contralateral ICA stenosis or occlusion compared with 9% overall. However, Benjamin et al. (*9*) observed significant cerebral ischemia during carotid clamping in only 16.6% of cases with a severe contralateral ICA stenosis, which did not differ from the overall rate of 16.0% or from the 15.4% in patients without severe contralateral ICA stenosis. In our study, patients with a severe contralateral ICA stenosis or occlusion required a higher incidence of carotid shunting (33% versus 13%), but the difference was not statistically significant ($P = 0.054$). A difference in collateral circulation through the posterior communicating artery, variable severity of the contralateral ICA stenosis, or different methods of determining the need for shunting may explain these controversial results. Schwarz et al. (*14*) reported that intraoperative EEG changes during CEA correlated with the presence or absence of collateral flow through the posterior communicating artery in 6 cases with occlusion of the contralateral ICA. Our study suggests that severe contralateral ICA stenosis does not always reflect the need for carotid shunting.

Although the rCVR was the only significant predictor of the need for carotid shunting, 19 patients with false-positive results would have undergone shunting unnecessarily and 3 patients with false-negative findings would not have undergone shunting had a reduced rCVR been used as the sole indication for carotid shunting. Whereas only 3 of 22 patients with a mildly reduced rCVR underwent carotid shunting, 6 of 7 patients with reduced rCBF and rCVR with significant contralateral carotid stenosis required carotid shunting. These findings suggest further refinement, including quantitative analysis, in the assessment of rCVR is needed. An additive role of rCBF or the presence of contralateral carotid stenosis needs to be clarified in a larger number of patients.

Our study has several limitations. First, because we did not perform the quantitative or semiquantitative analysis of cerebral hemodynamic status, the evaluation of cerebral hemodynamics was performed only by visual analysis. Visual assessment of abnormal rCBF or rCVR was often difficult in patients with a mild reduction of rCBF or rCVR. Subjective errors can result from inadequate normalization of SPECT images or bilateral severe carotid stenosis that may produce false-negative results. Quantification of the rCBF, rCVR, or oxygen extraction fraction determined by PET can produce objective results and prevent these subjective errors. However, those quantitative methods are not always available in routine clinical practice and also require a longer period of study time and necessitate blood sampling. To minimize inadequate normalization of SPECT images, we chose cerebellar activity as a standard reference point. Obviously, quantitative and precise assessment of the rCVR would provide a better definition of the role of ACZ-SPECT in detecting patients who will require carotid shunting.

Second, the status of collateral channels such as the anterior or posterior communicating artery was not assessed as a preoperative predictor because not all patients in this series underwent 4-vessel conventional angiography. Previous studies revealed the important role of the circle of Willis as a collateral pathway in patients with ICA occlusion (*28,29*). Schwartz et al. (*14*) reported that the inadequate collateral cerebral circulation correlated strongly with the development of intraoperative ischemia during CEA. However, patients were not randomly selected in their study.

Nonvisualization of collateral vessels does not necessarily mean that the artery is absent or incompetent (*30*). The lack of a relationship between angiographic collateral circulation and cerebral hemodynamic status has also been reported (*31*,*32*). Thus, the value of cerebral angiographic demonstration of collateral blood flow in predicting cerebral ischemia during CEA has not been fully clarified. We believe that evaluation of the circle of Willis would give us a better insight into the relationship between the need for carotid shunting and rCBF or rCVR on ACZ-SPECT.

Another limitation is that our results may not be applied to patients who underwent CEA under general anesthesia because brain metabolism is reduced under general anesthesia (*33*). Although the number of patients who need carotid shunting can be overestimated in the case of general anesthesia, our findings of a high negative predictability are of value in reducing the number of carotid shunts performed.

CONCLUSION

Our study showed that the reduced rCVR on ACZ-SPECT predicted the development of cerebral ischemia that required carotid shunting during carotid clamping. Preoperative ACZ-SPECT may be useful as a complementary method in determining selective carotid shunting during CEA.

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