

The effect of EC-IC bypass surgery on resting cerebral blood flow and cerebrovascular reserve capacity studied with stable Xe-CT and acetazolamide test

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Received: 3 August 1990

Summary. Cerebral blood flow (CBF) and cerebrovascular reserve capacity (CRC) were measured by stable xenon computerized tomography (Xe-CT) and acetazolamide test in 15 patients with cerebrovascular disease before and after extracranial-intracranial (EC-IC) bypass surgery for minor stroke, reversible ischemic neurological deficit or transient ischemic attack. All had angiographically shown occlusive lesions of the major arterial trunk. In the present series, global analysis showed that the bypass did not increase the resting rCBF, but did increase the rCRC. We divided the patients into four groups according to the preoperative resting rCBF and rCRC. All 3 patients with normal resting rCBF and reduced rCRC showed postoperative improvement of rCRC. Of 6 patients with reduced CBF and reduced CRC, three had postoperative increase in resting CBF and four had increased CRC. One of two patients with reduced CBF and normal CRC showed only an increase in CRC. We propose that reduced CRC or reduced CBF with reduced CRC are criteria for selection of candidates for bypass surgery. We conclude that Xe-CT with the Diamox test is a useful and simple method for evaluating cerebral hemodynamics. Preoperative grouping with a combination of preoperative resting rCBF and preoperative rCRC is useful for predicting the effect of EC-IC bypass surgery.

Key words: EC-IC bypass – Cerebral blood flow – Xe-CT – Cerebrovascular reserve capacity – Acetazolamide

The report of the Extracranial-intracranial Arterial (EC-IC) Bypass Study Group has demonstrated that this type of surgery has little value for preventing subsequent stroke [1]. However, this trial has been criticized for failing to identify and separately analyze the subgroup of patients with reduction in regional cerebral perfusion pressure distal to the symptomatic arterial lesion, who might be likely to benefit from such surgery [2, 3].

Vorstrup et al. reported that resting cerebral blood flow (CBF) was not changed in most patients after bypass

surgery because of preoperative matched low perfusion [4].

Therefore, other forms of examination, for example, oxygen extraction fraction (OEF), cerebral blood volume (CBV), CO₂ response or acetazolamide (Diamox) response, are needed for bypass evaluation [5–10]. Patients with “misery perfusion”, decreased CO₂ response, increased CBV/CBF or an acetazolamide-induced “steal effect” would belong to a subgroup that could benefit from bypass surgery [5–10].

The aim of this study was to preoperatively identify patients having a reduced CBF and/or reduced cerebrovascular reserve capacity (CRC) due to compromised collateral circulation. For this purpose, stable xenon computerized tomography (Xe-CT) and Diamox test were used. In this paper, we also evaluate postoperative changes in resting CBF and CRC, and propose criteria for the selection of appropriate candidates for EC-IC bypass.

Materials and methods

This study included a consecutive series of 15 patients who presented with cerebral ischemic symptoms (Table 1). There were 13 males and 2 females ranging in age from 46 to 71 years with a mean of 60 years. Clinical presentations were transient ischemic attack (TIA) in 4 cases, reversible ischemic neurological deficit (RIND) in 1 and minor stroke in 10. Indications for EC-IC bypass surgery were based on the clinical symptoms and the findings of angiography, CT scan and CBF measurement. All patients had stenosis or occlusion of the internal carotid or middle cerebral artery. Patients with a large infarct (≥ 20 cm²) on CT were excluded from this study. Fifteen EC-IC bypass operations were performed. These included 4 single superficial temporal artery – middle cerebral artery (STA-MCA) anastomoses, 5 double STA-MCA anastomoses and 6 STA-proximal MCA anastomoses. Postoperative angiography showed a patent bypass in all cases.

Table 1. Summary of cases

Case	Age/ sex	Clinical diagnosis	Angiographic findings	CT findings size of infarct	ST-MC anastomosis	Outcome
1	57 M	TIA	ICoc	None	Proximal	NRA
2	51 M	TIA	ICoc	None	Proximal	NRA
3	71 M	TIA	ICoc	None	Single	NRA
4	66 M	Min str	ICoc	Small	Double	Improve
5	60 M	Min str	ICoc	Small	Double	Improve
6	59 M	Min str	ICst	None	Single	NRA
7	60 M	Min str	ICst	None	Double	NRA
8	64 M	Min str	ICoc + ICoc	Moderate	Proximal	NRA
9	61 M	Min str	ICoc + ICoc	None	Single	Improve
10	59 M	Min str	ICoc + ICst	None	Double	NRA
11	46 M	Min str	MCoc	Moderate	Single	NRA
12	61 F	Min str	MCoc	Small	Proximal	NRA
13	57 F	TIA	MCst	None	Proximal	NRA
14	64 M	RIND	MCst	Small	Proximal	NRA
15	66 M	Min str	MCst	Small	Double	NRA

TIA, transient ischemic attack; *Min str*, minor stroke; *RIND*, reversible ischemic neurological deficit; *IC*, internal carotid artery; *MC*, middle cerebral artery; *oc*, occlusion; *st*, stenosis; *NRA*, no recurrent attack; *ST*, superficial temporal artery

Study protocol

The preoperative study was performed at least one month after the onset of stroke: it was repeated one month after surgery. The resting CBF studies were conducted on each subject with the eyes closed. Tidal CO₂, respiration rate, pulse rate and blood pressure were monitored. After measurement of resting CBF, an arterial blood sample was obtained to measure hematocrit, pH and PaCO₂, and 1 g of Diamox was administered intravenously. Twenty minutes after Diamox injection, a second CBF measurement following the arterial blood sample was taken.

The CBF studies were conducted with a Somatom DR3 CT scanner (Siemens Medical Co.), a Xetron III closed re-breathing xenon inhalator (Anzai Sogyo Co.), an AZ-723-XS end-tidal Xe monitor (Anzai Sogyo Co.) and EVAX CBF imaging software (Siemens Medical Co.). The theoretical background, validity and clinical applications of the xenon-enhanced CT method of CBF imaging have been discussed elsewhere [11]. In brief, after 2 baseline CT scans, the patient inhales a 30% Xe/70% O₂ gas mixture through a face mask, while a series of CT scans is obtained according to the inhalation protocol described below. Scan parameters are 96 kVp, 680 mAs, a 7-s scan time and an 8-mm slice thickness. The inhalator is equipped with an interface which provides automated transfer of the end-tidal xenon data and synchronizes the time scales of the xenon inhalator and the CT scanner. At the end of inhalation, the end-tidal xenon concentration data stored in a microcomputer are transferred automatically to the CT host computer, where, combined with the hematocrit value, it is converted into arterial xenon enhancement data. For calculating the parameter images of flow and lambda, the two-parameter optimization method described by Koeppe et al. is implemented [12]. This method consists of a modified algorithm which calculates a series of linear least-squares instead of a single iterative nonlinear least-squares calculation. In the first step, the convolution of the arterial xenon concentration and the exponential function is calculated for the expected range of k values and for the times of the

enhanced scans and stored in a table. The parameter optimization step consists of a grid search technique to fit the k value and a conventional least-squares fit for the flow, f. Lambda is then simply derived by dividing k by f.

Data analysis

The resting mean rCBF, Diamox-induced mean rCBF and rCRC of the middle cerebral artery distribution at the level of the basal ganglia were calculated in all cases, both pre- and postoperatively. CRC was defined as the difference between the Diamox-induced CBF and the resting CBF. We divided the patients retrospectively into four groups according to the preoperative values of resting rCBF and rCRC. Postoperative improvement of each parameter was analyzed in each group (Table 2).

Group I: resting CBF ≥ 40 ml/100 g/min, CRC ≥ 5 ml/100 g/min, meaning that the patient has normal resting CBF with normal CRC.

Group II: resting CBF ≥ 40 ml/100 g/min, CRC < 5 ml/100 g/min. Normal resting CBF with decreased CRC means that resting CBF is maintained by vasodilatation against decreased perfusion pressure.

Group III: resting CBF < 40 ml/100 g/min, CRC ≥ 5 ml/100 g/min. Decreased resting CBF with normal CRC means that even in areas without low density on CT, ischemic tissue damage has occurred and decreased metabolic demand is linked to decreased resting CBF.

Group IV: resting CBF < 40 ml/100 g/min, CRC < 5 ml/100 g/min. Decreased resting CBF with decreased

Table 2. Classification according to preoperative hemodynamics

	Resting CBF	CRC
Group I	≥ 40 ml	≥ 5 ml
Group II	≥ 40 ml	< 5 ml
Group III	< 40 ml	≥ 5 ml
Group IV	< 40 ml	< 5 ml

CRC, cerebrovascular reserve capacity

Table 3. Physiological parameters of 15 cases before and after bypass surgery*

Parameter	Preoperative state		Postoperative state	
	Resting	Diamox	Resting	Diamox
No. of cases	15	15	15	15
MABP (mm Hg)	101.2 ± 2.8	99.5 ± 2.2	99.8 ± 3.4	100.9 ± 3.7
pH	7.38 ± 0.02	7.41 ± 0.02	7.40 ± 0.01	7.41 ± 0.01
pO ₂ (mm Hg)	307.0 ± 15.6	294.4 ± 8.7	325.3 ± 18.9	306.2 ± 28.3
pCO ₂ (mm Hg)	38.6 ± 0.9	34.8 ± 1.1	39.1 ± 0.8	36.7 ± 0.8
Hematocrit	40.4 ± 1.0	41.1 ± 1.1	38.1 ± 1.0	39.0 ± 1.0

* Values are means ± standard error

MABP, mean systemic arterial blood pressure

CRC means that in the region of interest, severe reduction of perfusion pressure exceeding vasodilatation to maintain resting CBF has occurred. This group may include a state of "misery perfusion"; CBF reduction with increased OEF.

The values were expressed as mean ± standard error in ml/100 g/min. For statistical analysis, paired Wilcoxon test was used, and differences at $p < 0.05$ were regarded as significant. An increase in the resting rCBF or in the rCRC of 5 ml or more after bypass surgery was considered to be significant.

Normal control group

Eight normal volunteers with a mean age of 28 years were examined for resting CBF and CRC values. The mean rCBF and rCRC of the MCA territory at the level of the basal ganglia were 60.4 ± 3.1 ml/100 g/min and 19.0 ± 3.3 ml/100 g/min respectively.

Results

Regional cerebral blood flow and cerebrovascular reserve capacity

Mean arterial blood pressure (MABP), blood gas values and hematocrit showed no significant differences between the preoperative and the postoperative groups (Table 3).

Changes in rCBF and rCRC are shown in Figs. 1 and 2. The resting mean rCBF in the affected MCA area before bypass surgery was 37.3 ± 2.6 ml/100 g/min (Fig. 1). After the bypass surgery, the resting mean rCBF was 34.9 ± 1.6 ml/100 g/min, i.e. there were no significant differences in the values before and after bypass surgery. The mean rCRC in the affected MCA area was 4.4 ± 2.1 ml/100 g/min before bypass surgery, and 9.3 ± 1.8 ml/100 g/min after the bypass surgery (Fig. 2). There was, therefore, a significant difference in the values of postoperative rCRC compared with preoperative rCRC ($P < 0.05$).

Correlation between preoperative grouping and postoperative increase of rCBF and/or rCRC

In group I ($n = 4$), none of four patients had an increase in resting rCBF and rCRC. In group II ($n = 3$), only rCRC was increased postoperatively. In group III ($n = 2$), only

one of two patients had increased rCRC. In group IV, three of six patients had a postoperative increase in resting rCBF and four of six had a postoperative increase in rCRC (Fig. 3).

Results of bypass surgery

Three of 15 patients showed postoperative improvement of neurological deficits in cases of minor stroke. The other patients had no recurrent attacks of TIA or RIND. There

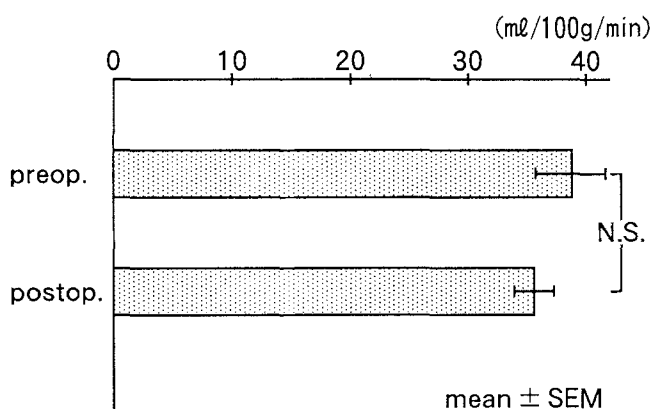


Fig. 1. The pre- and postoperative resting mean rCBF in the affected MCA area of all cases. There were no significant differences in the values before and after bypass surgery

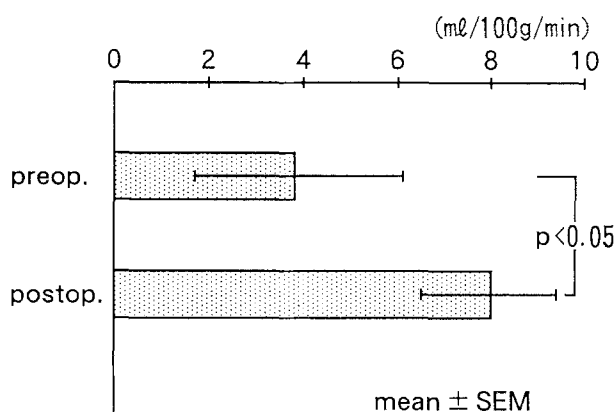


Fig. 2. The pre- and postoperative cerebrovascular reserve capacity (CRC = delta CBF with Diamox) in the affected MCA area of all cases. There was a significant difference in the values of postoperative rCRC compared with preoperative rCRC

		No. of cases	
Resting CBF (ml/100g/min)	II	rest CBF ↑	$\frac{0}{3}$
		C R C ↑	$\frac{3}{3}$
	IV	rest CBF ↑	$\frac{3}{6}$
		C R C ↑	$\frac{4}{6}$
		5	(ml/100g/min)
		Cerebrovascular reserve capacity	
		I	rest CBF ↑ $\frac{0}{4}$
			C R C ↑ $\frac{0}{4}$
		III	rest CBF ↑ $\frac{0}{2}$
			C R C ↑ $\frac{1}{2}$

Fig. 3. Postoperative hemodynamic changes in each group. The numerator (*number at the top*) shows number of patients who had a postoperative increase in the resting CBF or CRC. The denominator (*number at the bottom*) shows total number of patients in the each group

were no perioperative complications and the postoperative angiography showed patent bypass.

Representative case

A 66-year-old man had suffered sudden onset of left hemiparesis six months before admission. Neurological examination on admission showed mild hemiparesis and dysarthria. CT scan showed a small infarct in the right putamen. Right common carotid angiography revealed proximal occlusion of the internal carotid artery (Fig. 4a). Right double STA-MCA anastomoses were carried out. Postoperative angiography showed excellent filling of the middle cerebral artery from the bypass (Fig. 4b). Preoperative Xe-CT CBF images showed a low perfusion state and absent rCRC in the right hemisphere (Fig. 5). The postoperative CBF images indicated that the resting rCBF was increased by 5 ml from the preoperative value, and decreased hemispheric asymmetry was noted. Diamox increased the CBF in both hemispheres. Thus, in this case, it appeared that bypass surgery had not only increased the resting CBF but also improved CRC. The patient's hemiparesis improved after surgery.

Discussion

The report of the EC-IC Bypass Study Group has been criticized for failing to identify and separately analyze the subgroup of patients with "chronic hemodynamic insufficiency" who might be most likely to benefit from this type of surgery [2, 3]. To identify patients with "chronic hemodynamic insufficiency" preoperatively, CBF with CO₂ inhalation, acetazolamide injection or hypotension, or OEF and/or CBV were measured [5–10]. From these examinations, patients with a reduced CO₂ response, "misery perfusion" or an acetazolamide-

induced "steal effect" would appear to belong to a subgroup that could benefit from bypass surgery [5–10].

These data were obtained by positron emission tomography (PET), single-photon emission computed tomography (SPECT) or dynamic computed tomography. In this study, we used Xe-CT, which has the advantages of easily repeatable examination, cost effectiveness, high resolution and provision of absolute values as compared with PET, SPECT or dynamic CT.

Symptomatic arterial trunk occlusion produces reduction in regional cerebral perfusion pressure followed by dilatation of cerebral arterioles distal to the occlusion site. In this state, rCBF is increased little by the vasodilating agent, and rCBF decreases with hypotension, which means that decreased rCRC is present. CRC can be evaluated by CO₂ inhalation or hypotension. However, CO₂ inhalation makes the patient uncomfortable and hypotension has a risk of inducing an irreversible ischemic attack. Diamox is known to increase CBF due to vasodilatation, which occurs through tissue acidosis by inhibition of carbonic anhydrase [13]. Vorstrup et al. reported that the Diamox test evaluated CRC in the ischemic brain more conveniently than other methods [10]. In our institute, more than 100 Diamox tests have been carried out without complication.

Vorstrup et al. reported that the mean CBF value in the normal control group (mean age, 63 years) was 55 ml/100 g/min, and that the mean CBF increased by 31%, ranging from 13% to 46%, 20 min after venous injection of 1 g of Diamox [10]. In our data obtained from normal adult volunteers (mean age, 28 years), the resting rCBF of the MCA territory was 60.4 ± 3.1 ml/100 g/min, and the rCRC was 19.0 ± 3.3 ml/100 g/min. Our data thus agreed with those reported by Vorstrup et al. [10].

Vorstrup et al. stated that resting CBF did not change in most cases after bypass surgery because of the presence of a preoperative matched low-perfusion state [4]. Our study showed the same result, i.e., in the global analysis of all cases, EC-IC bypass was found not to increase the resting CBF, but did increase rCRC. These results suggest that bypass is more effective for improving rCRC than for increasing the resting CBF.

In order to analyze our data precisely, we divided the patients into four groups retrospectively according to the preoperative value of rCBF and rCRC. Group I had normal rCBF and rCRC. In group II, rCBF was normally maintained by vasodilatation. In group III, low rCBF with normal rCRC occurred due to matched low perfusion. In group IV, low rCBF with low rCRC occurred due to severe reduction of perfusion pressure exceeding vasodilatation in order to maintain resting CBF. Theoretically, patients in group II with normal rCBF and decreased rCRC, and those in group IV with decreased rCBF and decreased rCRC were expected to show postoperative increment of rCBF or CRC. This theory was supported by our findings that bypass surgery improved rCRC in group II, and improved rCRC and resting rCBF in group IV. EC-IC bypass certainly increases perfusion pressure in the area distal to the arterial occlusion and decreases vasodilatation, resulting in an increase in the

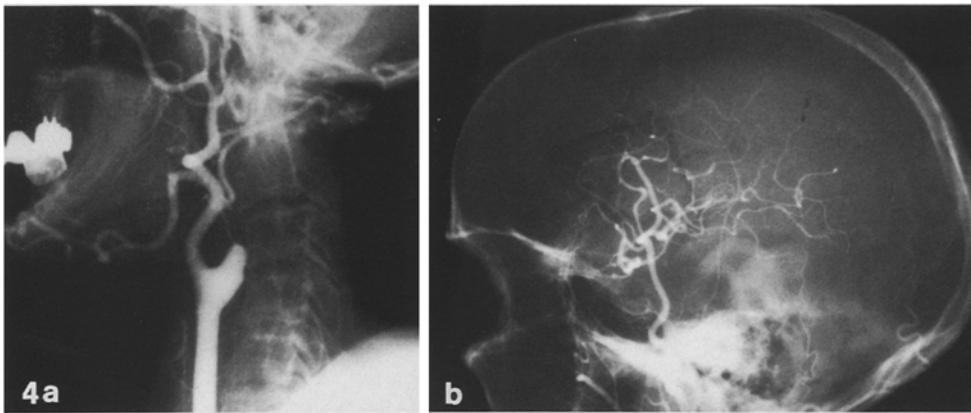


Fig. 4 a, b. Preoperative right common carotid angiography revealed proximal occlusion of internal carotid artery (a). Postoperative angiography showed an excellent filling of middle cerebral artery from the bypass

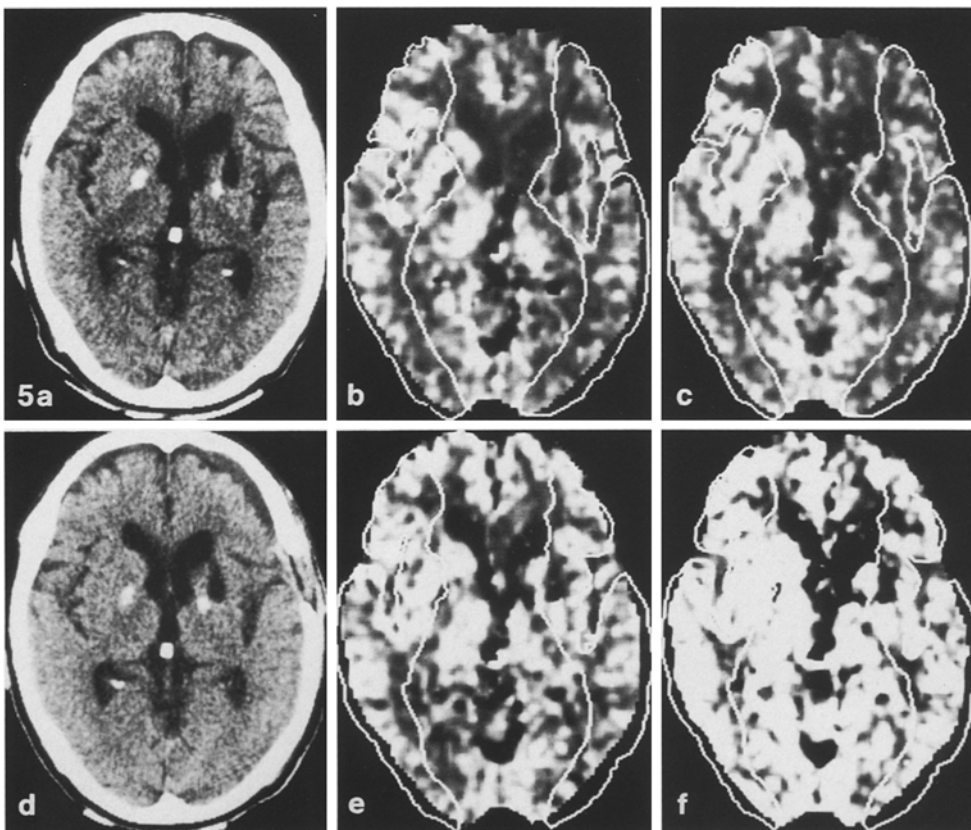


Fig. 5. a–c Preoperative images. **d–f** Postoperative images. **a, d** Plain CT. **b, e** Resting CBF. **c, f** Diamox induced CBF. Preoperative Xe CT CBF images showed a low perfusion state and absent rCRC in the right hemisphere. The postoperative CBF images indicated both the increased resting CBF and CRC. Dotted lines (region of interest) show the middle cerebral artery distribution

rCRC. In the area of severe perfusion pressure reduction that may include “misery perfusion”, bypass increases the resting rCBF.

Conclusion

We conclude that Xe-CT with the Diamox test is a useful and simple method for measuring cerebral hemodynamics. Preoperative grouping with a combination of preoperative resting rCBF and preoperative rCRC is useful for predicting the effect of EC-IC bypass surgery. Furthermore, we propose that compensated vasodilatation (as seen in group II) and severe perfusion pressure reduction (as seen in group IV) are appropriate criteria for selection of patients for EC-IC bypass surgery.

References

1. The EC-IC Bypass Study Group (1985) Failure of extracranial-intracranial arterial bypass to reduce the ischemic stroke. *N Engl J Med* 313: 1191–1200
2. Ausmann JI, Diaz FG (1986) Critique of the extracranial-intracranial bypass study. *Surg Neurol* 26: 218–221
3. Day AL, Rhoton AL, Little JR (1986) The extracranial-intracranial bypass study. *Surg Neurol* 26: 222–226
4. Vorstrup S, Lassen NA, Henriksen L, Haase J, Lindewald H, Boysen G, Paulson OB (1985) CBF before and after extracranial-intracranial bypass surgery in patients with ischemic cerebrovascular disease studied with xenon-133 inhalation tomography. *Stroke* 16: 616–626
5. Baron JC, Boussier MG, Rey A, Guillard A, Comar D, Castaigne P (1981) Reversal of focal “misery-perfusion syndrome” by extra-intracranial arterial bypass in hemodynamic cerebral ischemia; A case study with ^{15}O positron emission tomography. *Stroke* 12: 454–459

6. Gibbs JM, Wise RJS, Leenders KL, Jones T (1984) Evaluation of cerebral perfusion reserve in patients with carotid-artery occlusion. *Lancet* I: 310–314
7. Herold S, Brown MM, Frackowiak RSJ, Mansfield AO, Thomas DJ, Marshall J (1988) Assessment of cerebral haemodynamic reserve – correlation between PET parameters and CO₂ reactivity measured by intravenous ¹³³Xe injection technique. *J Neurol Neurosurg Psychiat* 51: 1045–1050
8. Norrving B, Nilsson B, Risberg J (1982) rCBF in patients with carotid occlusion – resting and hypercapnic flow related to collateral pattern. *Stroke* 13: 155–162
9. Sullivan HG, Kingsbury TB, Morgan ME, Jeffcoat RD, Allison JD, Goode JJ, McDonnell DE (1987) The rCBF response to Diamox in normal subject and cerebrovascular disease patients. *J Neurosurg* 67: 525–534
10. Vorstrup S, Henriksen L, Paulson OB (1984) Effect of acetazolamide on cerebral blood flow and cerebral metabolic rate for oxygen. *J Clin Invest* 74: 1634–1639
11. Kashiwagi S, Yamashita T, Abiko S, Aoki H, Maekawa T, Take-shita H, Suess C, Kalender W (1986) Measurement and imaging of cerebral blood flow with stable xenon and computed tomography (Xe-CT). *Electromedica* 54: 136–144
12. Koeppe RA, Holden JE, Ip WR (1983) Performance comparison of parameter estimation techniques for the quantitation of local cerebral blood flow by dynamic positron computed tomography. *J Cereb Blood Flow Metab* 5: 224–234
13. Vorstrup S, Brun B, Lassen NA (1986) Evaluation of the cerebral vasodilatory capacity by the acetazolamide test before EC-IC bypass surgery in patients with occlusion of the internal carotid artery. *Stroke* 17: 1291–1298

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