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Variability of cerebral blood volume and oxygen extraction: stages of cerebral haemodynamic impairment revisited

Colin P. Derdeyn,[1,2] Tom O. Videen,[2,3] Kent D. Yundt,[3] Susanne M. Fritsch,[3] David A. Carpenter,[3] Robert L. Grubb[2,3] and William J. Powers[2,3,4]

[1]*Neuroradiology Section,* [2]*Division of Radiological Sciences, Mallinckrodt Institute of Radiology,* [3]*Department of Neurology and Neurological Surgery and* [4]*The Lillian Strauss Institute of the Jewish Hospital of St Louis, Washington University School of Medicine St Louis, Missouri, USA*

Correspondence to: Dr C. P. Derdeyn, Mallinckrodt Institute of Radiology, 510 South Kingshighway Boulevard, St Louis, MO 63110, USA
E-mail: derdeync@mir.wustl.edu

Summary

The presence or degree of haemodynamic impairment due to occlusive cerebrovascular disease is often inferred from measurements of cerebral blood flow (CBF), cerebral blood volume (CBV), oxygen extraction fraction (OEF) and the cerebral rate for oxygen metabolism ($CMRO_2$). However, the relationship of these variables, in particular CBV, to regional cerebral haemodynamics is not clearly established in humans with subacute or chronic disease. In the present study, we investigated the relationship of CBV to OEF, CBF and $CMRO_2$, and to subsequent stroke risk in patients with unilateral carotid artery occlusion, in order to define better the associated haemodynamic and metabolic changes. We reviewed data from 81 patients with symptomatic carotid occlusion enrolled in a prospective study of haemodynamic factors and stroke risk. Measurements of CBV, CBF, OEF and $CMRO_2$ were made on entry using PET. Patients were divided into groups by hemispheric ratios and absolute ipsilateral values of OEF and CBV, based on comparison with normal controls. Haemodynamic and metabolic values, risk factors and stroke risk were compared between groups. Based on hemispheric ratios, 45 patients had increased ipsilateral OEF; CBV was increased in 19 of these 45 patients. No differences in CBF, $CMRO_2$ or clinical risk factors were found between these 19 patients and the remaining 26 patients with increased OEF and normal or reduced CBV. Thirteen ipsilateral strokes occurred during follow-up, and 10 of the 13 occurred in the 19 patients with increased OEF and CBV (log rank $P < 0.0001$). Thirty-two of the 68 patients with complete quantitative PET data had increased OEF by absolute ipsilateral values. CBV was increased in 20 of the 32 patients. No differences in CBF, $CMRO_2$ or clinical risk factors were found between these 20 patients and the remaining 12 patients with increased OEF and normal CBV. Seven of the nine ipsilateral strokes that occurred in the 68 patients occurred in those 20 patients with increased OEF and increased CBV (log rank $P = 0.003$). The higher risk of ischaemic stroke in patients with increased OEF and CBV suggests that their degree of haemodynamic compromise is more severe than those with increased OEF and normal CBV. In patients with chronic carotid occlusion and increased OEF, increased CBV may indicate pronounced vasodilation due to exhausted autoregulatory vasodilation. The physiological explanation for the measurement of normal CBV in patients with increased OEF is less certain and may reflect preserved autoregulatory capacity.

Keywords: haemodynamics; cerebral blood volume; oxygen extraction fraction; ischaemia; autoregulation

Abbreviations: CBF = cerebral blood flow; CBV = cerebral blood volume; $CMRO_2$ = cerebral rate of metabolism for oxygen; CPP = cerebral perfusion pressure; OEF = oxygen extraction fraction

Introduction

Since direct measurements of regional cerebral perfusion pressure (CPP) in patients with cerebrovascular disease are not practical, indirect methods have been developed. These indirect techniques are based on the identification of

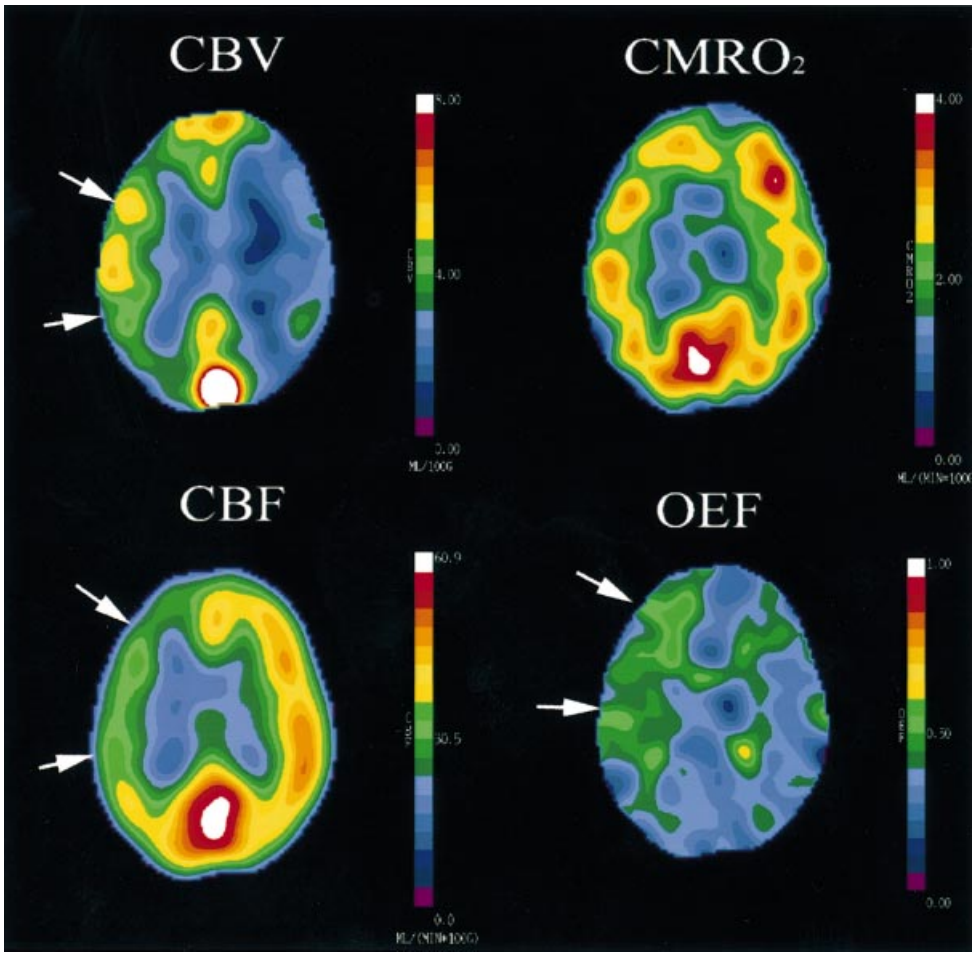

Fig. 1 Stage 2 haemodynamic failure. Increased CBV indicates autoregulatory vasodilation (CBV, arrows). This is insufficient to maintain flow, however, and flow falls (CBF, arrows). In this situation, the brain can increase the fraction of oxygen extracted from the blood (OEF, arrows) in order to maintain normal oxygen metabolism ($CMRO_2$) and brain function.

compensatory responses to reduced CPP that have been defined in animal studies involving acute global reductions in mean arterial pressure or increased intracranial pressure.

Two compensatory responses to acute reductions in CPP have been established: autoregulation and increased oxygen extraction. As CPP falls, cerebral blood flow (CBF) is maintained initially by vasodilation of resistance arterioles, a reflex known as autoregulation (Rapela and Green, 1964; MacKenzie *et al*., 1979). With further reductions in CPP, the autoregulatory capacity is exhausted and CBF falls as a function of pressure. When CBF falls, increases in the oxygen extraction fraction (OEF) will maintain cerebral oxygen metabolism and tissue function up to a point (Lennox *et al*., 1935; Kety *et al*., 1950; Boysen, 1973). CPP reductions beyond the point where increases in OEF can compensate will lead to true ischaemia, with an insufficient delivery of oxygen to meet metabolic demands. Energy failure will result and permanent injury may ensue, depending on the duration and degree of the ischaemia. It must be noted that the extent to which these compensatory responses are valid in humans with chronic regional reductions in CPP is incompletely known (Derdeyn *et al*., 1999*a*).

In 1987, we proposed a sequential, two-stage classification of chronic haemodynamic impairment for patients with atherosclerotic carotid artery disease, based on experimental data available at that time (Powers *et al*., 1987; Powers, 1991). Stage I (autoregulatory vasodilation) was identified as an increase in cerebral blood volume (CBV) or mean vascular transit time (mathematically equivalent to the CBV/CBF ratio) in the hemisphere distal to the occlusive lesion, with normal CBF, OEF and oxygen metabolism (cerebral rate for oxygen metabolism; $CMRO_2$) (Powers *et al*., 1987). Stage II (autoregulatory failure) was characterized by reduced CBF and increased OEF with normal oxygen metabolism (Fig. 1) (Baron *et al*., 1981). These stages were defined originally using PET techniques in patients with severe atherosclerotic

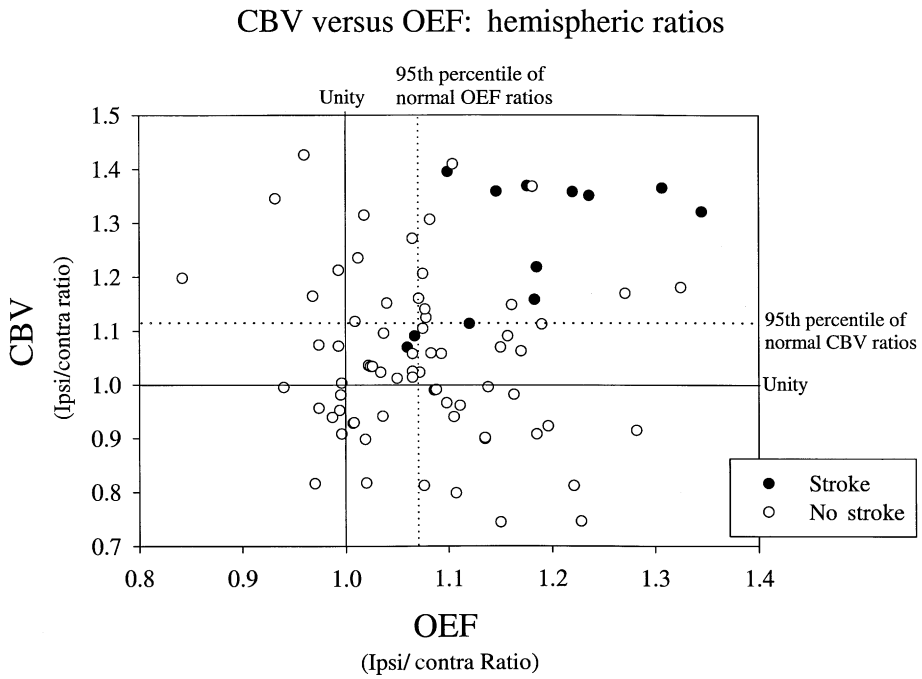

Fig. 2 Plot of ipsilateral to contralateral ratios of CBV versus OEF for all 81 patients. The solid vertical and horizontal black lines indicate unity for ipsilateral to contralateral OEF and CBV ratios, respectively. The 95th percentiles for normal OEF and CBV ratios are indicated by dotted lines. Ten of the 19 patients with increased OEF and CBV (upper right quadrant) had subsequent stroke (solid black circles). This relationship was highly statistically significant (log rank $P < 0.0001$).

carotid artery stenosis or occlusion and have been widely applied in the study of human cerebrovascular disease (Hirano *et al*., 1994; Yamauchi *et al*., 1996; Inao *et al*., 1998). In this sequential model, it was assumed that OEF did not increase until the capacity of autoregulation to maintain flow was exceeded. Increases in OEF would not be expected before CBV increased.

New experimental evidence has suggested that this sequential model is an oversimplification. First, CBF falls slightly through the autoregulatory range, leading to increases in OEF prior to exhaustion of autoregulatory capacity (Heistad and Kontos, 1983; Dirnagl and Pulsinelli, 1990; Schumann *et al*., 1998). Secondly, studies of CBV in the setting of reduced perfusion pressure have reported variable results. Some studies have found minimal or no increase until autoregulatory capacity is exceeded (Schumann *et al*., 1998; Zaharchuk *et al*., 1999), while others have reported CBV increases within the autoregulatory range (Grubb *et al*., 1973, 1975; Ferrari *et al*., 1992).

In the present study, we investigated the relationship between CBV, OEF and other haemodynamic and metabolic factors, as well as stroke risk in a large sample of patients with unilateral carotid artery occlusion enrolled in a prospective study of haemodynamic factors and stroke risk (Grubb *et al*., 1998). We undertook this study in order to define the haemodynamic and metabolic changes that occur with carotid occlusive disease and to determine if these data were consistent with the two-stage sequential haemodynamic model.

Methods

The material for this analysis was drawn from a retrospective analysis of clinical and haemodynamic data from 81 patients with symptomatic carotid artery occlusion enrolled in the STLCOS (St Louis Carotid Occlusion Study), a blinded prospective study of cerebral haemodynamics and stroke risk. The details of the overall study design of the STLCOS can be found in previous publications describing the analysis of baseline clinical, haemodynamic and epidemiological stroke risk factors (Derdeyn *et al*., 1998), and the primary outcome analysis (Grubb *et al*., 1998).

Subjects

At enrolment, and just prior to PET examination, each patient underwent neurological evaluation including detailed questioning regarding any symptoms. Focal ischaemic symptoms in the territory of the occluded carotid artery were categorized as cerebral TIA (transient ischaemic attack) (<24 h duration), cerebral infarct (>24 h duration) or retinal event (any duration), and as single or recurrent episodes. Times from

the first and the most recent ischaemic symptoms were recorded. The presence or absence of 17 known risk factors for stroke was recorded (Derdeyn *et al*., 1998). A study investigator reviewed pertinent medical records, CT or MRI scans, and angiograms. Specific imaging and angiographic data were recorded on a standardized form.

Patients were followed by the study coordinator for the duration of the study by telephone contact every 6 months with the patient or next of kin. The interval occurrence of any symptoms of cerebrovascular disease, other medical problems and functional status was determined. The occurrence of any symptoms suggesting a stroke was evaluated thoroughly by one designated (and blinded) investigator based on history from the patient or eyewitness and review of medical records ordered by the patient's physician. If necessary, follow-up neurological examination and brain imaging were arranged. This investigator remained blinded to the PET data. All living patients were followed for the duration of the study.

Eighteen normal control subjects aged 19–77 (mean $\pm$ standard deviation, 45 $\pm$ 18) years were recruited by public advertisement. Eight were female, 10 were male. All underwent neurological evaluation, MRI of the head and duplex ultrasound imaging of the extracranial carotid arteries.

Haemodynamic and metabolic measurements

Haemodynamic PET studies on patients with carotid occlusion were performed on study entry. Blood pressure was measured in the clinic prior to walking to the scanner suite. After positioning the patient on the scanner gantry, an individually moulded thermoplastic face mask was applied to ensure that the patient's head remained in a constant position during the scanning period. The exact position of the patient's head relative to the scanning plane was recorded on a lateral skull film obtained after head immobilization. Venous and, when possible, arterial catheters were placed for intravenous radiotracer administration and for arterial blood gas analyses and arterial time–activity curve determination, respectively. All PET studies were performed on one of two scanners (ECAT 953B or ECAT EXACT HR, Siemens/CTI, Knoxville, Tenn., USA) in 2D mode. A transmission scan was performed before radiotracer administration using germanium-68/gallium-68 rotating rod sources.

Each PET study consisted of three separate physiological studies. During each, arterial blood samples were collected in order to convert quantitative regional radioactivity data to quantitative physiological measurements. Additional arterial samples were drawn at intervals during the examination for determination of $PaCO_2$ stability, mean arterial oxygen content calculations and carboxyhaemoglobin content. First, a 5-min scan was obtained 2 min after inhalation of one or two breaths of air containing 75–100 mCi of ^{15}O-labelled carbon monoxide. After allowing this activity to decay for ~15 min, a 40-s scan was obtained after inhalation of one or two breaths of air containing 75–100 mCi of ^{15}O-labelled oxygen. After another 15 min, the last scan was acquired after the bolus injection of 50–75 mCi of ^{15}O-labelled water. The entire PET examination could be performed within 1 h because of the short half-life (122.2 s) of ^{15}O.

Image processing and analysis

All images were reconstructed using filtered back projection and scatter correction with a ramp filter at the Nyquist frequency. They were then filtered with a three-dimensional Gaussian filter to a uniform resolution of 16 mm full-width half-maximum. These images were transformed subsequently to stereotactic atlas space using the lateral skull film and the transmission scan (Fox *et al*., 1985). This was done to allow reproducible placement of regions of interest.

When combined with the arterial time–activity curve data and the haematocrit, the ^{15}O carbon monoxide image provided the quantitative regional measurement of CBV on a pixel-by-pixel basis (Martin *et al*., 1987; Videen *et al*., 1987). A regional map of quantitative CBF was generated from the ^{15}O water image using arterial time–activity data (Herscovitch *et al*., 1983; Videen *et al*., 1987). The [^{15}O] oxygen image provided the quantitative regional measurement of OEF, once combined with data from processed CBF and CBV images and the arterial time–activity curve information (Mintun *et al*., 1984; Videen *et al*., 1987). $CMRO_2$ images were generated on a pixel-by-pixel basis as the product of OEF, CBF and arterial O_2 content (Mintun *et al*., 1984).

For each patient and normal volunteer, seven separate spherical regions of interest 19 mm in diameter were placed in the territory of the middle cerebral artery in each hemisphere. Each region included grey and white matter and was placed automatically using stereotactic coordinates (Powers *et al*., 1985). Areas of prior infarction were identified by two investigators by review of $CMRO_2$ images as well as CT or MRI examinations. Neither the regions within these areas nor the corresponding contralateral regions were used for analysis. Mean absolute hemispheric values and left to right and ipsilateral and contralateral (relative to the occluded carotid artery) ratios of mean hemispheric values of all haemodynamic and metabolic measurements were calculated for patients and control subjects.

Data analysis for the original study

Complete quantitative studies of CBF, CBV, OEF and $CMRO_2$ were acquired for the 18 normal control subjects and for 68 of the 81 patients. Count-based estimates of OEF were obtained in the remaining 13 patients by a previously described method (Derdeyn *et al*., 1999*b*). The normal range of quantitative OEF ratios was 0.914–1.085 and the range for non-quantitative OEF ratios was 0.934–1.062 (Grubb *et al*., 1998). Based on this range, 39 of the 81 patients had elevated OEF in the hemisphere distal to an occluded carotid artery. A total of 15 strokes occurred in these 81 patients over a mean follow-up period of 3.1 years. All strokes were ischaemic and

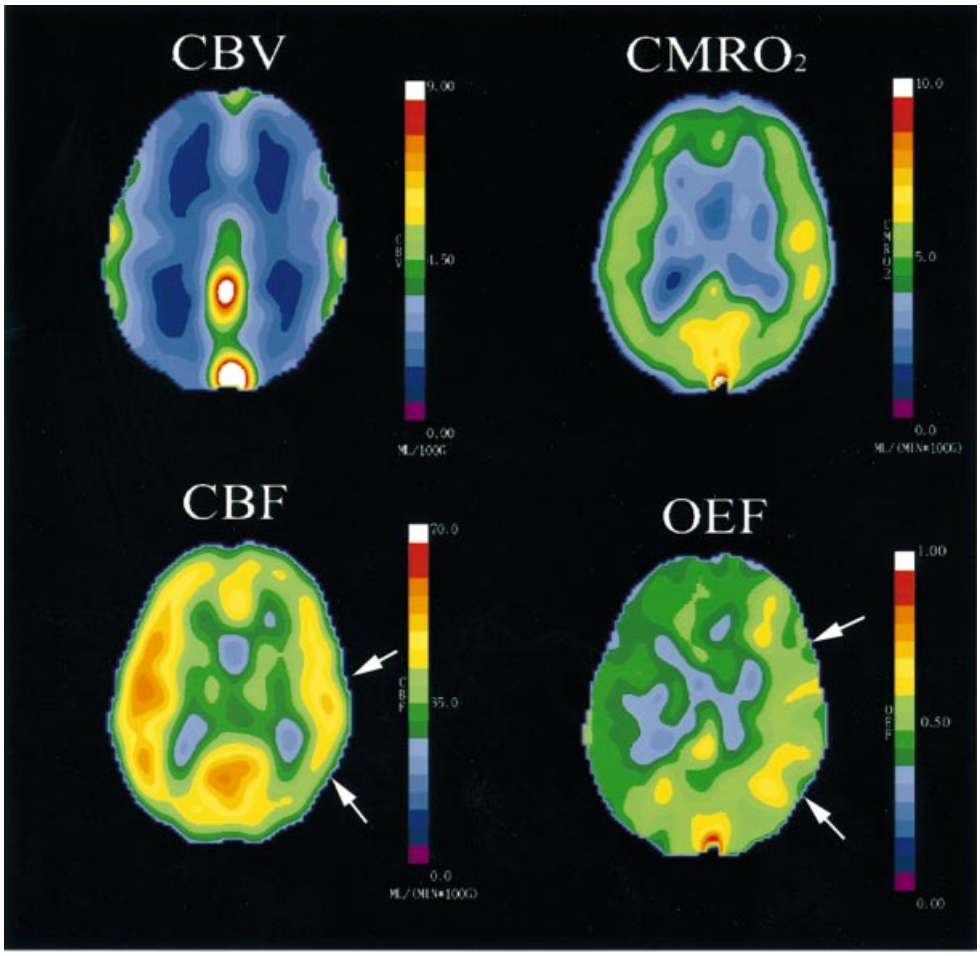

Fig. 3 Increased OEF without increased CBV. CBF is reduced (CBF, arrows) and OEF is increased (OEF, arrow) in order to preserve normal oxygen metabolism. The map of CBV is symmetrical, however. This phenomenon may reflect reductions in perfusion pressure within, and not beyond, the autoregulatory range. The abrupt cut-off of high counts at the periphery of the CBV image is due to a mask used for display purposes to reduce the counts from the skull and scalp appearing on the image due to partial volume effects.

13 occurred in the cerebral hemisphere ipsilateral to the occluded carotid artery. Twelve total and 11 ipsilateral strokes occurred in the 39 patients with increased OEF (Grubb *et al*., 1998).

Data analysis for the present study

Ipsilateral to contralateral ratios of CBF, CBV and $CMRO_2$ were calculated from absolute quantitative hemispheric values for the 68 patients with complete quantitative studies. Count-based CBV ratios were generated for the 13 remaining patients without arterial time–activity curve data. Hemispheric ratios of the counts from ^{15}O-labelled red blood cell scans are identical to hemispheric ratios of quantitative CBV values because of the linear relationship between CBV and PET counts (Martin *et al*., 1987). $CMRO_2$ and CBF data could not be recovered in these patients. The count-based hemispheric ratios of OEF and CBV allowed inclusion of these 13 patients in the outcome analysis, but not in the analysis of the relationship of OEF, CBV and other haemodynamic factors.

Patients were then divided into groups based on comparison of hemispheric ratios and absolute hemispheric values of OEF and CBV with normal controls. Hemispheric ratios falling beyond the 95th percentile and absolute values exceeding 95% confidence limits for OEF and CBV were considered increased. The 95th percentile was employed for the hemispheric ratio data as the use of confidence limits is not valid for ratios. Patients with increased OEF and increased CBV were compared with patients with increased OEF and normal or reduced CBV with regards to stroke risk (using Kaplan–Meier survival curve analysis), haemodynamic and metabolic measurements (Student's *t*-tests) and clinical risk factors for stroke (Student's *t*-test, χ^2 and Mann–

Table 1 *Comparison of haemodynamic and metabolic values of patients with increased OEF and increased CBV versus patients with increased OEF and normal or reduced CBV, measured in the hemisphere distal to an occluded carotid artery*

	CBF (ml/100 g/min)	$CMRO_2$ (ml/100 g/min)	OEF (%)
By hemispheric ratios			
Patients with increased OEF (n = 45)			
Normal or reduced CBV (n = 26)	0.829 ± 0.15 (n = 23)*	0.928 ± 0.10 (n = 23)*	1.14 ± 0.06
Increased CBV (n = 19)	0.776 ± 0.07 (n = 15)*	0.903 ± 0.05 (n = 15)*	1.18 ± 0.09
Student's t-test P value	0.20	0.41	0.07
By absolute ipsilateral values			
Patients with increased OEF (n = 33)			
Normal or reduced CBV (n = 13)	28.4 ± 8.1	2.66 ± 1.2	0.56 ± 0.11
Increased CBV (n = 20)	35.6 ± 8.3	3.12 ± 0.7	0.53 ± 0.08
Student's t-test P value	0.02	0.18	0.40

All values are ± standard deviation. *Complete quantitative CBF and $CMRO_2$ data available for 38 of the 45 with increased OEF by hemispheric ratios. Statistical significance accepted at $P < 0.05$ [0.017 with Bonferroni correction for multiple comparisons (0.05/3)].

Whitney U-tests). Statistical significance was accepted at $P < 0.05$. A Bonferroni correction for multiple comparisons was used for the assessment of haemodynamic and metabolic measurements and clinical risk factors.

Results

Hemispheric ratios

The range of hemispheric CBV ratios in the 18 normal control subjects was 0.824–1.213. The 95th percentile for the CBV ratio was 1.114. The 5th percentile for the CBV ratio was 0.854. The 95th percentile for the OEF ratio from quantitative studies in the normal control subjects was 1.067. The 95th percentile for the count-based OEF ratio technique for the normal control subjects was nearly identical (1.068). Forty-five of the 81 patients had increased OEF, based on these two thresholds (Fig. 2). CBV ratios were within the normal range in 21 of the 45 patients with increased OEF (Figs 2 and 3). Five patients with increased OEF had reduced ipsilateral CBV, with ipsilateral to contralateral hemispheric CBV ratios below the 5th percentile for CBV. Nineteen patients with increased OEF also had increased CBV. An additional 11 patients with OEF ratios in the normal range had increased CBV.

In the 45 patients with complete quantitative PET studies and increased OEF by hemispheric ratios, ipsilateral to contralateral hemispheric ratios of OEF, $CMRO_2$ and CBF were similar between patients with elevated CBV and normal CBV (Table 1). OEF ratios tended to be higher and CBF lower in the patients with increased CBV.

As previously reported, 13 ipsilateral strokes occurred during the mean follow-up period of 3.1 years (Fig. 2). No ipsilateral strokes occurred in the 11 patients with increased CBV and normal OEF (Fig. 2, upper left quadrant made by the dotted 95th percentile lines). Three ipsilateral strokes occurred in patients with CBV ratios below the 95th percentile and elevated or mildly elevated (still within the normal range) OEF ratios. The remaining 10 ipsilateral ischaemic strokes occurred in the 19 patients with increased OEF and increased CBV (log rank $P < 0.0001$, upper right quadrant of Fig. 3).

Baseline clinical risk factors recorded on study enrolment were similar between the 19 patients with increased OEF and CBV and those with increased OEF and normal or reduced CBV (Table 2). No difference in the time from first or last ischaemic symptom to the enrolment PET scan, a possible index of the duration of carotid occlusion, was noted (Table 2). Linear regression analyses of plots comparing CBV ratios with the duration from first or last symptoms to PET were not significant for the entire group of patients or for the subset with increased OEF. No differences in the imaging (CT or MRI) or angiographic findings were identified between the two groups (Table 3). The incidence of >50% stenosis of the contralateral carotid artery was higher in the patients with increased CBV, but this was not statistically significant (Table 3).

Absolute values

Sixty-eight patients had complete quantitative studies of CBV, CBF, OEF and $CMRO_2$. The range of quantitative OEF measured in the normal control subjects was 0.26–0.64 (mean 0.41). The upper 95% confidence limit for OEF was 0.44. Thirty-three of the 68 patients had increased ipsilateral OEF using this threshold. The range of quantitative CBV measured in the normal control subjects was 1.91–3.45 ml/100 g (mean 2.72 ml/100 g). The upper 95% confidence limit for CBV was 2.81 ml/100 g. CBV values were increased (above the 95% confidence limit) in 20 of the 33 patients with increased OEF (Fig. 4). An additional 21 patients with OEF ratios in the normal range had increased CBV.

No significant differences in absolute values of ipsilateral $CMRO_2$ and CBF were found between patients with increased OEF and elevated CBV and those with increased OEF and normal CBV (Table 1). Absolute ipsilateral values of CBF and $CMRO_2$ tended to be lower in patients with

Table 2 *Baseline clinical and laboratory stroke risk factors for patients with increased OEF in the hemisphere distal to an occluded carotid artery*

	Hemispheric ratios		*P* value	Absolute values		*P* value
	Increased CBV (n = 19)	Normal or low CBV (n = 26)		Increased CBV (n = 20)	Normal or low CBV (n = 13)	
Age (years, mean ± SD)	62.4 ± 8.2	65.0 ± 7.6	0.28	64.3 ± 7.2	66.6 ± 9.3	0.42
Gender						
Male	16 (84%)	18 (69%)	0.25	14 (70%)	12 (92%)	0.20
Female	3 (16%)	8 (31%)		6 (30%)	1 (8%)	
Cerebrovascular history						
Cerebral TIA	5 (26%)	7 (26%)	0.30	5 (25%)	3 (23%)	0.42
Cerebral stroke	14 (74%)	16 (62%)		12 (60%)	6 (46%)	
Retinal TIA	0	3 (12%)		3 (15%)	4 (31%)	
Total number of events	11 ± 24	8.9 ± 26	0.76	19 ± 23	10 ± 39	0.63
Recurrent symptoms	11 (58%)	14 (54%)	0.99	6 (30%)	6 (46%)	0.47
Duration of occlusion (median, in days)						
Time from first symptom to PET	–123	–138	0.78	–260	–180	0.71
Time from last symptom to PET	–30	–63	0.14	–60	–30	0.40
Hypertension	12 (63%)	17 (65%)	0.84	13 (65%)	7 (54%)	0.73
Heart disease						
Prior myocardial infarction	3 (16%)	4 (15%)	0.49	3 (15%)	3 (23%)	0.84
Diabetes mellitus	4 (21%)	5 (19%)	0.34	6 (30%)	2 (15%)	0.51
Smoking						
Never	2 (11%)	2 (8%)	0.50	0	2 (15%)	0.32
Past cigarettes	7 (37%)	14 (54%)		12 (60%)	6 (41%)	
Current cigarettes	9 (47%)	10 (38%)		7 (35%)	4 (31%)	
Current pipe or cigar	1 (5%)	0		1 (5%)	1 (8%)	
Alcohol consumption						
None	9 (47%)	16 (62%)	0.63	12 (60%)	7 (54%)	0.87
Drinkers (drinks/day)	1.0 ± 1.2	0.5 ± 1.1	0.44	0.9 ± 1.5	1.1 ± 1.0	0.85
Parental death from stroke	2 (11%)	6 (23%)	0.37	1 (5%)	3 (23%)	0.25
Laboratory results						
Haemoglobin (g/dl)	12.8 ± 1.6	12.7 ± 1.3	0.83	13.0 ± 1.1	12.8 ± 1.7	0.73
Fibrinogen (mg/dl)	381 ± 96	352 ± 72	0.27	404 ± 93	382 ± 102	0.56
HDL cholesterol (mg/dl)	39 ± 10	41 ± 11	0.46	42 ± 14	36 ± 11	0.19
LDL cholesterol (mg/dl)	171 ± 70	144 ± 36	0.11	149 ± 51	163 ± 72	0.59
Triglycerides (mg/dl)	235 ± 135	224 ± 219	0.85	224 ± 140	278 ± 312	0.43

TIA = transient ischaemic attack. Continuous variables, such as laboratory studies and age, are shown as mean values ± standard deviation. Statistical significance accepted at $P < 0.05$ [0.003 with Bonferroni correction for multiple comparisons (0.05/3)].

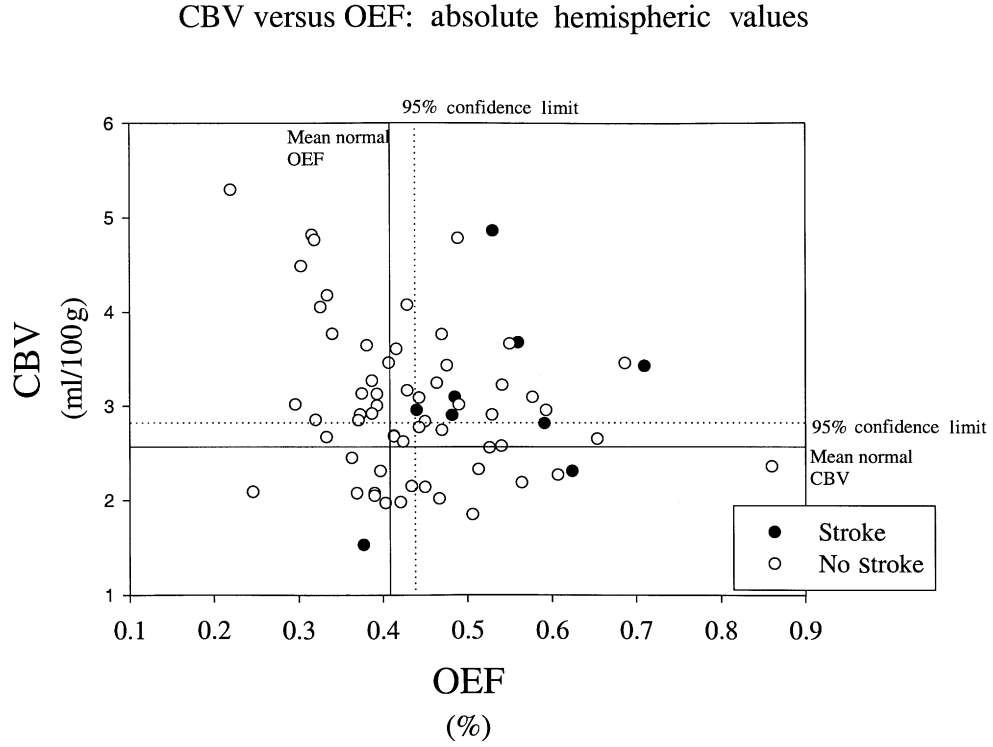

Fig. 4 Plot of absolute ipsilateral values of CBV versus OEF for all 68 patients with complete quantitative PET studies. The solid vertical and horizontal black lines indicate the mean ipsilateral OEF and CBV values for the normal control subjects, respectively. The 95% confidence limits for normal OEF and CBV values are indicated by dotted lines. Seven of the 20 patients with increased OEF and CBV (upper right quadrant) had subsequent stroke (solid black circles). This relationship was highly statistically significant (log rank $P = 0.003$).

increased OEF and normal CBV than in those with increased OEF and increased CBV. These differences were not statistically significant when a Bonferroni correction for multiple comparisons was applied (Table 1).

Nine ipsilateral strokes occurred during the mean follow-up period of 3.1 years in this group of 68 patients (Fig. 4). No ipsilateral strokes occurred in the 21 patients with increased CBV and normal OEF (Fig. 4, upper left quadrant). Eight of the nine ipsilateral strokes occurred in the 33 patients with increased ipsilateral OEF. Seven of these eight strokes occurred in the 20 patients with both increased OEF and CBV (log rank $P = 0.003$, upper right quadrant of Fig. 4). The 17 baseline clinical risk factors recorded on study enrolment were similar between the patients with increased CBV and those with normal or reduced CBV (Table 2). Linear regression analyses of plots comparing CBV values with the duration from first or last symptoms to PET were not significant for the entire group of patients or for the subset with increased OEF. The incidence of >50% stenosis of the contralateral carotid artery was higher in patients with normal or low CBV than in those with high CBV; however, this difference was not statistically significant when a Bonferroni correction for multiple comparisons was applied (Table 3). No other differences in the imaging or angiographic findings were identified between these two groups (Table 3).

Discussion

Two important observations emerge from this analysis. First, increased OEF in the territory of an occluded carotid artery often occurs in the absence of a measurable elevation in CBV. Secondly, patients with carotid occlusion who have both increased OEF and increased CBV are at much higher risk for subsequent ipsilateral stroke than those with increased OEF and normal CBV. These observations were consistent using either hemispheric ratios or absolute values of CBV and OEF. Assuming that the difference in outcome between these two groups reflects differences in the severity of CPP reduction, these data suggest that patients with increased OEF and normal CBV have a lesser degree of haemodynamic impairment than those with both increased OEF and increased CBV. This hypothesis is supported by experimental data.

Table 3 *Arteriographic and imaging characteristics of patients with increased ipsilateral OEF*

	Hemispheric ratios		*P* value	Absolute values		*P* value
	High CBV (n = 19)	Normal or low CBV (n = 26)		High CBV (n = 20)	Normal or low CBV (n = 13)	
Arteriographic						
Contralateral stenosis ⩾50%	6 (32%)	3 (11%)	0.17	1 (5%)	5 (34%)	0.02
Collaterals						
Anterior communicating	12 (63%)	19 (73%)	0.54	12 (60%)	8 (62%)	0.43
Posterior communicating	3 (16%)	7 (27%)		4 (20%)	5 (34%)	
External carotid	6 (32%)	12 (46%)		6 (30%)	6 (43%)	
Leptomeningeal	0	2 (8%)		1 (5%)	1 (8%)	
Imaging (CT or MRI)						
Normal	3 (16%)	6 (23%)	0.88	2 (10%)	6 (43%)	0.09
No. of ROIs placed (infarcted tissue excluded)	6.6 ± 0.7	6.2 ± 1.2	0.55	6.4 ± 0.9	6.5 ± 0.7	0.63
Single infarct	7 (37%)	7 (27%)	0.36	10 (50%)	6 (43%)	0.99

ROI = region of interest. Continuous variables, such as ROIs, are shown as mean values ± standard deviation. Statistical significance accepted at $P < 0.05$ [0.01 with Bonferroni correction for multiple comparisons (0.05/5)].

Fig. 5 Modified model of haemodynamic and metabolic responses to reductions in cerebral perfusion pressure after Powers *et al.* (1987). Point A represents baseline. The distance between points A and B represents the autoregulatory range. The distance between points B and C represents exceeded autoregulatory capacity where CBF falls passively as a function of pressure. Point C represents the exhaustion of compensatory mechanisms to maintain normal oxygen metabolism and the onset of true ischaemia. CBV may not change (Schumann *et al*., 1998; Zaharchuk *et al*., 1999) or may increase (Ferrari *et al*., 1992; Grubb *et al*., 1973, 1975) within the autoregulatory range (between A and B). Once autoregutory capacity is exceeded (between B and C), CBV may increase slightly (10–20%) (Schumann *et al*., 1998; Zaharchuk *et al*., 1999), remain elevated (Grubb *et al*., 1973, 1975) or continue to increase (up to 150%) (Ferrari *et al*., 1992). CBF falls slightly, down to 18%, through the autoregulatory range (between A and B) (Heistad and Kontos, 1983; Dirnagl and Pulsinelli, 1990). Once autoregulatory capacity is exceeded, CBF falls passively as a function of pressure down to 50% of baseline values (between B and C). OEF increases slightly, up to 18%, with the reductions in CBF through the autoregulatory range (between A and B) (Schumann *et al*., 1998). After autoregulatory capacity is exceeded and flow falls up to 50% of baseline, OEF may increase up to 100% from baseline (McHenry *et al*., 1961). $CMRO_2$ remains unchanged throughout this range of CPP reduction (between A and C), due to both autoregulatory vasodilation and increased OEF (McHenry *et al*., 1961; Grubb *et al*., 1975).

Slight reduction in CBF through the autoregulatory range is a well-documented phenomenon. Dirnagl and Pulsinelli (1990) conclusively demonstrated progressive reduction of CBF through the autoregulatory range. They plotted 399 measurements of CBF from 816 probes in eight lightly anaesthetized rats during pharmacologically induced hyper- and hypotension. They found a 2.9% change in CBF for each 10 mmHg change in systolic arterial pressure through the autoregulatory range. These data are consistent with several

other experimental studies, demonstrating 2–7% changes in CBF for each 10 mmHg change through the autoregulatory range (Heistad and Kontos, 1983).

With this reduction in CBF, a compensatory increase in OEF would be required to maintain normal oxygen metabolism (Fig. 5). Schumann *et al*. (1998) recently demonstrated this compensatory response. They found an 18% increase in OEF occurring within the autoregulatory range in a PET study of experimental global hypotension in baboons. This was associated with a slight decrease in CBF (not statistically significant). These data are also consistent with studies showing preserved vasodilatory capacity in regions with increased OEF. Kanno *et al*. (1988) measured increases in absolute OEF prior to exhaustion of vasodilatory capacity to CO_2 in 11 of 19 patients with occlusive cerebrovascular disease (moya-moya disease or atherosclerosis).

The physiological significance of CBV is difficult to interpret. Pial window studies during acute reductions of perfusion pressure through the autoregulatory range and beyond in animals consistently have found dilation of arteries and veins on the surface of the brain (Forbes, 1928; Fog, 1937; Kontos *et al*., 1978; MacKenzie *et al*., 1979; Auer *et al*., 1987). CBV is a more complex physiological parameter. It is composed of arterial, capillary and venous compartments, as well as parenchymal and pial components. The vasodilatory response of these different compartments to reduced perfusion pressure is variable (Kontos *et al*., 1978; Zaharchuk *et al*., 1999).

Studies of CBV in the setting of reduced perfusion pressure have reported variable results (Fig. 5). Some investigators have reported increases within the autoregulatory range (Grubb *et al*., 1973, 1975; Ferrari *et al*., 1992), while others have found minimal or no increase until autoregulatory capacity is exceeded (Schumann *et al*., 1998; Zaharchuk *et al*., 1999). Several decades ago, Grubb *et al*. (1973, 1975) demonstrated that CBV, measured with X-ray fluorescence or intracarotid radiotracers, increased with reductions in CPP produced by reductions in mean arterial pressure and increases in intracranial pressure, respectively. Animal studies of haemorrhagic hypotension by Ferrari *et al*. (1992) also reported increases in CBV within the autoregulatory range. In this study, CBV was calculated from independent measurements of CBF and mean transit time of an intravascular tracer. Schumann *et al*. (1998) found significant increases in CBV beyond, but not within the autoregulatory range in PET studies of experimental hypotension in baboons. Similar data were reported by Zaharchuk *et al*. (1999). In studies of experimental hypotension in rats, they found no increase in CBV through the autoregulatory range and a modest increase with further reductions in arterial pressure. These increases were greater on the cortical surface (21%) than in deeper structures (10%).

These discrepant results may be due to methodological differences. Different animal preparations, differential sensitivity to different vascular beds or differences in accuracy or precision for detecting small changes in CBV could all be operational. However, in carefully studying these reports, there is no obvious methodological reason for the variable CBV response to reduced CPP. Further examination of the individual published data by Grubb *et al*. (1975) indicates that the CBV change was variable from animal to animal, and that the range of that data encompassed the range of changes reported by these other authors (Schumann *et al*., 1998; Zaharchuk *et al*., 1999). Thus, there may be individual biological variability in the cerebral vasodilatory response to reduced CPP.

There are other possible mechanisms for the phenomenon of normal CBV in patients with increased OEF. One potential cause for normal or reduced CBV values is reduced metabolic demand. CBV falls when the metabolic activity of the tissue falls, due to either local or remote neuronal injury (diaschisis) (Baron *et al*., 1989; Sette *et al*., 1989; Yamauchi *et al*., 1994). In the present data, however, we found no significant difference in $CMRO_2$ between patients with increased OEF and increased CBV and those with normal or reduced CBV (Table 1).

Sette *et al*. (1989) noted the phenomenon of increased OEF associated with normal CBV and proposed a metabolically mediated vasconstriction, associated with the vascular collapse that may occur with severe reductions in perfusion pressure, to account for their observations. Based on CBF/CBV ratios, they considered these patients to have greater reductions in perfusion pressure than those with increased OEF and increased CBV. They studied four patients with carotid occlusion and found regions with reduced absolute ipsilateral values of CBF, increased OEF and normal CBV. $CMRO_2$ was slightly reduced in these areas as well. Our haemodynamic and metabolic data are similar, but are not entirely consistent with their hypothesis. While absolute values of CBF and, to a lesser extent, absolute values of $CMRO_2$ and hemispheric ratios of CBF were lower in patients with increased OEF and normal CBV (Table 1), these reductions were not statistically significant. It should be noted, however, that the reduction in absolute ipsilateral CBF would have reached statistical significance if no Bonferroni correction had been applied ($P = 0.02$). No evidence for reduced metabolism was present when patients were grouped by hemispheric ratios (Table 1). Importantly, the outcome data from the present study suggest that patients with increased OEF and normal CBV have less severe haemodynamic impairment than those with increased OEF and increased CBV. If the normal CBV values in patients with increased OEF were caused by reductions in the diameter of previously dilated vessels, secondary to severe reductions in intraluminal pressure, one would expect a higher risk of stroke in the patients with increased OEF and normal CBV than those with increased OEF and increased CBV. In our data, patients with increased OEF and increased CBV had a higher risk of stroke, suggesting that the degree of haemodynamic impairment is more, not less, severe in these patients.

The proposed model (Fig. 5) does not address two issues regarding the haemodynamic and metabolic effects of chronic reductions in perfusion pressure. First, bilateral hemispheric reductions in absolute $CMRO_2$ have been found in patients with unilateral carotid occlusion (Gibbs *et al*., 1984; Samson *et al*., 1985). Gibbs *et al*. reported haemodynamic and metabolic data for 32 patients with unilateral and bilateral carotid occlusions. They grouped their data by anatomy: contralateral hemisphere and ipsilateral hemisphere for unilateral occlusions, and both hemispheres for bilateral occlusions. Absolute hemispheric values of $CMRO_2$ were significantly lower than normal control values in all three groups. No difference between the three groups was seen, however. Incidentally, CBV was the highest in the group with bilateral carotid occlusion. In the present study, we observed a trend for an association between contralateral carotid stenosis (>50%) and lower, not higher CBV ($P = 0.02$). This association is probably due to chance, as it was not significant when the Bonferroni correction for multiple comparisons was applied.

Additionally, improvement in CBF and $CMRO_2$ in both hemispheres has been reported after extra-/intracranial bypass or with increased mean arterial pressure in selected patients (Samson *et al*., 1985, 1987). The nature of this phenomenon remains unclear. However, it does not appear that the variability in CBV observed in the present study is related to these metabolic changes, as we found no significant difference in $CMRO_2$ between patient groups.

Secondly, there are temporal factors regarding haemodynamic status that are poorly defined. Improved vasodilatory capacity over time has been shown in patients with carotid occlusion with transcranial Doppler (Widder *et al*., 1994). In a subset of patients from the STLCOS studied with follow-up PET, we found significant increases in CBF and improvement in OEF over time (Derdeyn *et al*., 1999*c*). We attributed this to an increase in flow through collateral channels. It is possible that vasodilatory capacity may improve before an improvement in blood flow, as suggested by Sette *et al*. (1989), although our data suggest that, if present, this compensatory mechanism may be independent of oxygen metabolism. One argument against this hypothesis is that we found no relationship between the time from first or last symptom and the enrolment PET scan, factors that might indicate the duration of occlusion.

The methods used for the measurement of CBV and OEF by PET are well validated (Mintun *et al*., 1984; Martin *et al*., 1987; Videen *et al*., 1987). The ^{15}O-labelled carbon monoxide CBV technique uses red cells as the tracer and requires assumptions regarding cerebral haematocrit (Martin *et al*., 1987). Yamauchi *et al*. (1998) reported reductions in cerebral haematocrit with chronic ischaemia. Despite this potential cause for low values of CBV, measurements of CBV in their study, using the same method as the present, were increased in regions with increased OEF and decreased CBF.

In conclusion, the data presented in this report support two modifications of the original model for chronic haemodynamic impairment (Powers *et al*., 1987) (Fig. 5): first, slight decreases in CBF lead to measurable increases in OEF through the autoregulatory range of perfusion pressure reduction (Schumann *et al*., 1998); and secondly, CBV measurements may be variable through the autoregulatory range. The higher risk of ischaemic stroke in patients with carotid occlusion and both increased OEF and CBV suggests that their degree of haemodynamic compromise is more severe than those with increased OEF and normal CBV. In patients with chronic carotid occlusion and increased OEF, increased CBV may indicate pronounced vasodilation due to exhausted autoregulatory vasodilation. The physiological explanation for the measurement of normal CBV in patients with increased OEF is less certain and may reflect preserved autoregulatory capacity.

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