Cerebral Hemodynamics in Relation to Patterns of Collateral Flow

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Background and Purpose—We sought to investigate the relation between collateral flow via different pathways and hemodynamic parameters measured by dynamic susceptibility contrast–enhanced MRI in patients with severe carotid artery disease.

Methods—Dynamic susceptibility contrast–enhanced MRI was performed in 66 patients and 33 control subjects. Patients had severe stenosis (>70%, n=12), unilateral occlusion (n=38), or bilateral occlusion (n=16) of the internal carotid artery (ICA). Cerebripetal flow and collateral flow via the circle of Willis were investigated with MR angiography. Collateral flow via the ophthalmic artery was investigated with transcranial Doppler sonography.

Results—Patients with ICA stenosis had well-preserved cerebral perfusion and were in general not dependent on collateral supply. Patients with unilateral ICA occlusion had impaired cerebral perfusion. However, appearance time, peak time, and mean transit time in white matter were less increased in patients with than in patients without collateral flow via the circle of Willis ($P<0.05$). Furthermore, patients with collateral flow via both anterior and posterior communicating arteries had less increased regional cerebral blood volume than patients with collateral flow via the posterior communicating artery only ($P<0.05$). Patients with bilateral ICA occlusion had severely compromised hemodynamic status despite recruitment of collateral supply.

Conclusions—In patients with unilateral ICA occlusion, the pattern of collateral supply has significant influence on hemodynamic status. Collateral flow via the anterior communicating artery is a sign of well-preserved hemodynamic status, whereas no collateral flow via the circle of Willis or flow via only the posterior communicating artery is a sign of deteriorated cerebral perfusion. **(*Stroke*. 1999;30:1432-1439.)**

Key Words: carotid artery diseases ■ collateral circulation ■ magnetic resonance imaging ■ perfusion

Severe atherosclerosis of the internal carotid artery (ICA) may lead to symptoms of transient retinal or cerebral ischemia and an increased risk of stroke.[1–4] At present it is difficult to determine with certainty whether the cerebral or retinal problems experienced by these patients are mainly of hemodynamic or of thromboembolic origin.[5–8] Therefore, knowledge of hemodynamic status may be important to elucidate the hemodynamic contribution to the symptoms. In the individual patient, cerebral perfusion is dependent not only on the degree of stenosis but also on the patency of collateral pathways.[5,8–14] Several collateral pathways may contribute to cerebral perfusion in patients with severe carotid artery disease. Collateral flow via the circle of Willis is considered the primary collateral pathway. These collaterals consist of cross-flow through the anterior communicating artery toward the hemisphere ipsilateral to the most severe ICA lesion, posterior to anterior flow through the ipsilateral posterior communicating artery, or both these systems.[5,11,15,16] Reversed flow through the ophthalmic artery and blood flow via leptomeningeal vessels are considered secondary collateral pathways.[5,11,15,16] Conflicting results have been published on the importance of each of these pathways, especially on the role of the anterior versus posterior communicating artery.[15,17–20] Moreover, the recruitment of collateral pathways is also dependent on the distribution of cerebripetal blood flow over the ICAs and the basilar artery.

Impaired hemodynamics in patients with severe carotid artery disease can be demonstrated by perfusion-weighted MRI.[21–25] The clinically most frequently used method is dynamic susceptibility contrast–enhanced (DSC) MRI, which is based on analysis of an intravenously injected bolus of contrast material. Analysis of the time-concentration curves per pixel yields hemodynamic parameter maps with relative values of regional cerebral blood volume (rCBV), mean transit time (MTT), time of appearance (TA), and time to peak (TP).

The aim of this study was to investigate the relation between the type of collateral supply and cerebral hemodynamic parameters as measured with DSC MRI in patients with stenosis or occlusion of the ICA.

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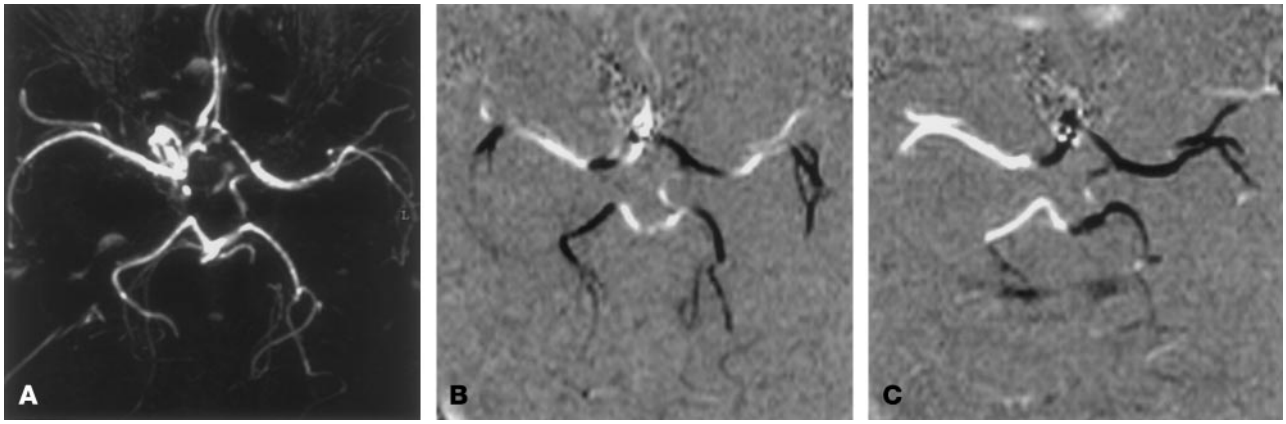

Figure 1. Example of MR angiography images of the circle of Willis of a patient with a left-sided occlusion of the ICA. A, Maximum-intensity projection of a 3-dimensional TOF investigation; B, 2-dimensional phase-contrast directional flow image with flow sensitivity in the anterior-posterior direction (flow in the anterior direction is black, and flow in the posterior direction is white); C, 2-dimensional phase-contrast directional flow image with flow sensitivity in the left-right direction (flow in the left direction is black, and flow in the right direction is white). Collateral flow from the right to the left hemisphere via the anterior communication artery and collateral flow via the left posterior communicating artery can be seen in this patient.

Subjects and Methods

Patients

Sixty-six patients (56 men, 10 women) with severe carotid artery disease and 33 control subjects were included in this study. Patients ranged in age from 35 to 92 years (mean age, 61±11 years). In the 6 months before investigation, 41 patients suffered from (minor) stroke, 12 patients experienced transient ischemic attacks, and 13 patients had transient or chronic ischemia of the eye. In all patients, the symptomatic hemisphere or eye corresponded to the side of most severe carotid artery disease. Symptomatic side was left in 37 and right in 29 patients. Patients were divided into 3 groups: 12 patients had ICA stenosis of >70% (mean, 76±10%), with a less severe contralateral stenosis (mean, 30±27%); 38 patients had unilateral ICA occlusion, with mild contralateral ICA stenosis (mean, 31±35%); and 16 patients had bilateral ICA occlusion. Occlusion or stenosis of the ICA was proven by intra-arterial digital subtraction angiography. Percent stenosis was determined from angiography by the use of North American Symptomatic Carotid Endarterectomy Trial criteria.[6] In none of the patients were abnormalities in the posterior circulation found. DSC MRI and cerebripetal flow measurements were performed at the same time in all patients.

Control subjects (20 men, 13 women) ranged in age from 40 to 81 years (mean age, 55±11 years) and were selected from an age-matched group (n=52) of patients who underwent MRI to exclude the presence of an acoustic neurinoma. Subjects with a tumor or any other abnormality at MRI of the cerebrum (n=19) were excluded. The age composition of the patient groups and the control subjects was not significantly different at the 0.05 level (Student's *t* test).

Informed consent was obtained from all subjects before examination. Study protocols were approved by the Human Research Committee of our hospital.

MR Investigation

All MR investigations were performed on a whole body system operating at 1.5 T (Gyroscan ACS-NT 15, Philips Medical Systems). Overall imaging time was ≈35 minutes.

MR Imaging

Conventional anatomic imaging consisted of a sagittal T1-weighted spin-echo sequence (repetition time [TR], 545 ms; echo time [TE], 15 ms; 19 slices of 4-mm thickness with a 0.6-mm interslice gap; 225-mm field of view [FOV]; and a 256×256 matrix) and a transaxial double-echo T2-weighted spin-echo sequence (TR, 2000 ms; TE, 20 and 100 ms; 19 slices of 7-mm thickness with a 1.5-mm interslice gap; 225-mm FOV; and a 256×256 matrix).

Additionally, 5 slices were imaged to match perfusion-weighted imaging. This additional imaging was used for region-of-interest definition and consisted of inversion recovery turbo spin-echo imaging (TR, 2200 ms; TE, 14 ms; inversion recovery delay, 300 ms; turbo spin-echo factor, 4; 90° flip angle; 5 slices of 8-mm thickness with a 2-mm interslice gap; 230-mm FOV; and a 256×256 matrix) and T2-weighted turbo spin-echo imaging (TR, 2000 ms; TE, 100 ms; turbo spin-echo factor, 6; 90° flip angle; 5 slices of 8-mm thickness with a 2-mm interslice gap; 230-mm FOV with 80% reduced field of view; reduced acquisition 60% [60% of data points acquired]; and a 256×256 matrix). The 5 slices were divided into 2 stacks: 4 slices were positioned with the central slices through the centrum semiovale, and the fifth slice was positioned through the cerebellum.

MR Angiography

Flow through the 2 ICAs and the basilar artery was measured with MR angiography. For the collateral vessels, the diameter is too small to reliably measure flow quantitatively. However, MR angiography can visualize patency of collateral flow via the circle of Willis. Data on collateral flow via the circle of Willis were available in 60 patients.

To visualize the circle of Willis, 50 slices were obtained with a 3-dimensional MR angiography time-of-flight (TOF) technique (TR, 31 ms; TE, 6.9 ms; 2 signals acquired; 20° flip angle; 1.2-mm slice thickness with a 0.6-mm overlap; 100-mm FOV; and a 128×128 matrix). These images were reconstructed in the transverse oblique plane with a maximum intensity projection algorithm (Figure 1A).

The direction of blood flow in the A1 segments of the anterior communicating artery and in the posterior communicating arteries was measured with a 2-dimensional phase-contrast method. This measurement was performed twice, once with phase encoding in the anterior-posterior direction and once in the left-right direction (TR, 16 ms; TE, 9.1 ms; 7.5° flip angle; 8 signals acquired; 13-mm slice thickness; 250-mm FOV; 256×256 matrix; and velocity sensitivity of 40 cm/s). Velocity sensitivity was chosen high enough such that no aliasing effects influenced the flow directions measured. Two collateral pathways were studied: (1) collateral flow through the anterior communicating artery with reversed flow in the A1 segment on the symptomatic side and (2) posterior-to-anterior flow through the ipsilateral posterior communicating artery (Figure 1B and 1C). The presence and direction of flow through the collateral pathways were independently evaluated by 2 of the authors (K.J. van E. and J. van der G.). Discrepancies between the 2 readings were reevaluated in a consensus reading.

Cerebripetal blood flow was investigated by nontriggered 2-dimensional phase-contrast flow measurements[26] through the ICAs and basilar artery at the level of the base of the skull (TR, 16 ms; TE, 9 ms; 7.5° flip angle; 8 signals acquired; 5-mm slice thickness; 250-mm FOV; 256×256 matrix; and velocity sensitivity of 100 cm/s). Flow

values were obtained by integrating across manually drawn regions of interest, which enclosed the vessel lumen as closely as possible.

Perfusion-Weighted Imaging

For perfusion-weighted imaging, 5 slices were imaged with a T2-weighted gradient echo sequence with echo-planar imaging (TR, 260 ms; TE, 30 ms; 9 echos per excitation; 30° flip angle; 230-mm FOV; 70% reduced FOV; 10-mm slice thickness; reduced acquisition 70%; 128×128 matrix; and 5 dummy scans and 50 dynamic scans with a time resolution of 1.5 seconds). Four slices were positioned in the centrum semiovale and the fifth through the cerebellum, corresponding to anatomic, inversion recovery, and T2-weighted imaging. Nine seconds after the start of the acquisition, a contrast bolus of 30 mL gadopentetate dimeglumine (Gd-DTPA^{2+}, Magnevist, Shering AG) was injected in 6 seconds by means of an MR-compatible injection pump (5 mL/s) (Spectris MR Injector, Medrad). The infusion line was prefilled with contrast, and the injection was immediately followed by a saline flush (10 mL saline: 5 mL at 5 mL/s followed by 5 mL at 2 mL/s). Perfusion maps were constructed offline on a clinical workstation. For each voxel in the dynamic data sets, time-intensity curves were converted into time-concentration curves, which were subsequently fitted by a gamma-variate function.[27] Curve fitting was performed by the downhill simplex method in multidimensions.[28] MTT, TA, and TP maps were expressed in time units (seconds), whereas rCBV was expressed in arbitrary units. Regions of interest for both hemispheres, white matter, and gray matter were defined by segmentation of inversion recovery images corresponding to the 5 perfusion-weighted imaging slices. Lesions were excluded on corresponding T2-weighted images. Segmentation was performed on a UNIX workstation (HP 9000/750) with the use of an image analysis package (Analyze, Mayo Foundation). [29] rCBV, MTT, TA, and TP data were averaged over the relevant regions of interest of the 4 cerebral slices. To allow interpatient comparison of hemodynamic parameters, data were normalized over the cerebellum; the hemodynamic parameters (rCBV, MTT, TA, and TP) for the hemispheres were divided by the corresponding values for the entire cerebellum. Throughout this report, even when not explicitly stated, normalized hemodynamic parameters are considered.

Transcranial Doppler Sonography

Collateral flow via the ophthalmic artery can be detected by transcranial Doppler sonography. The direction of blood flow was determined in the ophthalmic artery on the symptomatic side, with reversed flow indicating collateral circulation. Transcranial Doppler sonography examination was performed with a Multidop-X device (DWL) and a 4-MHz probe. Data on collateral flow via the ophthalmic artery were available in 56 patients; if the flow direction was uncertain or if the vessel was not found, it was considered a missing value and was not included in the statistical analysis.

Data Analysis

Patients were divided into 3 groups on the basis of the severity of obstruction of the ICAs: stenosis, unilateral occlusion, or bilateral occlusion. Hemodynamic parameters of symptomatic and asymptomatic hemispheres were compared between control subjects and patient groups. Hemodynamic parameters were studied for the whole hemisphere and for white and gray matter separately. One-way ANOVA was performed to reveal differences between groups. If differences were found, hemodynamic parameters were compared between groups by Student's *t* tests with Dunn's multiple comparison procedure.

For all 3 groups of patients, the presence of primary and secondary collateral pathways was investigated. Within the 3 groups, patients were divided into subgroups on the basis of recruitment of collateral pathways. Between those subgroups, differences were investigated in hemodynamic parameters of the symptomatic hemisphere with Student's *t* tests with Dunn's multiple comparison procedure.

Additionally, individual hemodynamic parameters for all patients were plotted against the pattern of division of total cerebripetal flow over the ICAs and the basilar artery to determine the anterior/posterior flow ratio. This ratio was calculated by summing the flow through both ICAs and dividing this sum by the flow through the basilar artery. Pearson correlation was calculated between hemodynamic parameters and cerebripetal anterior/posterior flow ratio. Because patients with bilateral occlusion differed significantly from the other patients, correlation was calculated with these patients included and also with these patients excluded.

In all statistical analyses a value of $P<0.05$ was considered statistically significant.

Results

Table 1 shows hemodynamic parameters of the symptomatic hemispheres for 3 groups of patients: patients with ICA stenosis, unilateral ICA occlusion, and bilateral ICA occlusion. Data are shown for the symptomatic hemisphere and for gray and white matter of the symptomatic hemisphere separately. Compared with control subjects, patients with severe ICA stenosis showed significantly increased TA and TP in the symptomatic hemisphere in both white matter and gray matter, reflecting a prolonged pathway of blood to reach the tissue, whereas rCBV and MTT were not increased. In patients with unilateral ICA occlusion, MTT, TA, and TP were increased in the symptomatic hemisphere in both white matter and gray matter. rCBV showed a small increase, which was statistically significant only for rCBV in white matter. Finally, in patients with bilateral occlusion, hemodynamic status was severely impaired: all hemodynamic parameters were significantly increased in the symptomatic hemisphere, in both white matter and gray matter, compared with control subjects.

In patients with an ICA stenosis, none of the hemodynamic parameters in the asymptomatic hemisphere were different from control values. In patients with unilateral ICA occlusion, TA was increased in the asymptomatic hemisphere (0.99), white matter (1.04), and gray matter (0.98) ($P<0.01$). In patients with bilateral occlusion, all perfusion parameters were significantly increased in the asymptomatic hemisphere compared with control values in both hemispheres (rCBV=1.02, MTT=1.11, TA=1.06, TP=1.06), white matter (rCBV=0.56, MTT=1.16, TA=1.12, TP=1.11), and gray matter (rCBV=1.33, MTT=1.09, TA=1.04, TP=1.05) ($P<0.01$).

Presence of Collateral Pathways

Severe ICA Stenosis

Table 2 shows that for the group of 12 patients with severe ICA stenosis, in 9 patients collateral flow of the circle of Willis could be assessed. Of these, 2 showed primary collateral flow (1 via the anterior communicating artery and 1 via the posterior communicating artery). The direction of ophthalmic artery flow was known in 10 patients with severe ICA stenosis. Of these, only 1 showed reversed flow (the same patient who had collateral flow via the anterior communicating artery).

Unilateral ICA Occlusion

Primary collateral flow data were available in 36 of the 38 patients with unilateral ICA occlusion (Table 2): 30 patients had collateral flow via the circle of Willis, of whom 17 were via the anterior communicating artery only, 6 via the symptomatic posterior communicating artery only, and 7 via both arteries. In the 6 patients in whom no primary collateral flow could be found, flow direction in the ophthalmic artery was reversed in 5 and unknown in 1. For the whole group, data on direction of ophthalmic artery flow were known in 30

TABLE 1. Hemodynamic Parameters for Control Subjects and Patients

DSC MRI Data (Symptomatic Hemisphere)	Control Subjects (Both Hemispheres) (n=66)	Patient Groups (Symptomatic Hemisphere)		
		Stenosis (n=12)	Unilateral Occlusion (n=38)	Bilateral Occlusion (n=16)
Hemisphere				
rCBV	0.80±0.17	0.76±0.11	0.88±0.20	1.01±0.25†
MTT	0.99±0.05	1.00±0.04	1.07±0.10†	1.12±0.11†
TA	0.98±0.03	1.01±0.04†	1.04±0.05†	1.07±0.04†
TP	0.98±0.03	1.01±0.03†	1.04±0.05†	1.07±0.04†
Gray matter				
rCBV	1.00±0.22	0.95±0.17	1.10±0.26	1.29±0.33†
MTT	0.99±0.05	1.00±0.05	1.06±0.09†	1.11±0.11†
TA	0.96±0.02	1.00±0.05†	1.03±0.05†	1.06±0.04†
TP	0.97±0.03	1.01±0.04†	1.04±0.05†	1.06±0.04†
White matter				
rCBV	0.40±0.08	0.39±0.05	0.50±0.16†	0.55±0.16†
MTT	1.00±0.07	0.99±0.09	1.13±0.15†	1.18±0.13†
TA	1.01±0.03	1.05±0.05†	1.10±0.06†	1.13±0.05†
TP	1.00±0.03	1.03±0.05*	1.09±0.07†	1.11±0.04†

Mean normalized hemodynamic parameters for control subjects (33 control subjects; hemispheres are pooled: n=66) and symptomatic hemispheres of patients with severe ICA disease (n=66) are shown. Patients were divided into 3 groups on the basis of severity of obstruction of the ICA: ICA stenosis, unilateral ICA occlusion, or bilateral ICA occlusion.

*$P<0.05$, †$P<0.01$, patients vs control subjects.

patients, of whom 23 had reversed flow. Patients with normal flow direction in the ophthalmic artery all had collateral flow via the circle of Willis.

Bilateral ICA Occlusion

Primary collateral flow data were available in 15 of the 16 patients with bilateral ICA occlusion (Table 2): 10 showed primary collateral flow via the posterior communicating artery, and 5 did not. Of the 5 patients without primary collateral flow, 4 had reversed ophthalmic artery flow, whereas 1 did not. For the whole group, direction of ophthalmic artery flow was reversed in 14 patients and was normal in 2.

TABLE 2. Presence of Primary and Secondary Collateral Flow

	Patients With Flow Via Specific Pathway, %		
	Stenosis	Unilateral Occlusion	Bilateral Occlusion
Circle of Willis	(n=9)	(n=36)	(n=15)
No collateral flow	78	17	33
ACoA	11	47	0
PCoA	11	17	67
Both ACoA and PCoA	0	19	0
Ophthalmic artery	(n=10)	(n=30)	(n=16)
Normal flow direction	90	23	13
Reversed flow direction	10	77	87

If data were not available, patients were excluded from the analysis (number of patients included is indicated). Pathways studied were circle of Willis (no primary collateral flow, via anterior communicating artery [ACoA], via posterior communicating artery [PCoA], or via both ACoA and PCoA and ophthalmic artery (normal or reversed flow direction).

Collateral Flow in Patients With ICA Stenosis

Hemodynamic Status in Relation to Collateral Flow

Because collateral flow was found in only 2 patients, no useful statistical comparison could be made between patients with and without collateral flow.

Collateral Flow in Patients With Unilateral ICA Occlusion

Hemodynamic Status in Relation to the Circle of Willis

Table 3 shows hemodynamic parameters of the symptomatic hemisphere of patients with unilateral ICA occlusion, subdivided into those with and those without collateral flow via the circle of Willis. Compared with control subjects (Table 1), both patients with and without collateral flow via the circle of Willis had increased MTT, TA, and TP in the symptomatic hemisphere, white matter, and gray matter ($P<0.01$) and increased rCBV in white matter ($P<0.01$). Comparison of hemodynamic data between the 2 subgroups showed that patients without primary collateral flow overall had more severely deteriorated hemodynamic parameters. This difference was statistically significant for TA and TP in the symptomatic hemisphere, gray matter, and white matter ($P<0.05$) and for MTT in white matter ($P<0.05$).

Table 4 shows the hemodynamic parameters of patients with collateral flow via the circle of Willis, further subdivided into those with collateral flow via the anterior communicating artery, posterior communicating artery, or both. Compared with control subjects (Table 1), different hemodynamic changes were found for the 3 subgroups. In patients with collateral flow via the anterior communicating artery, MTT, TA, and TP were increased in the symptomatic hemisphere, gray matter, and white

TABLE 3. Unilateral ICA Occlusion: Hemodynamic Parameters in Relation to Flow Via the Circle of Willis

DSC MRI (Symptomatic Hemisphere)	Collateral Flow Via Circle of Willis		
	No (n=6)	Yes (n=30)	*P*
Hemisphere			
rCBV	0.90±0.16	0.87±0.21	NS
MTT	1.15±0.12†	1.05±0.09†	NS
TA	1.08±0.06†	1.03±0.04†	0.015
TP	1.09±0.06†	1.03±0.04†	0.027
Gray matter			
rCBV	1.12±0.20	1.08±0.27	NS
MTT	1.12±0.11†	1.04±0.08†	NS
TA	1.08±0.06†	1.02±0.04†	0.009
TP	1.08±0.06†	1.03±0.04†	0.018
White matter			
rCBV	0.54±0.10†	0.48±0.16†	NS
MTT	1.25±0.18†	1.09±0.12†	0.024
TA	1.15±0.07†	1.09±0.05†	0.030
TP	1.14±0.08†	1.07±0.05†	0.027

Mean normalized hemodynamic parameters for patients with unilateral occlusion of the ICA are shown (38 patients, 2 incomplete collateral flow data; n=36). Patients are divided into subgroups on the basis of whether there was collateral flow via the circle of Willis (primary collateral pathways).

*†$P<0.01$, patients vs control subjects (control subject data in Table 1). *P* values in table refer to primary collateral flow vs no primary collateral flow.

matter (MTT: $P<0.05$; TA and TP: $P<0.01$), whereas rCBV was increased in white matter ($P<0.05$) only. In patients with collateral flow via the posterior communicating artery, MTT, TA, and TP were increased in the symptomatic hemisphere, gray matter, and white matter ($P<0.01$), while rCBV was increased in the symptomatic hemisphere ($P<0.05$) and in white matter ($P<0.01$). In patients with collateral flow via both anterior and posterior communicating arteries, only TA and TP were increased in the symptomatic hemisphere, in gray matter, and in white matter ($P<0.01$), and MTT was increased in white matter ($P<0.05$). No significant difference was found for rCBV. Comparison by ANOVA revealed significant differences between the subgroups. Patients with collateral flow via the posterior communicating artery showed a trend of deteriorated hemodynamic parameters compared with patients with collateral flow via the anterior communicating artery. Patients with collateral flow via the anterior communicating artery showed a trend toward less impaired hemodynamic parameters compared with patients with collateral flow via both the anterior and posterior communicating arteries. In patients with collateral flow via the posterior communicating artery, rCBV was significantly higher than in patients with collateral flow via both anterior and posterior communicating arteries ($P<0.05$).

Hemodynamic Status in Relation to Collateral Flow Via the Ophthalmic Artery

Table 5 shows hemodynamic parameters of the symptomatic hemisphere for patients with unilateral ICA occlusion with or without collateral flow via the ipsilateral ophthalmic artery. Compared with control subjects (Table 1), only TA and TP were statistically significantly increased in patients with normal ophthalmic artery flow ($P<0.01$), whereas TA, TP, MTT, and rCBV in white matter were significantly increased in patients with collateral flow via the ophthalmic artery ($P<0.01$). Although hemodynamic parameters tended to be more increased in patients with reversed flow in the ophthalmic artery, differences between the 2 subgroups were not statistically significant.

TABLE 4. Unilateral ICA Occlusion: Hemodynamic Parameters in Relation to Different Primary Collateral Pathways

DSC MRI (Symptomatic Hemisphere)	Collateral Flow Via Circle of Willis (Primary Pathway)		
	ACoA Only (n=17)	PCoA Only (n=6)	ACoA and PCoA (n=7)
Hemisphere			
rCBV	0.86±0.23	1.01±0.05*‡	0.76±0.15‡
MTT	1.03±0.10*	1.10±0.03†	1.05±0.10
TA	1.03±0.04†	1.05±0.02†	1.03±0.03†
TP	1.03±0.05†	1.05±0.01†	1.03±0.03†
Gray matter			
rCBV	1.10±0.31	1.21±0.10‡	0.93±0.18‡
MTT	1.03±0.09*	1.09±0.02†	1.04±0.09
TA	1.02±0.04†	1.04±0.02†	1.02±0.03†
TP	1.02±0.05†	1.04±0.02†	1.02±0.04†
White matter			
rCBV	0.48±0.18*	0.57±0.08†‡	0.41±0.10‡
MTT	1.07±0.13*	1.13±0.08†	1.08±0.13*
TA	1.08±0.05†	1.12±0.03†	1.08±0.05†
TP	1.06±0.06†	1.10±0.02†	1.07±0.05†

Mean normalized hemodynamic parameters of the symptomatic hemisphere for patients with unilateral occlusion of the ICA are shown (38 patients, 2 incomplete collateral flow data; n=36). Patients are divided into subgroups according to recruitment of primary collateral pathways: no collateral flow via the circle of Willis, collateral flow via the anterior communicating artery (ACoA) only (reversed flow in A1 segment indicating collateral flow from asymptomatic toward symptomatic side), collateral flow via the posterior communicating artery (PCoA) only (reversed flow PCoA on symptomatic side), or collateral flow via both the ACoA and PCoA.

*$P<0.05$, †$P<0.01$, patients vs control subjects (control subject data in Table 1).

‡$P<0.05$, PCoA only vs both PCoA and ACoA. For ACoA only vs PCoA only, *P*=NS. For ACoA vs both PCoA and ACoA, *P*=NS.

Collateral Flow in Patients With Bilateral ICA Occlusion

Hemodynamic Status in Relation to the Circle of Willis

Table 6 shows hemodynamic parameters of the symptomatic hemisphere of patients with bilateral ICA occlusion with and without collateral flow via the circle of Willis, which was in these patients via the posterior communicating artery only. In both patients with and patients without primary collateral flow, all hemodynamic parameters were significantly impaired ($P<0.01$). Direct comparison revealed no significant differences between the 2 subgroups.

TABLE 5. Unilateral ICA Occlusion: Hemodynamic Parameters in Relation to Collateral Flow Via the Ophthalmic Artery

DSC MRI (Symptomatic Hemisphere)	Flow Direction Ophthalmic Artery: Normal (n=7)	Flow Direction Ophthalmic Artery: Reversed (n=23)	P
Hemisphere			
rCBV	0.87±0.26	0.90±0.21	NS
MTT	1.03±0.08	1.10±0.11†	NS
TA	1.02±0.03†	1.05±0.05†	NS
TP	1.02±0.04†	1.05±0.06†	NS
Gray matter			
rCBV	1.14±0.36	1.11±0.25	NS
MTT	1.02±0.07	1.08±0.09†	NS
TA	1.01±0.03†	1.04±0.05†	NS
TP	1.01±0.04†	1.05±0.06†	NS
White matter			
rCBV	0.44±0.16	0.53±0.17†	NS
MTT	1.06±0.10	1.17±0.16†	NS
TA	1.08±0.05†	1.11±0.06†	NS
TP	1.06±0.05†	1.11±0.07†	NS

Mean normalized hemodynamic parameters of the symptomatic hemisphere of patients with unilateral occlusion of the ICA are shown (n=38). Patients are divided into subgroups on the basis of absence or presence of collateral flow via the ophthalmic artery on the symptomatic side (normal or reversed flow, respectively).

†$P<0.01$, patients vs control subjects (control subject data in Table 1). P values in table refer to normal vs reversed flow.

TABLE 6. Bilateral ICA Occlusion: Hemodynamic Parameters in Relation to Collateral Flow Via the Circle of Willis

DSC MRI (Symptomatic Hemisphere)	Patients With Bilateral Occlusion: No Primary Collateral Flow (n=5)	Patients With Bilateral Occlusion: Primary Collateral Flow (Via PCoA) (n=10)	P
Hemisphere			
rCBV	1.01±0.26†	1.07±0.26†	NS
MTT	1.08±0.06†	1.15±0.13†	NS
TA	1.06±0.04†	1.07±0.03†	NS
TP	1.06±0.02†	1.08±0.04†	NS
Gray matter			
rCBV	1.37±0.36†	1.27±0.34†	NS
MTT	1.06±0.05†	1.14±0.12†	NS
TA	1.04±0.03†	1.06±0.04†	NS
TP	1.04±0.02†	1.07±0.04†	NS
White matter			
rCBV	0.55±0.15†	0.57±0.16†	NS
MTT	1.14±0.05†	1.20±0.15†	NS
TA	1.11±0.06†	1.12±0.04†	NS
TP	1.09±0.03†	1.12±0.04†	NS

Mean normalized hemodynamic parameters patients with bilateral occlusion of the ICA are shown (16 patients, 1 incomplete collateral flow data; n=15). Patients are divided into groups on the basis of whether there was collateral flow via the circle of Willis (primary collateral pathways).

†$P<0.01$, patients vs control subjects (control subject data in Table 1). P values in table refer to primary vs no primary collateral flow.

Hemodynamic Status in Relation to Collateral Flow Via the Ophthalmic Artery

Because all but 2 patients had collateral flow via the ophthalmic artery, no useful statistical comparison could be made between patients with and without collateral flow.

Cerebripetal Anterior/Posterior Flow Ratio

Figure 2 shows hemodynamic parameters for the individual patients, plotted against the cerebripetal anterior/posterior flow ratio. We found a negative correlation between the distribution ratio and hemodynamic parameters (rCBV: $r=-0.33$ [$P<0.05$]; MTT: $r=-0.49$ [$P<0.01$]; TA: $r=-0.59$ [$P<0.01$]; TP: $r=-0.58$ [$P<0.01$]). When patients with bilateral ICA occlusion (with a cerebripetal anterior/posterior flow ratio of zero) were excluded from the analysis, for patients with subtotal ICA occlusion, correlation between the cerebripetal anterior/posterior flow was not significant for rCBV and MTT, whereas it was significant for TA and TP (TA: $r=-0.40$ [$P<0.05$]; TP: $r=-0.36$ [$P<0.05$]).

Discussion

In this study we investigated the role of collateral pathways on cerebral perfusion parameters in patients with ICA obstructions. The most important results of this study are as follows: (1) With increasing severity of the carotid artery lesion, cerebral hemodynamics deteriorate. (2) For patients with unilateral ICA occlusion, we found that compared with controls (a) patients with collateral flow via the circle of Willis have less impaired hemodynamic parameters than those without; (b) patients with collateral flow via the anterior communicating artery have less impaired hemodynamic parameters than those with collateral flow via the posterior communicating artery; (c) patients with collateral flow via both anterior and posterior communicating arteries have less impaired hemodynamic parameters than those with collateral flow via the anterior communicating artery only; and (d) patients with reversed ophthalmic artery flow have more impaired hemodynamic parameters than those without. (3) Finally, for both patients with unilateral and patients with bilateral ICA occlusions, hemodynamic parameters are significantly different from those of control subjects when collateral flow is via the posterior communicating artery.

We studied 4 hemodynamic parameters, each reflecting different perfusion characteristics. Increased rCBV reflects compensatory vasodilation, whereas increased MTT reflects slower passage of blood, both corresponding to reduced perfusion pressure. These parameters are directly related to the perfusion of the tissue, and for ideal "instantaneous" bolus passage, regional cerebral blood flow can be calculated by rCBV over MTT. TA and TP reflect the pathways of the blood to reach the tissue of interest rather than the perfusion characteristics of the tissue itself. This is, for example, reflected in the trend of more increased TA and TP in patients with collateral flow via the longer posterior communicating artery pathway than in patients with collateral flow via the anterior communicating pathway. In patients with large contribution of collateral circulation to the blood supply, TA and TP will be increased, whereas little or no increase in

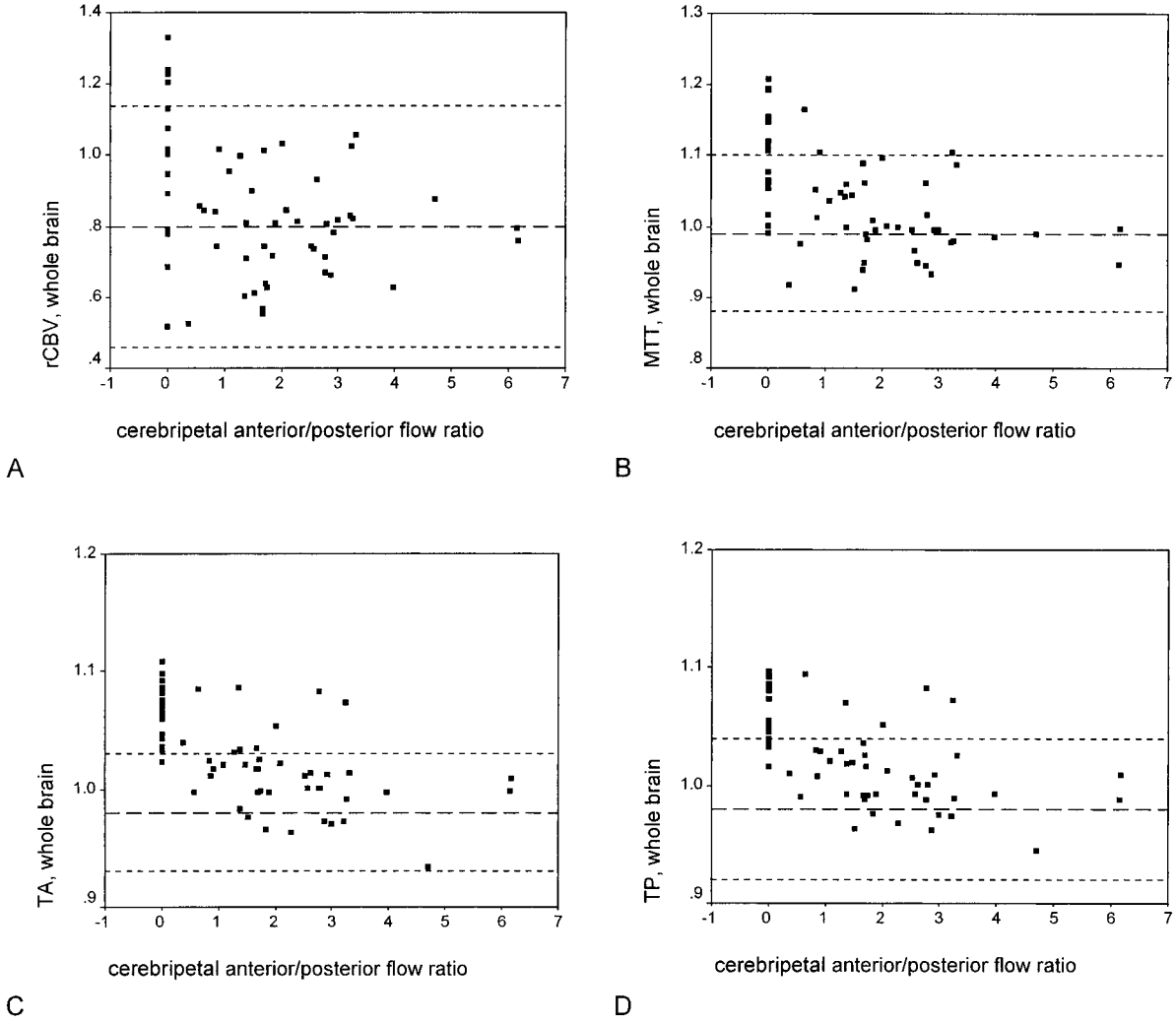

Figure 2. Scatterplot of the ratio of flow through both ICAs over the flow through the basilar artery with (A) rCBV, (B) MTT, (C) TA, and (D) TP, averaged over the whole brain. Horizontal lines indicate means (large dashed lines) and 95% CI limits (small dashed lines) of control subjects (for data of control subjects, see Table 1).

rCBV and MTT will be found. Only when collateral supply fails will rCBV and/or MTT increase significantly. This phenomenon is demonstrated in Figure 2. When the distribution of cerebripetal blood relies more on the basilar artery, no vasodilation and increased MTT occur unless the ICAs are both occluded, whereas TA and TP do increase when a larger part of the cerebripetal blood is supplied via the posterior communicating artery pathway.

We found less impaired hemodynamics in patients with collateral flow via the circle of Willis than in those without. In addition, we found differences based on which specific pathway was involved. Although several previous studies indicated that hemodynamic and metabolic changes were more severe in patients who lack the primary collateral pathways than in patients with well-functioning primary collaterals,[11,16,18] few studies investigated the role of both primary collateral pathways. In some studies only part of the circle of Willis could be studied,[9,11,14,30] while other studies restricted their inclusion criteria to either patients with a well-functioning collateral pathway through the anterior communicating artery,[31] asymptomatic patients,[12] or patients with low-flow infarcts.[8] Studies that investigated both primary pathways provided inconsistent results on the relative importance of each pathway. Contrary to a study that reported absence of flow through the posterior communicating artery as the only risk factor for watershed infarcts,[15] we found both in patients with unilateral ICA occlusion and in patients with bilateral ICA occlusion that the posterior communicating artery alone had little compensating capacity. Other studies indicated a key role in preservation of hemodynamics for the anterior communicating artery[17,32] or best-preserved hemodynamics if both primary pathways were recruited,[16] which is consistent with our results. Hemodynamic status tended to be worse in patients with reversed flow of the ophthalmic artery. This finding corresponds with the hypothesis that the ophthalmic artery is a secondary collateral pathway, which is only recruited when the primary pathways fall short.[11,16,30,32]

Despite large atherosclerotic lesions in the ICAs, we found that all patients showed a normal or increased flow in the basilar artery, as reflected in a decreased anterior/posterior ratio (Figure 2). This illustrates the dependency of these patients on the posterior circulation.

Prospective studies should show whether patients without primary collateral flow or with collateral flow via the posterior communicating artery only have a higher risk for low-flow infarcts than patients with collateral flow via the anterior communicating artery. In addition, reversed flow in the ophthalmic artery could prove an additional risk factor. If so, collateral flow via the ophthalmic artery and/or absence of primary collateral flow or collateral flow via the posterior communicating artery only could be an indication for treatment by bypass surgery or carotid endarterectomy of a stenosed contralateral ICA.

In conclusion, we found that in patients with unilateral ICA occlusion, collateral pathways have a significant influence on cerebral hemodynamic status. Collateral circulation via the anterior communication artery or via both anterior and posterior communicating arteries is a sign of well-compensated hemodynamic status. However, recruitment of the posterior communicating artery as the only primary pathway or recruitment of the ophthalmic artery can be regarded as an indication of impaired perfusion status of the brain.

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