Magnetic resonance angiography of collateral compensation in asymptomatic and symptomatic internal carotid artery stenosis

Jeroen Hendrikse, MD,[a] **Bert C. Eikelboom, MD, PhD,**[b] and **Jeroen van der Grond, PhD,**[a] *Utrecht, The Netherlands*

Objective: **In patients with stenosis of the internal carotid artery (ICA), the presence of collateral circulatory pathways may be crucial to maintain cerebral perfusion pressure, metabolism, and function. The purpose of the present study was to determine whether patients with asymptomatic stenosis of the ICA have a better collateral ability of the circle of Willis when compared with patients with symptomatic ICA stenosis.**

Method: **Magnetic resonance angiography consisting of the circle of Willis was performed in 19 patients with severe asymptomatic ICA stenosis and in 21 patients with severe symptomatic ICA stenosis prior to carotid endarterectomy and in 53 control subjects. Between group comparisons were made for function (directional flow) and anatomy (diameter).**

Results: **In patients with asymptomatic ICA stenosis, the prevalence of collateral flow via the anterior communicating artery was significantly increased (37%, 7 of 19) compared with symptomatic patients (10%, 2 of 21) and control subjects (0%; $P < .001$). Patients with asymptomatic ICA stenosis demonstrated the largest mean diameter of the anterior communicating artery (1.33 ± 0.18 mm) compared with patients with symptomatic ICA stenosis (1.22 ± 0.18 mm) and control subjects (1.06 ± 0.10 mm, $P < .05$). No differences in collateral flow pattern or diameter were found for the posterior communicating artery between the groups.**

Conclusions: **The present cross-sectional study demonstrates the importance of an adequate hemodynamic compensation via the circle of Willis in patients with ICA stenosis. Whether differences in collateral compensation can be used to select patients for CEA has yet to be determined. (J Vasc Surg 2002;36:799-805.)**

In patients with severe unilateral internal carotid artery (ICA) stenosis, carotid endarterectomy (CEA) decreases the risk of embolic stroke by removal of the atheromatous plaque.[1,2] Studies on carotid plaque morphology, distal microembolisms, and infarct location (ie, large artery strokes) have shown that the carotid plaque itself can be considered as a source of thromboembolisms.[3-7] Although in patients with stenosis of the ICA, the cause of stroke is primarily thromboembolic, the presence of low regional cerebral blood flow is also recognized as an additional risk factor.[8] The presence of low flow areas in the brain may lead to regionally impaired washout of emboli and, therefore, increased risk of infarction, predominantly in the border-zone areas of the brain. It has been shown that in patients with symptomatic ICA stenosis, absence of collateral flow via the circle of Willis and impaired vasomotor reactivity are both associated with increased stroke risk.[9-12] Moreover, in patients with symptomatic ICA stenosis, the absence of functional collateral pathways has been associated with a reduction in ipsilateral cerebral autoregulation,[13-15] decreased cerebral perfusion pressure,[16] and decreased cerebral blood flow.[17,18] In addition, it has been shown that patients with cross flow via the anterior communicating artery (ACoA) have a decreased incidence of electroencephalographic changes during carotid endarterectomy compared with patients without cross flow via the ACoA.[19-21] In this respect, it was also found that in patients with symptomatic ICA stenosis, the presence of collateral flow via the circle of Willis protects against stroke during carotid endarterectomy and the perioperative period.[11] On the basis of these studies, Barnett and Meldrum[22] recently noted that the determination of the adequacy of the collateral pathways of the circle of Willis could aid in the selection of patients at highest stroke risk for carotid endarterectomy. As a consequence, it is expected that differences in symptomatology of the ICA stenosis (symptomatic or asymptomatic) are not caused by differences in plaque morphology only, but may also be influenced by differences in collateral pathways distal to the ICA stenosis. We hypothesize that an asymptomatic severe ICA stenosis is associated with a better collateralization via the circle of Willis compared with a symptomatic ICA stenosis.

The aim of the present study was to compare the collateral ability of the circle of Willis between patients with asymptomatic and symptomatic severe unilateral ICA stenosis.

METHODS

Subjects. In total, 40 consecutive patients with severe unilateral ICA stenosis (>70%) were studied prospectively. Of these patients, 21 were symptomatic and 19 were

From the Departments of [a]Radiology and [b]Vascular Surgery, University Medical Center Utrecht.
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Reprint requests: J. Hendrikse, MD, University Medical Center, Department of Radiology (Hp E 01.132), PO Box 85500, 3508 GA Utrecht, The Netherlands (e-mail: j.hendrikse@azu.nl).
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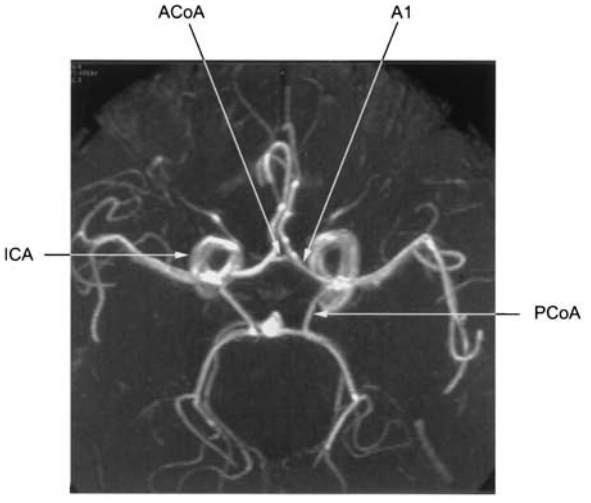

Fig 1. Three-dimensational time-of-flight MRA showing the anatomy of the circle of Willis. *ICA*, Internal carotid artery; *ACoA*, anterior communicating artery; *PCoA*, posterior communicating artery; *A1*, first segment of the anterior cerebral artery.

asymptomatic. Grading of the ICA lesions was performed with intraarterial digital subtraction angiography according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.[23] All patients had <30% stenosis on the contralateral side. Carotid endarterectomy was performed in all patients. Magnetic resonance angiography (MRA) examinations were performed 1 day before surgery. During CEA, cerebral monitoring was performed by using a 16-channel montage. The electroencephalogram was recorded on paper at 15 mm/sec with a 21-channel electroencephalograph (Siemens-Elema, Solna, Sweden). A clinical neurophysiologist monitored the recordings continuously during the surgical procedure. Both the neurophysiologist and the surgeon who performed the CEA were blinded to the preoperative MRA results. During the operation, the internal and external carotid artery were clamped after prior intravenous heparinization to test whether cerebral ischemia occurred. In these cases, a Javid shunt (Impra Inc, Tempe, Ariz) was introduced after which endarterectomy was performed.

The symptomatic patients (17 men, 4 women; mean age ± SD, 65.1 ± 9.4 years) had had transient (n = 10) or minor-disabling (n = 11) hemispherical neurologic deficits in the supply territory of the stenosed ICA within 12 weeks before the MRI examination. Transient neurologic deficits were defined as complaints lasting less than 1 day. A minor-disabling deficit indicated complaints lasting longer than 1 day, and which resulted in a mild or moderate invalidation (Rankin grade 3 or better).[24] The asymptomatic patients (16 men, 3 women; mean age ± SD, 63.9 ± 11.1) were detected in a general screening of patients with atypical complaints or bruits in the neck. All asymptomatic patients had absence of any neurologic ischemic symptoms in the past. The control group consisted of 53 volunteers aged 60-70 years (20 men, 33 women; mean age ± SD, 65.7 ± 2.5). The control group was recruited from a population-based study as described previously.[25] Informed consent was received from all subjects, and approval was received from the hospital's commission on scientific research on human subjects.

Magnetic resonance angiography. MRA of the circle of Willis was performed on a 1.5 Tesla system (Philips Gyroscan NT, Philips Medical Systems, The Netherlands). The MRA protocol consisted of a two-dimensional phase contrast (2D PC) sagittal localizer survey through the circle of Willis, followed by a three-dimensional time-of-flight (3D TOF) MRA sequence (Fig 1), which had the following imaging parameters: repetition time/echo time (TR/TE), 30 ms/6.9 ms; flip angle 20°; field of view, 100 x 100 mm; matrix size, 256 x 256; number of excitations, 2; slice thickness, 1.2 mm; gap width, −0.6 mm (ie, slices overlapped by 0.6 mm); slice orientation, transverse; number of slices, 50; stack volume, 30 mm. Diameter measurements were performed on the individual (transaxial) source slices of the 3D TOF MRA data set, by using a workstation (Easy Vision, Philips Medical Systems, The Netherlands). In all visible vessels on 3D TOF MRA, diameter measurements were performed. The investigators who performed the diameter measurements in the circle of Willis were blinded for the symptom status of the patient. Highly accurate measurements of even small-vessel diameters were made possible by means of interpolation programs linked to the magnification function, which was implemented in the software of the workstation.[26,27] The component vessels of the circle collaterals were measured in all patients and control subjects: ACoA, A1 segment of the anterior cerebral artery (ACA), and PCoA.

The direction of bloodflow in the A1 segment of the ACAs and in the PCoA were measured with two, 2D PC sequences, of which one was phase encoded in the anterior-posterior direction and another in the left-right direction. The imaging parameters of the 2D PC directional flow acquisition were: (TR/TE), 16 msec/9.1 ms; flip angle, 7.5°; field of view, 250 x 250 mm; rectangular field of view, 100%; matrix size, 256 x 256; number of excitations, 8; slice thickness, 13 mm; slice orientation, transverse; single slice, and a velocity sensitivity of 40 cm/s. According to the method described by Schomer et al,[28] two primary collateral pathways were analyzed; retrograde flow (toward the ICA) in the proximal segment of the anterior cerebral artery on the side of the stenosis (and symptoms), and posterior to anterior (retrograde) flow in the ipsilateral PCoA. Collateral flow via the A1 segment can be detected most clearly on the images that are phase encoded in the left-right direction. Collateral flow via the PCoA is detected only in the 2D PC images that are phase encoded in the anteroposterior direction. Collateral flow in the PCoA can not always be detected with phase encoding in the left-right direction because 2D PC images can hardly detect flow that is almost perpendicular to the direction of the phase encoding. Directional flow images were evaluated independently by two investigators (J.H. and J.vdG.) who were blinded to the

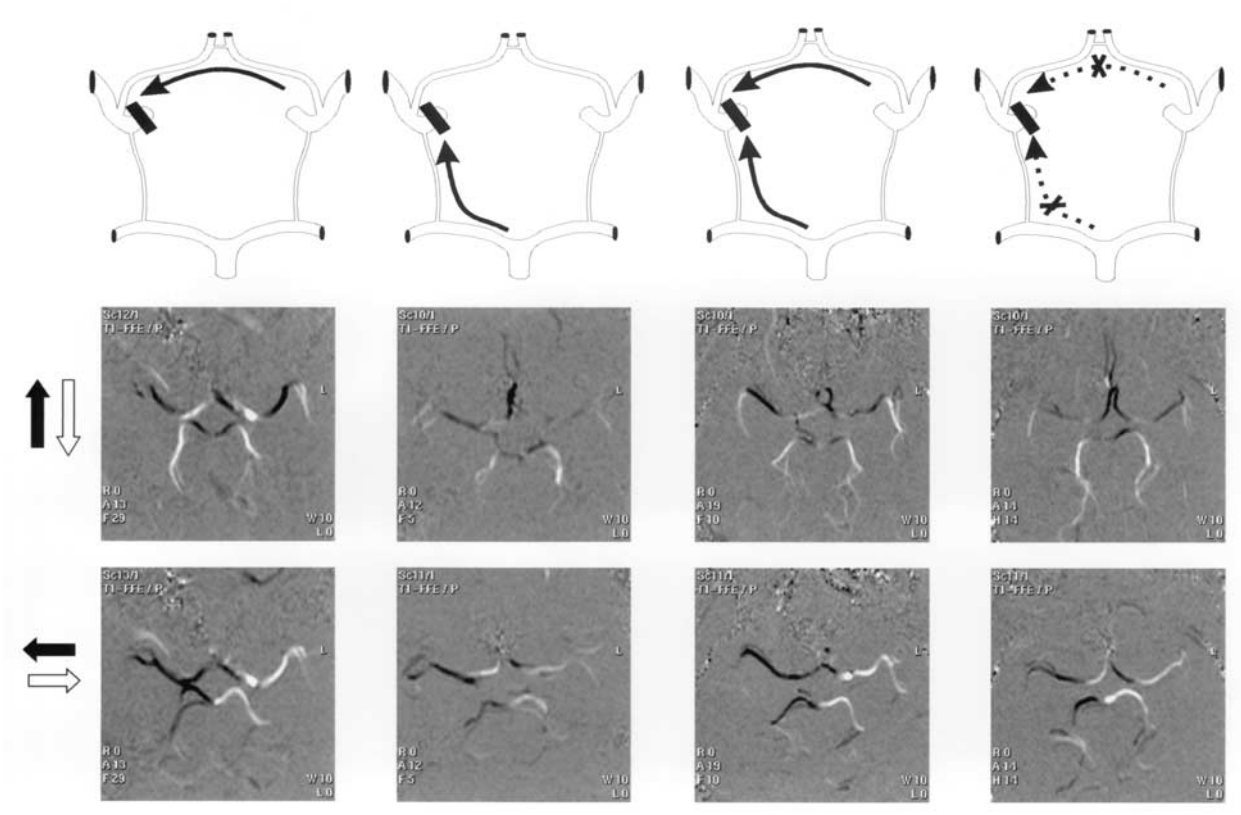

Fig 2. Patterns of collateral flow via the circle of Willis categorized as collateral flow via the A1 segment only, collateral flow via the PCoA only, collateral flow via both the A1 segment and the PCoA, and no collateral flow via the circle of Willis. **Middle row**, 2D PC images phase encoded in the anterior-posterior direction. Blood flowing in the anterior direction is black and blood flowing in the posterior direction is white. **Bottom row**, 2D PC images phase encoded in the left-right direction. Blood flowing to the right is *black* and blood flowing to the left is *white*. Collateral flow via the A1 segment can be detected on the images phase encoded in the left-right direction (bottom row). Collateral flow via the PCoA is detected only in the 2D PC images phase encoded in the anteroposterior direction (middle row).

status of the patient. Discrepancies between the evaluations of the two investigators were reevaluated in a consensus meeting. In each patient, the pattern of collateral flow via the circle of Willis was categorized as collateral flow (1) via the A1 segment only, or (2) via the PCoA only, or (3) via both the A1 segment and the PCoA, or (4) no collateral flow via either the A1 segment or the PCoA; Fig 2.

Statistical analysis. The null hypothesis tested was that the anatomy and function of the circle of Willis collaterals do not differ between asymptomatic and symptomatic patients with severe unilateral ICA stenosis and control subjects. Differences between asymptomatic and symptomatic patients in vessel diameters were analyzed with the analysis of variance (ANOVA) with Scheffe post hoc tests. Vessel diameters were expressed as means $\pm$ 2 $\times$ SEM. Collateral flow via the ACoA or PCoA was coded *yes* or *no* for the presence or absence of collateral flow. Between group comparisons (symptomatic, asymptomatic, and controls) for the presence of collateral flow were performed with χ^2-tests corrected for continuity. Individual comparisons between symptomatic patients, asymptomatic patients, and control subjects were performed with the two-tailed Fisher exact test. The comparison of the vessel diameter in patients with present or absent collateral flow was performed with the *t* test for equality of means. $P < .05$ was considered statistically significant.

RESULTS

ICA stenosis. For patients with asymptomatic and symptomatic ICA stenosis, no significant association was found between the degree of ICA stenosis on intraarterial angiography and the diameter measurements (ACoA, A1, PCoA). Furthermore no association was found between the degree of ICA stenosis and the absence and or presence of collateral flow. There was no significant difference in the mean degree of ICA stenosis when comparing asymptomatic ICA stenosis (76% $\pm$ 4%) with symptomatic ICA stenosis (79% $\pm$ 4%).

Collateral flow patterns. In Fig 3 and Table I the patterns of collateral flow are compared between patients with symptomatic ICA stenosis, asymptomatic ICA stenosis, and control subjects. Patients with asymptomatic ICA

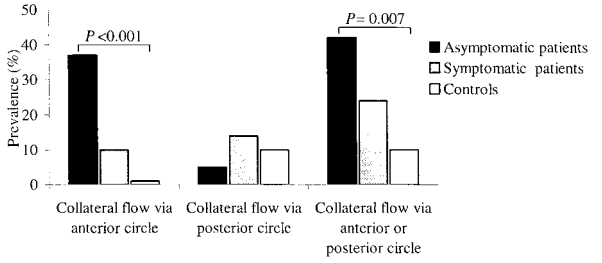

Fig 3. Prevalence of collateral flow patterns via the ipsilateral circle of Willis in asymptomatic (n = 19) and symptomatic (n = 21) patients with unilateral severe ICA stenosis and control subjects (n = 53). Probability values represent the comparison between asymptomatic patients, symptomatic patients and control subjects.

Table I. Prevalence of collateral flow patterns via ipsilateral circle of Willis

	Asymptomatic ICA stenosis (n = 19)	*Symptomatic ICA stenosis (n = 21)*	*Controls (n = 53)*
ACoA only	7 (37%)	2 (10%)	0
PCoA only	1 (5%)	3 (14%)	5 (9%)
ACoA or PCoA	8 (42%)	5 (24%)	5 (9%)

stenosis showed a significantly higher prevalence of collateral flow via the ACoA (37%; 7 of 19) compared with symptomatic ICA stenosis (10%; 2 of 21) and control subjects (0%, between group χ^2-test, $P < .001$). No significant difference was found in the prevalence of PCoA collateral flow (flow towards the ICA) among patients with asymptomatic ICA stenosis (5%), symptomatic ICA stenosis (14%), and control subjects (9%). Collateral flow via the ACoA or via the PCoA was found in 42% of the asymptomatic patients, in 24% of the symptomatic patients, and in 9% of the control subjects (between group χ^2-test, $P = .007$). The combined presence of collateral flow via both the A1 segment and the PCoA was not observed, neither in symptomatic patients nor in asymptomatic patients with unilateral ICA stenosis.

Vessel diameters. Fig 4 and Table II show the diameter comparison of vessel segments of the circle of Willis between asymptomatic ICA stenosis, symptomatic ICA stenosis, and control subjects. Patients with an asymptomatic ICA stenosis showed an increased ACoA vessel diameter compared with control subjects (1.33 ± 0.18 mm vs 1.06 ± 0.10 mm; ANOVA, $P = .021$), whereas patients with a symptomatic ICA stenosis did not. Patients with an asymptomatic ICA stenosis demonstrated a small, but not significant, increase in ACoA vessel diameter compared with patients with a symptomatic ICA stenosis (1.33 ± 0.18 mm vs 1.22 ± 0.18 mm). For three patients with an asymptomatic ICA stenosis and three patients with a symptomatic ICA stenosis, the diameter of the ACoA could not

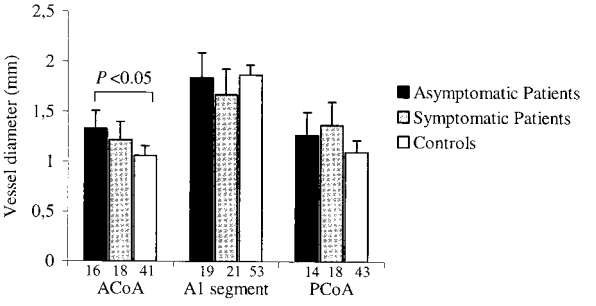

Fig 4. Mean diameters (mm ± 2 × SEM) of the collateral vessels of the circle of Willis in asymptomatic (n = 19) and symptomatic (n = 21) patients with severe unilateral ICA stenosis and control subjects (n = 53). *AcoA*, Anterior communicating artery; *A1*, A1 segment of anterior cerebral artery; *PCoA*, posterior communicating artery. Numbers at the bottom of table represent the number of vessel segments included in the diameter analysis. Probability value represents comparison of ACoA diameter between asymptomatic patients and control subjects.

be measured. No statisticaly significant differences in vessel diameter were found for the ipsilateral A1 segment and the ipsilateral PCoA between patients with asymptomatic ICA stenosis, symptomatic ICA stenosis, and control subjects.

The diameter of the ACoA in patients with present collateral flow via the anterior circle of Willis was significantly increased (*t* test for equality of means, $P = .012$) compared with patients without collateral flow via the ACoA (patients with collateral flow via the PCoA only or patients without collateral flow)(Fig 5).

Peroperative shunt. Eight of the 40 patients received a peroperative shunt. In the patients who received a shunt, no collateral flow was present via either the ACoA or PCoA on the preoperative MRA. In the patients who did not receive a shunt, in 13 of the 32 patients collateral flow via the ACoA or PCoA was present (Fisher exact test: $P = .037$). However, no statistically significant difference in vessel diameters of the ACoA, ipsilateral A1 segment, and ipsilateral PCoA were found when patients with and without peroperative shunt were compared. No statistically significant difference was found in the prevalence of peroperative shunt between patients with an asymptomatic (11%; 2 of 19) and a symptomatic (29%; 6 of 21) ICA stenosis.

DISCUSSION

The most important findings of the present study are threefold. Firstly, patients with an asymptomatic ICA stenosis have a higher prevalence of collateral flow via the anterior part of the circle of Willis compared with patients with a symptomatic ICA stenosis and control subjects. Secondly, patients with an asymptomatic ICA stenosis have an increased ACoA vessel diameter compared with control subjects. Thirdly, we found an association of the ACoA vessel diameter and the presence of collateral flow via the ACoA.

Collateral flow patterns. Our results show that the prevalence of collateral flow from the nonstenosed side to

Table II. Diameters of the collateral vessels of the ipsilateral circle of Willis

	Asymptomatic ICA stenosis (n = 19)	*Symptomatic ICA stenosis (n = 21)*	*Controls (n = 53)*
ACoA	(n = 16) 1.33 ± 0.18	(n = 18) 1.22 ± 0.18	(n = 41) 1.06 ± 0.10
A1 segment	(n = 19) 1.84 ± 0.25	(n = 21) 1.67 ± 0.25	(n = 53) 1.87 ± 0.10
PCoA	(n = 14) 1.27 ± 0.23	(n = 18) 1.37 ± 0.23	(n = 43) 1.10 ± 0.12

Vessel diameters are expressed as means (mm) ± 2×SEM; n, number of patients for each diameter calculation.

the stenosed side via the ACoA is increased in patients with an asymptomatic ICA stenosis. At present, very little is known about differences in function and anatomy of the circle of Willis between patients with asymptomatic and symptomatic ICA stenoses. Previous studies have shown that symptomatic stenosis is associated with an impaired hemodynamic status of the brain (eg, decreased cerebrovascular reactivity) compared with asymptomatic ICA stenosis.[9,29] Our results indicate that at least a subgroup of patients with asymptomatic ICA stenosis have well-developed collateral pathways that may preserve the arterial pressure distal to the stenosis and consequently maintain a normal cerebral blood flow. In this respect, it has been shown that patients with symptomatic ICA stenosis and collateral flow via the ACoA have increased poststenotic arterial pressure and a decreased incidence of electroencephalographic changes during carotid endarterectomy compared with patients without cross flow via the ACoA.[19-21] In our present MRA study we have had the opportunity to evaluate both the anatomy and function of the collateral pathways, and our findings support the hypothesis that the presence of collateral flow via the ACoA in patients with ICA stenosis points to a favorable hemodynamic situation. Furthermore, we found a trend towards a more frequent shunt use during CEA in patients with symptomatic ICA stenosis compared with patients with asymptomatic ICA stenosis; this is in accordance with the lower prevalence of collateral flow via the ACoA in the patient group with symptomatic ICA stenosis. Therefore, our findings strengthen the results of a recent transcranial Doppler study showing that in patients with an ICA occlusion and contralateral moderate-or-severe ICA stenosis, the cerebrovascular reactivity is preserved when a functional ACoA is present.[13] However, in our cross-sectional study we cannot prove that collateral flow via the ACoA indeed reduces the risk of future ischemic events.

In contrast to our findings concerning the prevalence of collateral flow via the ACoA, no difference in prevalence was found for the collateral flow via the PCoA between patients with asymptomatic and symptomatic ICA stenosis. Computational models of the circle of Willis showed that the ACoA is the major conduit of collateral blood supply to compensate for reduced arterial pressure caused by ICA lesions, whereas the PCoA is not recruited in patients with ICA stenosis only.[30,31] It appears that collateral flow via the posterior part of the circle of Willis is not a major collateral pathway in asymptomatic and symptomatic ICA stenosis and consequently does not play an important role in the occurrence of symptoms.

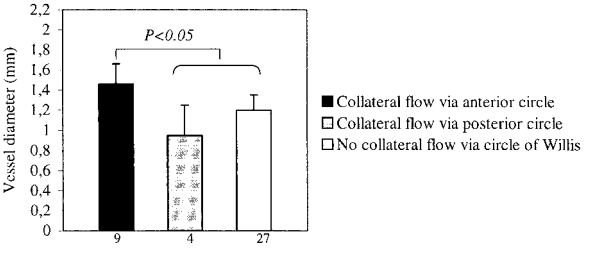

Fig 5. Mean diameters (mm ± 2 × SEM) of the anterior communicating artery in the total group of patients with unilateral ICA stenosis according to the flow pattern in the circle of Willis (n = 40). Numbers at the bottom of table represent the number of patients in each subgroup. Probability value represents the diameter comparison between present and absent collateral flow via the anterior communicating artery.

Vessel diameters. In addition, the present study shows that an increase in ACoA diameter is strongly associated with the presence of collateral flow in the ACoA. This correlation can be caused by two phenomena: better visualization of the ACoA on MRA caused by an increased sensitivity of MRA in case of higher ACoA (collateral) flow, or by a real anatomical increase in ACoA diameter. The potential of the collateral arteries in circle of Willis to increase in size is regarded as a mechanism to adapt to hemodynamic changes.[32-34] Our results are in accordance with a TCD study of Hoksbergen et al,[35] in which the adequacy of the collateral pathways of the circle of Willis was compared with postmortem diameters of these vessel segment, finding an association between an increased vessel diameter and an increased prevalence of collateral flow via these vessels. Furthermore, model-based studies pointed out that the diameter of the ACoA is important with respect to the adequacy to develop cross flow.[30] The importance of the vessel diameter is further addressed in studies finding an association between vessel diameters in the circle of Willis and the prevalence of ischemic infarction.[28,36] Still, a well-known problem of MRA is that visualization of cerebral arteries depends on flow through the arteries. When blood-flow is relatively low, the visibility of a vessel decreases, and diameter measurements may underestimate the actual value as the result of very slow flow near the vessel wall. In addition, a small underestimation in the prevalence of

collateral flow in small circle of Willis components may be expected. For instance, Patrux et al[37] showed that with techniques similar to those used in our study, the sensitivity of MRA to detect PCoA collateral flow was 81% with conventional angiography as gold standard. In general, MRA is regarded as a reliable technique to evaluate both the anatomy and function (flow direction) of the circle of Willis, and high correlations have been found between non-contrast-enhanced MRA and TCD ultrasonography or angiography measurements.[37,38]

Several potential limitations of the present study have to be addressed. With respect to the accuracy of the diameter measurements in vitro studies show that for a sufficiently high resolution (>3 pixel/diameter) the TOF MRA yields accurate diameter measurements with an error <5%.[39] With the transaxial resolution of 0.3 mm × 0.3 mm our mean vessel diameters were all above the 3 pixel/diameter range (> 1 mm). However, in the few individual patients or control subjects in which the diameter of the PCoA or ACoA was <0.9 mm, MRA may have underestimated the actual vessel diameter with 10% to 20%.[39] In the present study, gender differences were present between the control group and the patient group. The control group comprised a majority of women (62%), whereas the group of patients with carotid stenosis consisted of only 18% women. However, in a previous study in which 250 control subjects were included, the relation between gender and vessel diameters of the circle of Willis was studied. This study showed that no gender-related differences were present in the diameter of the ACoA, A1 segment, and PCoA.[25]

In the present study, we found an indication that the collateral ability of the collaterals of the circle of Willis is important with respect to symptomatology in patients with ICA stenosis. However, from our cross-sectional data we cannot identify patients at the highest risk of future stroke. These questions can only be answered in large prospective studies. Compared with patients having an ICA occlusion, the comparison of asymptomatic and symptomatic ICA stenosis is clinically more relevant. Miralles et al[40] showed that in patients with an ICA occlusion, a high prevalence of collateral flow through the ACoA was present in patients who did not have border zone infarcts. However, in contrast to most patients with unilateral ICA occlusion in whom surgery is not an option,[41,42] Barnett and Meldrum[22] mentioned that in patients with ICA stenosis the presence of hemodynamic compensation via the circle of Willis may be clinically useful to define (asymptomatic) patients who are not at risk, and, therefore, who may not benefit from surgery.

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