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Appraising the Plasticity of the Circle of Willis: A Model of Hemodynamic Modulation in Cerebral Arteriovenous Malformations

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Key Words
Cerebral arteriovenous malformations · Circle of Willis · Radiosurgery · Magnetic resonance angiography

Abstract
Objectives: Cerebral arteriovenous malformations (AVMs) harbor a network of abnormal vasculatures, namely the nidus between arterial and venous components. The pressure gradient between these two components results in abnormal high-velocity arteriovenous shunts flowing through the nidus and alternate intracranial hemodynamics. This study hypothesizes that the flow patterns of the circle of Willis (CoW) are modulated by the alternation of intracranial hemodynamics occurring in cerebral AVMs. The flow patterns of the CoW before and after AVMs had been corrected and the arteriovenous shunts closed by radiosurgery were assessed to validate the hypothesis. ***Patients and Methods:*** Fifty patients (32 men and 18 women; mean age 35.8 ± 4.2, range 23–52 years) with cerebral AVMs previously treated by radiosurgery were retrospectively investigated. This investigation used magnetic resonance angiography, performed prior to and after AVM surgery, to assess the CoW flow patterns. ***Results:*** The CoW flow patterns in nearly half of the subjects (20/50, 40%) altered after the AVMs had been corrected. The alterations included: (1) decreased size or ceased flow patterns in the CoW vascular segment: ipsilateral A1 (n = 1) of the anterior cerebral artery (ACA), ipsilateral posterior communicating artery (PCoA) segment (n = 7), contralateral PCoA collateral (n = 4), bilateral PCoA (n = 2); (2) increased size or opening of the previous 'hypoplastic' segment of CoW: ipsilateral A1 of ACA (n = 1), contralateral PCoA (n = 2), bilateral PCoA (n = 1), and (3) biphasic alteration of the CoW: ceased ipsilateral PCoA segment and opening ipsilateral A1 of the ACA (n = 1), ceased ipsilateral PCoA and opening contralateral P1 of the posterior cerebral artery (n = 1). ***Conclusion:*** The plasticity of the flow patterns in the CoW are modulated by intracranial hemodynamics as shown by the AVM model. The calibers of CoW arterial segments are not a static feature. Willisian collateralization with recruitment of the CoW segment may cease, or hypoplastic segments may reopen after closing arteriovenous shunts of the AVM.

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Introduction

Research has considered the circle of Willis (CoW), the primary intracranial physiological collateral pathway, as one of the buffers that salvage the brain from impaired cerebral hemodynamics [1, 2]. Nevertheless, the collateral pathway may be reversely closed after pathological hemodynamics have been corrected. One of our previous studies found that extracranial internal carotid artery occlusion might lead to a prompt initiation of CoW collaterals, while they promptly ceased in one third of the subjects after carotid artery stenting [3]. However, the number of blocked recruiting segments in the CoW was statistically higher than that of 'hypoplastic' segment openings in the CoW. The hemodynamic redistribution after carotid artery stenting was predominantly observed in the anterior circulation [3, 4]. Given this background, we hypothesized that the plasticity of CoW served as a reservoir for cerebral hypoperfusion stress and collateral demand. Could this vascular plasticity also be applicable to intracranial impaired hemodynamics?

In a previous study, we found that cerebral arteriovenous (AV) malformations (AVMs) disturbed brain perfusion [5]. Cerebral AVMs contain a cluster of pathological vascular networks, namely the nidus between arterial and venous components. With the pressure gradient between these two components, high-velocity AV shunts occur. The shunts with flow demand cause arterial hypotension in the neighboring vasculature owing to blood diversion from the vicinity of the adjacent brain tissues to the AVM. This is known as the cerebral 'steal phenomenon' [5, 6]. Could this intracranial hemodynamic disturbance be used as a model for CoW plasticity? To test our previous hypothesis of CoW plasticity, we conducted this retrospective longitudinal study focusing on the flow patterns of the CoW in cerebral AVM patients whose AVMs had previously been treated by radiosurgery. We assumed: (1) all CoW segments should open as an autoregulatory mechanism to the AV shunts with high blood flow demand, and (2) remodeling of the CoW should occur after AVMs had been corrected and the autoregulatory demand diminished.

Patients and Methods

Patient Population and Treatments

Ninety patients with cerebral AVMs were treated by Gamma Knife radiosurgery between 2001 and 2002 at our institute. We started radiosurgical service using the Gamma Knife in 1993. Since then, the imaging protocol and follow-up strategy have been standardized [5]. This work integrated stereotactic magnetic resonance (MR) imaging, 3-dimensional time-of-flight (3D-TOF) MR angiography (MRA) and X-ray angiography for radiosurgical targeting of AVMs. After radiosurgery, AVMs were followed up periodically by MR imaging and 3D-TOF MRA. Once observations showed that the AVM had been corrected on MR imaging, X-ray angiography was scheduled to verify the therapeutic results. Inclusion criteria for the current retrospective analysis were: (1) AVM had been corrected; (2) both AVM and CoW morphology were fully visualized in the scanning range of 3D-TOF MRA; (3) no history of previous treatments (radiosurgery, embolization, or microsurgery), and (4) AVMs were documented as corrected at the time of analysis. Among the 90 patients, 50 fulfilled the criteria and were recruited for the current analysis (32 men, 18 women; mean age 35.8 ± 4.2, range 23–52 years). According to the Spetzler-Martin staging system [6, 7], there were 24 grade II, 15 grade III, 6 grade IV, and 5 grade V AVMs.

Table 1. Baseline characteristics, time from neurological event to investigation, and time between consecutive investigations

Demographic characteristics	
Age, years	35.8 ± 4.2
M/F, n	38/12
Time from neurological event to investigation	
1st MRA, days	193 ± 48
Nidus size, ml	28 ± 3.8
Complete CoW	13 (26%)
Incomplete CoW	37 (74.1%)
1st–2nd MRA, days	582 ± 77
Nidus size, ml	0
Complete CoW	19 (38%)*
Incomplete CoW	31 (62%)
Altered CoW flow after GK	20 (40%)

GK = Gamma Knife. * = statistical significance.

Table 1 lists the timeframe of the MRA study. The AVMs were treated with mean (range) maximum/minimum target doses of 30.0 (28.2–32.5)/17.9 (15.5–18.5) Gy. The AVM volumes defined from the dose plan ranged from 15 to 56 (mean 28 ± 3.8) ml.

MR Imaging

The MR investigations were performed with a 1.5-T whole-body system (Sigma, CV/i, GE Medical Systems, Milwaukee, Wisc., USA). The flow patterns of the CoW were evaluated on the 3D-TOF MRA obtained with the following parameters: TR 31 ms; TE 6.9 ms; flip angle 20°; two signals acquired; 50 slices; slice thickness 1.2–1.5 mm; field of view 260 × 260 mm, and matrix size 512 × 512.

Flow patterns of the CoW were reviewed independently by 2 investigators (Y.-M.C., W.G.) with a consensus basis. The vascular segment of the CoW, namely A1, the posterior communicating artery (PCoA) and P1, were considered hypoplastic if their diameters were <1 mm or not visible on 3D-TOF MRA. The incidence of a complete CoW in the preoperative MRA was compared with that of the postoperative MRA (table 1). The number of cases with a decreased size/ceased CoW segment after complete radiosurgical AVM obliteration was compared with the number of patients with an increased size/opening CoW segment (table 2). The χ^2 test was used to compare the patient cohorts with different CoW flow pattern changes after radiosurgical AVM correction.

Statistical Analysis

The χ^2 test was used to compare the differences between patient groups with different CoW morphology changes after complete radiosurgical AVM obliteration. The incidence of a complete CoW in the preoperative MRA was compared with that of the postoperative MRA (table 1). The number of cases with a decreased size/ceased CoW segment after complete radiosurgical AVM obliteration was compared with the number of cases with an increased size/opening CoW segment (table 2).

Results

Table 1 shows the baseline characteristics of the 50 patients and the time interval between the relevant neurological manifestations and the various investigations. Table 1 also presents an overview of the baseline and postoperative cerebral MRA morphology. The baseline MRA consisted of only 13 subjects (26%) with a complete CoW configuration; the majority (n = 37) had an incomplete CoW configuration (74%) which included 36 hypoplastic PCoA segments, 18 hypoplastic A1 segments, and 6 hypoplastic P1 segments.

Postoperative MRA consisted of 19 subjects with complete CoW (38%); the remaining patients (n = 31) had an incomplete CoW configuration (62%) which included 30 hypoplastic PCoA segments, 16 hypoplastic A1 segments, and 3 hypoplastic P1 segments. Accordingly, the probability of a complete CoW is statistically higher in the postoperative setting (p = 0.04) which indicated a CoW normalization effect of complete radiosurgical AVM obliteration.

In the individual CoW morphology registration, nearly half of the subjects (40%) exhibited a significantly altered flow pattern in the CoW after complete AVM obliteration, including that which could be categorized into 9 patterns (table 2; fig. 1). The rest of the subjects (60%) remained the same. The probability of a decreased size or ceased recruitment segment of CoW after complete AVM obliteration was statistically higher than the increased size or opening of the hypoplastic segment of CoW (p = 0.011) which indicated that the normalization effect of radiosurgical AVM obliteration mainly shut down the previously provoked primary collaterals for cerebral AVM.

Table 2. Alterations in patterns of circle of Willis morphology after Gamma Knife obliteration in 50 subjects

	Nidus size
Static CoW after GK (n = 30)	18.5 ± 3.6
Altered flow pattern of CoW after GK (n = 20)	32.4 ± 4.3*
Monophasic decreased size or ceased recruitment segment of CoW after GK (n = 14)	25.8 ± 8.3
A Ceased ipsilateral A1 segment (n = 1)	
B Ceased ipsilateral PCoA segment (n = 7)	
C Ceased contralateral PCoA segment (n = 4)	
D Ceased bilateral PCoA segment (n = 2)	
Monophasic increased size or opening of hypoplastic segment of CoW after GK (n = 4)	35.6 ± 6.2
G Opening ipsilateral A1 segment (n = 1)	
H Opening contralateral PCoA segment (n = 2)	
I Opening bilateral PCoA segment (n = 1)	
Biphasic opening and ceased two distinct CoW segment (n = 2)	45.5 ± 8.8*
E Ceased ipsilateral PCoA segment and opening ipsilateral A1 (n = 1)	
F Ceased ipsilateral PCoA segment and opening contralateral P1 (n = 1)	
Number of ceased vs. opening of CoW segment	14:2* (p = 0.011)
Nidus size of monophasic vs. biphasic altered CoW, ml	30.2 ± 5.6 vs. 45.5 ± 8.8 (p = 0.02)

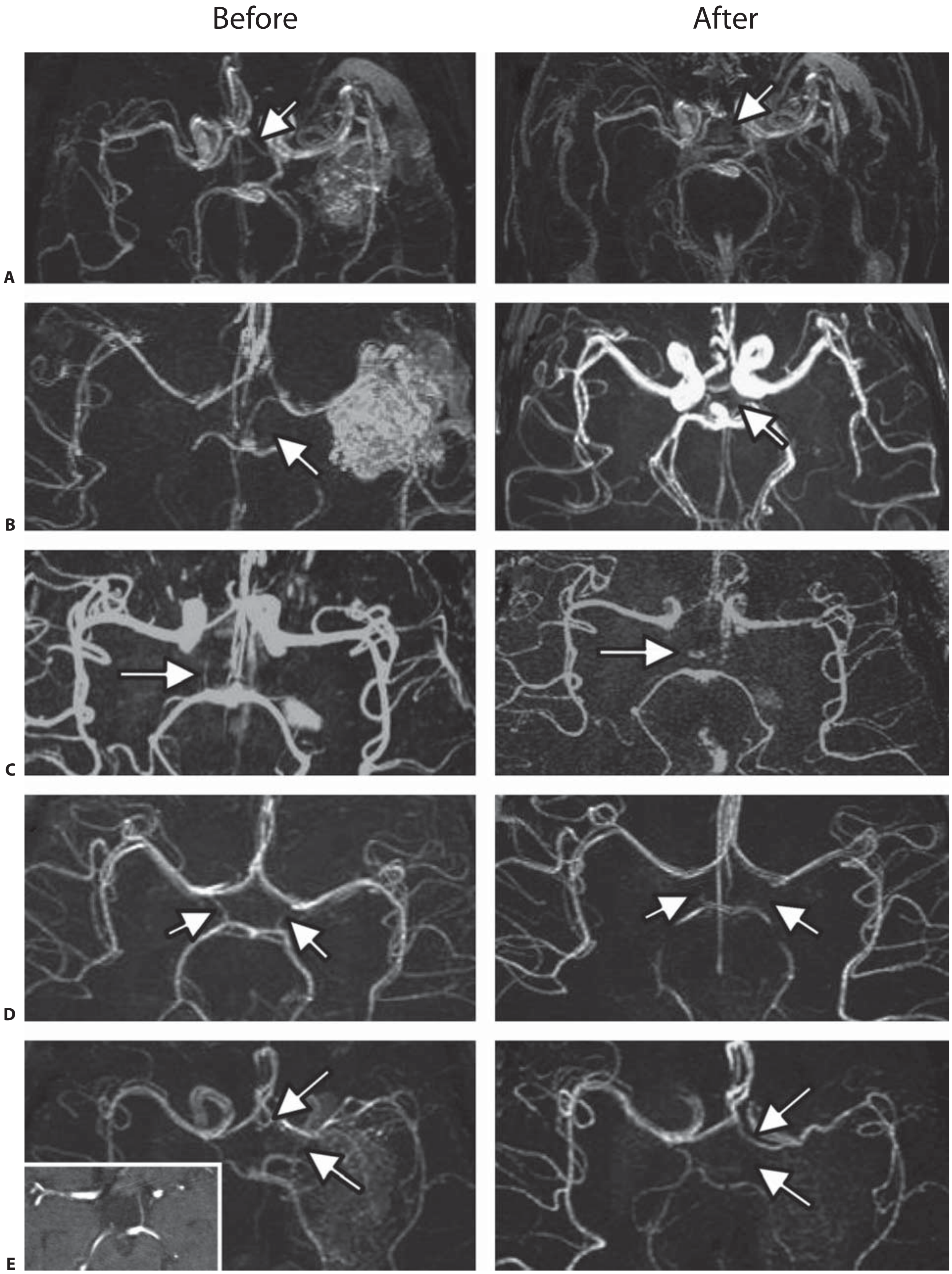
GK = Gamma Knife. * = statistical significance.

Decreased Size or Ceased Recruitment Segment of CoW after Complete AVM Obliteration

Decreased size or ceased recruitment of the ipsilateral and contralateral PCoA segments (n = 13) were the most common features after complete AVM obliteration. Seven subjects developed ceased recruitment of the ipsilateral PCoA (fig. 1B), 4 subjects developed ceased recruitment of contralateral PCoA (fig. 1C), and 2 subjects developed ceased recruitment of bilateral PCoA (fig. 1D).

Increased Size and Opening of the Hypoplastic Segment of CoW after AVM Obliteration

Opening of the bilateral and contralateral PCoA segment (n = 3) was the second most common feature after complete AVM obliteration (fig. 1H, I). Two subjects developed opening of the contralateral hypoplastic PCoA segment after complete AVM obliteration (fig. 1H). Opening of the ipsilateral hypoplastic A1 segment (n = 1)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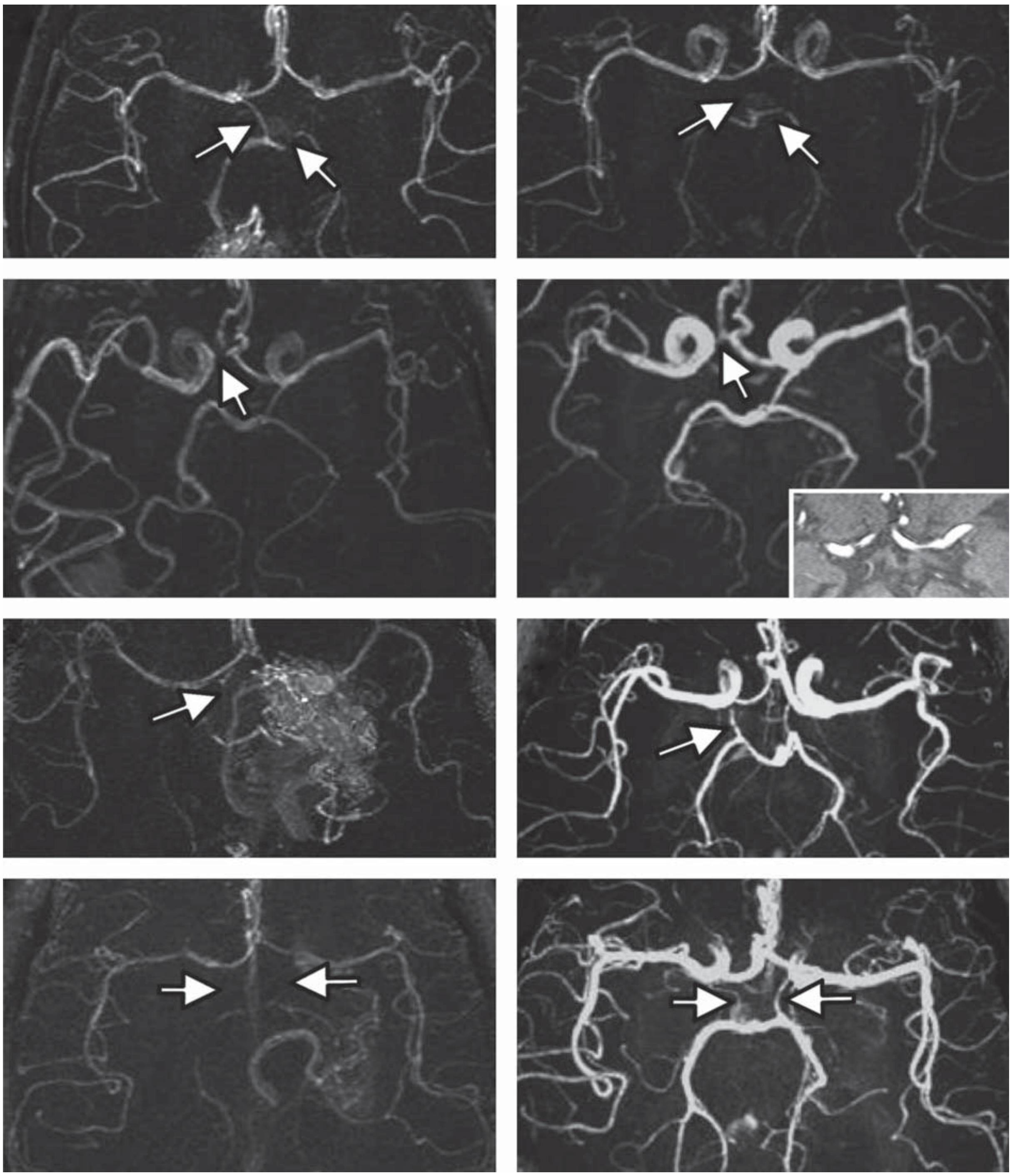

F G H I

Fig. 1. A comparison of baseline and postoperative MRA morphology of the circle of Willis (CoW). There were 8 patterns of CoW alteration after radiosurgical obliteration of arteriovenous malformations which are categorized into types A–I corresponding to the classification given in table 2. **A** Decreased size and ceased ipsilateral A1 segment (n = 1). **B** Decreased size and ceased ipsilateral PCoA segment (n = 7). **C** Decreased size and ceased contralateral PCoA segment (n = 4). **D** Decreased size and ceased bilateral PCoA segment (n = 2). **E** Ceased ipsilateral PCoA segment and opening ipsilateral A1 (n = 1). **F** Ceased ipsilateral PCoA segment and opening contralateral P1 (n = 1). **G** Increased size and opening ipsilateral A1 segment (n = 1). **H** Increased size and opening contralateral PCoA segment (n = 2). **I** Increased size and opening bilateral PCoA segment (n = 1).

was also noted after complete AVM obliteration (fig. 1G). The opening (n = 3) and ceased recruitment (n = 13) of hypoplastic PCoA accounted for 88.9% of the morphological alterations after complete AVM obliteration, which indicated that redistribution of the posterior circulation served as a major buffer after complete AVM obliteration.

Simultaneous Opening and Blocked Recruitment of Two Distinct CoW Segments

Two subjects developed biphasic CoW alterations with simultaneous opening and blocked recruitment of two distinct CoW segments after complete AVM obliteration. To the best of our knowledge, this biphasic pattern after complete AVM obliteration has never been described. Only 1 subject developed blocked ipsilateral PCoA and opened ipsilateral A1 (fig. 1E) and the other developed blocked ipsilateral PCoA and opened contralateral P1 after complete AVM obliteration (fig. 1F). Opening and blocked recruitment of the CoW segment served an opposite hemodynamic purpose. As we traced back the raw data of these 2 subjects, there was no comorbidity surrounding the intracranial arterial occlusion.

AVM Nidus Size Registration/Analyses

For comparison, subjects were divided into groups with or without CoW alterations after AVM obliteration. Subjects with an altered CoW morphology had a bigger AVM nidus size than the static group (nidus size 32.4 ± 4.3 vs. 18.5 ± 3.6 ml; $p < 0.01$).

Groups with monophasic alterations (increased/decreased segmental caliber) in CoW (n = 18) and biphasic alterations (simultaneous increased/decreased distinct segmental caliber of CoW; n = 2) were also compared. Biphasic alterations in the CoW group had a bigger AVM nidus size than the monophasic alteration group ($p = 0.02$; table 2).

Discussion

As TOF rather than phase contrast MRA was used, the direction of flow cannot be ascertained per se. We emphasize that despite the critique of TOF MRA in the literature, the modality is of interest precisely because of these flow effects [7]. Hoksbergen et al. [8] used MRA visibility of CoW as a sole criterion with a high sensitivity to identify functional collateral pathways. Based on Hoksbergen et al.'s criteria and the results of this cerebral AVM model, we interpreted that the change in functional anatomy of the CoW after radiosurgery might be caused by false-positive or false-negative findings in part of the circle [1, 9]. Lazorthes [9] described that the function of the CoW is to buffer and salvage our brain from impaired cerebral hemodynamics. Willisian collateralization with recruitment of a substantial hypoplastic segment contributes to a false-negative MRA diagnosis. Radiosurgery reduced the collateralization demand, which shut down recruitment and led to a false-positive MRA diagnosis of CoW vascular hypoplasia. CoW segmental hypoplasia is not only a variable feature, but is also enrolled as part of an autoregulatory mechanism [3, 4].

The morphological aspects of the CoW are well known but these functional aspects have undergone less study. Using the nidus size correlation, we addressed an emerging regulation model of CoW by considering the factor of AVM nidus size. We appraised the plasticity of CoW: a nidus size-dependent modulation in cerebral AVMs.

The nidus size refers to a bigger-sized AVM with turbulent transnidal shunting which increases the CoW autoregulatory demand and probability embedded with heterogeneous polyphasic homodynamic domains [10]. The complexity of CoW alterations after AVM obliteration is in accordance with the corresponding AVM autoregulatory demand. A biphasic alteration in CoW after complete AVM obliteration (n = 2) is a paradox in that two inverse autoregulatory domains coexist. Biphasic alterations in the CoW group had a larger nidus size than the monophasic alteration group ($p = 0.035$, $p = 0.04$).

The most common feature was decreased size or ceased recruitment of the ipsilateral/contralateral PCoA (n = 13). In hemodynamic physics, the anastomotic phenomena involving afferent and communicating arteries of the CoW strongly depend on the diameter [11]. A positive correlation between the caliber of the CoW and its collateral capability has been addressed [12]. A decreased PCoA size refers to a reduced collateralization demand after complete AVM obliteration.

On the contrary, AVM obliteration lead to opening of a new Willisian segment (n = 4) in the absence of comorbid cerebral arterial occlusion. Our explanation is that complete AVM obliteration restores the normal distribution of upstream blood flow which overcomes the opening pressure of previously closed CoW segments. Another explanation is that the CoW vascular segment constricts pre-surgically to block the 'steal phenomenon' from AVM which mimics a check valve to maintain surrounding satisfactory territorial perfusion [9, 10]. Iida et al. [13] depicted a similar phenomenon that CoW constricts as a hemodynamic barrier for a carotid-cavernous fistula. Cassot et al. [12] described a coupling effect of the CoW autoregulatory gain which initially altered with the diameter, but reversed to zero upon an out-of-phase hemodynamic catastrophe.

Some of our pre- and post-radiosurgical MRAs showed different levels of the CoW. Determining the flow alteration pattern on the segments of the CoW is inappropriate if MRA cutting is not at the same level. This study debated the feasibility of using MRA as an investigational tool. Despite a discrepancy between the resolution of MRA and conventional angiography, we made sure that the AVM was totally obliterated or the morphology of the CoW was alternated after radiosurgery with the conventional angiographic study.

In this study patients with previous treatments such as radiosurgery, embolization or microsurgery were excluded. However, 11 patients enrolled in this study had high-grade AVM (grades IV and V). These patients did not receive embolization before radiosurgery or fractionated radiosurgery. These procedures may interfere with the hemodynamic interpretation of CoW flow change [14].

Our conclusion is not straightforward. In fact, half of our subjects did not have any CoW configuration alteration after AVM obliteration. Clearly, a small sample size bias exists. For example, separate analyses for those with biphasic CoW alterations after complete AVM obliteration were performed due to the probable distinct pathophysiology.

The moderate inter-observer agreement is most probably a reflection of the difficulty in identifying very small communicating arteries with MRA. A certain false-negative rate of MRA in depicting intracranial collaterals may further enhance this bias. Sallustio et al. [15] used a supplementary transcranial color duplex sonography (TCCD) in evaluating MRA-invisible CoW segments and flow direction. However, the great disadvantages of TCCD include its dependence on the temporal bone windows, higher negative predictive rate of PCoA functional patency, and lower inter-observer agreement [15, 16].

Only 2 subjects had biphasic CoW alterations after complete AVM obliteration. Thus, the sample size was too small for statistical comparison. Data-snooping bias may exist in our Spetzler-Martin scoring-based analyses. A large-scale study utilizing quantitative hemodynamic parameters and CoW morphology correlation is needed to test the reproducibility of our findings. Despite these limitations, we believe that plasticity of the CoW is a real entity and its pathophysiology deserves greater attention [3].

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