The Clinical Relevance of Fetal Variant of the Circle of Willis and Its Influence on the Cerebral Collateral Circulation

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Abstract

In a fetal variation of circle of Willis (CoW) there is an embryological defect of the primary collateral circulation. Besides the fact that collateral flow cannot develop between anterior and posterior circulation, the tentorium namely prevents cerebellar vessels from connecting to the supra-tentorium territory. Therefore patients with a fetal variation of circle of Willis could be more prone to develop vascular insufficiency. An association between the regional cerebral blood volume (rCBV) inter-hemispheric asymmetry and CoW collateralization was observed with a topographic significance of corona radiate rather than centrum semiovale. An overview of the literature is given. We propose a fetal variation of circle of Willis as a risk factor for stroke should be subject of further investigation.

Key Words: circle of willis, fetal, cerebral collateral circulation.

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INTRODUCTION

Collateral circulation in the brain is important for maintaining a sufficient level of cerebral blood flow in case of obstructive disease in the main afferent arteries. This arterial network consists of extracranial and intracranial routes. The intracranial collateral vessels comprise the so-called primary collaterals, consisting of the arterial segments of the circle of Willis, which are used in case of acute need, and the secondary collaterals such as the ophthalmic artery and the leptomeningeal vessels, which develop after an ischemic stimulus when the primary collaterals are insufficient[(1)]. They can represent an important connection between the internal carotid artery (ICA) and the vertebrobasilar system.

However, variant of the circle of Willis makes collaterals between the ICA and the vertebrobasilar system impossible to develop since both the middle cerebral artery (MCA) and the posterior cerebral artery (PCA) are connected to the internal carotid system and not to the vertebrobasilar system. An important consequence of the fetal variant of the circle of Willis could be an increased stroke risk in patients with obstructive arterial disease, as has been described in postmortem studies[(2,3,4)]. Collaterals are regularly discussed as to their possible importance in relation to stroke risk, but little

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attention has been given to the variant of the circle of Willis in the literature. In this review we discuss the association between collaterals and a subsequent stroke risk.

THE CIRCLE OF WILLIS

The circle of Willis has a major role in redistributing the blood in case of diminished supply through the ICA and the basilar artery (Figure 1). This vessel structure enables inter-hemispheric flow through the anterior communicating artery and in two directions through the posterior communicating artery (PCoA). There is a considerable variation in the presence of the arterial segments of the circle of Willis. On the anterior side the anterior communicating artery or one of the A1 (proximal) segments of the anterior cerebral artery (ACA) can be missing or hypoplastic. On the posterior side, the PCoA can be absent uni- or bilaterally. In healthy individuals, a complete configuration of the circle of Willis is present in 42–52%[1,2]. In patients with ICA stenosis or occlusion, this percentage is higher[5].

ASSOCIATION BETWEEN COLLATERALS AND STROKE

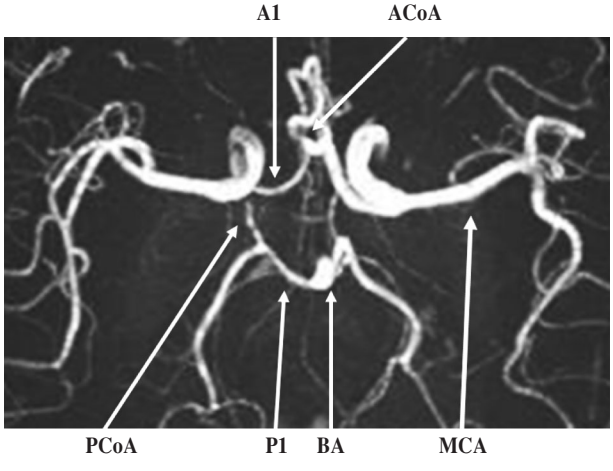


Figure 1. MR angiography image of the circle of Willis. ACoA: anterior communicating artery; A1: A1 segment of the anterior cerebral artery; MCA: middle cerebral artery; P1: P1 segment of the posterior cerebral artery; BA: basilar artery; and PCoA: posterior communicating artery.

The most rapidly recruited collaterals are the communicating arteries of the circle of Willis. A case-control study, assessing the collateral flow through the circle of Willis with transcranial color coded duplex ultrasonography in patients with acute ischemic stroke (n = 109) and in patients with peripheral arterial disease (n = 113), also showed that the presence of a nonfunctional anterior collateral pathway was associated with ischemic stroke (odds ratio = 7.3; 95% confidence interval 1.2–76.5)[1]. The authors described the highest infarct incidence in brains where 1 ICA mostly or exclusively supplied 2 ACAs, an MCA and a PCA[6].

Our previous study showed a topographic distribution of stroke in patients with A1 segment hypoplasia indicated an association with ipsilateral hemispheric ischemia, especially within the striatum (76.2%, n = 38). The rate of association of A1 hypoplasia with hemispheric infarction was 19.2% (n = 38), which was significantly higher than the association of A1 hypoplasia with brainstem/cerebellar ischemic stroke, at 4.87% (n = 4) (p value: 0.012). In addition, 71.4% of right A1 hypoplasia (10/14) and 64.3% of left A1 hypoplasia subjects (18/28) exhibited ipsilateral hemispheric infarctions[3].

Our previous study refer a topographic distribution of stroke in patients with PCoA hypoplasia indicated an association to ipsilateral thalamus (77.08%, n = 37), or mixed thalamic/occipital lobe (20.83%, n = 10)(Figure 2). The overall incidence of thalamic infarction in the hypoplastic PCoA group was significantly higher than was found for the non-hypoplastic PCoA group (27.2%, n = 68/250, p = 0.021). Furthermore, the rate of association of PCoA hypoplasia with hemispheric infarction (21.27%; n = 40), was significantly higher than its association with brain stem/cerebellar ischemic stroke (10%; n = 8, p = 0.032). Also, 83.33% of right PCoA hypoplasia (15/18) and 73.33% of left PCoA hypoplasia subjects (22/30) had ipsilateral hemispheric infarctions. The most common event found was an ipsilateral thalamic lacune (85.18%, 23/27). In contrast, this correlation of laterality was absent in the PCoA hypoplasia plus group. Additionally, all PCoA hypoplasia subjects with a contralateral major artery occlusion (ICA, n = 2/ MCA, n = 1/PCA, n = 1) developed a contralateral cerebral

infarct[4].

In the PCoA hypoplasia plus group, 33% of tandem ICA occlusion subjects developed a watershed infarction, which was significantly more frequent than what was found for the pure PCoA hypoplasia group (p = 0.021). Furthermore, patients with a tandem intracranial major vascular occlusion were more likely to develop a relevant territorial infarction than a thalamic lacune or a watershed infarct[4].

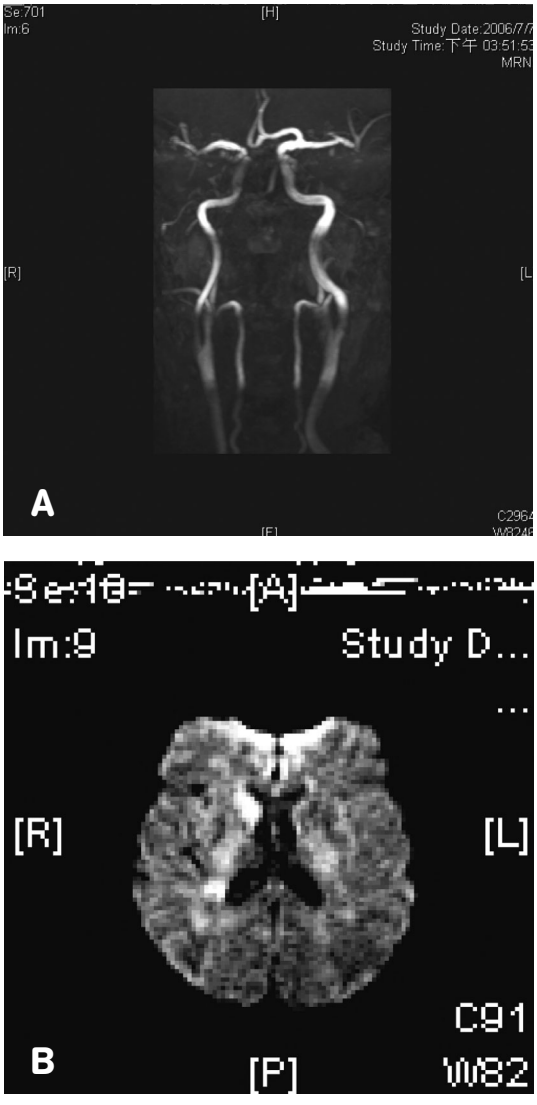


Figure 2. (A) Cerebral magnetic resonance angiogram of a 53-year-old male with a 10-year history of hypertension, who presented with acute onset of right hemiparesis, hemianesthesia and homonymous hemianopsia. (B) The corresponding MRI (diffusion-weighted imaging) disclosed multifocal hyperintense lesions involving the left thalamus and occipital lobe; which fulfilled the posterior choroidal artery occlusion 11 and TOAST subtype criteria for small-artery artherosclerosis. This image also revealed agenesis of the left posterior communicating artery (arrow). (TOAST = Trial of ORG 10172 in Acute Stroke Treatment).

We postulate a pathophysiological role for A1 segment hypoplasia based on the results of this small-scale study. Subjects with A1 segment hypoplasia have a (1) topographic preponderance of ipsilateral hemispheric stroke, (2) etiological preponderance of small-artery atherosclerosis, and (3) a correspondingly lower NIHSS score.

Our observation of the etiological preponderance of small-artery atherosclerosis was de novo. The majority (83.33%) of A1 segment hypoplasia-related strokes were associated with small vessel occlusion, especially within the striatum. One possible explanation is poor collateral capacity that would render arteries penetrating the striatum vulnerable to ischemic attack[7]. On the basis of the grading system of Brucker et al.[8], patients with A1 Contrary to our argument, van Everdingen et al. posited that one hypoplastic segment hypoplasia have impaired collateral circulation. Wang et al.[10], Kang et al.[7] and Caplan and Hennerici[9] posit that thromboembolism clearance is poor within the striatum with defective collateral circulation.

PCoA may be clinically irrelevant if at least one of the other primary collateral pathways is present, while Hoksbergen et al. suggested that PCoA hypoplasia is asymptomatic unless accompanied by an ipsilateral ICA stenosis[1]. Furthermore, Schomer et al. proposed that posterior communicating artery hypoplasia is a risk factor for ischemic stroke only in case of ipsilateral ICA stenosis[2]. Our result suggests that even in the absence of ICA occlusion, PCoA hypoplasia is an independent contributor to the risk of ischemic stroke.

DYNAMIC TRANSFORMATION OF CIRCLE OF WILLIS MORPHOLOGY

Catotid artery stenting model

In our previous study, we conducted a longitudinal observation of glow patterns in the circle of Willis one week after stenting for severe ICA stenosis (CAS).

Baseline MRA tested only 11 subjects (16.9%) with a complete CoW configuration; the majority (n = 54) had an incomplete CoW configuration (83.1%), which included 50 hypoplastic PCoA segments, 23 hypoplastic A1 segments and 4 hypoplastic P1 segments. Postoperative MRA tested 20 subjects (30.7%) with a complete CoW configuration; the remaining patients (n = 45) had an incomplete CoW configuration (69.3%), which included 45 hypoplastic PCoA segments, 20 hypoplastic A1 segments and 3 hypoplastic P1 segments. Accordingly, the probability of a complete CoW is statistically higher in the postoperative setting (p = 0.03), which indicates a normalization effect from CAS on the CoW. In individual CoW morphology registration, one third of the subjects (35.38%) had a significantly altered flow pattern in the CoW after unilateral CAS, including morphologies which could be categorized in 7 different patterns. The rest (64.62%) remained the same (Figure 3)[11].

The probability of a blocked recruitment segment in the CoW after CAS was statistically higher than an opening of a hypoplastic segment in the CoW (p = 0.021). This indicated a normalization effect from CAS,

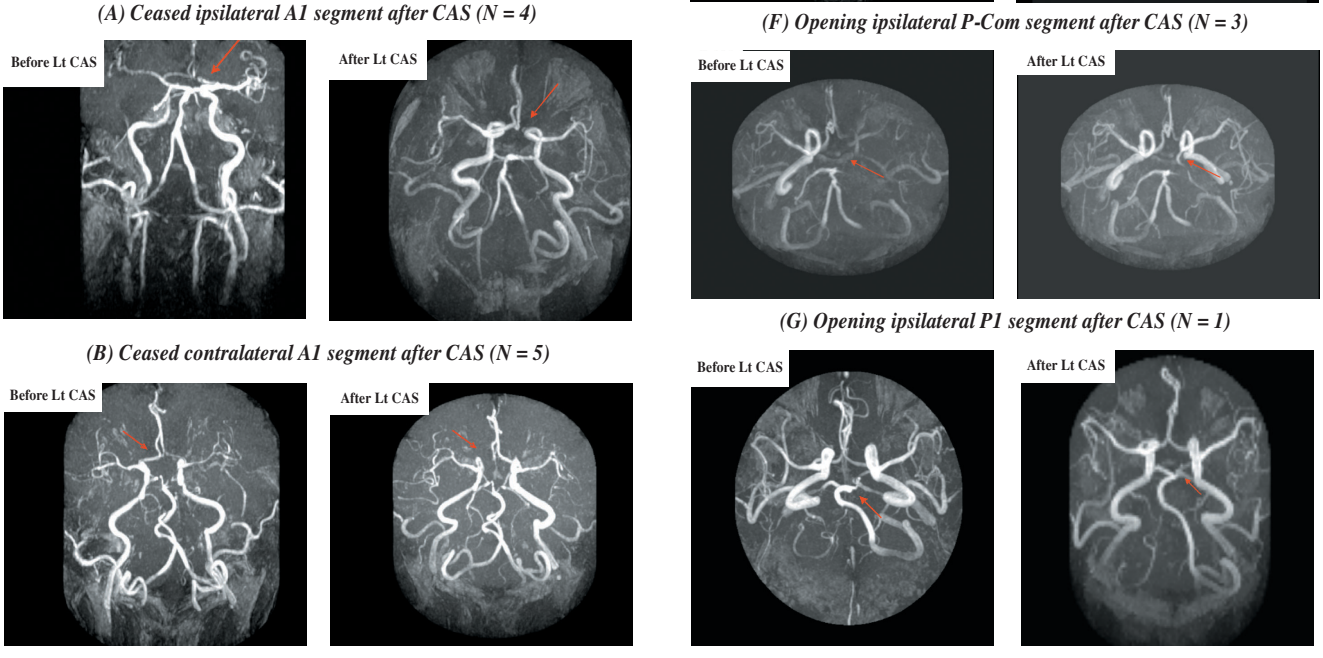


Figure 3. A comparison of baseline and post-operative MRA morphology of circle of Willis was shown as figure A to figure G. There were 7 patterns of CoW alteration after CAS which was categorized to type A to G which corresponds to Table 2 classification.

which mainly shut down the previously provoked primary collaterals of the ICA occlusion (Table 1).

The probability of recruitment of an open/blocked hypoplastic A1 occupied 60% of morphology alterations occurring after CAS, which was statistically higher than the total number of PCoA and P1 (p = 0.025; one subject with a simultaneous redistribution of ant. and post. Circulation was excluded). Accordingly, redistribution of anterior circulation served as a predominant major cushion after CAS (Table 2). Our observation that CoW segmental hypoplasia is not a static feature challenges the position of Schomer et al.[2] and Chuang et al.[3]

After acknowledging that CoW segmental hypoplasia is a variable parameter, the pathologic significance of PCoA and A1 hypoplasia was debated from a static observation. It is necessary to refine those assumed anatomical risk factors. The claims of Schomer et al.[2] should be revised to say that autoregulation failure to recruit a hypoplastic PCoA is a risk factor. In fact, our paper focusing on the hemodynamic aspects of ischemia is refreshing, as the current stroke literature has been focused on arterial anatomy, seemingly isolated from the pathophysiology of blood flow in the brain.

Table 1. Baseline Characteristics, Time from Ischemic Event to Investigation, and Time between Consecutive Investigat-ions

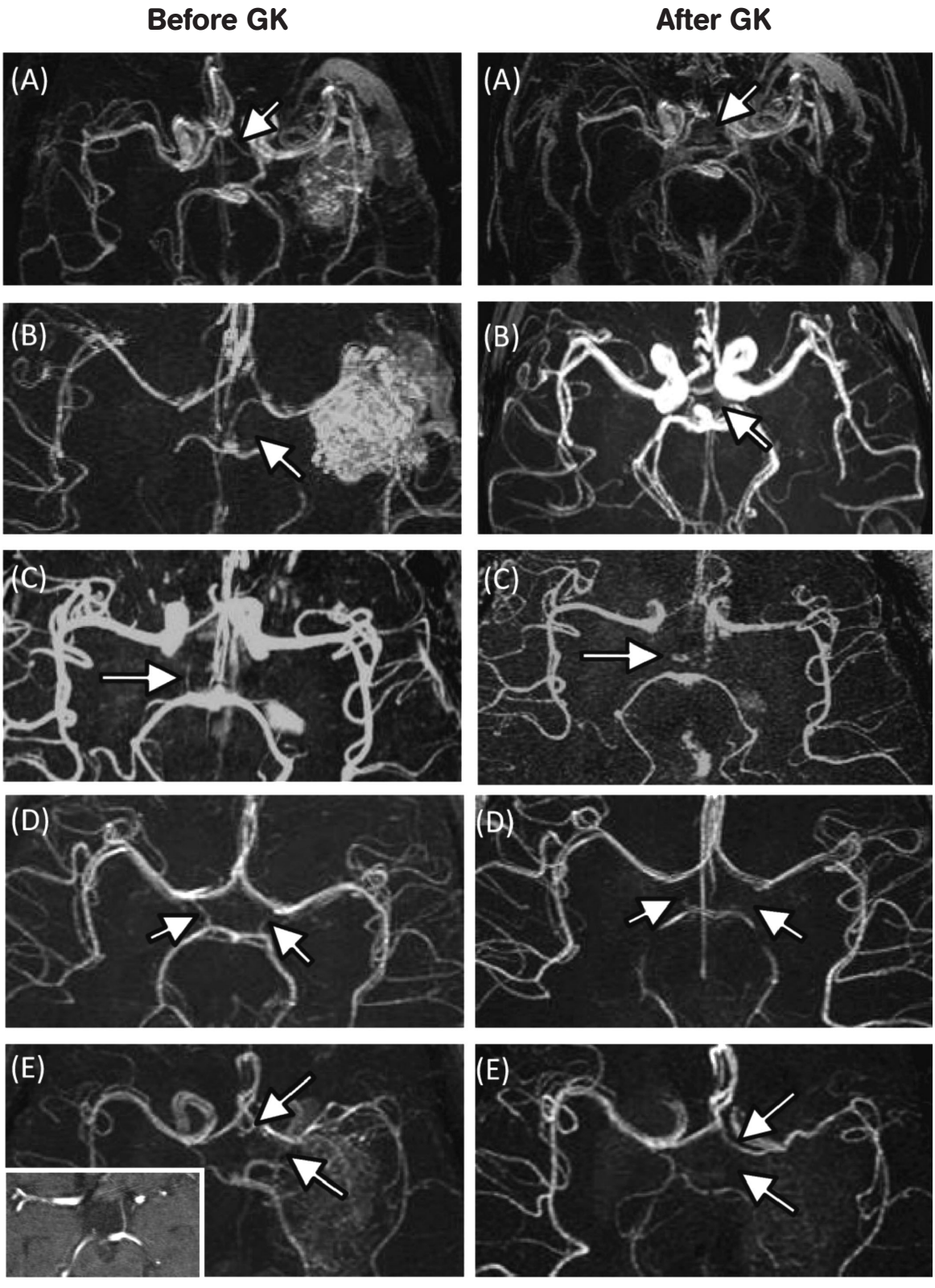
Demographic characteristics	
Age (mean ± SD), y	63.2 ± 8.4
M/F, n	51/11
Degree of contralateral ICA obstruction, n	
0–69%	55
70–99%	6
100%	4
Time from ischemic event to investigation	
1st MRA	93 ± 48 d
Complete CoW:	11 (16.9%)
Incomplete CoW:	54 (83.1%)
1st–2nd MRA	7 d
Complete CoW:	20* (30.7%)
Incomplete CoW	45 (69.3%)

Table 2. Patterns of circle of Willis morphology alteration after CAS of 23 subjects

No alteration of CoW after CAS	N = 62
Altered flow pattern of CoW after CAS	N = 23
Ceased recruitment segment of CoW after CAS (N = 14)	
(A) Ceased ipsilateral A1 segment	(N = 4)
(B) Ceased contralateral A1 segment	(N = 5)
(C) Ceased ipsilateral P-Com segment	(N = 4)
(D) Ceased ipsilateral A1 segment & P1 segment	(N = 1)
Opening of hypoplastic segment of CoW after CAS (N = 9)	
(E) Opening ipsilateral A1 segment	(N = 5)
(F) Opening ipsilateral P-Com segment	(N = 3)
(G) Opening ipsilateral P1 segment	(N = 1)
No of Ceased v.s Opening of CoW segment	14/9* (p = 0.021)
No of redistribution of Ant. v.s Post. Circulation	14/8* (p = 0.025)
(simultaneous redistribution of ant and post. circulation was excluded (N = 1))	

Cerebral arteriovenous malformations model

Latter, we conducted another longitudinal observation of glow patterns in the circle of Willis. 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 (Figure 4). The rest of the subjects (60%) remained the same. The probability of a decreased size or ceased recruitment segment of CoW


Before GK
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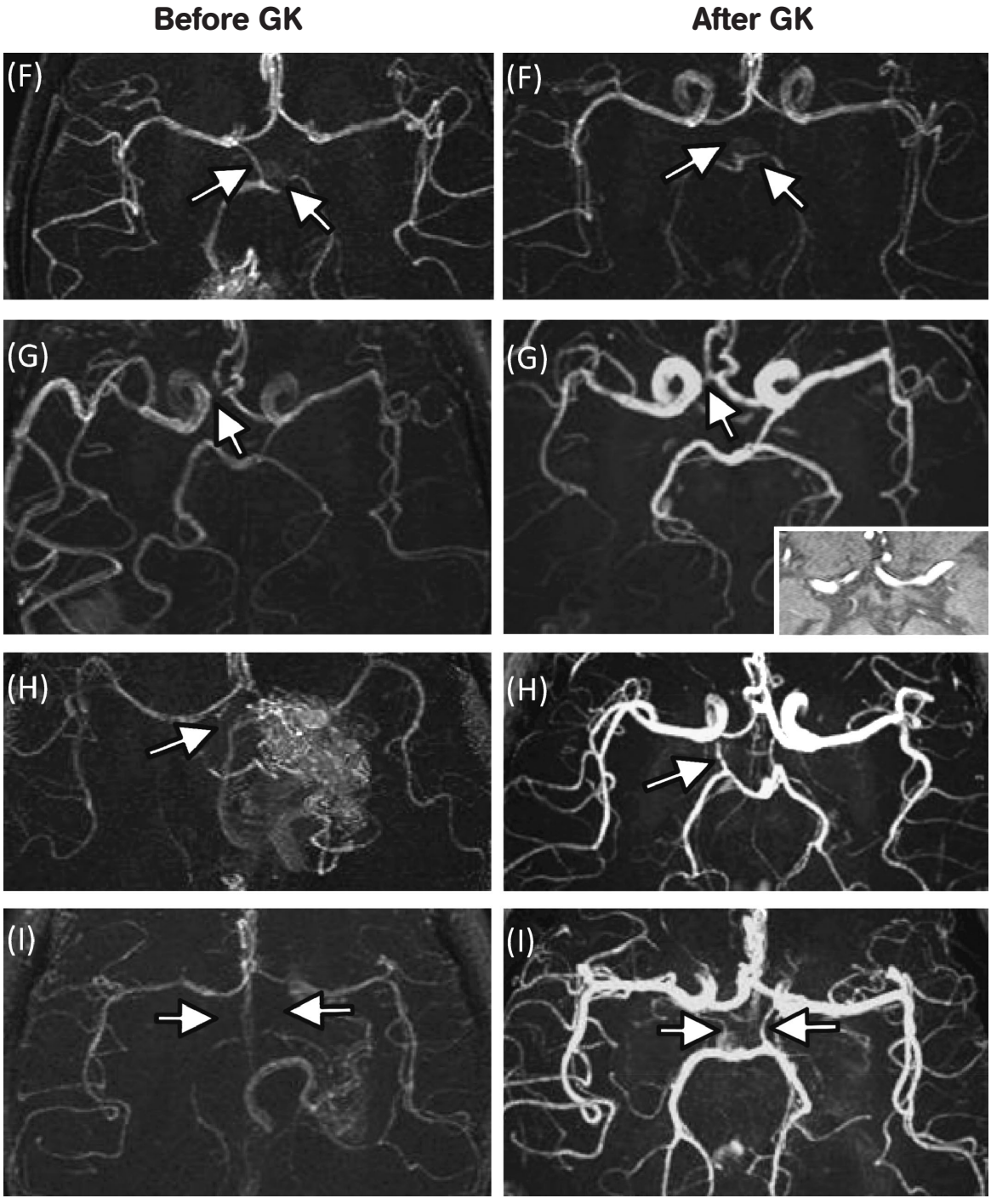

Figure 4. A comparison of baseline and post-operative MRA morphology of circle of Willis was shown as figure A to figure I. There were 8 patterns of CoW alteration after radio-surgical AVM obliteration which was categorized to type A to I which corresponds to Table 3 classification.

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[12].

AVM Nidus Size Registration/Analysis

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) (12)](Table 3).

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[13]. 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).

Correlation between the flow pattern of the circle of Willis and segmental perfusion asymmetry after carotid artery revascularization

Cerebral perfusion parameters were compared between the altered and static CoW group to determine the association of CoW morphology alteration and perfusion difference after CAS (Figure 5). The inter-hemispheric index of the relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF) was used to correlate the perfusion difference with the CoW alteration after CAS. A significant association between CoW alterations and rCBV can also be seen in the corona radiate (CR) and basal ganglia (BA) regions. An association between CoW alterations and rCBF was not found in these 65 patients; we did not observe a statistical difference in the rCBF index between the altered CoW group and the static group in all sampled regions.

Table 3. Patterns of circle of Willis morphology alteration after Gamma Knife (GK) obliteration of 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 contra-lateral PCoA segment	(N = 4)	
(D) Ceased bil. 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 contra-lateral PCoA segment	(N = 2)	
(I) Opening bil. PCoA segment	(N = 1)	
Biphasic opening and ceased two distinct CoW segment	(N = 2)	45.5+–8.8*
(E) Ceased ipsilateral PCoA segment & Opening ipsilateral A1 (N = 1)		
(F) Ceased ipsilateral PCoA segment & Opening Contralateral P1 (N = 1)		
No of Ceased v.s Opening of CoW segment	14: 2*	(P = 0.011)
Nidus size of Monophasic v.s Biphasic altered CoW	30.2+–5.6 v.s 45.5+–8.8ml (P: 0.02)	

The CR/CR1 ratio refers to the perfusion index of the CR. The altered CoW group had a significant increase in pre-stenting CBV (1.2 folds) in the stented CR area. In the pre-CAS setting, the RI index of the rCBV in the CR area of the middle cerebral artery (MCA) was significantly higher in the altered CoW group (1.23 ± 0.15) than in the static CoW group (0.87 ± 0.13; P = 0.03). The perfusion index of the rCBV in the CR area of the MCA regressed to 1.06 and 1.01 after carotid stenting in both the altered and static group. On the other hand, the RI index of the rCBV in the centrum semiovale (CS) area and occipital (O) region of the MCA (refer to the PCA territory) was comparable

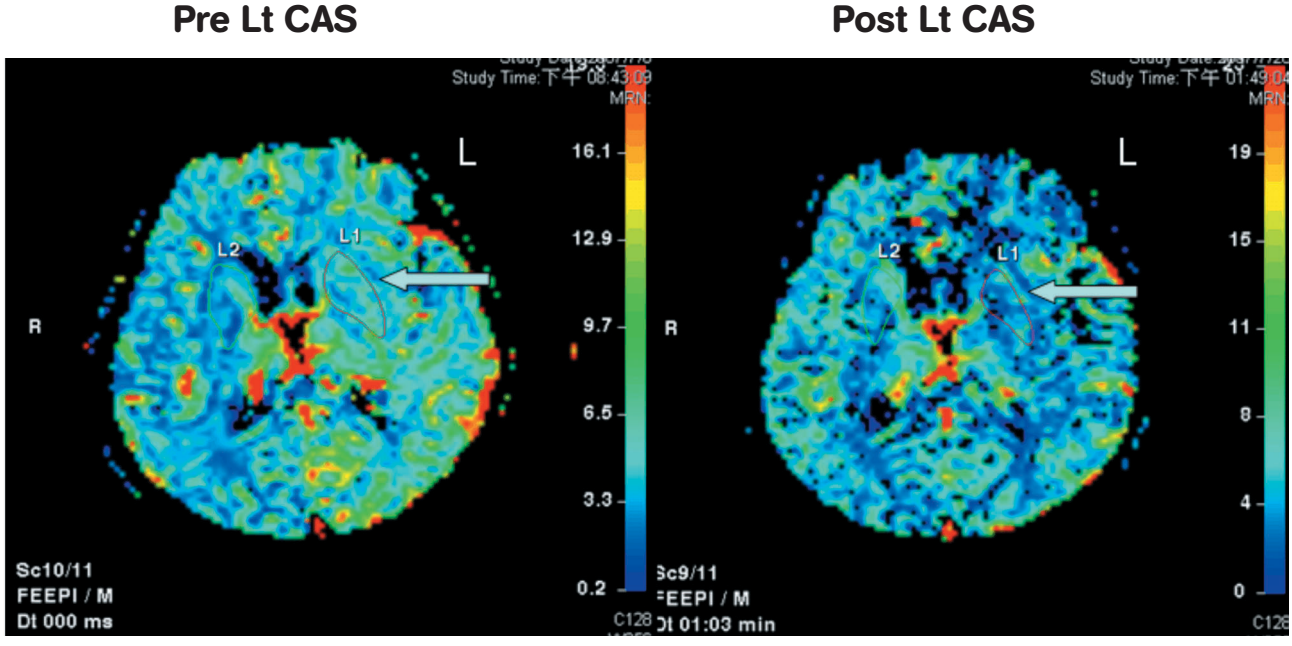

Figure 5. An increased relative cerebral blood volume (rCBV) in the left basal ganglia (arrow) pre-operatively with a significant interhemispheric perfusion asymmetry (BA/BA1 perfusion index: 1.22). The 7-day post-operative study shows decreased rCBV on the left basal ganglia with a regressed interhemispheric perfusion asymmetry (BA/BA1 perfusion index: 1.10).

between the altered and static group[14].

We compared the perfusion parameters between CAS in the ipsilateral and contralateral BA. In this carotid stenting model, the BA was supplied by a stenosed internal carotid artery (ICA) and PCA; BA1 was supplied by a patent ICA and PCA. We plotted this region of interest (ROI) to represent the mixed anterior and posterior circulation at the anastomosed site. As compared to the static CoW group, the altered CoW group showed a significant increase in pre-stenting CBV (1.25 ± 0.12 vs. 0.91 ± 0.11; $P = 0.03$) and post-stenting CBV (1.17 ± 0.07 vs. 0.85 ± 0.14; $P = 0.04$) in the BA. Unlike the RI index of the rCBV at the CR that regressed to 1.0 after carotid stenting, a higher RI index of the rCBV at the BA persisted despite carotid revascularization (Table 4).

An increased rCBV on MR perfusion images represents the vasodilatory-dependent status of the collateral circulation[15,16], which was self-evident in our study. Decreased size of CoW segments was the main characteristic, postoperatively. That is, carotid revascularization reduced the collateralization demand which shut down the dilated hypoplastic CoW segment and normalized the RI index of rCBV. Altered CoW group had a higher pre-CAS and post-CAS rCBV in the basal ganglia (rCBV perfusion index: 1.25 pre-operatively and 1.17 post-operatively). Prolonged higher rCBV at the basal-ganglia, reflecting hyperactivity of autoregulation after acute ischemic stroke, has already been documented[17]. Perforating arteries originating from the CoW occupy most of the basal ganglia. Collateral catastrophe from disintegration of the CoW primary collateral pathway[18] led to vulnerability to luxury perfusion post-operatively[18]. However, it should be noted that the cause and effect relationship of this link cannot be determined.

CONCLUSION

In this review, we gave an overview of the literature concerning fetal variant of the Circle of Willis. In fetal variant of the Circle of Willis, the possibility for collateral circulation to develop between the anterior and posterior part of the cerebral circulation is impeded, making collateral flow completely dependent on the anterior cir-

Table 4. Cerebral perfusion parameters measured before carotid stenting (Pre-CAS) and one week after carotid stenting (Post-CAS)

	Altered CoW group (N = 31)		Static CoW group (N = 34)	p-value
Age, year	48.55 ± 6.5		63.29 ± 8.5	0.00.019*
Risk factors (N)				
Hypertension	15		32	0.021*
Diabetes mellitus	08		28	0.011*
Smoking	12		18	0.321
Coronary artery disease	18		07	0.012*
Hyperlipidemia	18		22	0.422
Degree of contra-lateral ICA obstruction, n				
0–69%	9		26	0.017*
70–99%19	07		0.025*	
100%	03		01	0.435
	Pre-CAS	Post-CAS	Pre-CAS	Post-CAS
rCBV				
CR/CR1	**1.23 ± 0.15***	1.06 ± 0.13	0.87 ± 0.13	1.01 ± 0.13
CS/CS1	1.16 ± 0.15	0.96 ± 0.17	0.93 ± 0.11	1.08 ± 0.14
O/O1	0.99 ± 0.04	1.06 ± 0.14	0.97 ± 0.11	1.00 ± 0.12
BG/BG1	**1.25 ± 0.12***	**1.17 ± 0.07***	0.91 ± 0.11	0.85 ± 0.14
rCBF				
CR/CR1	**1.13 ± 0.12**	**1.05 ± 0.05**	0.91 ± 0.11	0.89 ± 0.12
CS/CS1	1.12 ± 0.11	1.02 ± 0.05	0.98 ± 0.11	1.01 ± 0.14
O/O1	**1.13 ± 0.12**	**1.08 ± 0.05**	0.92 ± 0.11	1.00 ± 0.13
BG/BG1	1.21 ± 0.14	1.18 ± 0.05	0.88 ± 0.11	0.87 ± 0.14

* Altered CoW group: altered flow pattern in the CoW after carotid stenting, static CoW group: static flow pattern in the CoW after carotid stenting, CR: stenting side in the corona radiata region; CS: CAS at the ipsilateral side of the centrum semiovale; O: CAS at the ipsilateral side of the occipital region; BG: CAS at the ipsilateral side of the basal ganglia. The similar ROIs of the non-stented hemisphere (CR1, CS1, O1, and BG1) were used as an internal reference. CR/CR1, CS/CS1, O/O1, and BG/BG1 infer to regional inter-hemispheric perfusion asymmetry index (RI index). Asterisks indicate a statistical difference between the altered CoW group and static CoW group. '*' symbol indicate a statistical significance.

culation of the contralateral side. Whether this is a risk factor for stroke should be subject of further investigation.

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