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Predisposing factors for recanalization of cerebral aneurysms after endovascular embolization: a multivariate study

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Abstract

Background—The recanalization of cerebral aneurysm after endovascular embolization (coiling or stent-assisted coiling) has been a matter of concern. We systematically evaluated the predisposing factors for cerebral aneurysm recanalization using multidimensional analysis in a large patient cohort.

Methods—In 238 patients with 283 aneurysms, patient baseline characteristics, aneurysm morphological characteristics, treatment-related factors, and changes in flow hemodynamics after endovascular treatment (coiling or stent-assisted coiling) were compared between the recanalization and non-recanalization groups. Multivariate logistic regression analysis was performed to determine independent risk factors correlated with recanalization.

Results—16 aneurysms treated by coiling recanalized, with a recurrence rate of 18.6%, and 24 recanalized in the lesions treated by stent-assisted coiling, with a recanalization rate of 12.2%. Large aneurysm (>10 mm, $P=0.002$) and follow-up interval >1 year ($P=0.027$) were demonstrated statistically significant between the recanalization and non-recanalization groups. Regarding flow

hemodynamics changes, three parameters (velocity on the neck plane, wall shear stress on the neck wall and wall shear stress on the whole aneurysm) showed relatively lower amplitude of decrease after endovascular treatment in the recanalization group. Interestingly, the velocity on the neck plane and wall shear stress on the neck wall may elevated after treatment. Specifically, the RR of velocity on the neck plane showed significant difference in the multivariate analysis ($P=0.013$), which was considered an independent risk factor for recanalization.

Conclusions—Besides the aneurysm size and follow-up interval, flow hemodynamic changes, especially the RR of velocity on the neck plane, played important roles in aneurysm recanalization.

Introduction

Endovascular therapy is now the first-line treatment for the majority of cases of cerebral aneurysms.¹ However, aneurysm treatment after endovascular embolization has a higher frequency of recanalization compared with surgical clipping, ranging from 6.1% to 33.6%.² Given the risk of recanalization, assessment of aneurysm recurrence is critical following endovascular treatment. Several risk factors have been proposed to explain aneurysm recurrence, including aneurysm morphological features, coil compaction and/or migration, and different types of endovascular embolization techniques.^{2, 3} Studies using computational fluid dynamics (CFD) have also suggested a key role of cerebral hemodynamics in aneurysm recurrence.^{4–6} However, these previous reports based on CFD were mainly performed in a relatively small patient-specific cases (for example: less than 10 cases) or in a subset of patients, which challenge the representativeness of hemodynamic findings.

Thus, the aim of the present study was to systematically develop a comprehensive assessment of the predisposing factors for aneurysm recurrence. From 283 consecutive aneurysms treated with endovascular embolization (coiling or stent-assisted coiling) in our institution, we performed a multivariate analysis including patient baseline characteristics, aneurysm morphological characteristics, treatment-related factors, and changes in aneurysmal hemodynamics to determine the independent risk factors of recanalization. To our knowledge, this was the first multidimensional report with hemodynamic analysis in such a large patient cohort.

Methods

Patient Selection

This study was conducted with the approval of our institution, and the ethics committee of our hospital approved the study protocol. We retrospectively reviewed the clinical and radiologic data of patients who underwent endovascular embolization between January 2012 and December 2014. Patient data with available angiographic follow-up that was performed at least 3 months after initial treatment were reviewed centrally by 2 experienced neuro-radiologists, independent of the study, to determine whether the aneurysm had recanalized. The angiographic results of aneurysm embolization were quantified according to the Raymond–Roy classification system;⁷ Class 1: complete obliteration, no filling of the aneurysm neck or dome; Class 2: a residual neck, the persistence of any portion filling of the

neck but not the dome; Class 3: a residual aneurysm, any opacification of the aneurysm sac. At follow-up, an aneurysm was considered recanalized if any further filling of the aneurysm neck or sac was observed compared with initial treatment findings.² Dissecting and fusiform aneurysms and patients who had insufficient three-dimensional digital subtraction angiography data were excluded from this cohort. For the purpose of this study, a total of 238 patients (283 aneurysms) with available medical and angiographic data, which were treated by coiling or stent-assisted coiling, were included in our research. All data were acquired for diagnostic purposes and computation of hemodynamics, and informed consent was obtained from each study patient or their closest relatives.

Demographic and Clinical Data

The following data were extracted from case record forms: patient baseline characteristics, including patient age and gender, smoking, drinking, and hypertension; aneurysm morphological characteristics, including large aneurysm (>10 mm),^{8, 9} wide neck aneurysm (>4 mm),^{8, 9} aneurysm status when receiving treatment (ruptured/unruptured), aneurysm locations and aneurysm geometry (sidewall/bifurcation) – aneurysm locations were categorized as anterior circulation (anterior cerebral artery, middle cerebral artery, internal carotid artery) and posterior circulation (basilar artery, vertebral artery, posterior cerebral artery); treatment-related factors, including initial angiographic result after treatment, stent-assisted, type of packing density (< 24% or >24%),^{10, 11} follow-up interval (< 1 year or >1 year); the stent was placed when the aneurysm was wide neck and/or the dome-to-neck ratio was less than 2; and packing density was calculated as the ratio of coil volume and aneurysm volume multiplied by 100% (see Supplementary File).

Computational Modeling and Hemodynamics Simulations

The patient-specific aneurysm morphologies were reconstructed from three-dimensional rotational angiography images. To calculate the hemodynamics of the aneurysms, we applied our previously developed computational modeling methods.¹² The novel virtual stenting technique^{13, 14} and the porous media method¹² were used to simulate the in vivo Enterprise stent and coil mass, respectively. Hemodynamics parameters based on CFD were performed under pulsatile flow conditions using commercial software (ANSYS CFX 14.0; ANSYS, Inc., Canonsburg, PA, USA). The computational results at the aneurysmal neck and the whole aneurysm were examined validly. For observation of hemodynamic variables, we extracted the average flow velocity and average wall shear stress (WSS) from both pre- and post- endovascular embolization at peak systole. The hemodynamic reduction ratio (RR), defined as pre-treatment parameter – post-treatment parameter/pre-treatment parameter, was calculated in each patient-specific aneurysm. The following hemodynamic changes were examined: the RR of velocity on the neck plane and inside-aneurysm, and the RR of WSS on the neck wall and the whole aneurysm wall (see Supplementary File).

Statistical Analysis

Statistical analysis was performed with statistical software (SPSS v19.0; IBM, Chicago, IL, USA). For continuous variables, the one-sample Kolmogorov–Smirnov test was used to test the normal distribution, followed by an independent-samples t-test for approximately normally distributed data. The Mann–Whitney U test was used to compare non-parametric

data, while the χ^2 test was used for categorical variables. Data are presented as frequencies (percentages) for categorical variables and mean $\pm$ SD or median (interquartile range) for continuous variables. Risk factors with a P value < 0.1 in univariate analysis were entered into a multivariate logistic regression analysis to assess the independent risk factors of recanalization. The odds ratio (OR) with 95% confidence intervals (95% CI) was calculated between the recanalization group and non-recanalization group. A 2-tailed P value < 0.05 was considered statistically significant in the multivariate logistic regression.

Results

During the study period, 283 consecutive intracranial aneurysms (40 recanalization, 243 non-recanalization) treated by endovascular embolization (coiling or stent-assisted coiling) in our hospital were included in our study. 16 aneurysms treated by coiling recanalized, with a recurrence rate of 18.6%, and 24 recanalized in the lesions treated by stent-assisted coiling, with a recanalization rate of 12.2%. Univariate analysis of patient baseline characteristics, aneurysm morphological characteristics, treatment-related factors, and hemodynamic changes are shown in Table 1. The results of multivariate logistic regression are presented in Table 2.

Patient Baseline Characteristics

There were 30% men in the recanalization group, and 27.2% men in the non-recanalization group. The mean patient age was 51.7 years in the recanalization group, and 53.6 years in the non-recanalization group. From univariate analysis, there were no differences in any patient baseline characteristics between the two groups (Table 1).

Aneurysm Morphological Characteristics

The mean aneurysm size was 10.1 ± 6.1 mm in the recanalization group, with a mean neck width of 5.6 ± 2.9 mm, and 6.8 ± 4.3 mm in the non-recanalization group, with a mean neck width of 5.1 ± 2.6 mm. By univariate analysis, there was a significantly higher proportion of large aneurysms (16, 40%) in recanalized aneurysms ($P < 0.001$, Table 1). There was a non-significant trend towards recurrence of wide neck aneurysms ($P = 0.075$, Table 1). 10 (25%) ruptured aneurysms were observed in the recanalization group, and 50 (20.6%) in the non-recanalization group, with no association of recanalization ($P = 0.526$, Table 1). There was also no association with recurrence regarding to the factors of aneurysm location (anterior circulation, posterior circulation) and the type of aneurysm geometry (sidewall, bifurcation). For aneurysmal morphological characteristics, the type of aneurysm size (> 10 mm) was the only independent risk factor for recanalization ($P < 0.001$, Table 1; OR, 4.63, 95% CI, 1.76–12.2, $P = 0.002$, Table 2).

Treatment-Related Factors

There were no differences in the initial angiographic result between the recanalization and non-recanalization groups ($P = 0.114$, Table 1). Aneurysms treated only by coiling showed a higher percentage in the recanalization group compared with the non-recanalization group (40% vs 28.8%, respectively), though it was demonstrated to be insignificant ($P = 0.154$, Table 1). Lower packing density ($23 \pm 7\%$ vs $26 \pm 6\%$, respectively) and longer interval of

follow-up (11.4 ± 7.5 months vs 9.4 ± 6.3 months, respectively) were observed in the recanalization group. However, there were no differences in the type of packing density ($P=0.203$, Table 1), whereas the interval of follow-up >1 year remained significant in the multivariate logistic regression analysis (OR, 2.51, 95% CI, 1.11–5.66, $P=0.027$, Table 2).

Hemodynamic Changes

There was a lower amplitude reduction of the velocity on the neck plane in the recanalization group (Figure 1A, C), resulting in a significantly lower median RR (19.5%) compared with the non-recanalization group (30.2%, $P<0.001$, Table 1). By contrast, the RR of velocity inside the aneurysm was similar. There were less streamlines inside the aneurysm caused by the inhibition of the stent and coils, indicating marked decrease of velocity after treatment (Figure 2D; Figure 3D), and showing no difference with a similar median value of RR in the recanalization and non-recanalization groups (71.7% vs 73.3%, respectively, $P=0.869$, Table 1). As observed for changes of velocity on the neck plane, there was a lower amplitude reduction, or potentially an even larger amplitude increase of the WSS on the neck wall in the recanalization group ($P<0.001$, Table 1). A larger area of elevated WSS may be seen on the circumference of the neck wall in the recanalization case (Figure 2C). Besides, a more marked decrease of WSS on the whole aneurysm wall between the pre- and post- treatment can be observed in the non-recanalization case compared with the recanalization one (Figure 2C; Figure 3C), which was also significantly different between the recanalization and non-recanalization groups ($P=0.026$, Table 1). Of all the significant factors in univariate analysis, only the RR of velocity on the neck plane was significantly correlated with recanalization in multivariate logistic regression analysis ($P=0.013$, Table 2).

Discussion

The durability of endovascular embolization (coiling or stent-assisted coiling) has been a major issue in the management of intracranial aneurysms. In the present study, we performed an overall evaluation of the predisposing factors correlated with recanalization in a large series of patients. Our main findings were that aneurysm size (>10 mm), follow-up interval >1 year, and the RR of velocity on the neck plane were significant independent risk factors of aneurysm recurrence.

Aneurysm Morphological Characteristics

Aneurysm size was significantly associated with recanalization in our patients, as previously reported.^{2, 15–17} What is more, we also found a 4.5-fold increase in the risk of recanalization with an aneurysm size >10 mm, similar to that reported in a systematic review and meta-analysis.¹⁷ It is possible that large aneurysms may be more susceptible to coil compaction/migration and/or coil loosening, attributed to the lower packing densities and resulting contrast filling within the aneurysmal neck or sac.^{11, 18} The precise mechanisms leading to coil changes (coil compaction, coil migration, coil loosening) remain unclear. Possibly, larger aneurysms may experience complex flow patterns caused by pulsatile flow, resulting in coil changes.^{11, 19} Based on the analysis of aneurysm morphological characteristics, we suggest that attention should be paid to large aneurysms after endovascular treatment. The use of flow-diversion embolization devices, which have a high metal surface area coverage

of the parent artery vessel, thus achieving aneurysm occlusion by marked reduction of flow velocity and endoluminal reconstruction of the parent artery,^{20, 21} may be a viable alternative for improved treatment of large aneurysms.

Treatment-Related Factors

In terms of treatment-related factors, follow-up interval >1 year was an independent risk factors for recanalization. In clinical practice, the first follow-up is routinely performed at 6 months as an index of occlusion,^{3, 22} while there is high interpersonal variability for follow-up beyond 6 months, with no safe time interval recommended.^{22, 23} Nguyen et al.¹⁶ reported follow-up strategies of 6 months, 1 year, and then every year until 5 years for ruptured aneurysms, and 1 month, 3 months, and then 5 years from initial coiling for unruptured aneurysms. Choi et al.²⁴ also suggested a first follow-up at approximately 6 months, and then annually for 4 years. However, in a series of 59 patients with coil embolization of 65 aneurysms, Jignesh et al.²⁵ reported that most occluded aneurysms at 6 months remained stable at 2-year follow-up, which questioned the need for imaging follow-up beyond 6 months. In contrast, our data suggest that a 6-month follow-up after embolization was insufficient for monitoring all recanalization, and that a further 6 months of rigorous imaging follow-up was required. In support, in a series of 501 aneurysms, Raymond et al. reported that majority of recurrence occurred at a mean of 12.31 months after embolization.¹⁵ Although repeated follow-ups provide additional expenses for patients, our findings imply that patients should receive reasonable follow-up at 1 year after initial treatment, in case early diagnosis recanalization was missed.

Hemodynamic Changes

The role of hemodynamics in aneurysm recurrence is widely reported.⁴⁻⁶ Many hemodynamic parameters have been proposed as potential indicators of aneurysm recurrence, of which velocity and WSS are considered the most important. In the largest population combined with CFD thus far, the most interesting finding in our current study was that the RR of velocity on the neck plane after embolization was a significant predictor of recanalization when controlling for other factors.

Different from previous reports, we used the RR of velocity as a normalized parameter to limit potential differences between individuals, which allowed more accurately comparisons. A relatively low amplitude RR of velocity on the neck plane was observed in the recanalization group. Of note, there were negative values for RR of velocity on the neck plane in most cases in the recanalization group, indicating elevated velocity after embolization. The higher residual velocity on the neck plane would have profound influence with later recurrence. One possibility is that the higher the residual velocity on the neck plane is, the higher the impingement occurs to the coils inside the aneurysm, which induce the coils compaction and further lead to recurrence. Another possibility is that the relatively fast blood flow may impair local blood coagulation and prevent thrombosis formation in the aneurysms.²⁶ Finally, the higher residual velocity may interfere with neointima formation of the aneurysmal orifice, which is considered essential for complete healing of the embolized aneurysms.²⁷

WSS, defined as the tangential drag force per unit area of the endothelial surface,²¹ is thought to play a significant role in recanalization. By constructing only one computational model of a curved artery, Feng et al.²⁸ proposed that high local WSS leads to degeneration of the arterial wall, and thus results in aneurysmal growth. Several later studies also reported that higher WSS promoted aneurysmal recanalization.^{4, 5, 26} By contrast, Waleed et al. found that aneurysm recurrence was related to a higher percentage of abnormally low wall shear stress, which may induce apoptosis of aneurysm endothelial cells.²⁹ In our study, a relatively low amplitude RR of WSS, or elevated WSS after embolization was observed in the recanalization group, which may be associated with recanalization but was marginally significant in multivariate analysis. The precise mechanisms underlying the biological relationship between WSS and recanalization need to be further determined.

Limitations

The current study has some potential limitations. First, we used simplified CFD analyses, including rigid walls, Newtonian blood properties, and physiological but not patient-specific flow-boundary conditions, but these parameters were previously reported to be useful for understanding flow hemodynamics in aneurysms.³⁰ Similarly, our computational modeling of the stents and coils did not fully reflect the actual situation of endovascular treatment. Besides, genetic factors and histopathological mechanisms are also important for aneurysm recanalization. The association between these aspects and aneurysm recurrence should be examined more comprehensively in future studies. Finally, flow diverter was not included in our current study because it was approved for operational use by the China Food and Drug Administration (CFDA) relatively late compared to other countries in the world. In addition, this was a retrospective single center study, and future prospective, large multicenter studies are required for detailed analysis of recanalization.

Conclusion

Using multi-dimensional analysis in a large patient cohort, we demonstrated that aneurysm size (>10 mm), follow-up interval >1 year, and RR of velocity on the neck plane were significant predisposing factors for aneurysm recurrence. These findings may be applied to clinical post-embolization management for the evaluation of recanalization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Representative velocity on the neck plane and wall shear stress on the neck wall in a recanalization (A, B) and a non-recanalization (C, D) case. First column, velocity on the neck plane (A, C). Second column, wall shear stress (WSS) on the neck wall (B, D). After embolization, there was lower amplitude reduction ratio (RR) of the velocity on the neck plane (A vs C) and obvious increases in WSS on the neck wall (B vs D) in the recanalization case.

Figure 2.

Illustrations of hemodynamics in a recanalized case, treated by stent-assisted coiling. A, angiographic images at pre-embolization (left), post-embolization (middle) and follow-up (right). B, reconstructed aneurysm model. C, wall shear stress (WSS) distribution at pre-embolization (left) and post-embolization (right). D, velocity streamlines at pre-embolization (left) and post-embolization (right). In illustration B, the green region (medium arrow) indicates the residual neck after endovascular treatment, the red region (large arrow) indicates the coiled aneurysm and the stent (small arrow) was deployed. After embolization, the WSS on the whole aneurysm wall and the flow velocity inside the aneurysm were decreased (C, D). However, the WSS on the neck wall (circumference of the black lines) increased markedly (C, black arrows).

Figure 3.

Illustrations of hemodynamics in a non-recanalized case, treated only by coiling. A, angiographic images at pre-embolization (left), post-embolization (middle) and follow-up (right). B, reconstructed aneurysm model. C, wall shear stress (WSS) distribution at pre-embolization (left) and post-embolization (right). D, velocity streamlines at pre-embolization (left) and post-embolization (right). In illustration B, the green region (large arrow) indicates the residual aneurysm after coil embolization, the red region (small arrow) indicates the coiled aneurysm. After embolization, the WSS on the whole aneurysm wall and the flow velocity inside the aneurysm were markedly decreased (C, D). In line with the changes of WSS on the whole aneurysm wall, the WSS on the neck wall (circumference of the black lines) decreased (C, black arrows).

Table 1

Univariate Analysis Between Recanalization and Non-Recanalization Groups

	Recanalization (n=40)	Non-recanalization (n=243)	P value
Patient baseline characteristics (n, %)			
age (mean $\pm$ SD)	51.7 $\pm$ 8.9	53.6 $\pm$ 9.8	0.582
male sex	12 (30%)	66 (27.2%)	0.71
smoking	9 (22.5%)	55 (22.6%)	0.985
hypertension	19 (47.5%)	117 (48.1%)	0.939
drinking	9 (22.5%)	50 (20.6%)	0.781
Aneurysm morphological characteristics (n, %)			
large aneurysm	16 (40%)	38 (15.6%)	<0.001 *
wide neck	23 (57.5%)	103 (42.4%)	0.075
ruptured aneurysm	10 (25%)	50 (20.6%)	0.526
anterior circulation	37 (92.5%)	217 (89.3%)	0.736
sidewall aneurysm	30 (75%)	178 (73.3%)	0.816
Treatment-related factors (n, %)			
initial angiographic result			0.114
complete obliteration	16 (40%)	140 (57.6%)	
residual neck	21 (52.5%)	75 (30.9%)	
residual aneurysm	3 (7.5%)	28 (11.5%)	
stent-assisted coiling	24 (60%)	173 (71.2%)	0.154
packing density >24%	22 (55%)	159 (65.4%)	0.203
interval of follow-up >1 year	13 (32.5%)	39 (16.0%)	0.013 *
Hemodynamic changes (median, IQR)			
RR of velocity on the neck plane	19.5 (−7.7~27.3)	30.2 (13.1~43.8)	<0.001 *
RR of velocity inside the aneurysm	71.7 (60.9~80.8)	73.3 (59.1~81.3)	0.869
RR of WSS on the neck wall	6.5 (−10.9~25.6)	22.7 (4.7~41.5)	<0.001 *
RR of WSS on the whole aneurysm wall	62.6 (49.1~71.7)	70.5 (53.6~78.7)	0.026 *

RR, reduction ratio; WSS, wall shear stress.

* $P < 0.05$

Table 2

Multivariate Analysis Between Recanalization and Non-Recanalization Groups

Variables	OR# (95% CI)	P value
Large aneurysm	4.63 (1.76–12.2)	0.002 *
Wide neck	0.45 (0.18–1.13)	0.089
Interval of follow-up >1 year	2.51 (1.11–5.66)	0.027 *
RR of velocity on the neck plane	0.98 (0.96–1.00)	0.013 *
RR of WSS on the neck wall	0.99 (0.98–1.00)	0.088
RR of WSS on the whole aneurysm	0.99 (0.98–1.01)	0.52

RR, reduction ratio; WSS, wall shear stress.

*
 $P < 0.05$