Risk Factor Analysis of Recanalization Timing in Coiled Aneurysms: Early versus Late Recanalization

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ABSTRACT

BACKGROUND AND PURPOSE: Long-term documentation of anatomic and angiographic characteristics pertaining to the timing of recanalization in coiled aneurysms has been insufficient. Our intent was to analyze and compare early and late-phase recanalization after coiling, identifying respective risk factors.

MATERIALS AND METHODS: A total of 870 coiled saccular aneurysms were monitored for extended periods (mean, 30.8 ± 8.3 months). Medical records and radiologic data were also reviewed, stratifying patients as either early ($n = 128$) or late ($n = 52$) recanalization or as complete occlusion ($n = 690$). Early recanalization was equated with confirmed recanalization within 6 months after the procedure, whereas late recanalization was defined as verifiable recanalization after imaging confirmation of complete occlusion at 6 months. A multinomial regression model served to assess potential risk factors, the reference point being early recanalization.

RESULTS: Posterior circulation ($P = .009$), subarachnoid hemorrhage at presentation ($P = .011$), second attempt for recanalized aneurysm ($P < .001$), and aneurysm size >7 mm ($P < .001$) emerged as variables significantly linked with early recanalization (versus complete occlusion). Late (versus early) recanalization corresponded with aneurysms ≤7 mm ($P = .013$), and in a separate subanalysis of lesions ≤7 mm, aneurysms 4–7 mm showed a significant predilection for late recanalization ($P = .008$). However, the propensity for complete occlusion in smaller lesions (≤7 mm) increased as the size diminished.

CONCLUSIONS: Although long-term complete occlusion after coiling was more likely in aneurysms ≤7 mm, such lesions were more prone to late (versus early) recanalization, particularly those of 4–7 mm in size. Long-term follow-up imaging is thus appropriate in aneurysms >4 mm to detect late recanalization of those formerly demonstrating complete occlusion.

Endovascular coiling is widely used in treating intracranial aneurysms. Despite continued improvement in related techniques and devices, the potential for recanalization remains. Risk factors linked to recanalization have been studied widely through comparative analysis, examining SAH at presentation, larger aneurysms, posterior locations, and other variables.[1,2] Coiled aneurysms showing major recanalization are subsequently in need of additional coiling, given the odds of rebleeding. Raymond et al[3] found that 46.9% of all recanalizations occurred within 6 months of procedures, with nearly 40% showing major recanalization.[4] As a function of the follow-up duration, aneurysm size and neck diameter and initial postembolization status were associated with the recanalization of coiled aneurysms monitored for 17 months.[3] However, in coiled aneurysms followed for <17 months, the initial postembolization status emerged as the sole significant risk factor for recanalization. Such a discrepancy may imply that risk factors inherent in aneurysm configuration have a greater long-term impact on recanalization.[4,5] Therefore, an association between the timing of recanalization and related risk factors is feasible. Most previous studies in this setting have limited risk factor analysis to patients showing either recanalization or complete occlusion, without considering time to recanalization. In this study, coiled saccular aneurysms were monitored over a longer term to analyze and compare early and late-phase recanalization, thereby identifying respective risk factors.

MATERIALS AND METHODS

A retrospective analysis of 898 patients (1035 aneurysms) took place, each patient having undergone coil embolization between

January 2008 and December 2010 at a single institution. Nonsaccular aneurysms (*n* = 70), specifically the fusiform/dissection, traumatic, or infectious types, were excluded from this analysis. The study end point was the timing of recanalization (early versus late) during follow-up. Another 66 patients lacking 6-month imaging data (lost to follow-up, 40; vegetative states, 16; deaths, 10) and 29 aneurysms followed for 6 months only were secondarily excluded. Ultimately, 746 patients with 870 saccular intracranial aneurysms who were monitored for more than 12 months met criteria for study enrollment.

In reviewing the medical records, sex, age, clinical presentation (unruptured intracranial aneurysm or SAH), and attempt at embolization (first versus second) were recorded, in addition to histories of hypertension, current smoking, and antiplatelet regimens. Patient angiographic variables included size of aneurysm (overall and at neck)[5]; circulatory location (anterior [including posterior communicating artery] versus posterior)[6]; aneurysm type (sidewall versus bifurcation) and depth-to-neck ratio; confirmed stent placement; initial postembolization status (successful occlusion versus residual sac)[4]; and coil technology (hydrogel-modified [HydroSoft; MicroVention, Tustin, California] or polyglycolic acid/lactide copolymer–coated [Matrix; Boston Scientific, Natick, Massachusetts]). Aneurysms were also grouped according to the extent of bioactive coil used (relative to the collective length of inserted coil) as bare (≤50%) or bioactive (>50%). This study was conducted with the approval of our institutional review boards. The requirement to obtain written informed consent for study participation was waived.

Endovascular Procedure and Angiographic Follow-Up
Most endovascular procedures were conducted under general anesthesia using an Integris V (Philips Healthcare, Best, the Netherlands) scanner in each instance.[4] Dual-agent antiplatelet therapy (loading doses [ie, 300 mg each] of clopidogrel and aspirin), given 1 day before procedures, plus additional clopidogrel (75 mg) and aspirin (100 mg) dosing on the mornings of procedures, were administered to patients with unruptured aneurysms for anticipated stent protection.[7] In poor responders to clopidogrel, signaled by the VerifyNow P2Y12 assay (Accumetrics, San Diego, California), cilostazol was added. If stent placement was unlikely, antiplatelet medications were not routinely used except in patients receiving such agents for other medical conditions. A bolus of heparin (3000 IU), given upon placement of the femoral arterial sheath, was thereafter sustained by hourly doses (1000 IU), and the activated clotting time was monitored each hour. Continuance of dual antiplatelet therapy was advised for at least 3 months postoperatively, followed by single-agent maintenance for at least 1 year in patients with stents deployed. In the absence of stent placement, antiplatelet therapy was selectively dispensed in instances of prior antiplatelet medication use, coil protrusion, or procedural thromboembolism.

Immediate postembolization angiographic results were graded as follows by using the 3-point Raymond scale: complete occlusion, residual neck, or residual sac. Complete occlusion and small residual neck were considered successful occlusive attempts.[4] Follow-up radiologic examinations, performed at 6, 12, 24, and 36 months postprocedure, relied on TOF-MRA, with 3D reconstruction and source images. Additional plain radiography was recommended at postembolization months 1 and 3 in patients presenting with hemorrhage. Conventional angiography was advised if MRA assessment of treated aneurysms was not feasible or if recanalization was suspected by noninvasive diagnostics (such as MRA or plain radiography) to gauge the need for further treatment. Anatomic outcomes in follow-up were categorized by the Raymond scale as follows: complete occlusion and recanalization (minor or major). Early recanalization was equated with confirmed recanalization within 6 months or upon postembolization follow-up imaging at 6 months, whereas late recanalization was defined as verifiable recanalization after imaging confirmation of complete occlusion at 6 months. Two qualified neurointerventionists (Y.D.C. [10 years' experience] and H.-S.K. [15 years' experience]) reviewed the radiologic data. In cases of discrepancy, a consensus was reached by the third interventional neuroradiologist (M.H.H. [>25 years' experience]).

Statistical Analyses
Continuous data are expressed as mean ± standard deviation by using χ^2 or Fisher exact test and unpaired *t* test to assess categoric and continuous variables, respectively. Univariate analysis was applied to evaluate between-group differences (early or late recanalization and stable occlusion). To examine the interrelationships of risk factors, a multinomial regression model was engaged, with early recanalization serving as the reference point. Risk factors differing by group at the $P < .10$ level were entered into the model. Nagelkerke R^2 was measured for explaining variation, which is estimated on the log-likelihood scale. A Kaplan-Meier estimate of cumulative survival (without recanalization) in coiled aneurysms according to aneurysm size was performed. All calculations relied on standard statistical software (SPSS v19; IBM, Armonk, New York), setting significance at $P < .05$.

RESULTS
Characteristics of Patient Enrollees
A total of 870 coiled saccular aneurysms were monitored for a mean period of 30.8 ± 8.3 months. Female patients accounted for 68.4% (595/870) of the aneurysms, and the mean age of all patients was 57.9 ± 11.0 years. Anterior circulation (*n* = 802; 92.2%) and bifurcation aneurysms (*n* = 388; 44.6%) predominated. Successful occlusion as an initial angiographic outcome was achieved in 657 coiled aneurysms (75.5%), with mean aneurysm size estimated at 5.3 ± 3.3 mm. Overall, 712 (81.8%) aneurysms were ≤7 mm. SAH was evident at presentation in 138 cases (15.9%), including 74 recanalized aneurysms (8.5%). In 707 aneurysms (81.3%), the coil inserted qualified as bare (≤50% bioactive). Stents were deployed in 222 instances (25.5%). During the follow-up period, 690 coiled aneurysms displayed complete occlusion, early recanalization was observed in 128 (minor recanalization, *n* = 45; major recanalization, *n* = 83), and late recanalization developed in 52 (minor recanalization, *n* = 34; major recanalization, *n* = 18). In terms of late recanalization, 31 (59.6%) instances were evident within 6–12 months, 19 (36.5%) within 12–24 months, and 2 (3.9%) within 24–36 months after procedures. Retreatment was recommended for major recanalized aneurysms and was actually performed as follows: 48 (57.8%) occurring early and 11 (61.1%) occurring late. During the follow-

up, no patients included in this study experienced SAH or re-bleeding. Detailed data on characteristics of the aneurysms in this cohort are shown in Table 1.

Risk Factors of Late Recanalization and Complete Occlusion

In between-group comparisons, female sex, age, history of hypertension, hyperlipidemia, smoking, aneurysm type, depth-to-neck ratio >1, initial postembolization status, and >50% bioactive coil usage did not reach statistical significance. However, aneurysm location, clinical presentation, second embolization for recanalization, aneurysm size >7 mm, and stent deployment differed significantly by group in the univariate analysis (Table 1).

The multinomial regression model further disclosed that posterior circulation (P = .009), SAH presentation (P = .011), required second embolization (P < .001), and aneurysm size >7 mm (P < .001) showed stronger associations with the early recanalization (versus complete occlusion) group (Table 2).

In comparing early and late recanalization, a link between aneurysm size >7 mm and early recanalization was apparent, whereas smaller lesions (≤7 mm) were associated with late recanal-ization (P = .013). Other group variables, such as posterior circulation, SAH presentation, second attempt (in recanalized lesions), antiplatelet agent use, and stent deployment did not differ significantly (Table 2). Further subanalysis of aneurysms ≤7 mm showed a significant relationship between aneurysms 4–7 mm in size and late recanalization (odds ratio, 3.00; P = .008). However, of those aneurysms ≤7 mm, diminishing size and stable occlusion were increasingly linked (On-line Table).

According to the Kaplan-Meier method, the cumulative survival rate without recanalization at 6 months was 90.7% in aneurysms ≤7 mm and 60.8% in aneurysms >7 mm. At 30 months after the procedure, the cumulative survival rate was 84.8% for aneurysms ≤7 mm and 52.8% for aneurysms >7 mm (P < .001) (On-line Fig).

DISCUSSION

Our findings indicate that small-sized aneurysms (≤7 mm) are relatively more susceptible to late (versus early) recanalization, despite a stronger association with complete occlusion. On the other hand, early recanalization correlated with locations in the posterior circulation, SAH presentation, second coiling for recanalization, and aneurysm size >7 mm. In particular, aneurysms ranging from 4–7 mm were more prone to late recanalization. Consequently, small-sized aneurysms >4 mm should be followed long-term for potential delayed recanalization, despite any proof of complete occlusion at midterm follow-up.

Patients presenting with SAH are also more likely to develop recanalization after coiling procedures.[3,8] The dynamic nature of ruptured aneurysms and clot lysis appears to promote recanalization. Wardlaw et al[9] reported that such aneurysms showed increased cross-sectional area expansibility (mean, 53%) during the cardiac cycle relative to adjacent normal arteries (mean, 20%). Recently, higher saccular pulsatile pressures have also been recorded in ruptured (versus unruptured) lesions,[10] and thinner, degenerative arterial walls, with significant macrophage infiltration, have been documented in histologic sections of ruptured aneurysms.[11] Mural instability and the increased pulsatile pressure of ruptured aneurysms may thus encourage greater coil compaction than that encountered in unruptured counterparts.[12] Lysis of clot may take place as well within thrombus or at rupture sites once related hypercoagulability subsides.[8]

Of particular importance, an increase in packing attenuation of near 30% may reduce intra-aneurysmal wall shear stress, promoting recanalization.[13] The probability of coil compaction declines if aneurysms are more densely packed (>20% in aneurysms <200 mm³; >24% in aneurysms <600 mm³).[14] Packing attenuation in our cohort (when excluding recanalized aneurysms) did not differ significantly in patients presenting with (36.3 ± 10.9) or without (36.1 ± 8.8) SAH (P = .859). Nevertheless, SAH proved significantly more frequent in aneurysms marked by early recanalization (versus complete occlusion) (P = .011). Further studies on the mechanism of recanalization in ruptured aneurysms are clearly needed.

Table 1: Baseline characteristics of study enrollees

Variables	Early (n = 128)	Late (n = 52)	Complete (n = 690)	P Value[a]
Female	94 (73.4%)	34 (65.4%)	467 (67.7%)	.389
Age, yr	58.0 ± 11.1	55.3 ± 12.1	58.1 ± 10.5	.330
HTN	80 (62.5%)	25 (48.1%)	375 (54.3%)	.134
Hyperlipidemia	15 (11.7%)	12 (23.1%)	123 (17.8%)	.126
Smoking	19 (14.8%)	6 (11.5%)	91 (13.2%)	.815
Location				
Anterior	104 (81.2%)	48 (92.3%)	650 (94.2%)	
Posterior	24 (18.8%)	4 (7.7%)	40 (5.8%)	<.001
Presentations				
UIA	99 (77.3%)	38 (73.1%)	595 (86.2%)	
SAH	29 (22.7%)	14 (26.9%)	95 (13.8%)	<.001
Second attempt	33 (25.8%)	7 (13.5%)	34 (4.9%)	<.001
Type				
Sidewall	66 (51.6%)	28 (53.9%)	388 (56.2%)	
Bifurcation	62 (48.4%)	24 (46.1%)	302 (43.8%)	.604
Maximum size, mm	8.3 ± 5.1	5.7 ± 2.2	4.6 ± 2.6	
Aneurysm size >7 mm	62 (48.4%)	12 (23.1%)	84 (12.2%)	<.001
D/N ratio (>1)	69 (53.9%)	35 (67.3%)	391 (56.7%)	.249
Balloon	22 (17.2%)	8 (15.4%)	162 (23.5%)	.141
Stent	45 (35.2%)	8 (15.4%)	169 (24.5%)	.009
Antiplatelet medication	48 (37.5%)	19 (36.5%)	183 (26.5%)	.018
Initial occlusion				
Successful occlusion	96 (75.0%)	42 (80.8%)	519 (75.2%)	
Residual sac	32 (25.0%)	10 (19.2%)	171 (24.8%)	.661
Bioactive coil (>50%)	26 (20.3%)	8 (15.4%)	129 (18.7%)	.743

Note:—D/N ratio indicates depth-to-neck ratio; HTN, hypertension; UIA, unruptured intracranial aneurysm.
[a] P < .05 is significant.

Table 2: Multinomial logistic regression; late recanalization versus complete occlusion (early recanalization serving as reference)[a]

Variables	Late Recanalization		Complete Occlusion	
	Odds Ratio (95% CI)	P Value[b]	Odds Ratio (95% CI)	P Value[b]
Posterior circulation	0.54 (0.17–1.72)	.301	0.42 (0.22–0.80)	.009
SAH presentation	1.16 (0.53–2.56)	.710	0.51 (0.30–0.86)	.011
Second attempt	0.65 (0.24–1.73)	.39	0.15 (0.08–0.27)	<.001
Stent	0.53 (0.21–1.32)	.172	1.39 (0.84–2.31)	.197
Antiplatelet medication	1.15 (0.58–2.30)	.689	0.73 (0.47–1.14)	.167
Aneurysm size >7 mm	0.38 (0.18–0.82)	.013	0.17 (0.10–0.26)	<.001

[a] Reference category: early recanalization. Nagelkerke R^2 = 0.214.
[b] P < .05 is significant.

Outcomes of the Unruptured Cerebral Aneurysm Study[15] have shown an association between aneurysms >7 mm in size and rupture. Relative to aneurysms 3–4 mm in size, larger lesions were at significantly greater risk (5–6 mm: hazard ratio = 1.13, P = .71; 7–9 mm: hazard ratio = 3.35, P < .001; 10–24 mm: hazard ratio = 9.09, P < .001). According to the International Study of Unruptured Intracranial Aneurysms,[16] 5-year cumulative rupture rates in anterior circulation aneurysms without previous SAH also varied decisively by lesion size (<7 mm, 0%; 7–12 mm, 2.6%; 13–24 mm, 14.5%). Larger aneurysms also are more likely to recanalize. Cognard et al[8] earlier determined that recanalization rates indeed are a function of aneurysm size (2–3 mm, 8.7%; 4–5 mm, 9.0%; and 6–8 mm, 22.0%). In addition, Jeon et al[5] have shown an association between large aneurysms (>7 mm) completely occluded in 6-month follow-up images and late recanalization, and reports by Ogilvy et al[17] and Niimi et al[18] similarly maintain that larger aneurysms (≥10 mm) are prone to recanalization. It is thus evident that large aneurysms are at peril of rupture and postprocedural recanalization. However, recanalization rates in small aneurysms have not been fully detailed, though they are considered to be low. Murayama et al[19] have cited a 5.1% overall recanalization rate for small aneurysms 4–10 mm in size with small necks, which was much lower than the 35.3% rate for larger aneurysms. The reported annual recanalization rate in aneurysms ≤7 mm showing complete occlusion at 6-month follow-up is 2.57%.[5] After some reflection, a subgroup analysis of our data was performed, examining recanalization rates in lesions <4 mm and in those 4–7 mm. Our findings showed that aneurysms 4–7 mm were more prone to late recanalization. Consequently, small-sized aneurysms >4 mm should be followed long-term for potential delayed recanalization despite confirming complete occlusion at midterm follow-up.

Stents are increasingly used in this setting if greater coil packing and flow diversion are anticipated.[20-23] Recanalization rates registered after stent-assisted coil embolization (6.6%–13%)[4,24,25] are notably lower than those encountered after simple coil embolization (10.7%–33.6%).[3,26] In our investigation, stent deployment differed significantly among 3 groups (early recanalization, n = 45 [45/128, 35.2%]; late recanalization, n = 8 [8/52, 15.4%]; and complete occlusion, n = 169 [169/690, 24.5%] [P = .009]) through univariate analysis. However, stent deployment held no significant association with complete occlusion or late recanalization in a multinomial logistic regression analysis using early recanalization as a reference. Although potential confounding factors related to the high probability of stent deployment in wide-neck aneurysms and the incorporation of arterial branches by aneurysms may have skewed our assessment of this presumptive benefit, Jeon et al[20] found that stents conferred no protective effects relative to progressive occlusion in small unruptured aneurysms with residual sac filling (P = .78). Still, after various corrections in the propensity score analysis, stent placement did promote progressive occlusion in coiled aneurysms.[20] In our opinion, the impact of stents is better investigated by considering the probability of stent deployment.

Hemodynamic force is another reputed factor in aneurysm recanalization and growth.[2] In recanalized aneurysms, maximum wall shear stress and spatially averaged wall shear stress exceed corresponding pretreatment values.[27] In addition, completely occluded aneurysms show diminished wall shear stress and flow velocity.[28] The efforts of Ortega et al[29] indicate that maximum wall shear stress increases at sites of blood flow impingement near remnant necks. Repetitive flow impingement and subsequent wall shear stress increments may thus lead to recanalization,[4] particularly in recanalized aneurysms. Our results also show that second attempts for recanalization were done with significantly greater frequency in early recanalized versus completely occluded aneurysms (P < .001), with no statistical difference between the early and late recanalization groups.

The HydroSoft coil was constructed as a platinum coil with an inner core of hydrogel and was designed to improve packing attenuation with low stiffness.[30] Lee et al[31] reported that the mean packing attenuation of the aneurysms treated with the HydroSoft coil was significantly higher than of those treated with a bare platinum coil (36.0% versus 32.1%; P < .001) without a difference in procedure-related complications. The use of the HydroSoft coil significantly lowered the retreatment rate at 12-month follow-up (adjusted risk ratio, 0.21; 95% CI: 0.07–0.64). Matrix detachable coils are covered with polyglycolic and polylactic acid and designed to enhance clot formation and fibrosis within the aneurysm sac.[32] A histology study showed a thick connective tissue formation that demarcated the aneurysm sac from the parent artery.[33,34] In our cohort, the number of treated aneurysms using bioactive coil (>50%) was 26/128 (20.3%) in early recanalization, 8/52 (15.4%) in late recanalization, and 129/690 (18.7%) in complete occlusion (P = .743). We speculate that the relative low proportion of bioactive coil (>50%) might lead to insignificant association among the 3 groups.

Although risk factors in recanalization have been well described through comparative studies of stably occluded and recanalized aneurysms, the potential difference between early and late recanalization is perhaps another issue to pursue in devising strategies for patient management. Herein, we have focused on analyzing risk factors with respect to the timing of recanalization. Our findings indicate that aneurysms of 4–7 mm are at significant risk of late recanalization, thereby mandating long-term follow-up.

Unfortunately, selection bias in this large (n = 870) and closely monitored sampling of aneurysms cannot be excluded, given the retrospective nature of this study. Furthermore, use of TOF-MRA in follow-up testing may entail some artifact because of stents obscuring recanalization.[20] Although the use of MIP in source images obtained by TOF-MRA has proved effective in estimating recanalization,[35] stent artifacts may still obscure instances of minor recanalizations, impacting calculated recanalization rates.[20] In addition, coil compaction and recanalization could be more pronounced in patients with small aneurysms who underwent MRA follow-up. On another note, anterior circulatory and unruptured aneurysms in our cohort accounted for 92.2% and 84.1% of lesions, respectively. Thus, lesions of the posterior circulation and ruptured aneurysms were not well represented.[5] Finally, and more specifically, recanalization of aneurysms may occur through growth of the lesions themselves, through poorly formed/degraded thrombus, or through failed

attempts at reconfiguring the saccular dome or neck.[36] More detailed investigations of recanalization are needed to better correlate angiographic outcomes with reciprocating effects of the healing process.

CONCLUSIONS

Risk factors related to early recanalization in this study were posterior circulatory location, SAH presentation, second coiling for recanalization, and aneurysm size >7 mm. Although aneurysms ≤7 mm in size were more prone to complete occlusion in long-term follow-up, a relative predisposition to late (versus early) recanalization was apparent, particularly in aneurysms of 4–7 mm. Long-term follow-up imaging is thus advisable in aneurysms >4 mm to exclude progression to recanalization, despite complete occlusion at midterm monitoring.

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