Wall enhancement, edema, and hydrocephalus after endovascular coil occlusion of intradural cerebral aneurysms

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Object. Symptomatic local inflammation, aseptic meningitis, and hydrocephalus are reported in a group of patients treated with second generation/modified platinum coils. The purpose of this study was to define the frequency and determinants of magnetic resonance (MR) imaging findings of aneurysm wall enhancement, perianeurysmal edema, and hydrocephalus in a cohort of coil-embolized intradural cerebral aneurysms treated with bare platinum or modified platinum coils (Matrix or HydroCoils).

Methods. The authors retrospectively reviewed 359 Gd-enhanced MR follow-up studies of 181 treated aneurysms (125 ruptured) for mural enhancement. Univariate and multivariate logistic regression analyses were used to define mural enhancement associations with demographic, clinical, angiographic, treatment, and follow-up data. Embolization-related edema and hydrocephalus were defined in 95 MR imaging studies of 56 unruptured aneurysms.

Results. Asymptomatic wall enhancement was observed in lesions treated with all coil types, occurring in 21 (18.6%) of 113 bare platinum coil–treated aneurysms. Independent associations were HydroCoil treatment (odds ratio [OR] 9.75, 95% confidence interval [CI] 3.45–30.75) and increasing aneurysm size (OR 3.58, 95% CI 1.99–6.95). Five (8.9%) unruptured aneurysms had asymptomatic de novo edema, and 3 (5.3%) demonstrated hydrocephalus; all had been treated with HydroCoils. Hydrocephalus presentation was delayed (8–31 months) and symptomatic in 2 patients.

Conclusions. Asymptomatic aneurysm wall enhancement occurred in 18.6% of embolizations performed with bare platinum coils, and probably represents a normal healing response. Perimal edema and hydrocephalus were observed only in patients treated with HydroCoils, but have been reported in patients treated with other modified platinum coils. These symptoms appear to represent an exaggerated inflammatory response during aneurysm healing. Increased vigilance for delayed hydrocephalus is required. Judicious clinical use of modified platinum coils is warranted until results of randomized trials are published. (DOI: 10.3171/JNS/2008/108/6/1074)

Key Words • aneurysm wall enhancement • coil embolization • edema • hydrocephalus

The use of standard or “bare” platinum coils has revolutionized cerebral aneurysm treatment, with a proven benefit of embolization with bare platinum coils compared with surgery in ruptured aneurysms.5,50 The major limitation of bare platinum coil embolization is the long-term recurrence rate of 14–21%.17,26,43,52,56 Modifications of bare platinum coils (which we will refer to as “modified platinum coils”) were developed to promote more stable aneurysm occlusion by inducing a more prolific inflammatory response or a more complete volumetric occlusion. Currently, there are only 2 basic types of modified platinum coils approved for clinical use. The first, which features the bioabsorbable polyester polymer PGLA, is available in different forms as Matrix (Boston Scientific), Cerecyte (MicroVention, Inc.), and Nexus (MicroTherapeutics, Inc.). These PGLA-based coils are designed to achieve aneurysm healing through stimulation of a vigorous chronic inflammatory response on degradation of the device’s polymeric braid, aiming to speed thrombus organization.53 In the second device, the expanding hydrogel in HydroCoils (MicroVention, Inc.) is designed to increase volumetric filling of the aneurysm sac to provide a stable coil mass, particularly at the lesion’s neck, thereby promoting thrombus organization.38 The safety and efficacy of modified platinum coils are unproven in the randomized trials published to date. Symptomatic local inflammation, aseptic meningitis, and hydrocephalus are complications that are being increasingly reported in patients treated with modified platinum coils.6,7,9,14,20,36,46 Reported MR imaging findings in these patients are aneurysm wall enhancement, perianeurysmal edema, and hydrocephalus.6,46 Our aim was to evaluate the frequency and determinants of the described MR imaging findings in a cohort of patients with intradural cerebral aneurysms treated with bare platinum coils, Matrix coils, and HydroCoils. We report on 3 cases of delayed hydrocephalus related to HydroCoil treatment in unruptured aneurysms.
Wall enhancement, edema, and hydrocephalus after coil embolization

We review the literature on inflammatory changes associated with coil-embolized aneurysms.

**Clinical Materials and Methods**

**Patient Population**

Patients registered in our institution’s Aneurysm Data Bank between January 2000 and December 2006 were included in the study if they met the following criteria: 1) they had undergone an endovascular coil embolization procedure performed on a previously untreated aneurysm during the study period; and 2) they had at least 1 posttreatment Gd-enhanced MR imaging study available for review. The cohort consisted of 181 aneurysms (125 of them ruptured) in 178 patients in whom a total of 329 Gd-enhanced MR studies were performed during the follow-up period. This cohort represented 55% of all endovascularly treated aneurysms during this period, 46% of endovascularly treated aneurysms during the years 2000–2003, and 71% of endovascularly treated aneurysms during 2004–2006. The increased use of MR imaging studies later in the series reflects a change in our practice; we began performing follow-up evaluations of coil-embolized aneurysms with Gd-enhanced MR angiography rather than catheter angiography. In our institution, follow-up MR imaging studies in ruptured aneurysms are performed at early time points (typically predischarge and at 2 and 6 months postdischarge) to act as a baseline and detect early recanalization. Aneurysms requiring additional coil embolization of previously coil-treated but reopened lesions (repeated coil embolization) were excluded. The clinical and treatment data in this study were prospectively acquired. The patients were clinically assessed and follow-up was performed in a multi-institutional setting. Clinical records and radiological images were reviewed in the event of incompletely recorded data. Demographic details, clinical presentations, and aneurysm characteristics of the study group are given in Table 1.

**Aneurysm Wall Enhancement, Edema, and Hydrocephalus Evaluation**

Two neuroradiologists who were blinded to clinical and treatment data retrospectively reviewed the MR imaging studies. Differences were resolved by consensus. The MR imaging studies of the brain were performed on a 1.5-T MR system (Signa Echospeed, version 8.2.3 software, GE Medical Systems) equipped with a standard head coil. Wall enhancement was defined as a complete enhancing ring around the coil-treated aneurysm on axial Gd-enhanced T1-weighted sequences (TR/TE 400/20 msec; section thickness/interspacing 5/2 mm). Also, T1-weighted sequences obtained without contrast were reviewed to exclude intrinsic T1 shortening due to hemorrhage. Source MR angiography images were examined to exclude enhancement arising from normal vessels. Mural enhancement was defined in the complete cohort of 181 aneurysms (both ruptured and unruptured lesions) to have sufficient outcome events to enable a number of independent variables to be included in a logistic model and to define the effect of clinical presentation on enhancement patterns.

The process of aneurysm rupture or the presence of parenchymal hemorrhage may cause edema in the brain parenchyma around an aneurysm. To avoid this potential confounding problem, perianeurysmal edema was defined only in unruptured aneurysms. The unruptured aneurysm cohort consisted of 56 aneurysms in 48 patients in whom a total of 95 MR imaging studies were obtained during the follow-up period. Edema was identified as the presence of perianeurysmal hyperintensity on axial FLAIR sequences (TR/TE/TI 9002/174/2200 msec; section thickness/interspacing 5/2 mm). Edema was attributed to the coil embolization process (de novo edema) if the following conditions were met: 1) pretreatment cross-sectional imaging studies showed absence of edema; 2) posttreatment studies confirmed edema; and 3) there was no major aneurysm recanalization or growth that could account for the edema. Figure 1 shows an example of wall enhancement and perianeurysmal edema. The presence or absence of coil-related hydrocephalus was defined on follow-up MR imaging studies in unruptured aneurysms. Hydrocephalus was defined as ventricular enlargement in relation to the baseline pretreatment study, with or without transependymal edema.

**Aneurysm Description**

The aneurysm dome and neck dimensions were calculated from 3D DS angiography data. The aspect ratio was calculated as the maximum dimension of dome/width of neck, and results were dichotomized as a ratio < 2 or ≥ 2. Aneurysm location was classified as the anterior or posterior circulation according to anatomical convention.

**Coil Type and Packing Density Calculation**

The type of coil used was recorded. The term “bare platinum coil” refers to aneurysms treated solely with uncoated platinum coils; “Matrix coil” and “HydroCoil” refer to aneurysms treated with bare platinum coils in conjunction with either Matrix coils or HydroCoils, respectively. For the entire group of 181 aneurysms, 113 (62.4%) were treated with bare platinum coils, 35 (19.3%) with Matrix coils, and 33 (18.2%) with HydroCoils. In the cohort of 56 unruptured aneurysms, the corresponding values were 31 (55.4%) for bare platinum, 8 (14.3%) for Matrix, and 17 (30.4%) for HydroCoils. The reason the interventionalist selected a particular coil was not documented, although trends in coil selection could be observed. HydroCoils tended to be used in aneurysms with a perceived greater risk of recurrence; namely, aneurysms with large domes or wide necks. These aneurysm characteristics were more frequently observed in our unruptured cohort, and probably reflect the more frequent use of HydroCoils in this group. Aneurysm sac volume was calculated based on the assumption that the aneurysm was ellipsoid in shape, by using the following formula: \[ V = \frac{4}{3} \pi (a/2)(b/2)(c/2) \], where \( V \) represents the calculated aneurysm volume, \( a \) is the width, \( b \) the length, and \( c \) the height of the aneurysm. The volume of a multilobed aneurysm was calculated as the sum of the individual components. The packing ratio was calculated for each aneurysm by taking the sum of the volumes of all the introduced coils and dividing it by the aneurysm volume. The volume of an introduced coil was calculated based on the supposition that coils are cylindrical, by using the following formula: \[ V_{coil} = \pi (d/2)^2(l) \], where
Vcoil represents the volume of the coil, d is the coil’s diameter, and l is its length. The calculated volume of the HydroCoil was based on the fully expanded state. The primary diameter of each type of coil we used is available from Boston Scientific, Microvention, and Micrus corporations.

Coil Insertion Technique

The technique applied to the endovascular treatment of aneurysms has been extensively reported, and is not discussed in detail here. In our practice, aneurysms were tightly packed with coils, stopping deposition only at the point when no more coils could be safely placed or when complete angiographically confirmed occlusion was obtained. Coil selection in each aneurysm was at the discretion of the treating interventionalist, and the reason for choosing a particular coil type was not recorded.

Angiographic Evaluation

Immediate postembolization DS angiograms and follow-up Gd-enhanced MR angiograms were used to assess the extent of aneurysm occlusion after coil embolization. The procedure and validation of our Gd-enhanced MR angiography technique has been reported previously. The extent of aneurysm occlusion was quantified according to the Raymond–Roy classification system, as follows: Class 1, no filling of the aneurysm neck or dome; Class 2, residual filling of the neck but not the dome; and Class 3, residual filling of the neck and dome. Aneurysm recurrence was defined as coil compaction, recanalization through the coil mesh, aneurysm regrowth, or aneurysm neck enlargement at follow-up angiography. No change in the Raymond–Roy class was required.

Clinical Follow-Up

Clinical follow-up was obtained in the multidisciplinary clinic attended by both interventional neuroradiologists and neurosurgeons. The GOS score was used to assess final clinical outcome.

Statistical Analysis

Differences between groups were examined using the Fisher exact test for categorical variables and the Mann–Whitney or Student t-test for continuous data, depending on the underlying distribution. Continuous data are report-

<table>
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<td>residual aneurysm</td>
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<td>aneurysm recurrence</td>
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<td>major aneurysm recurrence</td>
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<td>median clinical FU duration in mos (IQR)</td>
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<td>6.5 (2.9–12.2)</td>
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<td>46 (82.1)</td>
<td>158 (88.8)</td>
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<td>4 (7.1)</td>
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</table>

* Angio = angiographic; BC = bare platinum coil; FU = follow-up; HC = HydroCoil; MC = Matrix coil; NS = not significant; pts = patients. 
ed as the median and IQR. The significance of the difference of packing density and aneurysm size between and among the 3 coil types was assessed using the Kruskal–Wallis test and one-way analysis of variance. A two-tailed probability value of < 0.05 was chosen as the threshold for statistical significance. Multivariate logistic regression was used to assess predictors of aneurysm wall enhancement. The number of potential predictor variables was too large for them all to be considered in the same model while keeping the event-to-parameter ratio at < 10. To avoid overfitting, we used the best variables to create a model with ≤ 6 parameters. A sensitivity analysis was performed to examine whether the variables left out of this initial model were related to enhancement. Significant parameters were retained and other variables were switched in one at a time to create a new model, always keeping the number of parameters in each model at ≤ 6. The final multivariate model included only the risk factors (predictors) with a probability value of < 0.05. The results are presented as an OR as estimates of relative risk with the 95% CIs. The area under the receiver operating characteristic curve was calculated for the final multivariate logistic regression model to generate a concordance statistic. This statistic is a measure of the predictive ability of a prognostic model. A concordance statistic of at least 0.70 is considered necessary to provide acceptable discrimination. The le Cessie–van Houwelingen normal test statistic for the unweighted sum of squared errors (a measure of model calibration or goodness of fit) was evaluated for the final logistic model. A probability value of ≥ 0.10 is considered an acceptable calibration. Statistical analyses were performed using SPSS software version 15.0 (SPSS Inc.) and the R statistical package.

Results

Aneurysm Wall Enhancement

Univariate Analysis. Wall enhancement was observed in 57 aneurysms (31.5%) following endovascular treatment. Table I summarizes the demographic, clinical, angiographic, treatment, and follow-up findings in the total population and reports univariate analysis of the cohorts with and without wall enhancement. The demographic characteristics did not differ between groups. The clinical presentation, however, did differ significantly between aneurysms with and without enhancement (p = 0.008). As a percentage of the total presentation, aneurysms with wall enhancement were encountered less frequently with SAH and more frequently with other presentations: this finding predominantly involved aneurysms that were discovered incidentally and those presenting with mass effect. The frequency of wall enhancement differed significantly with aneurysm size, with the type of coil used (both p < 0.001), with the percentage packing density achieved (p = 0.001), and with the grade of aneurysm occlusion immediately after coil embolization (p = 0.006). Aneurysm location (anterior or posterior circulation) and dome/neck ratio did not differ between the groups. Mural enhancement occurred with all coil types, although it was significantly more frequent in HydroCoil-treated aneurysms (27 [81.8%] of 33; p < 0.001) compared with those treated with bare platinum (21 [18.6%] of 113) and Matrix (9 [25.7%] of 35) coils. HydroCoil-treated aneurysms had significantly greater packing density (median 53.8%, IQR 44.7–62.4%; p < 0.001) than those treated with either Matrix coils (32.2%, 24.9–41.7%) or bare platinum coils (27%, 19.6–34.1%). Packing density between Matrix and bare platinum coils was significantly different (p = 0.01). HydroCoil-treated aneurysms were also larger (median 11.8 mm, IQR 9.1–14.6 mm; p < 0.001) than those treated with either Matrix coils (7.2 mm, 5.6–8.9 mm) or bare platinum coils (8.6 mm, 5–8.5 mm), and had wider necks (median neck size [IQR] for HydroCoil-treated aneurysms was 4.3 mm [3.6–5.9 mm; p < 0.001]; for Matrix coils it was 3.4 mm [2.4–4.3 mm]; and for bare platinum coils it was 3 mm [2.4–3.9 mm]). There was no significant difference in aneurysm dome or neck size between Matrix-treated lesions and those treated with bare platinum coils.

There was a significant difference in the interval from the coil placement procedure to the first MR examination between the aneurysms with and without enhancement (median 1.3 months, IQR 0.2–5.6 months for those with enhancement, compared with 5.5 months, 1–6.7 months for those without [p < 0.001]). Magnetic resonance angiography follow-up was available in all aneurysms (median follow-up 6.7 months, IQR 4.7–17.4 months), with no significant difference in interval from treatment to final MR examination between groups. The final angiographic occlusion grade differed between groups; lesions with enhancement had fewer complete occlusions and more residual aneurysms. There was no significant difference in the overall frequency of aneurysm recurrences between the groups; however, major recurrences occurred more frequently during follow-up of aneurysms that showed enhancement. Clinical follow-up data were available in all patients (median follow-up 6.6 months, IQR 2.9–11.8 months), with no difference in the duration of follow-up between groups. There was no difference in the GOS score in patients with or without aneurysm wall enhancement (Table I) or when each group was dichotomized into patients with or without SAH (data not shown).

Multivariate Analysis. Logistic regression models were used to adjust for potentially confounding variables. Parameters with a probability value of < 0.05 on univariate analysis were investigated (Table I): these included clinical presentation, coil type, aneurysm size, packing density, initial and final angiographic occlusion grades, major aneurysm recurrences, and time between treatment and first MR imaging study. After analysis of these potential predictors, only coil type and aneurysm dome size remained as significant independent predictors of wall enhancement. Clinical presentation, coil packing density, treatment efficacy, and timing of the MR study did not influence or improve the prediction of wall enhancement in the logistic regression analysis once coil type and aneurysm size were taken into account. HydroCoil treatment had the strongest association with enhancement, with an OR of enhancement of 9.75 above bare platinum coils (95% CI 3.45–30.75; p < 0.001) and an OR of 5.37 above Matrix coils (95% CI 1.60–19.99; p = 0.008). Matrix coil treatment was not associated with increased enhancement compared with bare platinum coil embolization (OR 1.81, 95% CI 0.69–4.75; p = 0.21). Incremental 5-mm increases in aneurysm dome size increased the OR of enhancement by 3.58, with a 95% CI of 1.99–6.95 (p < 0.0001). The relationship between wall

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enhancement, aneurysm size, and coil type is illustrated in Fig. 2. The final model had an area under the receiver operating characteristic curve of 0.84, indicating very good discrimination. The le Cessie–van Houwelingen statistic (p = 0.53) confirmed no lack of fit.

Follow-Up Findings. Interval MR imaging follow-up was available in 42 (73.7%) of 57 aneurysms with wall enhancement (median follow-up 8.5 months, IQR 5.1–16.5 months). Wall enhancement was invariably present on follow-up MR imaging (41 [97.6%] of 42 aneurysms); there was only 1 aneurysm (2.4%) that demonstrated full resolution of wall enhancement. The observed enhancement was stable in 23 (54.8%), decreased but was still present in 11 (26.2%), increased in 5 (11.9%), and developed in 2 (4.8%) aneurysms at 4 and 10 months after coil placement.

Perianeurysmal Edema

Perianeurysmal edema was observed in 8 (14.3%) of 56 unruptured aneurysms following endovascular treatment. All of these aneurysms had wall enhancement (14% of the wall-enhancing cohort). Pretreatment MR imaging studies were available in 7 cases. There was surrounding edema on the pretreatment MR image in 2 cases; both of these were partially thrombosed aneurysms. The remaining 5 lesions with posttreatment edema were fully patent aneurysms and had shown no pretreatment edema. The aneurysm for which no pretreatment MR image was available was fully patent and computed tomography did not show edema. Therefore, edema occurred in 6 unruptured aneurysms after coil embolization; however, in 1 case the edema occurred at 44 months after treatment with bare platinum coils, corresponding to the development of massive recanalization, thrombus formation, and aneurysm growth. The perianeurysmal edema in this case was not observed on the follow-up MR image obtained at 17 months and could not be directly attributed to the coil placement procedure, but was secondary to aneurysm recanalization and regrowth. Thus, de novo edema that could be directly related to the coil procedure was seen in 5 unruptured aneurysms (8.9%). All patients were asymptomatic. These aneurysms were all treated with HydroCoils; this corresponds to 5 (29.4%) of 17 unruptured aneurysms treated with HydroCoils.

Unruptured aneurysms with de novo edema did not differ significantly in size from unruptured aneurysms without edema (median size 10.5 mm, IQR 9.4–13.2 mm, compared with 8.3 mm, 5.6–11.4 mm; p = 0.23); however, greater coil packing density was observed (median percentage packing density 49.8%, IQR 38.7–70.5% compared with 30.7%, 22–44.1%; p = 0.03). In the cohort of unruptured aneurysms treated with HydroCoils (17 lesions), there was no difference in the size or packing density of aneurysms with and without de novo edema (data not shown). Summary characteristics of the unruptured aneurysms with
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coil-related edema are given in Table 2. The number of aneurysms with edema was too small to allow for multivariate regression analysis.

Time of onset of edema was as early as 4 days after coil placement, with a median onset of 1.3 months (IQR 1.2–4.3 months); in 1 case the edema was not observed on the MR image obtained at 2.3 months but had developed by 8.3 months. Follow-up images obtained at set intervals after the onset of edema were available in 3 cases. The edema had resolved in 2 aneurysms by 5.1 and 6.2 months, and in 1 case the edema persisted but was stable at 24.4 months.

Incidence of Hydrocephalus

In 4 patients with unruptured aneurysms, delayed hydrocephalus developed. In 1 patient (not shown) this occurred at 44 months after treatment with bare platinum coils and corresponded to the development of massive recanalization, thrombus formation, and aneurysm growth, and was not observed on earlier follow-up MR images. The hydrocephalus in this case was probably secondary to the massive aneurysm regrowth and edema. The other 3 patients with hydrocephalus had aneurysms showing progressive occlusion or stable neck remnants on follow-up. In these cases the hydrocephalus was directly related to the coil placement procedure and coil type. The hydrocephalus was first detected on cross-sectional imaging. All 3 aneurysms had been treated with HydroCoils. This represented 3 (5.4%) of our total unruptured aneurysm cohort (56 patients), or 3 (17.6%) of 17 unruptured aneurysms treated with HydroCoils. The hydrocephalus presentation in these cases was delayed (7.8–30.6 months postprocedure). Two patients were symptomatic. The symptomatic rate in our total cohort of unruptured aneurysms was 2 (3.6%) of 56, or 2 (11.8%) of 17 unruptured aneurysms treated with HydroCoils. One patient’s family declined ventriculoperitoneal shunt surgery, whereas the other symptomatic patient is undergoing work-up for possible shunt surgery. Summary characteristics of the unruptured aneurysms with coil-related hydrocephalus are given in Table 3. In 2 of the patients with hydrocephalus there was wall enhancement, and none had perianeurysmal edema.

Unruptured aneurysms with de novo hydrocephalus did not differ significantly in size from unruptured aneurysms without hydrocephalus (median size 13.2 mm, IQR 7.8–13.7 mm, compared with 8.3 mm, 5.7–11.4 mm; p = 0.4); however, greater packing density was observed (median percentage packing density 76.7%, IQR 61–87%, compared with 31.4%, 22.7–43.7%; p = 0.01). In the cohort of 17 unruptured aneurysms treated with HydroCoils there was no difference in the size of lesions with and without de novo hydrocephalus (median size 13.2 mm, IQR 7.8–13.7 mm, compared with 10.4 mm, 8.2–12.6 mm; p = 0.7); however, the median percentage packing density with HydroCoils was greater (73.9%, 54.9–80.1%, compared with 39.3%, 20.4–50.4%; p = 0.04). A summary of the frequency of wall enhancement, edema, and hydrocephalus by coil type is given in Table 4.

Discussion

The MR findings of wall enhancement, perianeurysmal edema, and hydrocephalus are observed in cases of symptomatic inflammation following treatment with modified platinum coils. It was important to identify the frequency and factors associated with inflammatory changes after coil embolization for 3 reasons: 1) it was unknown whether MR imaging–detectable abluminal changes can be seen in asymptomatic cases treated with bare platinum coils and whether these changes represent part of the normal healing process in coil-embolized aneurysms; 2) perianeurysmal inflammation may become symptomatic if it is exuberant or excessive; and 3) there are reports that steroids administered in the peri- and postprocedural period may decrease this inflammatory risk.

Causes of Wall Enhancement

The cause of aneurysm wall enhancement observed on the Gd-enhanced MR images is unknown. To date, wall enhancement has been reported after modified platinum coil treatment, and in large aneurysms with recanalization and regrowth after bare platinum coil treatment. In these cases the wall enhancement was associated with perianeurysmal edema. We observed asymptomatic wall enhancement without surrounding edema in 18.6% of aneurysms treated with bare platinum coils. This surprisingly frequent observation suggests that wall enhancement by itself, in the absence of edema or hydrocephalus, may not be pathologic, but may represent a normal healing response.

Review of the histopathological changes in coil-embolized aneurysm specimens obtained in human patients supports the hypothesis that isolated wall enhancement may
be a normal healing response. Currently there are histological reports on ~ 50 bare platinum coil–embolized aneurysms obtained at autopsy or surgery. Most of the studies have centered on the inflammatory changes and scar formation that occur within the aneurysm lumen after coil placement; however, some investigators have reported changes occurring adjacent to or in the aneurysm wall. Healing has been reported to occur in a centripetal fashion, with the inflammatory and granulation tissue response starting at the periphery of the luminal clot adjacent to the aneurysm wall and extending to the luminal core. Inflammatory cells have been reported in nearly all human specimens, and consist initially of neutrophils, then macrophages, and subsequently foreign body giant cells. Specific wall changes have been reported following coil placement in animal and human specimens. In these cases platinum coils were seen to be partially incorporated into a thickened aneurysm wall composed of fibrovascular tissue, with chronic inflammatory cells present at the coil–tissue interface. These histological findings provide evidence of inflammatory and granulation changes in the wall of certain bare platinum coil–embolized aneurysms. We observed enhancement both early (within the 1st week) and late (within a time frame of months to years) following coil delivery, suggesting that the wall changes probably represent the acute inflammatory and chronic reparative phases of the healing response. We have observed that enhancement, once present, persists, suggesting that the chronic enhancement probably represents granulation tissue within the wall of the aneurysm.

**Wall Enhancement and Coil Type**

We observed aneurysm wall enhancement after treatment with all coil types. In our study the strongest independent predictor of wall enhancement was HydroCoil treatment. The wall enhancement rate with HydroCoils was > 4-fold higher than with bare platinum coils, and therefore should be considered an exaggerated response. In lesions treated with Matrix coils, we did not observe a significant difference in mural enhancement above levels found in bare platinum coils on multivariate analysis.

**Wall Enhancement and Aneurysm Occlusion**

The significance of asymptomatic wall enhancement in terms of long-term occlusion of aneurysms and protection from rebleeding is unknown. Böcher-Schwarz et al. speculated that chronic wall inflammation and thickening may be a protective mechanism to prevent aneurysm rupture. Bendszus and Solymosi proposed that the proinflammatory reaction with modified platinum coils may be a contributor to a possibly lower recanalization rate, and inflammatory complications should be considered a trade-off for a more stable aneurysm occlusion. There are some provisional data to suggest that HydroCoils may reduce long-term recurrence rates compared with bare platinum coils, particularly in aneurysms in which the final device placed was a HydroCoil or that were occluded with a high percentage of HydroCoils. Results of randomized trials are awaited. If the assumption that wall enhancement represents a more florid wound healing response is correct, then asymptomatic wall enhancement may be a favorable finding in terms of treatment efficacy, although an exaggerated reaction may manifest as edema, chemical meningitis, and hydrocephalus. However, we did not find evidence to support a more stable aneurysm occlusion in aneurysms with wall enhancement. On the contrary, on univariate analysis there was a suggestion that aneurysms with wall enhancement had more incomplete angiographically demonstrated occlusions and major recurrences; however, after adjusting for aneurysm size and the type of coil used in treatment, the angiographic occlusion grade and recurrence rate were not independently associated with wall enhancement. A multicenter study looking at wall enhancement, long-term recanalization, and rebleeding rates would be informative.

**Aneurysm Inflammation Prior to the Introduction of Modified Platinum Coils**

Prior to the introduction of modified platinum coils, symptomatic inflammation had only been reported in large and giant aneurysms and in large venous spaces. This inflammation manifested as menigitis and/or edema; there were no reported cases of “inflammatory” hydrocephalus. The symptomatic inflammation occurred in untreated large (> 15 mm) and giant aneurysms, and should therefore be considered an exaggerated response. In lesions treated with Matrix coils, we did not observe a significant difference in mural enhancement above levels found in bare platinum coils on multivariate analysis.
tured and unruptured aneurysms. The inherent wall inflammation in small or medium-sized aneurysms does not lead to complications, either because the inflammation resolves or because it remains in a quiescent state. Supporting earlier reports that inflammation can occur in untreated aneurysms, we observed asymptomatic perianeurysmal edema prior to treatment in 3 partially thrombosed unruptured aneurysms (11–15 mm). In these cases, the exuberant pro-inflammatory response in the vessel wall may be related to the relatively large mass of thrombus and coagulum, which acts as an inflammation promoter. Other mechanisms that may contribute to perianeurysmal inflammation include hemorrhage within the aneurysm wall, expression of angiogenesis growth factors within the aneurysm wall, and the “water-hammer effect” in incompletely coil- or balloon-occluded aneurysms (in this phenomenon, pulsatile blood flow striking the coil mass or balloon is transmitted repetitively to the aneurysm wall, producing perianeurysmal edema).

Aneurysm Inflammation After Treatment With Modified Platinum Coils

Symptomatic inflammation has now been reported in fully patent aneurysms < 15 mm in size that have been treated with modified platinum coils. More recently, 4 cases of symptomatic inflammation in small aneurysms (6–8 mm) have been reported. In our study the median size of aneurysms with either de novo edema or hydrocephalus was 11.7 mm. These lesions were all were treated with HydroCoils and were stable on follow-up evaluation. This contrasts with the report of perianeurysmal edema that was secondary to unstable aneurysm remnants after bare platinum coil embolization. Based on our findings and the reports in the literature, modified platinum coils, particularly but not exclusively HydroCoils, appear to cause an exuberant inflammatory response that is not usually seen in uncomplicated moderate-sized aneurysms.

Reported Inflammatory Complications With Modified Platinum Coils

There are currently 12 reported cases of symptomatic inflammation following aneurysm embolization with modified platinum coils (Table 5). Symptoms were related to either perianeurysmal inflammation or to hydrocephalus. Brisman et al. reported 2 cases of hydrocephalus in patients with unruptured aneurysms treated with stent-assisted HydroCoil embolization. These cases were probably included in the more recent, larger case series reported by the same group, and are not included in Table 5. DeShaises et al. reported 3 additional cases of postembolization headaches following HydroCoil treatment that also are not included in the table. These occurred in patients with cavernous ICA aneurysms and may have been related to dural compression from mass effect. Inflammatory changes have been reported after treatment with 3 of the currently available surface-modified coils: Matrix, HydroCoil, and Cerecyte. The inflammatory changes were identified based on clinical symptoms, MR findings of wall enhancement and edema, and nonspecific inflammatory changes in the CSF. The inflammatory changes may result in local, regional, or systemic effects. Local or perianeurysmal inflammation may cause symptoms, with the signs based on the severity of the dura mater, the proximity of the dura mater, and the eloquence of the adjacent brain.

Incidence of Inflammatory Complications With Modified Platinum Coils

The incidence of symptomatic inflammation following treatment with modified platinum coils is unknown. A review of published case series that specifically reported on the absence or presence of aseptic meningitis or hydrocephalus shows that the reported incidence varies widely, from 0 to 10% (Table 5). We observed delayed hydrocephalus in 3 (17.6%) of 17 unruptured aneurysms treated with HydroCoils. Based on postmarketing surveillance, MicroVention has reported the incidence of hydrocephalus with HydroCoil treatment in unruptured aneurysms at 1.7% in its internal newsletter (Clinical Update Newsletter, MicroVention, Inc., Vol. 2, No. 2, July 2006). In large and giant unruptured aneurysms, the incidence was 3.1%. We could find no published data on the incidence of hydrocephalus from the other manufacturers of modified platinum coils. Data on the true incidence will likely come from the large prospective randomized trials of surface-modified coils that are currently in progress.

### Table 3

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Max Aneurysm Dome Size (mm)</th>
<th>% Residual Aneurysm Coiling Density (% HC)</th>
<th>Occlusion Grade</th>
<th>Time From Op (mos)</th>
<th>Symptoms</th>
<th>Wall Enhancement</th>
<th>Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>56, M</td>
<td>terminal BA 6.0 BC, HC</td>
<td>90 (82) residual aneurysm</td>
<td>occluded</td>
<td>30.6</td>
<td>memory loss, gait disturbance, incontinence</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>67, F</td>
<td>paraophthalmic 13.2 BC, HC</td>
<td>77 (74) residual aneurysm</td>
<td>residual neck</td>
<td>11.8</td>
<td>confusion, gait disturbance, incontinence</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>45, F</td>
<td>terminal BA 13.9 BC, HC</td>
<td>56 (49) occluded</td>
<td>occluded</td>
<td>7.8</td>
<td>none</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

* All presentations were incidental, and none of the patients received intravenous corticosteroids. Abbreviation: BA = basilar artery.
We did not, however, find a statistically significant difference in the size of unruptured HydroCoil-treated aneurysms associated with hydrocephalus compared with aneurysms not associated with hydrocephalus, although this may be a Type II error due to small sample size and lack of statistical power. It is important to note that hydrocephalus does occur in patients with small aneurysms after HydroCoil treatment. We have observed hydrocephalus following HydroCoil embolization of a 6-mm aneurysm, and Im et al.7 have observed it after treatment of an 8-mm aneurysm. We found that unruptured HydroCoil-treated aneurysms associated with hydrocephalus had greater HydroCoil packing density than aneurysms not associated with hydrocephalus. This suggests that this disorder may be related to a critical packing density of the HydroCoil, although Berenstein et al.7 reported a case of hydrocephalus associated with an aneurysm with a HydroCoil packing density of 40%. It appears that mural or perimural inflammatory changes are not a prerequisite for the development of hydrocephalus, because one of our cases did not have wall enhancement, and none had perianeural edema. Similar to the report by Im et al., we have observed the development of delayed hydrocephalus after HydroCoil treatment. This suggests that a low-grade chronic inflammatory response may be important as a source of the hydrocephalus with modified coils. To support this suggestion of ongoing abluminal inflammatory activity in certain coil-embolized aneurysms, we have observed persistent enhancement and edema > 2 years after treatment of unruptured aneurysms with HydroCoils. Recent early work has suggested that hydrocephalus after embolization of unruptured aneurysms with HydroCoils is associated with elevated levels of specific interleukins (interleukin-6) and matrix metalloproteases (matrix metalloproteinase-9) in the CSF, implying an inflammatory process in the origin of the hydrocephalus (Clinical Update Newsletter, MicroVention, Inc., Vol. 2, No. 2, July 2006). Steroid administration in the peri- and postprocedural period has been suggested to decrease this inflammatory risk.30,28,33,36,42,46

Study Limitations

This study has several limitations. We do not have historical studies of the observed wall enhancement. Our assumption that in stable aneurysms asymptomatic wall enhancement represents a healing response to the coils is based on histopathological reports from the literature. We did not measure biochemical markers of inflammation in the serum or CSF. We looked at reported MR markers of inflammation; namely, wall enhancement, edema, and hydrocephalus. We have pretreatment Gd-enhanced MR imaging studies available in only 13 cases. In 1 case, wall enhancement was present in a partially thrombosed basilar artery aneurysm. The other 12 cases did not show pretreatment wall enhancement. In our cohort of 181 coil-embolized aneurysms we reviewed the MR imaging studies in 24 additional but untreated, fully patent aneurysms to evaluate them for mural enhancement and edema. We did not find wall enhancement or edema in any of these cases. In some small aneurysms the Gd filled the lumen of the aneurysm, making wall assessment difficult. There were relatively few patients with unruptured aneurysms treated with Matrix coils (8 patients). This may have contributed to the lack of perianeural edema and hydrocephalus observed in unruptured aneurysms treated with Matrix modified coils. Matrix embolization and treatment with other PGLA-modified coils have been associated with perianeural edema and hydrocephalus.6,46 Although we found no difference in the clinical grade in patients with or without wall enhancement, the follow-up is biased toward good-grade patients, because patients classified as poor grade following treatment are less likely to have a postprocedure MR imaging study.

Conclusions

Asymptomatic wall enhancement can be seen after embolization with all coil types and probably represents a normal healing response to the coils. Almost 20% of aneurysms treated with bare platinum coils demonstrate mural enhancement. Factors independently associated with increased rates of mural enhancement are HydroCoil treatment and increasing aneurysm size. We found no independent association between wall enhancement and treatment efficacy, in terms of angiographically confirmed occlusion and recanalization rates. Enhancement invariably persists on follow-up evaluations and probably represents granulation tissue within the aneurysm wall. In this study, unruptured aneurysms with de novo perimural edema were observed only in patients with HydroCoil embolizations. The patients with edema were asymptomatic. In other studies symptomatic edema has been observed in lesions treated

### TABLE 4

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No. of Lesions</th>
<th>MR Parameter*</th>
<th>BC</th>
<th>MC</th>
<th>HC</th>
<th>All Types</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>total</td>
<td>181</td>
<td>wall enhancement</td>
<td>21 of 113 (18.6)</td>
<td>9 of 35 (25.7)</td>
<td>27 of 33 (81.8)</td>
<td>57 of 181 (31.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>unruptured</td>
<td>56</td>
<td>wall enhancement</td>
<td>9 of 31 (29)</td>
<td>3 of 8 (37.5)</td>
<td>14 of 17 (82.4)</td>
<td>26 of 56 (46.4)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>edema</td>
<td>0 of 31 (0)</td>
<td>0 of 8 (0)</td>
<td>5 of 17 (29.4%)</td>
<td>5 of 56 (8.9)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hydrocephalus</td>
<td>0 of 31 (0)</td>
<td>0 of 8 (0)</td>
<td>3 of 17 (17.6%)</td>
<td>3 of 56 (5.4)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

* De novo edema and hydrocephalus by coil type in unruptured aneurysms.
<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Diagnosis</th>
<th>Incidence: No. Based on Unruptured Cases (%)</th>
<th>Age (yrs), Sex</th>
<th>Unruptured</th>
<th>Aneurysm Location</th>
<th>Max Dome Size†</th>
<th>Coils Used</th>
<th>Immediate Occlusion Grade</th>
<th>Symptoms Post-Coil Insertion</th>
<th>Time From Op</th>
<th>CSF Findings Reported‡</th>
<th>MR Findings</th>
<th>Intravenous Corticosteroids</th>
<th>Shunt Insertion</th>
<th>Symptom Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyers et al., 2004</td>
<td>aseptic meningitis, hydrocephalus</td>
<td>NA</td>
<td>52, F yes</td>
<td>yes</td>
<td>paraophthalmic</td>
<td>20 mm</td>
<td>BC, HC, &amp; MC</td>
<td>occluded</td>
<td>fever, meningism</td>
<td>26 hrs</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>aseptic meningitis, local inflammation, hydrocephalus</td>
<td>46, F no</td>
<td>PCA</td>
<td>20 mm</td>
<td>BC, HC, &amp; MC</td>
<td>occluded</td>
<td>fever, meningism, cranial nerve palses, hemiparesis, somnolence, inattention</td>
<td>3 wks; 7 wks</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td></td>
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<tr>
<td>Berenstein et al., 2006</td>
<td>hydrocephalus</td>
<td>3 of 56 (5.4)</td>
<td>75, F yes</td>
<td>yes</td>
<td>paraophthalmic</td>
<td>large</td>
<td>BC, HC</td>
<td>residual aneurysm</td>
<td>confusion &amp; gait disturbance</td>
<td>9 wks</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>hydrocephalus</td>
<td>46, M yes</td>
<td>terminal ICA</td>
<td>20 mm</td>
<td>BC, HC</td>
<td>residual aneurysm</td>
<td>9 wks</td>
<td>yes in 2 of 3 pts</td>
<td>NA</td>
<td>NA</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
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<tr>
<td>Bendszus et al., 2006</td>
<td>hydrocephalus</td>
<td>79, M yes</td>
<td>PCoA</td>
<td>large</td>
<td>BC, HC</td>
<td>residual aneurysm</td>
<td>11 mm</td>
<td>neck</td>
<td>confusion &amp; gait disturbance</td>
<td>6 wks</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
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<tr>
<td></td>
<td>local inflammation</td>
<td>1 of 10 (10)</td>
<td>43, M yes</td>
<td>yes</td>
<td>terminal ICA</td>
<td>large</td>
<td>Cerecyte</td>
<td>occluded</td>
<td>hypothyse of rt hand</td>
<td>6 days</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Cloft, 2007</td>
<td>aseptic meningitis</td>
<td>1 of 120 (0.8)</td>
<td>NA</td>
<td>yes</td>
<td>paraophthalmic</td>
<td>20 mm</td>
<td>BC, HC</td>
<td>NA</td>
<td>meningism</td>
<td>9 days</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
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<tr>
<td>Im et al., 2007</td>
<td>aseptic meningitis</td>
<td>3 of 30 (10)</td>
<td>56, F yes</td>
<td>yes</td>
<td>ICA</td>
<td>8.2 mm</td>
<td>BC, HC</td>
<td>NA</td>
<td>fever, meningism, memory loss, HA, &amp; gait disturbance</td>
<td>18 hrs; 6 mos</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
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<tr>
<td>Deshaies et al., 2007</td>
<td>hydrocephalus</td>
<td>1 of 32 (3.1)</td>
<td>66, F yes</td>
<td>yes</td>
<td>ICA</td>
<td>8.1 mm</td>
<td>BC, HC</td>
<td>NA</td>
<td>fever, meningism</td>
<td>22 hrs</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
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<tr>
<td></td>
<td>aseptic meningitis, hydrocephalus</td>
<td>68, M yes</td>
<td>MCA</td>
<td>6 mm</td>
<td>BC, HC</td>
<td>NA</td>
<td>fever, meningism, fever</td>
<td>20 hrs</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>aseptic meningitis, hydrocephalus</td>
<td>66, F yes</td>
<td>ophthalmic</td>
<td>large</td>
<td>HC</td>
<td>HA, normal-pressure hydrocephalus</td>
<td>1 of 32 (3.1)</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HA</td>
<td>1 of 32 (3.1)</td>
<td>NA</td>
<td>yes</td>
<td>ACoA</td>
<td>8 mm</td>
<td>HC</td>
<td>NA</td>
<td>HA</td>
<td>&gt;24 hrs</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

*ACoA = anterior communicating artery; HA = headache; PCA = posterior cerebral artery; PCoA = posterior communicating artery.
†Large designates lesions > 10–25 mm, and small designates lesions > 4–10 mm.
‡Analysis of CSF yielded findings of aseptic, nonspecific inflammation.
with PGLA-based coils. Clinically significant perimodal inflammation appears to depend on the severity of edema, the proximity of the dura, and the eloquence of the adjacent brain. We documented 3 cases of de novo, delayed hydrocephalus in patients treated with HydroCoils; 2 were symptomatic. Perimodal edema and hydrocephalus have not been reported in patients with stable bare platinum coil embolization, and should be considered an exaggerated inflammatory response. These findings suggest that modified coils, in particular HydroCoils, amplify the inflammatory response during aneurysm healing. Steroid administration in the periprocedural period may decrease the inflammatory risk. Increased vigilance for delayed complications is required. Gadolinium-enhanced MR imaging studies should be considered in patients with suspected inflammatory complications secondary to modified platinum coils. Judicious clinical use of modified platinum coils is warranted until results of randomized trials are published.

**Disclaimer**

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