Flow Diversion Versus Conventional Treatment for Carotid Cavernous Aneurysms

Mario Zanaty, MD; Nohra Chalouhi, MD; Robert M. Starke, MD; Guilherme Barros, BS; Mark Philip Saigh, BA; Eric Winthrop Schwartz, BS; Norman Ajiboye, MD; Stavropoula I. Tjoumakaris, MD; David Hasan, MD; Robert H. Rosenwasser, MD; Pascal Jabbour, MD

Background and Purpose—Several endovascular treatment options are available for cavernous carotid aneurysms. We compared pipeline embolization device (PED) versus conventional endovascular treatment in terms of evolution of mass effect, complications, recurrence, and retreatment rate.

Methods—One hundred fifty-seven patients harboring 167 cavernous carotid aneurysms were treated using PED placement, coil-assisted coiling, and carotid vessel destruction. Procedural complications, angiographic results, and clinical outcomes were analyzed and compared.

Results—There were no difference in age, sex, and mean aneurysm size between those treated with PED and those treated with conventional endovascular procedures. The patients treated with PED had a significantly lower proportion of small-size aneurysms (<10 mm) and a shorter follow-up duration. Multivariate analysis revealed treatment other than PED (PED: odds ratio [OR], 0.03; \( P=0.002 \)) and size >15 mm (OR, 4.27; \( P=0.003 \)) to be predictors of no improvement in symptoms. The rate of complete occlusion was 81.36% (48 of 59) for PED, 42.25% (39 of 71) for stent-assisted coiling, 27.27% (6 of 22) for coiling, and 73.33% (11 of 15) for carotid vessel destruction. Retreatment was needed in patients with aneurysm size >15 mm (OR, 2.67; \( P=0.037 \)) and those who were not treated with PED (PED: OR, 0.16; \( P=0.006 \)). The rate of major complications was 6.6% (11 of 167). Patients who were treated with PED or stent-assisted coiling had 3.84 lower odds to develop complications (OR, 0.26; \( P<0.05 \)).

Conclusions—The use of PED should be encouraged, especially in symptomatic patients. We found PED to be associated with less need for future treatment, higher improvement in symptoms rate, and lower rate of complications.

Key Words: cerebral aneurysm • complication intraoperative • complication peroperative • complication postoperative • endovascular procedure • endovascular technique • intracranial aneurysm

Because of the latest technology advances, there are several endovascular treatment options available for cavernous carotid aneurysms (CCA).1-5 These strategies include balloon-assisted coiling, stent-assisted coiling (SAC), carotid vessel destruction (CVD), and flow diversion, each varying in degrees of success. Recent studies have demonstrated the effectiveness and safety in treating patients with large, wide-neck CCAs with flow diversion techniques.6-8 There is increasing evidence that when treated with flow diversion such as the pipeline embolization device (PED), these aneurysms have higher rates of complete occlusion, with lower rates of recurrence and retreatment with less mass effect on the surrounding structures, as opposed to traditional endovascular methods.6-11 In our study, we compared each of these treatment modalities, PED, SAC, coiling, and CVD, in terms of morbidity, mortality, evolution of mass symptoms, aneurysm occlusion, and rate for retreatment.

Materials and Methods

Patient Cohort

After obtaining the institutional review board approval from our institution, we searched our prospectively maintained database for all patients with CCA undergoing endovascular treatment between 2005 and 2014. A total of 157 patients with 167 CCA were identified. Medical charts, angiographic studies, MRI, and computed tomographic scans were carefully reviewed. Patient’s age and sex, as well as aneurysm size and location were recorded. Treatment was dictated by the dual trained attending neurosurgeons. Asymptomatic patients were considered for treatment if there was a significant growth of the aneurysm. Any aneurysm that displayed a decreasing percentage of occlusion (>5%) on follow-up angiography was considered recurrent. Thromboembolic and ischemic complications were diagnosed clinically (new deficits or change in level of consciousness) or on computed tomographic scans or MRI (new infarcts) after excluding confounders such as vasospasm, hydrocephalus, and metabolic disorders.
Patient Outcome
The primary clinical outcome was the evolution of cranial nerve deficits produced by mass effect, which was classified as complete disappearance of symptoms, partial improvement in symptoms, no change in symptoms, and worsening of symptoms. Patients were initially evaluated before the treatment and at every follow-up. The final clinical status was assessed at the latest follow-up. The registered complications were symptomatic ischemic stroke, symptomatic hemorrhagic stroke, aneurysm rupture, and vessel perforation.

Angiographic follow-up (digital subtraction angiography or MR angiography) was scheduled at 6 months, 1 year, 2 years, 5 years, and >5 years after endovascular procedures. Patient clinical status was also subsequently assessed on the latest follow-up visit. Complete occlusion was defined as >95%, near complete occlusion as >90% but <95%, and incomplete occlusion if <90%. Patients without routine follow-up were contacted for assessment via a structured telephone interview, and medical records were obtained from outside hospital facilities. We evaluated the complication rates, the need for retreatment (because of recurrence of the aneurysm or worsening symptoms), the aneurysm occlusion rates, and the evolution of cranial nerve deficits.

Statistical Analysis
Data are presented as mean and range for continuous variables, and as frequency for categorical variables. Patients treated with CVD, endovascular coiling, SAC, and flow diversion were compared. Statistical analyses of categorical variables was performed using the χ² and Fisher exact tests; comparison of means was performed using Student t test, and ANOVA followed by Bonferroni post hoc testing was performed as appropriate. Univariate analysis was used to test covariates predictive of the following dependent post-treatment variables: treatment-related complications, aneurysm occlusion at latest follow-up, the need for retreatment, improvement of cranial nerve deficits, and favorable clinical outcome (modified Rankin Scale score 0–1 without worsening signs or symptoms). Factors predictive in univariate analysis (P<0.20) were entered into a multivariate logistic regression analysis. P values <0.05 were considered statistically significant.

Results
Patients Characteristics
Of 157 patients with CCA, the mean age was 61.4±12.7 years and 147 were women (93.6%). Mean aneurysm size was 15.1±9.0 mm. CCA were treated with endovascular coiling (22 of 167; 13.2%), CVD after balloon occlusion test was 15.1±9.0 mm. CCA were treated with endovascular coil- placement, failure of occlusion, or worsening of symptoms. Of 27, 3 were previously treated with PED, 8 with coils, 14 with SAC, and 2 with CVD. The need for retreatment for each intervention is given in Table 2. The only significant predictors on univariate and multivariate analysis were size >15 mm (OR, 4.27; P=0.003) to be predictors of no improvement in symptoms. People treated with PED had 33.33% higher odds to improve. We identified 25 patients with incidental CCA, 2 of whom developed ocular symptoms after treatment with SAC.

Rate of Retreatment
Twenty-seven aneurysms had >1 treatment because of recanalization, failure of occlusion, or worsening of symptoms. Of 27, 3 were previously treated with PED, 8 with coils, 14 with SAC, and 2 with CVD. The need for retreatment for each intervention is given in Table 2. The only significant predictors on univariate and multivariate analysis were size >15 mm (OR, 2.67; P=0.037) and treatment other than PED (PED: OR, 0.16; P=0.006). CVD was also found to decrease the risk of recurrence when compared with treatment other than PED (OR, 0.16; P=0.001). The rate of complete occlusion was 81.36% (48 of 59) for PED, 42.25% (39 of 71) for SAC, 50.84% (30 of 59) improved, and 40.67% (42 of 59) remained the same. Of the 22 symptomatic patients treated with endovascular coiling, 9 (of 18; 50.00%) improved, 2 (of 18; 11.11%) worsened, and 7 (of 22; 38.89%) remained the same. Finally, 11 of 14 (78.57%) patients had improvement in their symptoms; the remaining 3 did not show any change in their symptoms (3 of 14; 21.43%).

Table 1. Comparison of Patients’ Characteristics Between PED and Other Modalities

<table>
<thead>
<tr>
<th></th>
<th>PED</th>
<th>Other Treatments</th>
<th>Significance (P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, y</td>
<td>63.00</td>
<td>60.42</td>
<td>0.19</td>
</tr>
<tr>
<td>Female proportion</td>
<td>93.22%</td>
<td>93.62%</td>
<td>0.405</td>
</tr>
<tr>
<td>Size, mean, mm</td>
<td>16.75</td>
<td>14.27</td>
<td>0.12</td>
</tr>
<tr>
<td>Angiographic follow-up, mean, mo</td>
<td>7.31</td>
<td>18.24</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Symptoms at presentation</td>
<td>86.44%</td>
<td>84.26%</td>
<td>0.769</td>
</tr>
</tbody>
</table>

PED indicates pipeline embolization device.

Table 2. Comparison of Different Types of Treatments

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Improvement in Symptoms</th>
<th>Complication Rate</th>
<th>Retreatment Rate</th>
<th>Complete and Near-Complete Occlusion Rate (&gt;90%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PED</td>
<td>92.16% (47/51)</td>
<td>3.39% (2/59)</td>
<td>5.08% (3/59)</td>
<td>89.83% (53/59)</td>
</tr>
<tr>
<td>SAC</td>
<td>50.84% (30/59)</td>
<td>5.63% (4/71)</td>
<td>19.71% (14/71)</td>
<td>84.51% (60/71)</td>
</tr>
<tr>
<td>Coiling</td>
<td>50.00% (9/18)</td>
<td>13.64% (3/22)</td>
<td>36.36% (8/22)</td>
<td>54.54% (12/22)</td>
</tr>
<tr>
<td>CVD</td>
<td>78.57% (11/14)</td>
<td>13.33% (2/15)</td>
<td>13.33% (2/15)</td>
<td>86.67% (13/15)</td>
</tr>
</tbody>
</table>

CVD indicates carotid vessel destruction; PED, pipeline embolization device; and SAC, stent-assisted coiling.
combined was 89.83% (53 of 59) for PED, 84.51% (60 of 71) for SAC, 54.54% for coiling, and 86.67% (13 of 15) for CVD.

Treatment-Related Complications
The rate of major complications was 6.6% (11 of 167). Major complications are defined as symptomatic ischemic stroke, hemorrhagic stroke, aneurysm rupture, and vessel perforation that lead to neurological damage. We had 2 (of 167; 0.03%) post-treatment aneurysm ruptures, 1 occurred after PED placement and 1 after SAC. Hemorrhagic stroke developed in 2 cases (of 167; 0.03%), 1 after SAC and 1 after treatment with PED. Ischemic stroke occurred in 2 patients with SAC, 2 patients with CVD, and 1 patient treated with endovascular coiling, adding up to 5 cases in total (5 of 167; 2.99%). There were no procedural related deaths and only 2 (of 167; 0.03%) intraoperative ruptures, both of which occurred in patients treated with coils. The complication rate for each treatment modality is included in Table 2. Univariate predictors included in multivariate analysis were treatment modality, age, and aneurysm size. In multivariate analysis, the only factor predictive of major complications was the use of other than PED or SAC. Patients who have been treated with PED or SAC had 3.84 lower odds to develop complications (OR, 0.26; P<0.05). This was unchanged after controlling for duration of follow-up and patient/aneurysm characteristics. We presented 2 illustrative cases (Figures 1 and 2).

Discussion
Flow Diversion in CCA
CCA are associated with mass effect on adjacent cranial nerves, whereas their risk of rupture subarachnoid hemorrhage or fistulation is low,12,13 except for cases with giant aneurysms.14 Conventional endovascular techniques have been preferred for the treatment of symptomatic CCA. The reported recurrence rate and incomplete angiographic occlusion after treatment with conventional endovascular technique remains high,15,16 discouraging their use in complex aneurysms. Recently, flow diversion has been emerging as a novel treatment, but with not enough data to establish its superiority over conventional modalities. Still, many institutions are starting to consider flow diversion as first-line treatment for CCA.

Angiography and Clinical Outcome
Traditional methods for treatment of CCA such as carotid sacrifice with or without bypass have been effective, but suboptimally. Carotid sacrifice achieves a 93% (95% confidence interval [CI], 86.0–97.0) complete aneurysm occlusion and 83.0% (95% CI, 52.0–96.0) resolution of mass effect, but is associated with a 4.0% (95% CI, 1.0–9.0) risk of procedure-related neurological deficits.1 However, because these aneurysms are often very large or giant with a wide neck, standard endovascular coiling achieved a complete aneurysm occlusion rate of only 67.0% (95% CI, 55.0–77.0) in a meta-analysis from 2014.1 Furthermore, the coiling group demonstrated a retreatment rate of 18.0% (95% CI, 12.0–26.0) compared with 6.0% (95% CI, 2.0–12.0) for CVD without bypass (P=0.01). However, there were no differences in the improvement of mass effect between coiling, SAC, and CVD. On the contrary, van Rooij17,18 found no significant difference in overall occlusion rates between CCA treated with coil embolization versus CVD. Therefore, the superiority of CVD over coiling in terms of symptom improvement has not been established, but CVD
is still preferred given the higher occlusion rate demonstrated by meta-analysis and systemic reviews of nonrandomized controlled trials.

The experience with flow diversion has somewhat been different. Lanzino et al. have conducted a retrospective matched-pair comparison of paraclinoid aneurysms treated with PED versus conventional endovascular techniques. The aneurysm and patient characteristics were not different between the 2 groups. The second most common type of paraclinoid aneurysm was the CCA (18 in total). The authors report a significantly higher rate of complete occlusion in patients treated with PED (76.2%) versus the control group (21.4%) on follow-up. However, the small sample of CCA in the study imposes a major limitation. Puffer et al. reported a complete occlusion rate of 71% (25 of 35) for CCA treated by PED embolization. Improvement of symptoms was noted in 90% patients (26 of 29). Of the remaining patients with incomplete occlusion, 50% (4 of 8) were found to have progressed to complete occlusion at final follow-up. Hence, we included and accounted for follow-up duration in the multivariate analysis in our study. The Canadian trial reported complete occlusion rates of 70% to 100% and symptom improvement in upwards of 90% of patients. Starke et al. treated 3 CCA with PED after incomplete occlusion with coiling, with a 100% success rate. Our study supports these findings, because PED was associated with a significantly lower retreatment rates and a significantly higher rate of improvement in symptoms when compared with conventional treatments.

Flow diverters seem to be more effective than the conventional techniques because they completely seal the aneurysm neck, diverting flow away from the aneurysm and leading to its thrombosis and shrinkage while simultaneously providing a support for the diseased vessel allowing its reconstruction. The re-establishment of the homeostasis seems to be responsible for the favorable angiographic occlusion and evolution of symptoms. The resolution of mass effect might be because of the decreased pulsation in the aneurysm along with a decrease in its size when successfully excluded out of the aneurysm, as demonstrated by Szikora et al.

Complication Rates
The safety and efficacy of PED placement have to be compared with that of conventional endovascular therapy. Major concerns after flow diversion are delayed aneurysm rupture,
distal hemorrhage, and major ipsilateral stroke.\textsuperscript{26} In patients with intracranial aneurysms, the procedure-related morbidity and mortality are 5\% and 4\%, respectively; the rate of intraparenchymal hemorrhage is 3\% and that of stroke is 6\%, as reported by Brinjikji et al\textsuperscript{27} in their meta-analysis. Puffer et al\textsuperscript{1} treated 44 CCA using PED. They encountered in 36\% (16 of 44) of procedures minor technical complications (minor vasospasm, incomplete opening, vessel perforation). No patient who experienced intraprocedural or delayed complications had any clinical sequelae. Although Briganti et al\textsuperscript{28} reported a 4\% mortality rate (3 of 76) for treatment of CCA with flow diverters, the mortality rate in a multitude of studies,\textsuperscript{2,\textsuperscript{5} including ours}, is 0\%. The Canadian study\textsuperscript{4} reported a 0\% overall morbimortality in 70 CCA. In a meta-analysis of 316 patients with CCA performed in 2002, procedure-related neurologic deficits occurred in 5\% of patients treated with CVD and 0\% of patients treated with coils alone.\textsuperscript{29} More recently, in a series of 113 patients treated either by coil or SAC, the rate of neurological complications was 3.5\%.\textsuperscript{30} Recently, Turfe et al\textsuperscript{4} performed a meta-analysis to determine the complications associated with endovascular coiling and CVD for CCA. The perioperative morbidity rate for endovascular coiling was 3.0\%, significantly lower than that of CVD (7.0\%). There was no difference in the mortality rate between the 2 groups, which was 0\% for the coiling cohort and 4\% for the CVD. Therefore, it is safe to assume, based on the literature, that coiling is safer than CVD in the treatment of CCA. On the contrary, the literature does not allow such conclusion on PED versus coiling in terms of morbidity and mortality, because direct comparison has not been made. Our study, however, compared PED head to head with coiling and SAC and demonstrated that PED placement is associated with lower complication rates compared with coiling and CVD.

Risk–Benefit Analysis
A risk–benefit analysis should be assessed before deciding on whether or not to treat patients with CCA, and what type of treatment is most adequate. The analysis should factor in the patient’s age, interventionist experience, aneurysm size, morbimortality rate, occlusion rate, and presence or absence of symptoms. CVD is an effective treatment with high occlusion rates, but limited by the risk of complications, risk of aneurysm formation along the collateral pathways, and presence of contralateral mirror aneurysms.\textsuperscript{5,\textsuperscript{31–\textsuperscript{34}}} These limitations make flow diversion, a reconstructive technique, more appealing. Even more, CCA have a sidewall morphology and lack perforating side branches, which make them well suited for PED placement.\textsuperscript{3,\textsuperscript{5}} However, many authors still prefer CVD in elderly patients with excessive tortuous vessels or where traversing the aneurysm is thought to be challenging.\textsuperscript{3} The results of our study strongly suggest the use of flow diversion, which might help avoid the higher rate of complications that we are currently having with conventional treatments and to dodge the need for retreatment in the future. Additionally, the findings in this study demonstrate that patients treated with PED had the highest likelihood of improvement in symptoms and mass effect. We encourage the use of flow diversion in patients who present with symptomatic CCA. Finally, complete occlusion seems to be higher with pipeline placement; this along with vessel reconstruction and aneurysm shrinkage confers PED a potential advantage over other modalities when treating giant CCA in hope of avoiding subarachnoid hemorrhage.

Limitations
The limitations of the present study include retrospective design and possible selection bias. Patients in our cohort were treated at a tertiary referral hospital by dual trained neurosurgeons leading to a potential ascertainment bias, limiting the external validity of the results. The lack of an untreated control group limits assessment of intervention strategies. Nevertheless, our study is the only one comparing results of flow diversion, including mass effect evolution, head to head with other conventional endovascular studies in patients harboring CCA. It is also the cohort with the largest sample of CCA.

Conclusions
In the absence of randomized controlled trials, hard evidence guidelines are lacking. Randomized controlled trials have to overcome many obstacles, including an adequate sample size for analysis, given the low prevalence of CCA in the population. With the present findings in literature and with the results found in this study, the use of flow diversion should be encouraged, especially in symptomatic patients. We found PED to be associated with higher obliteration rate, less need for future treatment, higher improvement rates in mass symptoms, and lower complications when compared with traditional endovascular treatments.

Disclosures
Dr Jabbour is a consultant at Covidien. Dr Tjoumakaris is a consultant at Covidien and Stryker. The other authors report no conflicts.

References
Flow Diversion Versus Conventional Treatment for Carotid Cavernous Aneurysms
Mario Zanaty, Nohra Chalouhi, Robert M. Starke, Guilherme Barros, Mark Philip Saigh, Eric
Winthrop Schwartz, Norman Ajiboye, Stavropoula I. Tjoumakaris, David Hasan, Robert H.
Rosenwasser and Pascal Jabbour

Stroke. published online July 22, 2014;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/early/2014/07/22/STROKEAHA.114.006247

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/