ORIGINAL RESEARCH

Enterprise stenting for intracranial aneurysm treatment induces dynamic and reversible age-dependent stenosis in cerebral arteries

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ABSTRACT

Background Although intracranial stenting has been associated with in-stent stenosis, the vascular response of cerebral vessels to the deployment of the Enterprise vascular reconstruction device is poorly defined.

Objective To evaluate the change in parent vessel caliber that ensues after Enterprise stent placement.

Methods Seventy-seven patients with 88 aneurysms were treated using Enterprise stent-assisted coil embolization and underwent high-resolution three-dimensional rotational angiography followed by three-dimensional edge-detection filtering to remove windowing-dependence measurement artifact. Orthogonal diameters and cross-sectional areas (CSAs) were measured proximal and distal on either side of the leading stent edge (points A, B), trailing stent edge (points D, E), and at mid-stent (point C).

Results Enterprise stent deployment caused an instant increase in the parent artery CSA by 8.98% at D, which was followed 4–6 months later by significant in-stent stenosis (15.78% at A, 27.24% at B, 10.68% at C, 32.12% at D, and 28.28% at E) in the stented artery. This time-dependent phenomenon showed resolution which was complete by 12–24 months after treatment. This target vessel stenosis showed significant age dependence with greater response in the young. No flow-limiting stenosis requiring treatment was observed in this series.

Conclusions Use of the Enterprise stent is associated with a significant dynamic and spontaneously resolvable age-dependent in-stent stenosis. Further study is warranted on the clinical impact, if any, of this occurrence.

INTRODUCTION

For the past decade a significant proportion of wide-necked, fusiform, irregular, and complex intracranial aneurysms treated by endovascular means have used the stent-assisted technique.[1–3] In the USA, the initial intracranial stent used as an adjunct for aneurysm treatment has been the open-cell design Neuroform device (Stryker Neurovascular, Freemont, California, USA). Since its initial release, a number of studies have looked into its effect on the parent artery.[3–5] This stent continues to be popular and useful in the treatment of aneurysms. More recently, the Enterprise (EN; Codman Neurovascular, Raynham, Massachusetts, USA) vascular reconstruction device has seen increased use. The EN stent is a partially retrievable closed-cell design stent with a significantly lower profile.[6 7] Although there have been a few reports of delayed migration, the EN stent is easy to deploy and has gained significant use since its introduction more than 5 years ago. However, despite its wide use to date, the impact of EN stent implantation on the parent artery in a temporal fashion remains poorly defined, with only a few studies addressing this important parameter in stent placement in a qualitative or semi-quantitative fashion.[8–10]

The current study was performed to evaluate the quantitative response of the parent artery to EN stent deployment in stent-assisted treatment of cerebral aneurysms by accurately measuring vascular geometry and lumen caliber in a cohort of patients using three-dimensional digital rotational angiography (3DRA) along with edge-detection methodology to improve accuracy and evaluate the longitudinal response.

MATERIALS AND METHODS

Patient population

From June 2007 to December 2011, 77 patients with 88 intracranial aneurysms, two pseudoaneurysms, and one vascular dissection were managed using 84 EN stents. In this patient cohort there were 63 women and 14 men of mean age 56 years (range 13–88).

Aneurysms were located in the cervical internal carotid artery (ICA) (4), petrous ICA (1), cavernous ICA (5), supraclinoid ICA (22), ophthalmic artery (19), and at the bifurcation of the ICA (2). There were also aneurysms treated that involved the anterior cerebral artery (1), anterior communicating artery (4), middle cerebral artery (6), posterior communicating artery (6), anterior choroidal artery (1), superior cerebellar artery (1), vertebral artery (1), posterior cerebral artery (2), and the basilar apex (6). Four female patients had bilateral aneurysms of either the ophthalmic arteries or the supraclinoid ICA with only one aneurysm per patient being treated and included in this analysis. An additional patient had one large and three smaller adjacent aneurysms treated with stenting across all four aneurysms with coiling of the largest aneurysm. Furthermore, four patients, each with two adjacent aneurysms, were treated via stenting across both aneurysms with the larger aneurysm being coiled. Given the differing physiology and pathology in cervical ICA dissections and pseudoaneurysms, these patients were removed from further statistical analysis.

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Of the aneurysms mentioned above, 10 had ruptured previously and had been initially treated with endovascular embolization or surgical clipping 3.5–6 years prior to this analysis. These aneurysms were retreated using EN stent-assisted coiling due to aneurysm regrowth and were included in this analysis. One patient had a previously ruptured basilar bifurcation aneurysm that was treated with Neuroform stent-assisted coiling. Four months later, angiographic follow-up demonstrated coil compaction and residual aneurysm filling. EN stent-assisted coiling was performed to treat this residual. All other patients included in this study were undergoing their primary treatment.

All of our patients routinely undergo high-resolution 3DRA before and immediately after stenting and at each angiographic follow-up. Prospective clinical data are maintained on the occurrence of transient neurological ischemic events, cerebral infarction, and assessment of neurological outcome on follow-up.

Procedural details

The Codman EN stent is a flexible nitinol stent which has a closed-cell design with flared ends to enhance apposition to the wall of the vessel. The stent is compatible with a 0.021 inch Prowler Plus microcatheter (Codman Neurovascular), and measures 4.5 mm in diameter with different stent lengths of 14, 22, 28, and 37 mm. All stents were deployed under general endotracheal anesthesia with the administration of an antiplatelet regimen consisting of clopidogrel bisulfate 75 mg/day and acetylsalicylic acid 325 mg/day beginning at least 3–5 days before the procedure, as well as intravenous anticoagulation with heparin to an activated clotting time of 230–250 s. Stent coiling was performed either by using the sequential or jailing technique. Following the procedure, patients were maintained on an intravenous heparin drip for a goal partial thromboplastin time of 50–70 s for 12–24 h.

Angiographic follow-up

Patients were followed up both radiographically and clinically at 3–6 months. An angiogram was obtained at this time. A second follow-up angiogram or non-invasive MRI (MRI/MRA) was performed at 6 months to 1 year and then yearly depending on the findings. Clopidogrel was continued for 3 months post-procedure and discontinued over 1 week. Aspirin was maintained for at least 6 months post-procedure. If no clinical or radiographic concerns were found, aspirin was discontinued at the 6-month period.

3D modeling and quantitative vascular measurement

Biplane 2D digital subtraction angiography and 3DRA imaging were performed on a Siemens Axiom-Artis biplane system (Siemens Artis, Malvern, Pennsylvania, USA) in each case to assess for any branch occlusion, thrombus formation, degree of aneurysmal occlusion, stent position as well as in-stent stenosis. 3DRA was performed using 3 mL/s of contrast medium for 5 s with a 1.5 s pre-injection delay. All the reconstructed 3D imaging data sets were analyzed using Amira 3D visualization and modeling system software (Amira 5.3.3, Visage Imaging, San Diego, California, USA). Specifically, the patient's 3DRA volumetric dataset was subjected to 3D Sobel edge-detection filtering, which yielded the 3D corresponding output dataset. All measurements were made from this Sobel-filtered volume dataset, thereby removing the artifactual dependence of vessel diameter on the center and width of the windowing look-up table used in visualization. Using the Sobel edge-filtered dataset in 3D interactive space, the following points were chosen for vascular measurement along the path of the parent artery (figure 1): (1) 2–4 mm proximal to the stent (point A); (2) 2–4 mm distal to the proximal struts (point B); (3) midstent segment at the aneurysm neck (point C; for patients with multiple adjacent aneurysms treated with one stent deployment, point C would be chosen at the neck center of the major coiled aneurysm); (4) 2–4 mm proximal to the distal struts (point D); and (5) 2–4 mm distal to the distal struts (point E). The same corresponding vessel points (A, B, D, and E) were chosen for measurement before and immediately after stent coiling during the treatment procedure, and at each angiographic follow-up study. Point C was measured after stent coiling and at each angiographic follow-up because the absence of coils before treatment made the measurement point at the level of the aneurysm neck arbitrary and prone to variability. At each point, the stented vessel was sectioned perpendicularly to its major flow axis in 3D space and the cross-section was treated as an ellipse with major and minor axis diameters a and b, respectively (figure 2). An average luminal diameter was computed as (a+b)/2, and the cross-sectional area (CSA) of the parent vessel was calculated according to the formula ([π]×a×b/4).[5 11]

Statistics

The vascular diameters and CSA values were compared using paired t tests in the JMP software package, V.10.0 (SAS Institute, Cary, North Carolina, USA) before and after stent coiling and at each follow-up. A logistic regression model was used to evaluate the correlation between clinical events and the degree of luminal change and between patient characteristics (ie, age, presence of hypertension, aneurysm neck width), stent dimensions, duration at angiographic follow-up, and presence of luminal change. Statistical significance was assumed at a value of $p<0.05$, and highly significant at $p<0.01$.

RESULTS

Stent deployment and angiographic follow-up

Eighty-four EN stents were deployed in this series. All patients had one or more angiographic follow-up study. A follow-up angiogram was performed once in 77 patients within a range of 1–13 months (mean 3.5 months) following stenting, twice in 48 patients within a range of 3–41 months (mean 12.6 months), three times in 25 patients within a range of 4–52 months (mean 24.3 months), and four times in eight patients within a range of 8–40 months (mean 28 months).

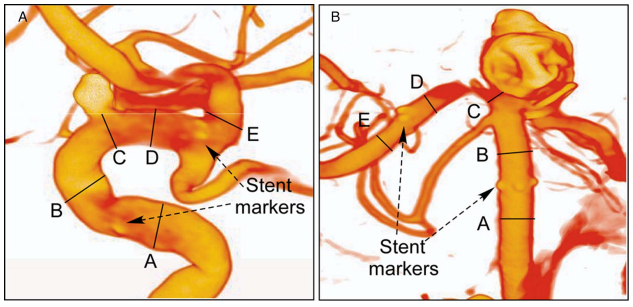


Figure 1 Three-dimensional rotational angiography (3DRA) reconstructions of two patients demonstrating points of measurement A–E. Orthogonal diameters and cross-sectional areas (CSAs) were measured 2–4 mm proximal and distal on either side of the leading stent edge (points A, B), trailing stent edge (points D, E) and at mid-stent (point C). (A) A sexagenarian patient with a 3 mm aneurysm with a wide neck involving the origin of the right ophthalmic artery. (B) An elderly patient who presented with a 12 mm aneurysm with an 8 mm neck at the basilar bifurcation.

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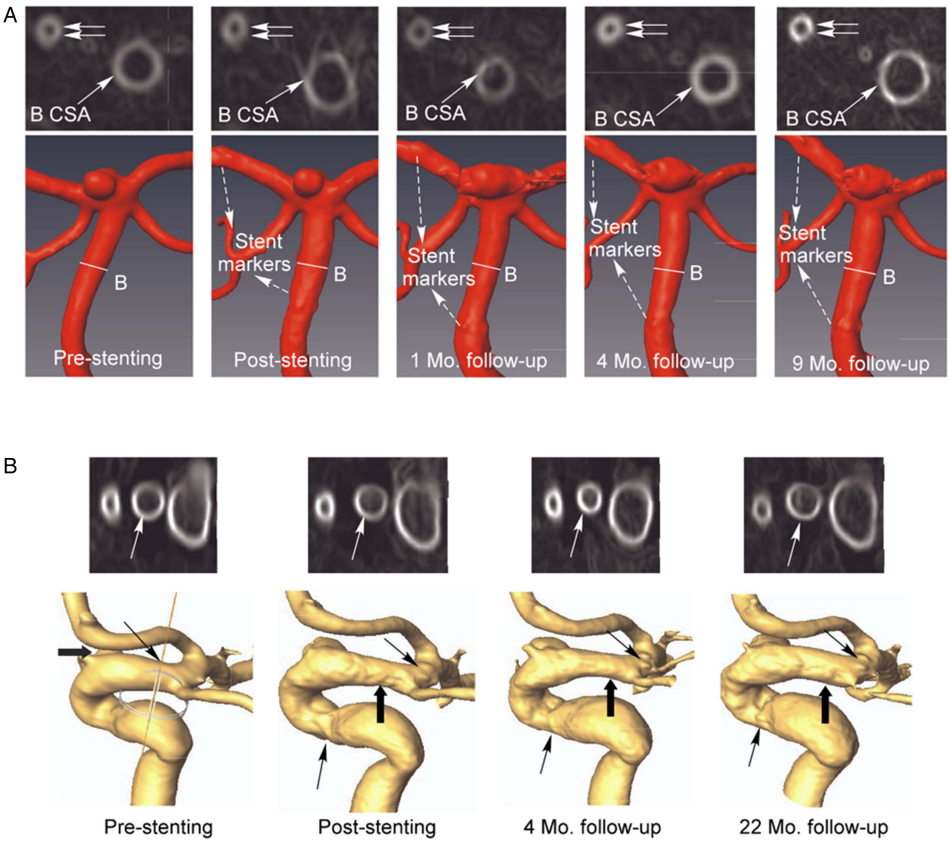


Figure 2 (A) A sexagenarian patient with a 3 mm aneurysm of the basilar artery bifurcation. A cross-sectional image of the Sobel three-dimensional edge detection filtered reconstructions (above) and three-dimensional rotational angiography (3DRA) reconstruction (below) are presented for each time point. The ellipse used to calculate the cross-sectional area (CSA) at point B is shown by a single arrow and a reference vessel without a stent is shown by a double arrow. The diameter of point B was 2.75 mm, 3.1 mm, 2.45 mm, 2.55 mm and 2.8 mm at the respective follow-up times. Similar findings were found for the CSA. The reference vessel diameter and CSA did not change. (B) A middle-aged patient with a right 5 mm paraclinoid segment aneurysm (thick black arrow, pre-stenting). The plane at point D in which the artery is orthogonally sectioned (thin black arrow, pre-stenting). The stent markers are demonstrated by thin black arrows and point D by the thick black arrow on post-stenting, 1-month and 4-month follow-up. The diameter at point D (white arrow, top row) was 3.3 mm, 3.6 mm, 2.55 mm and 3.4 mm at the respective follow-up times. The two reference vessels were unchanged throughout follow-up.

Dynamic vascular response to stent implantation

The deployment of the EN stent caused a statistically significant immediate increase in the average diameter of the parent artery at all points analyzed, with the greatest diameter increase noted at point D (0.13 mm, 4.4% increase, $p<0.005$). At points A, B, C, D, and E the mean vascular diameter was decreased compared with pre-stenting values at both 1–3 and 4–6 months post-treatment and returned to the post-stenting diameter by 7–9 months (table 1). The greatest reduction was noted at point D at 4–6 months post-treatment (0.53 mm, 18.09% decrease, $p<0.005$). Similar significant trends occurred with the CSA at all points. The CSA at 4–6 months post-treatment was reduced by 15.78% at point A, 27.24% at point B, 10.68% at point C, 32.12% at point D, and 28.28% at point E (table 1). At points A, B, C, D, and E the CSA was decreased compared with pre-stenting values at both 1–3 and 4–6 months post-treatment and returned to post-stenting CSA by 7–9 months (table 1).

The two reference points B and D were chosen to compare the percentage change in CSA of the parent artery versus the length of time post-treatment. Comparing percentages allowed us to eliminate the absolute values of each patient's natural parent artery diameter (figure 3). The CSA was increased immediately after stent deployment, with a gradual decrease in CSA to a nadir at 4–6 months post-treatment and then a subsequent return to pre-stenting CSA by 6–9 months. We analyzed whether this reaction had any age dependence at 2–4 months post-stenting. A significant correlation between younger age and a more significant reaction to stent deployment was noted at points A ($p<0.01$), B ($p<0.001$), D ($p=0.003$), and E ($p=0.02$) (figure 3, data displayed for points B and D).

We wished to evaluate the number of instances where the percentage reduction in CSA exceeded 30%, 50% and 70% for clinical relevance. We calculated this for points B and D at the 4–6 month time period since this time point showed the greatest reduction in both diameter and CSA. At point B, a 30% reduction in CSA was noted in 9/27 patients (33%), a 50% reduction in 2/27 patients (7.4%) and a 70% reduction in 0/27 patients (0%). At point D, a 30% reduction in CSA was noted in 11/27 patients (41%), a 50% reduction in 3/27 patients (11%) and a 70% reduction in 1/27 patients (3.7%). No in-stent stenosis that developed was flow-limiting or required any additional treatment for correction including angioplasty or further stenting.

DISCUSSION

The EN stent has become a commonly used adjunct to coil embolization of aneurysms due to its low profile, closed-cell design, ease of deployment, and ability to be retrieved in certain clinical situations.[6 7] This study aimed to quantitatively investigate the effect of EN stent implantation on the parent vessel. Our results suggest that there may be a significant intimal reaction with hyperplasia within the stented segment causing the in-stent stenosis observed. This process, however, seems to be dynamic and is spontaneously reversed.

We have demonstrated that EN stenting causes an immediate statistically significant increase in both the average diameter and CSA of the parent vessel. With time, an in-stent intimal hyperplasia probably begins, leading to stenosis that peaks at some time between 2 and 6 months after stent implantation. This in-stent stenosis, however, is dynamic and both the diameter and the CSA of the parent vessel are restored to pre-stenting values by 7–12 months. Interestingly, we have noted that this process tends to occur more aggressively with younger patients. We hypothesize that this is probably due to a greater and more intense parent artery reaction to the stent at younger ages. This

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Table 1 Mean vascular diameter (top rows, mm) and CSA (bottom rows, mm^2) at points A, B, C, D, and E

Point	Pre-stenting	Post-stenting	1–3 m	4–6 m	7–9 m	10–15 m	16–24 m	>25 m
A	3.65±0.09 (100%)	3.75±0.09*** (102.74%)	3.61±0.12 (98.90%)	3.31±0.18* (90.68%)	3.48±0.21 (95.34%)	3.52±0.23 (96.44%)	3.81±0.18 (104.38%)	3.55±0.19 (97.26%)
	10.90±0.49 (100%)	11.51±0.53*** (105.60%)	10.72±0.65 (98.35%)	9.18±0.94* (84.22%)	10.02±1.1 (91.93%)	10.37±1.23 (95.14%)	11.76±0.98 (107.89%)	10.33±1.09 (94.77%)
B	3.45±0.09 (100%)	3.55±0.09 ** (102.90%)	3.16±0.11*** (91.59%)	2.89±0.17*** (83.77%)	3.21±0.17 (93.04%)	3.23±0.16 (93.62%)	3.52±0.17 (102.03%)	3.22±0.20 (93.33%)
	9.73±0.46 (100%)	10.27±0.49 * (105.55%)	8.25±0.55*** (84.79%)	7.08±0.83*** (72.76%)	8.37±0.8 (86.02%)	8.47±0.77 (87.05%)	10±0.87 (102.77%)	8.62±1.05 (88.59%)
C		3.48±0.11 (100%)	3.19±0.11*** (91.67%)	3.24±0.21** (93.10%)	3.37±0.13 (96.84%)	3.06±0.18 (87.93%)	3.33±0.21 (95.69%)	3.22±0.18 (92.53%)
		9.74±0.69 (100%)	8.19±0.52** (84.09%)	8.70±1.15* (89.32%)	8.84±0.70 (90.76%)	7.68±0.78 (78.85%)	8.83±1.06 (90.66%)	8.3±0.8 (85.22%)
D	2.93±0.09 (100%)	3.06±0.09*** (104.44%)	2.55±0.11*** (87.03%)	2.40±0.14*** (81.91%)	2.95±0.18 (100.68%)	2.74±0.18 (93.52%)	3.01±0.14 (102.73%)	2.9±0.16 (98.98%)
	7.13±0.39 (100%)	7.77±0.42*** (108.98%)	5.53±0.43*** (77.56%)	4.84±0.53*** (67.88%)	7.22±0.85 (101.26%)	6.23±0.71 (87.38%)	7.29±0.6 (102.24%)	6.87±0.67 (96.35%)
E	2.74±0.09 (100%)	2.84±0.09*** (103.65%)	2.53±0.1* (92.34%)	2.30±0.14** (83.94%)	2.66±0.20 (97.08%)	2.47±0.18 (90.15%)	2.64±0.15 (96.35%)	2.59±0.19*** (94.53%)
	6.33±0.37 (100%)	6.78±0.4*** (107.11%)	5.34±0.38*** (84.36%)	4.54±0.55* (71.72%)	6±0.84 (94.79%)	5.2±0.77 (82.15%)	5.74±0.61 (90.68%)	5.69±0.78*** (89.89%)

Values reported as mean±SEM (percentage change compared with pre-stenting value).
*p<0.05; **p<0.01; ***p<0.005 compared with post-stenting data.
CSA, cross-sectional area; m, months of follow-up post-stenting.

concept is supported in both the coronary artery literature[12] as well as the Wingspan literature,[13] where elderly patients were found to have less neointimal hyperplasia compared with younger patients after stent placement.

Our finding of an immediate increase in parent artery diameter and CSA after EN stenting is an important result. This phenomenon probably occurs due to a mismatch between the EN stent dimensions and the diameters of the parent artery into which it is deployed. Currently, the EN stent has a single diameter of 4.5 mm with different lengths and so may cause expansion distally in the smaller vessels in which it is deployed. We have demonstrated that implantation of this stent causes an overexpansion of the parent vessels. In addition to the greater absolute dimension of the stent compared with the parent artery, the EN stent imparts a small but not negligible radial force to the artery. Both these factors are likely to contribute to the immediate increase in artery diameter and CSA noted in this study. It should be noted that this effect, however, is not limited only to the area of the artery that contains the stent as enlargement was demonstrated at the native vessel points A and E, suggesting that the stent has obvious effects on the parent artery at points both proximal and distal to it. Although this overexpansion may help to maintain the patency of the artery, we hypothesize that this enlargement likely leads to some component of vessel injury, possibly subjecting the artery to low wall shear stress, and therefore causing the subsequent intimal hyperplasia and in-stent stenosis demonstrated.[14–16] Numerous studies have shown that overexpansion of a parent artery by stenting can markedly increase the area of a vessel subjected to low wall shear stress and that this increased deployment pressure is associated with vascular damage, an index that directly influences the amount of neointimal hyperplasia that develops.[14–16] Furthermore, these studies have suggested that altered wall shear stress distributions in the stented segment of an artery may contribute to the development of in-stent stenosis.

LaDisa *et al*,[17] as well as a previous in vitro study,[18] have suggested that low wall shear stress is most pronounced at the proximal portion of stent placement and is less dramatic throughout the remainder of the stent. This would suggest that the inlet of the stent would be most susceptible to neointimal hyperplasia (point B in our study). However, these studies were conducted within an artery model of the same diameter throughout the vessel without consideration of the anatomical differences in the size of an artery at its proximal and distal ends. These studies do not take into consideration that more distal portions of a stented artery have a greater percentage expansion than proximal portions of the artery. Our data tend to support the notion that the distal portions of the parent artery (point D) are (1) being expanded to a greater amount than any other point in the artery and (2) that this greater expansion probably leads to greater vascular injury leading to an increase in the amount of neointimal hyperplasia and in-stent stenosis.[14–16] Furthermore, previous studies have supported this claim by demonstrating that low wall shear stress is more profound downstream than upstream of the stent struts (point E vs point A).[19–21] It is likely that EN stent implantation alters the distributions of wall tension more profoundly distally within the parent artery which, in turn, triggers many of the cellular responses and consequently results in neointimal hyperplasia and stenosis within and around the stented segment of the parent artery in addition to any low wall shear stress-mediated changes downstream of the leading edge.[22 23]

One of our most interesting findings in this study is that the initial decrease in diameter and CSA of the parent artery is dynamic and starts a reversal process 4–6 months post-

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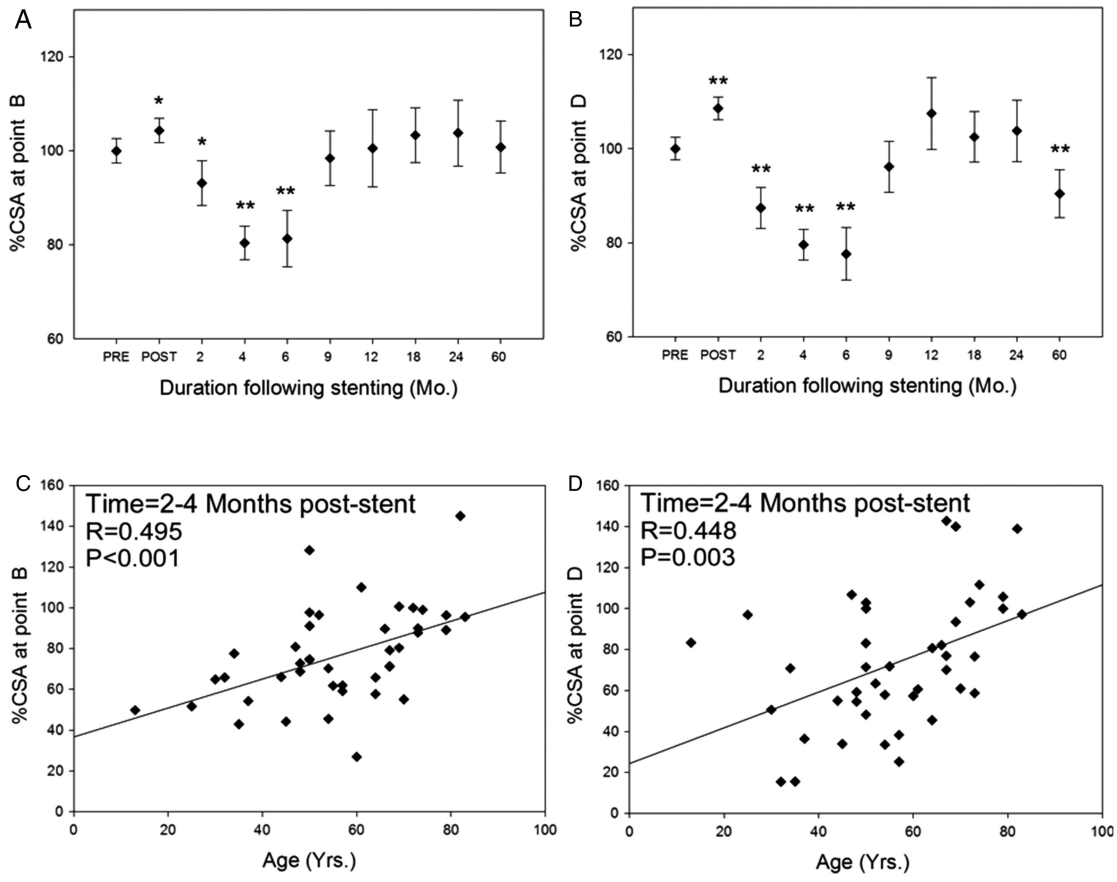


Figure 3 Time course of cross-sectional area (CSA) change at different follow-up times before and after stenting for point B (A) and point D (B). Values are all compared with the pre-stenting value (*p<0.05, **p<0.001). An immediate increase in CSA after stenting was followed by a gradual decrease in CSA to a nadir around 4–6 months post-treatment and then a return to baseline by 12–18 months. Age dependence using logistic regression model of CSA at points B (C) and D (D) at 2–4 months after stenting. Younger patients showed a greater percentage change in CSA following stenting. Pearson correlation coefficient (R) and p values are provided.

treatment. We, like others, hypothesize that this may reflect an initial neointimal fibrotic scar formation that over time contracts and is broken down.[8 24 25] Fiorella *et al*[4] demonstrated a similar finding with the Neuroform stent and reported that spontaneous resolution of in-stent stenosis occurred on average 9 months post-treatment. These findings have also been reported in the coronary circulation literature with balloon angioplasty[26] or implantation of balloon-expandable stents,[24 25 27 28] with a range of resolution occurring from 6 months to several years post-treatment.[24 25 27 28]

Although in-stent stenosis often has a negative connotation in the context of atherosclerotic disease, it may contribute to the positive effect seen in terms of lower rates of recanalization following coiling. In this series we had multiple aneurysms treated with stenting alone that showed aneurysm thrombosis and involution. The same neointimal hyperplasia that leads to this initial in-stent stenosis probably helps to seal the neck of the aneurysm whether or not coils are used.[29] It has repeatedly been shown in the literature that stent-assisted coiling methods tend to improve aneurysm thrombosis due to both denser coil packing ability as well as some aspect of flow diversion probably from the aforementioned neointimal hyperplasia.[30–32]

Finally, we report a 50% reduction in CSA at 4–6 months at point B in 2/27 patients (7.4%) and in 3/27 patients (11%, 1 patient with >70% reduction) at point D. Mocco *et al*[9] in a 10-center registry of 213 patients undergoing EN stent-mediated coil embolization reported a 3% rate of >50% in-stent stenosis at an average catheter-based angiographic follow-up of 175 days (range 30–395). Likewise, Fargen *et al*[10] reported on a nine-center registry of 229 patients undergoing EN stent-mediated coil embolization with a 2% rate of >50% in-stent stenosis visualized by catheter-based angiography, MRA and CT angiography at an average follow-up of 21 months. The current report demonstrates a higher rate of >50% stenosis than reported in both these series, albeit at an earlier time point than the average follow-up time of both the aforementioned studies. Since we have demonstrated that the most significant stenosis likely occurs 4–6 months after stent deployment, both these series may not be able to asses this higher rate of stenosis simply due to the angiographic follow-up time reported in their studies. However, similar to both of these series, we report no instances of the need for any additional endovascular intervention for any patient and demonstrate that this stenosis is a dynamic and reversible phenomenon that resolves 3–6 months after its initial peak at 4–6 months post-deployment.

In this study we report on the quantitative temporal parent artery response to the implantation of the EN stent in patients with wide-necked aneurysms. Although the in-stent stenosis has been asymptomatic in this patient cohort, long-term radiographic, clinical and histopathological correlation will be needed to determine whether this is a benign self-limiting remodeling process or a more concerning progressive clinically significant arteriopathy, and whether there is a second stenotic phenomenon after the relief of the initial in-stent stenosis.

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CONCLUSION

Enterprise stent deployment causes an age-dependent and dynamic spontaneously resolving in-stent stenosis of the parent artery that peaks at 4–6 months and resolves by 12–24 months post-treatment. Although of limited clinical impact except in some cases, this finding helps to increase our understanding of the intracranial vessel wall response to miniature self-expanding stent deployment.

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Ethics approval Ethics approval was obtained from the Tufts Medical Center IRB.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Patient level data and full dataset are available from the corresponding author.

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