Clinical Neurology and Neurosurgery 183 (2019) 105395

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Effect of aneurysm morphologic parameters on occlusion rates following pipeline embolization

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ARTICLE INFO

Keywords:
Pipeline embolization
Aneurysm morphology
Occlusion

ABSTRACT

Objective: Treatment failures with the use of Pipeline Embolization Device (PED) continue to be observed in up to 18% of patients in large case series. Adjunctive coiling and layering of multiple devices have been shown to improve occlusion rates; however, the optimal treatment strategy with the use of PED has not been established. The purpose of this study is to identify morphological characteristics predictive of treatment failure after PED.
Patient and methods: A case control design was used to evaluate the association of aneurysm morphologic parameters with failure after PED placement. Retrospective analysis of patients undergoing PED for elective aneurysm treatment between 2014 and 2017 was performed. Patients who underwent PED placement with at least 12 months follow-up using conventional cerebral angiography were included for further review.
Results: 84 patients met inclusion criteria for further analysis. ten patients (11.9%) experienced treatment failure defined by retained flow within the aneurysm and of those eight patients (9.5%) required additional retreatment. On multivariate analysis decreasing aspect ratio and increasing neck width were significant parameters that predicted treatment failure.
Conclusion: Aneurysms with small aspect ratio and large neck width may be more likely to experience treatment failure after PED embolization. This subset of aneurysms may therefore benefit from adjunctive coiling to improve occlusion rates. Future prospective studies are needed to validate these findings.

1. Introduction

Pipeline embolization device (PED) is a stand-alone therapeutic modality approved by the US Food and Drug Administration for treating large and complex aneurysms arising from the petrous and supraclinoid segment of the internal carotid artery. Initial indications for PED were aneurysms felt not to be amenable to conventional surgical and/or endovascular approaches; however, PED is now routinely used in the management of ruptured and unruptured aneurysms of all sizes in both the anterior and posterior circulation [4].

The PED has been used with increasing frequency due to its low complication rates and high technical and therapeutic success rates. Despite these favorable qualities, treatment failures continue to be observed in up to 18% of patients in large case series [2]. Initial treatment with PED limits retreatment options to re-stenting as the design of PED precludes the use of coil embolization and makes surgical clipping more technically challenging. Despite retreatment by deploying additional PEDs, there remains a specific subgroup of aneurysms that are particularly refractory to treatment with flow diversion [15]. One strategy to increase obliteration rates include concurrent coil embolization during initial stent placement which has been utilized by some authors to promote early aneurysm occlusion and avoid rare complications of aneurysm rupture after PED deployment [10].

Currently, there is no optimal treatment strategy with the use of PED. The decision to use concurrent coil embolization and layering multiple PED devices has been limited to the discretion of the practitioner. Although previous evidence suggests aneurysm size, location, and incorporation of a branch vessel predicts treatment failure, other morphologic parameters may be important but have not been evaluated [1,15]. The purpose of this study is to identify morphological characteristics predictive of treatment failure after PED as a stand-alone construct.

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https://doi.org/10.1016/j.clineuro.2019.105395
Received 24 April 2019; Received in revised form 21 June 2019; Accepted 23 June 2019
Available online 24 June 2019
0303-8467/

2. Patient and methods

A case control design was used to evaluate the association of aneurysm morphologic parameters with failure after PED placement. A retrospective analysis of patients undergoing PED for elective aneurysm treatment between 2014 and 2017 was performed. Patients who underwent PED placement with at least 12 months follow-up with conventional cerebral angiography were included for further review.

Patient characteristics and aneurysm morphologic parameters, which were obtained via magnified oblique digital subtraction angiogram and 4-dimensional rotational angiography with 3-dimensional reconstruction, include: 1) aneurysm width; 2) aneurysm depth; 3) neck width; 4) inflow angle; 5) aneurysm shape; 6) bottleneck factor (width/neck width); 7) aspect ratio (depth/neck width); 8) depth-width ratio; 9) size ratio (depth/diameter of parent artery; 10) number of devices; 11) presence of multiple lobes; 12) parent vessel diameter; 13) aneurysm volume; 14) presence of daughter sacs; 15) aneurysm location; and 16) presence of branching vessel (Fig. 2).

The Mann-Whitney Test was performed for continuous variables and the Fisher's exact and chi-square test was utilized for categorical variables to identify factors associated with treatment failure after PED. Receiver Operating Character (ROC) analysis was conducted for the significant variables to obtain an optimal cut-off value for logistic regression analysis and to understand the specificity and selectivity of the significant multivariate variables. Univariate logistic regression and stepwise, least-squares logistic multivariate regression was performed with a significance threshold of $P < 0.05$.

3. Results

During the study period 84 patients who underwent placement of PEDs to treat unruptured intracranial aneurysms met inclusion criteria and had at least 12 months follow-up with conventional cerebral angiography. Ten patients (11.9%) experienced treatment failure defined by retained flow within the aneurysm at 12 months follow-up and eight patients required additional retreatment (9.5%) consisting of placement of one or two additional PEDs. Of these eight cases, residual was total in one and subtotal in 7 cases. Of those who failed PED stand-alone therapy, three patients (37.5%) continued to be refractory to flow diversion therapy despite retreatment with an median follow-up of 1104 days compared to the 606 days of the nominal group (Tables 1 and 2). One patient continued to demonstrate subtotal filling and two patients demonstrated entry remnant filling at last follow-up.

Aneurysm size, neck location, and presence of an adjacent branching vessel were not significant predictors while the ROC area under curve (AUC) of neck width and aspect ratio had significant separation and specificity resulting in a multivariate curve with a specificity of over 0.7 for predicting PED failure (Table 3). Aneurysm aspect ratio and neck width both maintained significance for predicting treatment failure on multivariate analysis (Table 4).

4. Discussion

Treatment failure rates of nearly 20% have been reported in multiple large series evaluating the results of PED deployment [1,2]. To date, most studies evaluating the PED have focused on its safety and efficacy in treating aneurysms of different sizes and locations. Few studies have evaluated the factors affecting aneurysm obliteration and to the best of knowledge none have focused on studying the effect of aneurysm morphological parameters on occlusion rates beyond basic measurements such as volume, shape, and diameter [15]. Studies consistently suggest morphologic parameters are important in the formation, growth, and rupture of cerebral aneurysms [14]. We retrospectively analyzed 16 morphologic parameters of consecutive aneurysms treated with PED and identify decreasing aspect ratio and increasing aneurysm neck depth-width ratio as an independent predictors of treatment failure.

Table 1
Summary of continuous parameters of FDS treated patients. The table is divided into three sections; patients without re-stenting, patients with re-stenting, and the Mann-Whitney Test comparing those two cohorts. The population size, median, and p-value of the Mann-Whitney test are shown.

	Successful Cases (N = 73)	Refractory Cases (N = 11)	P-Value
Age	56	56	0.5866
Follow Up Time	606	1104	0.0625
# Devices	1	1	0.885
Size of Parent Vessel (mm)	4.37	4.34	0.9736
Branch Vessel Diameter (mm)	1.07	0.89	0.2844
Aneurysm inflow angle	98.5	131	0.2175
Aneurysm # Lobes	1	2	0.6203
Anerurysm # Daughter Sacs	0	0	0.414
Depth (mm)	4.67	7.22	0.3708
Width (mm)	4.98	8.86	0.2151
Neckwidth (mm)	4.46	7.74	0.0155
Volume (mm^3)	54.2997	265.7326	0.1323
Aspect Ratio	0.9551	0.8241	0.0312
Bottleneck Ratio	1.0871	0.9272	0.1072
Depth-Width Ratio	0.8442	0.796	0.1741
Size Ratio	1.135	1.5297	0.3637

Table 2
Summary of categorical parameters for FDS treated patients. The table is divided into three sections; patients without re-stenting, patients with re-stenting, and the Fisher's Exact/Chi-Squared test. The p-value of the Fisher's Exact/Chi-Squared test are reported.

		Successful Cases (N = 73)	Refractory Cases (N = 11)	P-Value
Sex	Male	8	2	0.6132
	Female	65	9	
HTN	None	44	7	1
	Present	29	4	
DM2	None	67	9	0,2805
	Present	6	2	
Smoking	None	28	8	0.0485
	Present	45	3	
CAD	None	71	11	1
	Present	2	0	
Renal Disease	None	69	7	0.0089
	Present	4	4	
Rheumatological Condition	None	71	11	1
Aneruysm Wall Location	Side	71	9	0.0813
	End-Wall	2	2	
Aneurysm Shape	Bulbous	73	9	0.0158
	Fusiform	0	2	
Branching Vessel	None	19	5	0.4108
	Adjacent	46	5	
	Arising off Fundus	8	1	
Adjunctive Coiling	None	63	10	1
	Present	10	1	

Most studies evaluating the predictors of incomplete occlusion after PED placement focus on clinical factors while few have fully evaluated the impact of morphology. In the largest series evaluating the predictors of occlusion after PED treatment of 465 aneurysms, Adeeb et al. identified increasing age and non-smoking status as independent predictors of aneurysm persistence [1]. Our study identified a similar trend of non-smoking status as a predictor of treatment failure but did not reach statistical significant on multivariate analysis possibly due to the small number of patients in our cohort.

Increasing aneurysm diameter and aneurysms incorporating a

Table 3
Results of the Receiver Operating Characteristics (ROC) curve analysis. The table demonstrates the area under the curve (AUC) its 95% confidence interval (CI), P-Value, Youden Index, and its associated criterion of both the individual significant variables of the Mann-Whitney Test and the combined multivariate regression curve itself.

	Neck Width (mm)	Aspect Ratio	Multivariate Regression
AUC	0.727	0.702	0.894
AUC (95% CI)	0.619–0.819	0.593–0.797	0.808–0.951
Youden Index	0.5579	0.4844	–
Associated Criterion	> 6.46 mm	≤0.93162	–

Table 4
Results of the univariate and multivariate logistic regression analysis of the significant parameters of Mann-Whitney Test, Fisher's Exact/Chi-Squared Test, and ROC curve analysis. We report the adjusted odds ratio in respect to the ROC curve criterion and p-value of the significant variables.

	Univariate		Multivariate	
	Adjusted Odds Ratio	P-Value	Adjusted Odds Ratio	P-Value
Neck Width > 6.46 mm	12.7895	0.002	38.8579	0.0002
Aspect Ratio ≤0.93162	13.5484	0.0154	45.3824	0.0017
Fusiform Morphology	–	NS		
History of Renal Disease	9.8571	0.0048	–	NS
No History of Smoking	4.2857	0.0428	–	NS

branched vessel were predictive of refractory cases in a the second largest published study to date on 445 patients by Bender et al [2]. Similar results have been independently reported by other authors and to date presence of a branch vessel within the aneurysm neck has been the most consistently reported predictor of aneurysm persistence [12,13]. In a review of 701 patients Kan et al. reported 15 aneurysms with a branching vessel arising from the fundus of the aneurysm and all 15 aneurysms were refractory at 6 months follow-up [7]. PED induces aneurysm obliteration by diverting flow away from the dome. A persistent hemodynamic demand through the distal branch vessel or aneurysms arising adjacent to a fetal type communicating artery may therefore prevent adequate flow diversion to induce aneurysm thrombosis [11].

O'Kelly et al. reported female gender and prior treatment with clipping or coiling as significant parameters associated with lower success rates on multivariate analysis [9]. McAulifffe et al. found previous treatment consisting of stent assisted coiling had a significantly lower occlusion rate of 50% in comparison to 80% in those who underwent previous coiling or clipping whereas an occlusion rate of 92.5% was attained in the virgin treatment group [8]. The authors hypothesized previous clipping or stent assisted coiling could result in poorer PED apposition along the parent vessel therefore resulting in endoleak and aneurysm persistence.

In our series only 11.9% of patients experienced treatment failure which may be explained by our report on only aneurysms undergoing PED as a stand-alone treatment without undergoing any form of prior treatment modality. Age and incorporation of a branched vessel were not identified as significant variables affecting aneurysm occlusion in our series likely due to the relative low numbers of aneurysms with branching vessels arising off the neck in our cohort. This finding is also affected by selection bias as these aneurysms are more likely to be treated at our institution via open surgery.

A recent publication evaluating the effect of size and shape features on incomplete occlusion following flow diversion showed that neither volume, diameter, surface area, sphericity, compactness, nor flatness were identified as significant variables [15]. The only significant factor identified on multivariate analysis to predict aneurysm occlusion was elongation feature. Elongation in this study was defined as the square root of the quotient of the largest and second largest principal component axes of the aneurysm and aneurysms. Aneurysms with decreasing elongation values are more likely to have a flatter and wider shape which was associated with increasing risk of incomplete occlusion [15]. The findings of this study support our current findings where we identify decreasing aspect ratio and increasing neck width as independent predictors of treatment failure after PED, consistent with aneurysm elongation.

Aspect ratio is the dimension of the dome height divided by the neck width of the aneurysm (Fig. 1). A lower aspect ratio is also due to a shallow dome or an elongated aneurysm neck. Wide neck aneurysms have increased surface area in apposition with PED (Fig. 2). This morphology increases the porosity of blood flow into the aneurysm dome and may therefore reduce the amount of flow diversion. In our series, the optimal cut-off value for aneurysm aspect ratio less than 0.93162 and neck width greater than 6.46 mm were strongly (greater than 70%) associated with treatment failure (Table 3). Aneurysms with a shallow fundus and wide neck width may experience similar hemodynamic properties as fusiform aneurysms which have historically had the lowest success rates after flow diversion therapy [5]. In the present study, fusiform morphology as a predictor of treatment failure did not reach statistical significance possibly due to the small number of patients in our cohort. Aspect ratio and neck width may therefore be a useful index as they might reasonably influence the surgical strategy for both saccular and fusiform aneurysms.

The aforementioned studies suggest older age, non-smoking status, increasing aneurysm size, and incorporation of a branch vessel may be predictive of treatment failure after PED. While these studies provide some insight into refractory cases, the optimal treatment strategy with PED remains unknown and is not significantly impacted by these variables. The current study provides new evidence that decreasing aspect ratio and increasing neck width are independent predictors of treatment failure after PED placement suggesting additional surgical strategies may be considered in such cases.

Adjunctive coiling and use of multiple PED devices during flow diversion therapy is performed for a variety of reasons and remains to the discretion of practitioner. Adjunctive coiling is often performed to prevent the rare complication of delayed rupture and also induce early aneurysm thrombosis to speed up the time to occlusion [10]. This is also not infrequently performed in giant and fusiform aneurysms to prevent stent foreshortening.

The use of multiple PEDs have been implicated by Kabbasch et al. to improve occlusion rates in comparison to use of a single device [6]. Although multiple other studies have been unable to confirm these results, treatment of refractory cases is typically limited to re-stenting as the design of PED precludes the use of coil embolization after PED placement and also reduces the compliance of the parent vessel thereby making surgical clipping more technically challenging [1,12]. Currently no optimal treatment strategies exist in respect to initial PED deployment beyond stent coverage across the neck of the aneurysm.

In the aforementioned study evaluating aneurysm persistence after PED, Bender et al. found the use of adjunctive coiling may facilitate aneurysm occlusion [2]. Their results led to a subsequent study evaluating the safety and efficacy of single stage flow diversion and adjunctive coiling in 72 aneurysms which yielded an occlusion rate of 85% at 6 months and 96% at 12 months with an average coil packing density of 14% [3]. Although no direct comparison was made with a single PED alone, flow diversion and augmentation with coil embolization may reduce the time to aneurysm occlusion and improve overall occlusion rates; however, the optimal scenario for which this technique should be employed has not been established. In a study on 171 patients, Park et al. reported occlusion rates of 68% with PED alone and 82% with adjunctive coiling [10]. Use of adjunctive coiling was an

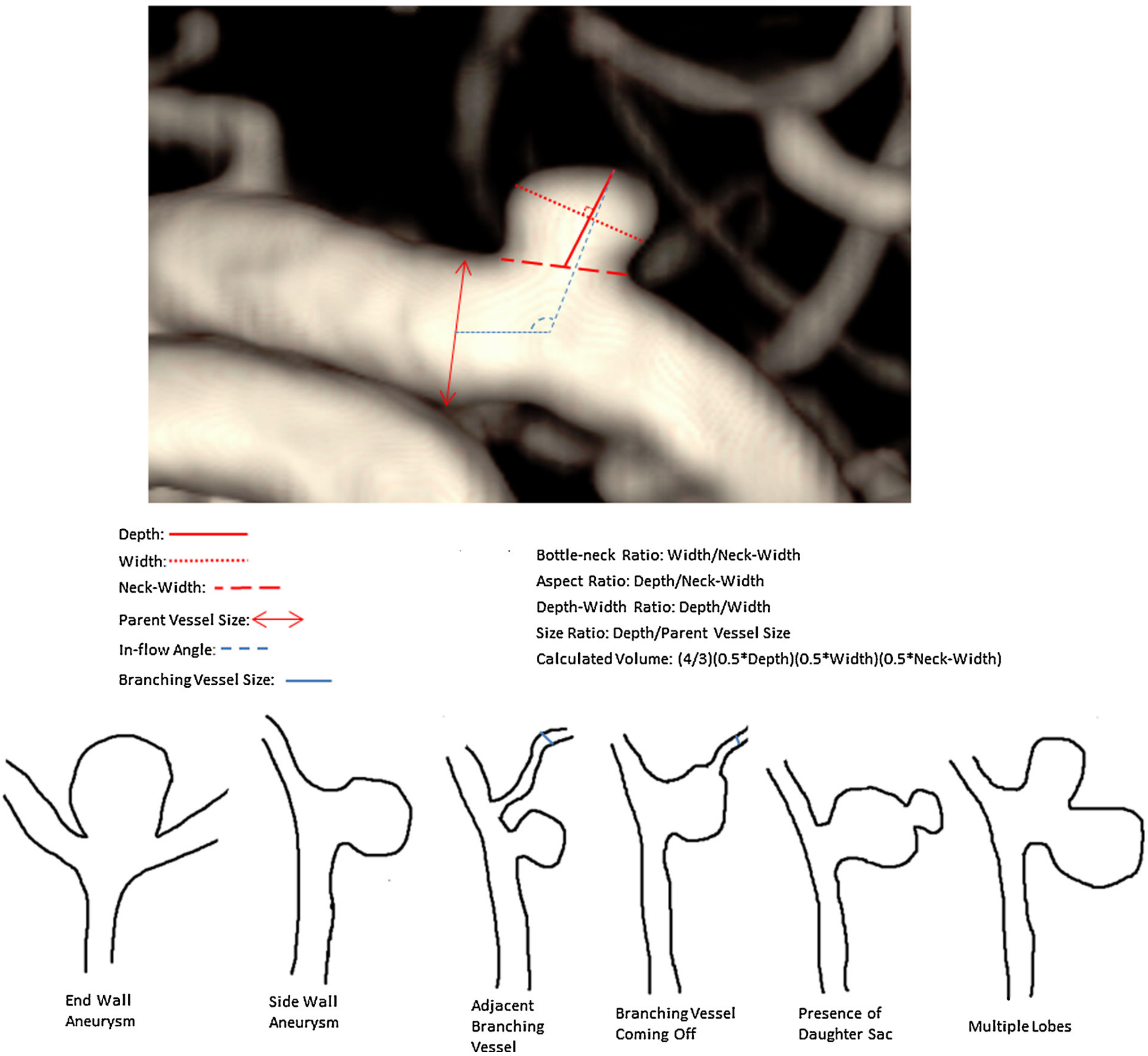

Fig. 1. List of morphometric aneurysm parameters. Depth was measured from the approximate midline of the opening to the highest projection point of an aneurysm. For complex and multi-lobulated aneurysms, the highest lobe, with the neck width axis as the origin, was chosen as the highest projection point. Width was obtained by measuring the widest point of an aneurysm approximately 90 degrees to the depth. Neck-width was obtained by measuring the widest point of the aneurysm opening. Parent vessel size was measured upstream and adjacent to an aneurysm. Inflow angle was obtained through the vertical axis of the midpoint of the aneurysm opening, the midpoint of the parent vessel diameter, and reaching the highest projection point of an aneurysm. Branching vessel size was the largest diameter of the branching vessel.

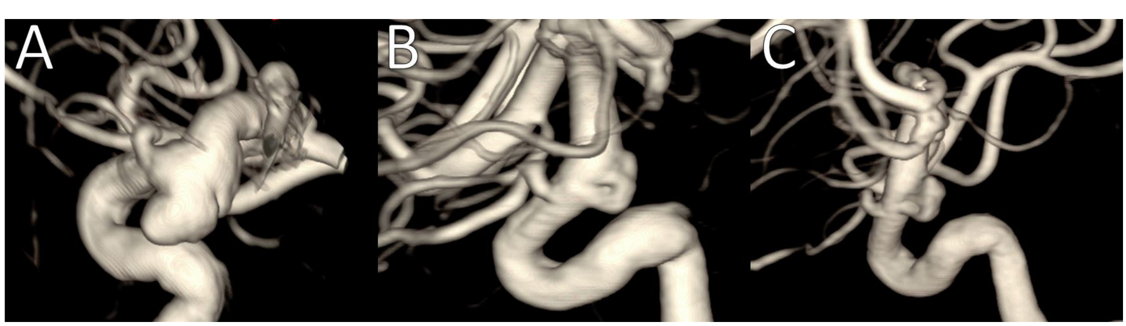

Fig. 2. 3D Angiograms of a 41-year-old female who undergo PED placement. The aneurysm (A) was initially treated with a single flow-diverting pipeline stent, but underwent re-treatment (B) 19 months post-procedure for residual filling. However, residual flow was still present and 14 months later the patient was re-treated (C). This aneurysm measured an aspect ratio of 0.824 and a neck width of 9.04 mm initially.

independent predictor of improved occlusion rates on multivariate analysis.

In the current study we have identified aneurysms with low aspect ratios and wide neck widths are more likely to be refractory to occlusion. This subset may therefore benefit from adjunctive coiling to improve occlusion rates or alternatively surgical clipping may be the best option in these cases. It is important to recognize however, that although aneurysms with smaller aspect ratio and wide neck width are less likely to attain occlusion after PED, these cases must be weighed against the potential risk and complexity of adjunctive coiling or placement of multiple overlapping devices. Aneurysms with necks wider than 6.5 mm are also often successfully treated with a single PED therefore neck width alone may simply be a substitution for more complex factors affecting flow dynamics that occur with different shapes and configurations of the aneurysm as well as proximal and distal parent vessel. At present, long term data on the risk of remnant aneurysms after PED is lacking and therefore the impact of our findings on altering surgical strategy remains unknown. Future prospective studies are needed to validate these findings.

This study is limited by its retrospective nature and although the overall sample size is modest. Angiographic follow-up at 12 months was performed in all cases as inclusion criteria for the study therefore reducing the mean follow-up time as we often perform follow-up using non-invasive imaging when indicated. Long term studies evaluating PED suggest that a certain subset of aneurysms will progress to full occlusion with time; however, it is unknown at this time if aneurysms with higher extents of residual filling (total or subtotal) would fit this subgroup. Selection bias may also limit the findings in this study as many aneurysms with less favorable morphologies for PED are treated using other surgical or endovascular methods.

5. Conclusion

In the current study we have identified aneurysms with low aspect ratios and wide necks are more likely to be refractory to occlusion with PED alone. This subset may therefore benefit from adjunctive coiling to improve occlusion rates. Future prospective studies are needed to validate these findings.

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