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Relationship between aneurysm occlusion and flow diverting device oversizing in a rabbit model

Simona Hodis¹, Yong-Hong Ding¹, Daying Dai¹, Ravi Lingineni², Fernando Mut³, Juan Cebal³, David Kallmes¹, and Ramanathan Kadirvel¹

¹Neuroradiology Research Laboratory, Mayo Clinic, Rochester, Minnesota

²Biomedical Statistics and Informatics, Mayo Clinic, Rochester, Minnesota

³Center for Computational Fluid Dynamics, College of Sciences, George Mason University, Fairfax, Virginia

Abstract

Background and Purpose—Implanted, actual flow diverter pore density is thought to be strongly influenced by proper matching between the device size and parent artery diameter. The objective of this study was to characterize the correlation between device sizing, metal coverage, and the resultant occlusion of aneurysms following flow diverter treatment in a rabbit model.

Methods—Rabbit saccular aneurysms were treated with flow diverters (iso-sized to proximal parent artery, 0.5 mm over-sized, or 1.0 mm over-sized, respectively, n=6 for each group). Eight weeks after implantation, angiographic degree of aneurysm occlusion was graded (complete, near-complete, or incomplete). The ostium of the explanted aneurysm covered with the flow diverter struts was photographed. Based on gross anatomic findings the metal coverage and pore density at the ostium of the aneurysm were calculated and correlated with degree of aneurysm occlusion.

Results—Angiographic results showed there were no statistically significant differences in aneurysm geometry and occlusion among groups. The mean parent artery diameter:flow diverter diameter ratio was higher in the 1.0 mm oversized group compared with other groups. Neither the percentage metal coverage nor the pore density showed statistically significant differences among groups. Aneurysm occlusion was inversely correlated with the ostium diameter, irrespective of the size of the device implanted.

Corresponding author: Ramanathan Kadirvel, Ph.D., Associate Professor of Radiology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, Phone: 507-266-3350, Fax: 507-255-7872, kadir@mayo.edu.

COMPETING INTERESTS STATEMENT

None

CONTRIBUTORSHIP STATEMENT

SH contributed to the conception and design, analysis and interpretation of data and drafting the article.

DD and YHD contributed to the animal experiments and analysis of angiographic data.

RL contributed to the statistical analysis and interpretation of data.

FM contributed to the virtual computational analysis and interpretation of data.

JC, DK and RK contributed to the conception and design and revising the article critically for important intellectual content

DATA SHARING

All authors in this manuscript have read and approved submission of the manuscript. All authors have access to the raw data.

Conclusion—Device sizing alone does not predict resultant pore density or metal coverage following flow diverter implantation in the rabbit aneurysm model. Aneurysm occlusion was not impacted by either metal coverage or pore density, but was inversely correlated with the diameter of the ostium.

Keywords

Aneurysm; flow diverter; metal coverage; rabbit model

INTRODUCTION

Even though flow diverters have demonstrated remarkably high rates of complete aneurysm occlusion in preclinical and clinical settings, the mechanism of action of flow diverters remains poorly understood. Leading theories of aneurysm occlusion following flow diverter implantation include the influence of the flow diverter on intrasaccular hemodynamics, with resultant stasis and subsequent thrombosis, versus the role of endothelial cell growth across the pores of the flow diverter, with subsequent exclusion of the sac from the circulation[1–3].

The exact “dose” of flow diversion, typically quantified as metal coverage (amount of metal surface area covered by the device) and pore density (number of pores per unit surface area), required for aneurysm occlusion, remains unclear in clinical practice. The pore density and metal coverage at the ostium have been hypothesized to play an important role in the occlusion of aneurysms[4–5]. Computational fluid dynamics studies predicted that oversizing the flow diverter increases the intra aneurysmal flow[6]. Improved understanding about the exact mechanism of action of flow diverters will both assist in customizing the treatment of individual patients and facilitate the development of next-generation flow diversion devices.

It has further been shown that, for flow diverters constructed of braided metal, resultant pore size is strongly influenced by the degree of matching between the device diameter and the parent artery diameter[7–8]. Specifically, close matching of sizes allows braided flow diverters to open fully and achieve trapezoidal shaped pores; incomplete opening results in relatively square shaped pores with resultant lower pore density than trapezoidal pores.

The objective of this current study was to characterize the correlation between device oversizing and parameters of metal coverage and subsequent occlusion of aneurysms treated with flow diverters in a rabbit model.

METHODS

The Institutional Animal Care and Use Committee approved all procedures before initiation of our study.

Aneurysm creation and flow diverter implantation

Some of the rabbits employed in this study were originally used as part of other investigations, where we probed the mechanism of endothelialization[2], developed

methodology for multi-modality image-based subject-specific computational models[9], assessed the relationship between hemodynamics and aneurysm occlusion[10], and analyzed flow changes in side branches[11] following flow diverter treatment. These publications were entirely unrelated to the present study. Elastase-induced, saccular aneurysms were created in 18 rabbits using well-described techniques[12]. At least 3 weeks following aneurysm creation, flow diverters (Pipeline Embolic Device™, Covidien Inc, CA) were placed across the aneurysm ostium. Rabbits were arbitrarily assigned to three groups; Group 1, in which iso-sized flow diverters were implanted, Group 2, in which flow diverters were oversized by >0.5 and 1.0 mm, Group 3, in which flow diverters were oversized by >1.0 mm to achieve varying degree of pore density and metal coverage at the ostium of the aneurysm. The size of flow diverters were chosen based on the diameter of the proximal parent artery. Two days before embolization, subjects were pre-medicated with aspirin (10 mg/kg PO) and clopidogrel (10 mg/kg PO); this medication regimen was continued for 1 month after embolization[13].

Tissue harvest

Eight weeks following flow diverter implantation, the animals were deeply anesthetized. Digital subtraction angiography (DSA) of the aortic arch was performed. The animals were then euthanized with a lethal injection of pentobarbital. Harvested aneurysms were immediately fixed in 10% neutral buffered formalin.

Angiographic evaluation

Aneurysmal dimensions (ostium, height and width) were determined with DSA measurements, which were calibrated by using an external sizing device of known diameter. Angiographic evaluation was performed for angiograms conducted immediately after device implantation as well as at the pre-sacrifice angiograms. The follow-up angiography assessed using a trichotomous scale (patent, near-complete occlusion, and complete occlusion).

Imaging of the aneurysm ostium

The flow diverter-implanted parent artery was bisected longitudinally to expose the luminal surface. Then the ostium of the aneurysm covered with the flow diverter struts was photographed and then used for metal coverage and pore density analysis. The lengths of the metal struts covering the aneurysm ostium and the angle of intersection of the struts were measured using Photoshop software (Adobe, CA). The metal coverage and pore density were calculated by the following formula

$$\text{Metal coverage(\%)} = \left(\frac{\text{Surface area} - \text{metal free surface area}}{\text{Surface area}} \right) * 100$$

$$\text{Surface area} = L1 * L2 * \sin(\alpha)$$

$$\text{Metal free surface area} = (L1 - N1 * \frac{d}{\sin(\alpha)}) * (L2 - N2 * \frac{d}{\sin(\alpha)}) * \sin(\alpha)$$

$$\text{Pore density (pores/mm}^2\text{)} = \frac{\text{Number of pores}}{\text{Surface area}}$$

where d represents the strut diameter, which is 0.03 mm, α denotes the angle between struts.

L1 and L2 represent the width and length of the struts covering the ostium of the aneurysm, respectively and N1 and N2 represent number of pores across L1 and L2, respectively.

Figure 1 illustrates the measurement of parameters. Due to the nonuniformity in the pore density, we calculated the porosity by using a sample area over multiple pores, between 6 and 8 pores across the ostium.

Similarly, porosity, pore size and pore density were estimated from a reference configuration taking into account the longitudinal stretching (foreshortening) due to oversizing as in computational models [6]. First, the effective (target) cell angle is computed based on the flow diverter reference angle and diameter, and the vessel (target) mean diameter following:

$$\frac{\text{Target Diameter}}{\sin(\frac{\text{Target Angle}}{2})} = \frac{\text{Reference Diameter}}{\sin(\frac{\text{Reference Angle}}{2})}$$

Second, a pixelization of the stretched stent design (straight cylinder of constant but smaller diameter) was performed by drawing each of the stent wires over a planar image that represented the stent surface. Next, measurements of porosity, pore size and pore density were taken from the pixelization, by counting marked (covered by metal) and unmarked (free space) pixels from the total image and from enclosed groups (pores). The procedure was repeated with different pixel sizes to ensure grid independence of the pixelization procedure.

Statistical analysis

The aneurysm geometry, metal coverage and pore density between groups were analyzed with Kruskal-Wallis test. The correlations between aneurysm occlusion and aneurysmal geometry, metal coverage and pore density were assessed by Spearman rank correlation. The association between aneurysm occlusion and effective factors were then analyzed using the logistic regression.

RESULTS

Angiographic findings

There were no statistically significant differences in ostium diameter or aneurysm width or height among groups (Table 1). Angiography showed incomplete occlusion of 4 aneurysms

and complete/near-complete occlusion of 2 aneurysms in Group 1, incomplete occlusion of 2 aneurysm and complete/near-complete occlusion of 4 aneurysm in Group 2, and incomplete occlusion of 5 aneurysms and complete occlusion of remaining one aneurysm in Group 3.

The mean of ratio of parent artery diameter to flow diverter diameter in Group 1, Group 2 and Group 3 were 1.0 ± 0.1 mm, 1.2 ± 0.1 mm, 1.5 ± 0.1 mm, respectively. There was a statistically significant difference in parent artery to flow diverter ratio in Group 2 ($p=0.02$) and Group 3 ($p=0.001$) compared to Group 1, but the difference between Group 2 and Group 3 was not statistically significant.

Metal coverage and pore density

The mean metal coverage and pore density were $25.9 \pm 4.9\%$ and 19.2 ± 7.1 pores/mm² in Group 1, $23.6 \pm 8.7\%$ and 15.2 ± 8.5 pores/mm² in Group 2 and $23.5 \pm 7.5\%$ and 14.2 ± 7.7 pores/mm² in Group 3, respectively. Neither the percentage metal coverage nor the pore density showed statistical significant differences among groups. Geometrical features of the proximal parent artery and devices implanted presented in Table 2. The actual measured porosity and pore density are comparable with that of computational models in most cases (Table 3). In virtual device oversizing, the pore geometry changes from a diamond shape, stretched in the circumferential direction to a diamond stretched in the longitudinal direction[6].

Aneurysm occlusion

Aneurysm occlusion was negatively correlated ($\rho=-0.76$, $p\text{-value}<0.001$) with larger ostium diameters, after adjusting for the groups. Logistic regression analysis (Table 4) showed that the odds of aneurysm occluding significantly decreased by 4.9 fold (Odds ratio (OR) 4.93, 95% confidence limit (CL) , 1.19 to 20.46, $p=0.03$) for every millimeter increase in the ostiumwidth. There was no significant association between aneurysm occlusion and percentage of metal coverage (OR 1.9, 95% CL, 0.92 to 1.29, $p=0.33$) and pore density (OR 1.06, 95% CL, 0.92 to 1.22, $p=0.42$) The relationship between metal coverage, ostium width and occlusion is plotted in Figure 2.

DISCUSSION

In our current study we purposefully varied the fidelity of size matching between flow diverter devices and the proximal parent artery. While we noted a strong trend toward higher pore densities with good matching between devices and parent arteries, degree of metal coverage did not vary substantially among groups. Further, final occlusion rates were not substantially impacted by the resultant pore density or metallic coverage, but were strongly influenced by aneurysm ostium width. Indeed, for each incremental increase in ostium width, the propensity for complete aneurysm occlusion decreased by nearly an order of magnitude. Ostium smaller than 3 mm in width is related to *complete* and *near complete* occlusion in all seven cases, except for two *near complete* cases, where the ostium width is 3.71 and 4.65 mm.

These findings suggest that it remains difficult to predict resultant pore density and metallic coverage based exclusively on sizing, and that other factors may strongly influence the morphology of flow diverters after implantation. In real deployment, we obtained different pore geometry than than one estimated from the device reference configuration and degree of oversizing, due to the user-dependent techniques of deployment. Therefore, the oversizing criterion shouldn't be the only parameter to analyze in order to explain the aneurysm occlusion, but the ostium size. Further, ultimate occlusion may not relate closely to implanted device morphology.

In the original pipeline embolization device study[13], similarly low rates of aneurysm patency were observed at 1 and 3 months, while those in the 6 month group showed a much higher occlusion rate (83%). It is possible that the current study's findings relating aneurysm non-occlusion rate to aneurysm ostium size are confounded by the relatively short follow-up interval. Previous work has shown that factors beyond simple device sizing may impact in vivo device morphology. For example, deformation of the flow diverter, where the device "herniates" into the aneurysm ostium, led to higher metal coverage over the ostium area as compared to coverage of adjacent parent arteries[14]. We did not notice any device deformation in our studies. Sadasivan et al. analyzed the occlusion of aneurysms implanted with flow diverters with three different porosities and metal coverage, and suggested that pore density is crucial for the occlusion of aneurysms[4 15]. In contrast, Wang et al. predicted that a flow diverter with a 35% actual metal coverage at the ostium can predict >95% of angiographic aneurysm occlusions in rabbits[5]. In our series, the average metal coverage of iso-sized flow diverters was much lower than the predicted 35%. This could partially be due to the smaller diameter of the struts of the device compared to the flow diverter used by Wang et al[5]. We achieved >35% metal coverage in only three case, however, of which two showed incomplete aneurysm occlusion while remaining one exhibited complete occlusion. Our findings suggest that other factors, such as the geometry of the aneurysm and parent vessel, endothelialization, wall apposition, and hemodynamic factors may strongly influence the closure of aneurysms.

Our study had several limitations. We did not use diameter of parent artery at ostium for choosing appropriate devices for treatment, instead we used proximal parent artery, as normally utilized in clinical practice. We used gross images of formalin fixed tissue samples for the calculation of metal coverage and pore density. To calculate the metal coverage, we measured the struts lengths and angle between the struts, from the gross images of the tissue sample at the ostium, which may subject to some measurement errors. The device configuration in the implanted vessel may have changed after tissue harvest. The majority of the periphery of the ostium was covered with a portion of the pore, which were counted as a single pore in our measurement. The pore density varies in different parts across the entire ostium. In addition, there is high variability in sizes of aneurysm and parent vessel size between animals and cohorts. A controlled study of aneurysms with similar geometries would be needed to validate our findings.

Conclusions

In the rabbits aneurysm model, device sizing alone does not predict resultant pore density or metal coverage following flow diverter implantation. Aneurysm occlusion was not impacted by either metal coverage or pore density, but was inversely correlated with the diameter of the ostium in the rabbit model.

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Clinical relevance

Numerous prior studies have addressed concerns about device sizing, especially regarding the propensity for lower pore density and less metal coverage with oversized devices. However, because current flow diverters are not tapered longitudinally and many or most vessels decrease in diameter as they go distal, one often is required to choose a device that is “oversized” at the level of the neck in order to achieve good apposition proximally. Our current study should temper those concerns about oversizing and give confidence that even slightly oversized devices will retain efficacy.

Figure 1.

Measurement of parameters at the ostium of the aneurysm implanted with flow diverter

- a) Gross image showing aneurysm ostium covered with flow diverter struts
- b) Schematics of measurements in the flow diverter struts

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Figure 2.

The relationship between metal coverage, ostium width and occlusion

Table 1

Characteristics of aneurysms by Groups

Variable	Iso-sized (Group 1, N=6)	Oversized by >0.5 and (Group 2, N=6)	1.0 mm	Oversized by >1.0 mm (Group 3, N=6)	p-value *
Ostium width in mm, Mean(SD)	3.9 ± 1.4	4.5 ± 3.1		5.8 ± 1.3	0.120
Aneurysm dome width in mm, Mean(SD)	4.9 ± 1.6	4.7 ± 1.5		5.8 ± 1.8	0.240
Aneurysm height in mm, Mean(SD)	9.7 ± 2.9	9.6 ± 4.0		12.5 ± 0.8	0.144
Metal coverage %, Mean(SD)	25.9 ± 4.9	23.6 ± 8.7		23.5 ± 7.5	0.324
Pore Density (pores/mm), Mean(SD)	19.2 ± 7.1	15.2 ± 8.5		14.2 ± 7.7	0.191
Incomplete aneurysm occlusion , N(%)	4 (66.7%)	2 (33.3%)		5 (83.3%)	0.195

* p-value from Kruskal-Wallis or chisq test; SD=standard deviation; % =percentage.

Table 2

Flow diverting devices and parent artery measurements calculated from the gross images taking at the ostium of aneurysm

Animal ID	Group	Diameter of PPA (mm)	Size of Flow Diverter (mmXmm)	Nominal Oversizing (mm)	Diameter of flow diverter to PPA	Ostium size (mm)	Occlusion at 8 weeks
279E	1	3.07	3.5X12	0.43	1.14	6.16	Incomplete
282E	1	3.95	4.0X10	0.05	1.01	3.60	Incomplete
292E	1	3.72	3.75X12	0.03	1.01	3.70	Incomplete
298E	1	3.97	4.0X10	0.03	1.01	4.82	Incomplete
376E	1	3.53	3.5X12	-0.03	0.99	2.53	Complete
401E	1	3.65	4.0X10	0.35	1.10	2.80	Complete
368E	2	4.24	4.75X10	0.51	1.12	2.81	Complete
378E	2	3.79	4.75X12	0.96	1.25	3.71	Near complete
383E	2	3.57	4.25X10	0.68	1.19	2.72	Near complete
402E	2	3.70	4.25X10	0.55	1.15	2.48	Near complete
426E	2	2.96	3.75X10	0.79	1.27	4.82	Incomplete
431E	2	3.23	3.75x10	0.52	1.16	10.52	Incomplete
290E	3	3.10	4.75X12	1.65	1.53	5.33	Incomplete
296E	3	2.86	4.75X10	1.89	1.66	5.80	Incomplete
299E	3	3.41	4.75X10	1.34	1.39	4.59	Incomplete
369E	3	3.25	4.75X10	1.50	1.46	4.65	Near complete
381E	3	3.16	4.5X12	1.34	1.42	8.04	Incomplete
432E	3	3.28	4.5x12	1.22	1.37	6.19	Incomplete

Table 3

Porosity, pore density and pore size of the flow diverting devices calculated from the gross iamges and from their reference configuration accounting for cell stretching due to oversizing.

Animal ID	Group	Porosity reference (%)	Pore density reference (pore/mm ²)	Porosity gross image (%)	Pore density gross image (pores/mm ²)	Pore size (mm)
279E	1	62.7	24.1	70.5	25.9	0.161
282E	1	77.3	14.8	75.5	16.6	0.228
292E	1	79.5	11.3	77.8	13.2	0.265
298E	1	60.6	27.3	75.8	15.8	0.149
376E	1	62.9	24.0	66.2	30.2	0.162
401E	1	60.3	27.5	79.1	13.5	0.148
368E	2	79.4	11.4	82.1	9.8	0.264
378E	2	64.4	21.6	82.5	7.7	0.172
383E	2	74.3	16.0	79.6	12.3	0.215
402E	2	62.5	24.3	79.7	12.7	0.160
426E	2	62.9	24.0	59.5	31.2	0.162
431E	2	76.0	16.8	75.1	17.5	0.212
290E	3	62.7	24.1	62.2	29.6	0.161
296E	3	82.1	9.8	83.0	8.7	0.290
299E	3	76.2	13.2	79.2	11.3	0.240
369E	3	79.6	11.2	78.6	11.4	0.266
381E	3	78.9	12.2	75.5	13.8	0.254
432E	3	81.5	10.7	80.8	10.6	0.275

Table 4

Results from Regression Analysis for Aneurysm Occlusion

Variable	Odds Ratio (95% Confidence Limit)	p-value
Ostium width in mm	4.93 (1.19, 20.46)	0.028
Metal coverage %	1.09 (0.92, 1.29)	0.325
Pore Density (pores/mm)	1.06 (0.92, 1.22)	0.421