Clinical impact of Sim & Size® simulation software in the treatment of patients with cerebral aneurysms with flow-diverting Pipeline stents.

DANIEL EDUARDO MANTILLA GARCÍA

ARTÍCULO DE TRABAJO DE GRADO PARA OBTENER EL TÍTULO DE MÉDICO ESPECIALISTA EN RADIOLOGÍA INTERVENCIONISTA.

Director de proyecto:

Dr. Oliverio Vargas Pérez.

MD Especislista en Radiología e Imágenes Diagnósticas.

FOSCAL-UNAB

Co-Investigadores:

Dr Melquisedec Galvis, Dr. Carlos Ferreira, Carolina Valenzuela, Dr. Vincent Costalat, Franck Nicoud.

Asesor Epidemiológico:

Dr. Miguel Ochoa.

NOVIEMBRE 2020

UNIVERSIDAD AUTÓNOMA DE BUCARAMANGA

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Clinical impact of Sim & Size® simulation software in the treatment of patients with cerebral aneurysms with flow-diverting Pipeline stents.

ABSTRACT

Objectives: To evaluate the clinical impact of the Sim & Size numerical simulation software in the treatment of patients with unruptured saccular brain aneurysms with Flow-Diverting Pipeline stents.

Materials and methods: A retrospective monocentric analytical study of patients treated for an intracranial aneurysm using the parent artery reconstruction technique with flow diverter stent, at FOSCAL clinic, from June 1st, 2014, to December 31st, 2019 was performed. Two population groups were evaluated: Patients treated with and without the use of Sim&Size intraoperative numerical simulation software. Univariate and bivariate analysis were performed.

Results: 73 records of interventions of 68 patients were analyzed. 56 (76.70%) interventions with simulation and 17 (23.30%) without simulation. In the simulation group, surgical time was 100 minutes (85-125) versus 118 (61-175) in the group without simulation (p= .20). The diameter of the stent was 4 mm (3.50-4.40) and 3.75mm (3-4) in the patients with simulation and without simulation respectively (p= .20). The stent length was 16 mm (12-20mm) in the patients with simulation and 20 mm (20-20mm) in the other group (p <.001). The number proportion of implanted stents for a patient was 1.03 vs 1.13, in the group with simulation vs. without simulation. There were no immediate thromboembolic complications in any group.

Conclusions: The use of the simulation software program (Sim & Size®) for the endovascular treatment of patients with unruptured saccular cerebral aneurysms decreases surgical time and the length of the flow-diverting pipeline stent, and the quantity of the used devices for the patient.

INTRODUCTION

The prevalence of unruptured cerebral aneurysms varies between 0.5 - 7% depending on the population; the main risk factors associated are age, female sex, smoking, high blood pressure, and the family history of a cerebral aneurysm. The treatment to avoid the rupture of cerebral aneurysms can be open surgery on selected cases or endovascular therapy(1).

There are different techniques used in endovascular therapy. Parent artery reconstruction with flow-diverting stents has shown to be an effective and safe treatment. Flow-diverting pipeline stents stimulate endothelial growth and provoke disruption of the blood flow of the aneurysm causing its thrombosis. They are used to treat aneurysms with complex morphology and locations where other techniques cannot be used. In 2011 the FDA approved Flow-diverting pipeline stents for the treatment of large or giant, wide-necked aneurysms of the internal carotid artery from the petrous segment to the pituitary(2,3)[2.3].

Stent size selection is an essential parameter for treatment safety. If a stent is exceedingly long, the implantation becomes more difficult, and the risk of stroke increases and, a short stent may be insufficient to cover the neck of the aneurysm. If the diameter is rather small, unfolding it becomes more difficult due to lack of anchorage and, incomplete coverage of the aneurysm may occur(4)[4]; stent malposition is associated with an increased risk of device migration, delayed aneurysm rupture, and stroke(5)[5].

Cerebral arteries are tortuous and irregular vessels with different diameters in each segment. Choosing the stent size can be done manually with digital subtraction angiography or with virtual simulation programs. These new programs are used in planning to select the optimal device for the patient. Sim&Size® software(6) (Sim&Cure, Grabels, France) numerically simulates the behavior of the Pipeline stent, considering the characteristics of the patient vessel and the device.

This monocentric study aims to evaluate the clinical impact of the Sim & Size numerical simulation software in the treatment of patients with unruptured saccular brain aneurysms with flow-diverting pipeline stents.

METHODOLOGY

Study type: Monocentric retrospective analytical study, approved by the institution's medical ethics committee. The information was obtained from the database of the service of the interventions performed for the treatment of patients with cerebral aneurysms with flow diversion stents from June 1, 2014, to December 31, 2019. Given the retrospective nature of the study, no informed consent was needed. Patients with unruptured saccular aneurysms treated with a flow-diverter pipeline stent were included. Numerical simulation using Sim&Size was performed after December 27, 2017, and cerebral aneurysms with morphology other than saccular or ruptured aneurysms were excluded. Results between treatment with the simulation software were compared to results without numerical simulation.

Data collection

Demographic data (age and sex), history of chronic arterial hypertension, history of smoking, and aneurysm in the family were included. Morphology, size, location, and previous treatment of the aneurysm, as well as the diameter, length, and the number of stents used were evaluated. Surgical time, intraoperative complications, immediate and 30 days outcomes after the procedure were compared between the two groups. Complications included: thromboembolism, hemorrhage, and vascular accesses. The sudden shortening and the need to correct position due to a suboptimal stent size were also assessed. Size, location, and the number of aneurysms were obtained from the 3D angiography. Surgical time was defined as the difference between the starting time of the procedure and the ending time.

Stent deployment technique

Under general anesthesia, by femoral artery puncture with 18G argon angiographic needle using the Seldinger technique, 3D digital subtraction angiography was performed. The Destination 6Fr catheter was then ascended, and anticoagulation was started with 5300 IU, followed by activated coagulation time measurement. The Navien 6Fr intermediate catheter was then positioned in the petrous segment of the internal carotid artery. The Marksman microcatheter was employed, and the Pipeline flow diverter stent was implanted in all cases. After the device was released, a low contrast CT control was performed to evaluate apposition, in cases in which the treating physician considered it was needed.

Choice of the stent with manual measurement

Conventionally, to ensure good wall apposition, the operator selects a target distal landing zone, as well as a proximal landing zone in a straight part of the main vessel. The first step was to select the implant diameter based on 2D-DSA measurements of the parent artery in the target proximal landing zone. The operator then attempted to anticipate areas of stent elongation, especially proximal to the aneurysm, as well as possible foreshortening, mainly depending on the length of the aneurysm neck. The centerline of the parent vessel is measured between the distal target landing zone and the proximal landing zone using the 3D-RA reconstruction of the angiosuite to select the length of the stent. All these measurements contributed to the final choice of stent diameter and length.

Sim&Size software sizing method

Sim & Size software is commercially available marked with CE and approved by the FDA. The software version used in this study was designed for a research project in Colombia. It predicts the movement of endovascular devices such as the Pipeline stent. Without the need to send data to the cloud, the software reconstructs the 3D arterial geometry using the 3D-RA acquisition data on a local personal computer. The accuracy of the reconstruction can be optimized

manually, if necessary. Once the trajectory from the microcatheter is selected into the parent vessel, the operator manually defines the distal and proximal stent landing zones, targeting straight vessel segments. Immediately afterward, the software proposes the first recommendation to achieve the best deployment within the chosen landing zones, with an appropriate wall apposition, in terms of device dimensions. The degree of wall apposition is simultaneously displayed as an interactive color scale along the length of the stent. The operator can evaluate in real time the different landing zones, device dimensions, and the amount of "push" applied during the deployment of the device, modifying the final position and the behavior of the device.

The first operator scrubs out downloads the 3D data, and executes the virtual simulation, immediately after the 3D acquisition, performed as the first series of the intervention; while the second operator organized the anteroposterior, latero-lateral and working projections. It takes approximately 3-6 min to carry out the extraction and processing process (See figure 1).

Statistical analysis

A univariate description of demographic, clinical, and background data was performed to characterize the patients. Means and standard deviations were used for the numerical variables; medians and interquartile ranges (IQR) depending on the distribution.

Bivariate analysis of the dependent variables was performed in both groups. 95% confidence intervals were utilized. A p value <.05 was considered statistically significant. Nonparametric analyses were performed when needed. All analyses were performed with STATA 14 statistical package.

RESULTS

From June 1, 2014, to December 31, 2019, 75 patients underwent embolization of a cerebral saccular aneurysm with a Pipeline stent. Seven patients were excluded (three fusiform aneurysms, two dissections, one Blister Like aneurysm, and one ruptured aneurysm). In total 84 aneurysms were treated in 68 patients

with 73 interventions performed; in two cases three aneurysms were treated simultaneously with the same device; in seven procedures two aneurysms were embolized in the same surgery, and in 64 of them, a single aneurysm was treated; 5 of the 68 patients were intervened twice to treat two aneurysms, one in each cerebral hemisphere.

The majority of patients were women (86.3%). The most prevalent comorbidities were high blood pressure (42.7%), followed by smoking (10.96%). The youngest patient had 22 years of age and the oldest 85 (median age of 62.94 ± 14.35). Patient characteristics are presented in table 1.

Aneurysm characteristics

The median of the greater diameter of the aneurysm was 6 mm (IQR 5-9), the smallest measured 2 mm and the highest 40 mm. Most of the aneurysms treated were located in a segment of the internal carotid artery; only three had different localizations: two in the anterior cerebral artery and one in the middle cerebral artery. Aneurysm locations are presented in graph 1.

Intervention and device

Of all 73 procedures, 56 (76.7%) included, and 17 (23.3%) didn´t include the use of Sim&Size simulation software. Additionally, five patients were treated twice because aneurysms were located on a different axis. A record of surgical time was not available in one of the patients that belonged to the group treated using the simulation software.

Procedure time, stent length, and diameter had a non-gaussian distribution; hence a non-parametric comparison based on median (p50) and interquartile range (IQR) was employed. The median of procedure time was 105 minutes (87.5-130), with the shortest procedure lasting 55 minutes and the longest 205 minutes. The median stent length was 16 mm (12-20 mm): the shortest was 12mm long and the largest 35mm. The median stent diameter was 4 mm (3.5 – 4.24), the smallest being 2.5 mm, and the largest 5 mm.

The simulation group had less surgical time (100 m vs 118 m p= .22), stent length (16mm vs 20mm p= <.001) and proportion of implanted stents (1.03 vs 1.13). There was only one failed stent implantation due to the technical failure of the device; it presented in the group without simulation. See table 2.

Complications

There were three intracranial hemorrhagic complications; one occurred during surgery secondary to aneury sm rupture during coiling. The other two happened after the surgical procedure, one on the immediate postoperative period and the other in the first 30 days secondary to antiplatelet therapy. These complications occurred in the group treated without simulation. Four hemorrhagic complications were related to the femoral vascular access, three in the simulated group and one in the non-simulated group. There were no thromboembolic complications. In the 30-day evaluation, no patient presented sequelae secondary to complications. 30-day mortality was 0%. In three patients, two stents were used to completely cover the neck of the aneurysm, one of them planned in the simulated group. In the two other cases, stent shortening was not predicted in the surgical planning in one patient of each group.

DISCUSSION

The selection of the device size used in the treatment of cerebral aneurysms is a challenge. The use of Sim & Size software helps the neuroradiologist in this decision. Only a few studies have evaluated its intraoperative impact(6)[6].

The study population was not homogeneous. The number of cases was greater in the group treated using simulation. This is consequent to the technique´s continuous evolution and to the confidence that the simulation program gives physicians. We can assume that this difference is related also to the development of the service and the availability of the software in clinical daily practice.

More women were treated in our series. 75% of the patients were older than 59 years. The most common comorbidity was high blood pressure, followed by smoking. This was similar to reports with unruptured aneurysms(1)[7].

Intervention time

Piergallini et al(7)[8], like in our study, compared the management of cerebral unruptured aneurysms with pipeline flow diverter with and without simulation software. They found a shorter procedure duration in cases that used simulation compared to those that did not (46-52 p=.002). In our study, there was a decrease in the median in the group of patients treated using simulation 100 min (85-125) vs 118 minutes (61-175). However, this difference was not significant (p=.22). Piergallini measured the surgical time from the positioning of the catheter in the internal carotid or vertebral artery until the end of the procedure. In our study, we measured the duration from beginning to end, which also includes the period between the start until the carotid artery catheterization. The Sim & Size software did not show an statistically significant impact, even though there was an 18 minutes decrease in the median when the software was used.

The surgical time in the operating room is valuable for several reasons: first, if it is optimized, more procedures can be performed. Second, patient exposure to radiation is directly proportional to surgical time(8)[9]. And last, longer interventions in the treatment of intracranial aneurysm are associated with an increased rate of ischemic events(9)[10].

In our study, the use of Sim & Size software showed a reduction in surgical time, this group also showed less variability in the duration of surgery compared to the non-simulated group. This means less risk of ischemic events, less radiation for the patient and indirectly lower treatment costs.

Device size

The Sim & Size simulation software helps the physician choosing the stent measurements (diameter and length) adapted to the characteristics of the patient vessel. We found a significant reduction in stent length in the group treated using the software 16 mm (12-20), compared to the group that did not use it 20mm (20-20); this decrease was statistically significant p <.001. Our results show a higher reduction in the median than that found by Piergallini et al(7)[8], and Ospel et

al(10)[11]. Ospel compared simulated patients with the Sim & Size program to non-simulated patients who underwent manual measurements with 2D angiographic acquisitions(10)[11].

Diameter is another parameter that the simulation program can calculate. In the present study, patients that underwent simulation had a greater stent diameter: 4mm (3.5-4.4 mm) compared to the non-simulated group 3.75mm (3-4 mm) p = .20, in contrast to studies that showed that the use of simulation decreased in diameter. Piergallini et al found a decrease in the median of 0.25mm between simulated (3.75mm) and non-simulated (4.00mm); however, the result was not statistically significant (p = .11)(7)[8]. Ospel et al found a mean (mean) 3.89mm in the non-simulated and 3.94mm in the simulated, with a median that did not show differences(10)[11]; a result that may be explained by physicians' decision to have a better apposition.

Selecting specific measures of the stent to treat the aneurysm allows adequate apposition to the parent artery, which reduces the risk of migration of the device, late rupture of the stent, stroke(5,11)[12.13] and acute thrombus formation(12)[14]. Performing intraoperative simulation to choose a stent adjusted to the characteristics of the vessel could quantitatively reduce the risk of malpositioning and associated complications. Additionally, using adequate measures reduces the probability of stent shortening and the need for a second device to completely cover the aneurysm neck. Also helps avoiding to cover branches emerging from the parent artery. In each group, we found a second stent was required to treat the aneurysm in two patients. The proportion of devices used was higher in the non-simulated group.

Complications

The percentage of complications in our study was similar in other studies of cerebral aneurysms treated with Pipeline flow diverter stent (3.5%); the rate of ischemic complications was less than that reported in the literature (4.7%)(13)[15]. Four complications presented in the puncture site; nevertheless, the simulation software did not influence this result. Of the intracranial hemorrhagic complications, none was directly associated with the stent placement. They were

related to antiplatelet therapy and coiling placement. All intracranial hemorrhagic complications were in the non-simulate group. No ischemic events or mortality were found after 30 days of the procedure.

Limitations

This is a retrospective monocentric, non-randomized study. The number of patients studied is small thus it is not possible to make statistically significant associations for all the studied variables.

Conclusion

The use of Sim & Size Software in the endovascular treatment of intracranial aneurysms with flow diverter stent reduces the length of the stent, the number of devices per treatment, and intervention time.

References

1. Giordan E, Sorenson TJ, Brinjikji W, et al. Risk factors for growth of conservatively managed unruptured intracranial aneurysms. Acta Neurochir. 2018;160(12):2419–23. DOI: 10.1007/s00701-018-3729-z

2. Caroff J, Neki H, Mihalea C, et al. Flow-Diverter Stents for the Treatment of Saccular Middle Cerebral Artery Bifurcation Aneurysms. AJNR Am J Neuroradiol. 2016;37(2):279-84. DOI: https://doi.org/10.3174/ajnr.A4540

3. Altschul D, Vats T, Unda S. Endovascular Treatment of Brain Aneurysms. In: Bozzetto P, Ahmad R, Abdullahi A, eds. New Insight into Cerebrovascular Diseases. First ed. Intechopen; 2020:177-126.

4. Nishimura K, Otani K, Mohamed A, et al. . Accuracy of Length of Virtual Stents in Treatment of Intracranial Wide-Necked Aneurysms. Cardiovasc Intervent Radiol. 2019;42(8):1168-1174. DOI: https://doi.org/10.1007/s00270-019-02230-9

5. Kühn AL, Wakhloo AK, Gounis MJ, et al. Use of self-expanding stents for better intracranial flow diverter wall apposition. Interv Neuroradiol. 2017;23(2):129–36. Doi: 10.1177/1591019916681981

6. Sim&Cure (Grabels, France). Available: https:// sim- and- cure. com [Accessed 25 May 2020].

7. Giordan E, Sorenson TJ, Brinjikji W, et al. Risk factors for growth of conservatively managed unruptured intracranial aneurysms. Acta Neurochir. 2018;160(12):2419-2423. DOI: 10.1007/s00701-018-3729-z. 2018.

8. Lorenzo Piergallini, Federico Cagnazzo, Giorgio Conte, et al. Virtual simulation with Sim&Size software for Pipeline Flex Embolization: evaluation of the technical and clinical impact. J NeuroIntervent Surg. 2020;0:1–6. DOI:10.1136/neurintsurg-2020-015813

9. Cheung N, Boutchard M, Carr M, et al. Radiation exposure, and procedure and fluoroscopy times in endovascular treatment of intracranial aneurysms: a methodological comparison. J NeuroIntervent Surg 2018;0:1–6. DOI:10.1136/neurintsurg-2017-013596.

10. Hahnemann ML, Ringelstein A, Sandalcioglu IE, et al. Silent embolism after stent-assisted coiling of cerebral aneurysms: diffusion-weighted MRI study of 75 cases. J Neurointerv Surg. 2014;6(6):461-5. DOI: 10.1136/neurintsurg-2013-010820.

11. Ospel JM, Gascou G, Costalat V, et al. Comparison of Pipeline Embolization Device Sizing Based on Conventional 2D Measurements and Virtual Simulation Using the Sim&Size Software: An Agreement Study. AJNR Am J Neuroradiol. 2019;40(3):524–30. DOI: http://dx.doi.org/10.3174/ajnr.A5973

12. Ku¨hn A, Macedo-Rodrigues K, Wakhloo A, et al. Endovascular techniques for achievement of better flow diverter wall apposition. Interv Neuroradiol. 2019;25(3):344-7. DOI: 10.1177/1591019918815294

13. Zhang H, Gao X, Liang H, et al. Incomplete stent apposition of low-profile visualized intraluminal support stents in the treatment of cerebral aneurysms. J Neurointerv Surg. 2020;12(6):591-7. http://dx.doi.org/10.1136/neurintsurg-2019-015505

14. Marel K, Gounis M, Weaver J, et al. Grading of Regional Apposition after Flow-Diverter Treatment (GRAFT): a comparative evaluation of VasoCT and intravascular OCT. J Neurointerv Surg. 2016;8(8):847-52. DOI: 10.1136/neurintsurg-2015-011843.

15. Salem M, Ravindran K, Enriques-Marulanda A, et al. Pipeline Embolization Device Versus Stent-Assisted Coiling for Intracranial Aneurysm Treatment: A Retrospective Propensity Score-Matched Study. Neurosurgery. 2020;4:nyaa041. DOI: https://doi.org/10.1093/neuros/nyaa041.

Table 1. Demographic and clinical characteristics of the patients

Characteristics n=73	With simulation	Without simulation	p
Sex			
Female	46 (82.14%)	17 (100%)	
Male	10 (17,86%)	0	
High blood pressure (n (%)	24 (41.18%)	7 (42.86%)	.902
Smoking (n (%))	7 (12.5%)	3 (17.65%)	.589
Current smoking (n(%))	4 (7.14%)	3 (17.65%)	.20
First degree relative with cerebral aneurysm(n(%))	7 (12.50%)	1 (5.88%)	.399
Multiple aneurysm	34 (60.71%)	7 (41.18%)	.155

Table 2. Intervention features according to simulation planning

	With simulation (n=56)	without simulation (n=17)	p
Time (median (IQR))	100 (85-125)	118 (61-175)	.22*
Stent diameter (median (IQR))	4 (3.5-4.4)	3,75 (3-4)	.2*
Stent length (median (IQR))	16 (12-20)	20 (20-20)	<.001*
Number of implanted stents			
One (n(%))	54 (96.43%)	15 (88.24%)	.19†
Two (n(%))	2 (3.57%)	2 (11.76%)	
Hemorrhagic complications of vascular Access (n(%))	3 (5.36%)	1 (5.88%)	.64†
unplanned stent shortening (n(%))	1 (1.79%)	1 (5.88%)	.36†

*Wilcoxon Rank-sum test

† Fischer exact test

Graph 1. Location of aneurysms

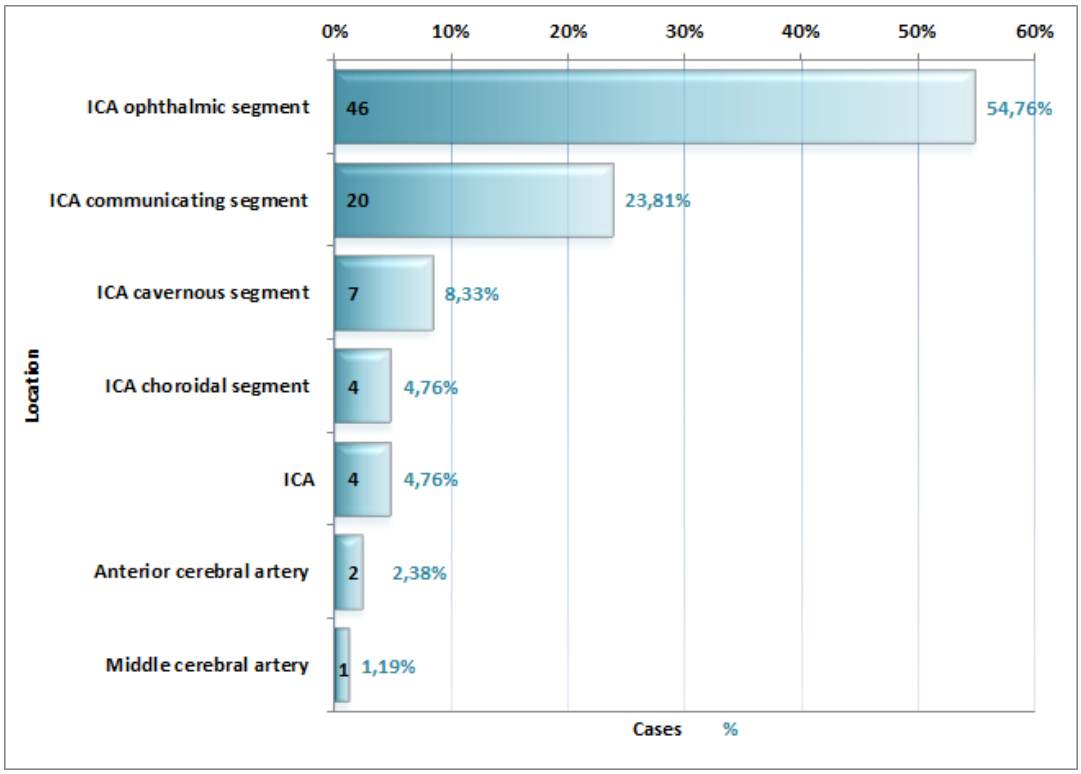

Figure 1.

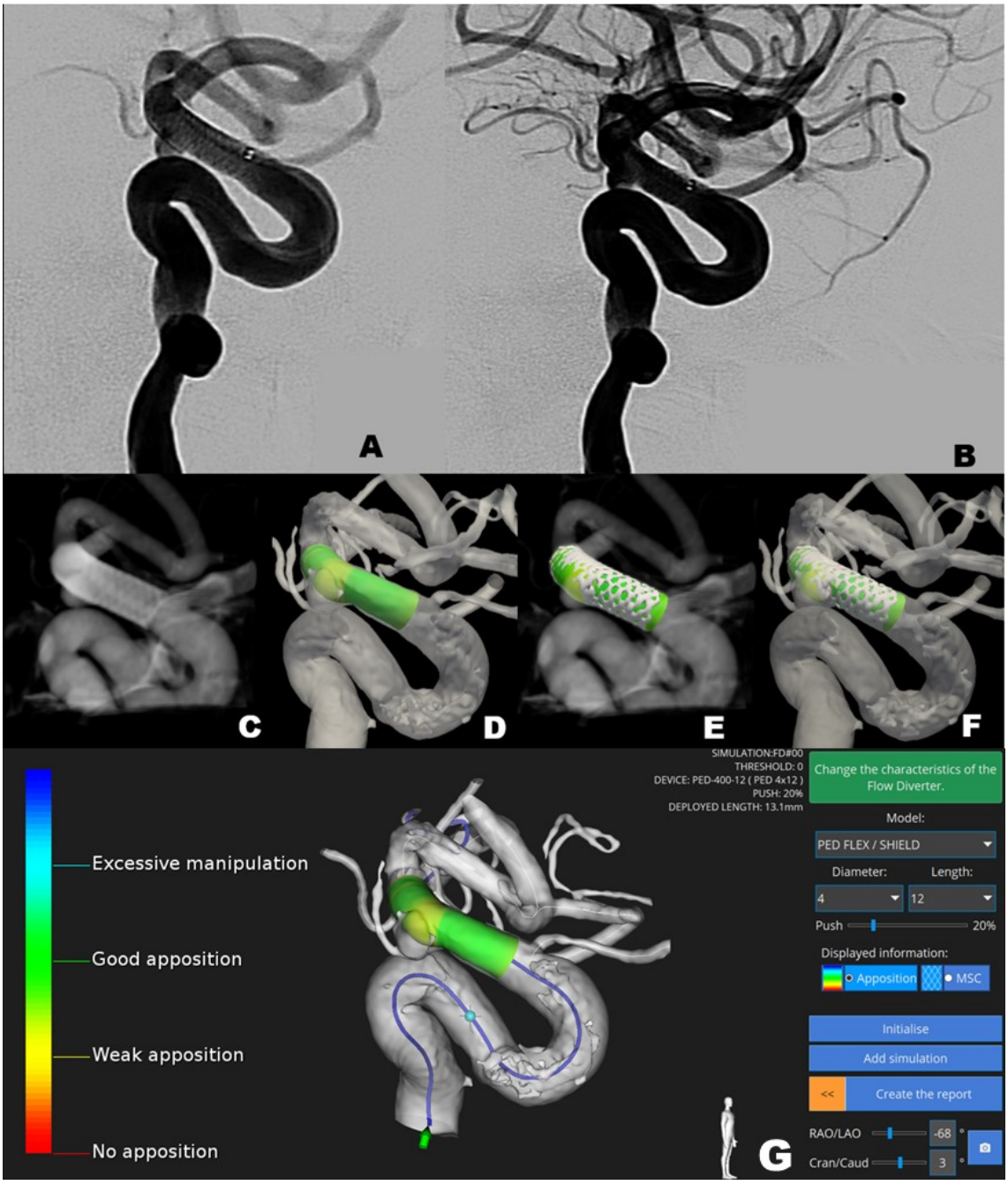

Figure 1: Example of the application of the Sim&Size software for one patient.

A: Zoomed working projection after stent deployment in the treatment of an anterior chöroidal aneurysm with a PED Device.

B: Lateral projection showing proximal stent landing zone.

C: Low contrast CT showing stent wall apposition and proximal landing zone.

D: Sim&Size simulation software result showing the stent proximal ending ad in green a good apposition to the vessel walls.

E and F: Overposition of the Low Contrast CT with the simulated stent, showing a good correlation of the proximal ending zone.

G. Sim&Size simulation result using a Pipeline Shield of 4x12 mm with a 20% push, not covering the ophthalmic artery. Color scale at the left side shows the apposition of the stent with the parent vessel wall.