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Impact of morphological factors in the recanalization of anterior communicating artery aneurysms treated by endovascular approach

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1 - INTRODUCTION

Intra-cranial aneurysms (ICA) are a frequent pathology with a prevalence estimated at 2%[1,2]. In the United States, 10 to 12 million people have an ICA[3]. In France, 1.3 million could be diagnosed with ICA. The global risk of a ruptured aneurysm is estimated to be 1.9% per year[2] and they are responsible for 75% of non-traumatic subarachnoid hemorrhage with a high level of morbi-mortality (30-45%)[4]. Every year in the United States, 27000 new cases of subarachnoid hemorrhage due to ruptured aneurysm are recorded[3]. The mean age of its occurrence is between 55 and 60 years old[3]. The risk of rebleeding in ruptured ICA is about 2 to 4 % in the first 24 hours and 15 to 20 % in the first two weeks[3].

Several prospective and randomized studies have shown that the first-line treatment is endovascular: the ISUA study described a morbidity of 7.3% versus 13.3% for surgery with a mortality around 1%[5] while the ISAT reported a morbi-mortality at one year of 23.5% versus 30.9% for surgery[6]. One of the major limitations of embolization is aneurysmal recanalization, which is estimated at 20.8% and requires subsequent endovascular treatment in 10.3% of cases[7]. Aneurysmal recanalization of ruptured brain aneurysm[8] is responsible for 2.2% to 2.5% of rebleeding in the first year and about 0.2% of non-ruptured aneurysmal bleeding in the first 6 months after endovascular treatment[9].

The major value of establishing the predictive risk of aneurysmal recanalization would be the ability to select patients who are at high risk of recanalization in order to be able to offer them more invasive treatments. In fact, technical progress in intracranial aneurysm embolization such as coiling assisted by stenting or flow-diverter stents helps to reduce the recanalization rate but increases the rate of morbimortality[10]. The risk factors for aneurysmal rupture are well known. An overview of the literature showed that age, female sex, posterior location, size of the aneurysm, high blood pressure and smoking are the major risk factors[11]. On the other hand, the risk factors of aneurysmal recanalization are less well known. Ruptured aneurysm status[12-14], size, aneurysm neck size and anterior location seem to be factors of recanalization[14-16]. Epidemiological factors like smoking have also been studied[17]. However, angioarchitecture of aneurysms has received very little attention, in particular the measurement of the branching angle between the parent vessel and the aneurysmal neck or with the daughter artery. The

« inflow angle » (IA), i.e. angle between parent artery and aneurysmal neck, seems to be a predictive factor of aneurysmal rupture[18]. However, it has not been studied in the framework of aneurysmal recanalization. Nor has the « outflow angle », i.e. angle between parent artery and daughter vessels, been analyzed[19,20].

To date, studies conducted on aneurysmal recanalization have taken the notion of recanalization to be a global event. However, aneurysms evolve differently according to their location [7,21], which probably could introduce a bias. Therefore we decided to focus only on Anterior communicating Artery (AcoA) aneurysms, which are one of the most common presentations [1] involving an increased risk of recanalization[22]. The minimal period of follow-up is one year because aneurysmal recanalization is most often required in the first year[8,22].

The purpose of our study was to analyze the morphological factors involved in AcoA aneurysm and their influence on recanalization after endovascular treatment with a minimal follow-up of one year.

2 - METHODS

This was a retrospective monocenter study performed in the interventional radiology department of a university hospital.

2-1 Patients

All the AcoA treated by an endovascular approach from 2006 to 2013 were analyzed. A senior and a junior neuroradiologists systematically re-examined every original arteriography and every angio-MRI and arteriography in the follow-up period. Follow-up was for at least one year.

Inclusion criteria were as follows: unruptured or ruptured aneurysms treated by endovascular approach; AcoA aneurysm; having 3-dimensional volumetric data sets. Exclusion criteria were as follows: antecedents of endovascular treatment for intra-cranial aneurysms, arterio-veinous malformations (treated or not), fusiform ICA, dissecant ICA; death not related to aneurysmal recanalization rebleeding; lost to follow-up.

2-2 Follow-up

Aneurysmal recanalization related to morphological parameters was the primary end-point. Patients treated by an endovascular approach were monitored in our center by angiography and/or angioMR. Follow-up was based on standard recommendations including the 2011 guidelines of the French Society of Neurosurgery: 3D TOF angioMR in the 3-6 months after endovascular treatment, then arteriography and a 3D TOF angioMR between 12 to 15 months, followed by an 3D TOF angioMR at 3 years and at 5 years of occlusion if the treatment is satisfactory[12,22-25]. The degree of occlusion was evaluated by the Raymond scale in 3 groups: complete obliteration (class 1), residual neck (class 2), and residual aneurysm (class 3). Recurrence of aneurysm was defined as the transition from class I to II, II to III and an increase in size of the residual aneurysm for class III[26,27].

2-3 Clinical and morphological parameters and angioarchitecture of aneurysm

Clinical data including age, sex, cardiovascular factors (high blood pressure, smoking and alcohol) were collected from neurosurgical hospitalization reports. The following morphological characteristics were collected: high size (h), neck size (c), ASPECT ratio (h/c)[20,28], and the high size/width ratio (h/l)[29]. A recent study[30] showed that ICA located anteriorly were more at risk of recanalization when a dominant anterior cerebral artery was found. This parameter was also investigated in our patients.

Dominance was defined as a diameter of precommunicating segment of anterior cerebral artery A1 ≥ A1 contralateral or asymmetric opacification of A2 segments. Codominance was defined as symmetric opacification of A2 segments or A1 diameter equal to A1 contralateral. Saccular aneurysms are preferentially located at the top of arterial bifurcations due to high shear forces[31]. The geometry and angioarchitecture of these arteries were therefore studied. For each aneurysm, 3 angles were calculated: IA, right OA (angle between A1 and right A2) and left OA (between A1 and left A2) using three-dimensional angiographic acquisition. These calculations were based on a scalar product derived from 3D spatial coordinates (x, y and z) of 3 points constituting each angle as measured with OsiriX software (v5.5.2 64-bit, PIXMEO SARL), including the formula shown in figure 2.

IA was defined as the angle formed between P1 (point in the middle of the aneurysmal neck), P2 (point in the middle of the A1 termination) and P3 (point in the middle of A1 5mm upstream from it) (Figure 3).
To calculate OA, we set the angle vertex (P4) to cross the lines P2 -P3 and P5-P6 formed by the point P5 (middle of A2 at its origin) and P6 (middle of A2 5mm downstream from it). OA were therefore defined as the angles between P3, P4 and P6 left and right (Figure 4). The sum of OAG and OAD was calculated and termed the "global outflow angle". A recent study showed the benefit of this parameter in assessing aneurysms that occur at the top of arterial bifurcations[31], due to the significant shear forces exerted at this level. We assumed that if this angle was correlated with the formation of the aneurysmal bifurcation, it could be implicated in aneurysmal recanalization.

2-4 Endovascular treatment, angiographic results and complications

The initial type of treatment was collected (single coils, coils associated with remodeling, coils associated with a stent or stent flow diverter). The possible complications (bleeding, thromboembolism, vasospasm and hydrocephalus) were analyzed.

2-5 Statistics

The Wilcoxon test was used to analyze non-parametric data (age, aneurysmal morphological characteristics and calculation of the angles). These variables were expressed as mean ± standard deviation. Fisher's exact test was used for parametric data such as cardiovascular risk factors, sex, aneurysm status (ruptured or not), dominance of the A1 segments of the anterior cerebral arteries, degree of initial occlusion and conventional complications of subarachnoid hemorrhage. These tests were used for univariate analysis. A multivariate analysis (logistic regression variables with $p < 0.20$ in the univariate analysis) was subsequently performed. The significance level was 5 % ($p < 0.05$). All analyses were performed with SAS software v 9.3.

3 - RESULTS

3-1 Characteristics of population

We included 156 patients (156 AcoA aneurysms) of initial 237 patients between 2006 and 2013: 40 died (16.9%), 35 procedures were performed without 3D acquisition (14, 8%), 4 patients had surgical treatment (1.7%) and 2 were not saccular but dissecant aneurysms (0.9 %) (Figure 5). Mean age was 57±12 years; sex ratio (F/M) was 1.3.
35.3 % of patients were hypertensive, 25% were smokers, 7.1% had chronic alcohol consumption and 5.8% were diabetics. 83% of the initial aneurysms included were ruptured (Table 1). The average height of the aneurysm was 6.02 ± 2.53mm, size of the neck was 2.92 ± 1.23mm, and ASPECT ratio was 2.2 ± 0.82. According to angular data, the average IA was 157.09 ± 15.93° and the sum of right and left OA (OAD + OAG) was 211.48 ± 39.53°.

3-2 Modalities of endovascular treatment

All the aneurysms included had endovascular treatment (aneurysms treated surgically were excluded). All the procedures were performed under general anesthesia and heparin was used as often as possible. In 62.8 % of cases, a remodeling balloon was used. Complete occlusion (grade 1) was obtained in 81% of cases and subtotal occlusion (grade 2) in 14.7 % of cases. Occlusion was incomplete (grade 3) in 4.4 % of cases.

3-3 Follow-up and recanalization rates

Aneurysmal recanalization was determinate in 59 patients (38 %) of cases with an average of 21.5 months of recanalization, (minimum: 2,9 months, maximum: 95 months). It was minor (grade 2) in 18 cases (11.5%) and grade 3 in 41 cases (26.5 %). In the first 18 months, the rate was 21%. Mean follow-up was 34 months. A new treatment was performed in 17 patients (10.9%). Among the classic complications of subarachnoid hemorrhage, there were 15.4% of hydrocephalus and 12.2% of vasospasm. Embolization complications were 16% of thromboembolic events and 3.2% rebleeding per procedure. During follow-up, no rebleeding occurred.

3-4 Recanalization factors

Univariate analysis (Table 3) identified the following as factors of significant morphological risk of recanalization: aneurysmal height 6.6 ± 2.9 mm ($p = 0.03$), size of the neck 3.4 ± 1.1 mm ($p < 0.0001$), width 4.9 ± 2 mm ($p = 0.0008$) and ASPECT ratio 1.9 ± 0.7 ($p = 0.007$). The dominance of one A1 segment over the other proved significant ($p < 0.007$). Global outflow angle was significant ($p < 0.0001$), unlike IA ($p = 0.38$). Multivariate analysis revealed three significant independent risk factors for aneurysmal recanalization: global outflow angle, aneurysmal height and ASPECT ratio (Table 4).

The threshold value of global outflow angle for predicting aneurysmal recanalization was calculated using ROC curves (Figure 5). The optimal global outflow angle was 207 ° with a sensitivity of 75% and a specificity of 77%, so an aneurysm with a global outflow angle < 207 ° was at greater risk of recanalization. The ROC curves of the three factors of significant and independent risk showed that the global outflow angle in the aneurysmal recanalization was more discriminating than the aspect ratio or aneurysmal height. The areas under the curves (AUC) were respectively 0.81, 0.627 and 0.61. However the inclusion of these three parameters was better than the single value of global outflow angle: AUC of the global outflow angle was 0.81, and AUC of the sum of these three parameters was 0.842.

3-5 Intra-reader agreement for calculation of angles

The reproducibility of calculating angles was tested with a Bland-Altman plot (fig 6). The average differences in calculating the Inflow Angle was 2, (SD = 7.5). 95% of the values of the differences between the two measurements were between -12.8 ° and 16.8°.

The average differences for the A1 angle was 1.6 (SD = 9.3). 95% of the values of the differences between the two measurements were between -16.7 ° and 19.9°.

The average differences for the A2 angle was 0.2 (SD = 10.4). 95% of the values of the differences between the two measurements were between -20.3 ° and 20.5°.

4 - DISCUSSION

While the endovascular procedure is the gold standard for ICA treatment[5,6], its main limitation is aneurysmal recanalization. We focused on aneurysms located at the AcoA owing to their high frequency, high risk of recanalization and to limit any bias due to studying very different morphological factors around the aneurysm.

4-1 Modalities of treatment and initial occlusion

All ICA included were treated by an endovascular approach. Initial occlusion rate was grade 1 in 81%, grade 2 in 14.7% and grade 3 in 4.3%. In the study by Pierot et al[32] initial occlusion was grade 1 in 75.8%, grade 2 in 18.8% and grade 3 in 5.4%. When two independent reviewers reexamined the data, there were 47.4% grade 1, 41.9% grade 2 and 10.7 % grade 3. If we used the same method of critical rereading, we would probably find a similar difference in our data.

4-2 Recanalization and re-treatment

Our recanalization rate was 38%, this rate is higher than the 20.8%[7] reported in a literature review of 33 studies for all aneurysmal locations. However, only eight of those studies had an average follow-up >18 months whereas our mean follow-up was 34 months. After 18 months of follow-up, our recanalization rate was 21.2% which is in agreement with the literature. In 2011, Ferns et al[25] found a lower recanalization rate for anterior locations of ICA compared to posterior locations. This difference is likely due to the high frequency of surgical treatment that the authors reported for AcoA aneurysms. In our center, surgical treatment is only rarely performed since only 4 of the 237 aneurysms initially included received surgical clipping (1.7%). Furthermore our re-treatment rate of 10.9 % is also consistent with the 10.3% rate reported in the literature[7].

4-3 Intraoperative complications

The rate of the most common complications thromboembolic and intraoperative rupture was 16% and 3.2%[33,34] respectively. The rate of these same complications in the CLARITY[35] study were 12.5 % and 4.4 % respectively. The retrospective nature of our study did not allow us to identify any symptomatic iatrogenic complications.

4-4 Morphological factors affecting recanalization

Univariate analysis demonstrated the same recanalization risk factors as those already reported such as aneurysmal dimensions (height and width) and the size of the neck[36]. An ASPECT ratio < 2 was also predictive of recanalization. In fact, the greater the size of the neck, the lower the ASPECT ratio. This ratio was not significant in the literature review. The dominance of the A1 segment was also significant ($p < 0.07$), in agreement with Tarulli et al[30].

Our analysis revealed a new morphological factor for locating recanalization of AcoA aneurysms. The global outflow angle was significant with values of 189.2 ± 37.8 in the recanalization group and 226.6 ± 33.2 in the group without recanalization ($p < 0.0001$). Baharoglu et al[31] recently studied the global outflow angle at the middle cerebral bifurcation artery. They showed that it was significantly lower in patients with aneurysms in the middle cerebral bifurcation. However, our method of calculating angles seems much more reliable since it is based on the spatial coordinates of the points defining an angle on a 3D angiography by using a 3D scalar product formula. In contrast, in the study of Baharoglu et al, the angles were calculated with a 2 - dimensional projection, which might not be very reproducible and does not correspond to the actual angle of the arteries. On the other hand, the clinical data we collected were not significant.

Multivariate analysis was used to objectify 3 risk factors for recanalization, " the global outflow angle ", the aneurysmal height and ASPECT ratio.

4-5 Limitations of the study

A major limitation of the study is that it was retrospective and conducted in a single center. The findings now need to be validated in a prospective study. Some patients who were lost to follow were called by phone to undergo a control angio MR. Recanalization proved necessary in some of them. In addition, this new method requires validation by inter-observer agreement. Finally, our results on the initial occlusion should be reviewed by independent neuroradiologists, as demonstrated Pierot and al[32], since the initial degree of aneurysmal occlusion is overestimated when analyzed by the operator who treated the aneurysm.

5 - CONCLUSION

The recanalization and angioarchitecture profiles of ICA differ depending on their location. Therefore, to limit any bias due to morphological factors, we focused on ICA of the anterior communicating artery, one of the most common sites with a high risk of recanalization. Multivariate analysis demonstrated aneurysmal height and ASPECT ratio to be morphological risk factors for aneurysmal recanalization. We also found a new risk factor: the global outflow angle ($p < 0.0001$). This finding should be taken into account when establishing the initial treatment strategy and when assessing the need to insert intracranial stents for unruptured aneurysms from the outset. It would also be interesting to calculate the global outflow angle for other aneurysmal locations such as the middle cerebral artery bifurcation and the top of the basilar artery.

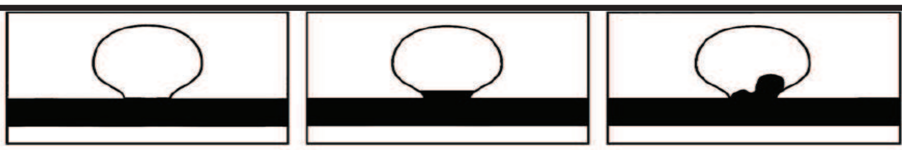
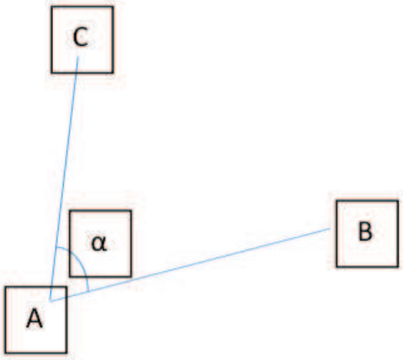


Fig. 1. Classification of anatomical results. Schematic representation (*bottom*) with corresponding clinical examples (*top*). (*A*) Complete occlusion. (*B*) residual neck (*arrow*). (*C*) Residual aneurysm (*arrow*).

Figure 1. Raymond scale



$$\overrightarrow{AB}.\overrightarrow{AC} = \|\overrightarrow{AB}\|.\|\overrightarrow{AC}\|.cos(\alpha)$$

$$\overrightarrow{AB}.\overrightarrow{AC} = (x_B - x_A).(x_C - x_A) + (y_B - y_A).(y_C - y_A) + (z_B - z_A).(z_C - z_A)$$

$$\|\overrightarrow{AB}\| = \sqrt{(x_B - x_A)^2 + (y_B - y_A)^2 + (z_B - z_A)^2}$$

$$\|\overrightarrow{AC}\| = \sqrt{(x_C - x_A)^2 + (y_C - y_A)^2 + (z_C - z_A)^2}$$

$$cos(\alpha) = \frac{(x_B - x_A).(x_C - x_A) + (y_B - y_A).(y_C - y_A) + (z_B - z_A).(z_C - z_A)}{\sqrt{(x_B - x_A)^2 + (y_B - y_A)^2 + (z_B - z_A)^2}.\sqrt{(x_C - x_A)^2 + (y_C - y_A)^2 + (z_C - z_A)^2}}$$

Figure 2. Scalar 3D product

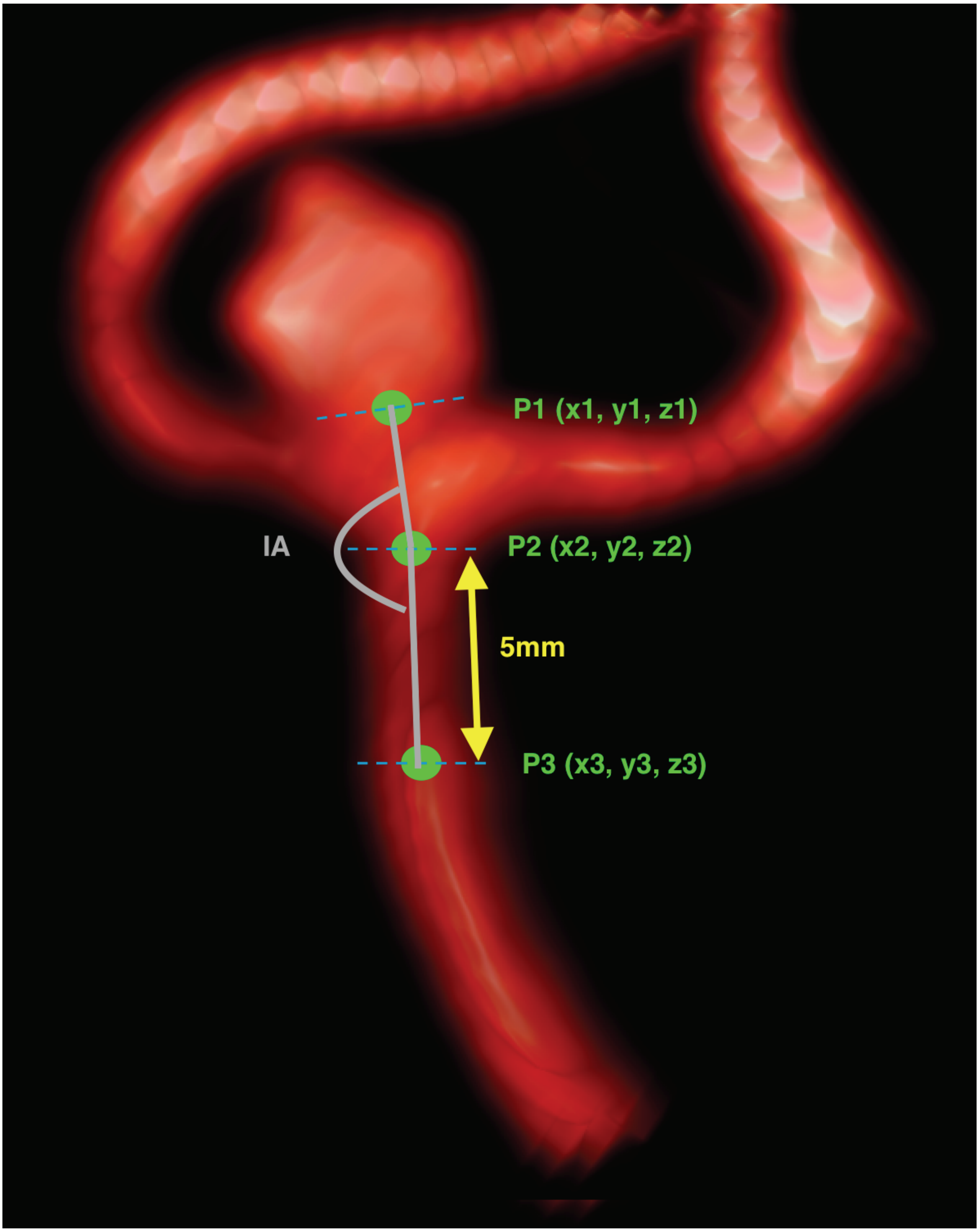


Figure 3. Inflow Angle

P1 : point in the middle of the aneurysmal neck.
P2 : point in the middle of the A1 termination.
P3 : point in the middle of A1 5mm upstream from it.

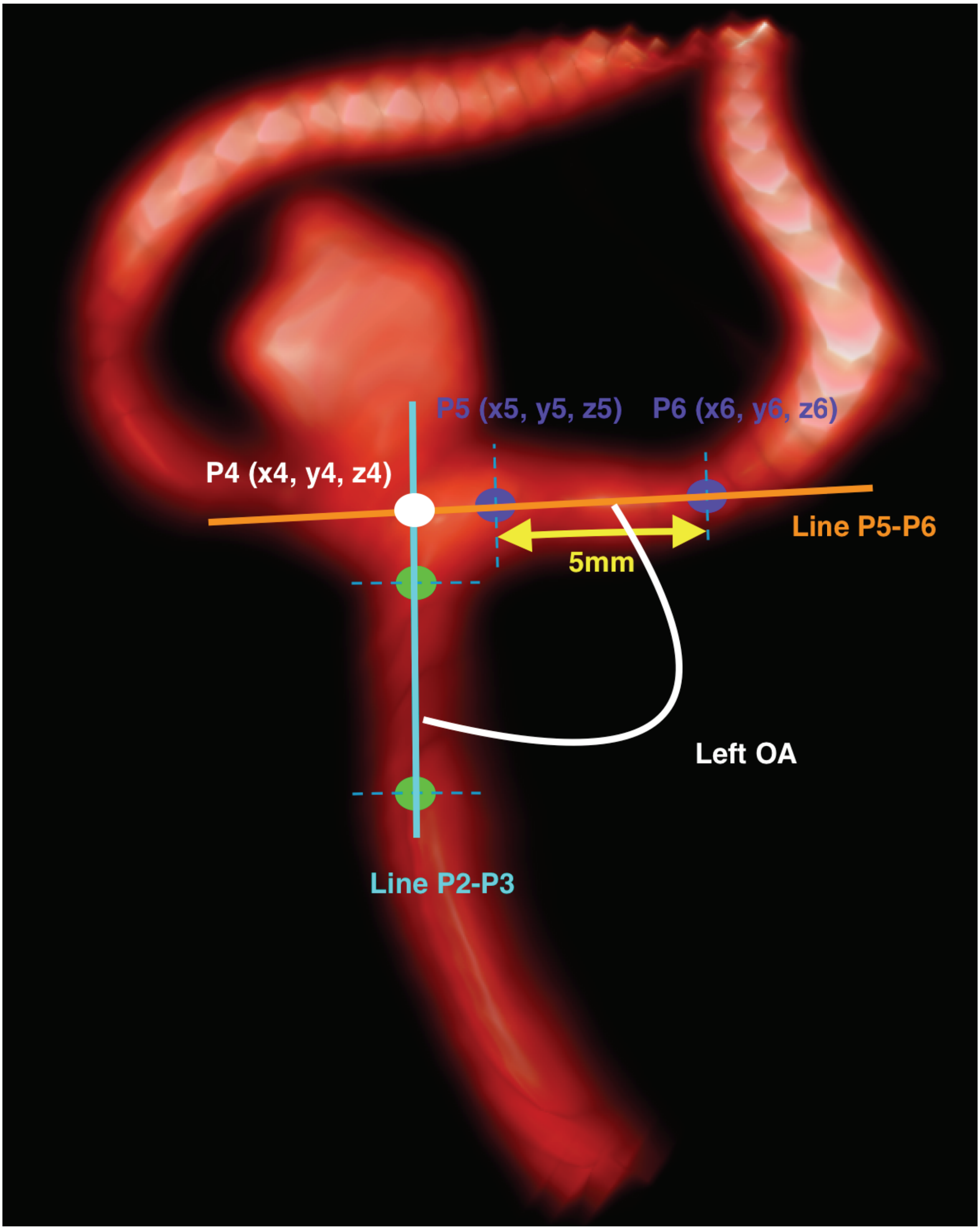


Figure 4. Left outflow Angle

To calculate OA, we set the angle vertex (P4) to cross the lines P2-P3 and P5-P6 formed by the point P5 (middle of A2 at its origin) and P6 (middle of A2 5mm downstream from it).
OA were therefore defined as the angles between P3, P4 and P6 left.

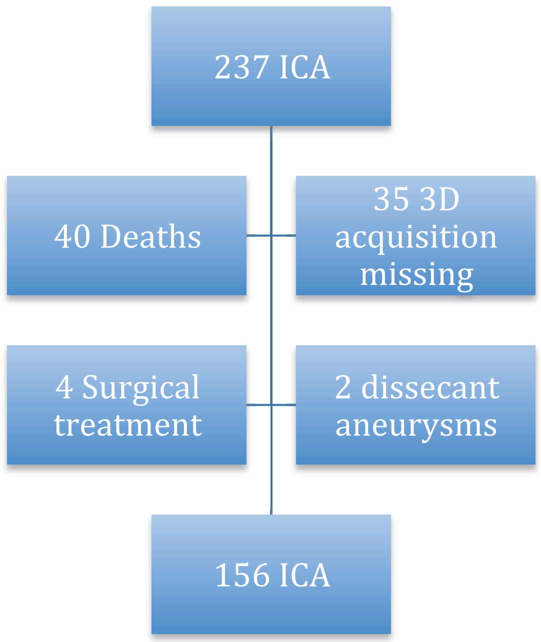


Figure 5. Flowcharts

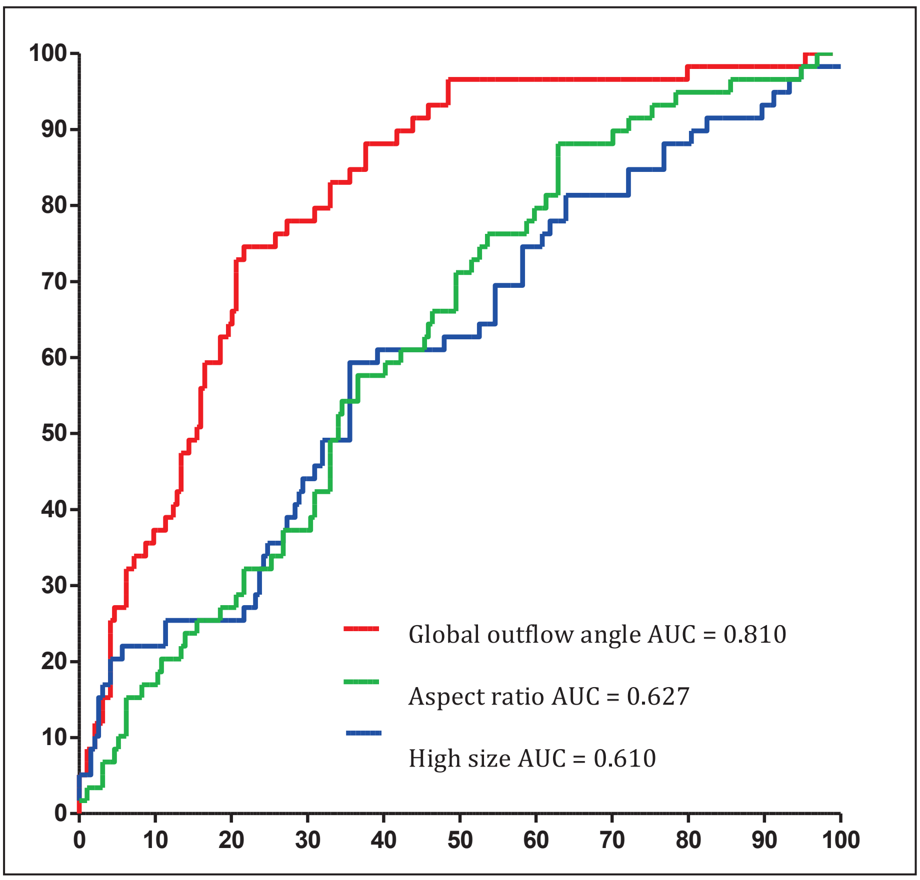


Figure 6. ROC curves

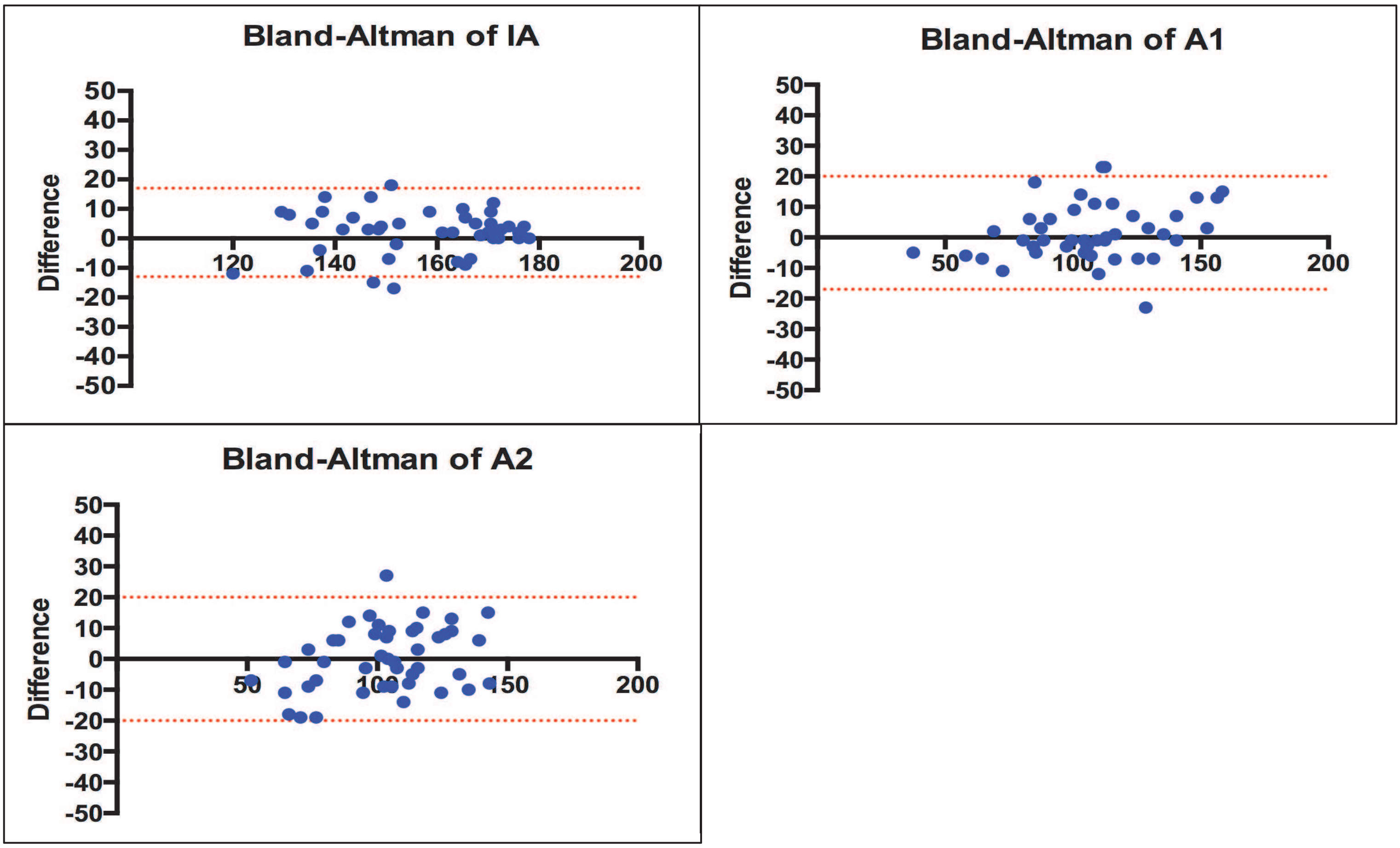


Figure 7. Intra-reader agreement for calculating angles

Variables	Patients (N= 156)
Age (mean ± SD)	57±12.3
Sex (%) Women Men	 88 (56.4) 68 (43.6)
High blood pressure (%)	55 (35.3)
Smoking (%)	39 (25)
Alcohol (%)	11 (7.1)
Diabetes (%)	9 (5.8)
Ruptured AIC (%)	130 (83)
Unruptured AIC (%)	26 (17)

Table 1. Characteristics of population

Risk factors	Recanalization	Not recanalization	« p »
Age (mean ± SD)	57.3±12.8	56.8±12	0.5
Sex			0.25
Women	32 (20.5)	56 (35.5)	
Men	31 (19.9)	37 (23.7)	
Clinical history No. (%)			
High blood pressure	24 (15.4)	31 (19.9)	0.6
Smoking	16 (10.3)	23 (14.7)	1
Alcohol	5 (3.2)	6 (3.9)	0.75
Diabetes	3 (1.9)	6 (3.9)	0.74
Ruptured	54 (34)	76 (48.7)	0.5
Unruptured	9 (5.8)	17 (10.9)	
Morphological characteristics (mean ± SD)			
High size (H)	6.6±2.9	5.6±2.2	**0.03**
Neck size	3.4±1.1	2.6±1.2	**<0.0001**
Width (W)	4.9±2	3.9±1.5	**0.0008**
ASPECT ratio	1.9±0.7	2.3±0.9	**0.007**
H/W	1.4±0.4	1.5±0.5	0.13
Inflow Angle	158.5±16	156.2±15.9	0.38
Global outflow angle	189.2±37.8	226.6±33.2	**<0.0001**
Dominance of A1	48 (30.8)	51 (32.7)	**0.007**
Co-dominance of A1	15 (9.6)	42 (26.9)	
Initial treatment. No. (%)			
Grade 1			
Grade 2	44(28)	82 (53)	
Grade 3	15(9.6)	8 (5.1)	
	4 (2.5)	3 (1.8)	
Complications			
Thromboembolic	10 (6.4)	15 (9.6)	1
Hydrocephalus	10 (6.4)	15 (9)	0.8
Peri-procedure bleeding	4 (2.6)	1 (0.6)	0.16
Vasospasm	5 (3.2)	14 (9)	0.22
Follow-up			
Average of recanalization (months)	21.5 months		
% of recanalization	38%		
Type of recanalization			
Grade 2	11.5%		
Grade 3	26.5%		

Table 2. Univariate analysis of recanalization risk factors

Risk factors	Odds ratio (95% IC)	« p »
Global outflow angle	0.97 (0.96-0.98)	**<0.0001**
High size	1.39 (1.1-1.7)	**0.0057**
ASPECT ratio	0.27 (0.14-0.5)	**0.0001**

Table 3. Multivariate analysis of recanalization risk factors

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ABSTRACT

Background and purpose: This study sought to identify morphological factors influencing recanalization aneurysms of the anterior communicating artery after endovascular treatment.

Methods: A retrospective study was conducted of 156 aneurysms of the anterior communicating artery treated by an endovascular approach between January 2006 and December 2013. Epidemiological data were gathered as well as morphological parameters (height, width, size of neck, height/width ratio, ASPECT ratio, and dominance of segment A1). New parameters were calculated: a) the global outflow angle which is the sum of the angles between the afferent artery and both efferent arteries of the aneurysm; b) the inflow angle. Univariate and multivariate analyses of all of these parameters were performed.

Results: 130 aneurysms were ruptured and 26 unruptured at the time of diagnosis. Mean follow-up was 34 months and the average time of recanalization was 21.5 months. Univariate analysis retained as recanalization factors: height (p = 0.03), size of neck (p < 0.0001), aneurysmal width (p = 0.0008), ASPECT ratio (p = 0.007), dominance of one segment A1 (p = 0.007) and global outflow angle (p <0.0001). The multivariate analysis established three factors of recanalization: the global outflow angle (OR 0.97; 95 % CI, 0.96 to 0.98), height (OR 1.39; 95 % CI, 1, 1 to 1.7) and ASPECT ratio (OR 0.27; 95 % CI, 0.14 to 0.5).

Conclusion: We have identified a new morphological factor of recanalization aneurysms in the anterior communicating artery: the global outflow angle. This factor should be taken into account when planning the embolization of unruptured aneurysms in order to anticipate the need for intracranial stents.

Key words: intracranial aneurysm, recanalization, risk factors.

SERMENT

En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses ! Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque !