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Thrombus burden management during primary coronary bifurcation intervention: a new experimental bench model

Ahmad Hayek et al., Thrombus burden management in coronary bifurcations

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Abstract

Background: Management of thrombus burden during primary percutaneous coronary intervention (pPCI) is a key-point, given the high risk of stent malapposition and/or thrombus embolization. These issues are especially important if pPCI involves a coronary bifurcation. Herein, a new experimental bifurcation bench model to analyze thrombus burden behavior was developed.

Methods: On a fractal left main bifurcation bench model, we generated standardized thrombus with human blood and tissue factor. Three provisional pPCI strategies were compared (n = 10/group): 1) balloon-expandable stent (BES), 2) BES completed by proximal optimizing technique (POT), and 3) nitinol self-apposing stent (SAS). The embolized distal thrombus after stent implantation was weighed. Stent apposition and thrombus trapped by the stent were quantified on 2D-OCT. To analyze final stent apposition, a new OCT acquisition was performed after pharmacological thrombolysis.

Results: Trapped thrombus was significantly greater with isolated BES than SAS or BES+POT (18.8 ± 5.8% vs. 10.3 ± 3.3% and 6.2 ± 2.1%, respectively; $p < 0.05$), and greater

with SAS than BES+POT ($p < 0.05$). Isolated BES and SAS tended show less embolized thrombus than BES+POT (5.93 ± 4.32 mg and 5.05 ± 4.56 mg vs. 7.01 ± 4.32 mg, respectively; p = NS). Conversely, SAS and BES+POT ensured perfect final global apposition (0.4 ± 0.6% and 1.3 ± 1.3%, respectively, p = NS) compared to isolated BES (74.0 ± 7.6%, $p < 0.05$).

Conclusions: This first experimental bench model of pPCI in a bifurcation quantified thrombus trapping and embolization. BES provided the best thrombus trapping, while SAS and BES+POT achieved better final stent apposition. These factors should be taken into account in selecting revascularization strategy.

Key words: primary percutaneous coronary intervention, trapped thrombus, embolized thrombus, nitinol self-apposing stent, provisional stenting

Introduction

Management of thrombus burden is one of the key-points in primary percutaneous coronary intervention (pPCI) during acute myocardial infarction. Distal thrombus embolization is directly correlated with cardiovascular prognosis, including final no-flow, stent thrombosis and death [1]. To limit this risk, direct stenting is strongly recommended [2]. At the same time, the pPCI is at risk of final stent malapposition, due to secondary resorption of thrombus “trapped” between stent and artery, and to acute ischemic vasoconstriction inducing stent undersizing [3]. Malapposition increases the risk of late stent thrombosis [4]. However, these concepts of thrombus embolization or “trapped” thrombus during the pPCI have never been clearly quantified.

Coronary bifurcation pPCI is even more complex [5]. The systematic difference in diameter between proximal and distal vessels, due to the fractal geometry [6], entails systematic proximal malapposition which usually needs to be corrected by post-dilatation. In the absence of thrombus burden, an initial proximal optimization technique (POT) is also recommended to correct these malappositions and to optimize the side-branch ostium [7]. But, in the specific context of pPCI, POT, like any post-dilatation, risks distal thrombus embolization in the branches. The mechanical properties of nitinol self-apposing stents (SAS) may, in bifurcation pPCI, enable spontaneous correction of proximal malapposition [8] without for need for POT [9], in contrast to BES [10].To date, all strategies to decrease thrombus burden before pPCI, whether mechanical thrombo-aspiration [11] or

pharmacological resorption as minimalist immediate mechanical intervention (MIMI) strategy [12], failed to improve the clinical prognosis.

The present experimental bench study developed a new coronary bifurcation model to analyze thrombus behavior during pPCI according to procedural strategy and stent properties.

Methods

Experimental design

All experiments were performed in fractal left-main coronary bifurcation bench models [7] (Segula Technologies, Saint-Priest, France), with diameters 4.25 mm, 3.40 mm and 2.9 mm in the proximal main branch (MB), distal MB and side-branch (SB), respectively. Thrombus was generated in the MB, centered on the SB. Three provisional stenting strategies (Fig. 1) were compared (n = 10/group): 1) isolated BES (Synergy™, Boston Scientific, USA), 2) BES followed by POT, and 3) isolated SAS (Xposition S™, STENTYS, France). SASs were implanted after controlled opening of the protective sheath by balloon inflation at 12 atm, as recommended by the manufacturer. BES diameters and POT balloon inflation pressures were determined so as to obtain a proximal and distal stent-artery ratio between 1.0 and 1.1, as recommended (Fig. 1) [13].

After each stent implantation, saline serum was injected (200 mL) as coronary circulation. To quantify the “embolized” thrombus in the branches (distal MB and SB) during saline injection, all serum seeping from the branches was sieved, and trapped thrombus was weighed blind to the procedure. Experiments were concluded by pharmacological thrombolysis. During all experiments, the bench models were kept in a 37° bath under thermostat control.

Thrombus synthesis and thrombolysis

Blood samples were taken in an EDTA tube, from a single healthy subject without medication or medical history of bleeding or thrombosis (FD). Thrombus was generated by mixing 500 µL of blood with a pro-coagulant reagent associating 50 µL tissule factor (300 pM) (Innovin, Behring, Marburg, Germany) and 10 µL $CaCl_2$ (1 M). The mixture was directly injected into the bench model, always in the same position, according to marks, to obtain a homogeneous thrombus with 30 mm length (10 mm in the distal MB and 20 mm in the proximal MB). After 15 min, the thrombus was considered to be formed, and experimentation was performed (Fig. 2). At the end of all the experiments, thrombolysis solution (100 µL tPA

(Actilyse, Boehringer, Ingelheim, France), diluted 50% in a Hepes-BSA tampon as previously described [14], was injected directly into the bench model for 24 h.

OCT analysis

OCT acquisitions with the Lunawave^{TM} OFDI system (Terumo Europe, Leuven, Belgium) were performed after the first saline wash and after complete thrombolysis at 24 h (Fig. 1). OCT analysis quantified lumen area, mean bench model diameter (D_{mean}) and stent diameter (D_{stent}). The stent-artery ratio was calculated as D_{stent}/D_{mean}. After millimetric cross-sectional stent analysis, global malapposition was calculated as percentage malapposed/total struts. Strut malapposition on OCT was defined by a 150 µm threshold (stent thickness + OCT axial resolution). The trapped thrombus was estimated by blind computational planimetry on millimetric cross-sectional stent analysis as equal to $A_1/A_2 \times 100$ (with A_1 = thrombus area and A_2 = lumen area) (Figs. 3, 4).

Statistical analyses

Quantitative variables were expressed as mean ± standard deviation after confirmation of normal distribution on the Shapiro-Wilk test. Quantitative effects were compared on ANOVA with Bonferroni correction and t-test, using SPSS® software, version 25 (IBM, NY, USA). The significance threshold was set at $p < 0.05$.

RESULTS

All experiments (n = 30) were successfully completed. Table 1 and Figure 5 summarize the main results after isolated BES, BES+POT and SAS. Trapped thrombus was greater with isolated BES than with BES+POT or SAS (18.8 ± 5.8% vs. 10.3 ± 3.3% and 6.2 ± 2.1%, respectively; $p < 0.05$) and with BES+POT than with SAS ($p < 0.05$). This was in concordance with a trend for lower distal thrombus embolization in isolated BES and SAS (5.93 ± 4.32 mg and 5.05 ± 4.56 mg, respectively) than with BES+POT (7.01 ± 4.32 mg, p = NS) (Fig. 5).

At 24 h, after complete thrombolysis, final global stent apposition was optimal with both SAS and BES+POT, unlike with isolated BES (0.4 ± 0.6% and 1.3 ± 1.3% vs. 74.0 ± 7.6%, respectively, $p < 0.05$). Moreover, stent area in the mother vessel increased significantly after thrombolysis in the SAS group (+9.7%; $p < 0.05$) (Table 1), whereas with isolated BES and BES+POT, area and diameters were unchanged.

DISCUSSION

According to available research, this bench study was the first experimental model specifically dedicated to analyzing thrombus behavior during pPCI, especially in coronary bifurcations. For the first time, to the ability to confirm and quantify the concept of thrombus "trapping" and distal thrombus embolization following stent implantation was demonstrated. Thanks to this new model, comparing thrombus burden management according to different strategies and stents (BES or SAS) was shown. Thus, the trapped thrombus was greater in case of isolated BES than BES+POT or SAS, and in SAS than BES+POT. However, this greater trapping with isolated BES was at the cost of greater global malapposition, mainly proximal, as expected in light of the specific fractal geometry of coronary bifurcations. On the contrary, nitinol SAS and BES+POT both ensured perfect final apposition. Finally, thrombus embolization did not significantly differ between the three strategies, probably due to unexpected thrombus behavior during stent implantation and the relatively small sample sizes. However, there were trends for lower embolization in favor of isolated BES and SAS, in agreement with the greater thrombus trapping.

Coronary bifurcation model

Specifically a fractal coronary bifurcation model was chosen in order to simulate the worst situation for thrombus management, given the differential of diameters between proximal and distal segments. In clinical practice, BES bifurcation revascularization requires systematic initial POT [7, 13] to correct the expected proximal malapposition [6]. Nitinol SAS experimentally demonstrated perfect spontaneous apposition in provisional stenting without need for specific bifurcation post-dilatation such as POT [9], and in contrast to balloon-expandable stents [7]. This may be useful in limiting the risk of embolization in the bench model. In this experimental model, exploring acute ischemic vasocontraction was not possible [3], which also increases the risk of global malapposition. However, according to the mechanical properties of nitinol, SAS seems to be able to optimize stent apposition secondarily by increasing the area and diameter, as seen after complete thrombolysis [8].

Embolized and trapped thrombus

According to available research, this is the time that this experimental model was able to quantify the trapped and embolized thrombus during stent implantation with large thrombus burden during pPCI. The best trapping and thus lowest embolization was obtained by BES implantation without post-dilatation, but at the cost of a greater final global

malapposition after thrombolysis. On the other hand, final apposition was perfect with SAS or BES+POT, with better trapping for SAS ($p > 0.05$). This greater trapping was probably at least partly due to a greater metallic cover area with SAS Xposition S™ (20%) than DES Synergy™ (12%) (data provided by the manufacturers for a 3.5 mm stent at nominal pressure). Moreover, SAS implantation required only a single small-diameter inflation to open the sheath, compared to the larger stent balloons used for BES deployment and additional post-dilatation. Large balloon and successive inflations in thrombus burden exposes to distal embolization, by cutting the thrombus protruding in the lumen between struts. Even so, however, embolization did not significantly differ in these small samples. Importantly, the poorer crossing profile of SAS Xposition S™ compared with BES Synergy™ and the "brutal" sheath opening could also decrease the expected theoretic benefits for thrombus mobilization and/or embolization with SAS.

Clinical implications

This first experimental demonstration of thrombus trapping and distal embolization must be taken into account in clinical practice, especially in case of large thrombus burden as found in large-diameter proximal arteries. Due to the higher risk of embolization, balloon inflation has to be cautious, and direct stenting should be preferred. Stent mobilization before implantation, because of the risk of positioning being destabilized by the thrombus, as observed in our experiments, has to be cautious and limited. SAS is no longer available, so when a BES is implanted in a bifurcation with high thrombus burden, especially in uncalcified lesions with large differences in diameter, final post-dilatation may be considered, to optimize apposition (as in POT) secondarily after the main pharmacological thrombus resorption, as in the MIMI strategy [12].

This first model is able to evaluate thrombus burden behavior (trapping, embolization) and could be useful for future evaluation of other new vascular devices or techniques specifically dedicated to acute artery reperfusion, in interventional cardiology or even neurology.

Limitations of the study

The main limitation of this study lay in the use of an experimental thrombus, unlike the usual formation after arterial wall plaque rupture. The potential effect of antithrombotic medication given in the acute phase of myocardial infarction was also not taken into account. All of this could influence thrombus structure and thus embolization and trapping

mechanisms. However, in the present experiments, the thrombus behavior was close to that observed in clinical practice, and the OCT images were similar to those usually observed (Fig. 4).

Moreover, the model used herein is a non-pathological cylindrical bench model and thus did not reproduce the impact of atherosclerotic plaque on SAS deployment. Due to the low spontaneous expansion force of nitinol, global post-dilatation should be considered after SAS implantation, especially if the lesion was calcified or stiff, to avoid potential under-deployment due to a resistant lesion.

CONCLUSIONS

This first experimental coronary bifurcation model of pPCI in large thrombus burden confirmed and quantified the phenomena of thrombus trapping and embolization. Greater trapped thrombus was observed with the classic BES implantation without post-dilatation, at the cost of severe malapposition. Conversely, provisional stenting with the nitinol SAS achieved perfect apposition, as good as that of BES followed by POT, but with a high level of thrombus trapping.

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Conflict of interest: None declared

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Table 1. Balloon-expandable and self-apposing stent implantation in coronary bifurcation with thrombus burden (n = 10/group).

	Balloon-expandable Synergy™ alone	**Balloon-expandable Synergy™ + POT**	**Self-apposing Xposition S™**
After stent implantation in thrombus burden			
Mother vessel			
D_{mean} [mm]	4.07 ± 0.08	4.20 ± 0.04†	4.15 ± 0.10
D_{stent} [mm]	3.32 ± 0.09	4.17 ± 0.09†‡	4.06 ± 0.07†
Stent area [mm^2]	8.68 ± 0.47	13.66 ± 0.57†	12.95 ± 0.45†
Stent-artery ratio	0.82 ± 0.02	1.01 ± 0.03†	0.99 ± 0.03†
Main branch			
D_{mean} [mm]	3.37 ± 0.07	3.40 ± 0.09	3.34 ± 0.09
Stent area [mm^2]	8.90 ± 0.36	9.08 ± 0.49	8.80 ± 0.49
Stent-artery ratio	1.06 ± 0.03	1.08 ± 0.02	1.06 ± 0.02
Embolized thrombus mass [mg]	5.93 ± 4.32	7.01 ± 4.32	5.05 ± 4.56
Total thrombus trapping [%]	18.8 ± 5.8	6.2 ± 2.1†‡	10.3 ± 3.3†
Thrombus trapping MB	13.8 ± 4.4	6.8 ± 1.9†	8.9 ± 2.9†
Thrombus trapping MoV	19.6 ± 6.6	6.1 ± 2.2†‡	10.7 ± 4.6†
After complete thrombolysis			
Mother vessel			
D_{mean} [mm]	4.05 ± 0.09	4.20 ± 0.07†	4.25 ± 0.11†*
D_{stent} [mm]	3.36 ± 0.09	4.20 ± 0.09†	4.25 ± 0.11†*
Stent area [mm^2]	8.87 ± 0.47	13.85 ± 0.54†	14.20 ± 0.73†*
Stent-artery ratio	0.83 ± 0.03	1.02 ± 0.02†	1.03 ± 0.02†*
Main branch			
D_{mean} [mm]	3.34 ± 0.07	3.35 ± 0.08	3.42 ± 0.06†
Stent area [mm^2]	8.80 ± 0.48	8.84 ± 0.42	9.16 ± 0.23
Stent-artery ratio	1.06 ± 0.03	1.07 ± 0.03	1.07 ± 0.02
Global malapposition [%]	74.0 ± 7.6	1.3 ± 1.3†	0.4 ± 0.6†

Values are expressed as mean ± standard deviation; *$p < 0.05$ vs. before thrombolysis; $^{\dagger}p < 0.05$ vs. balloon-expandable stent alone; $^{\ddagger}p < 0.05$ vs. self-apposing stent; D — diameter, MB — main branch

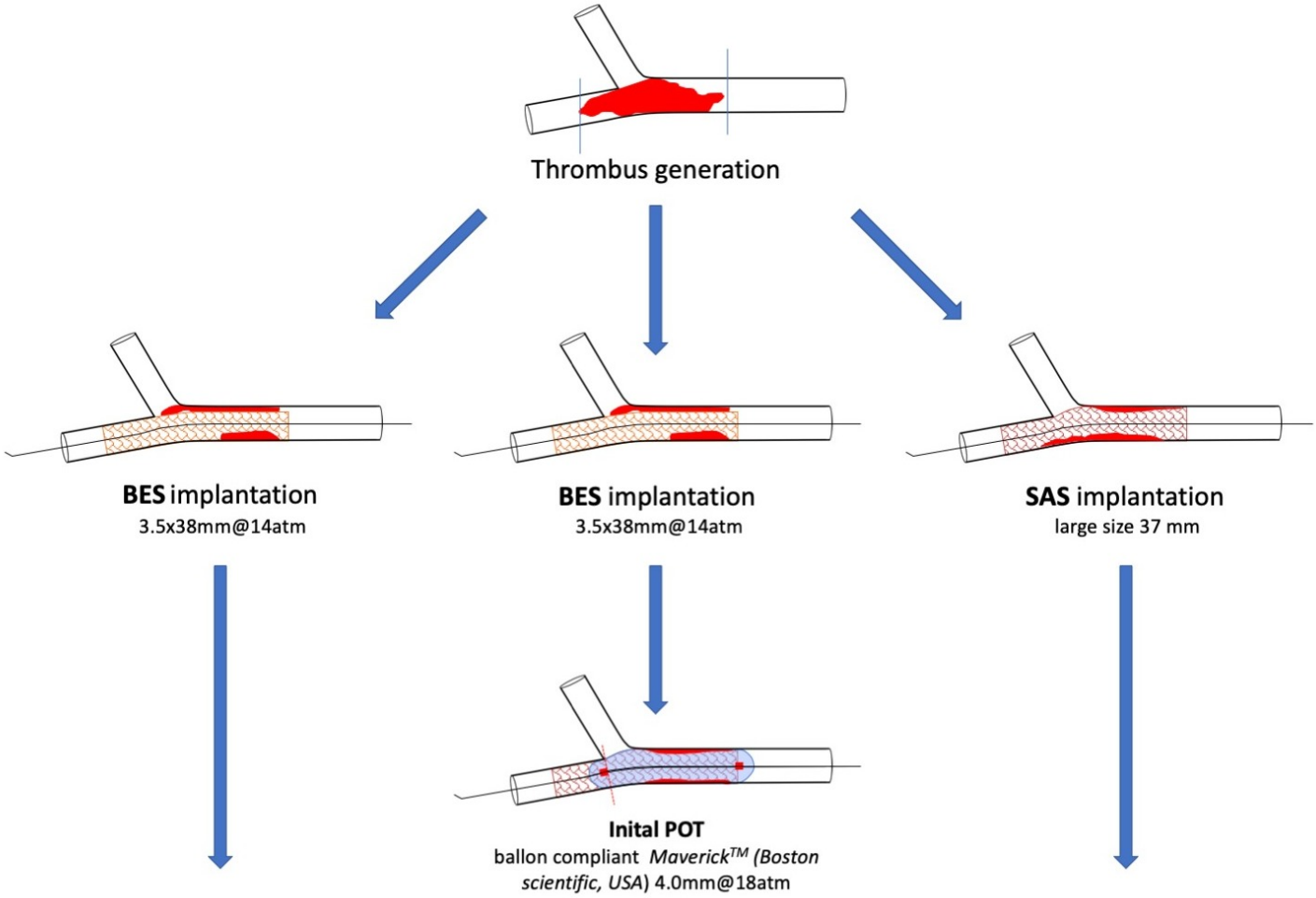
Figure 1. Study protocol; POT — proximal optimization technique.

Figure 2. Bench experimentation; **A.** Thrombus before stent implantation; **B.** Residual thrombus after washing; **C.** Thrombus trapped in sieve.

Figure 3. Quantification of trapped thrombus by computational planimetry by OCT. Cross-sections were taken at each millimeter of the stent; A1 — thrombus area; A2 — complete lumen area.

Figure 4. OCT acquisitions after provisional stenting in thrombus burden then after thrombolysis. Yellow arrows show thrombus, green arrows show malapposed struts; POT — proximal optimization technique.

Figure 5. Main results after balloon-expandable and self-apposing stent provisional stenting in thrombus burden (n = 10/group); *$p < 0.05$ vs. balloon-expandable stent implantation alone; $^{\dagger}p < 0.05$ vs. balloon-expandable stent implantation plus proximal optimization technique (POT).



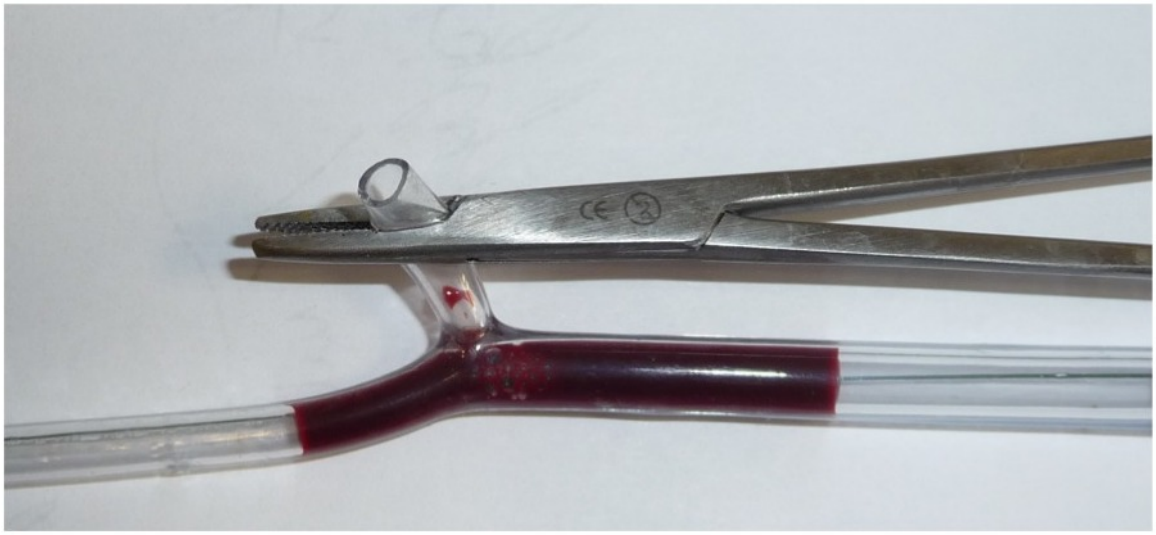
Washing with physiological serum

2D-OCT acquisition

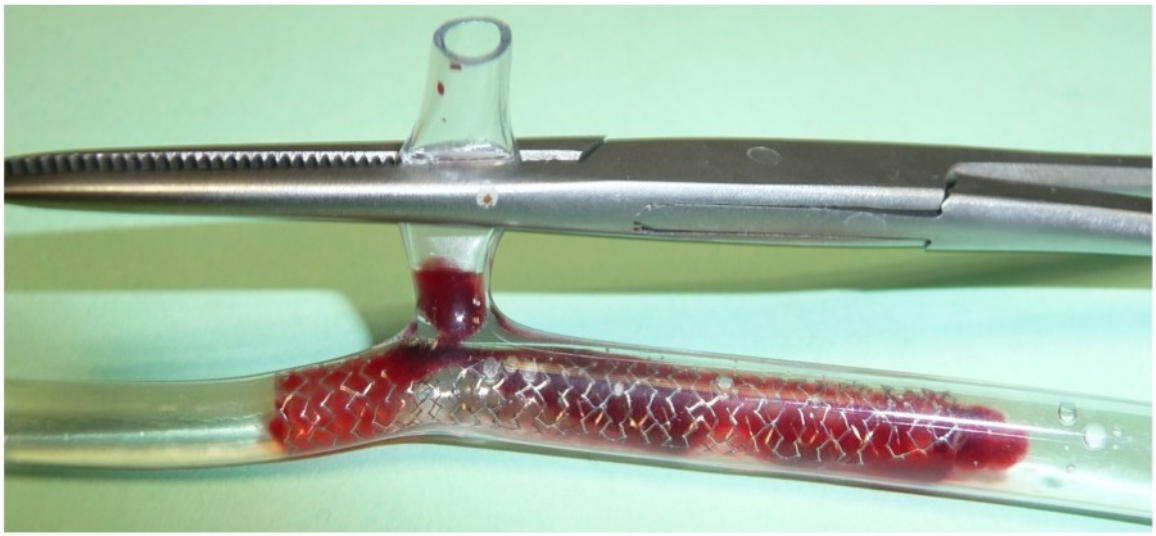
Pharmacological thrombolysis during 24h

2D-OCT acquisition

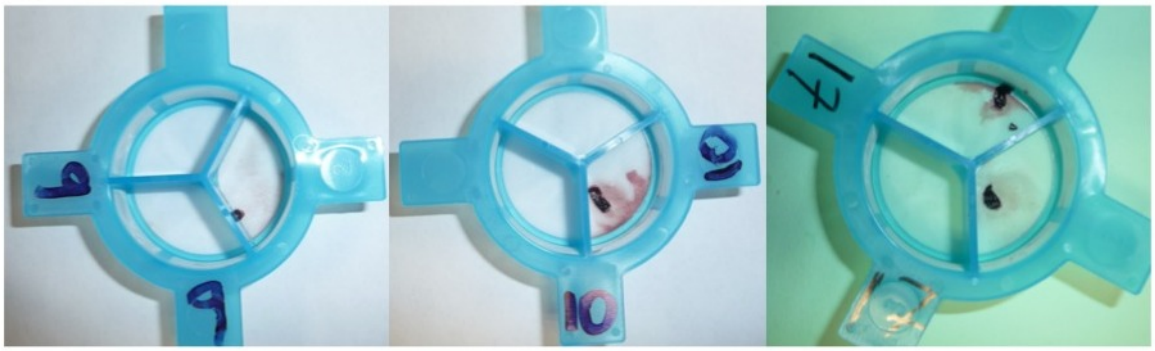
A



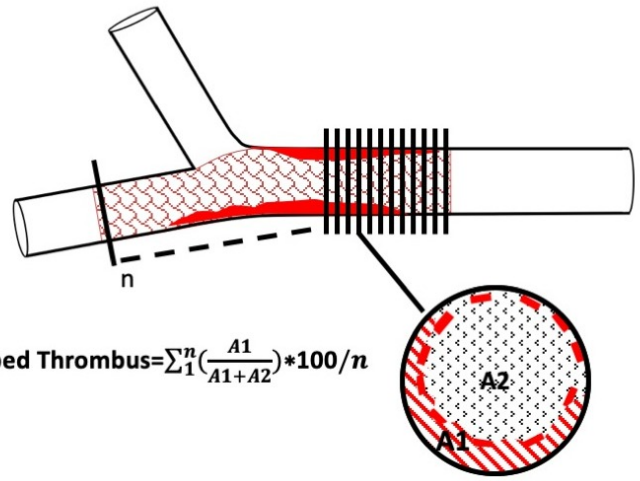
B



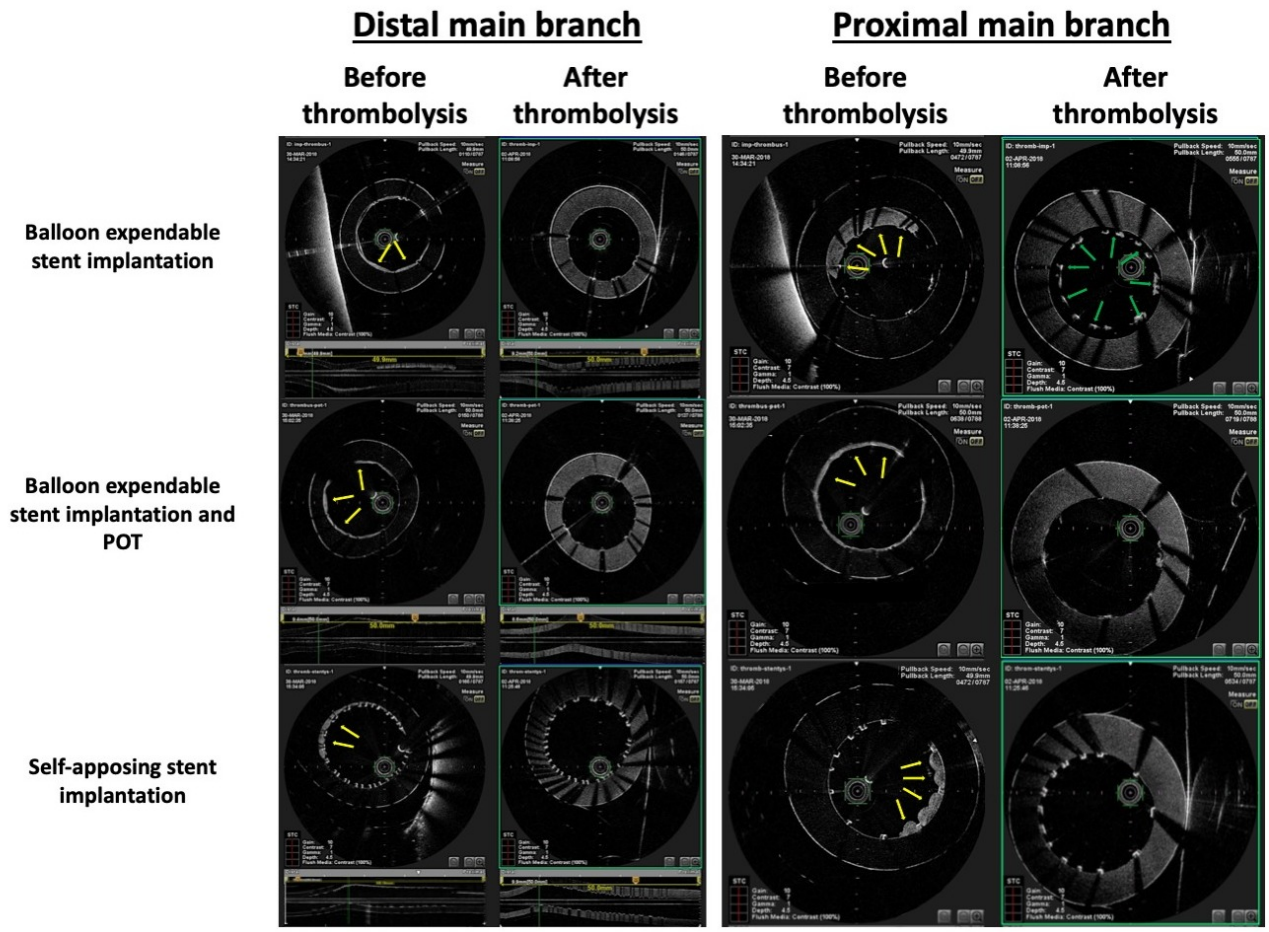
C

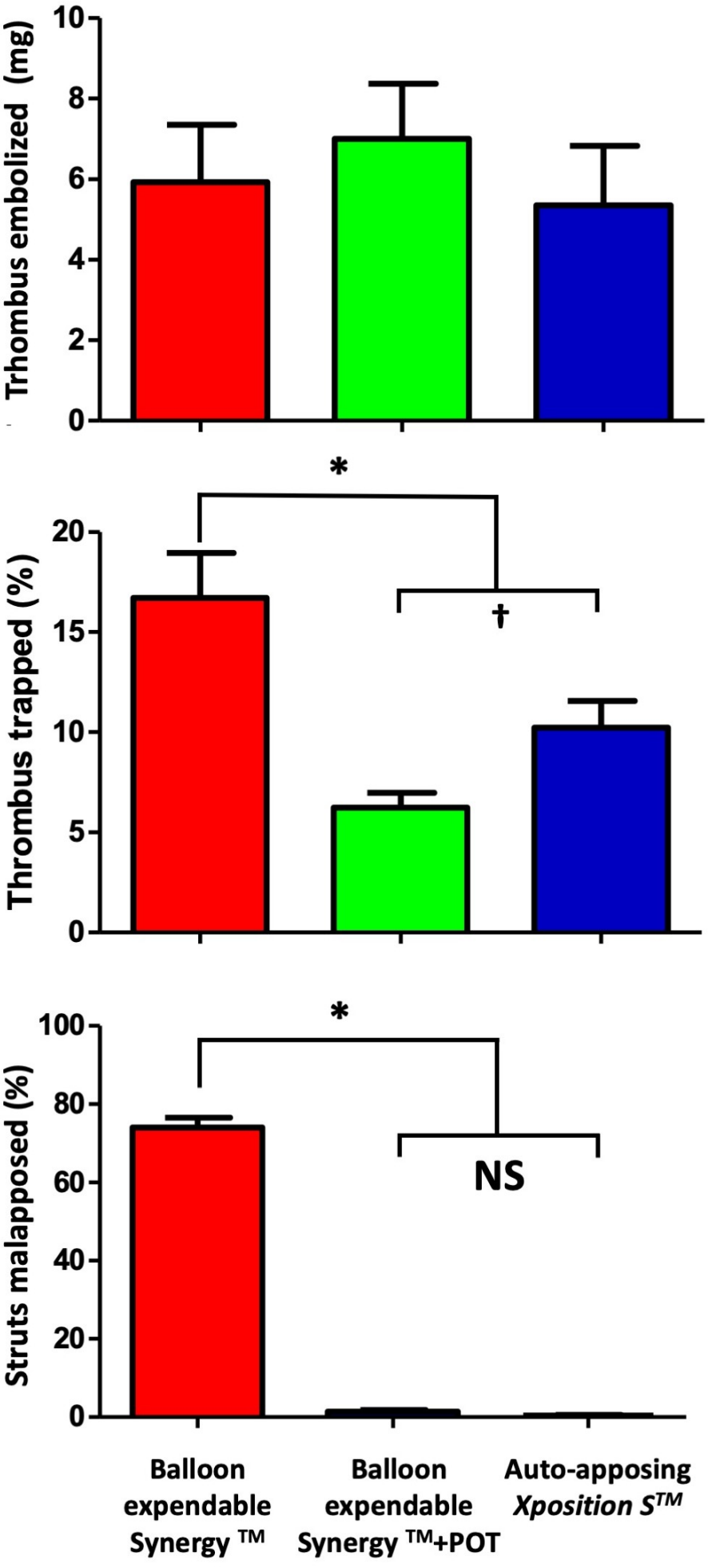


Thrombus=2.21mg Thrombus=5.64mg Thrombus=8.12mg



$$\%\text{Trapped Thrombus}=\sum_1^n\left(\frac{A1}{A1+A2}\right)*100/n$$


Distal main branch
Proximal main branch
Before thrombolysis
After thrombolysis
Before thrombolysis
After thrombolysis
Balloon expendable stent implantation
Balloon expendable stent implantation and POT
Self-apposing stent implantation


Trhombus embolized (mg)
10
8
6
4
2
0
*
Thrombus trapped (%)
20
15
10
5
0
†
Struts malapposed (%)
100
80
60
40
20
0
*
NS
Balloon expendable Synergy ™
Balloon expendable Synergy ™+POT
Auto-apposing Xposition S™