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Influence of Stent Expansion States on Platelet Deposition in an Extracorporeal Porcine Arteriovenous Shunt Model Using a Multichannel Perfusion Chamber

Limited data are available about incomplete stent expansion (SE) on platelet deposition (PD). We examined PD following different SE using an extracorporeal porcine arteriovenous shunt model to which a perfusion chamber with four parallel silastic tubes were connected. Blood flow was set at a 20 and 100 mL/min in 1.8 and 3.1 mm diameter tubes, respectively. P154 stents were deployed completely (Group A, n=15) or incompletely (Group B, n=15) in 1.8 mm (n=13) and 3.1 mm (n=17) tubes. ^{51}Cr-labelled platelet autologous blood was injected 1 hr before the perfusion. After 15 min-perfusion, the testing tubes were assessed for radioactivity counts. In-stent cross sectional area was measured by intravascular ultrasound. There was a significant difference in PD between group A and B regardless of channel size (118±18.4 vs 261.4±52.1 plts $\times 10^6/cm^2$, $p<0.05$). With adjusted shear rate and similar stenosis, PD was similar in both tubes. In smaller 1.8 mm tubes, a stenosis as subtle as 10% was associated with a significant PD difference (226.1±20 vs 112.9±20.5 plts $\times 10^6/cm^2$, $p<0.005$). This model enabled a repetitive, simultaneous comparison of PD following different SE states. It seems that the quality of SE remains crucial in smaller channels.

Key Words: *Blood Platelets; Stents; Porcine Model; Perfusion Chamber*

Taehoon Ahn, Eakkyun Shin, Yahye Merhi*, Pierre Thai*, Luc Bilodeau*

Department of Internal Medicine, Gachon University Hospital, Inchon, Korea
Montreal Heart Institute and University of Montreal*, Montreal, Quebec, Canada

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Address for correspondence
Taehoon Ahn, M.D.
Department of Internal Medicine, Gachon University Hospital, 1198, Kuwol-dong, Namdong-gu, Inchon 405-220, Korea
Tel: +82.32-460-3869, Fax: +82.32-460-3117
E-mail: Ahnth@ghil.com

INTRODUCTION

Acute stent thrombosis occurs within minutes to hours after the stenting procedure and is commonly due to incomplete stent expansion (SE) and/or vessel dissection (1). Recently, the incidence of thrombus appears to have been greatly diminished by technical modifications through the optimization of the stent deployment techniques and advanced antiplatelet therapy. With routine high pressure balloon expansion and use of new antiplatelet drugs, acute thrombosis is rare, occurring in less than 1% of stent procedures (2).

However, some particular conditions are still potentially associated with stent thrombosis, namely, stenting small diameter vessels (<2.0 mm) in which higher shear rate activates platelets, inadequate SE, in- and outflow obstructions and edge dissections. Coronary stenting has initially been restricted to vessels with a diameter ≥3.0 mm because of the increased risk of thrombotic occlusion in smaller vessels (3). According to previous observational studies (4, 5), stent thrombosis rate of 9.5% has been reported for vessels of 2.5 mm diameter, and rate as high as 25% for vessels with 2.0 mm diameter.

Now, very limited intravascular ultrasound (IVUS) guided criteria may allow the operator to optimize stent placement in smaller reference lumen to avoid stent thrombosis (6). In vivo animal studies using stents do not serve as an adequate model since stent placement is rarely associated with acute closure. Ex vivo arteriovenous (AV) shunt model closely simulates in vivo arterial thrombus formation and has been widely accepted for acute stent experimental model for the evaluation of platelet responses to vascular injury or thrombogenic materials, mechanism of thrombosis and therapeutic strategies (7-10).

Incomplete SE can result in acute or subacute stent thrombosis (11, 12). Limited data are available on platelet deposition (PD) and thrombus formation with incomplete SE (13, 14).

We examined the platelet activation with different SE states in different tubes mimicking small- and medium-sized coronary arteries using a multichannel perfusion

chamber connected to an ex vivo porcine AV shunt model. This shunt model serves to recreate the coronary interventional milieu with silastic channels in which stents are implanted. Using a porcine model, blood passes through these stents and platelets are labeled in order to quantify PD in each channel.

MATERIALS AND METHODS

Animal preparation

The animals studied were five male domestic pigs (mean weight, 32±2 kg), prepared according to the Canadian Counsil on Animal Care Regulation. Anesthesia was induced by an intramuscular injection of 200 mg Ketamine (Rogarsetic, Roger/STB Inc., Montreal, Quebec, Canada) and 100 mg azaperone (Strensil, Janssen Pharmaceuticals, Mississanga, Ontario, Canada). The pigs were intubated, and 0.5% halothane (Fluothane, Ayerest, Montreal, Quebec, Canada) was used to maintain the anesthetic state.

Left femoral artery and right femoral vein were canulated with 8F introducer sheath to establish an extracorporeal AV circuit with silicon tubes. Heparin was given 50 U/kg initially with additional 25 U/kg boluses hourly to prevent clotting on the catheters and stasis thrombosis on an extracorporeal AV circuit. Activated clotting time (ACT) was not checked consistently before the experiments. No antiplatelet agents were administered. Arterial blood pressure and ECG were continuously monitored. Mean blood pressure was maintained at 90 mmHg by adjustment of the depth of anesthesia and volume expansion with intravenous infusion of normal saline.

Isolation and labeling of platelets

On the day of experiment, 100 mL of autologous blood anticoagulated with acid-citrate-dextrose (ACD) was used to obtain a platelet-rich plasma by differential centrifugation, as described previously (16, 17). This platelet suspension was incubated with 300 μCi ^{51}Cr (Merck Frosst Canada Inc.) for 40 min. The suspension was then centrifuged to remove unbound ^{51}Cr, and the radiolabeled platelets were resuspended in plasma and reinjected into the animal one hour before the perfusion experiments. The labeling efficiency with ^{51}Cr averaged 51.4±2.4%, and a mean of 155±8 μCi ^{51}Cr was injected.

Experimental protocol with a perfusion chamber

The specially designed acrylic perfusion chamber (Fig. 1), in which four holes were located on each side, was connected via silicon tubes between the arterial and the venous circuits. Four parallel testing silastic tubes (3.5 cm long) were connected through Y connector to each

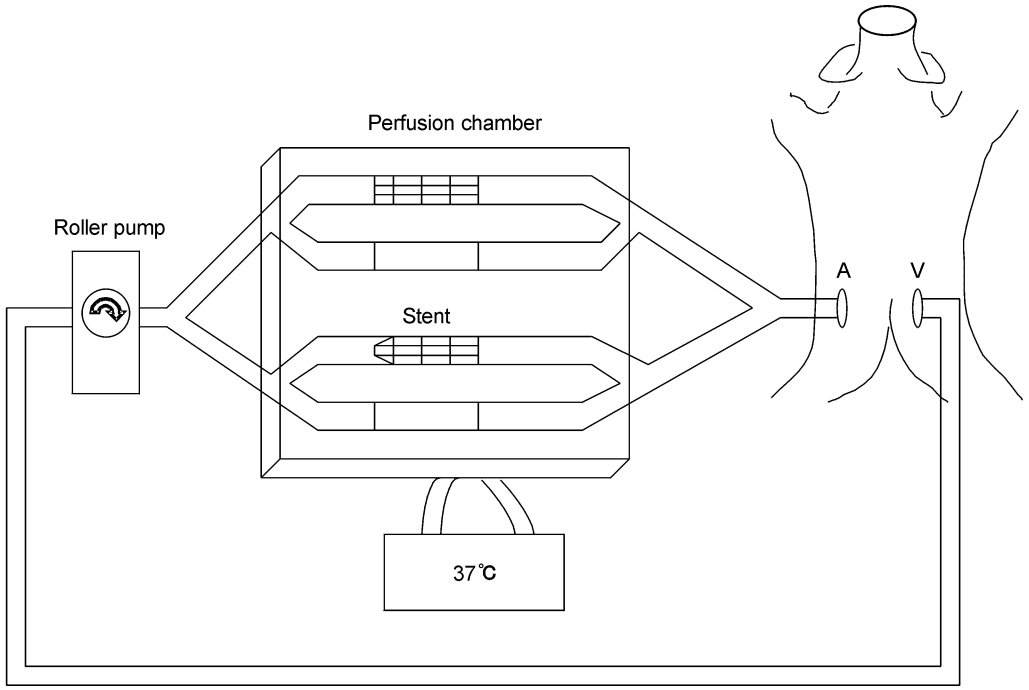

Fig. 1. Schematic illustration of the porcine extracorporeal arteriovenous shunt with a multichannel perfusion chamber. A, femoral artery; V, femoral vein.

circuit. In these experiments, arterial blood from the left femoral artery was circulated through the perfusion chamber for 15 min at a flow of 20 mL per min in 1.8 mm channels and 100 mL per min in 3.1 mm channels with the assistance of a peristaltic pump and then re-circulated back into the animal through the right femoral vein. These flow system generated a wall shear rates of 146/sec and 143/sec at the testing tube surfaces in the 1.8 mm and 3.1 mm tubes, respectively. The shear rates were calculated according to the flow formula of homogenous Newtonian fluid in a cylindrical tube: shear rate=$32\ Q/\pi D^2$, where Q is flow and D is diameter (15). During each perfusion, four parallel tubing systems were used at the same time and under the same test conditions. At the completion of each perfusion period, normal saline was circulated through the perfusion chamber for 30 sec to return unattached cells and blood to the femoral vein. After tubing segments were removed from the circuit of the perfusion chamber, the perfusion chamber and extracorporeal system were perfused with normal saline to clear any visible blood before insertion of another testing tube systems.

Stents

30 Palmaz P154 stainless steel stents (Cordis, Johnson & Johnson Interventional Systems, Warren, NJ, U.S.A.) were used for the perfusion studies. These stents are 15 mm long without articulation and may provide greater radial compressive strength than the most commonly used coronary articulated coronary Palmaz-Schatz stent (PS-153). They are also made for large vessels. Stents were hand crimped on a deflated balloon of a conventional semi-compliant 3.0 mm coronary angioplasty balloon catheter. The stents were then inserted into the allocated testing silastic tubes and deployed at 12 atm before perfusion initiation. The stents were deployed completely (Group A, n=15) or incompletely (Group B, n=15) in two or three silastic channels and remaining channel(s) as control(s). Thirteen stents were used in 1.8 mm channels and 17 stents were used in 3.1 mm channels. Incomplete expansion of stents deployed was created manually by external compression of the distal portion of the stent.

Quantification of platelet deposition

After each 15 min perfusion, tubing segments containing stents were cut at both distal ends and fixed overnight in 4% paraformaldehyde solution. The amount of platelet deposited on the tubes was quantified by counting the specific ^{51}Cr radioactivity. The radioactvities of reference blood samples were quantified using a gamma counter (Minaxi 5000, Packard Instruments Co.). Platelet deposition ($\times 10^6/cm^2$) on the tubes, was calculated as previously described (16, 17), knowing blood platelet count and the radioactivity in blood and on testing tubes.

Measurements of in-stent cross-sectional area by intravascular ultrasound

After radioactivity quantification, the maximum and minimum in-stent cross-sectional area (CSA) were measured by a 3.5F, 20 MHz Vision® Five-64F/X Endosonic ultrasound catheter (Rancho Cordova, CA, U.S.A.) for each stented channels. The portions of the stent with the largest and smallest area were selected for measurements for each pass of the IVUS catheter. % CSA stenosis was calculated as follows:

(maximum CSA−minimum CSA)×100 / maximum CSA

Statistics

All data were expressed as mean±SEM. An one-way analysis of variance (ANOVA) was performed to determine significant differences among the expansion states of the stent (fully expanded or incompletely expanded vs control). If the significant F (i.e., $p<0.05$) ratio was found, inter-group comparisons were made using Bonferroni t-test. For the different-sized tubes and subgroup analysis, unpaired t-test was performed for comparisons of the data. A value $p<0.05$ was considered significant.

RESULTS

Comparison of platelet deposition according to stent expansion states

A total of twelve 15-min-perfusion studies were performed for the evaluation of different stent expansion states on PD in five pig extracorporeal AV shunt model (Fig. 2). Platelet deposition in groups with SE, completely or incompletely (Group A and B) was increased when compared to that in control tubes without stent (189.7±30.8 vs 11.5±6.3 platelets$\times 10^6/cm^2$, $p<0.0001$). There was a statistical difference in PD between Group A and Group B (118±18.4 and 261.4±52.1 platelets$\times 10^6/cm^2$ respectively, $p<0.05$) regardless of perfusion channel size.

Effects of in-stent % CSA stenosis and shear rate on platelet deposition in 1.8 mm versus 3.1 mm perfusion channels

Thirteen stents in 1.8 mm perfusion channels were compared to 17 stents in 3.1 mm perfusion channels in

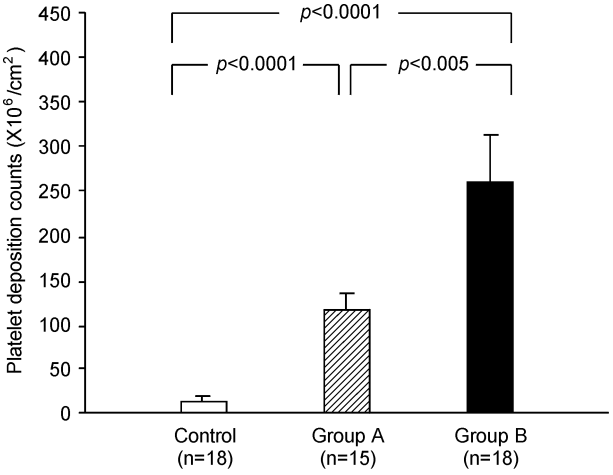

Fig. 2. Comparison of platelet deposition following stent expansion states: 15 mm P154 stents were deployed with complete expansion (Group A, n=15) and incomplete expansion (Group B, n=15) during 15 min of extracorporeal chamber perfusion.

regards to in-stent % CSA stenosis, local wall shear rate, and PD (Fig. 3). In 1.8 mm perfusion channels, in-stent % CSA stenosis and shear rate were 16.6±2.5% and 262 ±16/sec, respectively. In 3.1 mm perfusion channels, in-stent % CSA stenosis and shear rate were 23.2±2.6% and 309±20/sec, respectively, which were not statistically different with those in 1.8 mm tubes. With adjusted shear rate and similar in-stent CSA stenosis, stent PD was similar in 1.8 and 3.1 mm tubes (183.6±21.2 vs 195.1±51.3 platelets×10^6/cm^2, p=ns).

Platelet deposition according to in-stent cross-sectional area measured by intravascular ultrasound

Thirteen P154 stents were deployed in 1.8 mm tubes. Fig. 4 showed PD of stents with various stenoses in 1.8 mm tubes according to in-stent % CSA stenoses. Around 10% in-stent CSA stenosis was selected as a cut-off level to differentiate the degree of PD (left). A group with more than 10% in-stent CSA stenosis (n=8) as defined by IVUS was associated with a significant increase in PD compared to a group with less than 10% CSA stenosis (n=5) (226.1±20 vs 112.9±20.5 platelets×10^6/cm^2, p<0.005) (right).

Seventeen P154 stents were deployed in 3.1 mm tubes. Fig. 5 showed PD of stents with various stenoses in 3.1 mm tubes according to in-stent % CSA stenoses. Around 30% in-stent CSA stenosis was selected as a cut-off level to differentiate the degree of PD (left). A group with more than 30% in-stent CSA stenosis (n=5) was associated with a significant increase in PD compared to a group with less than 30% CSA stenosis (n=12) (428.3±117.7 vs 93.8±19 platelets×10^6/cm^2, p<0.0001) (right).

DISCUSSION

This porcine model using a multichannel perfusion chamber connected to an extracorporeal AV shunt enables a repetitive, simultaneous comparison of PD in different SE states. This study demonstrated that stented segments revealed increased PD compared to control tubes without stent. Incomplete SE showed more PD than complete SE regardless of the tube sizes.

The use of stents has initially been restricted to vessels with a reference diameter ≥3.0 mm to avoid thrombotic occlusions in smaller vessels (3). According to a substudy of the Benestent trial, the risk of subacute stent thrombosis when stents were deployed in small arteries was

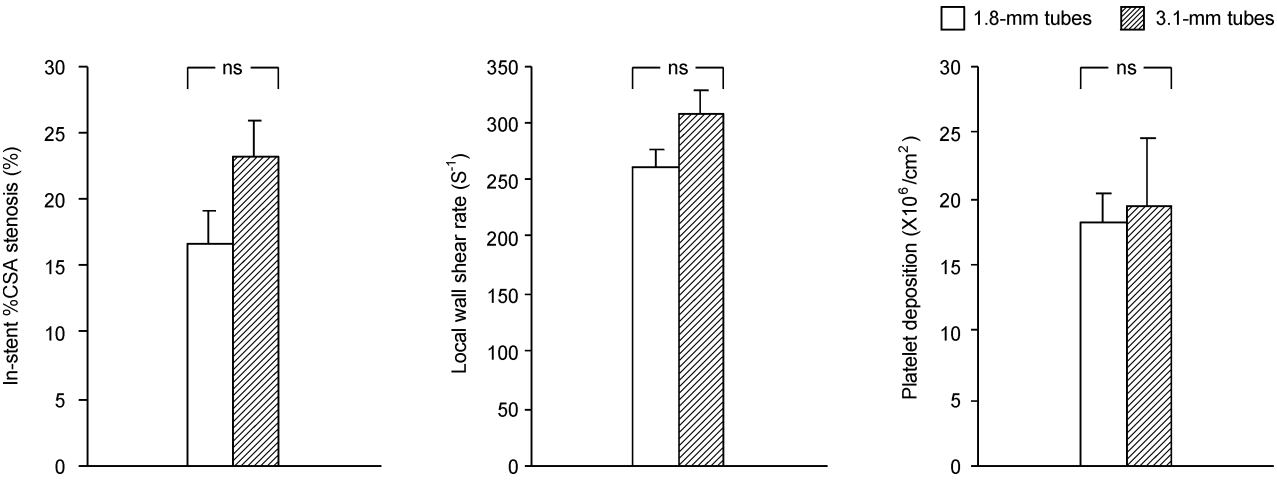

Fig. 3. Comparison of in-stent percent cross-sectional area (% CSA) stenosis, local wall shear rate and platelet deposition between 13 stents in 1.8 mm tubes (open bars) and 17 stents in 3.1 mm tubes (shadowed bars). ns, not significant.

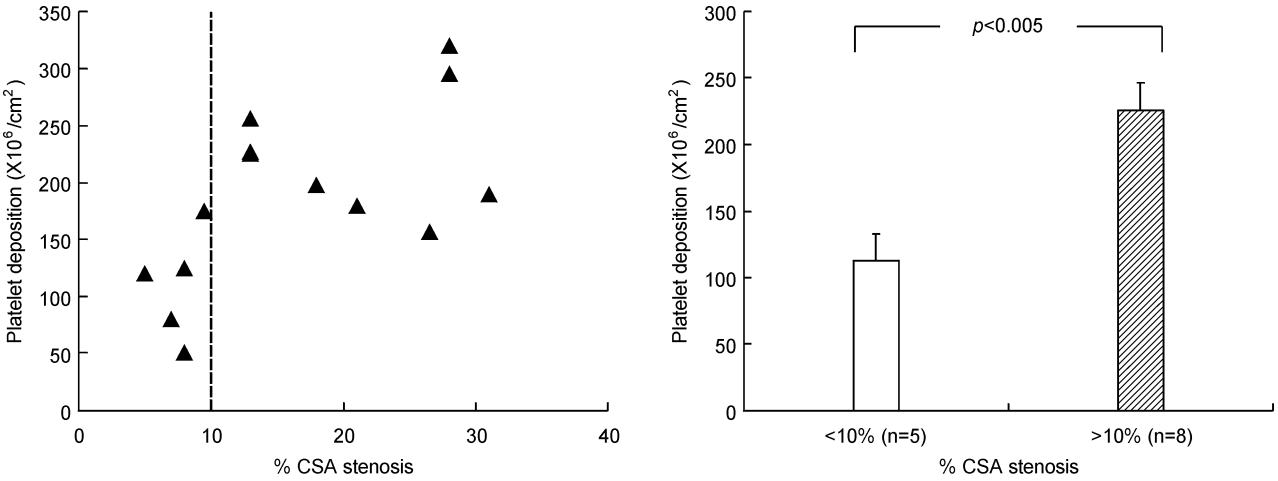

Fig. 4. Platelet deposition according to in-stent cross-sectional area (CSA) measured by intravascular ultrasound (IVUS) in 1.8 mm channels **(left)**. Thirteen stents showed platelet depositions following their % CSA stenoses **(right)**. Two groups defined by IVUS criteria of 10% CSA stenosis revealed a difference in platelet deposition.

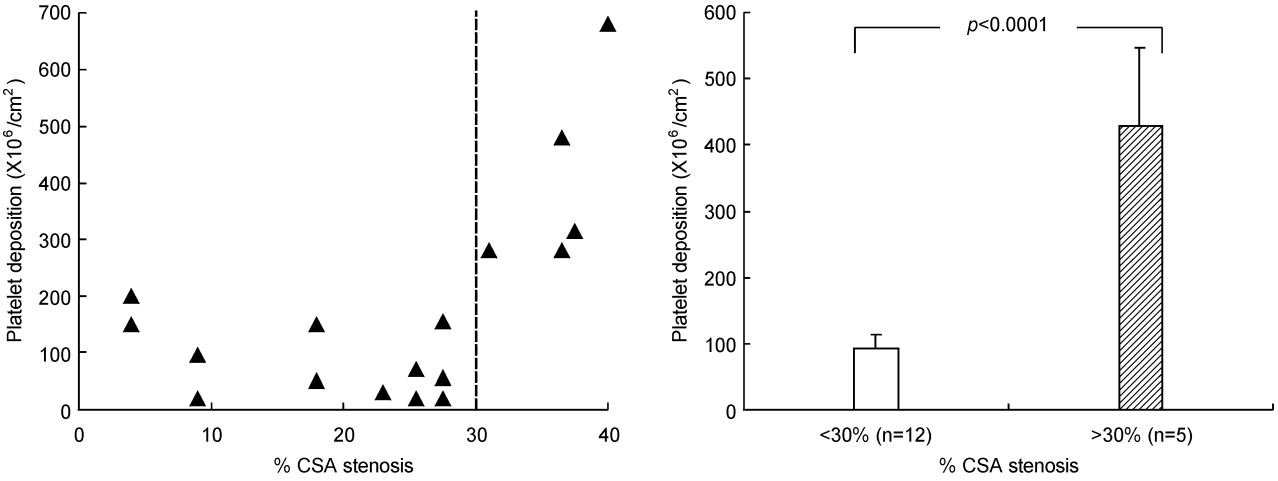

Fig. 5. Platelet deposition according to in-stent cross-sectional area (CSA) measured by intravascular ultrasound (IVUS) in 3.1 mm channels **(left)**. Seventeen stents showed platelet depositions following their % CSA stenoses **(right)**. Two groups defined by IVUS criteria of 30% CSA stenosis revealed a difference in platelet deposition.

6.9% compared to 0.9% for vessels >3.0 mm in diameter (18). Despite improved implantation techniques and advanced antiplatelet drugs, vessel size <3.0 mm remains an important predictor of stent thrombosis, likely a result of relatively more metal per lumen area and increased shear rates in smaller vessels (19, 20).

Recently, preliminary trials of stenting in small coronary arteries <3.0 mm in size were reported with a low incidence of stent thrombosis in a limited number of patients (21-23). Modern stent design, antithrombotic regimen, and accumulated operator's experiences have improved the results of stenting in small vessels. However, limited data are available on the efficacy of intracoronary stenting in smaller (<2.0-2.5 mm) vessels (4, 5).

All current available stents are made of metal and are thrombogenic in a varying degree. Coronary stenting produced a more remarkable platelet activation than balloon angioplasty (24). The use of a metal prosthetic device may lead to focal mural thrombus inside the stent (10). In addition, deeper arterial trauma with high pressure inflation provokes greater thrombotic response (25). Stenting also activates expression of the glycoprotein IIb/IIIa receptor on the platelet surface (26).

IVUS has played an essential role in developing an optimal strategy for stent deployment. IVUS criteria according to the AVID (Angiography Versus Intravascular ultrasound-Directed stent placement) (27) and MUSIC (Multicenter Ultrasound Stenting In Coronaries) (28) trials were based on adequate in-stent lumen area compared to distal reference vessel (or combination of proximal and distal reference vessels), full stent apposition on the vessel wall and the absence of significant dissection.

Stent geometry or eccentricity (minor/major axis) have not been affected by high pressure inflations. In spite of an optimal angiographic results, incomplete apposition of the stent struts to the vessel wall, narrowing of residual lumen, irregular and eccentric lumen in the stented segment were demonstrated by IVUS in 88% of cases (29). Moussa et al. (30) reported that subacute stent thrombosis was absent in very large final stent minimum lumen cross-sectional area (MLCSA) of ≥ 9 mm^2 and 0.5% when strict criteria of SE (MLCSA $\geq 90\%$ of average lumen CSA) among five empirical IVUS criteria proposed. By the POST registry (31), IVUS predictors of stent thrombosis were malapposition (64%), underexpansion (53%), plaque protrusion (27%), thrombus (23%), and edge tears (23%). Most IVUS criteria defined are based on studies done in vessels >3.0 mm in diameter. For the smaller vessels (<7.5 mm^2 area), criteria of >100% in-stent minimum luminal area to distal reference CSA was selected to decrease the risk of partial outflow obstruction (6). Even in small vessels <3.0 mm, absolute intrastent lumen area was reported as the most important determinant of target vessel revascularization (32).

Incomplete expansion of coronary stent can result in acute or subacute stent thrombosis despite better pharmacologic antiplatelet drugs (11, 12). Limited data were available on the effect of incomplete SE on platelet activation. Kocsis et al. (13) assessed the in vitro effect of incomplete expansion of stents and the effect of heparin coating in poorly deployed stents in 3.0 mm polyurethane tubes using a mechanical crimping device. In another study using the baboon AV shunt model (14), Palmaz-Schatz PS-153 stents were deployed in 3.2 mm silicon tubes with 25% and 50% stent constriction using a mechanical crimping device. Both studies showed that heparin coating reduced platelet adhesion in incompletely deployed stents. However, the inner diameter of the tubes used in these studies was >3.0 mm. The aim of our study was the assessment of effect of the SE states on PD in tubes of small diameter (<2.0 mm, inner diameter) and >3.0 mm diameter. More than 30% in-stent CSA stenosis was associated with a significant difference in PD in 3.1 mm tubes mimicking medium-sized coronary arteries. In smaller 1.8 mm tubes, an in-stent CSA stenosis as subtle as 10% was associated with a significant difference in PD. It seems that the quality of SE remains crucial in smaller channels. This may promote IVUS as a mandatory tool for optimization of stent implantation in stenting smaller vessels.

Ex vivo arteriovenous shunt model closely simulates in vivo arterial thrombus formation and has been widely accepted for studies in experimental animals for the evaluation of thrombotic materials and therapeutic strategies. We applied an in vitro perfusion chamber described by Beythein et al. (33), connected to the extracorporeal porcine AV shunt model. This extracorporeal perfusion chamber system has been used to study mechanisms and treatment of vascular thrombus formation in experimental animals. Cylindrical perfusion chambers that mimic vessel geometry have been used widely in baboon and pig AV shunt models (7-10, 34). Blood flow and shear rate are controlled by either a roller pump or a clamp placed distal to the thrombogenic device. The roller pump induced platelet activation and additional activation was developed probably by the stent surface and whirling between the meshes (33). With a simple tubular device of 2 to 4 mm inner diameter, blood flow rates from 20 to 240 mL/min yielded wall shear rates in the range of 100 to 2120/sec. The wall shear rate increases as the vessel diameter decreases: 100-1000/sec in large- to medium-sized arteries and 1500/sec in arterioles (35). Exposed local surface (stent and injured vascular vessel), rheology (local shear), and systemic thrombotic status were reported to interplay to affect stent thrombosis (36). In a porcine extracorporeal AV shunt model for 20 min perfusion, it has been demonstrated that acute thrombus formation is enhanced in conditions of higher shear rates and is affected by metal surface characteristics (37). In our study, with adjusted shear rate and similar CSA stenosis, stents in different tubes did promote similar PD under perfusion time of 15 min. Benis et al. (38) found the dry weight of thrombus accumulated in the plastic perfusion chamber increased with exposure time up to 20 min and decreased with increasing flow rate. Friedman et al. (39) reported the number of platelets per unit area adhering to a foreign surface sometimes decreased with exposure time greater than 30 min. In our study, 15 min of perfusion had been chosen as optimal interval to demonstrate the PD prior to thrombus formation according to our previous experiments (unpublished data). The multichannel perfusion chamber used in our study was able to compare the platelet adhesion to stent surfaces, simultaneously and repetitively in the same experiment.

The extracorporeal perfusion chamber model used in this study precludes the effect of vessel wall injury or underlying atherosclerotic stenosis with varying degree of plaques or thrombus on stent thrombosis. Previous studies have identified residual lesions and dissections after stent implantation as a major cause of subsequent early thrombotic events (40, 41). The effects of drugs (aspirin or ticlopidine) on stent thrombosis were excluded in this study. The shear rates generated in small tubes are much less than that of small vessels <2.0 mm. But this study emphasizes, under situation precluding high shear rate, the minimal change in in-stent lumen area may affect PD and probably acute stent thrombosis

especially in small vessels.

Concerning selection of the stents, large stents for vessels >3.0-4.0 mm were studied in small diameter tubes to compare the PD on stents. Because new designed stents for the small vessels are recently developed, these stents are impractical for the small vessels. In this study, stents with more metal surface to vessels and without articulation were selected to demonstrate enhanced and uniform PD on the testing tubes. A minimum of heparin was administered to prevent thrombosis in the extracorporeal AV circuit. Although ACT was not checked consistently in this study, available ACT data ranged 180-220 sec. Friedman et al. reported that the use of heparin in usual amounts (initial bolus of 10,000 U followed by continuous infusion of 5,000 U/hr) did not appear to affect the adhesion process (39).

In conclusion, this porcine model using a multichannel perfusion chamber connected to an extracorporeal AV shunt revealed the feasibility of repetitive and simultaneous comparative study of PD according to different SE states. Minimal changes as subtle as 10% in-stent cross-sectional area affected the PD on stents in small diameter tubes with diameter <2.0 mm. It seems that the quality of SE remains crucial in smaller channels. This suggest that IVUS might be a mandatory tool for optimization of stent implantation in stenting smaller vessels.

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