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Understanding the Mechanism of Drug Transfer and Retention of Drug-Coated Balloons

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Abstract

Objective: The purpose of this study was to determine the impact of varying inflation parameters on paclitaxel delivery and retention using a commercially available DCB.

Background: Drug-coated balloons (DCB) have become the standard treatment for peripheral artery disease. Clinical data suggest that varying DCB delivery parameters directly impact patient outcome. Differences in delivery parameters can potentially alter the retention of the drug coating on DCBs.

Methods: Harvested porcine carotid arteries were utilized in an *ex vivo* pulsatile flow bioreactor system. The DCBs were then deployed at a DCB-to-artery ratio of 1:1 or 1.25:1, an inflation time of 30 seconds or 1 minute and transit time of 30 seconds or 3 minutes. The amount of drug retention in arterial tissue was evaluated by pharmacokinetic analysis at 1 hour and 1 day post DCB deployment.

Results: Arterial paclitaxel levels were found to be less at an inflation ratio of 1:1 with 3-minute transit time as compared to 30 seconds of transit time at 1 hour (12.3 ± 1.6 ng/mg vs. 391 ± 139 ng/mg, $P = .036$). At 1-day, DCBs deployed at a ratio of 1:1 resulted in less drug retention as compared to 1.25:1 (61.3 ± 23.1 ng/mg vs. 404 ± 195 ng/mg, $P = .013$).

Conclusion: Arterial paclitaxel retention is reduced with extended transit times and sub-optimal expansion of the balloon. Optimization of delivery parameters can serve as an effective strategy to enhance clinical DCB outcomes.

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Author Contributions

Writing—original conceptualization: EVM, AL, and SKY; data acquisition, curation, and analysis: EVM, LS, AL, and MT; resources: SKY; writing—review and editing: EVM, LS, AL, MT, BWT, and SKY; supervision: SKY.

Declaration of Conflicting Interests

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Keywords

drug-coated balloon; pharmacokinetics; inflation parameters; *ex vivo* model; paclitaxel

Introduction

Peripheral arterial disease (PAD) impacts more than 200 million people globally each year.¹ PAD, which is characterized by cholesterol plaque buildup in the inner arterial wall, obstructs normal blood flow to distal tissue and organs and can potentially lead to gangrene, limb loss or death.² Endovascular intervention via percutaneous transluminal angioplasty (PTA) is the foundational method for PAD therapy and has remained as the standard treatment method for blood flow restoration.³ The major limitation of clinical success is the persistent post-procedural restenosis that oftentimes leads to necessary reintervention.⁴ Restenosis is the body's inflammatory response activated by PTA-induced injury to the vessel wall leading to vascular smooth muscle cellular proliferation, cellular migration and extracellular matrix production causing the re-narrowing of the lumen.⁵

Metallic stents, the gold standard in the treatment of coronary artery disease, were adopted for PAD to decrease restenosis rates and improve patency rates.⁶ However, the use of stents has shown limitations, leading to inconsistent outcomes, patient readmission, and repeat revascularization.⁷ Stents tend to fracture due to the severe biomechanical environment of peripheral arteries including compression, shortening, bending and twisting.^{8,9} Various approaches to improve PAD treatment have been developed as therapeutic alternatives to stents. More recently, drug-coated balloons (DCBs) have emerged as stent alternatives to locally deliver therapeutics to inhibit restenosis without the need of a permanent platform serving as a drug reservoir.¹⁰⁻¹⁴ Unlike drug-eluting stents which release their drugs over period of weeks to months, DCBs acutely transfer anti-proliferative drug over minutes by simple contact of the balloon surface to the luminal surface of the artery.¹⁵⁻¹⁷

Studies have shown that varying DCB delivery conditions impact drug transfer and retention and improving delivery conditions can lead to better clinical outcomes.^{12,18} To date, pre-clinical models have served as the primary process to evaluate and quantify DCB delivery outcomes.^{15,19-25} The objective of this study is to implement a bench-top system to optimize DCB drug transfer. Specifically, we investigated the impact of various transit time and balloon-to-artery ratios on acute drug transfer and retention in an *ex vivo* flow circuit using harvested porcine carotid arteries.

Methods and Materials

Ex Vivo Bioreactor System

Porcine common carotid arteries from large Yorkshire pigs (250-350 lbs.) were obtained from local and regional abattoirs. Vessels were then rinsed in saline and excess fat, connective tissue, and fascia removed from each artery and cut into approximately 8-cm segments. Arteries were stored in 15 mL falcon tubes at -20°C until needed.

To mimic cardiovascular flow conditions, an *ex vivo* bioreactor system was utilized that incorporated a computer-controlled gear pump and closed circuit hosted within a temperature-controlled incubator (Figure 1A). The end of each artery was connected to a luer fitting and assembled into our bioreactor housing. The space between the artery and the protective outer sleeve was then filled with tissue-simulating agent (Agarose, Thermo Fisher Scientific). To measure pressure within the flow circuit, a catheter-based pressure transducer (Millar Instruments, Houston, TX, USA) is positioned within the flow circuit. The volumetric flow rate was quantified using an ultrasonic flow meter (Transonic Systems Inc., Ithaca, NY, USA). The circulating medium consisted of Dulbecco's Modified Eagle's Medium containing low glucose (1000 mg/L), 4.0 mmol/L L-glutamine, 110 mg/L sodium pyruvate, pyridoxine hydrochloride, 10% fetal bovine (Gibco), and 1% antibiotic-antimycotic (Gibco).

Drug Delivery and Quantification of Paclitaxel Tissue Concentrations

Following bioreactor assembly, *ex vivo* arteries underwent endothelial denudation using an angioplasty balloon catheter. A commercially available DCB (Lutonix 035, BD, Franklin Lakes, NJ) was used to deliver paclitaxel into each vessel. The drug dosage of this DCB was 2 $\mu\text{g}/\text{mm}^2$ of paclitaxel. The DCBs were tracked over a guidewire to the target area. The transit time, the duration from insertion of DCB into the circulating flow until DCB inflation, was either 30 seconds or 3 minutes. The inflation pressures of the DCB were determined via cross-sectional ultrasound imaging in conjunction with manufacturer specifications to achieve balloon-to-artery ratios of 1:1 or 1.25:1. Balloons were inflated for either 30 seconds or 1 minute. The position of the treated arterial segments was marked on the outer sheath of the vessel housing compartment to record the specific region treated with paclitaxel. *Ex vivo* treated arteries (n = 4 per time point) were then harvested at 1 hour and 24 hours post-treatment for pharmacokinetic evaluation. The treated region, along with residual paclitaxel content on the balloons, were evaluated by a validated high-performance liquid chromatography (HPLC) electrospray Ionization-tandem, as previously described.^{20,22,26}

Statistical Analysis

All values were expressed as mean \pm standard deviation (SD). Continuous variables were compared between groups using one-way analysis of variance (ANOVA) using GraphPad Prism 9 (GraphPad Software, La Jolla, CA, USA). A value of $P < .05$ was considered statistically significant. If statistical significance was shown, comparison of quantitative data of multiple groups was performed by Tukey's multiple comparisons post hoc test.

Results

Figure 2 shows representative images of the harvested porcine carotid artery being treated by a DCB within the *ex vivo* bioreactor system (Figure 2A). The explanted vessels were pulsed for 1 hour or 24 hours within the *ex vivo* system, where they were subjected to physiological flow conditions. The flow consisted of a systolic pressure of 110 mmHg and a diastolic pressure of 80 mmHg (Figure 2B) with flow rates ranging from 45 to 56 mL/min (Figure 2C).

A total of 24 DCBs were deployed into our explanted porcine carotid arteries to evaluate arterial drug levels. All DCBs successfully transferred measurable paclitaxel levels from the balloon surface to the artery. At the 1-hour time point, 4 different groups were evaluated based on their transit time, inflation time and balloon-to-artery ratio (see Table 1). The results demonstrated a reduction in paclitaxel concentrations with transit time of 3 minutes versus 30 seconds (Group A: 12.3 ± 1.6 ng/mg vs. Group B: 20.7 ± 26.7 ng/mg vs. Group C: 391 ± 139 ng/mg vs. Group D: 450 ± 289 ng/mg, $P = .075$). Significant differences in paclitaxel concentrations were only observed between Group A and Group C (12.3 ± 1.6 ng/mg vs. 391 ± 139 ng/mg, $P = .036$), whereas others showed non-significant differences (Group B: 20.7 ± 26.7 ng/mg vs. Group C: 391 ± 139 ng/mg, $P = .06$). Paclitaxel levels were similar between Groups A and B (Group A: 12.3 ± 1.6 ng/mg vs. Group B: 20.7 ± 26.7 ng/mg, $P = .92$) along with Groups C and D (Group C: 391 ± 139 ng/mg vs. Group D: 450 ± 289 ng/mg, $P = .99$).

For the 24-hour time point, only Groups C and D were analyzed. The results demonstrated a significant reduction in paclitaxel concentrations in Group C as compared to Group D (1 day: Group C: 61.3 ± 23.1 ng/mg vs. Group D: 404 ± 195 ng/mg, $P = .013$) (Figure 3). Residual paclitaxel measurements on the balloon surface demonstrated that $93.8\% \pm 7.4\%$ and $94.7\% \pm 5.9\%$ of the drug was released from the balloons during the procedure for Group A and Group B, respectively. For Groups C and D, $91.9\% \pm 6.9\%$ and $89.1\% \pm 5.9\%$ of paclitaxel was released from the balloon. Overall, there were no differences among the groups ($P = .64$).

Discussion

This study was designed to determine the impact of varying delivery parameters on paclitaxel delivery and retention using a commercially available DCB. This was accomplished using an *ex vivo* system capable of rapidly evaluating arterial drug levels in isolated porcine carotid arteries. Four different groups were evaluated that differed in their transit time, inflation time and DCB-to-artery ratio. The results demonstrated increased arterial drug concentrations with shorter transit times and higher DCB-to-artery ratio. Overall, these results demonstrate a viable platform for the optimization of DCB to enhance drug transfer kinetics in an *ex vivo* setting.

Tissue pharmacokinetics have always been the focal aspect in the design of DCBs to ensure an effective drug transfer from balloon to the vessel wall.^{15,25,27} Typically, PK studies are performed *in vivo* using porcine peripheral models to determine temporal arterial drug levels.^{22,24,28,29} However, in this study, we performed delivery procedures with varying parameters to evaluate the uptake of drug using a validated *ex vivo* model.^{19,20,22,26,30,31} Transit time, a crucial procedural variable specific to DCB, was one of the variables evaluated. We selected to compare a transit time of 30 seconds versus 3 minutes as these are key time points identified by the manufacturer's procedural guidelines. Our results showed a decrease in drug uptake at a transit time of 180 seconds versus 30 seconds (Group B: 20.7 ± 26.7 ng/mg vs. Group C: 391 ± 139 ng/mg, $P = .06$).

The results of our *ex vivo* model supports previous *in vivo* studies showing significant drug loss of DCB coating in a prolonged aqueous environment. Schorn et al demonstrated a similar decrease in arterial drug levels with longer transit time using a porcine SFA model. Balloon deployment with a 30-second transit time and a 3-minute inflation time showed the highest drug concentration ($\sim 450 \pm 180$ ng/mg).¹⁸ Whereas balloon deployment with a 3-minute transit time and a 30-second inflation time showed the lowest drug concentration in tissue ($\sim 50 \pm 25$ ng/mg).¹⁸ Furthermore, the 30-second transit time was determined as a key procedural variable, identified by a post-hoc correlation of 12-month outcomes from the LEVANT 2 clinical study.^{18,32} Lee et al also demonstrated a critical time point of 25 seconds as a key attribute to success by reviewing and correlating clinical outcomes of 259 consecutive patients undergoing DCB treatment in the treatment of coronary artery disease.³³ It has been demonstrated that up to 6% of the total drug coating can be lost into the circuit during tracking of DCBs, and while that is a minimal percentage compared to the total amount, the aim to reduce that loss as much as possible remains relevant.^{25,28}

To gain better insight into the impact of the prolonged tracking time, we additionally analyzed the coating surface of a 30-second and a 3-minute hydrated DCB using scanning electron microscopy (SEM). The images demonstrated that at 30 seconds, the DCB coating was still intact and adhered to the balloon surface (Figure 4A and B). However, at 3 minutes, areas of bare balloon surface along with peeling of the DCB coating was visible (Figure 4C and D). Overall, these results reiterate the importance of short transit times, ensuring minimal drug loss from the DCB to the delivery site. It is worth noting that these SEM images represent surfaces of non-expanded DCBs. Loss of structural integrity of the 3-minute hydrated DCB coating will most likely be exaggerated during the expansion and may explain the lower drug uptake observed in arteries treated with longer transit time.

Appropriate balloon size selection has also been identified as another key procedural factor in the clinical outcomes of DCBs.^{13,18,34} In this study, we evaluated a DCB-to-artery ratio of 1:1 and 1.25:1, representing no overstretch of the artery and 25% overstretch of the artery during DCB expansion, respectively. It has been reported that a minimum of 4% of overstretch is needed for optimal drug delivery.¹⁸ Our results demonstrated no differences in drug transfer from the balloon surface to the arterial wall at 1 hour (Group C: 391 ± 139 ng/mg vs. Group D: 450 ± 289 ng/mg, $P = .99$). However, at 1 day, the retention of drug in the arteries treated at a DCB-to-artery ratio of 1.25:1 was significantly higher than DCB-artery-ratio of 1:1 (404 ± 195 ng/mg vs. 61.3 ± 23.1 ng/mg, $P = .013$). Thus, the mean drug loss in arteries treated with the DCB-artery-ratio of 1:1 was 84.3% from 1 hour to 1 day, whereas in arteries treated with a DCB-artery-ratio of 1.25:1, drug loss was 10.2%.

To better evaluate the impact of DCB-artery-ratio to retention, we evaluated the luminal surface of DCB-treated arteries within our *ex vivo* model. Specifically, we wanted to identify the region in which the drug coating could be visualized. SEM images demonstrated that the drug was mostly embedded and retained within grooves and gaps of the luminal surface (Figure 5A and B). This observation, as seen in Figure 5 could explain differences between drug retention in arteries treated with the DCB-artery-ratio of 1.25:1 as compared to 1:1. The overexpansion of the artery allows deeper penetration of the drug coating within grooves and cracks of the intimal layer, strengthening their adhesion to the luminal surface.

A more recent computational study also demonstrates the impact of elevated pressure during DCB deployment, leading to higher drug retention and deeper delivery of the drug.³⁵

A limitation of this study included the use of culture medium, rather than whole blood, as the working fluid in our *ex vivo* system. Additionally, the system utilized healthy carotid (non-diseased) arteries and physiological conditions mimicking below the knee tibial arteries. Lastly, this was a DCB-specific study and the data presented may not translate to other available DCBs.

Conclusion

Our *ex vivo* studies successfully demonstrated the impact of varying inflation parameters on paclitaxel delivery and retention using a commercially available DCB. Pharmacokinetic results showed an increase in arterial drug levels in arteries treated with shorter transit times and higher DCB-to-artery ratio. Optimization of delivery parameters can serve as an effective strategy to enhance clinical DCB outcomes.

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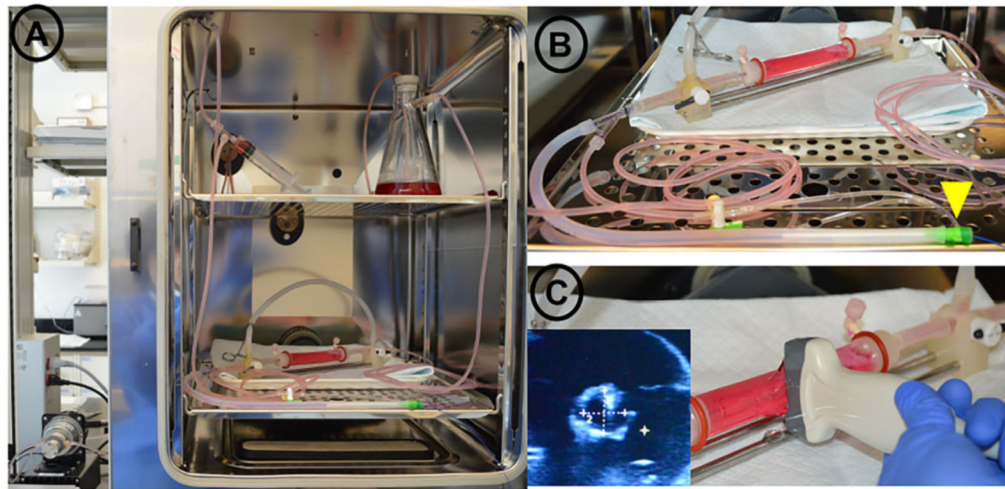


Figure 1.

Ex vivo bioreactor system. A, A gear pump generates a pulsatile flow driving cell culture medium through the explanted porcine carotid artery. B, A guide sheath (yellow arrowhead) is incorporated into the flow circuit permitting guidewires and balloons to be inserted into the flow and the artery. C, An ultrasound probe directly placed on the outer sleeve of the artery housing to measure the diameter. The insert shows an example of inner diameter measurement of the explanted artery.

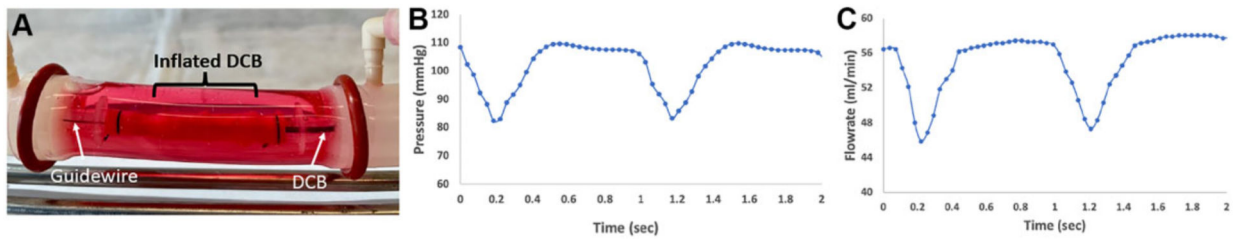


Figure 2. Deployment of DCB. A, Representative image of a DCB deployed within the explanted porcine carotid artery. B, A representative signal of the pressure within the flow system. C, A representative signal of the flow rate within the flow system.

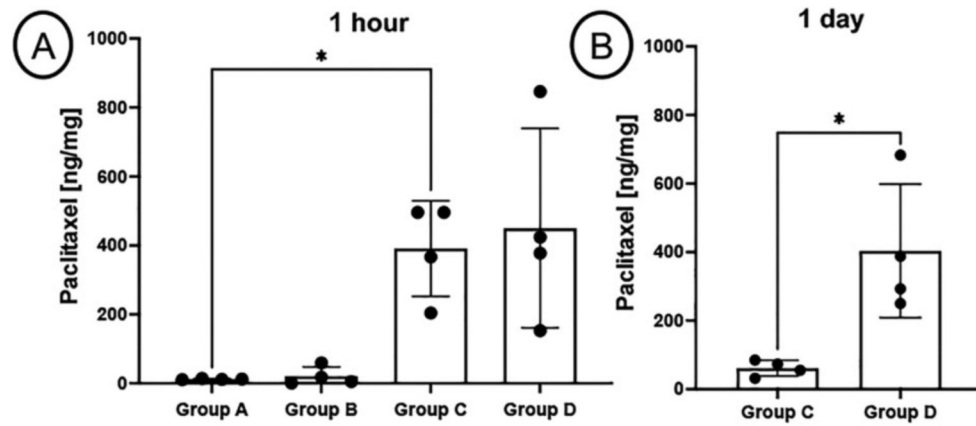


Figure 3. *Ex vivo* arterial drug retention. A, Scatter plots displaying measured arterial paclitaxel concentrations within the drug-coated balloon-treated segments expressed as ng/mg from the 1-hour experiments. B, Scatter plots displaying measured arterial paclitaxel concentrations within the drug-coated balloon-treated segments expressed as ng/mg from the 1-day experiments. Each bar represents the mean \pm standard deviation, * $P < .05$.

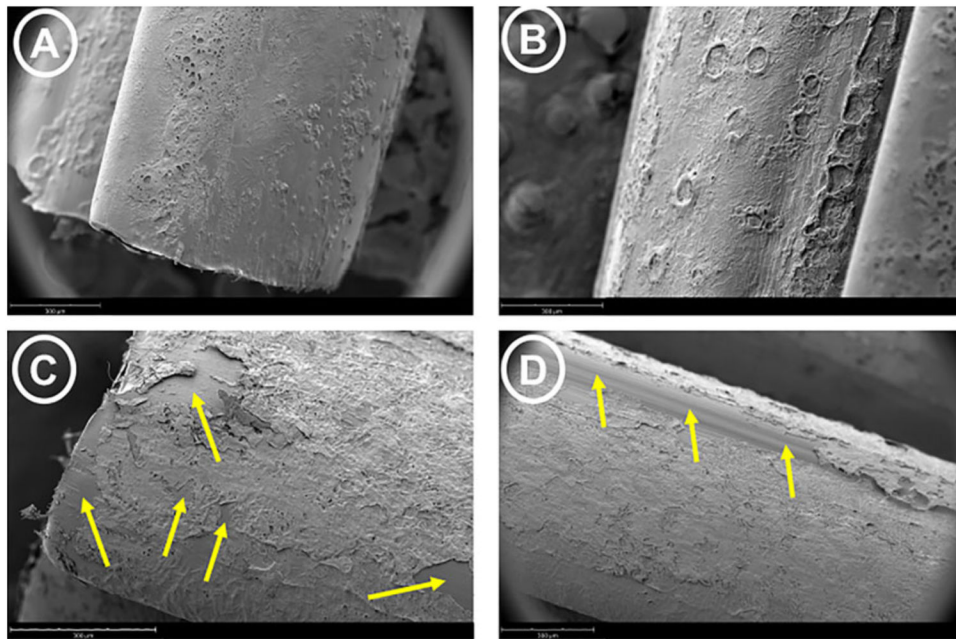


Figure 4. Scanning electron microscope images of hydrated DCBs. A and B, Representative SEM images of a 30-second hydrated DCB. No signs of coating damage were visible. C and D, Representative SEM images of a 3-minute hydrated DCB. Regions of coating defects, characterized as small defects with bare balloon surface exposure (arrows), were identified.

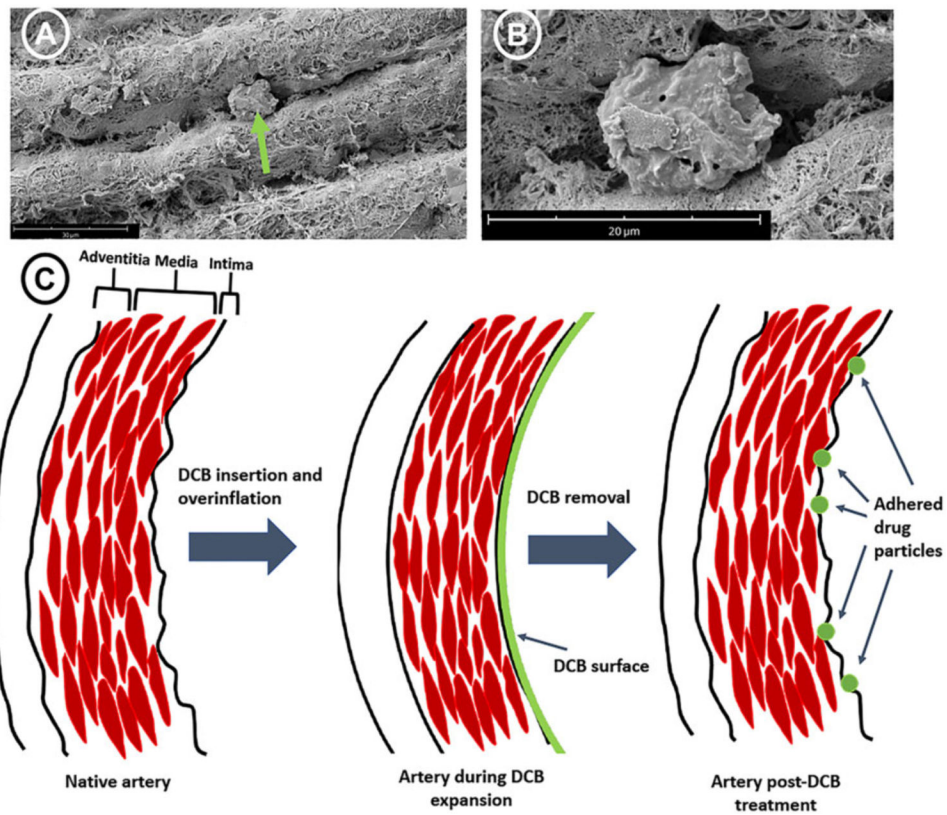


Figure 5. Drug-coated balloon adhesion. A and B, Representative low- and high-power SEM images of DCB-treated artery illustrating the presence of drug particle adhered into the luminal surface. C, Illustration of drug particle adhesion during drug-coated balloon deployment.

Table 1.

Delivery Parameters and Pacitaxel Levels of the Varying Groups at 1 Hour.

Group	Transit time (sec)	Inflation time (sec)	DCB-to-artery ratio	Pacitaxel levels (ng/mg)
A	180	30	1:1	12.3 ± 1.6
B	180	60	1:1	20.7 ± 26.7
C	30	60	1:1	391 ± 139
D	30	60	1.25:1	450 ± 289