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A Hybrid In Silico & In Vitro Approach To Study Coating Transfer In Drug-Coated Balloon Angioplasty

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Abstract

Drug-Coated Balloons (DCBs) have shown great promise as a minimally invasive therapeutic option for the treatment of stenotic arteries. However, recent animal studies have highlighted the challenge of limited coating transfer onto the arterial lumen short after the treatment. On this basis, studies have shown that the local transfer of the coating is highly influenced by the interaction between the balloon and the arterial endoluminal surface during balloon inflation. This sheds light on the significance of developing *ex vivo* strategies for the investigation of coating transfer efficiency. Therefore, this work aimed to propose a hybrid computational and experimental methodology to assess how the Contact Pressure (CP) and concurrent Balloon Stretch (BS) conditions may affect the coating delivery to the artery during the DCB inflation. On one hand, numerical simulations of a generic angioplasty balloon were implemented to study the CP at the balloon-artery interface and simultaneous BS. On the other hand, benchtop experiments of in-house and commercial DCBs were developed to study the effectiveness of local coating delivery after compression with pig aortic endothelium under the range of pressure and stretch values estimated from the numerical simulations. Coupling the effective or non-effective delivery of the coating under specific CP and BS conditions, the numerical simulations may predict the coating transfer maps under various procedure conditions. This approach is expected to provide significant insights for manufacturers of DCBs in terms of coating formulations and angioplasty platform devices.

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1. Intoduction

Cardiovascular diseases are the leading cause of death worldwide, primarily attributed to atherosclerosis, which is a pathological condition affecting the intimal layer of large and medium-sized arteries. Atherosclerosis leads to the development of atheromatous plaque, resulting in the thickening of the arterial wall, narrowing of the arteries and restricting the blood flow through the vessels.

To address arterial stenosis, DCBs have emerged as a promising minimally invasive therapeutic intervention. DCBs deliver various types of drugs to the arterial wall to prevent restenosis, initially, during their short inflation time (typically 30-180 seconds), with the aim of inhibiting the proliferation of smooth muscle cells. After balloon deflation, these devices are designed to transfer the drug-coating formulation onto the diseased vessel's endoluminal surface, which acts as a long-term drug repository for the lesion area (Bukka et al. (2018)). The morphological structure of DCBs has the potential to facilitate complete contact between the DCB surface and the stenosed vessel (Tesfamariam, (2016)), enabling uniform drug delivery on the lesion, which is suggested to hinder restenosis (Fanelli et al. (2014)).

Despite promising results from certain clinical trials, a number of studies disclosed restrained drug delivery to the vessel (Kempin et al. (2015); Petersen et al. (2013); Seidlitz et al. (2013)). Loss of the balloon's drug-coating can occur during transportation to the target area, resulting in incomplete coverage of the balloon surface prior to inflation (Speck et al. (2016)). Once inflated in the lesion, the interaction between the DCB and the arterial wall plays a critical role in the efficacy of local coating delivery (Cao et al. (2022)). Recent animal studies have shown limited coating adherence to the luminal wall shortly after DCB intervention (Tzafriri et al. (2020)), indicating the need for further enhancement of the treatment. Improving the device itself and optimizing the chemical formulation of the drug coating have been the primary focuses of research and development efforts (Rykowska et al. (2020)). However, only a few studies have so far examined the DCB interaction with arterial vessels (Azar et al. (2020); Chang et al. (2019); Galan et al. (2018); Lee et al. (2021)).

In light of this, the efficacy of coating transfer is considered an underexamined aspect in DCB angioplasty, while studies suggest that the restrained coating transfer may limit the efficacy of DCB angioplasty (Shazly et al. (2022)). The Contact Pressure (CP) between the balloon's external surface and the endoluminal surface of the artery has been identified as a crucial parameter influencing coating transfer. Higher CP enhances coating transfer, potentially increasing drug delivery to the vascular tissue. Previous studies have proposed that micromechanical indentation pressure, developed during the interaction of the coating with the vessel, is responsible for coating transfer (Chang et al. (2019); Tzafriri et al. (2020)), driven by macro-mechanical CP. Nevertheless, *in vivo* evaluation of CP is deemed unachievable, and the utilization of numerical methods can provide advantages in its measurement. However, the development of a numerical model capable of accurately computing the micro-mechanical aspects of CP resulting from the interaction between the coating and the artery would be highly complex.

Therefore, this study aimed to propose a coupled *in silico* and *in vitro* pipeline to investigate the effectiveness of the drug-coating transfer from the balloon's external surface onto the artery's endoluminal surface, during DCB angioplasty. The numerical simulations are conducted on a macroscale, i.e. the device-artery interaction, to analyze the overall mechanical behavior of the DCB in interaction with the arterial vessel during balloon inflation and concurrent circumferential Balloon Stretching (BS). On the other hand, the in vitro experiments are planned to be carried out on a mesoscale, where the complex artery wall/coating material interaction is investigated to examine the efficacy of coating detachment from DCB specimens obtained from drug-coated patches or commercial DCBs, and attachment of the detached coating onto the endothelial layer of pig arteries. These experiments are conducted using the calculated conditions of CP and BS derived from numerical simulations, as applied loadings. The experiments aim to investigate the complex mechanical and chemical/biological interactions between the coating and the artery as opposed to relying solely on intricate numerical simulations.

By employing this hybrid approach, in the future we may evaluate the effect of CP and BS during the balloon expansion of a DCB to deduce the optimal characteristics for balloon and coating features.

2. Methodology

The rationale underlying the approach employed in this study is illustrated in Figure 1. The focus of this research is to investigate the phenomenon of coating transfer, and it is examined at two distinct scales. At the macro/device scale, the macromechanical behavior of the DCB during its expansion within the vessel is analyzed. During the treatment, by applying inflation pressure to the internal surface of the DCB, the folded balloon initially expands until it reaches its fully distended configuration. As the inflation pressure continues to rise, the diameter of the balloon progressively increases, primarily through circumferential BS. Eventually, the expanded balloon comes into contact with the inner

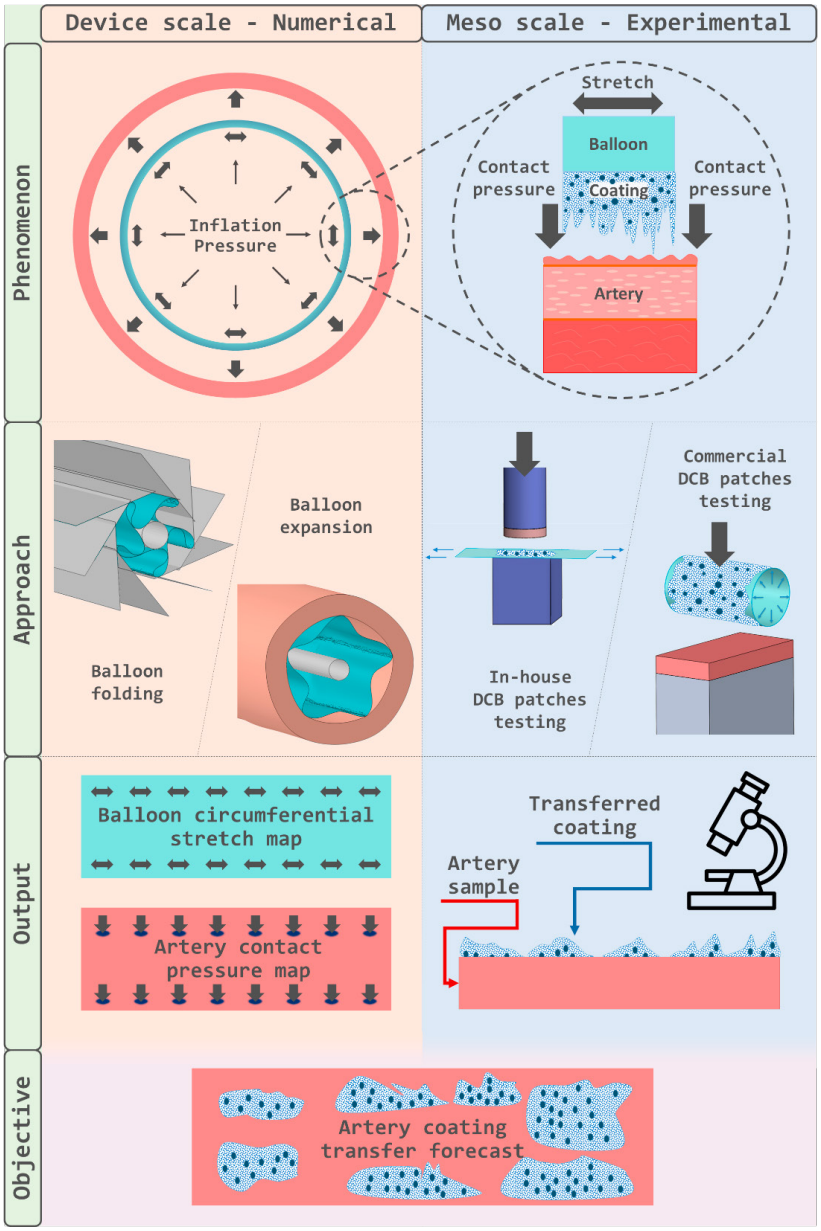

Figure 1. The rationale behind the coupled numerical and experimental approach to study the drug-coating transfer during the DCB expansion inside arterial vessels. The first raw presents the two scales of the problem, while the second and third raw depict the suggested methodological approach for each aspect and the respective expected output. The fourth raw represents the objective of the study, by merging the two techniques output to predict the coating transfer efficacy.

arterial surface. At this stage, the inflation pressure serves dual purposes: it stretches the balloon circumferentially and generates CP on the balloon-artery interface due to the radial resistance of the artery. After the balloon deflation, the coating may: i) remain on the balloon surface, ii) attach to the surface of the artery or iii) fragment and get partially transferred. Observing the phenomenon from a meso scale, the developed CP and BS during the maximum inflation of the balloon are suggested to influence the coating transfer to the arterial wall.

To approach the problem at a macro scale, we developed a finite element code in Abaqus/Explicit (Dassault Systemes Simulia Corp, Johnston RI) to simulate the folding and unfolding of a semi-compliant angioplasty balloon within simplified arterial vessels, as representative of healthy arteries which is the typical case during animal studies. The balloon was simulated as a bilinear elastoplastic material (Young's modulus =1150 MPa, Yield stress = 30 MPa and Plastic modulus =158 MPa) and the artery as 5 parameter Mooney Rivlin hyperelastic material (Prendergast et al. (2003)). The balloon-to-artery diameter ratio was 1.2. The folding of the balloon followed the method described by Geith (Geith et al. (2019)). Two different scenarios of balloon expansion were considered, one with 3 folds and the other with 5 folds.

To analyze the simulations, we visualized the circumferential BS of the balloon at a nominal inflation pressure of 7 atm, and the CP experienced by the inner surface of the artery at the same pressure using 2D heat map representation, where the intensity of the colors reflected the values of the variables.

To gain insights into the transfer of drug coating in the context of the DCB interaction with the artery, it is essential to approach the phenomenon from a material perspective. However, due to the intricate nature and computational complexity associated with incorporating numerical simulations to investigate the meso scale interaction between the DCB and the artery, a series of in vitro experiments are recommended. Conventionally, a compression experiment has been employed in the literature to study drug transfer to the arterial endothelium(Azar et al. (2020); Chang et al. (2019); Galan et al. (2018); Lee et al. (2021)). This experiment involves compressing a DCB patch ("flat stamping") onto an arterial endothelium. However, this method is limited to flat DCB specimens. Longitudinal cutting of commercial DCBs may lead to damage to the drug-coating layer due to remaining circumferential tension of the balloon. Hence, the authors propose an alternative technique that utilizes cylindrical commercial DCB specimens ("cylindrical stamping"). The objective of these experiments is to subject the DCB patches to a range of circumferential BS and compress them onto an arterial endothelium using a force that generates a similar range of CP as calculated in the numerical simulations. Following controlled compression for a duration equivalent to the DCB inflation time during treatment, the DCB patch is retracted, and both the DCB patch and the arterial endothelium are examined using laser microscopy to quantify the percentage of coating transferred to the vessel. To test the feasibility of the experiment, preliminary testing using commercial angioplasty balloons was performed. For the sample preparation, various types of resin and techniques were employed to expand the balloons and obtain solid cylindrical structures, which were then mounted onto the developed apparatus.

By establishing a correlation between the experimental effectiveness of coating transfer and the CP and BS values developed during DCB expansion, the proposed methodology aims to integrate the outcomes of the experimental approaches into the results of the numerical simulations. This integration allows the transformation of CP and BS maps obtained from the numerical simulations into coating transfer maps.

3. Results and Discussion

3.1. Numerical simulations

The results of the finite element analysis simulations demonstrated significant heterogeneity in both CP and circumferential BS at an inflation pressure of 7 atm, where the balloon and the artery have a circular cross-section (Figure 2). The values and patterns of these variables were heavily influenced by the number of folds incorporated in each simulation, showing a similar range of values. This suggests that the artery tracks initial contact with the balloon. In the case of the 5-folded balloon, it was observed that the areas with maximum balloon stretch corresponded to regions where the contact pressure was minimal. In parallel, regions with intermediate values of contact pressure exhibited significantly low levels of balloon stretch. This phenomenon can be attributed to the frictional interaction between the external surface of the balloon and the arterial endoluminal surface. When the balloon unfolds, certain areas of the balloon come into contact with the arterial wall first, resulting in these regions being obstructed by the

vessel. This obstruction increases the contact pressure and hampers the stretching of the balloon in those particular areas.

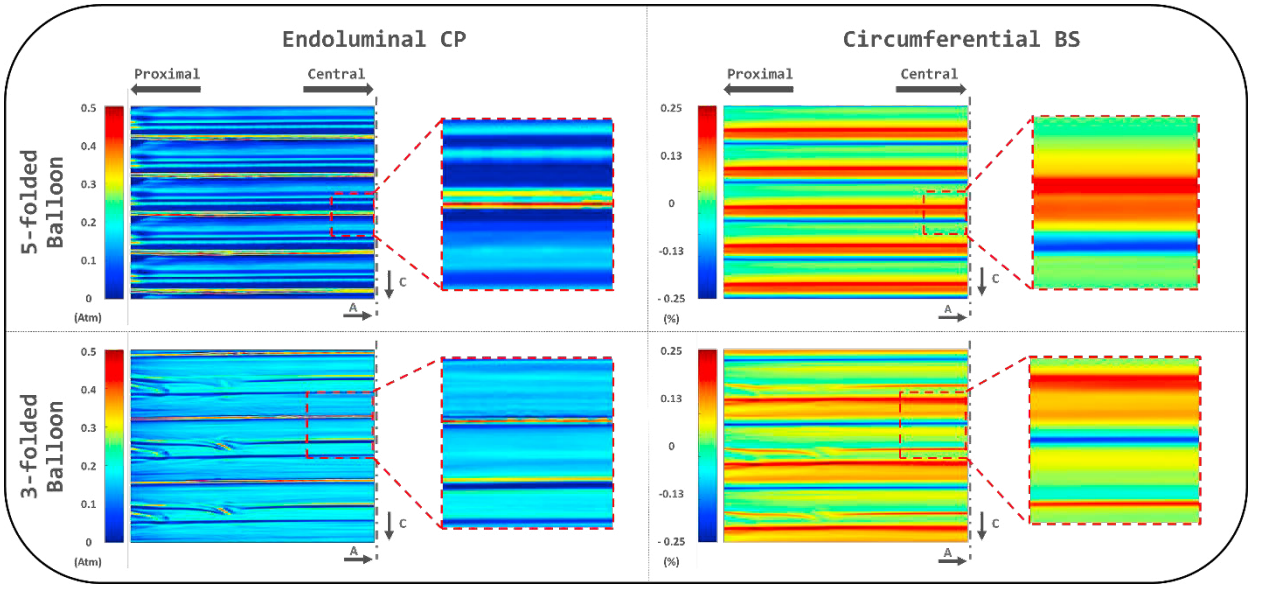

Figure 2. Results from the numerical simulations of balloon expansion inside the idealized vessels. The column of endoluminal CP depicts the CP map at the balloon-artery interface for the 3- and 5- folded balloon during the maximum balloon inflation. The column of circumferential BS represents the concurrent stretch on the balloon for the 3- and 5- folded balloon respectively. “A” and “C” on the bottom of the graphs denote the axial and circumferential directions respectively.

3.2. “Flat stamping”

To investigate the impact of the calculated CP and BS on the effectiveness of coating transfer, we developed an experimental setup capable of compressing arteries onto flat DCB specimens (Figure 3). The setup was specifically designed to be compatible with the uniaxial testing machine. The lower part of the setup consisted of a system that securely held the flat DCB patch at its ends, allowing for manual stretching of the specimen by a rotating screw. In the upper part of the setup a pig aorta was glued with the endothelium exposed on the underside. Numerical simulations were employed to assess the uniformity of the stretch caused by the grips and to calculate the required force for applying the range of CPs determined by the simulations. Following the compression process, both the balloon and the arterial patches are planned to be subjected to coating quantification using a confocal laser microscope.

3.3. “Cylindrical stamping”

A cylindrical stamping setup was developed to facilitate the utilization of commercial DCB devices and enable the testing of coating transfer efficacy on a large number of specimens (Figure 4). For sample preparation, a polyurethane resin was injected into the inner surface of the balloon. The volume expansion of the injected resin during solidification determined the extent of balloon expansion and circumferential balloon size. Once the resin solidified, it was cut into 1cm long DCB patches. A stereolithography 3D printed setup was specifically designed to be compatible with a uniaxial testing machine, allowing for the stamping experiment to be conducted on the cylindrical DCB specimens. After the specimens were cut, they were clamped laterally, and compression was performed between them and a flat pig aorta, which had the endothelium exposed on the top surface. The force applied during the compression was estimated through numerical simulations to correspond with the calculated CP derived from the balloon expansion simulations. So far, an angioplasty balloon was utilized to assess the feasibility of this experimental procedure.

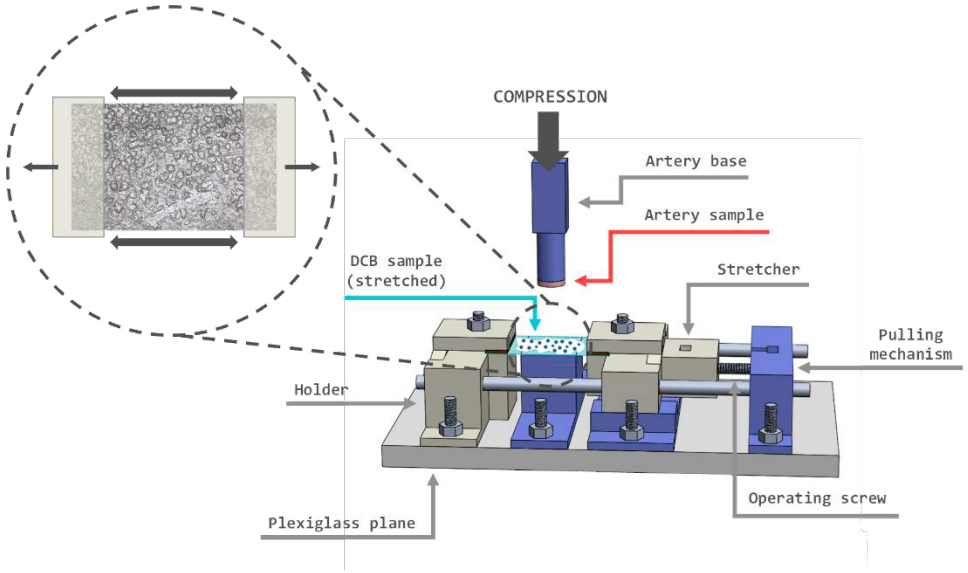

Figure 3.The flat "stamping" setup previously presented in literature with the addition of a stretching system facilitates the investigation of CP and BS to the coating transfer efficacy, The figure presents the system's design able to stretch a flat DCB patch and compress an arterial endothelium on the coated area of the patch.

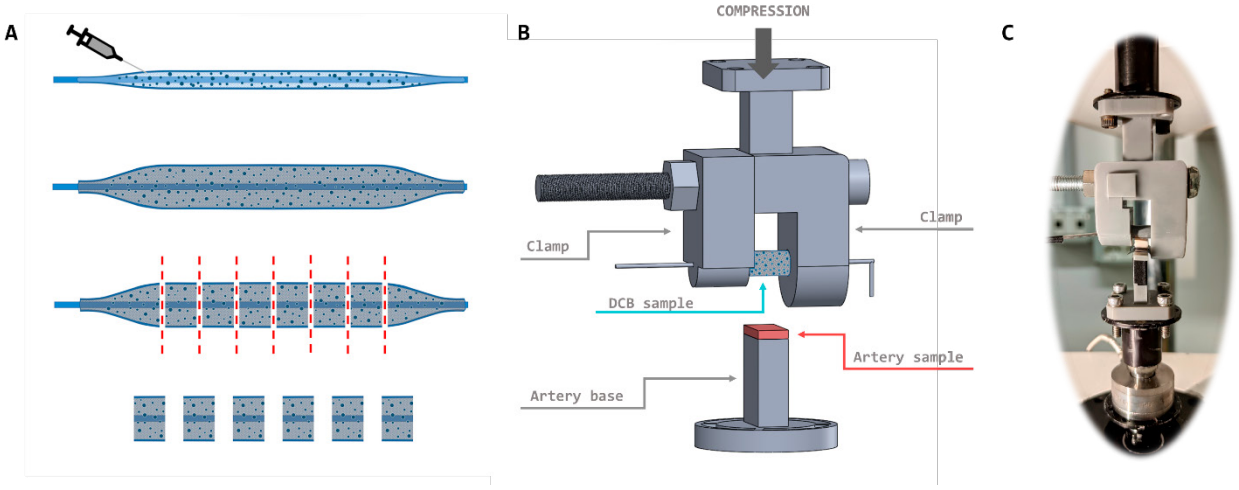

Figure 4. Experimental procedure to perform the "cylindrical stamping" experiment: A. The commercial DCB is initially inflated using a needle filled with a polyurethane resin and once solidified, cut in a number of specimens perpendicular to its longitudinal axis, B. the developed setup able to grab and compress DCB specimens on pig arteries and C. The feasibility of the experiment was tested with commercial angioplasty balloons.

4. Conclusion

This study presented a comprehensive approach combining numerical simulations and experimental methods to investigate the transfer of coating during balloon expansion in DCB angioplasty, conducted at two different scales. The numerical simulations performed on balloon expansion within simplified blood vessels demonstrated notable irregularities in CP and BS, indicating a wide range of values. To translate these results in coating transfer efficacy,

two benchtop experiments were proposed: one utilizing DCB patches developed in-house, and the other employing commercially available DCBs. The authors conducted a proof-of-concept study for these experimental approaches and plan to carry out a future experimental campaign that integrates the computational and laboratory findings to evaluate coating transfer under various procedural conditions.

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