Angiography-Based Computational Modeling for In Vivo Assessment of Endothelial Dynamic Strain in Coronary Arteries with De Novo Lesions: Comparison of Treatment Effects of Drug-Coated Balloons Between Small and Large Arteries

Lei Xu¹,²,³a, Zhouhao Tang²a, He Zou¹,², Yiqiu Jiang¹,², Youxian Shen¹,², Xinmin Zhang¹,², Ahmed Elkoumy⁴,⁵,⁶, Xueqiang Guan², Lianpin Wu¹,² and Xinlei Wu¹,²

¹Zhejiang-Ireland Joint Laboratory for Precision Diagnosis and Treatment of Valvular Heart Diseases, The Second Affiliated Hospital of Wenzhou Medical University, Wenzhou, China
²Department of Cardiology, Key Laboratory of Panvascular Diseases of Wenzhou, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University, Wenzhou, China
³Department of Radiology, The Second Affiliated Hospital and Yuying Children’s Hospital of Wenzhou Medical University, Wenzhou, China
⁴Islamic Center of Cardiology, Al-Azhar University, Cairo, Egypt
⁵Discipline of Cardiology, Saolta Group, Galway University Hospital, Health Service Executive, Galway, Ireland
⁶CORRIB Core Lab, University of Galway, Galway, Ireland

Received: 25 February 2024; Revised: 1 April 2024; Accepted: 22 May 2024

Abstract

Acute morphological changes in de novo coronary lesions after drug-coated balloon (DCB) angioplasty can affect endothelial mechanics and consequently clinical outcomes. Angiography-based computational modeling has been validated to assess endothelial dynamic strain (EDS) in coronary arteries in vivo. The EDS was calculated on the basis of pre- and post-DCB angiography. Parameters of quantitative coronary angiography and EDS were quantified at cross-sections in the treated segments. A total of 336 and 348 lesion cross-sections were included in the small/large vessel groups, respectively. The acute lumen gain after DCB was significantly higher in large than small vessels (relative changes: 21.3% [17.4%, 25.1%] vs. 7.4% [4.8%, 10.1%], P < 0.001). Before treatment, three indices of EDS were significantly higher in small than large vessels (for ED-EDS: 29.2% [19.8%, 44.8%] vs. 20.4% [14.3%, 30.2%]; for ES-EDS: 26.8% [18.9%, 37.7%] vs. 18.3% [13.9%, 25.4%]; for TA-EDS: 19.1% [13.9%, 27.8%] vs. 14.3% [10.5%, 20.1%], P < 0.001). After treatment, the EDS in small vessels significantly decreased (P < 0.001). ED-EDS showed the highest correlation with pre-DCB DSP (r = 0.43, P < 0.001) and post-DCB MLD (r = 0.35, P < 0.001). The levels of EDS parameters for small or large vessel lesions significantly differed. Further study is required to examine the clinical value of EDS in predicting cardiac events after DCB treatment.

Keywords: computational modeling; coronary angiography; endothelial dynamic strain; drug-coated balloon; de novo lesion
List of Abbreviations: AUC, area under the curve; DCB, drug-coated balloon; MLD, minimum lumen diameter; DS%, percentage diameter stenosis; AS%, percentage area stenosis; EDS, endothelial dynamic strain; ED, end-diastole; ES, end-systole; QFR, quantitative flow ratio; ROC, receiver operating characteristic; TA, time-averaged.

Introduction

Drug-coated balloons (DCBs), a new treatment approach currently used for diseased coronary arteries, enable rapid and homogeneous delivery of anti-proliferative drugs to lesions during balloon inflation without the use of permanent stents [1, 2]. Several studies [3–8] have demonstrated the efficacy and safety of DCBs in clinical scenarios such as in-stent restenosis or de novo lesions in small vessels. However, results regarding the safety of DCB-only treatment for large vessel lesions have been inconsistent, because large coronary arteries, owing to their larger amounts of elastic fibers, are more susceptible than small arteries to recoil and dissection [9].

The mechanical instability of the coronary arterial wall is widely understood to be associated with the occurrence of the acute recoil after DCB angioplasty [10]. Quantitative angiography assessment of the in vivo functional state of the coronary arterial wall might aid in identifying high-risk lesions in unstable vessels after DCB angioplasty to avoid potential adverse events [11]. In our previous studies, we have developed and validated angiography-based computational modeling of superficial wall stress [12, 13], called endothelial dynamic strain (EDS), thereby enabling evaluation of the mechanical strain of the coronary endothelial surface layer in vivo by extracting temporal variations in vessel morphological deformation from angiographic image sequences [14, 15]. This computational modeling has recently been applied to investigate the acute and long-term effects of EDS in vivo for native coronary arterial lesions treated with drug-eluting stents or bioresorbable scaffolds; device implantation has been found to significantly decrease EDS to a similar extent after treatment with polymer-based scaffolds or permanent metallic stents [16].

In this study, our aim was to investigate and compare the immediate effects of EDS in coronary arterial lesions de novo, before and after DCB treatment, between large and small vessels. Furthermore, the relationship between EDS and coronary artery stenosis was assessed to advance understanding of the mechanical state of the vascular wall in large and small vessels after angioplasty, and potentially increase the efficacy and safety of the DCB-only approach.

Methods

Patients and Angiography

Fifteen consecutive patients with 16 de novo coronary lesions (Supplementary Table 1) who underwent DCB-only angioplasty were retrospectively enrolled and provided informed consent to participate. The Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University approved this study (No. 2022-K-214–01), which was performed in accordance with the 1975 Declaration of Helsinki guidelines. Angiographic data from patients who underwent successful DCB treatment were selected for this post hoc analysis. The exclusion criteria were as follows: 1) excessive vessel imaging overlap or foreshortening (>90%); 2) insufficient angiographic image quality preventing delineation of lumen contours; 3) failure to achieve contrast filling consistently over at least one entire cardiac cycle; 4) availability of only one projection view of the stenotic artery; 5) angiographic appearance of dissection after lesion preparation; 6) requirement for bailout stent deployment; 7) treated in-stent restenosis lesions; and 8) frequent ventricular tachycardia. The inclusion criteria were as follows: 1) angiographic imaging with two projections ≥ 25° apart, obtained with flat-panel systems, and 2) complete contrast filling of the interrogated vessels. A 2.0 mm reference diameter cut-off at the
proximal and distal ends was selected to distinguish between small and large coronary arteries [17] (Figure 1).

**Treatment Procedure and Devices**

The interventions were performed according to the international DCB Consensus Group [1]. Specifically, pre-dilation with an undersized semi- or non-compliant balloon with a balloon-to-vessel ratio of 0.9–1.0 was mandatory [18]. After pre-dilatation, DCB angioplasty was conducted only in the absence of a major flow-limiting dissection and severe acute recoil. Shenqi (Shenqi Medical, Shanghai, China) or SeQuent Please (B Braun, Melsungen, Germany) DCBs were used in this study. The DCB size was chosen to exceed the length of both lesion ends by at least 2–3 mm. DCBs were delivered rapidly and inflated for 30–45 s under nominal pressure, depending on the characteristics of the lesion, such as calcification and tortuosity. After treatment with DCBs, the final assessment of angiograms with two projections was performed after at least 5 min, to identify early vessel recoil.

**Quantitative Coronary Angiography Analysis**

Angiographic images were recorded with X-ray systems (AXIOM-Artis, Siemens, Malvern, Pennsylvania; AlluraXper, Philips Healthcare, Best, the Netherlands). The 3D angiographic reconstruction at several key time points within one cardiac cycle was performed by an experienced analyst (X.W.). The synchronization between two projections was performed from electrocardiograms, according to the different stages of vessel motion during heart contraction and relaxation [15]. The proximal and distal ends of the interrogated arteries were selected according to anatomic landmarks such as bifurcations. The following quantitative coronary angiography (QCA) parameters were analyzed: minimum lumen diameter (MLD), percent age diameter stenosis (DS%), and percentage area stenosis (AS%).

**Endothelial Dynamic Strain Analysis**

The details of EDS analysis have been previously described [13–15]. Briefly, for each vessel, all
reconstructed geometries within one cardiac cycle were discretized into structured finite elements with identical node numbers in longitude and circumference. The predicted cyclic motion of the arteries was determined on the basis of the principle of minimum potential energy, when all nodes between two consecutive configurations were matched to generate the one-to-one mapping relationship. The initial configuration for cyclic computation was selected at diastasis (i.e., mid-diastole), because the heart is quiescent at this cardiac phase when the kinetic and strain energy of the coronary arteries are lowest throughout the entire cardiac cycle [12, 13]. Starting from diastasis, the EDS was calculated by dividing the finite element length of structured grids at the next time point by that at the previous time point, via a validated algorithm [13]. To quantitatively assess the mechanical status of the coronary endothelial surface layer, we obtained three parameters from the EDS analysis: end-diastole EDS, end-systole EDS, and time-averaged EDS within one cardiac cycle.

Definitions of Segments and Cross-Sections of Interest

To performed detailed assessment of the variations in morphological and mechanical variables of the local lesion segment, we calculated QCA and EDS parameters for each 0.4 mm cross-section. First, the treated segment on the 3D reconstructed vessel was determined according to the two radio-opaque markers on the deflated balloon at both ends on the post-DCB angiogram [19]. Subsequently, the major side branches next to the segment were identified, and the distances along the center line from both side branches to the end of the segment were measured. Finally, the distance between side branches on the center line was used for longitudinal matching of the segments of interest between serial angiograms. Therefore, the QCA and EDS parameters at each cross-section in the segments of interest were matched before and after DCB treatment.

Statistical Analysis

The normality of distributions was assessed with the Shapiro-Wilk test. Continuous variables are presented as mean ± standard deviation or median and interquartile range, as appropriate. Categorical variables are reported as percentages. Categorical variables were evaluated with the chi-square test, whereas continuous variables were compared with unpaired two-tailed Student’s t test or the Mann-Whitney U-test if normality assumptions failed (e.g., differences in morphological and endothelial strain variables between small and large vessels before and after DCB treatment). Spearman correlation analysis was applied to identify correlations between lumen morphology and endothelial strain variables. Furthermore, we evaluated the diagnostic performance of three strain variables alone versus lumen stenosis by using receiver operating characteristic (ROC) curves plotting sensitivity versus (100% – specificity %), thereby enabling calculation of the area under the curve (AUC). All calculations were two-tailed, and P < 0.05 was considered statistically significant. Statistical analyses were performed in both SPSS 23.0 (SPSS Inc., IBM Computing) and R 2.10.1 (The R Foundation for Statistical Computing).

Results

Data for 2339 cross-sections along vessels were derived through computational modeling and were matched before versus after DCB treatment in the small or large vessel groups. Figure 2 shows example coronary artery lesions in small or large vessels before and after DCB treatment. The small and large vessel groups included 336 and 348 cross-sections in the lesion segments of interest treated with DCB, respectively.

Quantitative Coronary Artery Analysis

Table 1 shows the QCA analysis of de novo lesions in small and large vessels before and after DCB treatment. Before the DCB intervention, no significant difference was observed in the DS% of the lesion segments between the small and large vessel groups [22.7% (10.4%, 37.7%) vs. 25.0% (11.1%, 37.4%), P = 0.093]. After treatment, the MLD increased from 1.5 (1.3, 1.8) to 1.7 (1.1, 2.2) mm (P < 0.001) in small vessels and from 2.0 (1.7, 2.4) to 2.7 (2.1, 2.9) mm (P < 0.001) in large vessels. Of note, the relative change in MLD was significantly higher in
large than small vessels [21.3% (17.4%, 25.1%) vs. 7.4% (4.8%, 10.1%), P < 0.001] (Table 1).

**Endothelial Dynamic Strain Analysis**

Before treatment, three indices of EDS were significantly higher in small than large vessels (P < 0.001) (Table 2). After treatment, the EDS variables in all (small + large) vessels significantly decreased with respect to pre-treatment values, whereas those in the large vessel group did not significantly decrease (P > 0.05). Two indices of EDS (ES-EDS and TA-EDS) in small vessels remained significantly higher than observed in large vessels (P < 0.001). The absolute and relative changes in EDS between pre- and post-treatment were significantly higher in small than large vessels (P < 0.05).

Representative examples of computation of EDS with different indices in small and large vessels before and after DCB treatment are shown in Figure 2. Before treatment, the highest EDS occurred at the proximal lesion shoulder in the small vessels at end-diastole (Figure 2A). After DCB treatment, the EDS decreased with increasing...
Lumen size (Tables 1 and 2). In the large vessel group, the EDS was lower than that in the small vessel group and did not change significantly despite the greater lumen size (Table 1 and Figure 2B).

**Correlation between Lumen Morphology and Endothelial Strain**

Figure 3 shows Spearman’s r correlation coefficients between lumen morphology and endothelial strain variables. Strong correlation was observed among these three morphological variables or three strain variables, in small, large, or overall vessels, either pre- or post-DCB. In the small vessel group, MLD showed a moderate negative correlation with endothelial strain variables pre-DCB, but a poor to weak positive correlation post-DCB (Figure 3A). Very weak negative correlations were observed between MLD and endothelial strain variables in the large vessel group. Overall, ED-EDS has the highest correlation coefficient with pre-DCB DSP (r = 0.43, P < 0.001) and post-DCB MLD (r = 0.35, P < 0.001).

### Table 1
Acute Changes in Morphological Indices at Cross-Sections along Lesion Segments in Small (n = 336) and Large (n = 348) Vessels Treated with Drug-Coated Balloons.

<table>
<thead>
<tr>
<th>Indices</th>
<th>Lesion vessel</th>
<th>Pre-DCB</th>
<th>Post-DCB</th>
<th>Absolute difference (95% CI)</th>
<th>Relative change (%) (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD (mm)</td>
<td>Small</td>
<td>1.5 (1.3, 1.8)</td>
<td>1.7 (1.4, 2.0)</td>
<td>0.1 (0.1, 0.2)</td>
<td>7.4 (4.8, 10.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>2.0 (1.7, 3.7)</td>
<td>2.7 (2.1, 2.9)</td>
<td>0.4 (0.3, 0.5)</td>
<td>21.3 (17.4, 25.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>1.8 (1.4, 2.1)</td>
<td>2.1 (1.7, 2.7)</td>
<td>0.2 (0.2, 0.3)</td>
<td>13.3 (10.3, 16.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>DS%</td>
<td>Small</td>
<td>22.7 (10.4, 37.7)</td>
<td>14.8 (5.6, 26.3)</td>
<td>−6.6 (−9.0, 5.0)</td>
<td>−30.0 (−41.0, 24.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>25.0 (11.1, 37.4)</td>
<td>7.0 (1.4, 14.9)</td>
<td>−13.2 (−16.2, 11.3)</td>
<td>−91.4 (−92.1, 90.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>23.9 (11.0, 37.4)</td>
<td>10.8 (3.0, 19.5)</td>
<td>−10.1 (−11.4, 8.3)</td>
<td>−82.3 (−85.0, 77.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P</td>
<td>0.522</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>AS%</td>
<td>Small</td>
<td>26.0 (6.0, 50.5)</td>
<td>17.4 (0.5, 37)</td>
<td>−9.4 (−11.7, 5.4)</td>
<td>−30.5 (−36.3, 22.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>35.8 (11.1, 55.3)</td>
<td>5.1 (−5.3, 17.4)</td>
<td>−20.0 (−24.3, 16.4)</td>
<td>−80.9 (−84.8, 74.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>31.6 (8.8, 53.7)</td>
<td>9.2 (−3.1, 25.9)</td>
<td>−14.0 (−16.3, 11.7)</td>
<td>−65.0 (−71.2, 58.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P</td>
<td>0.010</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Values are reported as median (interquartile range). DCB, drug-coated balloon; MLD, minimum lumen diameter; DS%, percentage diameter stenosis; AS%, percentage area stenosis.

### Table 2
Acute Changes in Endothelial Dynamic Strain at Cross-Sections along Lesion Segments in Small (n = 336) and Large (n = 348) Vessels Treated with Drug-Coated Balloons.

<table>
<thead>
<tr>
<th>Indices</th>
<th>Lesion vessel</th>
<th>Pre-DCB</th>
<th>Post-DCB</th>
<th>Absolute difference (95% CI)</th>
<th>Relative change (%) (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED-EDS (%)</td>
<td>Small</td>
<td>29.2 (19.8, 44.8)</td>
<td>20.3 (10.7, 34.9)</td>
<td>−8.1 (−20.2, 0.1)</td>
<td>−34.5 (−58.5, 0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>20.4 (14.3, 30.2)</td>
<td>19.8 (13.1, 26.1)</td>
<td>−1.6 ± 11.9</td>
<td>−8.7 (−36.6, 45.7)</td>
<td>0.056</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>24.3 (16.2, 35.4)</td>
<td>19.9 (11.9, 29.4)</td>
<td>−5.1 (−14.3, 4.4)</td>
<td>−20.8 (−47.6, 24.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>0.554</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ES-EDS (%)</td>
<td>Small</td>
<td>26.8 (18.9, 37.7)</td>
<td>22.0 (16.5, 34.8)</td>
<td>−4.8 (−15.0, 7.2)</td>
<td>−7.4 (−42.9, 27.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>18.3 (13.9, 25.4)</td>
<td>16.3 (12.1, 25.9)</td>
<td>−2.0 (−7.6, 6.6)</td>
<td>3.0 (−34.4, 46.8)</td>
<td>0.245</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>21.7 (15.8, 30.7)</td>
<td>19.7 (14.4, 28.9)</td>
<td>−0.8 (−10.0, 7.0)</td>
<td>−3.3 (−38.6, 39.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>TA-EDS (%)</td>
<td>Small</td>
<td>19.1 (13.9, 27.8)</td>
<td>16.3 (12.1, 25.9)</td>
<td>−2.2 (−9.5, 3.8)</td>
<td>−11.8 (−42.6, 23.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>14.3 (10.5, 20.1)</td>
<td>13.2 (9.5, 18.5)</td>
<td>−0.7 ± 7.6</td>
<td>−6.9 (−34.3, 39.3)</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>16.7 (12.2, 23.3)</td>
<td>14.9 (10.7, 21.7)</td>
<td>−1.4 (−7.7, 4.2)</td>
<td>−9.2 (−37.7, 32.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Values are reported as mean ± SD or median (interquartile range). DCB, drug-coated balloon; ED, end-diastole; ES, end-systole; TA, time-averaged; EDS, endothelial dynamic strain.
A DS% cutoff of 40% was used in this cohort to test the performance of endothelial strain in detecting coronary stenoses in cross-section analyses. In all three groups, ED-EDS had the highest AUC of the ROC curves, whereas ES-EDS had the lowest AUC (Figure 4). ED-EDS was the best index, associated with the optimal cutoff (22.2%), AUC (0.72), sensitivity (77.4%), and specificity (55.3%) in the overall cohort; the optimal cutoff (63.2%), AUC (0.73), sensitivity (37.7%), and specificity (96.8%) in the small vessel group; and the optimal cutoff (18.2%), AUC (0.72), sensitivity (88.0%), and specificity (48.3%) in the large vessel group (Table 3). The AUC difference between ED-EDS and ES-EDS was significantly greater in small than large vessels. Of note, the sensitivity of EDS in small vessels was higher than that in large vessels when (1 – specificity) was low, whereas the sensitivity in small vessels
was lower than that in large vessels when \((1 - \text{specificity})\) was high.

**Discussion**

The present study describes the first use of computational modeling of EDS to assess the treatment effects of DCBs on de novo lesions in small and large coronary arteries. The main findings were as follows: 1) Angiography-based EDS enabled comprehensive assessment of the morphological and mechanical status of de novo lesions pre- and post-DCB. The acute lumen gain between before and after DCB treatment was significantly higher in large than small vessels. 2) Pre-DCB, the EDS of lesion segments was significantly higher in small than large vessels. After treatment, the EDS variables significantly decreased in small but not large vessels. 3) Among three strain indices, the highest correlation coefficients were observed between ED-EDS and pre-DCB DSP and post-DCB MLD for the overall cohort. 4) ED-EDS had the largest AUC of the ROC curves and noticeably higher sensitivity in small vessels at low false positive rates.

DCBs are a treatment option increasingly used for various clinical situations in patients with coronary artery disease [4]. For treatment of bare metal and drug-eluting stent restenosis, DCBs are an established therapeutic option supported by guideline recommendations [1]. Although some studies conducted in small coronary vessels (<2.75 mm) have concluded that the DCB-only approach has similar target lesion revascularization rates to treatment with drug-eluting stents [20, 21], limited data are available for de novo large vessel disease treatment with DCB-only strategies [6, 7, 22], probably because of the more complex mechanical status of large than small vessels. DCBs could be affected by the interactions between internal (e.g., variable anatomic structure and lumen morphology) and external factors (e.g., mechanical force and blood pressure). In this study, the lumen changes before versus after DCB treatment were significantly higher in large than small vessels when the DS% was comparable between both groups. These findings might be explained by large arteries with abundant elastic fibers still having higher elasticity and expansibility than small arteries under high balloon inflation pressure, even after pre-dilation for lesion preparation before DCB delivery.

Before DCB treatment, the EDS in the overall group was significantly higher than that after interventional treatment. This finding was consistent with previous observations [16], thus suggesting a nonlinear negative relationship between MLD and EDS, wherein EDS decreases with increasing MLD. Therefore, our findings might be explained by the complex lumen geometrical perturbations and heterogeneous distribution of plaque compositions before treatment, such as the presence of local tortuosity, or protruding calcific mass. After treatment, the EDS variables significantly decreased in small but not large vessels. Several reasons may explain this finding. First, the geometry of the lumen surface at the lesion segment might become smoother and more uniform under the compression of low and long DCB inflation pressure. Second, the EDS might already have decreased to some extent with mild to moderate lumen stenosis after plain balloon angioplasty. Finally, in contrast to

<table>
<thead>
<tr>
<th>Indices</th>
<th>Lesion vessel</th>
<th>Optimal cutoff (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED-EDS</td>
<td>Small</td>
<td>63.2</td>
<td>37.7 (29.1, 47.2)</td>
<td>96.8 (95.0, 98.0)</td>
<td>11.9</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>18.2</td>
<td>88.0 (78.7, 93.6)</td>
<td>48.3 (44.4, 52.2)</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>22.2</td>
<td>77.4 (70.7, 82.8)</td>
<td>55.3 (52.4, 58.1)</td>
<td>1.7</td>
</tr>
<tr>
<td>ES-EDS</td>
<td>Small</td>
<td>49.5</td>
<td>36.8 (28.2, 46.3)</td>
<td>92.2 (89.7, 94.2)</td>
<td>29.0</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>19.1</td>
<td>77.3 (66.7, 85.3)</td>
<td>60.2 (56.3, 64.0)</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>21.3</td>
<td>71.3 (64.3, 77.4)</td>
<td>55.7 (52.8, 58.5)</td>
<td>1.6</td>
</tr>
<tr>
<td>TA-EDS</td>
<td>Small</td>
<td>33.9</td>
<td>39.6 (30.8, 49.1)</td>
<td>90.8 (88.2, 92.9)</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>Large</td>
<td>13.2</td>
<td>90.7 (82.0, 95.4)</td>
<td>52.0 (48.1, 55.9)</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>15.4</td>
<td>82.3 (76.1, 87.2)</td>
<td>52.5 (49.6, 55.3)</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Abbreviations are as shown in Table 2.
the large vessel group, with a median MLD of 2.0 mm before DCB, the smaller MLD in small 1.5 mm vessels was likely to have resulted in greater variability in lumen contour segmentation, thereby leading to the overestimated EDS, which was calculated as the ratio between the absolute lumen morphology parameter and the difference between lumen changes within the cardiac cycle.

Stronger correlations were observed within the same category of variables (morphological or strain) compared to those between different categories. In addition, among the three strain indices, ED-EDS had the highest correlation coefficients with pre-DCB DSP and with post-DCB MLD. These findings might have been associated with the relationship between morphological and strain variables in this cohort which was consistent in small vessels before DCB treatment and in large vessels after DCB treatment. Notably, ED-EDS had the highest AUC of the ROC curves among three strain indices in the overall cohort. The true positive rate in small vessels was clearly higher when the false positive rate was low, thus suggesting that EDS might have greater diagnostic value for stenotic lesions in small vessels compared to large vessels, which is precisely what is challenging to discern through visual observation alone.

Previous studies have demonstrated that the quantitative flow ratio or its gradient within lesion segments is a promising predictor of adverse events after DCB angioplasty [23, 24]. Of note, the quantitative flow ratio is a physiological index based on 3D QCA at a specific static frame within the cardiac cycle (e.g., end-diastole), which is used to estimate fractional flow reserve without hyperemia or a pressure guide wire, and enables both anatomical and functional lesion assessments. In our study, angiography-based EDS was measured from the dynamic deformation of coronary vessels during the cardiac cycle, thereby providing a realistic measurement of mechanical status of the vessel segment, which might also be associated with the late outcomes after DCB angioplasty of de novo lesions.

Whether our findings suggest potential improved outcomes of DCB in de novo large vessels remains hypothetical. Generating smooth and uniform surfaces of lesion segments following DCB treatment could be challenging, therefore it might be related to the less sensitive to EDS of the vessel segment. Decreasing and making the endothelial strain at the lesion segment uniform is highly recommended, given that large variations in strain might lead to lumen surface instability and recoil. Moreover, achieving desirable pre-dilation has been suggested to be key to successful DCB treatment for coronary de novo lesions [6]. All included cases were well-prepared after plain balloon angioplasty, and showed clear lumen contours without dissections, thus potentially resulting in the low level of EDS at pre-DCB.

Many angiography-based computational models have been developed and evaluated for the determining the physiological status of coronary arteries in vivo, to achieve optimal interventional treatment; these models include the quantitative flow ratio (QFR), superficial wall stress/strain, and endothelial shear stress. A large-scale trial has demonstrated that QFR-guided PCI lesion selection, compared with standard angiography guidance, improves 1-year clinical outcomes in patients [25], and has indicated the superior prognostic value of post-PCI physiological assessment by μQFR after angiographically successful left main bifurcation PCI, with 13.2% of patients showing elevated risk of 3-year cardiovascular death [26]. QFR is calculated on the basis of a static model of coronary arteries at end-diastole from 3D reconstruction of angiography and subsequent fluid dynamics measurements. In contrast, the EDS approach focuses on the dynamic mechanical status of the endothelial layer, and is directly calculated from the deformation of arteries according to angiography during the entire cardiac cycle. In theory, non-uniform distribution of strain or stress caused by dynamic vessel deformation might be likely to cause wall instability and trigger adverse events. Therefore, measuring EDS and evaluating its acute stability after DCB treatment on a large scale is clinically important.

Although this is the first study using computational modeling to assess EDS in de novo coronary arteries, several limitations should be acknowledged. First, the matching of the segments of interest between pre- and post-DCB might have been affected by variations in arterial length during the cardiac cycle. However, we used a relatively small value (0.4 mm) as the interval between adjacent cross-sections to limit deviations in the data between pre- and post-DCB at the same cross-section. Second, the patient sample included two vessel groups and was relatively small. The 16
available patients resulted in 684 cross-sections in the segment of interest, which enabled detection of significant differences in statistical analysis. Finally, outcome data should be obtained to assess the value of integrating this method for the assessment of DCB treatment significance into routine clinical practice. Although previous studies have assessed periprocedural myocardial biomarkers associated with mortality after left main PCI [27, 28], the effects of DCB treatment on periprocedural cardiac adverse events were unclear. The current study attempted to assess arterial wall stability by using the EDS method from a biomechanical viewpoint, but caution should be still exercised in predicting future events in small or large vessels.

Conclusion

Angiography-based computational modeling for assessing EDS of de novo coronary arteries enables evaluation of local mechanical deformation forces and lumen morphologies before and after DCB treatment in small and large vessels. DCB treatment following lesion preparation leads to larger increases in lumen size in large vessels compared to small vessels, while causing a more pronounced reduction in EDS in small vessels than in large vessels. Further study is required to examine the clinical value of EDS in detecting lesions with high instability after angioplasty that are likely to cause adverse events.

Author Contributions

L. Xu, Z. Tang, and X. Wu gathered, analyzed, and interpreted data; wrote the first draft of the article; and contributed to all revisions. Y. Jiang, H. Zou, and Y. Shen analyzed and interpreted data. X. Zhang, A. Elkoumy, X. Guan, and X. Wu designed the study; gathered and interpreted data; and contributed to all revisions.

Data Availability Statement

The datasets generated and analyzed for this manuscript are not publicly available but may be obtained from the corresponding author on reasonable request.

Funding

This research was supported by the Zhejiang Provincial Natural Science Foundation of China (LTGY24H180019), Basic Medical and Health Science Technology Projects of Wenzhou City (Y20220132), and Medical and Health Science and Technology Project of Zhejiang Province (2023RC210 and 2024KY160).

Ethics Approval Statement

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Institutional Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University on November 28, 2022 (No. 2022-K-214–01). Informed consent was obtained from all participants involved in the study.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Supplementary Materials

Supplementary material for this paper can be obtained online at the following links: https://cvia-journal.org/wp-content/uploads/2024/05/CVIA-424-Supplementary-Table-1.pdf; https://youtu.be/WitWxQ71S-M; https://youtu.be/myArObMC-ZUM; https://youtu.be/lMeOdcI3zE.

REFERENCES


