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# Impact of vessel curvature on neointimal healing after stent implantation as assessed by optical coherence tomography

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**Abstract**

**Purpose:** Previous studies have indicated that stent implantation could alter the vessel geometry, which may impact the neointimal healing process. Curvature is an important parameter for evaluating vessel geometry. The purpose of our study was to investigate the relationship between vessel curvature and neointimal healing after stent implantation.

**Methods:** Fifty-nine patients with acute coronary syndrome (ACS) who underwent stent implantation were enrolled in the study. According to the post-percutaneous coronary intervention vessel curvature measured by quantitative coronary angiography, patients were divided into high (n = 30) and low (n = 29) curvature groups. Neointimal thickness and area together with the neointimal type were assessed by optical coherence tomography at a 6-month follow-up.

**Results:** Baseline clinical characteristics were comparable between the 2 groups. The vessel curvature at pre- and 6-month follow-up was significantly higher in the high curvature group than the low curvature group. At 6-month follow-up, neointimal thickness (0.22 [0.08–0.32] mm vs. 0.10 [0.07–0.16] mm, $P = .043$) and neointimal area (1.86 [0.66–2.66] vs. 0.82 [0.60–1.41] $mm^2$, $P = .030$) were significantly higher in the high curvature group than the low curvature group. In the high curvature group, the incidence of the heterogeneous neointimal type was higher than that in the low curvature group (50.00% vs. 17.20%, respectively, $P = .004$), whereas the frequency of the homogeneous neointimal type was lower (43.30% vs. 82.80%, respectively, $P = .004$) in the high curvature group than the low curvature group.

**Conclusion:** Higher vessel curvature after stent implantation may potentially have an impact on the neointimal healing with a higher incidence of heterogeneous neointimal.

**Abbreviations:** ACS = acute coronary syndrome, DES = drug eluting stent, MLD = minimum lumen diameter, OCT = optical coherence tomography, PCI = percutaneous coronary intervention, QCA = quantitative coronary analysis, WSS = wall shear stress.

**Keywords:** neointimal healing, optical coherence tomography, vessel curvature

## 1. Introduction

Drug-eluting stent (DES) implantation is regarded as an effective strategy for patients with narrowing of the coronary arteries. However, in-stent restenosis, one of the major events, which may cause late-stent failure, has imperiled the long-term clinical outcome after percutaneous coronary intervention (PCI).[1] Several mechanisms have been revealed relating to the excessive neointimal healing including patient factors (diabetes), lesion factors (longer stent), or PCI procedure (stent under expansion), among others.[2] In addition, recently, researchers have demonstrated that the local geometric remodeling changed after stent implantation, which results in the redistribution of wall shear stress (WSS), could be another crucial factor related to the neointimal healing process.[3–5] However, few in vivo studies have given evidence that neointimal healing involves altered vessel curvature after PCI.

Coronary geometry is the major determinant of WSS, which could be semievaluated by the tortuosity or vessel curvature. Comparing the geometry in a bended vessel with that in a straight vessel, the variation can cause the change of WSS.[6] Moreover, low WSS could promote the migration of smooth muscle cells and increase the inflammation status during the development of atherosclerotic plaques.[7,8]

Curvature is an important parameter to evaluate the coronary geometry, which can be measured by quantitative coronary angiography analyses (QCA) software directly. Optical coherence tomography (OCT) is a new technology of intravascular imaging with a high-resolution ratio up to 5 to 10 μm. The neointimal area, thickness, and tissue characteristics can be qualitatively and quantitatively analyzed by OCT. Our study

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Ethical Approval: This research was approved by the institutional review committee of our hospital and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients provided written informed consent before inclusion in the study.

The authors report no conflicts of interest.

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aimed to observe the relationship between vessel curvature and neointimal healing. To address this issue, we used OCT and QCA to verify this viewpoint.

## 2. Materials and methods

### 2.1. Study population

We retrospectively enrolled patients with acute coronary syndrome (ACS) who underwent stent implantation and OCT follow-up from January 2010 to November 2013 at the 2nd Affiliated Hospital of Harbin Medical University. In accordance with the ACC/AHA guideline, the definition of ACS involves ST-segment elevation acute myocardial infarction, non-ST-segment elevation acute myocardial infarction, and unstable angina. All the patients underwent a single stent implantation and 6-month coronary angiography and OCT follow-up. Patients who have left main disease, extended long, severe calcified, or complex lesion; overlapping stents; or unsatisfactory OCT image quality were excluded from this study. Finally, 59 patients with ACS with 59 stents were enrolled and analyzed. This study was approved by the institutional review committee of our hospital, and all patients provided written informed consent.

### 2.2. QCA

The 2-dimensional angiograms were analyzed by an independent core laboratory with the CAAS 5.10.1 analysis system (Pie Medical Imaging BV, MA). Coronary angiograms were analyzed by 2 expert observers who were blinded to the OCT findings. The angiographic images were collected and measured at baseline, post-PCI, and at 6-month follow-up. We measured the following QCA parameters: curvature of vessel, percentage of diameter stenosis, minimal lumen diameter (MLD), reference diameter, and lesion length. Curvature was defined as the infinitesimal rate of change in the tangent vector at each point of the centerline, and the measurement has a reciprocal relationship with the radius of a perfect circle defined by the curve at each point, which was calculated as 1/radius of the circle (in $cm^{-1}$).[9] Curvature was measured at pre-implantation, post-implantation, and 6-month follow-up in the same angiographic position using clear landmarks or radio-opaque markers (Fig. 1). Furthermore, acute gain was calculated as post-implantation MLD minus pre-implantation MLD. Late luminal loss was calculated as post-implantation MLD minus MLD at the 6-month follow-up.[10,11]

### 2.3. OCT imaging analyses

OCT images were performed after implantation with a Frequency Domain system (C7-XR, LightLab Imaging, Westford, MA) or Time-Domain system (M2/M3, LightLab Imaging). The analysis of all images was accomplished using the offline software. Two experienced investigators analyzed all OCT images and were blinded to the histological and QCA results. Stent segments were analyzed every 1 mm from distal to proximal frames. If any section of the struts was exposed to the lumen, it was defined as uncovered struts.[12,13] Neointimal thickness was

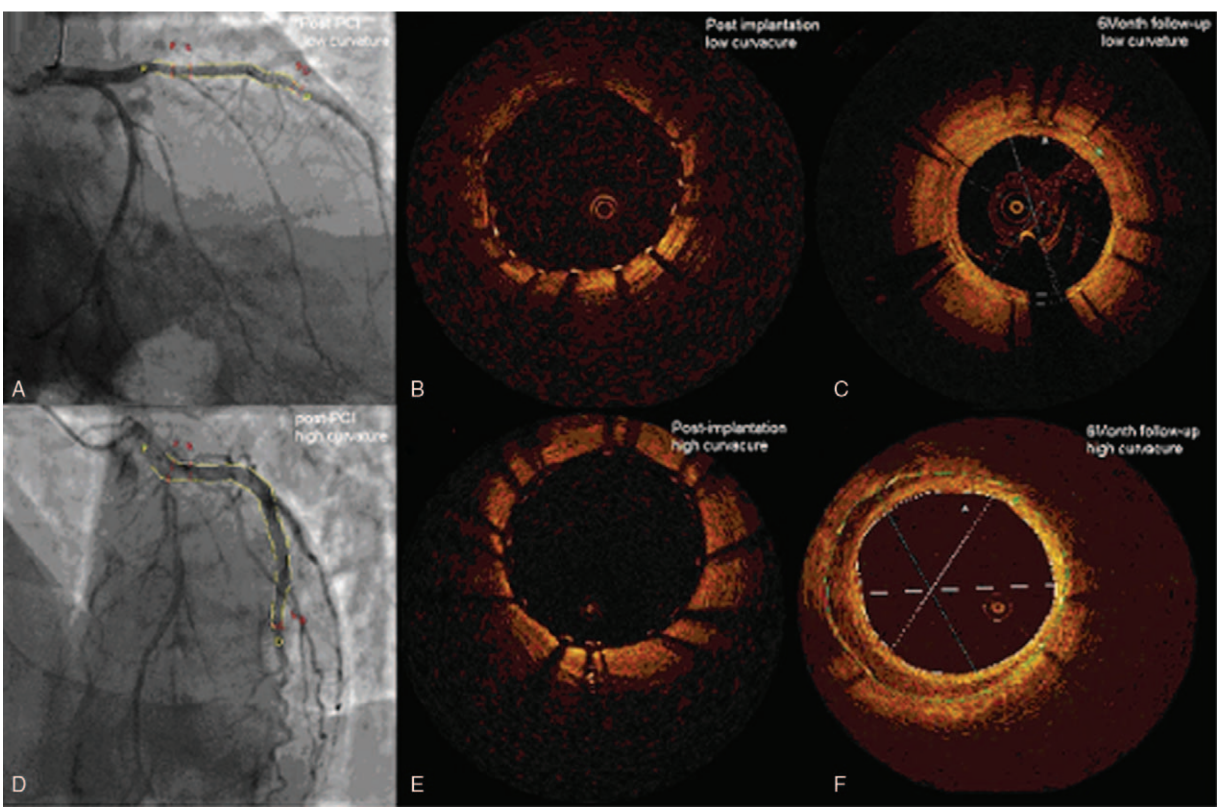


Figure 1. Representative quantitative coronary angiography (QCA) and optical coherence tomographic (OCT) images. (A) Coronary angiography after stent implantation in the low curvature group. (B) OCT image immediately at post-implantation in the low curvature group. (C) OCT image at the 6-month follow-up in the low curvature group. (D) Coronary angiography after stent implantation in the high curvature group. (E) OCT image immediately at post-implantation in the high curvature group. (F) OCT image at the 6-month follow-up in the high curvature group.

defined as the distance between the luminal surface and each strut, and the luminal surface was measured in the direction of the stent center of gravity. The stent area was calculated by multiple tracing the outline of the struts along its inner contour and was automatically depicted using the stent circumference. The lumen area was described as the area along the leading edge of the circumferential hyper-reflective zone covering the stent struts. This zone was delimited, and its area was calculated in a manner identical to that of the stent area. The neointimal area was calculated by subtracting the lumen area from the stent area. The percentage of neointimal area was calculated according to the following formula: (stent area – lumen area)/stent area $\times$ 100% (Fig. 1). For qualitative analyses, neointimal tissue was classified into 3 patterns: homogeneous, heterogeneous, and layered. Homogeneous neointimal was defined as the uniform optical properties with no focal change in the backscattering pattern. Heterogeneous pattern was identified as neointimal tissue with focal change optical properties and diverse backscattering patterns, and concentric layers with different optical properties were recognized as the layered pattern.[14,15]

### 2.4. Statistical analyses

Continuous variables were presented as the means ± standard deviations (mean ± SD). When continuous variables did not have a normal distribution, they were expressed as medians (interquartile range). Categorical variables were presented as numbers with a percentage. The Mann-Whitney *U* test was used for testing overall differences when variables were non-normally distributed, whereas Student *t* test was performed for normally distributed variables. Comparisons of categorical variables were evaluated with the $\chi^2$ test. All statistical analyses were conducted using SPSS version 23.0 (IBM, New York, NY). A *P* value <.05 was considered significant.

## 3. Results

### 3.1. Baseline clinical characteristics

In total, 59 patients with 59 stented lesions were divided into 2 groups according to the post-implantation vessel curvature. The clinical characteristics were compared between patients with high (n=30) and low (n=29) curvatures (Table 1). There were no significant differences in regard to age, sex, cardiovascular risk factors, clinical presentation, or medication between the 2 groups.

### 3.2. QCA

Table 2 shows the angiographic findings. All patients were managed with routine interventional techniques and underwent conventional DES implantation. Comparing the high and low curvature groups, the location of the target lesions in the coronary artery was similar. There were no significant differences between the two groups with respect to stent type, stent diameter, stent length, and PCI procedure. Diameter stenosis and lesion length were similar between the high and low curvature groups. Acute gain post-PCI and late loss at the follow-up procedure were also comparable between the high and low curvature groups (Table 3). When comparing the high and low curvature groups, we observed a significant difference in the curvature values (0.54 [0.35–0.64] and 0.36 [0.16–0.44], respectively, *P*=.002) between the 2 groups before stent implantation. Moreover, the curvature values post-implantation (0.49 ± 0.18 vs. 0.18 ± 0.08/cm, *P*<.001) and at the 6-month follow-up (0.42 [0.21–0.55], 0.20 [0.12–0.36]/ cm, *P*=.005) were also significantly different between the high and low curvature groups.

### 3.3. OCT finding

The OCT findings are shown in Table 4. There are 687 and 631 cross-sectional OCT images for the high and low curvature groups, respectively, which included 4356 and 4004 discernible stent struts, respectively; all of which were analyzed at 6 months of follow-up (Fig. 1). Compared with the low curvature group, the mean neointimal thickness was greater in the high curvature group (0.22 [0.08–0.32] vs. 0.10 [0.07–0.16] mm$^2$, *P*=.043) (Fig. 2A). Mean neointimal area was significantly larger in the high curvature group than the low curvature group (1.86 [0.66–2.66] vs. 0.82 [0.60–1.41] mm$^2$, *P*=.030) (Fig. 2B). The percentage of neointimal area was also significantly different between the 2 groups (23.47 [9.67–40.18] % vs. 11.92 [9.35–19.33] %, *P*=0.041) (Fig. 2C). Neointimal pattern type was significantly different between the high and low curvature groups (*P*=.012). Homogeneous neointimal pattern type was significantly different between the high and low curvature groups (43.30% vs. 82.80%, respectively, *P*=.004)

**Table 1**

**Baseline clinical characteristics.**

| Variables | High curvature (n=30) | Low curvature (n=29) | *P* |
|---|---|---|---|
| Age, yrs | 54.80 ± 11.48 | 56.07 ± 9.13 | .640 |
| Male, n (%) | 19 (63.30) | 19 (65.50) | .861 |
| Hypertension, n (%) | 15 (50.20) | 18 (62.10) | .350 |
| Diabetes, n (%) | 20 (66.70) | 16 (55.20) | .365 |
| Hyperlipidemia, n (%) | 10 (33.30) | 5 (17.20) | .153 |
| Smoker, n (%) | 16 (55.30) | 14 (48.30) | .698 |
| Clinical presentation | | | .219 |
| STEMI, n (%) | 11 (36.70) | 5 (17.20) | |
| NSTEMI, n (%) | 6 (20.00) | 9 (31.00) | |
| UA, n (%) | 13 (43.30) | 15 (51.80) | |
| Medication at discharge | | | |
| Aspirin, n (%) | 30 (100.00) | 28 (96.60) | .492 |
| Clopidogrel, n (%) | 29 (96.70) | 29 (100.00) | >.99 |
| Statin, n (%) | 29 (96.70) | 28 (96.60) | >.99 |

NSTEMI = non-ST-segment elevation myocardial infarction, STEMI = ST-segment elevation myocardial infarction, UA = unstable angina.

**Table 2**

**Angiographic and procedural characteristics.**

| Variables | High curvature (n=30) | Low curvature (n=29) | *P* |
|---|---|---|---|
| Location | | | .596 |
| LAD, n (%) | 14 (46.60) | 12 (41.40) | |
| LCX, n (%) | 5 (16.70) | 8 (27.60) | |
| RCA, n (%) | 11 (36.70) | 9 (31.00) | |
| Stent type | | | .137 |
| SES, n (%) | 15 (50.00) | 20 (69.00) | |
| EES, n (%) | 15 (50.00) | 9 (31.00) | |
| Stent diameter, mm | 2.89 (2.50–3.13) | 3.00 (2.50–3.50) | .839 |
| Stent length, mm | 24.00 (21.75–28.00) | 28.00 (18.00–33.00) | .529 |
| Balloon size, mm | 2.50 (2.50–3.00) | 2.50 (2.50–3.00) | .681 |
| Balloon pressure, atm | 16.00 (11.50–18.00) | 12.00 (8.00–17.50) | .060 |

EES = everolimus-eluting stent, LAD = left anterior descending, LCX = left circumflex, RCA = right coronary artery, SES = sirolimus-eluting stent.

**Table 3**

**Quantitative coronary angiography analysis.**

| Variables | High curvature (n=30) | Low curvature (n=29) | P |
|---|---|---|---|
| Curvature, /cm | | | |
| Pre-stent | 0.55 (0.35–0.64) | 0.36 (0.16–0.44) | .002 |
| Post-stent | 0.49±0.18 | 0.18±0.08 | <.001 |
| Follow-up | 0.42 (0.21–0.55) | 0.20 (0.12–0.36) | .005 |
| Pre-stent | | | |
| MLD, mm | 0.59 (0.34–0.99) | 0.53 (0.34–0.76) | .699 |
| RVD, mm | 2.26 (1.87–2.68) | 2.32 (2.09–2.70) | .570 |
| DS% | 74.73±16.20 | 75.65±12.65 | .808 |
| LL, mm | 9.20 (7.51–13.62) | 8.90 (7.09–12.62) | .744 |
| Post-stent | | | |
| MLD, mm | 2.39±0.41 | 2.35±0.45 | .688 |
| RVD, mm | 2.88±0.45 | 2.88±0.42 | .959 |
| DS% | 16.83±7.30 | 18.28±12.14 | .585 |
| LL, mm | 23.50 (18.00–28.00) | 28.00 (23.00–33.00) | .285 |
| Follow-up | | | |
| MLD, mm | 2.24±0.66 | 2.40±0.43 | .259 |
| RVD, mm | 3.05 (2.45–3.30) | 3.04 (2.80–3.33) | .554 |
| DS% | 24.77±13.92 | 21.33±11.19 | .296 |
| LL, mm | 24.00 (21.75–28.00) | 28.00 (18.00–33.00) | .529 |
| Acute gain, mm | 1.76±0.44 | 1.67±0.71 | .566 |
| Late loss, mm | 0.16±0.60 | -0.05±0.51 | .151 |

DS=diameter stenosis, LL=lesion length, MLD=minimal lumen diameter, RVD=reference vessel diameter.

**Table 4**

**Optical coherence tomography finding.**

| Variables | High curvature (n=30) | Low curvature (n=29) | P |
|---|---|---|---|
| Discernible struts | 4356 | 4004 | |
| Cross-section | 687 | 631 | |
| Uncovered struts | 407 | 495 | |
| Uncovered struts, n (%) | 6.70 (0.00–12.25) | 7.84 (1.83–21.69) | .075 |
| Thickness of NIH, mm | 0.22 (0.08–0.32) | 0.10 (0.07–0.16) | .043 |
| Lumen area, $mm^2$ | 5.10 (4.16–6.96) | 5.48 (4.77–7.44) | .370 |
| Stent area, $mm^2$ | 6.80 (5.87–8.99) | 6.77 (5.61–9.50) | .733 |
| NIH area, $mm^2$ | 1.86 (0.66–2.66) | 0.82 (0.60–1.41) | .030 |
| NIH area, n (%) | 23.47 (9.67–40.18) | 11.92 (9.35–19.33) | .041 |
| Malapposed struts | 2.09±3.22 | 3.11±4.10 | .232 |
| Neointimal type | | | .004 |
| Homogeneous, n (%) | 13 (43.30) | 24 (82.80) | |
| Heterogeneous, n (%) | 15 (50.00) | 5 (17.20) | |
| Layered, n (%) | 2 (6.70) | 0 (0.00) | |

NIH=neointimal hyperplasia.

(Fig. 3A), and the heterogeneous neointimal pattern type was also significantly different between the two groups (50.00% vs. 17.20%, respectively, $P=.004$) (Fig. 3B). At 6-month follow-up, the amount and percentage of uncovered struts and malapposed struts (including persistent and late acquired) were comparable within the two groups. Stent and lumen areas were also similar (Table 4).

## 4. Discussion

The leading discoveries of our research are listed below. First, the vessel curvature of both groups constantly changed from pre-stent implantation to post-stent implantation and from post-stent implantation to follow-up. Significant differences were found between the high and low curvature groups at the three periods. Second, compared with the low curvature group, the high curvature group has a bigger neointimal hyperplasia area, percentage of neointimal hyperplasia area, and neointimal thickness. Third, the high curvature group has less homogeneous neointimal type and more heterogeneous neointimal type compared to the low curvature group. Our research clearly indicated that neointimal thickness, neointimal area, and percentage of neointimal area are higher in the high curvature group than the low curvature group.

Curvature is an important parameter of the regional geometry in a coronary artery. The change of curvature varies with the change of vessel geometry. The local vessel geometry of an implanted stent may contribute to the redistribution of WSS and influence the characteristics of blood flow.[16–21] A curved vessel has lower WSS than a straight vessel. Moreover, curvature is higher in a curved vessel than a straight one. Bended vessels after stent implantation are more likely to cause endothelial injury and inflammation, which result in the migration of smooth muscle cells and promotion of excessive neointimal healing compared to straight vessels.[6] Excessive neointimal healing may be responsible for the development of atherosclerosis and is related to a high risk of restenosis.[22–26]

Previous studies considered that thrombogenesis is the main mechanism of stent restenosis,[2] whereas recent research has shown that the remodeling of vascular geometry and excessive neointimal healing are independent mechanisms of stent restenosis.[3] Although neointimal healing is influenced by multiple

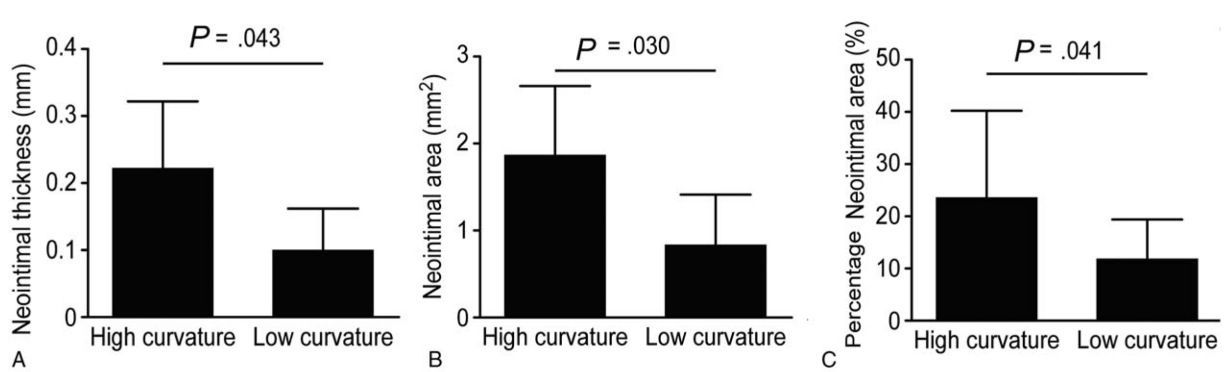


Figure 2. OCT findings for the high and low curvature groups. (A) Neointimal thickness ($P=.043$). (B) Neointimal hyperplasia area ($P=.030$). (C) Percentage of neointimal area ($P=.041$).

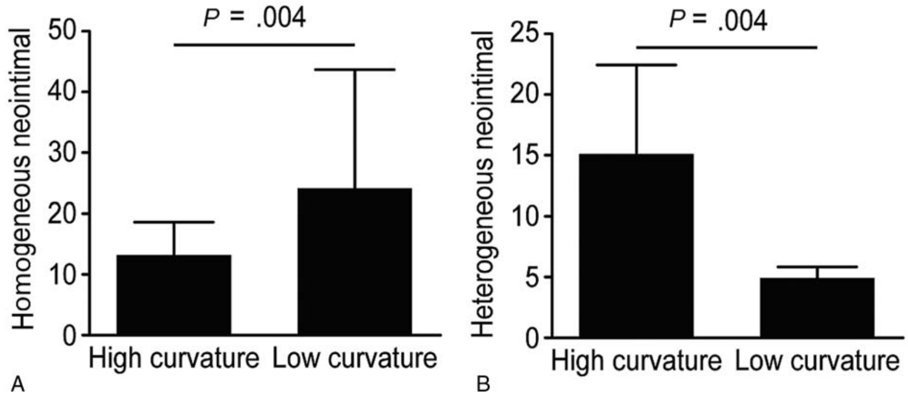


**Figure 3.** Comparison of neointimal type in the high and low curvature groups. (A) Homogeneous neointimal type ($P$ = .004). (B) Heterogeneous neointimal type ($P$ = .004).

factors, including the type of coronary heart disease, plaque morphology, age, sex, smoking, diabetes, hypertension, high cholesterol, drug-coated stent type, and stent design.[15] In our study, we fully consider these factors. Our research showed that there is no statistical difference in baseline data between 2 groups. The dilatation have no statistical difference in high curvature group and low curvature group (16.00 [11.50–18.00] vs.12.00 [8.00–17.50] atm, $P$ = .060). Most patients needs post dilatation in our center to optimize the stent implantation. But there was a few patients don't need post dilatation if the stent is well attached and expansive, although it is more convincing if the type of stent is consistent. But our study is retrospective. Our center used more sirolimus-eluting stent (SES) stents before and more everolimus-eluting stent (EES) stents resently. This is our research's limitation. Although EES stent is better than SES stent in design, drug coating, and preventing in stent thrombus, the distribution of stent type has no statistical difference between two groups ($P$ = .137). There are 15 SES patients in high curvature group and 20 SES patients in low curvature group. And there are 15 EES patients in high curvature group and 9 EES patients in low curvature group. Lesion length before stent implantation is not statistically different in high curvature goup and low curvature group (9.20 [7.51–13.62] vs. 8.90 [7.09–12.62], $P$ = .744). And there is no statistical difference in stent length in high curvature group and low curvature group (24.00 [21.75–28.00] vs. 28.00 [18.00–33.00], $P$ = .529). Before stent implantation, the lesion length was automatically identified by the computer as the narrowest part of the lesion on angiographic image with QCA, so the measured lesion length was smaller than the actual lesion length. The stent length is larger than the lesion length because the stent length must cover the lesion length. Whereas after stent implantation and at 6-month follow-up, the lesion length was identified according to the stent length. In concusion, our study excluded the effect of baseline data, lesion length, stent length, stent type, and surgical operaions and so on factors on neointima. This experiment aimed to study the effect of curvature on neointimal healing, under the condition where in the 2 groups had no difference in terms of these factors.

At the 6-month follow-up, although there was no difference in the degree of uncovered stents between the 2 groups, the high curvature group had greater neointimal area and thickness compared to the low curvature group. The degree of uncovered stent is the ratio of the uncovered struts to the total struts, which represents the rate of stent malapposition and the level of stent endothelialization. No difference in the degree of uncovered stent indicated that the rate of stent malapposition was similar between the 2 groups. The degree of uncovered stent is used to evaluate the incidence of thrombosis in stent and guide the antiplatelet therapy, whereas the neointimal area and thickness are used to predict stent restenosis.

In this research, the high curvature group had a relationship with the heterogeneous neointimal pattern type. The heterogeneous neointimal type consists of a proteoglycan-rich myxomatous matrix, microvessels, and pyknotic calcium deposition. The heterogeneous neointimal pattern type might have a greater ability to promote distal embolization compared to other neointimal pattern types.[27–29] Therefore, the high curvature group is more likely to cause thrombotic events. The low curvature group was associated with the homogeneous neointimal pattern type in our study. Earlier reports illustrate that the homogeneous neointimal pattern correlated with high proportion of connective tissues and smooth muscle cells, which are beneficial for vascular healing.[30] Similarly, we found that the homogeneous type consisted of a higher proportion of fibrous connective tissues. According to the histological features, the homogeneous intimal type had more benefits and greater prognosis after stent implantation.[31,32]

At 6-month follow-up, no death and recurrence of myocardial infarction occurred in either group. After stent implantation, there were 10 patients in high curvature group and 4 patients in low curvature group who have angina after stent implantation, but the extent of pain was more moderate. High curvature group has large degree of vascular curvature, so the blood flow has slower velocity. And then the myocardial energy metabolism maybe poor. Therefore, the symptoms of myocardial ischemia improve slowly. It requires large clinical research to confirm.

Our research also showed that the blood vessel curvature underwent dynamic changes; consequently, the vessel geometry also constantly changed. Moreover, our study showed that although vessel curvature of the individual patients in the high curvature group reduced, and that of the individual patients in the low curvature group increased at the 6-month follow up, the curvature was still statistically different between the 2 groups. Our study aimed to confirm that the remodeling of vascular geometry after stent implantation can lead to excessive neointimal healing, and that compared with straight vessels, curved vessels have excessive neointimal healing, which more likely lead to the development of in-stent restenosis.

### 4.1. Study limitations

First, our research was a small, single-center, and retrospective study, which most likely resulted in a selection bias. Second, our research was limited to patients with ACS. It is necessary to evaluate the effect of curvature on long-term prognosis of normal patients. Third, there was no comparision between the first generation stent type and the second generation stent type. Additionally, the curvature was measured by 2-dimensional QCA software instead of 3-dimensional software, which might have impacted the results of the study. Finally, a long-term follow-up period would be more convincing and give a comprehensive understanding about the relationship between vessel curvature and neointimal healing. Support from future studies involving large sample sizes is needed to confirm this opinion.

## 5. Conclusions

The present study demonstrated that vessel curvature after stenting may potentially impact the neointimal healing process. The higher vessel curvature in the coronary artery correlated with the larger neointimal tissue hyperplasia area and bigger neointimal thickness after stent implantation. Higher vessel curvature is related to heterogeneous neointimal type, and lower vessel curvature is linked to homogeneous neointimal type.

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