How to Fix the Edge Effect of Catheter-Based Radiation Therapy in Stented Arteries

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Background—Edge stenosis remains a serious limitation of catheter-based vascular brachytherapy (VBT). This study aims to identify the mechanisms and evaluate strategies to minimize edge restenosis in patients treated with VBT.

Methods and Results—Thirty-four porcine stented coronary arteries were irradiated (doses of 15 or 22 Gy) with $^{192}$Ir trains of either 6 seeds (23 mm) with 0 mm coverage at the distal stent edge and 10 mm at the proximal stent edge or 14 seeds (55 mm) centered at the distal edge of the stent with 27.5 and 14.5 mm coverage at the distal and proximal edges, respectively. After VBT, an additional 13-mm stent was positioned overlapping the distal margin of the first stent. Animals were killed at 28 days, and arteries were analyzed. Longer radiation margins were associated with reduced intimal area (IA) at the stent edge: $2.3/\pm 0.9$, $3.6/\pm 2.0$, and $5.3/\pm 2.2$ mm$^2$ with 15 Gy for a radiation margin of 14.5, 10, and $13$ mm ($13$ versus 10, $P=0.06$; 10 versus 14.5, $P=0.06$). Additional stenting was associated with an increase of IA: $4.0/\pm 2.3$ mm$^2$ at the overlapped segment. Increasing the dose to 22 Gy resulted in a reduction of the IA at the overlap segment to $1.3/\pm 0.57$ mm$^2$ with 14 seeds (27.5 mm coverage) but was not helpful with 6 seeds (0 mm coverage): IA, $5.56/\pm 2.28$ mm$^2$.

Conclusions—Extending the radiation margins to 14.5 mm from each end of the stent minimized the edge-effect phenomenon. A higher dose is essential to eliminate further increases in IA at the overlapped segment with additional stents. (Circulation. 2002;106:2271-2277.)

Key Words: stents • brachytherapy • restenosis

Vascular brachytherapy (VBT) has emerged as a promising therapy to inhibit restenosis after percutaneous coronary interventions.$^{1,2}$ Clinical studies that used both $\beta$ and $\gamma$ radiation have demonstrated potency to reduce the recurrence of in-stent restenosis.$^{3,4}$ However, angiographic follow-up identified the edge-effect phenomenon as a major limitation to VBT.$^5$ Angiographic and intravascular ultrasound (IVUS) studies on patients who underwent VBT showed nearly complete inhibition of the neointima within the stent body but detected stenosis at the edge of the stented segments and the radiation field. Unfavorable angiographic results were also observed when additional stents were implanted at the time of the radiation procedure.$^6$

The cause of the edge effect is not completely understood. The combination of dose falloff and stent injury has reproduced the edge effect with radioactive stents in animal models and in clinical trials,$^{7,8}$ but the relationships between edge effect and inadequate coverage of the injured segment by the radioactive source were never tested prospectively. The optimal margin coverage necessary to eliminate the edge effect, its consequences on nonstented segments, and the decremental effects of stenting after the brachytherapy procedure on the late outcome are unknown. Therefore, we performed a series of experiments to further explore a strategy that will enable us to minimize the edge-effect phenomenon by lengthening the radiation margin and to optimize the brachytherapy procedure when additional stents are deployed.

Methods

Animal Preparation

The protocol was approved by the Institutional Animal Care and Use Committee of the Medstar Research Institute, Washington, DC. Thirteen domestic juvenile swine (Thomas D. Morris, Inc, Reisterstown, Md), 3 months old and weighing 25 to 30 kg, were used. Animals were treated with aspirin 325 mg and with clopidogrel 75 mg/d 3 days before the procedure and continued until euthanization. The pigs were sedated with a combination of ketamine (25 mg/kg), xylazine (2 mg/kg), and acepromazine (0.2 mg/kg) by intramuscular injection. The animals were ventilated with oxygen (2 L/min) and room air (1.5 L/min). Anesthesia was maintained with 0.9 vol% isoflurane. An introducer sheath was placed in the left carotid artery by surgical cutdown, and heparin (3 mg/kg) was given.
Reference Stent Implantation
A baseline angiogram was performed, and 2 of the major coronary vessels (right, left anterior descending, and circumflex arteries) were selected for stenting. An implantation of an oversized stent (3.0 mm in diameter and 13 mm long centered on a 3.0×15-mm balloon; Tristar Stent, Guidant) was performed to obtain a stent-to-artery ratio of 1.1:1 to 1.3:1 compared with the baseline vessel diameter.

Radiation Protocol and Treatment Groups
After successful implantation, the VBT procedure was performed. A noncentered delivery catheter, Checkmate (Cordis), over a flexible 0.014-in wire was placed into the stented arteries. Three groups of radiation protocols were conducted with commercially available 192 Ir source trains and additional distal stenting. In the first group (n=9), a train of 6 seeds (23 mm) was placed, with the distal seed positioned at the distal end of the stent, leaving 10 mm of margin coverage at the proximal end of the stent; a dose of 15 Gy at 2 mm (mean dwell time, 20 minutes) was prescribed for this group of arteries.

The second group of arteries (n=9) was treated with a train of 14 radioactive 192 Ir seeds (55 mm). This train was centered on the distal edge of the reference stent with a margin of 14.5 mm of coverage at the proximal edge and 27.5 mm at the distal segment of the stent; this group was also treated with a dose of 15 Gy at 2 mm.

The third group of arteries (n=8) was also treated with a source train of 14 seeds, the same as that used for the second group, positioned at the same location but with an increase in the prescribed dose to 22 Gy at 2 mm from the source (mean dwell time, 29 minutes). The purpose of this group was to test whether a higher dose could minimize the gradient of the neointima formation seen in the overlapped segment versus the edges of the stent under sufficient coverage of the source.

In all arteries, a simulation of a nonradioactive train was used to plan accurate positioning by the protocol and documented by cineangiography.

Additional Stent Implantation
For all 3 groups, after the radiation treatment, an additional stent was implanted distal to the reference stent, overlapping ≤1 mm with the distal edge of the reference stent. Additional stent characteristics and delivery pressure were the same as the reference stent (13 mm long, 3 mm in diameter). An angiogram and IVUS documented the final result after the radiation therapy. Pigs were allowed to recover, and 50 mg of subcutaneous heparin was administered before the animals were returned to routine care.

Experimental Group With High Dose and Short Radiation Margins
To assess the impact of radiation dose on optimal margin length, an additional group of 8 arteries in 4 animals was irradiated at 22 Gy with 6-seed 192 Ir trains: radiation margins were −13 mm at the distal stent edge, 0 mm at the overlap segment, and 10 mm at the proximal stent edge. Follow-up and analysis similar to those in other groups were performed.

Follow-Up and Pathological Evaluation
Twenty-eight days after the intervention and the radiation therapy, the animals underwent follow-up angiogram and IVUS imaging and then were killed. The coronary arteries were perfusion-fixed in situ with 10% parafomaldehyde. The arteries were embedded in methyl methacrylate and cut, leaving the stent wires intact. Sections (50 to 100 µm thick) were obtained as follows: 1 section every 0.5 mm of proximal edges, distal edges, and overlapping segments, and 1 section every 6 mm in nonedge segments. The nonstented segments were sectioned every 6 mm from the stent edges (at 6, 12, 18, and 24 mm from stent edges). All sections were stained with toluidine blue/fuchsin and were assigned an injury score, an inflammation score, and a smooth muscle cellularity score.

Definitions of Subsegments
The edge segment was defined as the segment from 2.5 mm inside the stent edge extending up to 2.5 mm outside of the stent edge. The overlapping segment was defined as the segment extending 2.5 mm on each side from the middle of the overlapped stent. The body of the stent was defined as the stent, excluding the edge and the overlapped segments.

The radiation margin was the distance from the tip of the radiation source to the edge of the stent. The margin value was positive for stents covered by the radiation source and negative for the distance of the segments not covered by the source to the stent edge. Figure 1 illustrates the treated groups and the positioning of the source. The neointima formation for the following radiation margins was tested: −13, 0, 10, 13, 14.5, and 27.5 mm.
TABLE 1. Histomorphometric Measurements in the Body of Stents: Influence of Radiation Margin and Radiation Dose

<table>
<thead>
<tr>
<th>Radiation Dose, Gy</th>
<th>15</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−13-mm</td>
<td>0-mm</td>
</tr>
<tr>
<td></td>
<td>Margin</td>
<td>Margin</td>
</tr>
<tr>
<td>VA, mm²</td>
<td>13.10±1.49</td>
<td>13.16±1.72</td>
</tr>
<tr>
<td>LA, mm²</td>
<td>5.10±2.17</td>
<td>9.19±1.81*</td>
</tr>
<tr>
<td>IA, mm²</td>
<td>5.83±2.46</td>
<td>2.70±1.25*</td>
</tr>
<tr>
<td>IA/IS</td>
<td>3.02±4.93</td>
<td>1.43±0.22</td>
</tr>
<tr>
<td>% Stenosis</td>
<td>53±20</td>
<td>22±12*</td>
</tr>
<tr>
<td>Lum/Ar</td>
<td>39±16</td>
<td>66±11*</td>
</tr>
<tr>
<td>Inj score</td>
<td>1.44±0.95</td>
<td>0.90±1.20</td>
</tr>
<tr>
<td>Infl score</td>
<td>1.33±0.71</td>
<td>1.50±0.71</td>
</tr>
<tr>
<td>Int SM score</td>
<td>2.39±0.93</td>
<td>1.50±0.97</td>
</tr>
<tr>
<td>Adv fibrosis</td>
<td>0.94±0.53</td>
<td>0.70±0.82</td>
</tr>
</tbody>
</table>

VA indicates vessel area; LA, lumen area; IS, injury score; Lum/Ar, lumen/artery ratio; Inj, injury; Infl, inflammation; Int SM, intima smooth muscle cell; Adv, adventitia; r, reference stent; and a, additional stent. Margins are given from the stent edge.

*p indicates proximal edge; d, distal edge. Other abbreviations as in Table 1.

IVUS Equipment and Measurements

IVUS imaging was performed with a commercially available system (Atlantis 40 MHz, Cardio Vascular Imaging System, Inc). The ultrasound catheter was advanced 20 mm beyond the additional stent and was withdrawn by an automatic pullback at 0.5 mm/s. Data were recorded on high-resolution S-VHS videotapes for offline analysis. The analysis of the tapes was performed by use of computer planimetry (Tape Measure, Indec Systems) at the core laboratory independent of treatment information. At each stent edge, cross-sectional images were digitized every 1 mm from 10 mm distal to the additional stent to 10 mm proximal to the reference stent. Measurements included stent, external elastic membrane (EEM), lumen, plaque ± media (EEM − lumen), and intimal hyperplasia (IH, stent − lumen) cross-sectional areas.

Statistical Analysis

Data are expressed as mean ± SD. Comparisons of continuous variables between groups were performed by ANOVA with Bonferroni’s multiple comparison test for post hoc analysis. Significance was established at a value of P < 0.05.

Results

Overall, 13 animals (26 arteries) underwent successful stent implantation and radiation therapy. Two animals died prematurely at 25 days and 26 days: 1 treated with 15 Gy and the other with 22 Gy to both vessels. Postmortem analysis revealed coronary occlusion by a thrombus without evidence of intimal proliferation at the stented-irradiated site in both

TABLE 2. Histomorphometric Measurements at the Stent Edges: Influence of Radiation Margin and Radiation Dose

<table>
<thead>
<tr>
<th>Radiation Dose, Gy</th>
<th>15</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>−13-mm</td>
<td>10-mm</td>
</tr>
<tr>
<td></td>
<td>Margin</td>
<td>Margin</td>
</tr>
<tr>
<td>VA, mm²</td>
<td>13.04±1.62</td>
<td>13.27±1.13</td>
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<tr>
<td>LA, mm²</td>
<td>5.35±2.15</td>
<td>7.66±2.49*</td>
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<tr>
<td>IA, mm²</td>
<td>5.32±2.25</td>
<td>3.57±2.02</td>
</tr>
<tr>
<td>IA/IS</td>
<td>3.23±1.28</td>
<td>2.94±1.17</td>
</tr>
<tr>
<td>% Stenosis</td>
<td>50±19</td>
<td>33±21</td>
</tr>
<tr>
<td>Lum/Ar</td>
<td>41±16</td>
<td>57±19</td>
</tr>
<tr>
<td>Inj score</td>
<td>1.67±0.87</td>
<td>0.44±0.73</td>
</tr>
<tr>
<td>Infl score</td>
<td>1.33±0.87</td>
<td>1.22±0.67</td>
</tr>
<tr>
<td>Int SM score</td>
<td>2.56±1.01</td>
<td>1.78±1.20</td>
</tr>
<tr>
<td>Adv fibrosis</td>
<td>0.78±0.67</td>
<td>2.94±1.17</td>
</tr>
</tbody>
</table>

*p indicates proximal edge; d, distal edge. Other abbreviations as in Table 1.

*p < 0.05 vs 15 Gy/−13-mm margin; †p < 0.05 vs 15 Gy/10-mm margin; ‡p < 0.05 vs 15 Gy/14.5-mm margin (d); §p < 0.05 vs 15 Gy/14.5-mm margin (p).
animals. Eleven surviving animals were killed at 4 weeks, and all arteries were available for histomorphometric analysis.

**Histomorphometry**
A summary of histomorphometric measurements is displayed in Tables 1 to 3.

**Body of the Stents**
For the groups treated with 15 Gy, the neointimal formation within the body of the stents was lower by 42% in the group with a wide radiation margin of 14.5 mm: intimal area (IA) of $2.46 \pm 1.89$ mm$^2$ compared with the neointima formation in the group with no radiation coverage ($-13$-mm radiation margin), IA of $5.83 \pm 2.46$ mm$^2$, $P<0.05$. The group treated with 22 Gy and 14.5-mm radiation margins had a further reduction of IA: $1.06 \pm 0.69$ mm$^2$ in the body of the stent. The IA was similar within the body of reference and additional arteries treated with 22 Gy, IA was reduced across the entire analyzed segments to $1.31 \pm 0.57$ mm$^2$ at the overlapped segment versus $0.97 \pm 0.41$ mm$^2$ at the edge segment ($P=NS$) (Figure 3).

**Overlapping Stent Segments**
For the group treated with 15 Gy, IA was larger at the overlap segment than the body of the stent. Moreover, IA at the overlap segment was not influenced by the radiation margin. IA was $5.19 \pm 2.98$ mm$^2$ at the overlap segment covered by 0-mm radiation margin and $4.01 \pm 2.27$ mm$^2$ at the segment covered by 27.5-mm margin ($P=NS$). However, for the arteries treated with 22 Gy, IA was reduced across the entire analyzed segments to $1.31 \pm 0.57$ mm$^2$ at the overlapped segment versus $0.97 \pm 0.41$ mm$^2$ at the edge segment ($P=NS$) (Figure 3).

**Experimental Group With High Dose and Short Radiation Margins**
By histomorphometry, IA at the stent edge was $1.32 \pm 1.45$ mm$^2$ with a 10-mm radiation margin and $4.69 \pm 3.10$ mm$^2$ with $-13$ mm ($P<0.05$ versus 10 mm). With a 10-mm margin, the lumen area at the stent edge was smaller than at the body ($8.70 \pm 1.95$ and $9.78 \pm 0.37$ mm$^2$, respectively, $P=0.06$). At the overlap segment with 22 Gy and 0-mm margin, IA was $5.56 \pm 2.28$ mm$^2$ and was similar to the IA observed with 15 Gy and 0-mm margin ($5.51 \pm 2.87$ mm$^2$, $P=NS$).

**Nonstented Segments**
Selective analysis of the nonstented segments did not detect adverse histopathological findings. Throughout the artery, IA was less than $0.15 \pm 0.14$ mm$^2$ and was not correlated to the radiation margin. Injury and inflammation were rarely observed within these segments, with no correlation to the radiation margin: maximal injury score was $0.78 \pm 0.97$, maximal inflammation score was $0.33 \pm 0.50$, and there was no fibrin deposition in these segments.

**IVUS Measurements**
Results are expressed as the change in plaque, lumen, and EEM cross-sectional area from initial procedure to 28-day follow-up. Lumen loss throughout the nonstented segments was $<2$ mm$^2$. At all edges, the greatest lumen loss occurred in stented segments and was caused by IH. IH occurred primarily within edge segments and at the overlapped seg-

### TABLE 3. Histomorphometric Measurements at the Overlap Segment: Influence of Radiation Margin and Radiation Dose

<table>
<thead>
<tr>
<th>Radiation Dose, Gy</th>
<th>15 (0-mm Margin)</th>
<th>15 (27.5-mm Margin)</th>
<th>22 (27.5-mm Margin)</th>
<th>P, ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA, mm$^2$</td>
<td>13.14±1.31</td>
<td>13.71±0.81</td>
<td>12.60±1.05</td>
<td>0.17</td>
</tr>
<tr>
<td>LA, mm$^2$</td>
<td>5.48±2.04</td>
<td>7.53±2.21</td>
<td>9.11±1.00*</td>
<td>0.03</td>
</tr>
<tr>
<td>IA/Lum/art</td>
<td>5.51±2.87</td>
<td>4.01±2.27</td>
<td>1.31±0.57*</td>
<td>0.007</td>
</tr>
<tr>
<td>IA/IS</td>
<td>3.33±1.26</td>
<td>3.29±3.54</td>
<td>0.93±0.12</td>
<td>0.28</td>
</tr>
<tr>
<td>% Stenosis</td>
<td>49±22</td>
<td>36±17</td>
<td>13±5*†</td>
<td>0.004</td>
</tr>
<tr>
<td>Lum/art</td>
<td>42±17</td>
<td>55±15</td>
<td>72±5*†</td>
<td>0.003</td>
</tr>
<tr>
<td>Inj score</td>
<td>1.44±1.01</td>
<td>1.00±1.00</td>
<td>0.83±0.98</td>
<td>0.47</td>
</tr>
<tr>
<td>Inf score</td>
<td>1.22±0.83</td>
<td>1.33±0.50</td>
<td>1.00±0.63</td>
<td>0.64</td>
</tr>
<tr>
<td>Int SM score</td>
<td>2.22±0.97</td>
<td>1.67±1.00</td>
<td>0.00±0.00*†</td>
<td>0.0003</td>
</tr>
<tr>
<td>Adv fibrosis</td>
<td>1.11±0.60</td>
<td>1.33±0.71</td>
<td>0.83±0.75</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

*P<0.05 vs 15 Gy/0-mm margin; †P<0.05 vs 15 Gy/27.5-mm margin.
In arteries treated with 15 Gy, IH increased from 0.7 ± 0.6 mm² at 1 mm outside the stent to 3.3 ± 1.1 mm² at the stent edge with −13-mm radiation margin (outside versus stent edge; P < 0.01), from 0.9 ± 1.8 to 2.0 ± 0.8 mm² with 10-mm radiation margin (P = 0.11), and from 1.0 ± 0.4 to 2.4 ± 0.3 mm² with 14.5-mm radiation margin (P < 0.05).

At the overlap segment, maximal IH was 4.79 ± 1.26 mm² with 0-mm radiation margin and 3.39 ± 1.23 mm² with 27.5-mm radiation margin (P = 0.06).

In nonstented segments, maximal EEM gain (positive remodeling) was 2.4 mm² and maximal EEM loss (negative remodeling) was 1.6 mm², but no correlation was observed between EEM changes and radiation margins.

**Discussion**

This study shows that the edge effect after VBT is the consequence of neointimal proliferation at the edge of the stent and is preventable by lengthening the radiation margins. Additional stenting promotes neointimal proliferation at the overlapped segment despite long radiation margins. However, an increase of the radiation dose by 50% can prevent the neointimal proliferation triggered by additional stent.

The potential of intravascular radiation to inhibit neointimal hyperplasia after stent placement was demonstrated previously in animal models and in human clinical studies. Edge effect as a complication of VBT was seen first with the radioactive stent. Experimental work in porcine coronary arteries demonstrated that the main mechanism of edge effect with a $^{32}$P radioactive stent is a combination of dose falloff and stent injury. Edge effect was also reported with the use of catheter-based systems and was attributed primarily to geographical miss, in essence the lack of adequate coverage of the injured segment with the full radiation prescribed dose. Conversely, because activity of radioactive stents did not reduce the edge-effect phenomenon, the radiation dose did not appear to affect this phenomenon.

This study demonstrates that the radiation margin length influences the IA at the edge segment and that neointima formation is directly related to the source coverage, regardless of the injury. In our experiment, the lack of radiation coverage is associated with a 2.3-fold increase in neointimal formation compared with the maximal radiation coverage of 14.5 mm. By definition, the coverage of the edge segment is adequate when IA and lumen area at the edge segment do not differ from measurements within the body of the stent. This optimal coverage is obtained with a 14.5-mm margin beyond the stent edge, whereas a slight gradient between edge and body segments is still observed with 10-mm margin with either 15 or 22 Gy. This suggests that 14.5-mm margin is superior in eliminating the edge effect. However, because the effect on the IA was minimal between 10 and 14.5 mm with 22 Gy, it is possible that a higher dose minimizes the radiation margins.

The present study demonstrates that radiation therapy in noninjured, nonstented segments is free of neointimal formation and negative remodeling at 4 weeks. The absence of adverse histopathological and angiographic findings for those segments is consistent with previously reported 6-month IVUS and angiographic observation of irradiated, noninjured, and nonstented segments from the WRIST study.
suggests that these radiation doses do not stimulate aberrant neointimal formation in the absence of vascular injury. In addition, the IVUS findings of our study support this concept, because the changes in EEM in the nonstented segments are not related to the radiation margins. The lumen loss attributable to EEM changes never exceeds 2.0 mm² and is comparable to what is commonly observed in conventional stenting.15 Thus, we conclude that VBT does not induce any negative remodeling and that the extension of source coverage beyond the stent edge does not provoke any adverse effect.

This suggests that the edge effect is the consequence of the placement of the dose falloff; aberrant intimal proliferation observed with intermediate dose radiation might be triggered when the dose falloff is located close to injured segments and the prescribed dose is not delivered all along the stent.10 Most of the radiation trials reported an increase in adverse events when stents were placed as part of the VBT intervention.16 This was seen for patients treated with brachytherapy for in-stent restenosis and also for de novo lesions.6 One explanation of this unsuccessful marriage between radiation and stenting was attributed to delay in reendothelialization and excess in late thrombosis.17 Although late thrombosis was reported to be controlled by prolonged antiplatelet therapy,18 the negative influence of additional stenting continued to be observed. For example, in the BetaCath trial, a higher target revascularization rate was reported in patients treated with stent and concomitant VBT than in patients treated with stent alone, despite similar rates of late thrombosis, whereas in the balloon arm and VBT, patient outcome was better than that in control subjects.19 Our experiments attempt to mimic the clinical scenario practiced in the BetaCath trial by placing the second stent after the radiation therapy. Our study demonstrates that despite margin coverage of 27.5 mm, the neointima formation is increased at the overlap segment of stents with the use of the conventional dose that is used in human clinical trials. Interestingly, increasing the dose by 50% with adequate coverage is sufficient to eliminate the gradient seen between the overlap segments and the stent edge segment.

Study Limitations
First, this study was performed in normal coronary arteries of juvenile swine, which might not be comparable to human atherosclerotic arteries. Second, the analysis was conducted for only 28 days after the procedure, and this short-term follow-up might not characterize the full process of healing and potential late effects after stent injury and radiation. Still, we were able to demonstrate how to provoke an edge effect and how to control it. Margin lengths were determined by the available commercial sources and therefore were arbitrary;
other margin lengths might be effective. Finally, the study design was limited to radiation performed after stenting and does not mimic a clinical scenario in which stents are added after the radiation procedure.

**Clinical Implications**

Clinical recommendations can be proposed on the basis of this study and might potentially reduce the target-vessel revascularization rate after VBT. This study showed that the edge stenosis is a result of neointimal proliferation and is inversely correlated to the radiation margin.

Additional stenting after VBT increases the neointimal formation at the overlap segment. This localized proliferation can be inhibited by increasing the radiation dose but not by extending the radiation margin. Additional stenting should be minimized and if needed should be performed before the radiation therapy and coupled to a higher radiation dose.

**References**


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