

# Balloon-Assisted Angioplasty for the Treatment of In-Stent Restenosis After Vertebral Artery Ostium Stenting

## *Experiences From One Single Center*

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**Background:** Stenting appears to be a safe means of treatment for vertebral artery ostium stenosis with low complication rates and positive long-term effects, but the incidence of in-stent restenosis (ISR) after stenting is high. Different treatment strategies are applied for the revascularization of ISR; however, currently the optional approach is not recommended. The study was designed to investigate the feasibility, safety, and effectiveness of balloon-assisted angioplasty for the treatment of ISR after vertebral artery ostium stenosis.

**Methods:** In this study, we included patients from the Department of Neurology, Lishui Hospital of Zhejiang University, who were treated with balloon-assisted angioplasty as a result of suffering from ISR after previously undergoing vertebral artery ostium stenting. We retrospectively analyzed the clinical and functional outcomes of the patients.

**Results:** From January 2015 to December 2019, 11 patients were included in the study. The technical success rate reached 100% and the average operation time was 73 minutes. The Thrombolysis in Cerebral Infarction Score 2b-3 was acquired in all patients except 1 patient, who was presented with symptoms of hypoperfusion syndrome. The remaining 10 patients did not experience any intraoperative or postoperative complications. No restenosis, new cerebral infarction or transient ischemic attack were reported within 6 months of follow-up.

**Conclusion:** Balloon-assisted angioplasty could be feasible for the treatment of ISR after vertebral artery ostium stenting, however, more research is needed to confirm this.

**Key Words:** balloon-assisted angioplasty, in-stent restenosis, vertebral artery ostium stenting

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X. Cai and J.S.: conceived and designed research and supervised the study. Y.X. and X. Chen: collected and analyzed the data. X. Chen, and L.C.: analyzed the data and wrote the manuscript.

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Approximately 20% to 25% of all ischemic strokes occur in the posterior circulation, and vertebral artery ostium stenosis (VAOS) is one of the major factors contributing to posterior circulation ischemic events.<sup>1</sup> So far, antiplatelet and anticoagulant therapy are the basic treatments for VAOS; however, if the patient still has symptoms after optimal medication, endovascular treatment should be considered.<sup>2,3</sup> Some studies have suggested that stenting appears to be a safe means of treatment for VAOS with low complication rates and positive long-term effects.<sup>4,5</sup> The success rate of recanalization using stenting reached 99% to 100%.<sup>6–8</sup> However, the incidence of in-stent restenosis (ISR) after stenting is high and the incident rate varies significantly between different studies.<sup>2,9</sup> Various treatment strategies are applied for the revascularization of ISR, including pharmacological therapy, endovascular therapy, and surgery; however, no optimal therapeutic approach is recommended at present.<sup>10</sup> Up to now, balloon-assisted angioplasty has been proven to be an effective method to treat ISR after percutaneous coronary intervention, but there is still a lack of research regarding the use of angioplasty to treat ISR after vertebral artery ostium (VAO) stenting.

In this study, we assessed the feasibility and safety of balloon-assisted angioplasty for the treatment of ISR after VAO stenting and we also share our experience on how to improve the successful rate of interventional therapy in cases of complex ISR.

## METHODS

### Patient Selection

In this study, we retrospectively reviewed 11 cases of an ISR patients, who were treated with balloon-assisted angioplasty between January 2015 and December 2019 in Lishui Hospital of Zhejiang University. The ISR was defined as a stenotic lumen > 50% within or immediately adjacent (within 5 mm) to the stent.<sup>11</sup> Inclusion criteria were: (1) patients age 18 years or older; (2) ISR or occlusion of VAO; (3) recurrent strokes or transient ischemic attacks (TIAs) refractory to best medical treatment; (4) the lesions were treated with the balloon-assisted angioplasty; (5) available clinical and angiographic follow-up data after primary treatment and after angioplasty for ISR.

The local ethics committee approved the study and informed consent from the patients was obtained.

### Preprocedural Medical Management

All the patients underwent preprocedural routine examinations to determine whether the operation could be tolerated. The restenosis degree was based on a multimodality imaging approach (computed tomography angiography, magnetic resonance angiography, and/or ultrasound) that was needed to be confirmed by conventional angiography. Meanwhile, all patients were given aspirin (Bayer, Leverkusen, Germany) 100 mg/d and clopidogrel (Plavix, Sanofi Aventis, France) 75 mg/d at least

**TABLE 1.** Summary of Patients Clinical Data

Variable	1	2	3	4	5	6	7	8	9	10	11
Sex/age	M/63	M/66	F/67	M/65	M/71	M/65	M/64	F/68	F/60	M/67	M/73
Smoking	+	+	-	-	-	+	-	-	-	+	+
Diabetes mellitus	-	-	+	-	+	-	-	-	-	-	+
Hypertension	+	+	-	-	+	-	+	+	+	-	+
Hyperlipidemia	-	+	+	+	-	-	+	-	+	-	-
Coronary heart disease	-	-	-	-	-	-	+	-	-	-	-
Restenosis time (mo)	10	35	18	15	20	23	19	23	13	7	15
The time from puncture to recanalization (min)	69	75	68	89	73	77	63	71	81	73	65
Residual stenosis (%)	0	15	10	10	15	0	20	10	0	20	0
Complication	-	-	-	-	+	-	-	-	-	-	-
Stroke/TIA	-	-	-	-	-	-	-	-	-	-	-

+ indicates yes; -, no; F, female; M, male; TIA, transient ischemic attack.

3 days before intervention; atorvastatin 20 mg/d (Pfizer, Dalian, China) was also routinely given before surgery. Patients were asked to fast for at least 6 hours before the procedure, and their blood pressures were controlled at 110 to 120/70 to 80 mm Hg.

### Intervention Technique

Every procedure began with local anesthesia and puncture of the right common femoral artery. Blood pressure and blood oxygen saturation were monitored during the surgery. Intravenous heparin boluses (0.75 mg/kg body weight) were administered to maintain an activated clotting time between 250 and 300 seconds during the procedure. After a 6 Fr sheath was placed in the femoral artery, an 8 or a 6 Fr Envoy/MPD guide catheter was carefully advanced towards the subclavian artery over a guidewire (Stryker, Kalamazoo, MI). Multiangle magnified contrast angiography was used to ensure that the stenosis of the VAO was well displayed. Angiographic calculation of the VAO stenosis was calculated with the following formula: VAO stenosis =  $(1 - [\text{narrowest VA diameter}/\text{diameter normal distal VA}]) \times 100\%$ .<sup>12</sup> Subsequently, under the guidance of the route, the micro guidewire and the microcatheter (Micro Therapeutics Inc. dba ev3 Neurovascular, Irvine, CA) were inserted into the true vascular cavity through the restenosis segment and a microcatheter angiography was used to make sure that the distal end of the catheter was located in the true lumen of the vessel; it was also used to evaluate the blood circulation condition of the distal branch. All restenosis segments were dilated with a balloon (Apollo 4008; Microport, Z.J High-Tech Park, Shanghai, China) under the pressure of 6 to 12 atm. It should be noted that it is important to slowly dilate the balloon at the initial phase to avoid balloon displacement. Also, it is important to maintain the pressure for about 5 to 8 seconds before withdrawal. However, its prolonged onset can lead to chronic ischemia and increase the risk of complications. Follow-up angiography was performed to confirm whether the vessel was recanalization. After the uncomplicated procedure, the patient received heparin for 3 days, anticoagulant therapy, aspirin 100 mg/d and clopidogrel 75 mg/d for at least 3 months. Then, according to the results of the reexamination, the aspirin tablets were prescribed long term.

### Data Collection and Follow-up Outcome

All patients were followed up clinically after 2 weeks, and after 1, 3, 6, 9, and 12 months. Subsequently, the patients were followed up every half of the year. They were scheduled to return for a vascular imaging examination (ultrasound first; if the ultrasound showed a decreased blood flow velocity; computed tomography angiography or digital subtraction

angiography (DSA) were used for further examination). Demographic, clinical feature, angiographic, and procedural data were collected.

### Statistical Analysis

Descriptive statistics were used in this study. Continuous data are expressed as mean  $\pm$  SD or as the median with interquartile range (IQR), whereas categorical data were presented as numbers and percentages. Statistical analyses were performed using the SPSS software (SPSS Inc., Chicago, IL).

## RESULTS

### Clinical Characteristics

From January 2015 to December 2019, we completed a total of 11 cases (3 female and 8 male) of ISR balloon dilation of patients suffering from VAOS. The median age was 66 years (IQR, 64 to 68 y). Complications included tobacco smoking in 5 (45.45%) patients, hypertension in 7 (63.64%), hyperglycemia in 5 (45.45%), coronary heart disease in 1 (9.09%), and diabetes mellitus in 3 (27.27%). The ISR was identified at

**TABLE 2.** Patients Baseline Demographic and Clinical Characteristics (N=11)

Characteristics	n (%) or Median (IQR)
Restenosis time (mo)	18 (13-23)
The time from puncture to recanalization (min)	73 (68-77)
Age (y)	66 (64-68)
Male	8 (72.73)
Medical history	
Smoking	5 (45.45)
Hypertension	7 (63.64)
Diabetes mellitus	3 (27.27)
Cardiovascular diseases	1 (9.09)
Hyperlipidemia	5 (45.45)
Angiographic and procedural characteristics	
Successful recanalization	11 (100)
Complication rate	
Dissection	0 (0.00)
Perforation	0 (0.00)
Sympathetic intracranial hemorrhage	0 (0.00)
Hyperperfusion syndrome	1 (9.09)
Branch embolization	0 (0.00)

Successful recanalization: residual stenosis of occluded segment <20% at the end of the intervention. Residual stenosis: residual stenosis of occluded segment  $\geq$ 20% stenosis at the end of the intervention.

IQR indicates interquartile range.

**TABLE 3.** Clinical and Imaging Outcomes in Hospital and During Follow-up

Outcome	n (%) or Median (IQR)
<b>In-hospital</b>	
Stroke	0 (0.00)
Death	0 (0.00)
<b>Follow-up</b>	
Stroke/TIA	0 (0.00)
Death	0 (0.00)
mRS score at the sixth month	1 (0-1)
Imaging follow-up time	18 (13-23)
Angiographic restenosis	0 (0.00)
Symptomatic restenosis	0 (0.00)

IQR indicates interquartile range; mRS, modified Rankin Scale; TIA, transient ischemic attack.

the median follow-up duration of 18 months (IQR, 13 to 23 mo). The clinical data and outcomes of all patients are summarized in Table 1.

**Procedural Characteristics**

The technical success rate reached 100% and the median time from puncture to recanalization was 73 minutes (IQR, 68 to 77 min). The Thrombolysis in Cerebral Infarction Score 2b-3 was acquired in all patients. The mean residual stenosis rate is 9.09% (range: 0% to 20%). Except for 1 of the patients who presented with symptoms of hypoperfusion syndrome, such as a headache after surgery. The remaining 10 patients were not affected by any intraoperative or postoperative complications. The details are listed in Table 2.

**Follow-Up Evaluation**

As shown in Table 3, no new minor ischemic stroke was reported in any of the patients after the procedure and no deaths were reported. During the clinical follow-up period, no restenosis, no new cerebral infarction or TIA were reported and no death or recurrent symptoms occurred.

**Representative Case Illustrations**

**Patient 1**

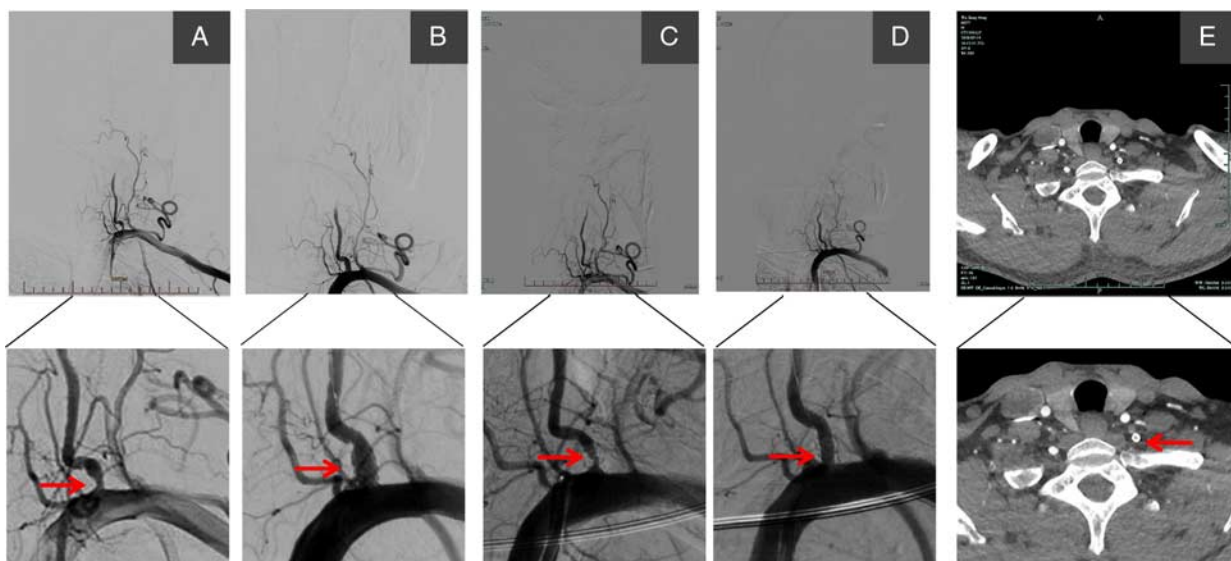
A 63-year-old male with a history of gout was hospitalized in our department in May 2018 due to recurrent complaints of vertigo for 2 years. Cerebral DSA showed left VAO severe stenosis (Fig. 1A). A 4 mm×8 mm stent (3.5 mm×8 mm, Apollo 4008, Microport; Z.J High-Tech Park) was placed in the left VAO. Ultrasound follow-up in March 2019 later revealed a decreased blood flow in the left VA. Furthermore, the arteriography confirmed severe restenosis in the stent of the VAO (Fig. 1C). Using a similar method described above, we treated the restenosis in its stent with balloon-assisted angioplasty. Follow-up angiography showed successful recanalization (Fig. 1D). The time from puncture to recanalization was 69 minutes. During the follow-up period, there were no symptom recurrence or abnormal imaging findings (Fig. 1E).

**Patient 2**

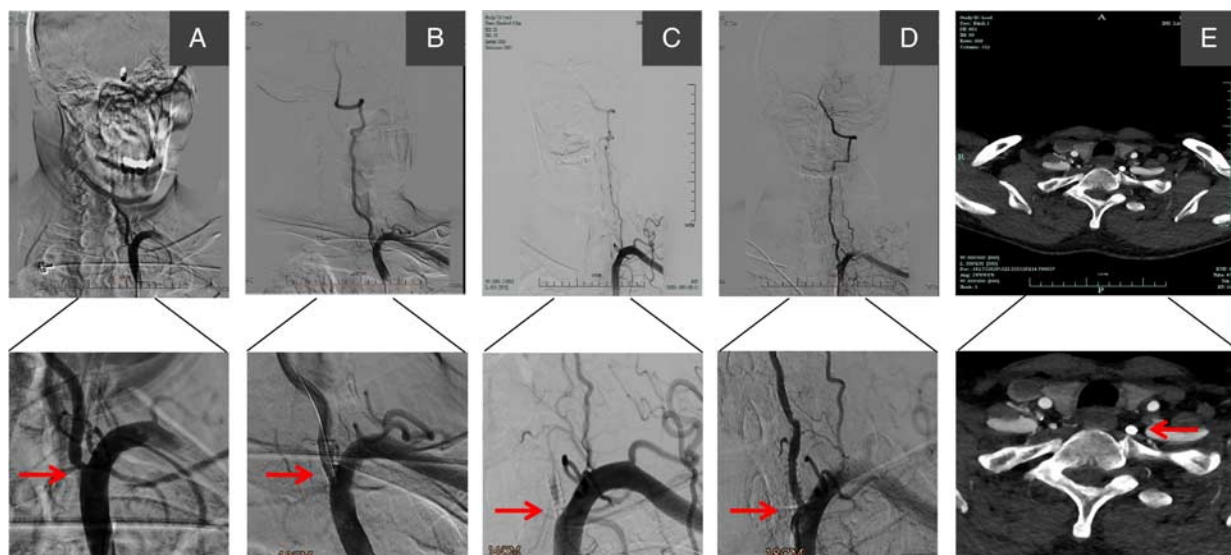
In October 2018, a 67-year-old man with a history of stroke was admitted in our hospital with a 7-month history of recurrent dizziness. Cerebral DSA showed carotid artery and severe bilateral VA stenosis (Fig. 2A). To treat the stenosis, 3 stents were implanted into the left carotid artery as well as the bilateral vertebral arteries. Follow-up angiography showed successful recanalization of all 3 arteries (Fig. 2B). In May 2019, he was again admitted to the hospital due to ISR of the left VAO, which was identified during a follow-up ultrasound. Further arteriography showed severe restenosis in the stent of the right VAO (Fig. 2C). Therefore, balloon-assisted angioplasty was used to treat the restenosis (Fig. 2D). Follow-up angiography showed successful recanalization of the left VA (Fig. 2E). The time from puncture to recanalization was 73 minutes.

**DISCUSSION**

At present, endovascular therapy is increasingly credited as a means of treatment for cerebrovascular diseases.<sup>13</sup> However, with the use of intravascular stent implantation in the



**FIGURE 1.** Case example 1. (A) Severe stenosis of the left vertebral artery ostium (arrow). (B) Left subclavian arteriography immediately after stent placement (arrow). (C) In-stent restenosis of left vertebral artery (arrow). (D) Arteriography immediately after treatment (arrow). (E) Follow-up computed tomography angiography after 12 months showed that the stent was in a good position without restenosis (arrow).



**FIGURE 2.** Case example 2. (A) Severe stenosis of the left vertebral artery ostium (arrow). (B) Arteriography immediately after stent placement (arrow). (C) In-stent restenosis after 7 months (arrow). (D) Arteriography immediately after treatment (arrow). (E) Follow-up computed tomography angiography in 12 months showed that the stent was in a good position without restenosis (arrow).

treatment of cerebrovascular disease, increased restenosis in the stent, has become a concerning issue that needs to be solved.<sup>14</sup>

For the treatment of VAOS, VAOS stenting has been proved for safety and efficacy and has become an alternative to standard medical management.<sup>15</sup> However, the incidence of ISR remains high, which ranges from 12% to 48%.<sup>16,17</sup> Vascular elasticity, vascular remodeling, thrombosis, excessive proliferation, and migration of vascular smooth muscle cells are important factors leading to restenosis. In addition, excessive proliferation of vascular smooth muscle cells may play a significant role in the process. Some studies have indicated that diabetes, postoperative residual stenosis, body mass index  $\geq 25$  kg/m<sup>2</sup> and ischemic heart disease are high-risk factors for restenosis.<sup>12,18</sup> Therefore, controlling blood sugar, blood pressure and lipid levels, as well as the use of long-term antiplatelet therapy can prevent restenosis. Intervention techniques also have an impact on ISR; stent diameter is an independent predictor of ISR.<sup>19,20</sup>

In addition to identifying risk factors for restenosis and preventing it, more optimized research is needed to identify the most beneficial treatment for ISR. In 2006, Scheller et al<sup>21</sup> introduced drug-coated balloon into the treatment of ISR after percutaneous coronary intervention and achieved good clinical outcomes. The PEPCAD-DES Study showed that the application of drug-coated balloon for ISR can significantly reduce the recurrence rate of ISR at 6 months after surgery (58.1% vs. 17.2%,  $P < 0.001$ ).<sup>22</sup> However, there are few reports on the treatment of cerebral vascular ISR. A recent study reported using hybrid revascularization technique, a combination of endarterectomy and endovascular intervention technique to treat 12 patients with internal carotid artery and vertebral artery (VA) ISR or occlusion, achieved 100% technical success with acceptable complications.<sup>23</sup> Meanwhile, in our study, we achieved good results with 11 patients with ISR in the VOA using balloon dilation only. For patients with ISR after VAO stenting, the condition in the restenosis segment was more complicated, and it was more difficult to pass the micro guidewire in such situations. Similarly, the micro guidewire may pass through the stent mesh, the outside of the stent, or the subendovascular pseudocavity, which means that it is important to make sure that the micro guidewire enters the true

lumen of the blood vessel by using multiple angiographies. In addition to this, higher levels of technical expertise are required for operators. Consequently, this technique is only carried out in experienced intervention centers.

Our research has several limitations. Since this is a retrospective, single-center study with a small sample size, further multicenter prospective studies are needed to confirm the feasibility and safety of this technique. Nonetheless, our study proved a satisfactory rate of technical success and a very low incidence of complications.

## CONCLUSIONS

In this study, we reported 11 cases in which balloon-assisted angioplasty was used to treat ISR after VAO stenting. The technical success rate reached 100% and all the cases achieved great outcomes during follow-up. This study suggests that balloon-assisted angioplasty has a promising potential as a treatment for ISR after VAO stenting. The feasibility and safety of this kind of treatment deserves to be further studied.

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