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ORIGINAL ARTICLE

Long-Term Risk of In-Stent Restenosis and Stent Fracture for Extracranial Vertebral Artery Stenting

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Abstract

Purpose Stenting and angioplasty of the vertebral artery (VA) is used to treat symptomatic stenosis but the long-term outcomes and complications are unclear. This study evaluated the long-term clinical outcomes and procedure-related complications in patients who underwent extracranial VA stenting and angioplasty, in particular the risks of in-stent restenosis (ISR) and stent fracture.

Methods This was a retrospective review of consecutive patients suffering from symptomatic extracranial VA stenosis who were treated with balloon-expandable bare metal stents. The clinical and angiographical outcomes were reviewed for procedural complications, recurrent stroke, ISR and stent fracture.

Results In this study 22 patients (17 male, 5 female) with a mean age of 63.4 years (SD 9.1 years) were included. The median follow-up was 56 months (interquartile range IQR 51.8 months). There were no periprocedural complications. The cumulative ISR risk was 45% with 6 cases detected at 1 year and 3 cases detected at 3 years post operation. The cumulative stent fracture rate at 1 year, 3 years, 5 years and the entire follow-up period were 5%, 15%, 25%, and 30%, respectively. Posterior circulation stroke occurred in 1 patient (4.5%), and 3 patients died of non-cerebrovascular causes during follow-up. Of the patients 2 with ISR and stent fracture required additional treatment.

Conclusion The long-term ISR and stent fracture risks were high in extracranial VA stenosis treated with balloon-expandable bare metal stents. The risk of stent fracture increased over time during the follow-up period. Further studies should be conducted to clarify the long-term safety and efficacy of extracranial VA stenting.

Keywords Angioplasty · Vertebral artery stenting · Stroke · In-stent restenosis · Stent fracture

Abbreviations

ISR	In-stent restenosis
TIA	Transient ischemic attack
VA	Vertebral artery

Introduction

Vertebral artery (VA) stenosis accounts for 20–40% of posterior circulation ischemic stroke [1]. Stenosis of 50% or more of the lumen is associated with vertebrobasilar insufficiency, and an increased risk of infarct [2–7].

Endovascular stenting and angioplasty have been used to treat symptomatic VA stenosis. Nevertheless, the efficacy of such procedures in reducing the long-term stroke risk remains controversial. The VAST study showed a higher same territory stroke risk in the stented group compared with the medicinal treatment group after a median follow-up of 3 years [8]. In contrast, another randomized trial (VIST) demonstrated a non-significant benefit of VA stenting in reducing stroke or transient ischemic attacks (TIA) over best medical treatment [9]. These studies, however, were not designed to address the long-term complication risks, such as in-stent restenosis (ISR) and stent fracture, and follow-up imaging was not mandated beyond 1 year. An

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ISR rate of up to 7–10% was reported in observational studies [10–12], while the incidence of stent fracture varied from 4–25% [13, 14]. The clinical impact of stent fracture and ISR on recurrent ischemia is unclear.

The aim of this study was to analyze the long-term clinical outcomes and procedure-related complications of patients who received balloon-mounted bare metal stents of the extracranial VA, with a focus on ISR and stent fracture risks.

Material and Methods

Study Design and Patient Selection

This was a single-center retrospective study of symptomatic VA stenosis patients treated with stenting and angioplasty between January 2007 and October 2017. Consecutive patients who received stenting of the extracranial VA were identified from a prospectively maintained database. The baseline demographic data, pre-existing cardiovascular risk factors, indications for treatment, procedural parameters, and clinical and angiographical follow-up outcomes were reviewed. The study was approved by the local institution review board.

Endovascular Procedure

All patients received at least 3 days of aspirin (300 mg daily) and clopidogrel (150 mg daily) prior to intervention and were fully heparinized with a target activated clotting time of 2–3 times that of the baseline. With the patient under general anesthesia, transfemoral access was established with a 6 Fr arterial sheath. The stenotic segment of the VA was cannulated with a 0.017 inch microcatheter over a 0.014 inch microguidewire, followed by deployment of an embolic protection device (Filterwire EZ, Boston Scientific, Boston, MA, USA) distal to the stenosis. An appropriately sized balloon-mounted stent (Express SD, Boston Scientific) was delivered and deployed over the entire stenotic segment. Predilatation with a Gateway PTA balloon (Stryker, Kalamazoo, MI, USA) was performed before stenting if there was critical stenosis of <2 mm limiting the stent delivery. A control angiogram was performed immediately after the procedure, and subsequent follow-up was carried out with computed tomography angiography (CTA) at 6 months, 1, 3 and 5 years in all patients. Digital subtraction angiography (DSA) was performed in persistently symptomatic cases if retreatment was planned or when CTA was unclear in documenting the degree of stenosis. The double antiplatelet regimen (aspirin 100 mg daily, clopidogrel 75 mg daily) was continued for at least 3 months, followed by lifelong aspirin monotherapy.

Outcomes

The primary outcome of this study was the occurrence of fatal or nonfatal stroke in any arterial territory during the follow-up period. Secondary outcomes included procedure-related complications, mortality rate, delayed ISR and stent fracture.

Statistical Analysis

Continuous baseline and clinical data were presented as means and standard deviations, while categorical data were presented as numbers. Statistical analyses were performed using IBM SPSS Statistics Software (Version 24, 2017). p value of 0.05 or less was considered significant.

Results

Patient Characteristics

In total 22 patients (17 male, 5 female) with a mean age of 63.4 years (SD 9.1 years) were treated in the study period. The most common cardiovascular risk factors were previous stroke (63.6%), hypertension (54.5%), hyperlipidemia (31.8%), and previous radiation therapy for malignancies (31.8%). Recent TIA or stroke was the indication for stenting in 13 patients (59.1%), and the remaining patients presented with vertebrobasilar insufficiency symptoms refractory to maximum medical therapy. These were defined as

Table 1 Risk factors, clinical characteristics and procedural details

Characteristics	Number (%)/mean (SD)
Male gender	17 (77.3%)
Age	63.4 ± 9.1
Laterality	
Left:Right	1:1
Indication for treatment	
TIA/ischemic stroke	13 (59.1%)
Vertebrobasilar insufficiency	9 (40.9%)
Risk factors	
Stroke history	14 (63.6%)
Hypertension	12 (54.5%)
Hyperlipidemia	7 (31.8%)
Prior radiotherapy	7 (31.8%)
Smoker status	5 (22.7%)
Ischemic heart disease	5 (22.7%)
Diabetes mellitus	4 (18.2%)
Peripheral artery disease	2 (9.1%)
VA tortuosity > 90°	13 (65.0%)
Follow-up period (months)	56 (29.4)

TIA transient ischemic attack; *VA* vertebral artery

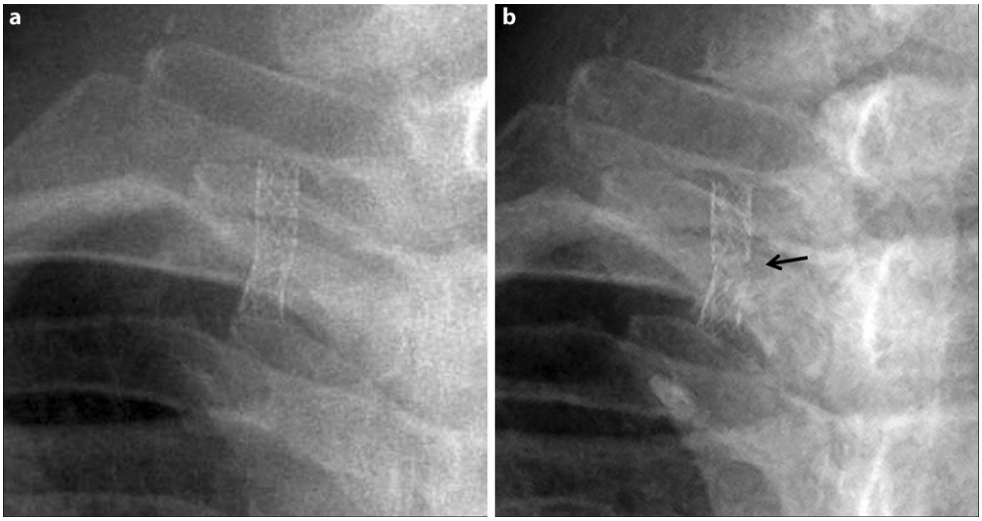

Fig. 1 **a** A 65-year-old woman with symptomatic right VA ostium stenosis was treated with an Express SD 4 × 15 mm stent. **a** Plain radiographs 3 years after intervention showing the intact stent, and **b** 5-year follow-up showing delayed stent fracture (*arrow*). This patient remained asymptomatic and was treated conservatively

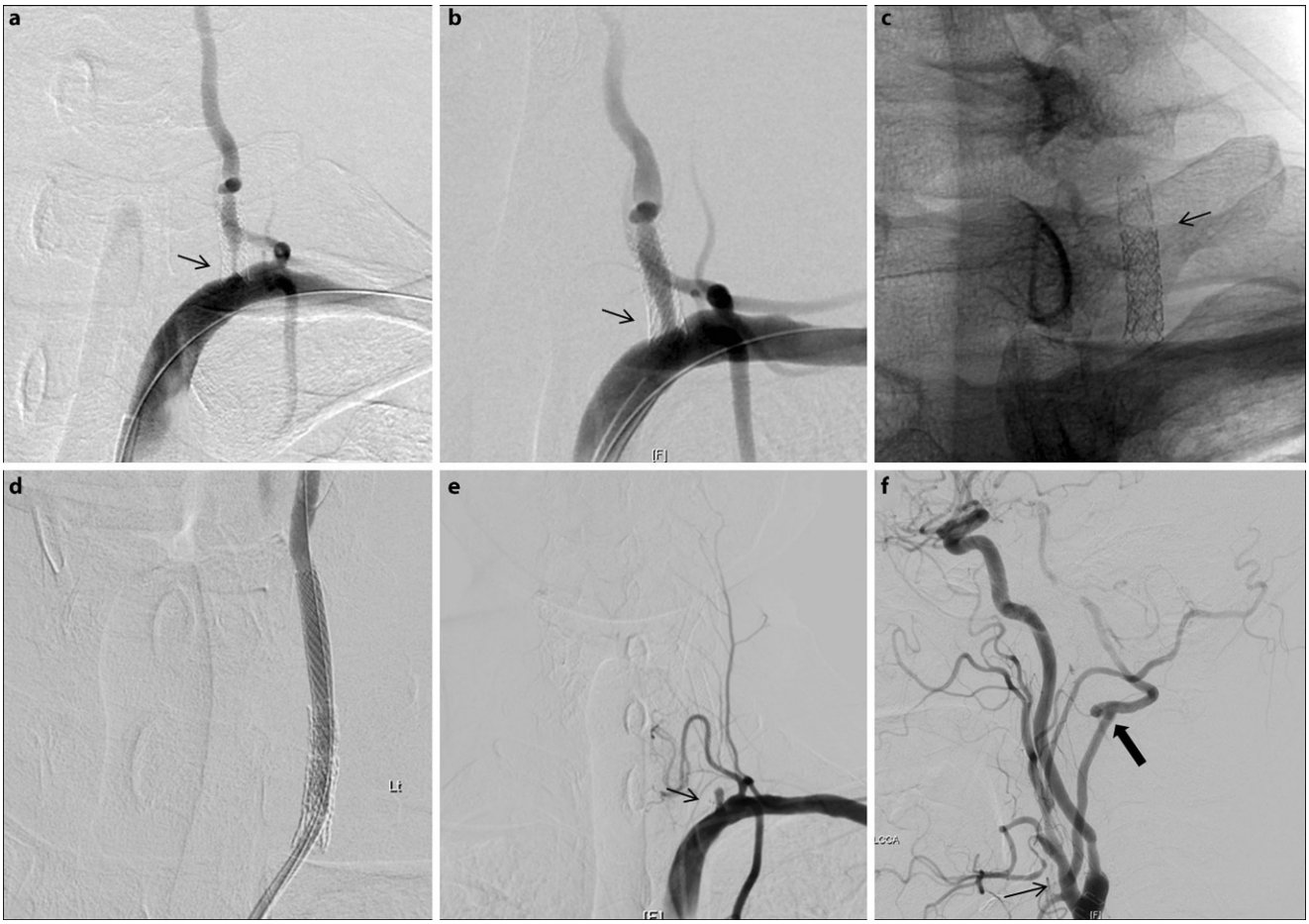

Fig. 2 A 46-year-old man with hypoplastic right VA and postirradiation stenosis at the left VA ostium was treated with an Express 5 × 15 mm stent after repeated posterior circulation TIAs despite medical treatment. **a** Catheter angiogram showed 80% ISR (*arrow*) at 8 months, **b** which was treated with balloon angioplasty (*arrow*). **c** At 3 years, the stent fractured (*arrow*). **d** The fractured stent segments were covered by a 5 × 30 mm Wallstent, followed by balloon angioplasty. **e** The proximal VA thrombosed with recurrence of symptoms 6 months after re-stenting (*arrow*). **f** The patient underwent vascular bypass with a saphenous vein graft, with the proximal anastomosis at external carotid artery (*arrow*) and the distal anastomosis at V3 segment of the VA (*broad arrow*)

neurological symptoms attributable to posterior circulation hypoperfusion, which were blood pressure dependent, secondary to vascular steal phenomenon or exertion coupled with angiographic evidence of hemodynamically significant stenosis along the vertebral arteries. The detail risk factor profile, clinical characteristics and procedure details are presented in Table 1.

Primary Outcome

During a median clinical follow-up of 56 months (IQR 51.8 months), 1 patient (4.5%) developed nonfatal ischemic stroke in the posterior circulation with a post-stroke modified Rankin score (mRS) of 2.

Secondary Outcomes

All patients were treated with a single Express SD stent at the VA ostium. There were no periprocedural complications. There were 3 mortalities (13.6%) due to unrelated causes, including 2 from pneumonia (2 and 5 years after intervention, respectively) and recurrent nasopharyngeal carcinoma at 11 months after stenting.

An ISR was defined as interval narrowing within the stented segment of the vessel compare to the immediate postoperative angiogram. Of the patients 2 who were asymptomatic did not consent to further angiogram follow-up and were not included in the analysis on delayed ISR and stent fracture. An ISR occurred in 6 patients in the first year, and another 3 patients at 3 years post operation, leading to an overall rate of 45% (9 out of 20 patients). During the follow-up 6 stents fractured, 4 of which were detected by CT angiography and two by DSA. The cumulative stent fracture rates at 1 year, 3 years, 5 years and the entire follow-up period were 5%, 15%, 25%, and 30%, respectively (Fig. 1) and 3 patients had both ISR and stent fracture.

Among the 12 patients with ISR or stent fracture, all but 2 remained asymptomatic and were managed conservatively with maintenance dual antiplatelet therapy. One patient with 50% ISR in the dominant VA was treated with a second balloon-mounted stent and angioplasty. The other patient who suffered from posterior circulation stroke 8 months after stenting developed recurrent symptomatic ISR despite repeated balloon angioplasty. The stent subsequently fractured at 3 years post operation and was replaced with another stent. Angiography performed 6 months after the second stent showed complete occlusion of the proximal VA. As the contralateral VA was hypoplastic and the patient remained symptomatic with vertebrobasilar insufficiency, a salvage with external carotid artery-vertebral artery bypass using a saphenous vein graft was performed. The graft was patent and the patient remained asymptomatic afterwards (Fig. 2). Univariate analysis was performed for ISR and stent fracture but did not identify any statistically significant risk factors (Table 2).

Discussion

This study of extracranial VA stenosis patients treated with stenting and angioplasty showed that while the periprocedural risk and recurrent stroke rate were low, the long-term ISR and stent fracture risks were high. The recent VAST and VIST trials did not demonstrate superiority of endovascular stenting and angioplasty for VA stenosis over best medical treatment. Nevertheless, this procedure has been commonly performed in symptomatic patients in the hope of preventing recurrent stroke [8, 9]. In a review of 27 studies on stenting of the extracranial VA, the periprocedural stroke risk of stenting was 1.1% [11]. These studies, however, were limited by a relatively short follow-up duration of 2–3.5 years and failed to address long-term complications.

The cumulative stent fracture risk in our cohort was higher than most reported cohorts and increased over time during the follow-up period [13–16]. Out of the 6 patients whose stent was fractured, 1 stent fractured at 1 year, 2 at 3 and 5 years, respectively, and 1 fractured 7 years after treatment. Half of these stent fractures were associated with ISR. The 2 patients who had delayed stent fracture

Table 2 Univariate analysis of factors associated with ISR and stent fracture

	ISR		Stent fracture	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Hypertension	0.46 (0.08–2.76)	0.65	6.67 (0.61–73.03)	0.16
Hyperlipidemia	2.13 (0.33–13.81)	0.64	2.50 (0.35–18.04)	0.61
Prior radiation	2.13 (0.33–13.81)	0.64	0.27 (0.02–2.92)	0.35
Smoker status	0.33 (0.03–3.93)	0.59	0.00 (N/A)	0.27
Diabetes mellitus	0.56 (0.05–7.44)	1.00	6.50 (0.46–91.92)	0.20
VA tortuosity	1.11 (0.16–7.51)	1.00	3.43 (0.30–39.64)	0.60
VAO calcification	0.50 (0.04–6.68)	1.00	1.50 (0.09–25.39)	1.00

ISR in-stent restenosis; *VA* vertebral artery; *VAO* vertebral artery ostium, *CI* confidence interval

at 5 years post operation were preceded by ISR earlier in the follow-up period, which led to recurrent stroke in 1 of them. Werner et al. postulated that ISR often arises from stent fractures, as the mechanical disruption caused by the fracture can induce abnormal smooth muscle and endothelial proliferation [14]. Our results suggested that the development of ISR could also precede that of stent fractures and may be an early sign of mechanical stress associated with delayed stent fractures.

The most common type of stent used to treat VA ostium stenosis was the balloon-expandable bare metal stent, which was also the predominant type used in the VIST, VAST and the present study. The use of newer stent designs may be associated with a lower incidence of delayed ISR and stent fracture. Drug-eluting stents, frequently used in coronary artery interventions, have the advantage of inhibiting endothelial proliferation and thereby reducing the chance of ISR occurrence. Meta-analysis of comparative studies on drug-eluting versus bare metal stents found a significantly higher ISR rates in those who were treated with bare metal stents [17]. In addition, self-expandable stents made of nitinol may be better suited for the VA ostium, as they are more flexible and compliant to the frequent motions at the branching site than balloon-expandable stents made of 316L stainless steel [18]. A prospective randomized trial reported a lower ISR rate of 3.1% in the self-expanding stent group compared with 22.9% in the balloon-expandable stent group after a short mean follow-up of 18 months [19]. The long-term efficacy and safety of these newer stents in the setting of VA stenosis remains unclear.

The anatomical configuration of the VA ostium may also affect stent survival [20]. A recent study showed that tortuosity at the V1 segment was an independent predictive factor of ISR and may be associated with stent fracture [21]. The authors postulated that stenting the acute angled vessel and hence correcting the tortuosity may induce extensive smooth muscle and endothelial proliferation, leading to subsequent ISR. We analyzed the VA tortuosity and calcification at the VA ostium in our cohort. While two thirds of patients in our study demonstrated significant extracranial VA tortuosity, we did not observe a significant association between tortuosity and ISR or stent fractures.

Currently, there is no standard treatment regimen or indications for ISR and stent fractures at the extracranial VA. Similar to other reported series, most of the patients with ISR or stent fracture were asymptomatic in this study [14, 22]. In symptomatic patients, re-stenting, balloon angioplasty, cerebrovascular bypass and aggressive antiplatelet drug treatment have been employed as treatment options [13, 14, 21, 23, 24]. We only considered retreatment if patients with >50% ISR developed recurrent ischemic symptoms or occurred at the dominant VA, in which the contralateral VA was hypoplastic or occluded. Surgical vascular bypass could be considered as a salvage treatment if repeated stenting or angioplasty failed.

Our study had limitations related to the inherent biases associated with retrospective studies. The small number of patients limited the statistical analysis in identifying potential factors associated with ISR and stent fracture. Cone-beam CT would be valuable to visualize the stent fracture but was not routinely available in our center at the time these patients were treated. All patients in this cohort were uniformly treated by the same protocol with balloon-expandable stents and the findings may not be applicable to other devices, such as self-expandable or drug-eluting stents.

Conclusion

Stenting and angioplasty of extracranial VA stenosis with balloon-mounted bare metal stents was associated with high long-term risks of ISR and stent fractures. The incidence of stent fractures increased over time and could occur more than 5 years after treatment. Further studies are needed to identify the optimal type of stents and assess the long-term safety and efficacy of extracranial VA stenting.

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Conflict of interest M.K.A. Li, A.C. On Tsang, F.C. Pong Tsang, W.S. Ho, R. Lee, G.K. Kit Leung and W.M. Lui declare that they have no competing interests.

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