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**Abstract:** Stenting has become one of the primary procedure to treat vertebral artery ostium stenosis patients. Postoperative in-stent restenosis (ISR) of the stenting is still one of the unsolved issues and requires systematic and further investigation. Through imaging assessments, ISR could be identified and evaluated in clinical practice and researches.

**Key words:** Vertebral, stenosis, stenting, in-stent restenosis, imaging

Ischemic stroke has emerged as a highlight in the field of medical and health care worldwide with more than 70 000 stroke events reported each year [1]. Posterior ischemic stroke accounts for only about 25%–30% of these patients [2,3]. However, it has a higher rate of morbidity and mortality than anterior ischemic stroke and causes the majority of the disability and death. Although multiple etiological factors predict onset of posterior ischemic stroke, vertebral artery ostium stenosis (VAOS) has been reported to contribute to most posterior circulation ischemic events [4].

For therapies of VAOS there exists an extensive history in medical practice over the past century, with endovascular treatments dating back to the 1980s [5]. This technique has undergone nearly 40 years of continuous refinement and initially began from a simple balloon angioplasty and evolved to stent implantation. Numerous studies have demonstrated the safety and efficacy of stenting of VAOS patients [6–8]. However, it should be noted that compared with the carotid artery lesions, interventional treatment strategies for VAOS have not been well established. Currently antiplatelet and anticoagulant combined therapy is still the standard treatment principle for VAOS. The American Heart Association guidelines for stroke prevention recommended the endovascular treatment be limited to the medicine refractory patients with symptomatic extracranial vertebral artery stenosis [9,10]. Current debate is mainly due to the high incidence of in-stent restenosis (ISR) after stent implantation with various follow-up studies showing that the incidence is 12%–48% [11–14].Consequently, the study of stenting for VAOS treatment and its restenosis has become one of the major topics of post-treatment recurrent stroke.

## Progress in VAOS stenting

Prior to development of endovascular procedures, open surgical operation was the primary treatment of VAOS with pharmacological therapy. The surgical procedures involved vertebral artery endarterectomy and vertebral to carotid artery end-to-end anastomosis to improve the distal vertebral artery and posterior circulation perfusion [15]. However, because of the deep anatomic location and the complex tissue surrounding the vertebral artery the surgical trauma was often counterproductive and frequently resulted in complications after the surgery such as Horner's Syndrome, vocal cord paralysis and myocardial infarction [16]. In the context of endovascular treatment occurrence and development, open surgery has been replaced gradually and is now rarely performed to treat

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VAOS. Premature endovascular therapy of VAOS is mainly based on the use of percutaneous transluminal angioplasty where a balloon reached the stenosis site, and then the balloon is inflated in the artery lumen to alleviate stenosis. The safety and efficacy of this procedure had been confirmed decades ago [17]. However, percutaneous transluminal balloon angioplasty possessed a high restenosis incidence (approaching 71% [18]). The reason for restenosis is attributed to the elastic retraction and other vascular reactions caused by the mechanical force of the balloon inflation. Therefore, as a respite therapy method, percutaneous transluminal balloon angioplasty currently has limited application in clinical practice. On the other hand, series of follow-up clinical investigations in recent years have confirmed that endovascular stenting is less invasive and also provides a high safety profile. Song et al. [19] reported a follow-up study on 219 lesions in 206 patients and showed that the technical success rate of the procedure was 99% (217/219), and that perioperative complications only occurred in seven cases (3%). Afterward, a study by Sun et al. [14] demonstrated similar results when 188 lesions in 188 VAOS patients demonstrated a 100% success rate and no postoperative complications.

As mentioned previously, endovascular treatment strategies for carotid artery lesions have been well established but less so in VAOS due to a lack of clinical trial evidence. To date, there are only two randomized control clinical trials compared stenting with medicinal therapy in VAOS. Unfortunately, neither results of either study showed sufficient evidence to support difference between the two treatments. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) trial randomized 16 patients with symptomatic VAS to an endovascular treatment (including stenting or angioplasty) or drug-treated groups with an average follow-up of 4.7 years [20]. There was no posterior circulation stroke in either group, but stroke occurred in three patients with myocardial infarction or anterior circulation stroke in each group. Compter et al. [21] recruited 115 patients with perioperative stroke that underwent stenting followed by 3-year follow-up. Findings were similar to the CAVATAS trial in that there was no significant difference between the intervention and drug treatment groups. Therefore, although enormous retrospective studies confirm the effectiveness and safety of stenting, large simple prospective randomized controlled trials are still required.

## Impact factors of ISR

In 1996, Storey et al. [22] reported on stenting performed in 3 VAOS patients who were medicine refractory and had obvious restenosis after percutaneous transluminal balloon angioplasty. None of these patients developed ISR after an average of 9-month follow-up. However, just 1 year later, another study reported on two VAOS stenting patients with 6-month follow-up and both patients demonstrated ISR (with one requiring percutaneous transluminal balloon angioplasty to alleviate the restenosis) [23]. Sample size reported in publications about VAOS stenting have continued to increase over time. However, the reported incidence of restenosis was still high. In 2009, 72 patients with a total of 77 lesions treated by VAOS stenting were followed up and demonstrated a high ISR rate of 48% [11]. This was the highest ISR incidence reported after VAOS stenting with more than 50 cases. Additionally, Sun et al. [14] described even a larger simple size, reporting on188 VAOS patients that underwent stenting. The incidence of ISR was 21% with a mean follow-up of 16 months. Similarly, another recent study with 204 patients illustrated that the incidence of ISR after VAOS stent was 19.4% [24]. Consequently, the true rate of ISR occurrence following VAOS remains controversial due to varied reports in the literature using small sample sizes and limited follow-up time. [25,26].

## Anatomical factors

Normally, the vertebral artery is the dominant source of perfusion of posterior cerebral circulation. The vertebral artery is typically the first large branch of the subclavian artery and bilateral arteries originate from the ipsilateral subclavian artery and then enter the 6th or 7th cervical vertebrae. Once they have passed through the transverse foramen of the 1st cervical vertebrae (also known as the atlas), the vertebral arteries travel across the posterior arch of C1 and through the suboccipital triangle before entering the foramen magnum. Intracranially, the two vertebral arteries join to form the basilar artery at the base of the pons, which is the main perfusion supply to the brainstem and connects to the Circle of Willis. The circle potentially supplies the rest of the cerebral vasculature if there is compromise to one of the carotids. Also, the vertebral artery gives off branches to the surrounding musculature via the anterior spinal arteries at each cervical level.

It should be noted that the incidence of anatomical variation in the vertebral artery is relatively high, and that these variations could potentially impact the treatment of vertebral artery stenosis in clinical practice. Anomalous origin is one of the most frequently reported types of vertebral artery variation. Vertebral arteries originate from the aortic arch, commonly on the left side [27], with an incidence of approximately 5%–15% [28,29]. It is generally acknowledged that abnormalities

of origin may influence the operation and selection of interventional procedures and may consequently influence the incidence of ISR [30]. Other relatively rare types of anatomical variations have been reported, such as the origin of the vertebral artery in the carotid artery [31,32]. Compared with the carotid artery, the incidence of vertebral artery hypoplasia is also higher, and the incidence of physiological hypoplasia or absence of the intracranial vertebral artery is roughly 6% [33] and 2%–6% of vertebral arteries occur entirely hypoplasia [34]. However, the impact of anatomical variation on the ISR is still unclear and unexplored.

## Stent type

Since the anatomical features of the vertebral artery are similar to the coronary arteries normally, the original stenting system applicated for VAOS was the coronary stenting system [35,36]. The majority of these systems were bare metal stents (BMS) which resulted in a higher incidence of ISR. The first drug-eluting stent (DES) in VAOS patients was reported in 2004 by Ko et al. [37]. Several similar studies were published after this and demonstrated a satisfactory effect on VAO [38–40]. In 2008, Akins et al.[41] did the first follow-up study of comparison between DES and BMS in VAOS. No restenosis (0%) was found in five patients in the DES group while restenosis occurred in three of seven patients (42.9%) in the BMS group. The study concluded that DES was able to reduce the occurrence of ISR. A later follow-up study by Song et al. [19] confirmed these findings. However, discrepant results still exist. For example, Raghuram et al.[42] found no significant difference in the incidence of ISR between the DES and BMS groups (30.8 % vs. 26.7%, $p > 0.05$), and pointed out that there were many factors influencing restenosis such as tortuosity and diameter of vertebral artery. A systematic meta-analysis of DES versus BMS in VAOS was published in 2014. The results showed that DES had a significantly lower rate of ISR compared with BMS (DES, 4.7%; BMS, 11.6%; $p = 0.005$), and no other risk factors for ISR were observed in the meta-analysis [43]. However, the literature included in this meta-analysis was not randomized controlled trials. Thus, the conclusion still needs to be further validated.

Self-expanding stents (SES) are widely used in the interventional treatment of carotid artery stenosis due to their high flexibility and strength [44]. For the specific anatomical characteristics of the vertebral artery, SES can also be applied to treat VAOS. The first experimental report of this approach was carried out on the canine vertebral artery in 1996 [45]. The earliest reported case was described in 2010 by Chung et al. [46]. A total of 20 VAOS patients were implanted SES then followed for approximately 14 months. Results showed that no recurrence of perioperative stroke and TIA occurred. Even while stent intimal hyperplasia appeared in five cases (25%), no significant ISR occurred. Comparable results were obtained by Li et al. [47] , with only one (1/32, 3.4%) patient developing asymptomatic ISR. Thus, the safety and efficacy of SES in VAOS have also been illustrated, providing another potential option for stenting in VAOS.

## Stent fractures

Stent fractures were originally investigated and reported in lower extremity arterial angioplasty [48,49], and shown to be a major contributor to long-term efficacy. With the widespread application of DES, numerous studies revealed that fractures had become an important factor in ISR. The incidence of fracture in coronary arteries was about 1%–8% [50], and was mainly related to location, distortions and stent length. Likewise, carotid stent fractures have been reported in the literature as an operative complication, with rates ranging from 7.8% [51] to 29.2% [52] . However, the investigation on the fracture of vertebral artery stents was relatively rare. In 2007, Kim et al. [53] reported on two fracture cases during VAOS stenting. Both patients underwent DES implantation and were observed to have broken stent related ISR at 5-month follow-up. Both ISR patients were then retreated with a second stenting procedure (stent-in-stent) to alleviate restenosis. Tsutsumi et al. [54] described that the incidence of stent fracture was 25% in VAOS (3/12 cases) after a mean follow-up time of 33.6 months, and that fractured stents were all coronary stents. The fracture of stents was suggested to be related to the stent knit structure. Werner et al. [55] found one case of stent fracture in 28 VAOS stenting patients, and 11 cases of them developed morphological deformation or retraction due to compression. Thus, they proposed that these factors were the main reasons leading to the development of ISR, not the previous consideration of intimal hyperplasia. Subsequently, Teraa et al. [56] reported on a case with VAOS stent fracture, and indicated the fracture was related to stent characteristics and vascular factors such as severe distortions and calcification of the vessel wall. Also, it was noted that position movement could increase the mechanical pressure on the stent and lead to fracture. Recently, Tang et al. [57] published their findings on the effect of dynamic respiration vertebral artery tortuosity on ISR and stent fracture. The research recruited 56 patients with VAOS stents and four ISRs occurred after an average of 28-month post-stenting. Two patients had occlusion due

to stent fractures and were significantly associated with tortuous vertebral artery (Spearman $\rho = 0.81$, $p < 0.01$). In addition, several studies mention cases of ISR caused by stent fracture in their findings [13,42,58]. However, the sample sizes were small, and all recognized during the follow-up and thus, stent fracture of ISR cannot be ignored.

## Influence of pharmacological therapies

Perioperative medication is another crucial factor which could affect the incidence of ISR after VAOS stenting. Literature reports that the application of antiplatelets has become an important part of preoperative preparation and postoperative monitoring. Conventionally, patients take aspirin (100 mg/d) and clopidogrel (75 mg/d) for 2–5 days, or high doses of aspirin (300 mg) and / or clopidogrel (300 mg) within 24 hours prior to the procedure to prevent perioperative stroke and thrombosis. Postoperative pharmaceutical therapy varies widely, but typically consists of dual antiplatelet therapy for 1–6 months, followed by long-term (> 1 year) single aspirin or clopidogrel [8,21,57,59–61]. In addition, statins have been shown to effectively reduce the risk of major vascular events (such as cardiogenic death, myocardial infarction, stroke, etc.) by lowering low density lipoprotein cholesterol [62]. Therefore, statins are widely used in the treatment of atherosclerotic disease. Initial evidence on the effectiveness of statins was found in coronary angioplasty. Several studies showed that statins could reduce the incidence of thrombosis and myocardial infarction during the peri- and post-operation because of improved endothelial function, stabilizing of atherosclerotic plaque, and reduced oxidative stress and inflammation [63–65]. Similar outcomes have also been reported in studies of carotid angioplasty [66,67]. Meanwhile, it has been described that statins can also be moderately absorbed by smooth muscle and endothelial cells, thereby inhibiting their cell proliferation and reducing ISR caused by in-stent intimal hyperplasia [68]. A comparative clinical trial divided 59 VAOS cases into two separately groups with randomized administration atorvastatin or standard of care. After an average 12-month follow-up, the atorvastatin group (29 patients, 49%) had significant lower ISR (20.7% vs. 50.0%, $\chi^2 = 5.526$, $p < 0.05$) compared with the control group, indicating that statins have a protective effect on reducing ISR [69].

Furthermore, atherosclerosis risk factors such as hyperlipidemia, diabetes, smoking and other underlying diseases are also considered as risk factors for ISR. Administration of medication in glucose and cholesterol control has shown to be effective in reducing ISR [8,19,70].

## Imaging assessment

It is important to evaluate ISR effectively and precisely by using imaging techniques. To date, digital subtraction angiography (DSA) remains the gold standard for the diagnosis of ISR after VASO stenting and is the principal follow-up modality. DSA provides a dynamic observation of the vertebral artery to diagnose stent fracture, distortion, or displacement. Also, it allows for direct measurement of the residual diameter for calculation of stenosis rate when ISR occurs. A systematic review of 53 studies of VAOS stenting illustrated that 1942 (85%) of the 2292 stents were followed up for an average 16.7 months and diagnosed ISR by DSA [71]. In recent follow-up studies, DSA has been shown to play a decisive role as an imaging modality for the diagnosis of ISR [1,57]. However, the cost of DSA is unsatisfactory and there are some complications such as pseudoaneurysm and contrast agent allergy. Furthermore, repeated application is subject to certain restrictions as the procedure is relatively invasive.

Magnetic resonance angiography (MRA) is a noninvasive imaging modality in the diagnosis of vascular stenosis. However, the impact of MRA artifacts is significant due to the metallic material structure of the stents. Thus, the observation of stent diameter is limited and even can often be contraindicated. Kono et al. [72] found that MRA could not display the diameter of the stent lumen after a carotid artery stenting procedure instantly due to metal artifacts. However, because the metal artifacts are reduced through the in-stent vascular endothelialization, a few cases exhibited the in-stent lumen by MRA at 3-month follow-up [73]. Additionally, MRA is susceptible to generating false-positives or overestimation of stenosis due to flow-empty actions [72]. Therefore, the application of MRA as a follow-up study of major follow-up imaging modalities after VAOS stenting is limited.

As another noninvasive imaging modality, computed tomography angiography (CTA) presents a relatively high sensitivity and specificity compared with MRA for the observation of stent lumens and is an alternative to DSA in postoperative VAOS stenting follow-up assessment. However, Lee et al. [74] found that there were still cases with unsatisfactory in-stent lumen display on CTA due to blooming artifacts. In this study, CTA offered a positive detection rate comparable with DSA ($p = 0.625$), but the diagnosis of ISR degree was significant different compared with DSA as a reference standard ($p = 0.001$). This literature also pointed out that CTA was unable to display the in-stent lumen in cases implanted with a thinner stent (diameter $\leqslant 2.75$ mm) and presented a higher false positive rate.

Color Doppler ultrasonography (CDU) is a simple repeatable and noninvasive imaging examination and can be applied for follow-up of VAOS stenting. As a metal material, stent typically shows hyperechoic knit structure on ultrasound imaging. CDU can provide measurements of stent diameters and hemodynamic data to comprehensively evaluate the occurrence of ISR postoperatively. A systematic review analyzed 27 studies that recruited 993 patients, and showed that DSA was used in approximately 50% (498/993) of patients during the follow up, and that CDU was applied in 152 cases (making it the second most common follow-up imaging modality). In contrast, neither MRA or CTA was frequently used [75], indicating that CDU has become the primary noninvasive imaging modality in follow-up studies. The application protocol in VAOS stenting patients is typically to undergo CDU examinations within 1 month, 3 months, 6 months, and 12 months postprocedural, and annually thereafter [2,76]. Jia et al. [77] published the ultrasound diagnostic criteria of restenosis after VAOS stenting in 2015, which called for acquisition of the in-stent velocity to differentiate and identify severity of the restenosis. Such hemodynamic-based diagnostic criteria have been shown to present a high sensitivity and specificity (85.5%–100%) based on comparisons with DSA as the gold standard.

## Conclusion

In summary, stenting is an established and reliable procedure and has become one of the primary procedures to treat VAOS patients. However, large randomized controlled trials are still required to validate their therapeutic effect compared with pharmacologic therapies. In addition, postoperative ISR of the stent is still one of the unsolved issues restricting its development and widespread use. Imaging assessment criteria of ISR should be identified and evaluated in clinical practice and researches. In particular, CDU is gaining in popularity and appears to be an ideal noninvasive method for monitoring ISR.

## Conflicts of interest

The authors have no conflict of interest to declare.

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