

In-Stent Restenosis after Carotid Stenting

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Carotid artery stenosis is a major risk factor for ischemic stroke. Currently, carotid endarterectomy (CEA) is the surgical treatment of choice for carotid artery stenosis. Carotid artery stenting (CAS) increases the risk of carotid artery stenosis. CAS is one of the treatment options available, particularly for high-risk CEA patients. Although CAS has the advantages of being less invasive, causing less patient discomfort, and requiring a shorter hospital stay, some patients may develop in-stent restenosis (ISR). ISR is closely related to clinical events such as transient ischemic attacks and ischemic stroke recurrence. The author examines the mechanism, influencing factors, and research progress of ISR following CAS, as well as its prevention and treatment, in order to provide clinical insights for clinicians.

Keywords: Carotid Artery Stenosis; Endarterectomy; Stenting; In-Stent Restenosis; Outcomes

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Carotid artery stenosis is a major cause of ischemic stroke, accounting for 10% to 20% of all ischemic stroke causes (1). Ischemic stroke has a high morbidity, disability, and mortality rate. Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are the main surgical treatments for carotid artery stenosis currently (2). CEA remains the most commonly used treatment for carotid artery stenosis, and the best surgical treatment option for the arterial stenosis (3, 4). However, CAS has the advantages of being less invasive, causing less patient discomfort, and requiring a shorter hospital stay. If there is a history of neck radiation therapy or surgery in some patients who are at high risk of CEA surgery, cervical spinal fixation is limited, anatomical exposure is difficult, lesions extend beyond the second cervical vertebra, contralateral carotid artery occlusion occurs as a result of cardiovascular complications and/or patients who cannot tolerate general anesthesia, and less invasive CAS treatment is available. In-stent restenosis (ISR) is a common complication that oc-

curred in 5.6% of carotid artery stenosis patients (5). ISR refers to the loss of lumen in the entire stent and/or 5 mm segments at both ends of the stent, resulting in a lumen stenosis rate of 50% (6), which not only affects patients' long-term prognosis and reduces quality of life, but it is also easy to cause ischemic stroke recurrence, causing serious economic losses and family burdens to patients.

Mechanisms of ISR formation following CAS

The following are the currently accepted views on the mechanism of ISR formation:

- (i) Neointimal formation is associated with increased production of cytokines and chemokines in smooth muscle cells (7), and surgical stress causes an increase in the production of reactive oxygen species, which triggers neointimal formation. ISR occurs when vascular smooth muscle cells die, causing adventitial myofibroblasts or medial vascular

smooth muscle cells to proliferate, migrate, and remodel, resulting in ISR (8).

- (ii) Post-vascular trauma-induced inflammation. The sac squeezes the plaque and destroys the intima and media of the vascular wall during interventional therapy, resulting in damage to vascular endothelial cells, causing an acute inflammatory response and inducing tissue factor release (9). Inflammatory cells in the blood (such as neutrophils) also participate in and exacerbate the inflammatory response to the damaged local area, and inflammatory cell aggregation further contributes to lumen stenosis. Furthermore, activated neutrophils can aggravate endothelial injury and stimulate platelet aggregation, which leads to neointimal hyperplasia and smooth muscle cell proliferation, which eventually leads to ISR (10).
- (iii) Endothelial repair is delayed. Long-term inhibition of vascular endothelial cell repair following drug-eluting stent placement results in a loss of homeostasis and a greater proclivity to adsorb leukocytes and platelets (11). According to this theory, ISR occurs in patients with drug-eluting stents because the drug-covered stent inhibits intima repair, resulting in poor endothelial coverage. Because of poor endothelial repair, the subsequent inflammatory reaction and hyperplasia eventually form ISR after the drug is fully released (12).
- (iv) Following drug-eluting stent placement, stent fracture is associated with the formation of new atherosclerosis as well as the restenosis rate in the stent fracture group. The rate was significantly higher in the stent-free group (38.0% vs. 8.2%) (13). Accordingly, in-stent neoatherosclerosis is a common pathological feature of ISR, and stent placement can help prevent it. Within one month of implantation, the pathogenesis of ISR involves an inflammatory response that leads to the formation of plaques rich in fibroblasts and smooth muscle cells, a phenomenon known as endomysial hyperplasia; ISR 12 weeks after stent placement is primarily due to recurrence and progression of atherosclerotic disease (14). If neovascularization occurs in atherosclerotic plaques, such intraplaque vessels may function as nutrient vessels for intimal growth beneath stents. Study has compared improved neck muscles arterial ultrasonography revealed that 6 of 10 patients with stent intimal hyperplasia had plaque enhancement of neovascularization, while 4 patients did not have plaque enhancement signs (15). Because stent intimal hyperplasia can cause ISR, plaque enhancement under contrast-enhanced carotid ultrasound Signs can be used as a risk factor for ISR (16). This study's sample size, however, was small, and its conclusions needed to be confirmed further.
- (v) ISR-related molecular mechanisms. The expression levels of 44 proteins in the rat carotid artery balloon injury model show significant changes within 3 days of arterial injury (17). Through research on the rabbit carotid artery balloon injury model, it was discovered that overexpression of heme oxygenase 1 can inhibit the expression of endothelin 1, thereby reducing vascular restenosis after rabbit carotid artery balloon injury (18). By inhibiting the nuclear tran-

scription factor B signaling pathway, four-and-a-half LIM domain proteins 2 reduce the inflammatory response of vascular smooth muscle cells (19). Furthermore, oxidized low-density lipoprotein receptor 1 can promote the proliferation and migration of vascular smooth muscle cells, which could be beneficial. Direct activation of the nuclear transcription factor B pathway mediates oxidized low-density lipoprotein-induced monocyte adhesion and promotes platelet-derived growth factor receptor activation, inducing vascular smooth muscle cell migration and proliferation (20). The findings indicated that numerous molecular pathways are involved in the pathological mechanism of ISR, providing new experimental evidence for the search for biomarkers and therapeutic targets of ISR.

Factors Influencing ISR after CAS

The factors that cause ISR after CAS are a result of the interaction and superposition of several factors (21, 22). According to the findings, the factors that cause ISR primarily focus on: (i) Variations in mean platelet volume. A study on Caucasians compared the mean platelet volume after CAS between the ISR group and the non-ISR group and discovered that there was no significant difference in the mean platelet volume after CAS between the groups (23), however, this is not the case post carotid endarterectomy (24). This could be due to ethnic differences, vascular structure, plaque biology, and preventive drugs (including anti-platelet aggregation therapy). (ii) Alterations in inflammatory markers. A study of 194 patients with carotid artery stenosis who underwent CAS found that ISR primarily occurred within 1 year of surgery, while CAS An elevated white blood cell count following surgery can be used as an independent risk factor for ISR (25). Another study found that CAS elevated C-reactive protein levels 48 hours after surgery were related to ISR 6 months later (26). Preoperative neutrophil to lymphocyte ratio was found to be a predictor of ISR in CAS patients (27). To investigate the relationship between residual stenosis and ISR, the results showed that over a 5-year period, residual stenosis increased the risk of ISR in patients, but this only exists in some event-specific models (such as the Wei-Lin-Weissfeld model) (28). (iii) Accordingly, hypertension and decreased cerebrovascular reactivity were both associated with ISR after CAS (29). Furthermore, Nishihori et al. found that ISR after CAS may be related to stent length and width, indicating that the longer the stent length and the narrower the width, the greater the risk of ISR after CAS (30).

ISR Prevention and Treatment Following CAS

ISR Prevention after Surgery

To begin, prevent ISR by intervening from the stent itself. Some studies had investigated the effectiveness of biological factor-eluting stents in preventing ISR, and an Arg-Gly-Asp peptide stent coating with an integrin-binding loop has been shown to inhibit the new generation of endothelial progenitor cells by recruiting endothelial progenitor cells (31). Drug-eluting stents have been shown in studies to reduce the incidence of ISR by 5% to 10% when compared to bare metal stents (32), but the effect of different drugs on improving stenosis remains unknown. The

ultrasonic spray system-designed 316L stainless steel double-layer vascular stent has good blood compatibility and can effectively inhibit the proliferation of vascular smooth muscle cells and thrombosis (33). Another method of preventing ISR is to modulate the patient's inflammatory response status, such as early and/or high-dose statin administration, which can reduce the patient's systemic and local inflammatory response (34). Given that the neutrophil-to-albumin ratio may play a role in the mechanism of ISR, nutritional interventions that increase or stabilize serum albumin levels may be a way to lower the risk of ISR in patients with a high neutrophil-to-albumin ratio (35). Some researchers have investigated vinpocetine in the hopes of reducing postoperative ISR in CAS patients, but the current efficacy is uncertain, and more research data is required in the future (36). Yang et al. believed that CAS ISR is related to postoperative residual stenosis, and recanalization by reducing residual stenosis may have an effect on reducing the occurrence of ISR (37).

Management of Postoperative ISR

Currently, the most common treatments for ISR after CAS are drug therapy, endovascular intervention, surgical therapy, and gene therapy.

- (i) *Medication.* Cilostazol can dilate arteries and inhibit blood vessels as an anti-platelet aggregation drug (38). The study's findings revealed that after one year of cilostazol treatment in CAS patients, the incidence of ISR was significantly lower than in the control group (39). Cases about the effect of argatroban on ISR were reported and found that CAS patients were followed up to 9 months after surgery. ISR was significantly lower in the class group than in the blank control group (7.1% vs. 21.6%), indicating that intravenous argatroban can effectively prevent ISR after CAS (40, 41). Furthermore, statins can inhibit the systemic inflammatory response, and high-dose atorvastatin (20 mg/d) can reduce both the systemic and local inflammatory responses in patients, inhibiting endothelial cell proliferation and smooth muscle cell migration. In patients with CAS, postoperative high-dose oral atorvastatin therapy significantly reduced the incidence of ISR (42, 43).
- (ii) *Endovascular therapy and surgical intervention.* Stent removal, carotid artery bypass grafting, CEA, and repeat CAS are the most common surgical treatments for severe ISR after CAS (44). All ISR treatment measures can effectively improve blood flow insufficiency caused by carotid artery stenosis and repeat CEA after ISR may result in a

better long-term prognosis but repeat CAS complications may occur (recurrent stroke or thrombosis). Carotid artery bypass grafting with a Gore hybrid vascular graft is a viable and dependable surgical option for ISR management (45).

- (iii) *Molecular therapy.* Several recent animal studies investigating the effect of gene therapy on restenosis after stent placement have yielded promising results, with the majority of them focusing on inhibiting the proliferation of vascular smooth muscle cells. Jing et al. created the Lenti-SM22a-p27-EGFP lentiviral vector, in which the smooth muscle 22 protein acts as a promoter to increase the expression of the cyclin-dependent protein kinase inhibitor p27kip1, inhibiting the proliferation of vascular smooth muscle cells (46). The lentivirus was used in a balloon injury model of the rat carotid artery. The experimental group had a lower ratio of carotid artery intima thickness to medial thickness, and the restenosis rate was significantly lower. Furthermore, Lipskaia et al. used the vascular smooth muscle cell proliferation inhibitor sarcolemmic reticulum calcium ATPase 2a to construct in a rat model of carotid balloon injury, the use of this recombinant vector can also reduce intimal hyperplasia after carotid balloon injury (47).
- (iv) *Gene therapy.* However, in the case of gene therapy, current research is still centered on animal experiments. Future theoretical research in this area may become a hot spot and focus in the future.

Conclusion

Carotid artery stenosis is a common clinical disease, and CAS is increasingly being used in the treatment of severe carotid artery stenosis, but the main problem that plagues clinical treatment is ISR after CAS. ISR is caused by a variety of factors, and various mechanisms are involved in the final cause of ISR. There is no agreement on the best treatment for ISR, but drugs that inhibit the inflammatory response locally in the stent can reduce the occurrence of ISR. Following ISR, stent removal and CEA are more invasive procedures that bypass the blood vessels. Stent implantation and repeated stenting have advantages and can be considered appropriate. Endovascular intervention may be appropriate for some patients, and biofactor-eluting stents can improve endothelial repair and reduce in-stent neointimal formation, potentially preventing ISR. In the future, gene therapy may provide new clinical treatment options. ■

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