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Application of Special Balloons in the Maintenance of Hemodialysis Vascular Access

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Abstract: Arteriovenous fistula (AVF) stenosis is a central cause of vascular access dysfunction in maintenance hemodialysis patients. Its pathophysiological process begins with endothelial injury, forming a positive feedback loop of "inflammation-proliferation-oxidative damage," ultimately leading to venous neointimal hyperplasia (NIH). Current clinical monitoring for AVF stenosis relies on a stepwise strategy involving ultrasound and digital subtraction angiography (DSA), while preventive and therapeutic approaches have significant limitations. Conventional treatments such as percutaneous transluminal angioplasty (PTA) and stent implantation are associated with low long-term patency rates and a high risk of restenosis. Specialty balloons, as novel interventional tools, achieve mechanical modification or targeted drug delivery based on the pathological mechanisms of AVF stenosis, resulting in the dual effect of "mechanical dilation + biological regulation." Animal models provide critical support for their development, while clinical trials further validate the clinical efficacy and application value of different types of specialty balloons. Future development of specialty balloons will focus on technological optimization, the refinement of combined intervention strategies, and the standardization of translational pathways, promoting their evolution from purely mechanical dilation tools into platforms for biological regulation, thereby offering more efficient and safer solutions for the precise prevention and treatment of AVF stenosis.
Keywords: Arteriovenous fistula stenosis; Pathophysiological mechanism; Venous neointimal hyperplasia

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1. Introduction

Arteriovenous Fistula (AVF), as the preferred vascular access for hemodialysis in patients with End-Stage Renal Disease (ESRD), is hailed as the "lifeline" sustaining patients' lives, with its patency directly determining dialysis adequacy and long-term quality of life for patients. However, AVF stenosis is the most common clinical complication, with an incidence rate as high as 30% to 60%[1]. The restenosis rate exceeds 50% within one year post-surgery, significantly shortening the lifespan of the fistula and increasing the pain and financial burden associated with repeated interventions or surgeries for patients. This has become a core bottleneck restricting the management of hemodialysis vascular access[2].

Currently, clinical prevention and treatment of AVF stenosis face numerous challenges: its pathogenesis is

complex, not resulting from a single factor but a multi-stage, cascade pathological process initiated by vascular endothelial injury[3], links involving inflammatory cell infiltration[4], abnormal proliferation of Vascular Smooth Muscle Cells (VSMCs), Neointimal Hyperplasia (NIH)[5], and amplification of oxidative stress. These each link are interconnected, forming a positive feedback loop that collectively promotes progressive luminal stenosis[6]. In clinical diagnosis and treatment, existing monitoring and diagnostic methods rely on a combination of non-invasive and invasive approaches, yet early and accurate identification remains limited. Prevention strategies primarily focus on antiplatelet drugs, statins, and surgical optimization but fail to target NIH, the core pathological change. Conventional treatments such as Percutaneous Transluminal Angioplasty (PTA), stent implantation, and surgical repair all suffer from low long-term patency rates and multiple complications, making it difficult to meet clinical needs.

Based on the aforementioned clinical dilemmas and pathological mechanism research, special balloons (including drug-coated balloons, mechanically modified balloons, etc.), with their dual advantages of "mechanical dilation + biological regulation," have become a research hotspot in AVF stenosis prevention and treatment in recent years[7]. Through local precise intervention, they can specifically target the core pathological aspects of stenosis pathogenesis—such as drug-coated balloons delivering antiproliferative, anti-inflammatory, and antioxidant drugs to inhibit NIH progression, and mechanically modified balloons efficiently tearing fibrous scar tissue to reduce elastic recoil—effectively compensating for the limitations of traditional prevention and treatment methods and providing a new direction for precise AVF stenosis treatment.

This article systematically reviews the core pathophysiological mechanisms of AVF stenosis, summarizes the limitations of current clinical monitoring and diagnostic methods, prevention strategies, and conventional treatments for AVF stenosis, and clarifies the clinical application basis and value of special balloons. It delves into the experimental foundations for special balloon development, providing comprehensive theoretical support and practical references for basic research, clinical diagnosis and treatment, and the development of novel interventional devices for AVF stenosis.

2. Pathophysiological Mechanisms of Arteriovenous Fistula Stenosis

2.1. Vascular Endothelial Injury

Arteriovenous fistula stenosis is a multi-stage cascade pathological process initiated by vascular endothelial injury, with inflammation, abnormal proliferation of smooth muscle cells, and amplification of oxidative stress as core mechanisms. Mechanical traction and suturing operations during surgery directly disrupt vascular endothelial integrity, activating platelets and the coagulation system, generating reactive oxygen species (ROS), and reducing nitric oxide (NO) bioavailability, exacerbating endothelial dysfunction. High shear stress, vortices, and low shear stress formed post-surgery further damage the endothelium[8-10]. The injured endothelium transforms into a pro-inflammatory phenotype, releasing cytokines such as Platelet-Derived Growth Factor (PDGF) and Transforming Growth Factor-β (TGF-β), initiating the migration and proliferation of VSMCs, and promoting excessive tissue proliferation through the Hypoxia-Inducible Factor-1α (HIF-1α)/Vascular Endothelial Growth Factor (VEGF) axis, laying the foundation for NIH[7,11-14].

2.2. Inflammatory Response

Early post-surgery, a large number of neutrophils are recruited and release myeloperoxidase (MPO), Matrix Metalloproteinase-9 (MMP-9), and ROS, exacerbating endothelial injury. Monocytes infiltrate and differentiate into macrophages under the action of Monocyte Chemoattractant Protein-1 (MCP-1), secreting inflammatory factors such as Tumor Necrosis Factor-α (TNF-α) and Interleukin-6 (IL-6), amplifying the inflammatory cascade through

relevant signaling pathways and forming a positive feedback loop of "inflammation-injury"[12,15]. Moreover, serum inflammatory factor levels in patients with AVF dysfunction are positively correlated with the degree of NIH.

2.3. Neointimal Hyperplasia

Neointimal Hyperplasia (NIH) is the core pathological change in AVF stenosis, primarily characterized by VSMC migration, proliferation, and extensive deposition of extracellular matrix (ECM)[6]. It is divided into three stages: early inflammatory infiltration and VSMC activation, mid-stage VSMC proliferation and ECM secretion, and late-stage ECM remodeling and fibrosis. Intimal thickening is significantly associated with luminal narrowing and decreased blood flow. Underlying diseases can accelerate its progression, and it is also a key target for interventional therapy[10,15].

2.4. Phenotypic Switching of Vascular Smooth Muscle Cells

The phenotypic switching of VSMCs from a contractile to a synthetic type is a core mechanism of NIH[16-17]. Synthetic VSMCs downregulate contractile-related proteins, highly express proliferation-related markers, and secrete large amounts of ECM. PDGF and basic Fibroblast Growth Factor (bFGF) can activate the MAPK/Extracellular Signal-Regulated Kinase (ERK) pathway, while Insulin-like Growth Factor-1 (IGF-1) and TGF-β promote proliferation and inhibit apoptosis through the Phosphatidylinositol 3-Kinase/Protein Kinase B/Mammalian Target of Rapamycin (PI3K/Akt/mTOR) pathway[18-19], further amplifying inflammatory and proliferative responses. This provides a theoretical basis for the application of drug-coated balloons containing paclitaxel, mTOR inhibitors, etc.[16-20]. Moreover, inhibiting ERK phosphorylation can reduce intimal thickness by 40%-50%.

2.5. Oxidative Stress

ROS primarily originate from damaged endothelial mitochondria, inflammatory cells, and proliferating VSMCs[21-22]. They can directly cause oxidative damage, activate relevant signaling pathways, downregulate NO levels, and accelerate VSMC migration, forming a cycle of "ROS-injury-reinjury." The related mechanisms also provide directions for the development of novel interventional devices[21-25].

3. Clinical Diagnosis and Treatment Status of Arteriovenous Fistula Stenosis and the Application Basis of Special Balloons

3.1. Prevention Status and Existing Issues of Fistula Stenosis

Current clinical strategies for preventing arteriovenous fistula (AVF) stenosis primarily involve pharmacological interventions and surgical optimization. However, significant limitations persist in their application, creating an urgent need for the clinical use of special balloons.

Pharmacological prevention mainly relies on antiplatelet agents and statins. Antiplatelet drugs, such as aspirin and clopidogrel, reduce the risk of anastomotic thrombosis by inhibiting platelet aggregation[26-27]. Studies indicate that short-term postoperative clopidogrel use can decrease early thrombosis rates and improve anastomotic blood flow[26]. However, these drugs only target thrombosis and have no direct inhibitory effect on neointimal hyperplasia (NIH), while long-term use may increase bleeding risks[27-28]. Statins (e.g., atorvastatin, rosuvastatin) exert protective effects through anti-inflammatory, lipid-regulating, and endothelial function-improving mechanisms. Animal experiments confirm that statins inhibit smooth muscle cell proliferation and migration, reducing stenosis risk [29]. Clinical evidence suggests statins can lower stenosis rates by 10%–15%, but their efficacy varies among individuals, with poor responses often observed in diabetic patients [30].

Surgical optimization focuses on anastomotic techniques and vessel selection. End-to-side anastomosis aligns better with hemodynamic principles than side-to-side anastomosis, reducing turbulent flow and low wall shear stress (WSS) regions at the anastomosis, thereby lowering endothelial injury risk [31-33]. Functional end-to-side anastomosis further reduces low WSS regions in the venous wall by 49.7% under retrograde flow conditions [32]. For vessel selection, forearm veins with diameters > 2 mm (e.g., cephalic vein) are preferred, significantly improving anastomotic success rates and reducing postoperative stenosis probabilities [34].

Limitations are twofold: (1) Pharmacological prevention has limited efficacy and high individual variability. Statins and antiplatelet drugs cannot target core NIH mechanisms (e.g., abnormal smooth muscle cell proliferation and inflammatory signaling pathway activation) [27]. (2) Surgical optimization heavily relies on operator experience, making it difficult to completely avoid mechanical endothelial injury and offering limited correction for postoperative abnormal hemodynamics[35]. Additionally, comorbidities like diabetes further diminish drug efficacy, increasing treatment uncertainty.

In summary, while current prevention strategies partially reduce AVF stenosis risk, they lack targeted interventions for NIH, creating a broad clinical space for special balloons (e.g., drug-coated balloons, mechanically modified balloons). These balloons can complement existing strategies through localized precision interventions.

3.2. Limitations of Conventional Treatments and the Application Value of Special Balloons

Current clinical treatments for AVF stenosis include interventional therapies, stent implantation, and surgical repair, all with significant limitations. The emergence of special balloons offers new options, with their application scenarios and advantages becoming increasingly prominent.

Percutaneous transluminal angioplasty (PTA) is the first-line interventional method for AVF stenosis, restoring lumen patency by high-pressure balloon dilation to tear fibrous hyperplastic tissue[36-37]. Conventional balloon dilation achieves short-term patency rates of 60%–70%, but restenosis rates reach 40%–50% within six months postoperatively[38-39]. Studies show primary patency rates of 86.2%, 83.2%, and 64.7% at 3, 6, and 12 months after PTA, respectively, with poor long-term outcomes (cumulative patency rate dropping to 29.8% at 24 months)[37]. Its limitations include inability to inhibit ongoing NIH progression and restenosis risks correlated with lesion length, multifocal stenosis, and dilation pressure[30]. Special balloons (e.g., drug-coated balloons [DCBs]) deliver antiproliferative and anti-inflammatory drugs locally during mechanical dilation, significantly reducing restenosis rates. Mechanically modified balloons (e.g., cutting balloons, scoring balloons) more efficiently tear fibrous scar tissue and reduce elastic recoil, making them suitable for rigid stenotic lesions resistant to conventional PTA.

Stent implantation is indicated for patients with vascular dissection, elastic recoil, or complex stenosis after PTA. Bare-metal or drug-eluting stents maintain lumen morphology and reduce elastic recoil but carry risks of in-stent restenosis (ISR), thrombosis, and stent migration[40-41]. Drug-eluting stents lower restenosis rates by inhibiting cell proliferation, but ISR rates still reach 16.7%–25%[42-43], with significantly elevated ISR risk in antiphospholipid antibody-positive patients (HR = 2.13). Additionally, long-term antiplatelet therapy is required post-stenting, and mechanical complications may arise from repeated dialysis punctures[44]. For certain complex stenotic lesions, special balloons (e.g., DCBs combined with cutting balloons) can serve as alternatives to stenting, avoiding stent-related complications while maintaining lumen patency long-term.

Surgical repair involves resecting stenotic segments followed by reanastomosis or autologous vein/prosthetic graft transplantation, suitable for patients with long-segment or multifocal stenosis. This method effectively restores blood flow but is associated with significant trauma, long recovery times, and postoperative complications (e.g., infection, hematoma) in ~10%–15% of cases[13,45]. Studies show primary patency rates of 68.4% and secondary patency rates of 94.7% at 9 months postoperatively[46], but its applicability is narrow, and it fails to address core NIH

pathomechanisms (e.g., smooth muscle cell proliferation and inflammation)[47]. For patients at high risk of surgical trauma, special balloon interventional therapy offers minimally invasive advantages as the preferred treatment option. For long-segment stenosis, multiple special balloons can be used segmentally to reduce surgical trauma and complication risks.

In summary, traditional treatments have limitations in long-term efficacy and complication control. Special balloons, through mechanical modifications or targeted drug delivery, address these issues effectively. Their clinical applications include conventional PTA failures, complex stenotic lesions, stent alternatives, and minimally invasive treatment demands, providing superior options for AVF stenosis therapy.

4. Clinical Trial Efficacy Analysis of Special Balloons

Different types of special balloons, designed based on varying principles, are suitable for distinct AVF stenosis lesions. Multiple multicenter, randomized controlled clinical trials have systematically validated their therapeutic effects, patency rates, and complication incidences, providing evidence-based guidance for clinical selection.

4.1. Cutting Balloons

Cutting balloons (CBAs) feature microblades on their surface to precisely tear fibrous scar tissue in the vessel wall during dilation, reducing elastic recoil. They are primarily indicated for localized fibrotic stenotic lesions resistant to conventional PTA. A multicenter controlled trial showed that CBAs achieved a 97.4% immediate technical success rate for localized fibrotic AVF stenosis (diameter 2–4 mm, length < 10 mm), with primary patency rates of 91.3% and 71.4% at 3 and 6 months postoperatively, respectively[48]. Another study enrolled hemodialsis patients with dysfunctional AVFs unresponsive to conventional PTA (residual stenosis > 30%). CBAs demonstrated significantly superior primary and secondary target lesion patency rates compared to high-pressure balloons (HPBAs). For AVF stenosis resistant to conventional PTA, CBAs serve as a superior second-line therapy due to their higher patency rates[49].

4.2. Drug-Coated Balloons

Drug-coated balloons (DCBs), the most widely clinically applied special balloons, are coated with antiproliferative and anti-inflammatory drugs (e.g., paclitaxel, sirolimus). During mechanical dilation, drug delivery to the vessel wall inhibits vascular smooth muscle cell (VSMC) proliferation and NIH, preventing postoperative restenosis in mild-to-moderate fibrotic stenosis. Their core advantages include no foreign body retention and no need for long-term antiplatelet therapy. A study evaluated clinical and imaging data from hemodialysis patients treated with paclitaxel-coated DCBs (length: 4 cm), following up on access patency. Kaplan-Meier analysis assessed primary and secondary patency rates, while univariate and multivariate Cox proportional hazards regression identified predictors of primary patency after DCB treatment. The study enrolled 173 patients, with median primary and secondary patency durations of 443 and 1035 days, respectively. Primary patency rates at 6, 12, 18, 24, 30, and 36 months were 85.9%, 64.1%, 34.1%, 21.3%, 12.0%, and 6.0%, respectively; secondary patency rates were 98.8%, 93.8%, 89.8%, 81.9%, 76.1%, and 48.6%, respectively[50]. Another international multicenter, single-blind, 1:1 randomized trial (330 patients) found that paclitaxel-coated balloons significantly outperformed standard balloons in 6-month target lesion primary patency (82.2% vs. 59.5%, $P < 0.001$), demonstrating non-inferior safety and superior efficacy[51].

4.3. Scoring Balloons

Scoring balloons (SBs) are pressure-focusing interventional balloons with nickel-titanium alloy scoring elements

integrated on non-compliant balloon surfaces. During inflation, expansion force concentrates at scoring contact points, creating localized high pressure for controlled micro-incision and directional dilation of fibrotic/calcified plaques while reducing vascular dissection and elastic recoil risks. A retrospective analysis evaluated SB performance in 428 patients with severe AVF and arteriovenous graft (AVG) stenosis. Postoperative primary patency rates were 98.1%, 90.8%, and 78.0% at 1, 3, and 6 months, respectively. Subgroup analysis showed 6-month primary patency rates of 79.9% for AVFs and 75.4% for AVGs, indicating efficacy in refractory and recurrent cases[52].

4.4. Combined Use of Special Balloons

For complex AVF stenosis (e.g., calcified+fibrotic, long-segment, multifocal stenosis), single special balloon therapy has limited efficacy. Clinical trials confirm that combining different special balloons achieves complementary advantages, improving treatment outcomes. A study showed that residual stenosis after conventional balloon angioplasty was (48.8 ± 11.3)%, which decreased to (18.7 ± 10.4)% after combined cutting balloon and DCB treatment. Technical success (residual stenosis < 30%) was achieved in 94.7% of lesions (18/19). At 6 months, target lesion patency was 100%, and vascular access primary patency was 94.7% (18/19), with no venous rupture or severe complications[53-54].

5. Experimental Basis and Translational Research Progress in Special Balloon Development

5.1. Targeted Drug Screening and Coated Balloon Development

Mechanistic studies in animal models have identified targeted drug interventions as a key direction for preventing AVF stenosis, providing core research evidence for drug selection and dose optimization in drug-coated special balloons. Drugs targeting different pathological pathways show significant efficacy in specific models.

5.1.1. Anti-inflammatory Targeted Interventions

In rat AVF models, postoperative intraperitoneal injection of anti-TNFα monoclonal antibodies significantly reduced TNFα expression (30%–40%) at injury sites, decreased macrophage infiltration, and lowered NIH thickness by 25%[55-56]. In rabbit AVF models, IL-6 receptor antagonists inhibited VSMC proliferation, improving lumen patency by 20% at 3 months postoperatively[57-58]. These findings support the development of anti-inflammatory drug-coated special balloons (e.g., TNFα antibody- or IL-6 receptor antagonist-coated balloons).

5.1.2. Antiproliferative Targeted Interventions

In porcine AVF models, local rapamycin (an mTOR inhibitor) delivery inhibited VSMC synthetic phenotype switching, reducing NIH area by 35% and restenosis rate by 30% at 6 months postoperatively[59]. In mouse models, paclitaxel reduced intimal thickening by 28% by inhibiting VSMC migration; in rabbit models, local application significantly improved lumen area (68% improvement rate)[60]. These data underpin the development of antiproliferative drug-coated special balloons. Currently, clinically used paclitaxel- and rapamycin-coated balloons optimize drug concentration and release rates based on these animal experiment results.

5.1.3. Antioxidant Targeted Interventions

In rat models, glutathione intervention reduced reactive oxygen species (ROS) levels by 40%, minimizing oxidative stress-induced endothelial injury and maintaining endothelial integrity[61]. This provides a new rationale

for developing antioxidant drug-coated special balloons that deliver antioxidants locally to inhibit ROS-mediated damage amplification.

These experimental data confirm that targeted drugs against inflammation, proliferation, and oxidative stress effectively inhibit NIH, providing critical evidence for clinical special balloon design (e.g., drug coating or targeted release systems). However, species differences (e.g., pharmacokinetics) and drug delivery optimization require further study[57,62].

5.2. Anti-inflammatory Immunomodulation and Balloon Functional Optimization

Anti-inflammatory and immunomodulatory strategies show key potential in AVF stenosis prevention, focusing on targeted interventions of macrophages, T lymphocytes, and innate immune pathways.

5.2.1. Macrophage Chemotaxis Regulation

CCR2-mediated monocyte/macrophage chemotaxis is critical for early inflammatory responses. Studies show that nano-carrier-delivered CCR2 antagonists (e.g., RS-504393) block the CCL2/CCR2 signaling axis, significantly reducing macrophage infiltration at injury sites (by 50%) and lowering NIH thickness by 32%[63]. This strategy further inhibits early focal macrophage aggregation and delays stenosis progression in porcine AVF models[59,64], providing a basis for developing CCR2 antagonist-coated special balloons that deliver antagonists locally to suppress macrophage recruitment and enhance anti-inflammatory effects.

5.2.2. T Lymphocyte Immunosuppression

CD4+ T cell activation promotes inflammatory cytokine (e.g., IFN-γ, IL-17) release, exacerbating vascular injury. In rabbit AVF models, CD4+ T cell inhibitors reduced lymphocyte infiltration and IFN-γ expression, lowering lumen stenosis rate by 25% at 4 months postoperatively. Clinical studies also find a positive correlation between CD4+ T cell proportion and AVF stenosis risk, suggesting potential value in immunomodulatory therapy [65-66]. These results guide the development of immunomodulatory drug-coated special balloons that combine anti-inflammatory and antiproliferative drugs for multi-target intervention.

5.2.3. Innate Immune Pathway Intervention

TLR4 signaling activation drives innate immune responses, amplifying inflammatory cascades. In porcine AVF models, TLR4 inhibitors (e.g., TAK-242) reduced neutrophil infiltration and TNF-α/IL-6 expression, while decreasing early thrombosis formation and improving patency by 22% at 5 months postoperatively[67]. This effect correlates with oxidative stress inhibition and endothelial protection. These findings support the development of TLR4 inhibitor-coated special balloons that block innate immune pathways locally to further enhance stenosis prevention.

In summary, targeting immune cell recruitment and innate immune activation effectively inhibits AVF stenosis progression, but clinical translation requires optimizing drug delivery strategies (e.g., local sustained-release systems) and evaluating long-term immune safety[63,68]. Combining anti-inflammatory and antiproliferative therapies may represent a future breakthrough direction.

5.3. Antioxidant Interventions and Balloon Design Directions

Antioxidant stress modulation plays a crucial role in preventing and treating arteriovenous fistula (AVF) stenosis, primarily through strategies such as Nrf2 pathway activation, mitochondrial-targeted antioxidation, and vitamin E

derivatives. These approaches provide experimental evidence for the design and development of specialized balloons with antioxidant functions.

5.3.1. Nrf2 Pathway Activation

Sulforaphane (SFN), a natural Nrf2 activator, significantly upregulates antioxidant enzyme (HO-1, SOD) expression through oral administration in a rat AVF model, enhancing reactive oxygen species (ROS) scavenging capacity by 50%, reducing endothelial cell apoptosis by 35%, and mitigating neointimal hyperplasia (NIH) by 30% [69-70]. The mechanism involves SFN binding to Keap1, promoting Nrf2 nuclear translocation, and activating antioxidant response element (ARE)-driven gene transcription[71]. Studies also indicate that Nrf2 expression increases significantly in the early stages of AVF models, inversely correlating with tissue oxidative damage[72]. This experiment confirms the antioxidant effects of Nrf2 pathway activators, providing drug selection and mechanism-based evidence for the development of Nrf2 activator-coated specialized balloons.

5.3.2. Mitochondrial-Targeted Antioxidation Mitochondrial-derived

ROS are a key trigger for vascular smooth muscle cell (VSMC) proliferation. In a rabbit AVF model, local injection of MitoQ (a mitochondrial-targeted ubiquinone) specifically accumulates in the mitochondrial matrix, inhibiting superoxide generation caused by electron leakage, improving mitochondrial membrane potential, and reducing intimal thickness by 27% at three months post-surgery[72]. MitoQ also reduces mitochondrial permeability transition pore (mPTP) opening, inhibiting VSMC apoptosis and abnormal migration[73]. This provides a rationale for developing mitochondrial-targeted antioxidant drug-coated specialized balloons, enabling precise elimination of mitochondrial-derived ROS through local delivery of drugs like MitoQ.

5.3.3. Vitamin E Derivative Protection

Alpha-tocopherol reduces vascular wall oxidative stress by 38% in a mouse AVF model by scavenging lipid peroxyl radicals (e.g., LOO·) and inhibiting NADPH oxidase (NOX2) activity[74]. Its hydrophobic side chain embeds into cell membranes, blocking oxidative stress chain reactions, reducing collagen deposition and matrix metalloproteinase (MMP-9) expression, ultimately alleviating luminal stenosis by 24%[75]. These results support the development of vitamin E derivative-coated specialized balloons, utilizing local sustained-release technology to maintain antioxidant drug concentrations in the vascular wall.

Despite the significant effects of antioxidant strategies in animal models, human AVFs face persistent oxidative stress in the uremic microenvironment (e.g., accumulation of advanced glycation end products), necessitating the development of local sustained-release systems (e.g., nanocarrier-encapsulated antioxidants) to maintain effective concentrations[76]. Combining Nrf2 activators with mitochondrial-targeted antioxidants may represent a future breakthrough direction[77].

5.4. Exploration of Advanced Biotechnology Combinations

Advanced biotechnologies offer novel strategies for preventing and treating AVF stenosis, including gene therapy, stem cell therapy, and biomaterial interventions.

5.4.1. Gene Therapy Targeting VSMC Proliferation

c-Myc, a key regulatory gene for smooth muscle cell proliferation, can effectively inhibit neointimal hyperplasia (NIH) when silenced. Studies show that delivering siRNA targeting c-Myc via adeno-associated virus (AAV) vectors

in a porcine AVF model specifically silences c-Myc expression, reducing NIH area by 40% and improving patency by 35% at six months post-surgery[78-79]. AAV serotype selection (e.g., AAV1's high affinity for muscle tissue) and promoter optimization (e.g., SM22α promoter-driven VSMC-specific expression) are critical for enhancing targeting efficiency[73,80]. This experiment provides evidence for developing siRNA-delivering specialized balloons, utilizing local pressure during balloon expansion to promote efficient siRNA carrier penetration into the vascular wall, achieving synergistic gene silencing and mechanical dilation.

5.4.2. Stem Cell Therapy Promoting Endothelial Repair

Endothelial progenitor cells (EPCs) accelerate re-endothelialization by homing to injury sites and differentiating into mature endothelial cells. In a rat AVF model, intravenous EPC infusion increases $CD34^+/VEGFR2^+$ cell homing efficiency by 2.1-fold, shortens endothelial integrity recovery time by 50%, and reduces restenosis by 30% at four months post-surgery[81-82]. The mechanism involves EPC secretion of VEGF and stromal cell-derived factor-1 (SDF-1), activating the PI3K/Akt pathway to inhibit apoptosis[83-84]. This provides a rationale for developing EPC-loaded specialized balloons, utilizing balloon surface modification technology to load EPCs and precisely deliver stem cells to high-damage regions during lumen expansion, promoting endothelial repair.

5.4.3. Biomaterial Regulation of Local Microenvironment

Biodegradable scaffolds (e.g., polycaprolactone, PCL) loaded with VEGF enable controlled release of growth factors. In a rabbit AVF model, PCL scaffolds sustain VEGF release (release cycle > 28 days), maintaining local VEGF concentrations > 50 ng/mL, promoting endothelial regeneration and inhibiting VSMC migration, improving luminal patency by 28% at five months post-surgery [85-86]. The scaffold degradation rate (typically 8-12 weeks) must match tissue regeneration to avoid early mechanical support failure [87-88]. These results provide references for developing biodegradable drug-eluting specialized balloons, combining biodegradable biomaterials with balloons to achieve synergistic long-term drug release and mechanical dilation.

Current technologies still face challenges such as low in vivo delivery efficiency (e.g., AAV neutralizing antibody interference), insufficient stem cell survival (apoptosis rate > 60% at 72 hours post-transplantation), and material biocompatibility issues[89-90]. Future efforts should focus on developing more targeted carriers (e.g., ligand-receptor targeting systems modified with nanoparticles) and smart-responsive scaffolds (e.g., pH- or enzyme-triggered release), combined with multi-omics technologies to screen optimal intervention timelines.

6. Summary and Outlook

The core pathological mechanism of AVF stenosis lies in the cascade reaction triggered by endothelial injury, encompassing inflammatory infiltration, phenotypic switching and abnormal proliferation of VSMCs, as well as ROS-mediated oxidative stress. These factors collectively drive neointimal hyperplasia, ultimately leading to pathway dysfunction. Current clinical approaches, primarily involving imaging monitoring, pharmacological prevention, and PTA, struggle to fundamentally block the aforementioned core pathways, resulting in persistently high restenosis rates. Special balloon technology, which combines mechanical dilation with local drug delivery, effectively expands the lumen and reduces elastic recoil while directly inhibiting VSMC proliferation and inflammatory responses, thereby significantly addressing the limitations of traditional PTA. Future research will focus on technological optimization (such as drug coatings and biodegradable materials), combined therapeutic strategies (such as synergistic effects with gene or stem cell therapies), as well as the standardization and personalization of clinical

translation, aiming to comprehensively enhance the long-term patency and safety of vascular pathways.

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