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Risk factors and possible mechanisms of saphenous vein graft failure after coronary artery bypass surgery

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Coronary heart disease (CHD) is a complex metabolic syndrome, resulting in atherosclerotic lesions in one or more coronary arteries. CHD is associated with high morbidity and mortality worldwide. Coronary artery bypass grafting (CABG) is the gold standard for invasive treatment of severe CHD, especially triple-vessel disease and left main disease. Saphenous veins (SVs) are typically used in CABG because of their sufficient length and convenience, but SV graft (SVG) failure is a common finding in patients. Approximately 20% of SVGs fail within 1 year after CABG, and the 10-year post-CABG patency rate is 60%.[1]

Vein graft failure can be affected by numerous potential risk factors, mainly including endothelial cell (EC) dysfunction, instantaneous shear stress change, structure of SVs, and surgical techniques. ECs are a thin layer of specialized epithelial cells located between the blood and blood vessel wall. In normal circumstances, ECs, as a barrier, are tightly arranged and play a crucial role in vascular homeostasis. ECs can synthesize and release a large variety of mediators. For example, vasodilators (nitric oxide [NO], prostacyclin, etc) and vasoconstrictors (angiotensin-converting enzyme, endothelin, etc) can regulate vascular tone and matrix products (fibronectin, collagen, etc). Growth factors (insulin-like growth factor, transforming growth factor, etc) can manage the remodeling of blood vessel walls. Antithrombotic factors (thrombomodulin, heparin, etc) and procoagulant factors (von Willebrand factor [vWF], thromboxane A2 [TXA2], etc) can affect blood coagulation and fibrinolysis homeostasis, and inflammatory mediators (interleukin [IL]-1, IL-6, IL-8, etc) involved in inflammatory responses. Once ECs are damaged, a complex network of adhesion, chemotaxis, and inflammatory responses is triggered and influences vascular smooth muscle cells (VSMCs), platelets, and peripheral leukocytes through autocrine, paracrine, and endocrine effects.[2] Harvesting of SVs results in ischemia reperfusion injury. It has been reported that ultrastructural changes in ECs can be observed using transmission electron microscopy after 30 min of ischemia in canine veins. Long ischemic times are associated with more severe damages in the ECs of grafted veins. EC dysfunction decreases the activity of endothelial NO synthase and associated reduction in NO. The dysregulation of NO balance has profound effects on the impairment of vasodilatation, especially in the vein graft, and increased reactive oxygen species production, which can directly regulate the proliferation and migration of VSMCs. The Rho/Rho-kinase pathway may negatively regulate endothelial NO synthase and is involved in intimal hyperplasia. Long-term oral Rho-kinase inhibition suppresses the proliferation of VSMCs and intimal thickening in vein grafts after surgery in rabbits.[3] This method may provide a new treatment for vein graft failure. Instantaneous shear stress change is one of the risk factors of vein graft failure. The wall shear stress of SVs is normally 1 to 6 dyn/cm^2, and the hydrostatic pressure of SVs is 5 to 10 mmHg. After implantation, SVs experience higher wall shear stress (10–70 dyn/cm^2) and higher hydrostatic pressure (120/80 mmHg). The endothelium lining of the cardiovascular system is highly sensitive to hemodynamic shear stresses. The immediate increases in the wall shear stress and hydrostatic pressure result in damage and exfoliation of ECs, which further destroy the function of the vascular endothelial barrier. The structure of SVs is another risk factor of vein graft failure. Compared with arteries, SVs have a narrower medial layer composed primarily of collagen, fenestrated elastic laminae, less elastin, and fewer VSMCs. Ephrin B2 and ephrin B4 are the key factors in arteries and veins, respectively. Previous studies have

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demonstrated that EphB4 expression reduces on SVG adaptation in humans and adult rats. Reduction in EphB4 expression in ECs in a mouse vein graft model results in diminished proliferation and migration of ECs and VSMCs.[4] These results indicate that the loss of EphB4 plays a role in vein graft adaptation, and stimulation of EphB4 function may be a candidate strategy for vein grafting in human clinical trials designed to inhibit venous neointimal hyperplasia. Vascular endothelial growth factors (VEGFs) are a sub-family of growth factors. They are important signaling proteins involved in vasculogenesis and angiogenesis. VEGF-A plays a critical role in down-regulating EphB4 expression (venous identity) in adult venous ECs without inducing Ephrin B2 expression (arterial identity). These changes in adult ECs *in vitro* recapitulate the changes in identity described during vein graft adaptation to the arterial environment *in vivo*. However, it has been suggested that the effect of VEGFs on grafted veins should be understood from two opposing aspects. In the early post-implantation period, VEGF may be a beneficial repair factor for EC damage. In the long-term after vein grafting, the increased expression of VEGFs may result in VSMCs proliferation and/or neointimal formation.[5] The mechanism of action of VEGFs in vein grafts needs further confirmation. In addition, surgical techniques are associated with vein graft failure. The "no-touch" technique of SV harvesting can improve the patency of SVGs, including short-term and long-term patencies. Perivascular adipose tissue, releases cytokines, adipokines, and inflammatory factors via autocrine and/or paracrine pathways and participates in the regulation of vascular tone, proliferation and migration of VSMCs, atherosclerosis, and even restenosis. The "no-touch" technique seems to retain perivascular adipose tissue, provides a protection medium for SVs, maintains the integrity of ECs, and preserves EC function.[6] Some studies have focused on the vein patency of "off-pump" CABG in comparison to "on-pump" CABG. The Randomized On/Off Bypass Trial (ROOBY) randomized 2203 patients ("on-pump" or "off-pump" CABG), and the angiographic results showed that the graft patency after 1 year of "off-pump" CABG was significantly lower than that after "on-pump" CABG. Furthermore, the technique of harvesting the vein was also studied. The sub-analysis of the ROOBY trial showed that endoscopic vein harvesting is associated with lower SVG patency after 1 year than open-vein harvesting.[1] In summary, surgical techniques are important in determining vein graft failure.

Vein graft failure is the result of a complex physiopathological process, and the possible mechanisms include thrombosis, intimal hyperplasia, atherosclerosis, and inflammation. Thrombosis is the main cause of early failure of vein grafts (usually defined as less than 1 month after CABG). After SVG, intimal damage leads to the denudation of ECs, causing exposure of the sub-endothelial extracellular matrix to the flowing blood. Platelets are directly activated by sub-endothelial extracellular matrix proteins, including laminin, fibronectin, vitronectin, and collagen. Following initial platelet activation and adhesion, additional platelets and fibrinogen are recruited to form thrombi. This process involves a variety of factors, including glycoprotein Ib, vWF, adenosine diphosphate, TXA2, and fibronectin. Activated platelets further release a number of vasoactive substances, such as growth factors (platelet-derived growth factors, tumor growth factor-β), chemotactic factors, IL-1β, and thrombin, which further stimulate thrombosis. The initial thrombosis is closely related to EC dysfunction and instantaneous shear stress changes in SVs.[1] Intimal hyperplasia is the primary cause of delayed failure of vein grafts (1–12 months after CABG). Abnormal proliferation and migration of VSMCs play a critical role in the pathogenesis of intimal hyperplasia. After EC injury, many different cell types, including ECs, platelets, and inflammatory cells, release mediators. These mediators promote changes in VSMCs from the quiescent contractile state to the active synthetic state. This process contributes to the proliferation and migration of VSMCs. Meanwhile, EC damage and dysfunction also lead to extracellular matrix protein deposition, which promotes the induction of VSMCs migration and proliferation.[1] Atherosclerosis is the leading cause of late failure of vein grafts (1 year after CABG). Foam cells and intimal thickening appear 1 year after SVG. Two to five years after SVG, a necrotic core may develop, which is involved in plaque rupture and thrombosis. More than 5 years after SVG, a large number of necrotic cores are observed, and intra-plaque hemorrhage and fibrous plaque rupture are observed in the lumen. The pathogenesis of atherosclerosis involves foam cell accumulation, cellular proliferation, inflammatory cell infiltration, fibrous plaque formation, intra-plaque hemorrhage, and plaque rupture. These pathological processes are triggered by endothelial damage. Grafted SVs are more likely to develop atherosclerosis with more rapidly progressing pathological changes than those in coronary arteries.[1] In recent years, studies have found that inflammation plays an important role in the pathological process of vein graft failure.[7] SV distention pressure is significantly correlated with inflammatory markers, including toll-like receptors 2 and 4, platelet endothelial cell adhesion molecule (PECAM), vascular cell adhesion molecule, and intercellular cell adhesion molecule. Toll-like receptors are central in the inflammatory responses and activate monocyte chemoattractant protein-1 (MCP-1) to induce the release of cytokines generally through the myeloid differentiation primary response protein 88 – nuclear factor-κB pathway. Inhibition of nuclear factor-κB can inhibit the inflammatory response and accumulation of VSMCs in neointimal hyperplasia in rabbit models. In addition, arterialization of vein grafts results in the activation of p38 mitogen-activated protein kinases (MAPKs) in canine models. Rat models of vein grafts with p38 MAPK inhibitors significantly ameliorate intimal, medial, and adventitial thickening of SVGs. The new results show that MAPKs may be a key mechanism involved in SVG failure.[8] Some studies of anti-inflammatory treatment for vein graft failure have also confirmed that inflammation plays an important role in the pathological process of vein graft failure. MCP-1 is a specific chemokine of monocytes and macrophages. Local blockade of the MCP-1/CCR-2 signaling pathway by adenoviral gene transfer of the N-terminal deletion mutant of *MCP-1* significantly attenuates inflammation and proliferation and suppresses neointimal formation in dogs with vein grafts.[9] A recent study of SVG patency in patients with chronic peripheral arterial disease has indicated that low levels of anti-phosphorylcholine immunoglobulin M, an

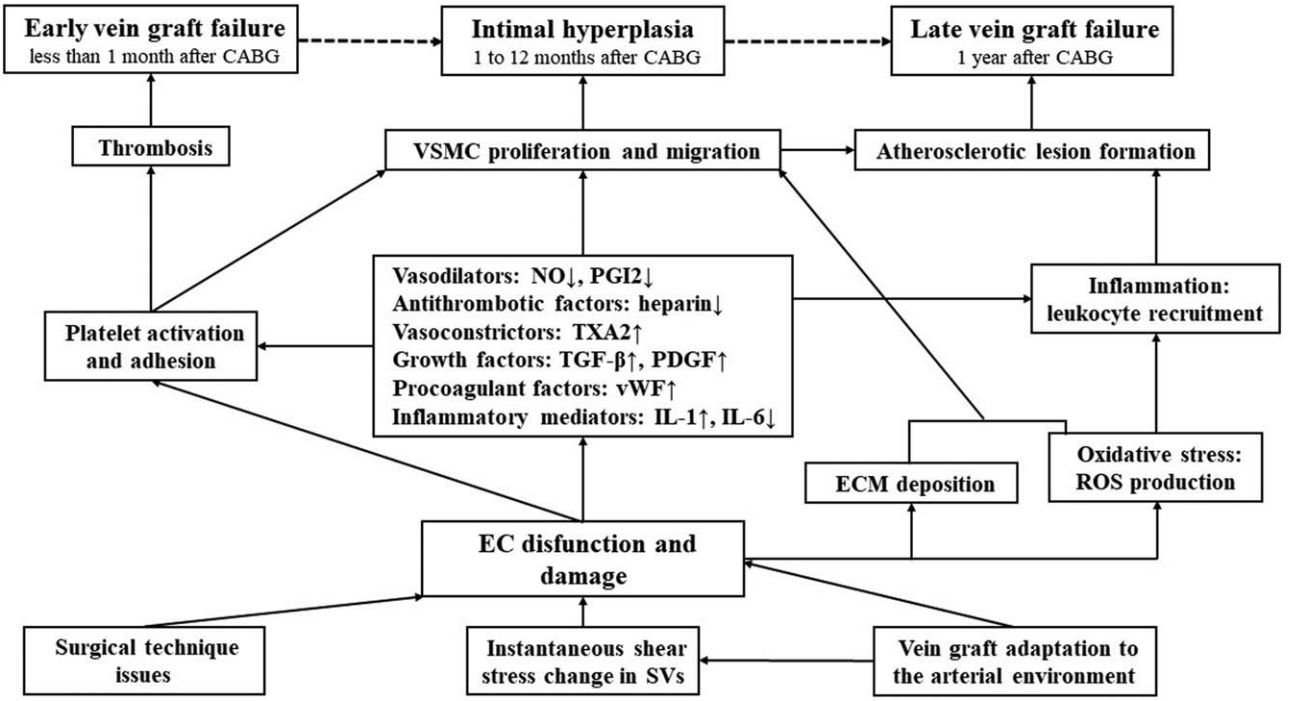

Figure 1: Possible mechanisms of vein graft failure. CABG: Coronary artery bypass grafting; VSMC: Vascular smooth muscle cell; NO: Nitric oxide; PGI2: Prostacyclin; TXA2: Thromboxane A2; TGF-β: Tumor growth factor-β; PDGF: Platelet-derived growth factor; vWF: von Willebrand factor; IL: Interleukin; ROS: Reactive oxygen species; ECM: Extracellular matrix; EC: Endothelial cell; SV: Saphenous vein.

anti-inflammatory mediator, are associated with vein bypass graft failure.[10]

In conclusion, SVG failure is an urgent problem to be solved. Previous studies have suggested that thrombosis, intimal hyperplasia, and atherosclerosis are involved in the pathogenesis of vein graft failure [Figure 1]. With further research, especially of inflammation, some progress has been made. Although the inflammatory mechanism of vein graft failure has not been fully elucidated, the studies described in this article suggest that there are potential and novel anti-inflammatory therapies for vein graft failure.

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Conflicts of interest

None.

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