Saphenous vein graft disease, pathophysiology, prevention, and treatment. A review of the literature

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Funding information
NIHR Biomedical Research Center at University Hospitals Bristol NHS Foundation Trust

Abstract

Background: The saphenous vein remains the most frequently used conduit for coronary artery bypass grafting, despite reported unsatisfactory long-term patency rates. Understanding the pathophysiology of vein graft failure and attempting to improve its longevity has been a significant area of research for more than three decades. This article aims to review the current understanding of the pathophysiology and potential new intervention strategies.

Methods: A search of three databases: MEDLINE, Web of Science, and Cochrane Library, was undertaken for the terms “pathophysiology,” “prevention,” and “treatment” plus the term “vein graft failure.”

Results: Saphenous graft failure is commonly the consequence of four different pathophysiological mechanisms, early acute thrombosis, vascular inflammation, intimal hyperplasia, and late accelerated atherosclerosis. Different methods have been proposed to inhibit or attenuate these pathological processes including modified surgical technique, topical pretreatment, external graft support, and postoperative pharmacological interventions. Once graft failure occurs, the available treatments are either surgical reintervention, angioplasty, or conservative medical management reserved for patients not eligible for either procedure.

Conclusion: Despite the extensive amount of research performed, the pathophysiology of saphenous vein graft is still not completely understood. Surgical and pharmacological interventions have improved early patency and different strategies for prevention seem to offer some hope in improving long-term patency.

KEYWORDS
cardiovascular pathology, clinical review, coronary artery disease

1 | INTRODUCTION

Coronary artery bypass grafting (CABG) remains the gold standard treatment for severe coronary artery disease, especially for patients with diabetes and low ejection fraction. The most frequently used conduits for CABG are the left internal thoracic artery (LITA) and the long saphenous vein (LSV). While the LITA has been shown to have an excellent long-term patency rate, it is limited by its length and therefore it is not generally suitable for multiple grafts. The LSV, on the other hand, is readily available in greater lengths to construct...
more than one graft and can be harvested at the same time as the LITA. For these reasons, the LSV remains one of the most commonly used conduits for CABG. Other conduits not extensively used are the radial artery and the right internal thoracic artery.

Despite its extensive use, the LSV graft suffers short-term failure and has a low long-term patency rate resulting in lower long-term survival and event-free survival compared with arterial grafts.

Over the years, there has been increased interest in understanding the pathophysiology involved in the development of vein grafts disease as although many therapeutics have been suggested, none has been successful enough to make them widely adopted. This is in part related to our limited understanding of the complex pathological processes involved in the development of the disease starting from vascular inflammation (VA) to superimposed atherosclerosis, the cross-talk between the different cells forming the LSV and the influence of the circulating cells and other molecules. The overall process is thought to be marked by complex interactions between several factors owned to either the patient or the technique which will ultimately impact the pathophysiology of the disease, making its study challenging.

2 | METHODS

Original research articles and reviews were selected as they related to the pathophysiology, prevention, and treatment of SV graft failure. A literature search was performed using MEDLINE, Web of Science, and Cochrane Library. The search was focused on human, translational, in vitro, and animal studies.

3 | RESULTS

3.1 | Pathophysiology of LSV graft failure

The pathophysiology of LSV graft failure has been described as driven by four interconnected and related processes: early acute thrombosis (AT), VA, intimal hyperplasia (IH), and late accelerated atherosclerosis.

3.1.1 | Acute thrombosis

It is widely accepted that AT is responsible for the majority of early vein graft failures. This process starts from the harvesting of the LSV, where surgical injury combined with hypoxia caused by damage to the vasa vasorum, oxidative stress, wall distention, and acute elevation of shear stress can lead to endothelial dysfunction and activation and make it switch to a prothrombotic state, or even deendothelialize the vessel exposing the extracellular matrix (ECM) to the blood in the lumen. This results in a loss of balance between antithrombotic and prothrombotic systems in favor of the latter with a marked reduction of nitric oxide (NO), prostacyclin (PGI2), thrombomodulin, and heparin-like substances in injured endothelium associated with increased expression of adhesion molecules and the sensitivity of the vascular smooth muscle cells (VSMC) to vasoconstrictors. Furthermore, there is simultaneous activation of the coagulation cascade resulting in platelet activation and adherence to the de-endothelialized areas with the generation of different pro-coagulation factors such as thromboxane A2, fibrinogen, fibronectin, thrombospondin, von Willebrand factor, platelet factor IV, and b-thromboglobulin. These processes combined can culminate in 3% to 12% early graft occlusions.

It has been described that the endothelial lining of the grafts can recover after this initial process, although, as described below, the new endothelium can be dysfunctional.

3.1.2 | Intimal hyperplasia

IH is a chronic disease where the VSMCs in the medial layer switch from a quiescent state to a synthetic proliferative, resulting in migration to the intimal layer where they proliferate causing further thickening of the intimal. The function of both VSMCs and endothelial cells (ECs) is linked by their physical and paracrine interactions, which controls vascular tone, cell proliferation and response to inflammation. In a healthy state the interaction between ECs and VSMCs keeps the VSMCs in a quiescent state; via EC-derived homeostatic molecules like NO which help regulate the tone of the medial layer and suppress VSMC phenotypic switching to synthetic cells. Local inflammation and endothelial injury cause the ECs to switch to a prothrombotic state and, therefore, this interaction is disrupted. This, can be further enhanced by the release of cytokines like interleukin-6 (IL-6), IL-8, and thromboxane A2 and growth factors like platelet-derived growth factor and fibroblast growth factor from activated platelets and leukocytes contributing to VSMC phenotypic switching to synthetic phenotype and proliferation. Also, it is known that both ECs and VSMCs secrete ECM proteins, and this may be a way of indirect communication, which induces VSMC phenotypic switching and proliferation. ECs may also induce VSMCs proliferation via microRNAs. For example, increased levels of endothelial-derived miR-126 resulted in higher VSMC turnover (proliferation and apoptosis). On the other hand, ECs microRNAs miR-143/145 have been associated with decrease IH possibly through downregulation of VSMC phenotypic switching mechanism; while miR-126 seems to contribute to the formation of IH since its depletion in mice resulted in IH suppression. However, these studies relate specifically to IH and not in the context of LSV graft. After the initial denudation, new ECs can be seen as early as the first week after surgery in experimental models, however, after the endothelium is restored the process of IH does not reverse, this is thought to be in part due to the increase of shear stress on the wall which makes the new endothelium dysfunctional and partly due to the now chronic localized inflammatory response.

Some studies on VSMCs have identified the importance in the development of IH, of Kruppel-like factor 4 (KLF4) and Kruppel-like
factor 5 (KLF5), both protein-coding genes. KLF4 acts as a down-regulator of VSMCs contractile markers such as smooth muscle α-actin, SM22α, and smooth muscle myosin heavy chain, thus switching the cell to a synthetic state. However, KLF4 may serve as an athero-protective factor, its overexpression in ECs induces the upregulation of anti-inflammatory and anti-atherosclerotic factors. KLF5 has been seen to increase in response to vascular injury and atherosclerotic lesions. KLF5 may activate VSMCs to switch, migrate and proliferate as is preferentially expressed in de-differentiated VSMCs. A study also found an association between KLF5 positive VSMCs and a higher risk of graft restenosis in rabbits. Other important factors in the development of IH that have been studied are p38 mitogen-activated protein kinase (p38), and nuclear factor kappa-light-chain-enhancer of activated B cells both have been evidenced to induce VSMC proliferation in vitro using models of cultured VSMCs and on coculture models of VSMCs and ECs.

The development of IH is a complex process in which the VSMCs and the ECs play a crucial role, but the entire process is not yet completely understood, and by expanding our comprehension of this process we may find new therapeutic targets to reduce the rate of LSV graft failure.

3.1.3 Accelerated atherosclerosis

Atherosclerotic disease progresses much rapidly in LSV grafts as compared to native arteries, as its lipolysis is slower and suffers from accelerated lipid uptake. Compared to native atherosclerotic plaques, the LSV plaque is more highly populated with foam cells and other inflammatory cells, including multinucleated giant cells. It has been detected that some of these cells may originate from venous VSMCs rather than from circulating cells, making IH an important contributor to the speed and severity of atherosclerosis in vein grafts.

Like the native artery atherosclerosis, the vein graft atherosclerosis can suffer plaque rupture and AT, which has been described in necropsy samples. However, the vein graft atherosclerosis tends to be diffuse, concentric, and friable with a poorly developed or absent fibrous cap and little evidence of calcification, making it more prone to rupture than native artery atherosclerotic plaques.

3.1.4 The role of inflammation

At any time during the development of the previous three mechanisms of LSV graft failure, there can coexist a certain degree of localized acute or chronic inflammation, which exacerbates the pathophysiological stage of the graft failure. During the initial phase of this process the exposure of the ECM to the lumen of the vessel in an area of de-endothelialisation recruits leukocytes and platelets. These cells infiltrate the intima, this process will alternate between acute and chronic with more or less leukocyte activation. IH is enhanced by growth factors and cytokines IL-1, IL-6, and tumoral necrosis factor-alpha released by inflammatory cells. In a later stage, monocytes infiltrate the IH layer and differentiate into macrophages as is developing into an atherosclerotic plaque and develop into foam cells as they would on the artery’s atherosclerosis due to uptake of lipid, but the localized chronic inflammatory changes make this process happen faster than in native arteries. Intimal macrophages secrete matrix metalloproteinases which lead to ECM and cell-to-cell contact cleavage further inducing VSMCs migration into the intima and proliferation. The presence of VSMCs within the intimal layer, triggers further inflammation, attracting additional macrophages into the IH layer, thus accelerating atherosclerosis (see above).

During this process of inflammation damage to perivascular fat will release cytokines and recruit lymphatic cells in the vessel’s adventitia which will, in turn, secrete proinflammatory cytokines, disruption of perivascular fat also reduces the bioavailability of NO which acts as a regulator of vascular tone and signals the VSMCs to stay in a contractile state.

3.2 Prevention of LSV failure

The quest for modifiable factors that influence graft failure has occurred for more than three decades. Some of the following are methods that may reduce the incidence of graft failure.

3.2.1 Reducing atherosclerosis risk factors

Atherosclerosis associated risk factors are still present in the patient after CABG, some of which have been directly associated with poor prognosis of the LSV grafts.

- Smoking: Multiple studies have identified the role of smoking habit in the development of both long and short-term LSV graft disease and inferior survival after CABG.
- Dyslipidaemia: Evidence points towards hyperlipidaemia as one of the main risk factors in the development of vein graft disease; cholesterol levels higher than 240 mg/dL have shown a significant increase in the rate of LSV graft obstruction, similarly as found in native coronary disease with the relation between LDL cholesterol and HDL cholesterol is as important as the total serum cholesterol. The elevation of triglycerides in the serum has also been related to late vein graft failure. Furthermore, there is a strong association between dyslipidaemia and long-term morbidity and mortality after CABG. Aggressive treatment and prevention of hyperlipidaemia has been associated with better long-term outcomes.
- Hypertension: Despite its role in systemic atherosclerosis, studies looking at hypertension as a risk factor for LSV failure have found no such association.
- Diabetes mellitus (DM): There is conflicting evidence regarding the influence of DM on vein graft disease. Some studies have found that poorly controlled DM is associated with worse survival after CABG, while others found no significant difference in the rate of
No prospective study has explicitly looked at DM as a risk factor for LSV graft failure, and several laboratory studies have shown that DM impairs some of the vasodilator mechanisms, suggesting a role in graft disease.  

3.2.2 | Surgical technique

There is compelling evidence that a technique or surgical strategy affects LSV graft failure.

- Endoscopic vs Open LSV harvesting: Minimizing surgical trauma and improvement in patient’s quality of life was the driving for the development of endoscopic vein harvesting. However, there is now concern over this technique due to lower long-term patency rates of LSV grafts retrieved endoscopically.

- Distention: There is a large body of evidence that harvesting and subsequent distention of the LSV at more than 150mm Hg causes endothelial denudation exposing the ECM to the lumen, and increases rates of long-term graft failure.

- Harvesting, skeletonized vs “no-touch” LSV harvesting: Preserving the vein adventitia and the perivascular fat let to the development of the “no-touch” technique, which consists of harvesting the LSV with its perivascular fat and ligating the tributaries at least one centimeter away from the vein. This technique associated with nonabove-arterial pressure distention has demonstrated in some studies to provide substantially better long-term outcomes in terms of vein graft patency. However, it has the disadvantage of being associated with a higher incidence of graft site complications in the early postoperative period.

- Vein preservation media: The choice of preservation media during storage of the LSV prior to its use has been associated with increased concentration of free oxygen radicals and ischemia in all layers of the vein. On this subject, ex-vivo studies have shown a benefit in using the patient’s heparinized blood, but this benefit has not been able to be demonstrated in clinical practice. However, recent studies have demonstrated that a pH buffer in either crystalloid or blood media has provided a significant clinical benefit.  

- Technical aspects: Anastomotic technique is thought to be crucial for graft longevity, with poor technique and excessive surgical trauma associated with early vein graft failure. Accurate graft length is critical, both too short and too long grafts suffer from worse outcomes. There is evidence that graft longevity is dependent on the target vessel and its capacity to provide a good runoff flow. Advocates of the good runoff theory suggest that sequential anastomoses achieve a better runoff and lesser peripheral resistance to flow and therefore, improved long-term patency. While some evidence supports this statement a recent paper found worse rates of LSV graft failure with sequential anastomoses.

- Flow measurement: Transit time flow measurement (TTFM) may provide the surgeon with a tool for assessing both anastomosis quality and distal runoff while still in the operating theater; the current guidelines are that it should be considered. However, there are discrepancies in what values are considered acceptable and studies looking at this technique as a predictor for graft failure tend to use different values which are sometimes arbitrary. Despite these limitations, TTFM has shown to be useful in determining technical graft problems as is highly specific when a graft has a negative flow or high resistance, which can be caused by problems in the anastomosis.

3.2.3 | External graft support

External stenting has been proposed to reduce the rate of IH on vein grafts, by imposing LSV graft symmetry, more laminar flow and the subsequent reduction of shear stress, and also by providing a protective environment for the formation of new adventitia. However, despite promising results in animal models, early clinical trials have shown conflicting results such as a higher failure rate on right-sided grafts. Further trials will be needed before its application in clinical practice.

3.2.4 | Topical pretreatment

Storage of the LSV before its use provides a window of opportunity for topical treatments.

Gene therapy of the graft before implantation, have shown encouraging results in experimental animal models but contrasting results in the clinical context. There has been a success in ex-vivo models with TIMP-3 gene therapy and a clinical trial has been proposed.

3.2.5 | Pharmacological therapy

- Aspirin: Several prospective randomized trials have looked at the influence of aspirin vs placebo after CABG and demonstrated an increase in graft patency in patients receiving aspirin. Current trials recommend that aspirin therapy should be started as soon as possible after the operation as it has shown that if it started after the third day after surgery, it provides no benefit. Consequently, its implementation in the first-day postoperation showed a significant reduction of both early and late graft failure. Another important consideration is that it has been demonstrated that part of the population appears to be nonresponsive to aspirin and does not experience the same benefits as responding to patients.

Current indications suggest starting aspirin as early as 6 hours after surgery and continuing high dose aspirin for at least a year, also if tolerated low dose aspirin is indicated after that for secondary prevention of atherosclerosis.

- Dual antiplatelet: Recent guidelines recommend dual antiplatelet therapy with clopidogrel and aspirin for patients undergoing
Recent studies have shown a decrease in cardiovascular mortality in patients with dual antiplatelet therapy; however, it is still unclear whether different antiplatelet therapies combined with aspirin provide different outcomes. There is a need for trials that evaluate the efficacy of different antiplatelet agents when compared to each other.

- Statins: Hyperlipidaemia is a major contributor to LSV graft disease, and statin therapy has a beneficial effect on event-free survival after CABG. The American Heart Association recommends the use of statins after CABG in the absence of contraindications.

3.3 | Treatment after LSV failure

When vein graft failure results in clinical events or symptoms, it will require treatment. Deciding the appropriate therapy after LSV graft failure is often problematic and should be a decision taken by a multidisciplinary heart team. The treatment options are usually percutaneous coronary intervention (PCI) and repeat CABG; both have significantly increased risks as compared to first-time intervention. Therefore, some patients will be deferred to medical management instead.

3.3.1 | Vein graft angioplasty

PCI after vein graft failure accounts for 5% to 10% of all PCIs performed in the United States in a year, the procedure is technically challenging, especially if treating early graft failure, the risk of distal embolization is high, and some authors suggest the use of distal embolic protection devices. Regarding the choice of the stent, recent studies suggest that drug-eluting stents may offer an advantage over bare-metal stents. Long-term results are better with PCI than with medical treatment alone but are far from ideal and are indeed worse than outcomes of patients without vein graft failure.

3.3.2 | Reoperation

Repeat CABG may be an option for patients with LSV graft disease. However, it is with a significantly higher risk of mortality and morbidity, which is increased in cases when one or more of the grafts are patent, or for lack of available conduits. Comparison between long-term outcomes between reoperation and PCI is difficult as there is a substantial selection bias, but similarly to PCI long-term outcomes after reoperation are worse than those of patients with no graft failure.

3.3.3 | Medical management

Although both PCI and reintervention offer better long-term outcomes than medical therapy sometimes the initial elevated risk may preclude patients from receiving either intervention, in those cases patients will be managed with a combination of medical therapy and control of risk factors to achieve at least symptomatic control.

4 | CONCLUSIONS

Vein graft failure is a multifactorial process embedded in an already complex disease, atherosclerosis. Recent studies have helped further our understanding of the pathophysiology of this condition and have already yielded advancements in its secondary prevention; there is still to be seen the impact of these advancements in the reduction of long-term vein graft failure.

The clinical significance of LSV graft failure remains debated. The main limitation to research on this subject is the lack of a standardized classification of graft failure as some authors consider flow limitation and occlusion as comparable and others think this should be analyzed separately. This is also important when researching factors that affect LSV graft patency as there is much discrepancy in the literature in the definition of patency and of what constitutes early-, mid-, and long-term failure; this makes a comparison between studies particularly difficult in this subject.

Another problem in ascertaining the real clinical consequences of LSV failure is the wide variety of techniques used on bypass grafting, which have demonstrated to influence the rate of failure and long-term survival and symptoms, an example will be a study that demonstrated that LSV failure impaired long-term survival when it was grafted in the left anterior descending artery. This may no longer be valid as currently, most surgeons prefer to use the LITA for this coronary graft.

In the variety of studies that have investigated the clinical impact of LSV failure, most have found an increased need for reintervention as compared with patients who underwent CABG but did not have LSV failure, on the long-term survival. however, studies have shown opposing results with some showing a decrease on survival with graft failure and others no difference.

Research in this area is still required as the saphenous vein remains an essential conduit for CABG and by further our understanding of the mechanism of its failure, we may discover even more therapeutic approaches to both the treatment and the prevention of this condition.

ACKNOWLEDGMENTS

This study was supported by the NIHR Biomedical Research Center at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

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How to cite this article: Guida G, Ward AO, Bruno VD, et al. Saphenous vein graft disease, pathophysiology, prevention, and treatment. A review of the literature. *J Card Surg.* 2020;35:1314–1321. https://doi.org/10.1111/jocs.14542