Chapter 2
Pathogenesis and Prevention of Early Saphenous Vein Graft Occlusion following Coronary Artery Bypass Grafting

Philemon Gukop, Georgios T Karapanagiotidis, Kavitha Mattam, Amber Jiskani, Rajdeep Bilkhu, Alessandro Montecalvo, Damian Balmforth, Aziz Momin

Department of Cardio-thoracic Surgery, St George’s Hospital NHS Trust, London, UK

*Corresponding Author: Philemon Gukop, Department of Cardiac-thoracic surgery, St George’s Hospital NHS Trust, London, SW17 0QT, UK, Tel: +44(0) 2087253551; Fax: +44-(0)2087252170; E-mail: gukop@doctors.org.uk

First Published October 23, 2015
Copyright: © 2015 Philemon Gukop et al.

This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source.

Introduction

Saphenous vein graft (SVG) is a common technique of coronary artery bypass surgery. SVG occlusion is a significant source of morbidity and mortality in the post-operative period [1,2]. The pathogenesis of SVG occlusion is not completely understood and many factors have been implicated; these include thrombus formation, SVG spasm, [3], neointimal formation, Vascular smooth muscle hyperplasia, yellow plaque and small calibre of the grafted vessel [4]. Various studies have identified grafted vessel calibre, the grafted artery, type of graft (sequential or not) and the use of post-operative anti-platelet as independent predictors of graft failure [5]. Graft failure has been classified into early and late. The incidence of early graft failure is 5-10% while late failure rate at 10 years is up to 50% [6]. Late graft failure has been extensively discussed in the literatures, our focus is to illuminate on early SVG failure. We critically appraise the etiopathogenesis of early SVG occlusion and then propound an all-encompassing hypothetical explanation and suggested preventive measures in the light of this hypothesis.

Definition

Early SVG failure is the inability of SVG to provide adequate perfusion of target myocardium within the first 28 days of surgery due to luminal compromise, caused by thromboembolism or kinking of the graft. This can be sub-classified into acute within 48 hours and sub-acute
beyond 48 hours.

In acute SVG failure the patient remains unstable without immediate intervention by reoperation, PCI or IABP \([7,8]\). Late or chronic SVG failure is when this event occurs beyond 28 days.

The treatment of SVG failure is revascularisation. Its prevention can be classified into surgical, pharmacologic, lifestyle changes and possible gene therapy.

**Pathogenesis**

SVG failure is a continuum process arbitrary divided into early and late. The two most important cells involved in the initiation of the process are platelets and vascular endothelial cells. The normal endothelium functions as an active antithrombotic interface that facilitates laminar flow of plasma and cellular components in the vasculature. SVG failure requires an initiating stimulus to occur and a maintenance substrate to be sustained. The single and most important initiating stimulus is injury to the vascular endothelium \([9]\) either by direct trauma or due to high hydrodynamic shear stress; cytokines are released by the damaged endothelium and the underlying connective tissue is exposed for interaction with circulating platelets. Damaged endothelial cells release pro-inflammatory cytokines like endothelin 1, endothelium derived growth factors, interleukin8, monocyte chemo-tactic protein 1 \([10, 11]\). The release of this pro inflammatory cytokines is mediated via P38 mitogen activated protein (MAP) kinase and this can be obtund by brief treatment with dexamethasone which induces MAK kinase phosphatase 1 to suppress the pro inflammatory process \([11]\). Endothelial nitrous oxide and prostacyclin are lost as a result of injury \([12]\). These agents have antithrombotic properties. Consequently the endothelium is converted to a thrombogenic and an antifibrinolytic interface. Platelets adhere to the underlying collagen occurs via adhesion molecules \(\alpha_2\beta_1, \text{Gp1a2a, Gp5, Gp1bixv and VWF}\) this leads to platelet activation and degranulation with release of cytokines like thromboxane A2, ADP, and serotonin leading to platelet aggregation and plug formation, with activation of the coagulation and fibrinolytic cascade. In a normal laminar flow pattern this process culminates in a minimal fibrin plug formation and repair of the endothelial damage implying the absence of a maintenance substrate and consequent termination of the process. In the presence of a maintenance substrate which implies turbulent or non-laminar flow, the process persists and progresses to SVG failure. SVG with a narrow ‘anastomotic window’ will generate non laminar flow and high shear stress in the segment of the vein graft, this destabilises the endothelium further and constitutes the maintenance substrate for SVG failure. This explains why graft failure occurs less in good calibre anastomosis with good flow. The rate of progression of SVG failure is proportional to the magnitude of the initiating stimulus and maintenance substrate. This explains why non-touch technique or minimal damage to the endothelium during vein harvesting reduces the
rate of graft failure [13,14]. A good calibre anastomosis on a graft that is not kinked implies a small magnitude maintenance substrate and low graft failure rate. Although the vein endothelium cell is not adapted to high shear stress unlike arterial endothelium [11] a narrow ‘anastomotic window’ constitute a significant escalation of shear stress on the endothelium and can be quantified by the Hagen-poiseuille equation \( Q = \pi a^4 P / 8nL \). Decrease in Lumina calibre by ½ at the ‘anastomotic window’ will cause 16 times increase in resistance and slows flow rate 16 times. This causes stasis and increase shear stress in the segment of SVG. The high shear stress disturbs the endothelium with consequent release of cytokines and exposure of underplaying collagen. As a result of the stasis lamina flow is lost. In lamina flow the cellular component of blood are axial or central in location while the plasma is peripheral and in contact with endothelium. But with turbulent flow cellular form have access to the disturbed endothelium. Endothelial cytokines attract inflammatory cells and stimulate acute inflammation. Platelet adhesion, degranulation, aggregation and plug formation occurs. The coagulation, fibrinolytic and complement pathways are activated. This process is amplified by a positive feedback mechanism and maintained by a substrate.

**Hypothesis**

Tunica intima disruption as a result of turbulent blood flow is the major culprit of earlysaphenous vein graft occlusion.

**Explanation**

The tunica intima is the endothelial lining of the blood vessel and disruption of this layer is critical to SVG thromboticocclusion, as this triggers both an intravascular thrombogenesis and an acute inflammatory response [15].

The disruption of the intimal leads to exposure of subjacent connective tissue with consequent platelet adhesion, platelet aggregation, degranulation and plug formation, ultimately this leads to a thrombus formation if there is stasis [10]. The thrombus could be preserved and propagated if a non-lamina flow and or stasis persists.

The degranulation process coupled with endothelial damage leads to the release of cytokines and an acute inflammatory response, some of these cytokines include platelet derived growth factor PDGF, endothelium derived growth factor EDGF, histamine, endothelia \([4]\) and thromboxane \([16]\) etc. These cytokines mediate neointimal formation, vascular smooth muscle hyperplasia, SVG spasm and thrombosis.

If turbulent flow persisted then the thrombus is preserved and propagated. It then forms a nidus for further artherosclerosis and organisation with consequently long term graft occlusion [17].

We suggest that non lamina flow is the major culprit
for intraluminal intimal disruption as the consequent turbulent flow and high shear stress generated is disruptive to the delicate intima and as this persists the thrombotic process is initiated and preserved.

Non laminar flow could be generated by a graft to a small calibre vessel ≤ 2.0 mm or flow through a kinked graft, the pressure of flow from a wider lumen vein through the small calibre vessel (anastomotic window) generates a high resistance with turbulent flow and stasis in the proximal vein graft. As a consequence of this the above process is orchestrated [18]. This explains why SVG occlusion is not common in graft to large calibre vessels like the LAD where flow through the anastomotic window is laminar and non-turbulent due to good luminal calibre, [19]. Although some intimal damage does occur during the process of saphenous vein harvesting and handling [20]. This in itself is not sufficient to cause graft failure unless in the presence of turbulent flow through a narrow anastomotic window which preserves and perpetuates it. Studies have shown that wherever early thrombotic SVG occlusion occurred distal narrowing at the anastomotic site or beyond was present [17].

**Prevention**

Saphenous vein graft Harvest: The process of preventing SVG occlusion starts at the stage of conduit harvesting [13]. It is important to handle the vein gently to avoid damage to the vessel wall especially the intima [12], there should be no handling of the vein with crushing instruments like forceps and artery clamps, it should be handled with the hand gentle instruments like Duvall or non-touch technique [6,21]. The side branches should be tied flush to the main vessel lumen to avoid narrowing of the lumen or out-pocketing when the tie is further off along the side branch, these could lead to stasis and turbulent flow which are culprit for thrombotic occlusion. During testing of the vein it is recommended to avoid high distending pressure and repeated testing as this could be injurious to the intima and predispose to thrombotic occlusion by stimulating cytokine release [16,22,23].

Intra-operatively as much as possible significant discrepancy in lumina calibre between the SVG and the vessel to be grafted should be avoided as this is a recipe for turbulent flow, stasis and intima disruption which leads to graft failure [24].

Where an anastomosis between vessels with significant calibre discrepancy was necessary then an aggressive preventive measures addressing all the culprit factors of SVG occlusion should be instituted as follows:

There are class 1a evidence suggesting that starting early low dose aspirin within 6hrs of CABG significantly reduces the incidence of early thrombotic SVG failure [1].

Studies have shown that a vein graft in a hypercholesterolemia milieu exhibit enhanced and sustained tissue factor synthesis. These tissue factors could stimulate hyperplasia and thrombosis leading to early
SVG failure. Early administration of statin may be preventative of early SVG failure by enhancing endothelial function, reducing inflammation, oxidative stress and inhibiting smooth muscle proliferation and migration [25,26].

A new class of nitric oxide donating aspirin (NO-ASA) drugs have been shown to reduce the incidence of early SVG failure not only by preventing thrombosis but also by preventing SVG spasm and proliferation of vascular smooth muscle, a property attributed to nitric oxide [27].

Good hydration with crystalloids reduces the viscosity of blood and reduces hypercoagulable states. The increases fluidity of blood and enhances lamina and could reduce the incidence of early thrombotic SVG failure.

Endothelin-1 is a potent constrictor proinflammatory peptide released by traumatised SVG. It has also been shown to stimulate SVG smooth muscle proliferation and neointimal thickening. These actions are mediated via endothelin (A and B) receptors. Experimentally endothelin receptor antagonist has been shown to inhibit this process and could have a potential role for the prevention of SVG failure [4,28].

Angiotensin-2 has recently been implicated in the pathogenesis of intimal hyperplasia. Modulation of the renin-angiotensin pathway by angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers may have a role in preventing graft failure. The medications are powerful inhibitors of arteriosclerosis and cardiovascular remodelling, class 1 evidence suggest that they slow progression of cardiovascular disease and improve survival [29].

Gene therapy promising to be a viable strategy for prevention of vein graft failure. Vein graft can be genetically modified ex vivo prior to grafting during CABG. Matrix-degrading metalloproteinase is known to stimulate intimal thickening and smooth muscle proliferation in vein graft to provoke occlusion [30,31]. Adenoviral-delivered overexpression of an endogenous inhibitor of metalloproteinase 3 (TIMP3) has been shown to significantly suppress both intimal thickening and smooth muscle proliferation thereby enhancing vein graft patency. Transfection of endothelial nitric oxide synthase gene in human saphenous vein graft enhances vein graft patency by preserving the production of nitric oxide [32-34].

Multiple factors contribute to the pathogenesis of early thrombotic saphenous vein graft occlusion. It is obvious that some mechanical and cytokine factors play a significant role.

The crucial mechanical factor is the calibre of the ‘anastomotic window’. A relatively narrow ‘anastomotic window’ would cause a high resistance to flow with consequent turbulent flow and stasis. This generates high shear stress that predisposes to intimal disruption. Endothelial disruption exposes the subjacent collagen with
resultant platelet adhesion and the release of numerous cytokines which are prothrombotic, vasospastic and lead to neointimal proliferation. These are the milieu in which early SVG failure occurs. When this persists it progresses to late graft failure in the long term due to super added arteriosclerosis and fibrosis.

**Conclusion**

Saphenous vein graft disease and consequent graft failure is a significant source of morbidity and mortality. Several measures have been advocated for the prevention of vein graft failure. Surgical technique involving minimal trauma to the conduit and large calibre anastomosis could alleviate the burden of the problem alongside prompt use of antiplatelet agents in the postoperative period to optimise vein graft patency. More research is need in the area of prevention and treatment of vein graft failure.

**References**


