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Saphenous Vein Conduit in Coronary Artery Bypass Surgery — Patency Rates and Proposed Mechanisms for Failure

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1. Introduction

Coronary artery disease is the single leading cause of death in the United States. Every year more than 1 million open coronary revascularization procedures are performed in the United States. Most commonly the greater saphenous veins and internal mammary and/or radial arteries are used as bypass conduits. Long term patency and avoiding repeat revascularization is every surgeon's goal following coronary artery bypass grafting. Unfortunately it is estimated that during the first year after surgery; between 10 - 15% of venous grafts occlude. The graft attrition rate is estimated to be 1 - 2 % per year during the first five years following surgery. By 10 years only 50 % of vein grafts remain free from significant stenosis [1].

The reasons for premature graft closure include; biologic, conduit quality, unsatisfactory harvest/preparation, and inappropriate operative strategy or poor surgical technique [2]. Many of these factors can be avoided with proper technique and experience of the surgical team. Currently much of the research being performed on graft failure is leading to the hypothesis of early thrombosis and neointimal hyperplasia as the physiologic basis for graft failure, although the exact mechanism is not well established.

This chapter will discuss current knowledge and ongoing research regarding the thrombosis, intimal hyperplasia and atherosclerosis of vein grafts. It will highlight harvesting techniques and preservation methods, as well as discuss proposed mechanisms that lead to intimal

hyperplasia, graft atherosclerosis, and the evolving strategies and current research for long-term prevention of graft failure.

2. How vein harvesting methods can affect patency rates

Dr. Rene Favaloro developed the first saphenous vein harvesting technique in 1967 [2]. This technique required a longitudinal incision along the length of the greater saphenous vein entering the fascial canal surrounding the vein and thus causing inadvertent damage to the adventitial layer. Following vein isolation from the surrounding tissues, ligation of side branches, as well as a transection of the vein for completion of the harvest is performed. Since that original description, many methods have evolved from Dr. Favaloro's original technique. As well, research has focused on the best method of harvesting grafts without damage. In addition to Favaloro's original technique, current and popular harvesting techniques included; "no touch", stab phlebectomy, and most recently endoscopic techniques. It is inherent that manipulation of the vein conduit causes damage to the vein itself, but the extent was unknown. Multiple studies have been done to compare; "open", "no touch", and "endoscopic vessel harvesting (EVH)" techniques [3]. The traditional open technique which is performed under direct visualization of the vein was found to preserve the endothelium of the vein quite well, but also came with the complications of leg pain i.e. wound healing, post operative cellulitis, and increased length of hospital stay [4], [5]. Initial studies performed on the long-term outcome of vein grafts harvested using the open technique did show that the vein was often stripped of the beneficial adventitial layer as well as distended to high pressures to overcome the associated vasospasm [6]. Unfortunately, the increased distention pressures caused shear stress damage to the vein intima and subsequent endothelial wall [7]. When viewed histologically the endothelial cells appeared deformed, flattened, polymorphic, and contained an abundance of cytoplasmic vesicles [8]. As a method to avoid over-handling of the vein and increased distention pressures a pedicle technique was developed and named the "no touch" technique. It was thought that veins procured in this manner would eliminate the need for conduit distention and its associated morbidities since the perivascular adipose tissue surrounding the vein was left intact [9]. It had been shown that this surrounding tissue in internal thoracic mammary arteries provided a vasodilatory effect with less arterial conduit vasospasm. Increased patency rates were demonstrated with the "no touch" technique compared to the conventional open technique [9]. 1997 began a new era in coronary artery bypass grafting with the use of EVH to harvest the saphenous vein. Endoscopic harvesting techniques were found to eliminate the need for invasive incisions, and decrease the associated risks that accrued with an open technique. Furthermore veins harvested via an EVH method were hypothesized to be promising for graft patency, since endothelial integrity was maintained following EVH harvest compared to other conventional harvesting techniques. This new technique soon became the standard of care with greater than 70% of saphenous vein conduits being retrieved in this manner [10]. Endoscopic harvesting had lower complication rates including less post-operative pain, and decreased patient length of stay. However, controversy arose about the long-term patency of the vein conduits after coronary artery

bypass grafting; depending upon what vein harvest method was used in surgery. It was felt veins harvested using an EVH technique failed more often and earlier than veins harvested in the traditional open technique. Studies performed by Desai et al in 2011, confirmed the relationship between the learning curve of EVH and the patency rates based on beginner and expert level of experience in harvesting vein tissue [11]. It has since been shown that when a novice is performing the procedure the vein is subjected to much more stress from trying to better visualize the vein, and 50% of the veins had discrete areas of injury [11]. It was noted that if a section of vein had more than 4 areas of injury, it had a greater than 50% risk of failure of patency [11]. Early studies, which compared the traditional open harvest method to EVH, were published in the infancy stages of EVH when all harvesters were novices to this new technique. Thus, it is now recognized that this confounding issue may have contributed to the decreased long-term patency that was noted. However, this has changed in the past years with “novice” level practitioners becoming experts. It has recently been found that when procured by expert level harvesters the physical damage to the vein is similar to that of open harvest [12], [13]. Thus, it is hypothesized that EVH and open harvest when performed by an expert will have similar patency rates if all other factors are equal.

3. The role of pressure distention and wall stress during harvest

Standard procedure in the United States is to distend the saphenous vein graft after procurement prior to myocardial implantation to ensure that all branches are ligated. The majority of the time during harvest, the vein is distended to supra-physiologic pressures [14]. While saphenous veins *in vivo* are rarely subjected to pressures greater than 60 mmHg, recorded pressure measurements during harvest easily reach 300-400 mmHg [15]. This supra-physiologic pressure severely damages the endothelium and ultimately leads to premature graft closure. This high pressure is inadvertently used to overcome vasospasm as well as to ensure ligation of all side branches [16]. The pressure causes shear wall stress that denudes the protective endothelial layer (Figure 1). As a mechanism to protect itself, the endothelium releases basic fibroblast growth factors and platelet-derived growth factors [17]. Basic fibroblast growth factor, a heparin-binding polypeptide that is present in the nucleus and cytoplasm of smooth muscle and endothelial cells and in the intracellular matrix, is normally a non-secreted cell product [18]. Platelet derived growth factor is also widely acknowledged in the process of angiogenesis and most specifically in cell migration and proliferation. The release of these 2 mitogens together initiates intimal hyperplasia [17].

4. The graft “environment” at a cellular level

The vascular endothelium has many protective functions, and it releases factors that maintain vein graft patency. The endothelium serves as the physical barrier between the blood components and the sub-endothelium, damage to this endothelium by either direct or indirect stress can disrupt this protective environment causing the formation of atheromas and subsequently

graft failure. Injury to the endothelium in addition to surgical manipulation also increases the risk for vasospasm, stenosis, and intimal hyperplasia. Studies have shown that many factors can affect the viability of endothelium; these include temperature, distention, and the composition of solution used in vein preparation. Nitric oxide controls vascular tone in addition to causing vasodilatation. Vascular endothelium contains L-arginine which when combined with nitric oxide synthase forms nitric oxide¹. The main target of nitric oxide is to stimulate guanylate cyclase and subsequently form guanosine 3 prime 5 prime-cyclic monophosphate (cGMP). The cGMP leads to vasodilatation and inhibition of platelet aggregation [19]. Furthermore, nitric oxide also has been shown to interfere with cell migration, specifically white cells by reducing the adhesion of neutrophils to the endothelial surface. Several cytoprotective properties are conferred through nitric oxide including; scavenging of oxygen free radicals and blocking release of prostaglandin E2 and F2 alpha. These are anti-inflammatory effects, and are quite intricate in detail, but are based on regulation of transcription factors [20], [21]. Nitric oxide also has some cytotoxic effects including decreasing protein synthesis, increasing lipid peroxidation, and decreasing acute phase proteins [22]. Injury to the endothelium directly causes a decrease in nitric oxide release by the endothelial cells and destroys the integrity of the vein. Studies performed by Kown et al. showed that vein grafts treated with L-arginine (nitric oxide is a by-product created when L-arginine is converted to citrulline) can increase levels of nitric oxide and subsequently decrease hyperplasia [23].

5. Reperfusion injury

Approximately 12% of patients experience thrombosis of saphenous vein grafts within 30 days of surgery [24]. It has been shown that this acute thrombosis is likely a combination of multiple factors including ischemia and hemostasis during coronary procedures which favors thrombogenesis [25]. The ischemic period in which the vein has been harvested but not yet re-implanted into the myocardium, marks the beginning of the cascade to possible thrombosis. Upon re-establishment of blood flow through the vein it has been shown that neutrophils in the oxygenated blood are attracted to the areas of endothelial injury [26]. This ischemia-reperfusion results in a reduction in both basal and stimulated nitric oxide release, yet attenuates the vaso-relaxation responses to the agonist stimulators of endothelial nitric oxide acetylcholine and bradykinin. Together this impairs the release of nitric oxide and down regulates nitric oxide production after an ischemic event.

After the saphenous vein is harvested, the initial injury causes a decrease in nitric oxide due to the traumatic endothelial cell injury from manipulation and distention. Following the ischemic period and after implantation, nitric oxide synthesis will increase due to the reperfusion. Re-implantation causes release of multiple growth factors, and cytokines that cause the migration and proliferation of vascular smooth muscle cells and formation of extracellular matrix into the intimal compartment of the vein graft. Once neutrophils are adherent they initiate further endothelial damage and activation of the coagulation cascade which can lead to thrombosis [1]. The release of nitric oxide at this time can limit neointimal hyperplasia by inhibiting this proliferation and promoting apoptosis [27].

6. The role of neointimal hyperplasia in graft patency

Neointimal hyperplasia is the accumulation of smooth muscle cells and extracellular matrix that occurs in the intimal layer of vein. This thickening leads to a narrowing of the lumen and subsequent stenosis of the vein graft. Neointimal hyperplasia is the most widely accepted reason for graft failure at the present time. Many theories exist as to why this occurs but none have been completely proven. Work is currently being performed evaluating the up regulation of genes or proteins that may cause the phenomenon of intimal hyperplasia [15]. Nearly all vein grafts placed into an arterial system develop some areas of hyperplasia within the first four weeks. This acute hyperplasia can narrow the lumen of the vein conduit by as much as 25%.

Many studies have related extensive endothelial injury to neointimal hyperplasia development. Injury can be in the form of extreme venous distention, denudation of the endothelium itself, and degree of vasospasm overcome during harvest [28]. Intimal growth is stimulated by several factors including platelet derived growth factor, transforming growth factor beta, and epidermal growth factor which cause proliferation and subsequent invasion of the smooth muscle cells into the intimal layer [1]. When veins are injured, basic fibroblast growth factor is released from the endothelial cells and smooth muscle cells. This is a very potent mitogen that causes the increased production of multiple regulatory proteins, kinases, and genes that participate in DNA synthesis [29]. The sequential activation and inactivation of the cyclin dependent regulatory kinases (Cdk) leads the smooth muscle cells through the cell cycle [30]. Each cyclin exhibits a cell cycle phase specific pattern of expression with several cell cycle checkpoints at the G1/S station. At these points the kinases interact with a cyclin, specifically D and E interacting with Cdk 4/6, and 2. To progress the cell into the M phase cyclin B is activated. These Cdk proteins are inhibited by activating Cdk 1. The G1 Cdk is part of the retinoblastoma pocket proteins that when phosphorylated can sequester cell cycle regulatory transcription factors. This phosphorylation by retinoblastoma proteins as well as specific cyclin dependent kinases during late G1 leads to activation and release of genes that participate in DNA synthesis. It is this complex cascade of cellular activities that leads to proliferation of smooth muscle cells causing neointimal hyperplasia, [30]. Further research has shown that other theories also exist as to the mechanism of neointimal hyperplasia that includes a role for perivascular fibroblasts and matrix metalloproteinases (MMP's). It is thought that fibroblasts invade through the media of the saphenous vein graft and differentiate into myofibroblasts. MMP's are the mediators of matrix deposition and degradation, which can cause neointimal hyperplasia. Theories exist that a strategy to avoid hyperplasia would be to use MMP inhibitors. MMPs compose a super family of 66 known zinc peptidases that degrade collagen, gelatin, and elastin³¹. MMPs are critical for cell growth and proliferation, cell migration, organ development, reproduction, and tissue remodeling. In all of these biological phenomena, matrix degradation is needed to facilitate changes in cell phenotype. For example, ligand-dependent cell-matrix associations are critical for modulating cell function, and matrix degradation. These interactions can thereby modulate responses of the cell to its microenvironment within the saphenous vein.

Vascular smooth muscle cells, monocytes/macrophages, and endothelial cells have all been shown to express MMPs. Vein graft stenosis appears to be associated with increased expression of MMP-9 and increased activation of MMP-2 [32]. Pharmacological inhibitor studies demonstrate that MMPs are, indeed, involved in the formation of the neointima. Therefore, with this data it appears that MMPs are critical for smooth muscle cell migration and proliferation, which serve as the cellular basis for neointimal proliferation *in vivo*. Tissue inhibitors of metalloproteinases (TIMPs) are four naturally occurring proteins that inactivate MMP's by binding to them. Kranzhofer et al showed that three of these TIMPs are found on saphenous vein grafts [33]. Several regulatory mechanisms exist to keep a precise balance between enzymes that degrade matrix and proteins that inhibit their action. Cytokines and growth factors, specifically platelet derived growth factor BB act together through a protein kinase C dependent mechanism to increase the expression of MMP-9, whereas transforming growth factor-beta and platelet derived growth factor BB induce TIMP-3 expression in vascular smooth muscle cells [31]. However, they do not have any influence on TIMP-1, or TIMP-2 expression. Baker et al. transfected grafts with a gene for TIMP-3 and observed an 84% reduction in neointima at 14 days and 58% reduction at 28 days in porcine vein grafts [34]. This shows promise for a potential preventative treatment of neointimal hyperplasia, but problems such as weakening of pre-existing atherosclerotic plaques need to be addressed and the longer-term benefits of this therapy remain unknown.

7. Upregulation of innate inflammatory markers and graft failure

Studies have shown that patients who present with unstable angina after revascularization by previous bypass procedures do so because of an obstructive atherosclerotic lesion in the saphenous vein conduit, and graft stenosis. These plaques have been seen as early as 1 year after bypass procedures [35]. When the vein conduit plaque is viewed histologically, it is found to have an increased number of foam cells than in arterial atheromatous plaques. Recent studies support the theory that a stimulus must exist that induces the expression of inflammatory mediators and may be the inciting factor leading to intimal hyperplasia and eventual graft failure [15].

Scavenger receptor proteins play a vital early role in vascular inflammation. Scavenger receptor proteins on the surface of vascular endothelial cells and macrophage have been shown to upregulate NF-kappaB inflammatory pathways. Studies focusing on upregulation of inflammatory markers following distention compared to non distended vein segments have shown that expression of scavenger receptor-A, scavenger receptor- B, and CD36 are upregulated in the distended saphenous vein tissue [15]. This suggests that the process of distention is an inciting event that allows for the upregulation of scavenger receptors, leading to graft failure through atherosclerotic lesion progression initiated by the formation of foam cells in these saphenous vein grafts.

Pressure distention of saphenous vein conduits has been part of the standard vein preparation procedure for decades. The longer the vein is exposed to pressure distention the higher the

expression of biomarkers. These biomarkers include; toll like receptors (TLRs), intracellular adhesion molecules (ICAM), vascular cell adhesion molecule-1 (VCAM-1), and platelet endothelial cell adhesion molecule-1 (PECAM-1). An upregulation of ICAM, VCAM-1, and PECAM-1 was seen in veins that had undergone distention when compared with the nondistended vein [15]. The expression of these cell adhesion molecules is important because an interaction of VCAM-1 and ICAM-1 with monocytes facilitates the monocytes' recruitment to the vein [36]. Additionally, interactions of ICAM-1 and VCAM-1 with PECAM-1 mediate the process of diapedesis of the monocytes into the vessel wall. These initial cell-mediated events facilitate recruitment of more inflammatory cytokines to the area of injury caused by the damage from distention. PECAM-1 is constitutively expressed on all endothelium regardless of cytokine activation.

Toll-like receptors play a very important role in the signaling pathway of inflammation. Traditionally, TLR4 costimulates with CD14 in chronic conditions. Interestingly TLR4 has also been shown to bind directly to lipopolysaccharide without CD14 costimulation, leading to subsequent NF-kappa B activation. Studies in TLR4-deficient mice have shown that despite the presence of lipopolysaccharide, these mice do not develop neointima, suggesting that neointimal hyperplasia is a TLR4-dependent process [15], [37]. TLR4 in cooperation with interleukin-1 receptor plays a significant role in the formation of neointima. TLR4 signaling also promotes a proinflammatory phenotype and plays a role in the early response to vascular injury. Therefore, the upregulation of TLR4 may play a role in the development of graft failure in terms of neointimal hyperplasia. TLR2 activation with MYD88 leads to cytokine production through NF-kappa B pathways. Thus, these data suggest that vein graft failure is likely a multifactorial process that includes neointimal hyperplasia and inflammation. Immediate vein graft failure is most probably due to inflammatory cytokines whereas late failure (1 year after CABG) is due to neointimal hyperplasia. However, the common cause of both of these processes is quite possibly exacerbated by SV pressure distention [15].

8. The future of prevention: from the research bench to the operating room

Much interest in reducing neointimal hyperplasia by blocking gene expression is arising. The cell cycle of endothelial cells is now better understood and therefore has allowed for genetics to help play a role in preventing stenosis, thrombosis, and ischemia. If the genetic pathways that are associated with the above process can be fully identified this may ultimately influence coronary graft patency. Ex-vivo work has been promising to show that blocking of the cell cycle via gene therapy has slowed down the atherosclerosis that can lead to graft failure [1].

Repeat coronary vascular procedures will continue to be problematic until an understanding of the mechanisms of vein graft have been elucidated. Thus far, extensive research has been done on this topic, but an overall consensus exists that the saphenous vein is a very fragile and easily injured conduit. Great care must be taken while handling the vein during harvest and preparation to avoid damage or stress to either the external or internal surface of the vein. Avoiding supra-physiologic pressure, prolonged distention periods and manipulations which

result in tissue inflammation and injury should be employed to prevent graft failure. Such efforts are expected to reduce the morbidity associated with saphenous vein graft disease and repeat coronary artery bypass interventions.

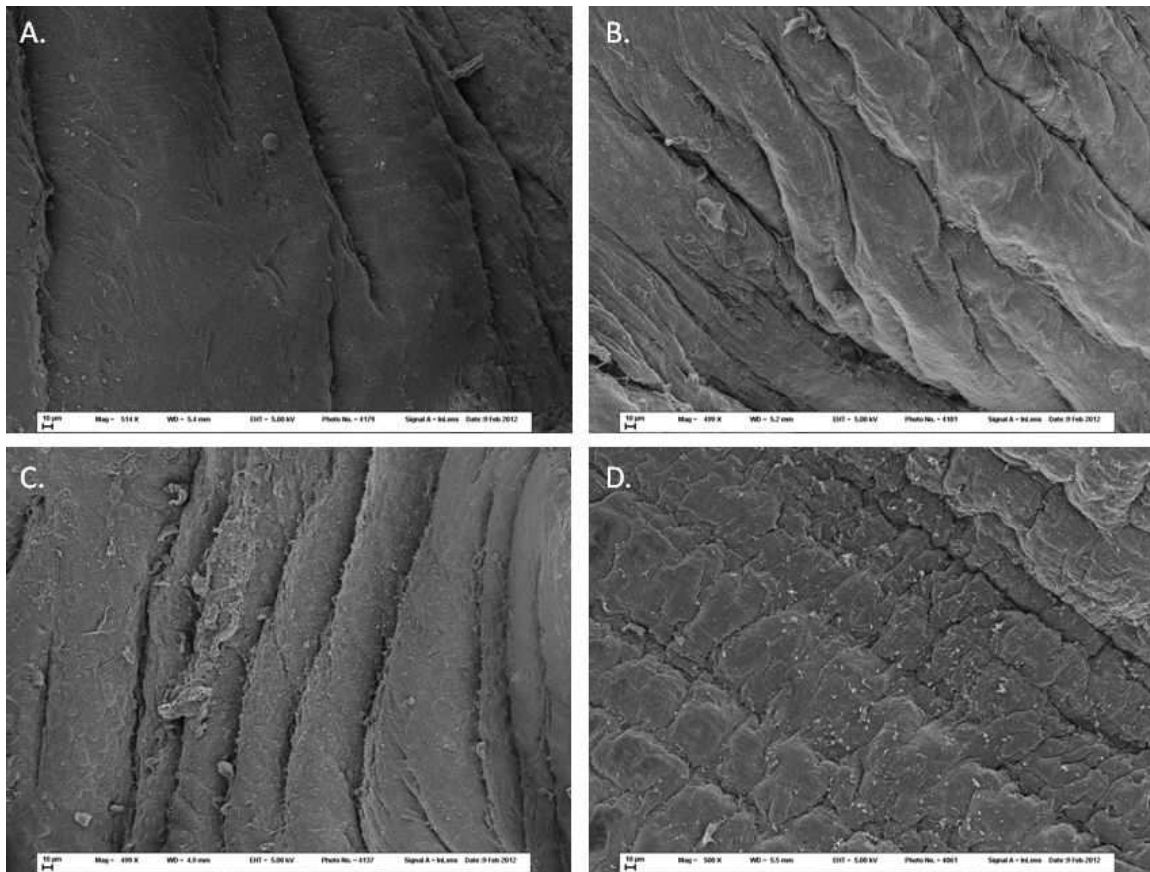


Figure 1. Scanning electron microscopy photomicrographs of vein tissue following harvest and distention. Saphenous veins underwent endoscopic harvest during bypass grafting procedures with routine pressure distention to ligate side branches. Vein distention was performed by attaching a syringe to the most anatomically distal portion of the vein. A segment of vein was obtained prior to distention and several segments along the length of the vein were harvested after distention and subjected to scanning electron microscopy. Pictures shown in the figure are (A) non-distended vein (B) most distal portion of vein from origin of distention (C) mid section of saphenous vein graft (D) vein segment closest to the syringe. Shown in the pictures are endothelial layer starting to change from a smooth flat surface to a rounded up rough surface.

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