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Vein Graft Disease and Vein Graft Failure
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Background

Vein Grafting

Vein grafting is a surgical technique in which a vein(s) is removed and grafted to another blood vessel to bypass a blockage, repair a blood vessel or connect blood vessels of a tissue or digit graft to recipient blood vessels. Vein grafting can be performed utilizing either free vein grafts or integral veins located within tissue grafts.

Free vein grafts are isolated veins harvested from one part of the body and grafted elsewhere in the body. Saphenous vein grafts for example, are harvested as free veins from the leg for use as coronary artery and peripheral bypass grafts in CABG and peripheral bypass surgeries, respectively. Free vein grafts are also used frequently during reconstructive surgery in situations where recipient vessels are damaged or are otherwise inadequate and require bridging vein grafts to connect graft and recipient blood vessels or to restore vessel length in situations where recipient vessels have been surgically debrided. Integral vein grafts refer to those blood vessels located within a flap or digit graft that are micro-surgically connected to recipient blood vessels. Regardless of the type of vascular graft; free vein, free artery and integral vein grafts are all subject to post-grafting Vein Graft Disease (VGD) and the mechanism of disease initiation and progression is similar across all graft types. This is not surprising given the similar anatomy and physiology between types of vein grafts and given that vascular grafts experience similar stresses, including the physical trauma of harvesting and handling, post-harvest ischemia, oxidative stress, reperfusion injury and adaptive stress in the new post grafting environment.

Unfortunately, the durability and patency of these grafts are significantly compromised by Vein Graft Disease (VGD) in a process that begins during the grafting surgery itself. VGD is the principal cause of both early (within 30 days) and intermediate/late Vein Graft Failure (VGF). VGD encompasses the pathophysiological changes that occur in vein grafts following their use in surgical grafting. These changes, apparent within minutes to hours of grafting, are manifested as endothelial dysfunction and include pro-inflammatory, pro-thrombogenic and proliferative changes within the graft. As VGD progresses, vein grafts lose their ability to adapt to the post-grafting environment leading to thrombus formation, intimal hyperplasia and atherosclerosis resulting in graft stenosis, occlusion and loss of graft patency.

There has been relatively little change over the past several decades in the occurrence of VGD and VGF and the rates of both VGD and VGF remain unacceptably high[1] despite the introduction of medications such as aspirin and statins to treat or mitigate the disease. Approximately 45-50% of patients undergoing CABG and peripheral bypass surgery respectively will have a graft failure within 12 months. The percentage of patients with underlying VGD that will manifest as VGF after one year is even higher.

VGD that progresses to VGF may result in death, myocardial infarction, the need for repeat revascularization and/or lower limb amputation. The success rate of revascularization or re-intervention of a failed graft is very poor[2] and therefore addressing early vein graft disease in the primary graft is crucial.[1]

As such, VGD represents a staggering disease burden to the patient and a tremendous cost burden to health care systems. It also represents a disease for which there has been no significant improvement in several decades.

Pathophysiology of VGD and VGF

Vein Graft Disease (VGD) is comprised of three temporally distinct but pathophysiological related processes: thrombosis, intimal hyperplasia, and atherosclerosis. Vein Graft Disease that has progressed to significant graft stenosis or occlusion is called Vein Graft Failure (VGF). Thrombosis-mediated graft failure is an early event causing about 10-15% of Saphenous Vein Grafts (SVGs) to occlude within the first month of CABG surgery. Intimal hyperplasia represents the foundation for later graft atheroma development and is the basis of intermediate- to late-stage VGF that occurs months to years after bypass surgery.

The principal mediator of VGD following grafting in bypass surgeries is the initial endothelial damage and denudation that occur during intra-operative vascular graft handling and graft arterialization.[3,1] Endothelium can be destroyed or damaged intraoperatively through the acute physical stress of harvesting, storage, handling and arterialization and through more insidious processes such as those associated with ischemia reperfusion injury and oxidative damage. Endoscopic vein graft harvesting increases the risk of stretching and blunt surgical trauma. This has been shown in some studies to result in higher VGF rates and adverse clinical outcomes as compared to the open technique.[4] Between the time after harvest and before grafting, Saphenous Veins (SV) are often stripped of surrounding tissue and are exposed to either saline or blood-based solutions; actions that decrease conduit quality and graft patency.[5-7] After grafting, the luminal surface of a damaged vein is exposed to the bloodstream, eliciting local biochemical and inflammatory signals that trigger a cascade of events that ultimately promote VGF. Loss or reduction in expression of endothelial-based molecules such as Nitric Oxide (NO) disturbs the graft's ability to mitigate shear stress, further exacerbating damage and inflammation. It is therefore clear that even minor injury to the vascular graft during the surgical procedure can trigger a cascade of downstream events that can be mitigated by optimizing handling and preservation of the graft.

Although some types of arterial grafts may remain patent longer and while the pathophysiology of VGD is complex, it is mechanistically similar for vein and arterial grafts following CABG, peripheral and other bypass and grafting surgeries. An intact, functional endothelial layer is critical for vein graft adaption to the post grafting environment and plays a protective role post-grafting by conferring protection from damage caused by increases in pressure, pulsatile hemodynamics and exposure to blood.[8,9] Moreover, it is important for the graft's survival and for maintaining its functional capacity. Functional endothelium, for example, has been invoked as the mediator in observed shear-dependent early remodeling (within 1 month) making it a critical factor in the graft's ability to respond to increased blood flow.[8] Loss or damage to the endothelium therefore pre-dispose the endothelium to subsequent damage in the post-grafting environment. A functional and intact endothelial layer is not only required for correct vein graft functioning and vasomotor activity but also presents an anti-inflammatory and anti-coagulant surface to flowing blood and blood cells. This is largely due to the role of the endothelium and endothelium-derived molecules such as nitric oxide (NO) and prostacyclin enabling vein grafts to respond quickly and efficiently to changes in blood flow[8] and enabling the maintenance of an anti-inflammatory and anti-thrombogenic state.[10] A damaged or dysfunctional endothelium also promotes production of reactive oxygen species leading to oxidative damage that chemically alters endothelial cell components further, injuring an already damaged endothelial layer. In the absence of an intact, functioning endothelial layer, vein adaptation is lost or mitigated and in the absence of vein graft adaptation, VGD progresses — leading to the end state of VGD and VGF. Therefore, presenting an intact functional endothelial layer at the time of grafting is paramount to protecting the graft and its associated endothelium from damage that can occur post-grafting. It is of utmost importance to protect the endothelium initially during the surgical grafting procedure to mitigate the development of VGD, and to ensure optimal vein graft patency and performance in the short and long-term settings.

Progression of VGD and VGF

Preclinical models show that the process of intimal hyperplasia begins within 24 hours of grafting.[10] Within hours, an inflammatory response is generated. Within 24 hours, smooth muscle cells begin to proliferate and within several days proliferating cells migrate into the intima, where proliferation continues at a peak rate for at least a few weeks. The limited available clinical data support these observations.[11,12] The initiation of intimal hyperplasia, clinically measured by wall thickening, presents within 4-6 weeks in SVGs used in both CABG and peripheral bypass procedures. Following the initial development of intimal hyperplasia, the disease can further progress, stabilize, or regress. Clinical regression and/or stabilization can occur in grafts within the first year of grafting.[11] However, disease progression can also occur when the balance of endothelial repair is disturbed by chronic vascular inflammation and associated endothelial dysfunction. Studies have shown that wall thickness measurements as early as 4-6 weeks may provide an important surrogate marker for grafts at risk of further development of intimal hyperplasia, atheroma and subsequent graft failure.

Endothelial damage/disruption is also the principal underlying mechanism of early VGF manifested as graft thrombosis.[12] Loss or disruption of the endothelium causes a cascade of cellular, biochemical, and immune-modulatory events creating a pro-thrombogenic state within the graft; in part due to loss of endothelial-derived anti-thrombotic molecules such as NO and prostacyclins. The resultant pathophysiology is abrupt, manifesting as early graft failure due to thrombosis, when mural thrombus propagates into an occlusive thrombus in up to 15% of SVGs within the first month of bypass surgery.[13] Many of these failures initially are clinically silent but are detected as incidental findings using radiological methods such as a CT angiogram.

Clinical Complications Associated with VGF

"Early Vein Graft Failure is associated with worse long term outcomes after CABG", and "non-occlusive VGF was the strongest predictor of the composite outcome (following CABG) of death, MI and revascularization".[14]

The correlation between graft failure and adverse outcomes is known to exist; "bypass graft failure (CABG) has been shown in a number of studies to be independently correlated with a variety of adverse clinical outcomes including death, myocardial infarction, revascularization, and worsening of symptoms such as angina".[15] Vein Graft Failure following Peripheral Vascular Surgery directly results in the need for revascularization, and lower limb amputation. Venous failure represents the most common complication in free flap surgery[16] and venous thrombosis mediated early failure is frequent[17] and requires re-exploration and revision surgery for flap salvage.

VGD and VGF Represent an Unmet Clinical Need

"The early promise of Coronary Bypass Grafting has not been fulfilled and an insidiously deadly variety of atherosclerosis progressively chokes most vein grafts and in the end extinguishes their benefit".[18]

There are currently no approved vein graft treatments that reduce the incidence of VGF or the clinical complications associated with VGF. Given the sobering clinical and health care costs statistics on VGD and VGF following CABG and Peripheral bypass surgeries and the fact that there have been no significant improvements in VGD over the past several decades, this disease represents a significant unmet need that may be quite simply addressed by an appropriate treatment for the prevention of VGF and associated clinical complications.

VGD is Preventable:

DuraGraft®, a one-time intra-operative vein graft treatment designed to prevent VFD and VGF has been shown to reduce with statistical significance the incidence of clinical complications following coronary bypass surgery by addressing vascular endothelial damage that occurs intra and peri-operatively. DuraGraft is ionically balanced and buffered containing potent antioxidants that prevent damage to vascular grafts and support the production of nitric oxide thus protecting the associated endothelium during *ex vivo* intraoperative procedures. The treatment is formulated into a ready-to-use solution for intraoperative use, and is consistent with current surgical practice. Therefore, the treatment obviates the need for solutions such as saline, blood or other solutions used during this interval. DuraGraft treatment has been shown to better maintain the structural and functional integrity of both human vein and arterial segments as compared to standard practice in which no vein treatment is utilized.[7] This is likely due to its additional ability to protect the vein graft from oxidative and metabolic stress and in preventing damage that occurs in the lack of ionic homeostasis.[19]

Clinical evidence from two unpublished retrospective studies encompassing almost 3,000 CABG patients in the E.U. and the U.S. also supports the safety and performance of DuraGraft.[20] In the larger U.S. study, use of DuraGraft was associated with significant reductions in the rates of MI (*pValue* <.0001), repeat revascularization (*pValue* <0.031) and MACE (*pValue* <0.042).

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