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Vein graft adaptation and fistula maturation in the arterial environment

Daniel Y Lu^{1,2,*}, Elizabeth Y Chen^{1,2,*}, Daniel J Wong^{1,2}, Kota Yamamoto, MD PhD^{1,2,3}, Clinton D Protack, MD^{1,2}, Willis T Williams, MD^{1,2}, Roland Assi, MD^{1,2}, Michael R Hall, MD^{1,2}, Nirvana Sadaghianloo, MD^{1,2,3}, and Alan Dardik, MD PhD^{1,2,4}

¹Yale University Vascular Biology and Therapeutics Program, New Haven, CT

²Department of Surgery, Yale University School of Medicine, New Haven, CT

³University Hospital of Nice, Department of Vascular Surgery, Nice, France

⁴VA Connecticut Healthcare System, West Haven, CT

Abstract

Veins are exposed to the arterial environment during two common surgical procedures, creation of vein grafts and arteriovenous fistulae (AVF). In both cases veins adapt to the arterial environment that is characterized by different hemodynamic conditions and increased oxygen tension compared to the venous environment. Successful venous adaptation to the arterial environment is critical for long term success of the vein graft or AVF, and in both cases is generally characterized by venous dilation and wall thickening. However, AVF are exposed to a high flow, high shear stress, low pressure arterial environment, and adapt mainly via outward dilation with less intimal thickening. Vein grafts are exposed to a moderate flow, moderate shear stress, high pressure arterial environment, and adapt mainly via increased wall thickening with less outward dilation. We review the data that describe these differences, as well as the underlying molecular mechanisms that mediate these processes. Despite extensive research, there are few differences in the molecular pathways that regulate cell proliferation and migration or matrix synthesis, secretion, or

Correspondence: Alan Dardik, Yale University School of Medicine, 10 Amistad Street, Room 437, PO Box 208089, New Haven, CT 06520-8089, Phone: (203) 737-2082 Fax: (203) 737-2290 alan.dardik@yale.edu.

*These authors contributed equally to this work.

Author Roles

Conception and design:	DL, AD
Analysis and interpretation:	DL, EC, AD
Data collection:	DL, EC, DW, KY, CP, WW, RA, MH, NS
Writing the article:	DL, EC, DW, KY, CP, NS, AD
Critical revision of the article:	AD
Final approval of the article:	DL, EC, DW, KY, CP, WW, RA, MH, NS, AD
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degradation currently identified between vein graft adaptation and AVF maturation that account for the different types of venous adaptation to arterial environments.

Keywords

vein graft; arteriovenous fistula; remodeling; hemodynamic forces; environment

Introduction

Vascular surgeons expose veins to the arterial environment during two common procedures, creation of vein grafts and arteriovenous fistulae (AVF). Adaptation of veins to the arterial environment, including the different hemodynamic conditions and increased oxygen tension, is characterized by venous wall dilation and thickening as an integration of the underlying processes of cellular migration and proliferation, as well as extracellular matrix deposition and remodeling. Successful venous adaptation is critical for long term success of the vein graft or AVF, whereas unsuccessful adaptation, either insufficient or exuberant, may be a source of conduit failure that leads to patient morbidity and even mortality. Although our understanding of venous adaptation has substantially increased, this knowledge has not translated into successful therapy, and, accordingly, the failure rates of both vein grafts and AVF remain high, resulting in both patient suffering as well as significant health care expenditure.^{1, 2}

AVF are the current optimal and preferred conduit for vascular access for hemodialysis. Compared to arteriovenous grafts and central venous catheters, AVF have the longest patency with fewest complications.^{3–6} Despite their superiority among dialysis access choices, AVF still exhibit relatively high failure rates, as high as 60% failing to mature adequately to support hemodialysis in some reports,^{7, 8} and primary patency rates of approximately 60–65% within 1 year.^{9, 10} Similarly, vein grafts are the most commonly used and preferred vascular conduit for bypass surgery.^{11, 12} Like AVF, vein grafts also mature after surgical placement, a step thought to be necessary for long term patency.¹³ Vein grafts also have a significant rate of complications and failure, with 1-year primary patency rates reported to be as low as 60%.^{14–17} Coronary artery vein grafts have higher patency rates, with 1-year patency rates of approximately 75–90%, and 5–10 year patency rates above 75% that decrease to 50% at 15 years or more.^{18–21} The similarities and differences between AVF and vein grafts are summarized in Table 1.

The surgical formation of a vein graft or an AVF exposes the vein to the arterial environment of high blood flow and pressure that are typically considered injurious and that stimulate venous adaptation to the new environment.¹² This review compares both physiological and molecular adaptation of veins (“venous remodeling”), as either vein grafts (“vein graft adaptation”) or AVF (“AVF maturation”), to this different environment, using literature specific to venous adaptation and not based on arterial data.

Surgical Procedure

Several aspects of the surgical procedure are noteworthy and likely to affect venous remodeling. Vein grafts can be performed either in reversed, nonreversed, or in situ fashion, generally at the discretion of the surgeon. Reversed vein grafts create a flow environment in which the endothelial cells remain aligned to the direction of flow and the valves remain in their normal alignment, allowing antegrade flow with minimal resistance or disturbance. Nonreversed vein grafts are prepared similarly but require valve destruction, creating flow disturbance and even turbulence near the valve remnants; the endothelial cells remain aligned to the direction of flow but the flow direction is 180 degrees reversed compared to

the native venous flow. In situ vein grafts similarly require valve destruction and have reversed flow on the endothelial cells, but the veins are not removed from the native tissue bed, leaving the venous adventitia, as well as the vasa vasorum and nervous innervation, intact. Vein grafts, both reversed and nonreversed, require extensive handling and irrigation, resulting in spasm as well as endothelial damage and inflammation.^{22–24} During coronary artery bypass, veins may be exposed to the colder environment of the bypass flow circuit and cardioplegia.

Similarly, AVF may be created directly or transposed from a deeper bed, although transposition in reversed configuration with valve destruction is distinctly less common. The AVF procedure is usually performed with less mobilization and surgical manipulation of the vein compared to vein grafts, resulting in AVF being performed more quickly and with less trauma, ischemia, and endothelial injury compared to vein grafts.

The systemic environment created by the comorbid conditions of the patient is often quite different between vein grafts and AVF. Vein grafts are typically created in patients with cardiovascular disease that is similarly frequently present in patients needing AVF. However, patients with AVF have advanced renal disease and uremia that is not present in many patients requiring vein grafts. Uremia is an independent factor that predisposes the AVF to failure to mature.^{25–28} AVF are also cannulated for dialysis multiple times a week, unlike vein grafts that reside in atraumatic environments.

Flow and Pressure

The minimum blood flow for hemodialysis in the United States is generally 350–450 ml/min, and in order to prevent venous collapse, the flow rate should exceed this minimum rate by at least 100 ml/min.²⁹ High flow rates correlate with successful access maturation, with 84% of fistulae with flows greater than 500 ml/min eventually being adequate for dialysis, while only 43% of fistulas with flows less than 500 ml/min becoming adequate.²⁹ The National Kidney Foundation Clinical Practice Guidelines recommend a flow rate of 400–500 ml/min as a minimal threshold for re-evaluation of a fistula.³⁰ In Europe and Japan, however, hemodialysis is currently performed with lower flow rates but with longer sessions compared to those performed in the US.^{31, 32} For example, in Europe, a minimal flow rate of 300 ml/min is the threshold for re-evaluation.³³

The blood flow in the cephalic vein in healthy, non-hemodialysis patients is approximately 28 ± 14 ml/min.³⁴ Studies evaluating successful radial-cephalic AVF reveal normal flow rates averaging between 600–1000 ml/min, with many individual AVF exposed to even higher peak flows, and this magnitude of flow increases substantially in the larger diameter brachial-cephalic AVF (Table 2). Dixon et al. reported that 90% of forearm AVF have flow between 500–2000 ml/min, whereas 90% of upper arm AVF have flow between 500–3000 ml/min.³⁵ Corpataux et al. reported that shear stress increases from 5–10 dyne/cm² to 24.5 dyne/cm² after one week, which then normalizes to 10.4 dyne/cm² over 3 months.^{5, 36} The substantially increased magnitude of blood flow in the AVF, typically much higher compared to arterial flow, we call “supra-arterial” magnitudes of flow (Table 1). With these high magnitudes of flow in the AVF, the character of the flow may be disturbed, e.g. non-laminar and highly disordered, even turbulent.^{37–40}

The blood flow within vein grafts varies depending on several variables, including type of procedure, length and diameter of conduit, as well as the amount of resistance in the runoff bed distal to the vein graft. Accordingly, average flow rates for lower extremity bypasses typically vary from <100 to >300 ml/min, while average flow rates for coronary artery bypass are often <100 ml/min (Table 2). Flow rates over time are extremely difficult to assess, as the presence of a failing graft, even sub-clinically, as well as advancing proximal

and/or distal disease, are significant confounding variables that usually precipitate intervention. Nevertheless, most studies show that vein grafts are exposed to flows of the arterial circulation that are typically much lower magnitude than to which AVF are exposed.

In lower extremity vein grafts, average intraoperative shear stress was measured to be 23–27 dyne/cm², which decreases by 1 year to 12 dyne/cm².^{17, 41, 42} Fillinger et al. showed that smaller diameter vein grafts are associated with much higher values of shear stress, with these values normalizing to 6–10 dyne/cm² by 12 months.⁴³ Coronary vein grafts generally dilate little and have lower magnitudes of flow, with shear stress values reported to be 5 dyne/cm².^{44, 45}

Fewer studies examine pressure, but pressure measurements in an AVF are generally significantly less than measurements in a vein graft.^{36, 46} Corpataux et al. measured the cephalic vein pressure to be 49 ± 19 / 24.5 ± 6 mmHg (systolic / diastolic) immediately after radial-cephalic AVF creation, and this did not increase 13 months later.³⁶ Animal studies are also generally consistent with this small increase in pressure.^{37, 47} Vein grafts are typically exposed to arterial pressure.^{2, 46} In toto, extensive examination shows that vein grafts are exposed to arterial magnitudes of pressure and flow whereas AVF are exposed to supra-arterial magnitudes of flow at pressures typically much lower than arterial systolic pressure (Table 1).

Outward remodeling

Adaptation of the vein to the increased flow and shear stress of the arterial environment requires dilation by outward remodeling of the venous wall, described by Poiseuille's law, whereas increases in pressure and tensile stress require wall thickening, described by Laplace's law. These changes are thought to be mediated by the venous endothelium that senses hemodynamic forces and integrates these forces to allow successful adaptation without loss of luminal area and vessel patency.^{10, 13, 48}

Diameter expansion is thought to be a critical element of venous outward remodeling and predicts clinical success for both AVF and vein grafts.^{17, 49–51} Although mediated by the endothelium, this process may require destruction of the internal elastic lamina to allow subsequent wall dilation.^{47, 52} Several studies examining venous dilation in AVF reported mean diameter increases from 2.3–3.2 mm to 5.8–6.6 mm, three months after fistula creation. These values reflect a 45–86% increase within the first month and an increase of up to 179% after 3 months, correspond to an average cross-sectional area of approximately 10–12 mm², and were associated with normalization of the shear stress.^{36, 50, 53, 54}

Lower extremity vein grafts are associated with average dilation of approximately 20–30% during the first few months after surgery, with minimal dilation afterwards.^{17, 41, 42} Fillinger et al. reported that at 1 year postoperatively, initially smaller-diameter vein grafts tended to dilate 20–25%, whereas initially larger-diameter vein grafts tended to constrict 10–15%, achieving similar final diameters.⁴³ Vein grafts in the coronary circulation may also show flow-mediated diameter remodeling, although they frequently exhibit a small amount of inward remodeling, consistent with their lower flow.^{55, 56} Thus both vein grafts and AVF remodel their diameters, usually by dilation, depending on the magnitudes of flow in the new environment, normalizing the shear stress sensed by the venous endothelium.

Wall Thickening

Wall thickening is the adaptation of the vessel wall to increased pressure; thickening has been studied extensively in several models of vascular injury and adaptation, especially in the arterial angioplasty and hypertension models. These models have shown that this process

involves expansion of all the layers of the vessel via both extracellular matrix (ECM) deposition, as well as via cell proliferation and migration.^{13, 14, 22, 41, 57} Several types of cells are involved in wall thickening, including smooth muscle cells, adventitial fibroblasts, and bone-marrow-derived progenitor cells. In addition to proliferation, smooth muscle cells may migrate from the medial to the intimal layer and differentiate from a contractile to synthetic phenotype; fibroblasts may similarly differentiate into myofibroblasts.^{10, 13, 23, 25, 52, 58–66} Bone marrow-derived progenitor cells are capable of differentiation into both endothelial and smooth muscle cells within both AVF and vein grafts, although whether this occurs in humans is not clear.^{61, 67–70} Neoangiogenesis also occurs during wall thickening, although its contribution to normal adaptation or maladaptive pathology is unclear.^{39, 59, 67, 71}

Jacot et al. reported increased wall thickness during human vein graft adaptation, from 0.47 ± 0.03 to 0.61 ± 0.004 mm, during the first 6 months after implantation.⁷² Using intravascular ultrasound, Higuchi et al. reported similar wall thickening that accompanied outward remodeling in saphenous vein coronary artery bypass grafts.⁷³ Similarly, Corpataux et al. reported increased wall cross sectional area in AVF although the small increase in the AVF is likely due to the lower pressure in the AVF compared to the coronary vein graft.³⁶

Venous remodeling integrates outward remodeling and wall thickening

AVF are exposed to a high flow, high shear stress, low pressure arterial environment, and adapt mainly via outward dilation and less intimal thickening. Vein grafts are exposed to a moderate flow, moderate shear stress, high pressure arterial environment, and adapt mainly via increased wall thickening with less outward dilation (Figure 1). Schwartz et al. confirmed this behavior using a rabbit model, showing that AVF are exposed to higher flow than vein grafts (AVF: 82 ± 17 ml/min; vein grafts: 16 ± 4 ml/min) as well as increased shear stress (AVF: 71 ± 50 dyne/cm²; VG: 0.96 ± 0.38 dyne/cm²) that was associated with increased dilation (AVF: 194%; VG: no change); vein grafts are exposed to higher pressure (VG: 62 ± 3 mmHg; AVF: 6 ± 2 mmHg) and had increased myointimal area (VG: 4.72 ± 0.83 mm²; AVF: 1.9 ± 0.55 mm²).⁷⁴ Interestingly, Zilla et al. recently showed in a nonhuman primate model that vein grafts in the coronary circulation had lower mean velocity and shear stress, and lumen constriction and increased intimal thickening, compared to peripheral vein grafts that dilate.⁷⁵

Molecular Mechanisms of Venous Remodeling

Vascular Identity

The developmental origin of vascular endothelial cells and smooth muscle cells is different, with Ephrin-B2 being a determinant of arteries and Eph-B4 a determinant of veins in the developing embryo; these determinants persist as markers of identity on adult vessels.^{14, 76–79} Vein graft adaptation is characterized by loss of Eph-B4 expression, e.g. loss of venous identity, but Ephrin-B2 is not expressed, e.g. arterial identity is not gained.⁸⁰ However, similar characterization of the changes that occur during AVF maturation is not yet available. Downstream signaling in the Ephrin-Eph pathway may mediate many effects of venous remodeling, but the significance of this pathway as a potential source of therapeutic manipulation is not yet known. However, since Eph signaling is upstream of the E2F pathway, modulation of the Eph pathway may provide therapeutic benefit, unlike the disappointing failure of the PREVENT trials.^{15, 81}

Endothelial Signaling

The venous endothelium releases mitogens and chemotactic agents, regulators of extracellular matrix remodeling, as well as vasoactive signals that regulate wall dilation to

allow vessel adaptation to flow, shear stress, pressure, and tension (Figure 2).⁸² Endothelial injury and denudation disrupt endothelial signaling leading to impaired adaptation. Flow-related endothelial denudation can occur within hours of AVF creation, and chronic kidney disease may delay reendothelialization; denudation leads to barrier dysfunction, exposure of subendothelial collagen, thrombus formation, and inflammatory cell extravasation into the vein wall.^{27, 39} A similar process occurs in vein grafts, where endothelial denudation can occur within an hour after implantation.^{83, 84} Both the stress of the arterial environment and the surgical injury likely contribute to endothelial loss and dysfunction. The endothelium is regenerated 2 weeks after both vein graft implantation and AVF creation, although endothelial proliferation continues for several weeks afterwards.^{39, 83}

In endothelial cells, nitric oxide (NO) is produced by endothelial nitric oxide synthase (eNOS), and is a potent vasodilator and signaling molecule with anti-inflammatory and anti-platelet properties.^{14, 23} eNOS may contribute to adaptive vein wall remodeling both through its anti-inflammatory and anti-thrombotic properties as well as through its anti-proliferative properties.² Both eNOS and inducible nitric oxide synthase (iNOS) are upregulated in the AVF and may mediate adaptation; inhibition of eNOS results in increased MCP-1 and IL-8, leading to neointimal hyperplasia.^{67, 85} Similarly in vein grafts, NO limits neointimal thickening, cell proliferation, and macrophage infiltration,^{86, 87} while iNOS may inhibit intimal and adventitial thickening.^{87, 88}

Endothelin-1 (ET-1) is an inflammatory mediator of vasoconstriction and endothelial proliferation. ET-1 expression is upregulated in the venous wall and within areas of neointimal hyperplasia in AVF as well as in the plasma of patients with chronic renal failure and hemodialysis. ET-1 may mediate wall thickening in response to localized hemodynamic forces.^{58, 89, 90} Similarly in vein grafts, high densities of ET-1 receptors are present within subintimal regions that coincide with areas of proliferating cells. In a pig vein graft model, treatment with an ET-1 receptor antagonist resulted in decreased cell proliferation, decreased intimal and medial vein graft thickening, and increased luminal dilation.^{91, 92}

The opposing roles played by ET-1 and NOS are balanced by the venous endothelium during vein graft adaptation; however, arterial stress-induced endothelial injury and denudation disrupts this balance and likely is a mechanism of impaired venous adaptation. This pathway may be fruitful for consideration of modulation in future clinical studies. However, differences between arterial and venous ET-1 function suggest that results derived from arterial models may need to be interpreted cautiously in the context of venous remodeling.²³

Inflammatory and Coagulation Pathways

Numerous inflammatory mediators are present during venous remodeling. In an AVF, inflammatory cells accumulate rapidly, with additional accumulation in segments that thrombose.^{47, 93, 94} IL-6, IL-8, MCP-1, and PAI-1 expression are upregulated in the AVF, and these mediators are associated with fistula failure.^{58, 85, 95} IL-6 and TNF- α are more highly expressed in thrombosed AVF, and both CRP and fibrinogen are associated with AVF failure.^{93, 96}

The anti-inflammatory molecule heme oxygenase-1 (HO-1), an inducible stress protein involved in heme metabolism, regulates ECM deposition, endothelial proliferation, oxidative stress, and smooth muscle proliferation. HO-1 expression is upregulated within AVF, and reduced HO-1 activity is associated with AVF failure.^{67, 97, 98} HO-1 knockout mice develop increased neointimal hyperplasia and decreased AVF patency, with corresponding increased expression of PAI-1, MCP-1, matrix metalloproteinase (MMP)-2 and MMP-9.^{97, 99}

Inflammatory cells such as macrophages and granulocytes are recruited to vein grafts rapidly after implantation, and are associated with expression of both pro-inflammatory and anti-inflammatory mediators; increased expression of inflammatory mediators may result in negative wall remodeling and intimal hyperplasia.^{2, 100–102} Interestingly, there is significantly higher induction of the pro-inflammatory IL-1 β and less induction of the anti-inflammatory IL-10 within low flow vein grafts that correlates with increased intimal hyperplasia.¹⁰³ Elevated hsCRP, a marker of systemic inflammation, is associated with impaired positive remodeling, increased wall stiffness, suggesting an increased risk of failure in vein grafts.⁴² Failing vein grafts are also associated with increased levels of PAI-1 and diminished tPA.¹⁰⁴ Similar to the data reported for AVF, HO-1 is also protective against vein graft failure, as vein grafts derived from HO-1 knockout mice demonstrate enhanced neointima compared to veins from wild type mice.¹⁰⁵ Finally, a variety of anti-inflammatory agents decrease vein graft neointimal proliferation in animal models.¹⁴

Reactive Oxygen Species

Oxidative stress and injury stimulates synthesis and secretion of reactive oxygen species (ROS) that in turn regulate numerous signaling pathways, regulating diverse processes such as smooth muscle cell migration and proliferation, as well as activate latent MMP, potentially mediating many aspects of venous remodeling.^{2, 12, 22, 89} For example, superoxide can deplete NO, resulting in disruption of numerous pathways.^{2, 106}

Oxidative stress is associated with end stage renal disease and dialysis, and therefore is likely to be present at all times an AVF is present.⁸⁹ In the artery proximal to an AVF, ROS mediate arterial flow-dependent remodeling via MMP activation.¹⁰⁷ In the venous limb of the AVF markers and products of oxidative stress are elevated in neointimal lesions, often colocalizing with the cytokines of growth and proliferation.⁸⁹ AVF demonstrate increased superoxide and decreased superoxide dismutase (SOD) coordinately with induction of HO-1; addition of a superoxide scavenger decreases venous neointimal thickening and calcification within the AVF.⁹⁷

With increased surgical manipulation, including removal from the surrounding tissues and disruption of vasa vasorum, vein grafts are associated with oxidative stress as well as ischemia-reperfusion injury that lead to generation of ROS.^{2, 108} Superoxide is produced in vein grafts and released from intimal smooth muscle cells, mediated by NAD(P)H oxidase.¹⁰⁶ Superoxide is reciprocally related to NO function, as decreased intimal hyperplasia is associated with decreased superoxide production and increased NO-mediated vein graft relaxation.^{109, 110} A variety of free radical scavengers such as desferoxamine manganese and SOD reduce intimal hyperplasia in vein graft models.^{108, 111}

Extracellular Matrix

Venous adaptation depends on coordinate synthesis, secretion, and degradation of extracellular matrix (ECM). The MMP family regulate ECM remodeling and allow cell migration through degradation of collagen and elastin and is stimulated by a variety of factors present during vein graft adaptation including flow, stretch, mechanical injury, inflammation, and oxidative stress.^{22, 46, 47, 60, 99, 112, 113} In AVF, MMP-2 and MMP-9 expression are upregulated, and a high serum ratio of MMP-2 to TIMP predicts AVF maturation.^{46, 47, 60, 85, 94, 112} However, MMP-2 and MMP-9 are also elevated in AVF stenoses and may play a role in thrombosis.^{60, 93, 99, 112} Decreased expression of MMP-1, MMP-3, and MMP-9 have been linked to increased AVF failure and stenosis that may be due to accumulation of ECM and impaired wall remodeling.¹¹⁴ The role of the TIMPs is not consistent and thus difficult to assess.^{46, 47, 60, 115} Other elastases such as cathepsin S and

cathepsin K are also upregulated in the AVF and may be associated with degradation of the internal elastic lamina.⁴⁷

In vein grafts, ECM deposition is likely to be the major mechanism of adaptation after 4 weeks.^{71, 83, 116} Both MMP-2 and MMP-9 expression are upregulated in the early developing neointima of vein grafts, but decline to baseline between 3–6 months, suggesting their role in early remodeling and cell migration.^{102, 113, 116} Interestingly, surgical preparation of vein grafts, including harvest, adventitial removal, distention, exposure to cold temperature, etc., activates MMP-2 and MMP-9 and coincides with partial endothelial denudation.¹¹⁷ Upregulation of MT1-MMP (MMP-14), an activator of MMP-2, also occurs after vein graft implantation.¹⁰² Elastase is also upregulated in vein grafts, and expression of an elastase inhibitor, elafin, protects against vein graft neointimal hyperplasia and inflammation within the venous wall.¹¹⁸ TIMP-2 is downregulated early during vein graft adaptation, followed by a return to normal levels.¹⁰² TIMP-1, however, increases in vein grafts.¹¹⁹ Overexpression of TIMP-3 leads to decreased vein graft thickening.¹²⁰

Matrix degradation is regulated by MMP whereas matrix deposition is regulated by transforming growth factor- β (TGF- β) that is produced by a variety of cell types, including endothelial, smooth muscle, and inflammatory cells, potentially contributing significantly to intimal and medial thickening.^{58, 121, 122} TGF- β is upregulated at both early and later time points after AVF formation, depending on the model, and this expression correlates with ECM accumulation; TGF- β is also expressed within stenotic AVF, and correlates with areas of ECM deposition.^{58, 85, 99, 123, 124} Higher expression of TGF- β is associated with decreased AVF patency, likely due to increased deposition of ECM.¹²¹

TGF- β is similarly a potent stimulator of ECM deposition during early stages of vein graft adaptation.¹²² TGF- β 1 mRNA expression is upregulated after vein graft implantation, while inhibition of TGF- β 1 expression decreases neointimal hyperplasia and MCP-1 expression.^{119, 122} Upregulation of TGF- β mRNA expression in vein grafts is associated with increased expression of collagen I and collagen III mRNA.¹²⁵ Both TGF- β and connective tissue growth factor (CTGF) expression are upregulated in vein graft neointima despite diminished neointima cellularity.¹¹⁶

Growth Factors and Cell Adhesion Molecules

Numerous growth factors and cytokines play a role during venous adaptation, both through pathways that control ECM synthesis, secretion, and degradation, as well as through control of cell proliferation and migration. For example, insulin-like growth factor-1 (IGF-1) induces ECM synthesis, smooth muscle proliferation and migration, and inhibits apoptosis in AVF.¹²⁴ Platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) also play significant roles in stimulating cell proliferation and migration.^{14, 22} Both PDGF- α/β and IGF-1 expression are upregulated in AVF.^{85, 99} Vascular endothelial growth factor (VEGF) plays several roles in vascular remodeling, including stimulation of endothelial proliferation and differentiation, modulation of smooth muscle cell proliferation and migration, angiogenesis, and modulation of the inflammatory response.^{126–128} Interestingly, VEGF may play an inhibitory role in AVF adaptation, since inhibition of VEGF-A is associated with increased lumen area and decreased inward remodeling.¹²⁷

Similarly in vein grafts, PDGF and bFGF expression are upregulated and correlate with intimal thickening.¹⁰⁰ Inhibitors of the PDGF receptor and bFGF inhibit smooth muscle cell migration and proliferation leading to diminished neointimal hyperplasia.^{14, 22, 129} IGF-1 receptor expression is upregulated by mechanical stretch and deletion of the IGF-1 receptor leads to diminished neointimal hyperplasia in vein grafts.¹³⁰ VEGF expression is upregulated during vein graft implantation and is a negative regulator of intimal hyperplasia;

inhibition of VEGF activity increases thickness of the vein graft intima-media.^{71, 80} Interestingly, the effects of VEGF-A during vein graft adaptation may be mediated by the Eph signaling pathway.⁸⁰ Conversely, incubation of vein grafts in VEGF decreases intimal thickening.¹³¹

Monocyte chemoattractant protein-1 (MCP-1) regulates chemotaxis, endothelial activation, and stimulation of smooth muscle proliferation and migration, and plasma MCP-1 levels are increased in patients with kidney disease.^{7, 132} MCP-1 is increased in AVF, and reduced MCP-1 activity is associated with increased AVF patency, increased luminal area and decreased wall thickness.^{7, 58, 85} Increased serum MCP-1 is also associated with AVF failure.⁹⁵ In vein grafts, MCP-1 expression is increased immediately after implantation and remains elevated for several weeks.¹³² Treatment of vein grafts with an antagonist to the MCP-1 receptor CCR2 diminished thickening.¹³³

Selectins facilitate leukocyte adhesion. P-selectin is present on endothelial cells and platelets, and E-selectin is present on endothelial cells; ICAM and VCAM facilitate additional binding and migration.¹³⁴ P-selectin and E-selectin expression are both upregulated early after AVF creation, followed by decreased P-selectin expression after 1 month.⁸⁵ VCAM-1, but not ICAM-1, is highly expressed in thrombosed and stenotic AVF.⁹³ β -catenin and c-Myc expression are increased 1 week after AVF creation, correlating with decreased N-cadherin and associated with smooth muscle cell proliferation.¹³⁵ In vein grafts, ICAM-1 expression is increased soon after implantation, and vein grafts derived from ICAM knockout mice have fewer adherent macrophages and 30–50% less neointimal hyperplasia.¹³⁶

Failure of venous remodeling

Despite the ability of vein grafts and AVF to remodel and adapt successfully to the arterial environment, vein grafts and AVF still exhibit significant rates of failure. AVF show two distinct phases of failure; AVF failure can occur early due to lack of sufficient maturation, as well as failure later, after successful maturation, due to neointimal hyperplasia that may result in stenosis or thrombosis. Vein grafts show similar patterns of early and later failure. We believe that despite somewhat different mechanisms of vein graft and AVF remodeling to the arterial environment, failure of successful remodeling leads to the early phase of clinical failure in both cases; similarly, later failure is generally associated with progression of disease in both cases as well. However it is still not known whether the mechanisms that regulate successful venous remodeling become dysregulated and lead to later conduit failure. Therapeutic approaches to prevent failure include both cell-based therapies and gene therapy targeting many of the molecular pathways addressed in this paper. While a detailed review of these approaches is beyond the scope of this paper, several excellent reviews have addressed this topic in detail.^{2, 10, 14, 22, 25, 59, 81, 82}

Conclusions

The molecular mechanisms leading to cell proliferation and migration, as well as ECM synthesis, secretion, and degradation, are remarkably similar during vein graft and AVF adaptation to the arterial environment. Despite differences in vein graft adaptation, characterized mainly by wall thickening, and AVF maturation, characterized mainly by outward remodeling, the lack of identifiable molecular differences between these two processes remains a gap in our understanding of venous remodeling. Research directed towards understanding the effects of different hemodynamic and other environmental forces on veins may identify molecular differences between vein graft adaptation and AVF maturation, and may depend on understanding the fundamental biological differences

between responses of arteries and veins to these stimuli. Additional areas of research include regulation of apoptosis, endothelial phenotype, and the role of endothelial progenitor cells in venous remodeling.

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Figure 1.

Schema of vein graft adaptation and AVF maturation. AVF adapt largely through outward remodeling in response to supra-arterial flow, whereas vein grafts adapt largely through intimal/medial thickening in response to arterial pressure.

Figure 2.
Diagram depicting molecular pathways mediating venous adaptation to the arterial environment.

Table 1

Basic characteristics of vein grafts compared to arteriovenous fistulae (AVF)

	Vein Graft	AVF
Preferred conduit?	Yes (bypass)	Yes (access)
Maturation in the arterial environment Outward remodeling	Yes	Yes
Wall thickening	Yes	Yes
1-year Patency	60–80%	50–65%
Typical patient environment	Cardiovascular risk factors	Uremia / renal disease
Runoff	High Resistance	Low Resistance
Flow	Arterial	Supra-Arterial
Pressure	High (arterial)	Low
Branches	Ligated	Patent
Vein left intact	No (reversed vein graft) Yes (in situ vein graft)	Yes
Surgical mobilization	Extensive	Minor (typical) Extensive (transposed)
Conduit diameter after remodeling	Medium	Large
Disturbed post-surgery	Undisturbed	Frequently Cannulated

Table 2

Studies measuring flow in human arteriovenous fistulae and vein grafts.

Study	Measurement	Flow (mean $\pm$ SD)
Wong et al. 1996 ⁵⁰	AVF (Radiocephalic) – Cephalic vein	125 $\pm$ 102 ml/min intraoperatively 710 $\pm$ 318 ml/min at 12 weeks
Lin et al. 1997 ⁵³	AVF (Radiocephalic) – Cephalic vein	825.6 $\pm$ 424.3 ml/min in successful fistulae at 2–3 weeks
Yerdel et al. 1997 ¹³⁷	AVF (Radiocephalic and Brachiocephalic) – Cephalic vein	58 $\pm$ 23 ml/min intraoperatively 472 $\pm$ 315 ml/min at day 1 861 $\pm$ 565 ml/min at day 7
Lin et al. 1998 ⁵⁴	AVF (Radiocephalic) – Cephalic vein	750.4 $\pm$ 392.2 ml/min – younger 634.2 $\pm$ 310.3 ml/min – elderly at > 1 week
Robbin et al. 2002 ²⁹	AVF (Upper arm and forearm) – draining veins	780 $\pm$ 401 ml/min in successful fistulae within 4 months
Dixon et al. 2002 ³⁵	AVF (Brachiocephalic and Radiocephalic)	Brachiocephalic: 1247 ml/min Radiocephalic: 938 ml/min
Albayrak et al. 2007 ³⁴	AVF (Radiocephalic and Brachiocephalic) – Cephalic vein	Brachiocephalic: 1983 $\pm$ 1199 ml/min Radiocephalic: 870 $\pm$ 322 ml/min
Saucy et al. 2010 ¹³⁸	AVF (Radiocephalic) – Pre-anastomotic radial artery minus post-anastomotic radial artery flow	230 $\pm$ 194 ml/min intraoperatively 753 $\pm$ 269 ml/min at 1 week 915 $\pm$ 393 ml/min at 1 month in successful radiocephalic fistulae
Fillinger et al. 1994 ⁴³	VG (Infrainguinal Bypasses) – Greater Saphenous Vein	104–206 ml/min at 1 week 57–82 ml/min at 1 year
Owens et al. 2006 ⁴¹	VG (Lower-Extremity Bypass) – Greater Saphenous, Cephalic, or Basilic Vein	161 $\pm$ 21.7 ml/min intraoperatively 302.2 $\pm$ 47 ml/min (Mean $\pm$ SEM) at 6 months
Owens et al. 2009 ¹³⁹	VG (Femoral-Popliteal) – Greater Saphenous Vein	348.0 $\pm$ 153.2 ml/min (average age of graft: 1195.6 days)
Greenfield et al. 1972 ¹⁴⁰	VG (Coronary Artery Bypass) – Saphenous Vein	35 $\pm$ 2 ml/min (Mean $\pm$ SEM) at 30 minutes after bypass
Hamby et al. 1979 ²¹	VG (Coronary Artery Bypass) – Saphenous Vein	Early (8–12 days postoperatively): To LAD: 79 $\pm$ 39 ml/min To Right Circumflex: 65 $\pm$ 17 ml/min To Left Circumflex: 68 $\pm$ 25 ml/min Late (average 2.5 years): To LAD: 67 $\pm$ 31 ml/min To Right Circumflex: 42 $\pm$ 17 ml/min To Left Circumflex: 60 $\pm$ 24 ml/min
Gurné et al. 1999 ¹⁴¹	VG (Coronary Artery Bypass) – Saphenous Vein	Early: 56 $\pm$ 19 ml/min (average 9 days) Late: 50 $\pm$ 16 ml/min (average 23 months)
Walpoth et al. 2008 ¹⁴²	VG (Coronary Artery Bypass) – Greater Saphenous Vein	58 $\pm$ 29 ml/min intraoperatively 50 $\pm$ 27 ml/min at 3 months 46 $\pm$ 27 ml/min at 10 months

AVF = Arteriovenous Fistula, VG = Vein Graft, LAD = Left Anterior Descending Artery, SD = Standard Deviation, SEM = Standard Error of the Mean.