Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Research review

# Vein graft adaptation and fistula maturation in the arterial environment

*Daniel Y. Lu, BS,*[a,b,1] *Elizabeth Y. Chen, BS,*[a,b,1] *Daniel J. Wong, BS,*[a,b] *Kota Yamamoto, MD, PhD,*[a,b,d] *Clinton D. Protack, MD,*[a,b] *Willis T. Williams, MD,*[a,b] *Roland Assi, MD,*[a,b] *Michael R. Hall, MD,*[a,b] *Nirvana Sadaghianloo, MD,*[a,b,c] *and Alan Dardik, MD, PhD*[a,b,d,*]

[a] *Yale University Vascular Biology and Therapeutics Program, New Haven, Connecticut*
[b] *Department of Surgery, Yale University School of Medicine, New Haven, Connecticut*
[c] *Department of Vascular Surgery, University Hospital of Nice, Nice, France*
[d] *VA Connecticut Healthcare System, West Haven, Connecticut*

ARTICLE INFO

*Article history:*
Received 26 October 2013
Received in revised form
25 December 2013
Accepted 24 January 2014
Available online 30 January 2014

*Keywords:*
Vein graft
Arteriovenous fistula
Remodeling
Hemodynamic forces
Environment

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 with 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 degradation currently identified between vein graft adaptation and AVF maturation that account for the different types of venous adaptation to arterial environments.

Published by Elsevier Inc.

## 1. 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,

* *Corresponding author*. Yale University School of Medicine, Vascular Biology and Therapeutics Program, 10 Amistad Street, Room 437, PO Box 208089, New Haven, CT 06520-8089. Tel.: +203 737 2082; fax +203 737 2290.
E-mail address: alan.dardik@yale.edu (A. Dardik).
[1] These authors contributed equally to this work.
0022-4804/$ – see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.jss.2014.01.042

**Table 1 – Basic characteristics of vein grafts compared with AVF.**

| | Vein graft | AVF |
|---|---|---|
| Preferred conduit? | Yes (bypass) | Yes (access) |
| Maturation in the arterial environment | | |
| Outward remodeling | Yes | Yes |
| Wall thickening | Yes | Yes |
| 1-y 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)<br>Yes (*in situ* vein graft) | Yes |
| Surgical mobilization | Extensive | Minor (typical)<br>Extensive (transposed) |
| Conduit diameter after remodeling | Medium | Large |
| Disturbed postsurgery | Undisturbed | Frequently cannulated |

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 and significant health care expenditure [1,2].

AVF are the current optimal and preferred conduit for vascular access for hemodialysis. Compared with 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 y [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-y primary patency rates reported to be as low as 60% [14–17]. Coronary artery vein grafts have higher patency rates, with 1-y patency rates of approximately 75%–90%, and 5- to 10-y patency rates >75% that decrease to 50% at ≥15 y [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.

## 2. 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° reversed compared with 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 with vein grafts, resulting in AVF being performed more quickly and with less trauma, ischemia, and endothelial injury compared with 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.

## 3. Flow and pressure

The minimum blood flow for hemodialysis in the United States is generally 350–450 mL/min, and 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 >500 mL/min eventually being adequate for dialysis, whereas only 43% of fistulas with flows <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 with those performed in the United States [31,32].

**Table 2 – Studies measuring flow in human AVF and vein grafts.**

| Study | Measurement | Flow (mean ± SD) |
|---|---|---|
| Wong *et al.* [50] | AVF (radiocephalic)-cephalic vein | 125 ± 102 mL/min intraoperatively<br>710 ± 318 mL/min at 12 wk |
| Lin *et al.* [53] | AVF (radiocephalic)-cephalic vein | 825.6 ± 424.3 mL/min<br>in successful fistulae at 2–3 wk |
| Yerdel *et al.* [137] | AVF (radiocephalic and brachiocephalic)-cephalic vein | 58 ± 23 mL/min intraoperatively<br>472 ± 315 mL/min at d 1<br>861 ± 565 mL/min at d 7 |
| Lin *et al.* [54] | AVF (radiocephalic)-cephalic vein | 750.4 ± 392.2 mL/min—younger<br>634.2 ± 310.3 mL/min—elderly<br>at >1 wk |
| Robbin *et al.* [29] | AVF (upper arm and forearm)-draining veins | 780 ± 401 mL/min in successful fistulae within 4 mo |
| Dixon *et al.* [35] | AVF (brachiocephalic and radiocephalic) | Brachiocephalic: 1247 mL/min<br>Radiocephalic: 938 mL/min |
| Albayrak *et al.* [34] | AVF (radiocephalic and brachiocephalic)-cephalic vein | Brachiocephalic: 1983 ± 1199 mL/min<br>Radiocephalic: 870 ± 322 mL/min |
| Saucy *et al.* [138] | AVF (radiocephalic)-pre-anastomotic radial artery minus post-anastomotic radial artery flow | 230 ± 194 mL/min intraoperatively<br>753 ± 269 mL/min at 1 wk<br>915 ± 393 mL/min at 1 mo<br>in successful radiocephalic fistulae |
| Fillinger *et al.* [43] | VG (infrainguinal bypasses)-greater saphenous vein | 104–206 mL/min at 1 wk<br>57–82 mL/min at 1 y |
| Owens *et al.* [41] | VG (lower-extremity bypass)-greater saphenous, cephalic, or basilic vein | 161 ± 21.7 mL/min intraoperatively<br>302.2 ± 47 mL/min (mean ± SEM) at 6 mo |
| Owens *et al.* [139] | VG (femoral-popliteal)-greater saphenous vein | 348.0 ± 153.2 mL/min (average age of graft: 1195.6 d) |
| Greenfield *et al.* [140] | VG (coronary artery bypass)-saphenous vein | 35 ± 2 mL/min (mean ± SEM) at 30 min after bypass |
| Hamby *et al.* [21] | VG (coronary artery bypass)-saphenous vein | Early (8–12 d postoperatively):<br>To LAD: 79 ± 39 mL/min<br>To Right Circumflex: 65 ± 17 mL/min<br>To Left Circumflex: 68 ± 25 mL/min<br>Late (average 2.5 y): To LAD: 67 ± 31 mL/min<br>To Right Circumflex: 42 ± 17 mL/min<br>To Left Circumflex: 60 ± 24 mL/min |
| Gurné *et al.* [141] | VG (coronary artery bypass)-saphenous vein | Early: 56 ± 19 mL/min (average 9 d)<br>Late: 50 ± 16 mL/min (average 23 mo) |
| Walpoth *et al.* [142] | VG (coronary artery bypass)-greater saphenous vein | 58 ± 29 mL/min intraoperatively<br>50 ± 27 mL/min at 3 mo<br>46 ± 27 mL/min at 10 mo |

LAD = left anterior descending artery; SD = standard deviation; SEM = standard error of the mean.

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 and1000 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.* [35] reported that 90% of forearm AVF have flow between 500 and 2000 mL/min, whereas 90% of upper arm AVF have flow between 500 and 3000 mL/min. Corpataux *et al.* reported that shear stress increases from 5–10 dyne/cm$^2$ to 24.5 dyne/cm$^2$ after 1 wk, which then normalizes to 10.4 dyne/cm$^2$ >3 mo [5,36]. The substantially increased magnitude of blood flow in the AVF, typically much higher compared with 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, for example, nonlaminar 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, and 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, whereas 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 subclinically, 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/cm$^2$, which decreases by 1 y to 12 dyne/cm$^2$ [17,41,42]. Fillinger *et al.* [43] showed that smaller diameter vein grafts are associated with much higher values of shear stress, with these values normalizing to 6–10 dyne/cm$^2$ by 12 mo. Coronary vein grafts generally dilate little and have lower magnitudes of flow, with shear stress values reported to be $\leq$5 dyne/cm$^2$ [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.* [36] measured the cephalic vein pressure to be 49 $\pm$ 19/24.5 $\pm$ 6 mm Hg (systolic/diastolic) immediately after radial-cephalic AVF creation, and this did not increase 13 mo later. 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).

## 4. 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 to 5.8–6.6 mm, 3 mo after fistula creation. These values reflect a 45%–86% increase within the first month and an increase of up to 179% after 3 mo, correspond to an average cross-sectional area of approximately 10–12 mm$^2$, 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 afterward [17,41,42]. Fillinger *et al.* [43] reported that at 1 y 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. 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.

## 5. 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.* [72] reported increased wall thickness during human vein graft adaptation, from 0.47 $\pm$ 0.03 to 0.61 $\pm$ 0.004 mm, during the first 6 mo after implantation. Using intravascular ultrasound, Higuchi *et al.* [73] reported similar wall thickening that accompanied outward remodeling in saphenous vein coronary artery bypass grafts. Similarly, Corpataux *et al.* [36] 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 with the coronary vein graft.

## 6. 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 (Fig. 1). Schwartz *et al.* [74] confirmed this behavior using a rabbit model, showing that AVF are exposed to higher flow than vein grafts (AVF: 82 $\pm$ 17 mL/min; vein grafts: 16 $\pm$ 4 mL/min) as well as increased shear stress (AVF: 71 $\pm$ 50 dyne/cm$^2$; VG: 0.96 $\pm$ 0.38 dyne/cm$^2$) that was associated with increased dilation (AVF: 194%; VG: no change); vein grafts are exposed to higher pressure (VG: 62 $\pm$ 3 mmHg; AVF: 6 $\pm$ 2 mmHg) and had increased myointimal area (VG: 4.72 $\pm$ 0.83 mm$^2$; AVF: 1.9 $\pm$ 0.55 mm$^2$). Interestingly, Zilla *et al.* [75] 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 with peripheral vein grafts that dilate.

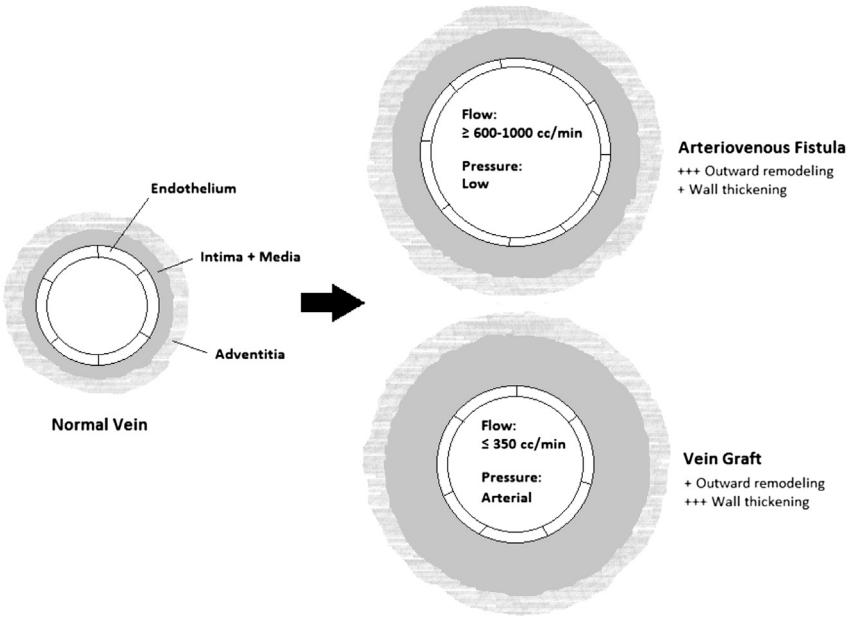


**Fig. 1 – Schema of vein graft adaptation and AVF maturation. AVF adapt largely through outward remodeling in response to supra-arterial flow, whereas vein grafts adapt largely through intimal/medial thickening in response to arterial pressure. + = positive; +++ = significantly positive.**

## 7. Molecular mechanisms of venous remodeling

### 7.1. *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, for example, loss of venous identity, but Ephrin-B2 is not expressed, for example, 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, because Eph signaling is the upstream of the E2F pathway, modulation of the Eph pathway may provide therapeutic benefit, unlike the disappointing failure of the PREVENT trials [15,81].

### 7.2. *Endothelial signaling*

The venous endothelium releases mitogens and chemotactic agents, regulators of extracellular matrix remodeling, and vasoactive signals that regulate wall dilation to allow vessel adaptation to flow, shear stress, pressure, and tension (Fig. 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 re-endothelialization; 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 wk after both vein graft implantation and AVF creation, although endothelial proliferation continues for several weeks afterward [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 antiplatelet properties [14,23]. eNOS may contribute to adaptive vein wall remodeling both through its anti-inflammatory and anti-thrombotic properties and through its anti-proliferative properties [2]. Both eNOS and inducible nitric oxide synthase are upregulated in the AVF and may mediate adaptation; inhibition of eNOS results in increased monocyte chemoattractant protein-1 (MCP-1) and interleukin (IL)-8, leading to neointimal hyperplasia [67,85]. Similarly in vein grafts, NO limits neointimal thickening, cell proliferation, and macrophage infiltration [86,87], whereas inducible nitric oxide synthase 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 and 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

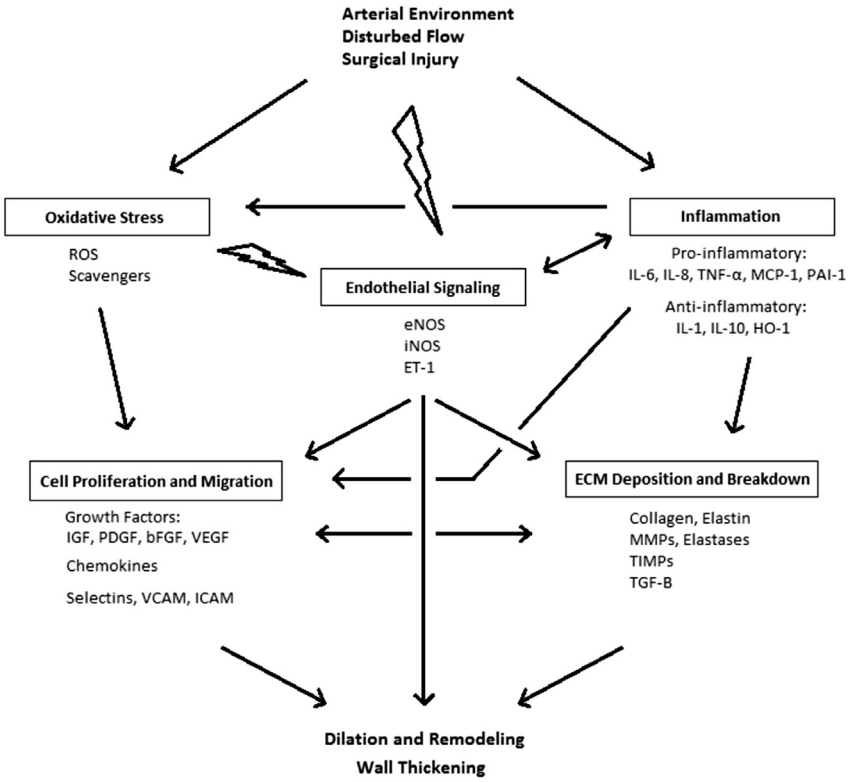


**Fig. 2 – Diagram depicting molecular pathways mediating venous adaptation to the arterial environment. iNOS = inducible nitric oxide synthase; TNF-α = tumor necrosis factor-α.**

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].

### 7.3. *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 plasminogen activator inhibitor-1 (PAI-1) expressions are upregulated in the AVF, and these mediators are associated with fistula failure [58,85,95]. IL-6 and tumor necrosis factor-α are more highly expressed in thrombosed AVF, and both C-reactive protein (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 proinflammatory 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 proinflammatory IL-1β and less induction of the anti-inflammatory IL-10 within low flow vein grafts that correlates with increased intimal hyperplasia [103]. Elevated high-sensitivity C-reactive protein (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 tissue plasminogen activator (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 with veins from wild-type mice [105]. Finally, a variety of anti-inflammatory agents decrease vein graft neointimal proliferation in animal models [14].

### 7.4. *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, and 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 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 superoxide dismutase reduce intimal hyperplasia in vein graft models [108,111].

### 7.5. *Extracellular matrix*

Venous adaptation depends on coordinate synthesis, secretion, and degradation of 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 expressions are upregulated, and a high serum ratio of MMP-2 to tissue inhibitor of metalloproteinases (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 expressions 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 wk [71,83,116]. Both MMP-2 and MMP-9 expressions are upregulated in the early developing neointima of vein grafts but decline to baseline between 3 and 6 mo, 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, and so forth, activates MMP-2 and MMP-9 and coincides with partial endothelial denudation [117]. Upregulation of Membrane type 1-MMP (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-β1 messenger RNA (mRNA) expression is upregulated after vein graft implantation, whereas inhibition of TGF-β1 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 expression are upregulated in vein graft neointima despite diminished neointima cellularity [116].

### 7.6. *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 and through the 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 expressions 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 because inhibition of VEGF-A is associated with increased lumen area and decreased inward remodeling [127].

Similarly in vein grafts, PDGF and bFGF expressions 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].

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; intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) facilitate additional binding and migration [134]. P-selectin and E-selectin expressions are both upregulated early after AVF creation, followed by decreased P-selectin expression after 1 mo [85]. VCAM-1, but not ICAM-1, is highly expressed in thrombosed and stenotic AVF [93]. β-catenin and c-Myc expressions are increased 1 wk 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].

## 8. 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 article. Although a detailed review of these approaches is beyond the scope of this article, several excellent reviews have addressed this topic in detail [2,10,14,22,25,59,81,82].

## 9. Conclusions

The molecular mechanisms leading to cell proliferation and migration, and 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 toward 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.

## Acknowledgment

This work was supported by the National Institutes of Health R01-HL095498 (A.D.) and TL1-RR024137 grants (D.Y.L.), the Yale Department of Surgery Ohse award (K.Y. and C.D.P.), the Yale University Medical Student Research Fellowship (E.Y.C.), the Society of Vascular Surgery Student Research Fellowship (E.Y.C.), the Doris Duke Foundation Clinical Fellowship (D.J.W.), as well as with the resources and the use of facilities at the VA Connecticut Healthcare System, West Haven, CT (K.Y. and A.D.).

## Disclosure

The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

## REFERENCES

[1] Dember LM, Beck GJ, Allon M, et al. Effect of clopidogrel on early failure of arteriovenous fistulas for hemodialysis: a randomized controlled trial. JAMA 2008;299:2164.
[2] Wan S, George SJ, Berry C, Baker AH. Vein graft failure: current clinical practice and potential for gene therapeutics. Gene Ther 2012;19:630.
[3] Gibson KD, Gillen DL, Caps MT, Kohler TR, Sherrard DJ, Stehman-Breen CO. Vascular access survival and incidence of revisions: a comparison of prosthetic grafts, simple autogenous fistulas, and venous transposition fistulas from the United States Renal Data System Dialysis Morbidity and Mortality Study. J Vasc Surg 2001;34:694.

[4] Schwab SJ, Harrington JT, Singh A, et al. Vascular access for hemodialysis. Kidney Int 1999;55:2078.
[5] Asif A, Roy-Chaudhury P, Beathard GA. Early arteriovenous fistula failure: a logical proposal for when and how to intervene. Clin J Am Soc Nephrol 2006;1:332.
[6] Ravani P, Palmer SC, Oliver MJ, et al. Associations between hemodialysis access type and clinical outcomes: a systematic review. J Am Soc Nephrol 2013;24:465.
[7] Juncos JP, Grande JP, Kang L, et al. MCP-1 contributes to arteriovenous fistula failure. J Am Soc Nephrol 2011;22:43.
[8] Vazquez MA. Vascular access for dialysis: recent lessons and new insights. Curr Opin Nephrol Hypertens 2009;18:116.
[9] Rooijens PP, Tordoir JH, Stijnen T, Burgmans JP, Smet de AA, Yo TI. Radiocephalic wrist arteriovenous fistula for hemodialysis: meta-analysis indicates a high primary failure rate. Eur J Vasc Endovascular Surg 2004;28:583.
[10] Roy-Chaudhury P, Spergel LM, Besarab A, Asif A, Ravani P. Biology of arteriovenous fistula failure. J Nephrol 2007;20:150.
[11] Bradbury AW, Adam DJ, Bell J, et al. Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL) trial: an intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy. J Vasc Surg 2010;51(5 Suppl):5S.
[12] Anwar MA, Shalhoub J, Lim CS, Gohel MS, Davies AH. The effect of pressure-induced mechanical stretch on vascular wall differential gene expression. J Vasc Res 2012;49:463.
[13] Owens CD. Adaptive changes in autogenous vein grafts for arterial reconstruction: clinical implications. J Vasc Surg 2010;51:736.
[14] Muto A, Model L, Ziegler K, Eghbalieh SD, Dardik A. Mechanisms of vein graft adaptation to the arterial circulation: insights into the neointimal algorithm and management strategies. Circ J 2010;74:1501.
[15] Conte MS, Bandyk DF, Clowes AW, et al. Results of PREVENT III: a multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery. J Vasc Surg 2006;43:742. discussion 51.
[16] Conte MS, Owens CD, Belkin M, et al. A single nucleotide polymorphism in the p27(Kip1) gene is associated with primary patency of lower extremity vein bypass grafts. J Vasc Surg 2013;57:1179.
[17] Gasper WJ, Owens CD, Kim JM, et al. Thirty-day vein remodeling is predictive of midterm graft patency after lower extremity bypass. J Vasc surg 2013;57:9.
[18] Zeff RH, Kongtahworn C, Iannone LA, et al. Internal mammary artery versus saphenous vein graft to the left anterior descending coronary artery: prospective randomized study with 10-year follow-up. The Ann Thorac Surg 1988;45:533.
[19] Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. J Am Coll Cardiol 1996;28:616.
[20] Desai ND, Cohen EA, Naylor CD, Fremes SE. Radial Artery Patency Study I. A randomized comparison of radial-artery and saphenous-vein coronary bypass grafts. The New Engl J Med 2004;351:2302.
[21] Hamby RI, Aintablian A, Handler M, et al. Aortocoronary saphenous vein bypass grafts. Long-term patency, morphology and blood flow in patients with patent grafts early after surgery. Circulation 1979;60:901.
[22] Collins MJ, Li X, Lv W, et al. Therapeutic strategies to combat neointimal hyperplasia in vascular grafts. Expert Rev Cardiovasc Ther 2012;10:635.
[23] Mitra AK, Gangahar DM, Agrawal DK. Cellular, molecular and immunological mechanisms in the pathophysiology of vein graft intimal hyperplasia. Immunol Cell Biology 2006;84:115.
[24] Osgood MJ, Hocking KM, Voskresensky IV, et al. Surgical vein graft preparation promotes cellular dysfunction, oxidative stress, and intimal hyperplasia in human saphenous vein. J Vasc Surg; 2013; epub Jul 30.
[25] Dixon BS. Why don't fistulas mature? Kidney Int 2006;70:1413.
[26] Kokubo T, Ishikawa N, Uchida H, et al. CKD accelerates development of neointimal hyperplasia in arteriovenous fistulas. J Am Soc Nephrol 2009;20:1236.
[27] Liang A, Wang Y, Han G, Truong L, Cheng J. Chronic kidney disease accelerates endothelial barrier dysfunction in a mouse model of an arteriovenous fistula. Am J Physiol Renal Physiol 2013;304:F1413.
[28] Wali MA, Eid RA, Dewan M, Al-Homrany MA. Intimal changes in the cephalic vein of renal failure patients before arterio-venous fistula (AVF) construction. J Smooth Muscle Res 2003;39:95.
[29] Robbin ML, Chamberlain NE, Lockhart ME, et al. Hemodialysis arteriovenous fistula maturity: US evaluation. Radiology 2002;225:59.
[30] National Kidney Foundation. Clinical Practice Guidelines and Clinical Practice Recommendations, 2006 Updates.: Available from: http://www.kidney.org/professionals/kdoqi/guideline_uphd_pd_va/va_guide4.htm.
[31] Gallieni M, Saxena R, Davidson I. Dialysis access in Europe and North America: are we on the same path? Semin Intervent Radiol 2009;26:96.
[32] Saran R, Bragg-Gresham JL, Levin NW, et al. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. Kidney Int 2006;69:1222.
[33] Tordoir J, Canaud B, Haage P, et al. EBPG on vascular access. Nephrol Dial Transplant 2007;22(Suppl 2):ii88.
[34] Albayrak R, Yuksel S, Colbay M, et al. Hemodynamic changes in the cephalic vein of patients with hemodialysis arteriovenous fistula. J Clin Ultrasound 2007;35:133.
[35] Dixon BS, Novak L, Fangman J. Hemodialysis vascular access survival: upper-arm native arteriovenous fistula. Am J Kidney Dis 2002;39:92.
[36] Corpataux JM, Haesler E, Silacci P, Ris HB, Hayoz D. Low-pressure environment and remodelling of the forearm vein in Brescia-Cimino haemodialysis access. Nephrol Dial Transplant 2002;17:1057.
[37] Krishnamoorthy MK, Banerjee RK, Wang Y, et al. Hemodynamic wall shear stress profiles influence the magnitude and pattern of stenosis in a pig AV fistula. Kidney Int 2008;74:1410.
[38] Ene-Iordache B, Remuzzi A. Disturbed flow in radial-cephalic arteriovenous fistulae for haemodialysis: low and oscillating shear stress locates the sites of stenosis. Nephrol Dial Transplant 2012;27:358.
[39] Manning E, Skartsis N, Orta AM, et al. A new arteriovenous fistula model to study the development of neointimal hyperplasia. J Vasc Res 2012;49:123.
[40] Ojha M, Cobbold RS, Johnston KW. Influence of angle on wall shear stress distribution for an end-to-side anastomosis. J Vasc Surg 1994;19:1067.
[41] Owens CD, Wake N, Jacot JG, et al. Early biomechanical changes in lower extremity vein grafts—distinct temporal phases of remodeling and wall stiffness. J Vasc Surg 2006;44:740.
[42] Owens CD, Rybicki FJ, Wake N, et al. Early remodeling of lower extremity vein grafts: inflammation influences biomechanical adaptation. J Vasc Surg 2008;47:1235.

[43] Fillinger MF, Cronenwett JL, Besso S, Walsh DB, Zwolak RM. Vein adaptation to the hemodynamic environment of infrainguinal grafts. J Vasc Surg 1994;19:970; discussion 8–9.
[44] Shimizu T, Ito S, Kikuchi Y, et al. Arterial conduit shear stress following bypass grafting for intermediate coronary artery stenosis: a comparative study with saphenous vein grafts. Eur J Cardiothorac Surg 2004;25:578.
[45] Isobe N, Kaneko T, Taniguchi K, Oshima S. Comparison of the rheologic parameters in left internal thoracic artery grafts with those in saphenous vein grafts. Circ J 2005;69:700.
[46] Chan CY, Chen YS, Ma MC, Chen CF. Remodeling of experimental arteriovenous fistula with increased matrix metalloproteinase expression in rats. J Vasc Surg 2007;45:804.
[47] Chang CJ, Chen CC, Hsu LA, et al. Degradation of the internal elastic laminae in vein grafts of rats with aortocaval fistulae: potential impact on graft vasculopathy. Am J Pathol 2009;174:1837.
[48] Langille BL, O'Donnell F. Reductions in arterial diameter produced by chronic decreases in blood flow are endothelium-dependent. Science 1986;231:405.
[49] Feldman HI, Joffe M, Rosas SE, Burns JE, Knauss J, Brayman K. Predictors of successful arteriovenous fistula maturation. Am J Kidney Dis 2003;42:1000.
[50] Wong V, Ward R, Taylor J, Selvakumar S, How TV, Bakran A. Factors associated with early failure of arteriovenous fistulae for haemodialysis access. Eur J Vasc Endovasc Surg 1996;12:207.
[51] Schanzer A, Hevelone N, Owens CD, et al. Technical factors affecting autogenous vein graft failure: observations from a large multicenter trial. J Vasc Surg 2007;46:1180; discussion 90.
[52] Tomas JJ, Stark VE, Kim JL, et al. Beta-galactosidase-tagged adventitial myofibroblasts tracked to the neointima in healing rat vein grafts. J Vasc Res 2003;40:266.
[53] Lin SL, Chen HS, Huang CH, Yen TS. Predicting the outcome of hemodialysis arteriovenous fistulae using duplex ultrasonography. J Formos Med Assoc 1997;96:864.
[54] Lin SL, Huang CH, Chen HS, Hsu WA, Yen CJ, Yen TS. Effects of age and diabetes on blood flow rate and primary outcome of newly created hemodialysis arteriovenous fistulas. Am J Nephrol 1998;18:96.
[55] Nishioka T, Luo H, Berglund H, et al. Absence of focal compensatory enlargement or constriction in diseased human coronary saphenous vein bypass grafts. An intravascular ultrasound study. Circulation 1996;93:683.
[56] Lau GT, Ridley LJ, Bannon PG, et al. Lumen loss in the first year in saphenous vein grafts is predominantly a result of negative remodeling of the whole vessel rather than a result of changes in wall thickness. Circulation 2006;114(1 Suppl):I435.
[57] Owens CD, Ho KJ, Conte MS. Lower extremity vein graft failure: a translational approach. Vasc Med 2008;13:63.
[58] Nath KA, Kanakiriya SK, Grande JP, Croatt AJ, Katusic ZS. Increased venous proinflammatory gene expression and intimal hyperplasia in an aorto-caval fistula model in the rat. Am J Pathol 2003;162:2079.
[59] Lee T, Roy-Chaudhury P. Advances and new frontiers in the pathophysiology of venous neointimal hyperplasia and dialysis access stenosis. Adv Chronic Kidney Dis 2009;16:329.
[60] Misra S, Fu AA, Anderson JL, et al. The rat femoral arteriovenous fistula model: increased expression of matrix metalloproteinase-2 and -9 at the venous stenosis. J Vasc Interv Radiol 2008;19:587.
[61] Roy-Chaudhury P, Wang Y, Krishnamoorthy M, et al. Cellular phenotypes in human stenotic lesions from haemodialysis vascular access. Nephrol Dial Transplant 2009;24:2786.
[62] Shi Y, O'Brien JE Jr, Mannion JD, et al. Remodeling of autologous saphenous vein grafts. The role of perivascular myofibroblasts. Circulation 1997;95:2684.
[63] Kalra M, Miller VM. Early remodeling of saphenous vein grafts: proliferation, migration and apoptosis of adventitial and medial cells occur simultaneously with changes in graft diameter and blood flow. J Vasc Res 2000;37:576.
[64] Zhang WD, Bai HZ, Sawa Y, et al. Association of smooth muscle cell phenotypic modulation with extracellular matrix alterations during neointima formation in rabbit vein grafts. J Vasc Surg 1999;30:169.
[65] Borin TF, Miyakawa AA, Cardoso L, de Figueiredo Borges L, Goncalves GA, Krieger JE. Apoptosis, cell proliferation and modulation of cyclin-dependent kinase inhibitor p21(cip1) in vascular remodelling during vein arterialization in the rat. Int J Exp Pathol 2009;90:328.
[66] Mima A. Hemodialysis vascular access dysfunction: molecular mechanisms and treatment. Ther Apher Dial 2012;16:321.
[67] Caplice NM, Wang S, Tracz M, et al. Neoangiogenesis and the presence of progenitor cells in the venous limb of an arteriovenous fistula in the rat. Am J Physiol Renal Physiol 2007;293:F470.
[68] Zhang L, Freedman NJ, Brian L, Peppel K. Graft-extrinsic cells predominate in vein graft arterialization. Arterioscler Thromb Vasc Biol 2004;24:470.
[69] Xu Q, Zhang Z, Davison F, Hu Y. Circulating progenitor cells regenerate endothelium of vein graft atherosclerosis, which is diminished in ApoE-deficient mice. Circ Res 2003;93:e76.
[70] Diao Y, Guthrie S, Xia SL, et al. Long-term engraftment of bone marrow-derived cells in the intimal hyperplasia lesion of autologous vein grafts. Am J Pathol 2008;172:839.
[71] Westerband A, Crouse D, Richter LC, et al. Vein adaptation to arterialization in an experimental model. J Vasc Surg 2001;33:561.
[72] Jacot JG, Abdullah I, Belkin M, et al. Early adaptation of human lower extremity vein grafts: wall stiffness changes accompany geometric remodeling. J Vasc Surg 2004;39:547.
[73] Higuchi Y, Hirayama A, Shimizu M, Sakakibara T, Kodama K. Postoperative changes in angiographically normal saphenous vein coronary bypass grafts using intravascular ultrasound. Heart Vessels 2002;17:57.
[74] Schwartz LB, O'Donohoe MK, Purut CM, Mikat EM, Hagen PO, McCann RL. Myointimal thickening in experimental vein grafts is dependent on wall tension. J Vasc Surg 1992;15:176.
[75] Zilla P, Moodley L, Scherman J, et al. Remodeling leads to distinctly more intimal hyperplasia in coronary than in infrainguinal vein grafts. J Vasc Surg 2012;55:1734.
[76] Kullander K, Klein R. Mechanisms and functions of Eph and ephrin signalling. Nat Rev Mol Cell Biol 2002;3:475.
[77] Foo SS, Turner CJ, Adams S, et al. Ephrin-B2 controls cell motility and adhesion during blood-vessel-wall assembly. Cell 2006;124:161.
[78] Adams RH. Molecular control of arterial-venous blood vessel identity. J Anat 2003;202:105.
[79] Swift MR, Weinstein BM. Arterial-venous specification during development. Circ Res 2009;104:576.
[80] Kudo FA, Muto A, Maloney SP, et al. Venous identity is lost but arterial identity is not gained during vein graft adaptation. Arterioscler Thromb Vasc Biol 2007;27:1562.
[81] Conte MS. Molecular engineering of vein bypass grafts. J Vasc Surg 2007;45(Suppl A):A74.
[82] Rothuizen TC, Wong C, Quax PH, van Zonneveld AJ, Rabelink TJ, Rotmans JI. Arteriovenous access failure: more

than just intimal hyperplasia? Nephrol Dial Transplant 2013;28:1085.
[83] Zwolak RM, Adams MC, Clowes AW. Kinetics of vein graft hyperplasia: association with tangential stress. J Vasc Surg 1987;5:126.
[84] Dilley RJ, McGeachie JK, Prendergast FJ. A review of the histologic changes in vein-to-artery grafts, with particular reference to intimal hyperplasia. Arch Surg 1988;123:691.
[85] Croatt AJ, Grande JP, Hernandez MC, Ackerman AW, Katusic ZS, Nath KA. Characterization of a model of an arteriovenous fistula in the rat: the effect of L-NAME. Am J Pathol 2010;176:2530.
[86] Ohta S, Komori K, Yonemitsu Y, Onohara T, Matsumoto T, Sugimachi K. Intraluminal gene transfer of endothelial cell-nitric oxide synthase suppresses intimal hyperplasia of vein grafts in cholesterol-fed rabbit: a limited biological effect as a result of the loss of medial smooth muscle cells. Surgery 2002;131:644.
[87] Wu J, Wadsworth RM, Kennedy S. Inhibition of inducible nitric oxide synthase promotes vein graft neoadventitial inflammation and remodelling. J Vasc Res 2011;48:141.
[88] Meng QH, Irvine S, Tagalakis AD, McAnulty RJ, McEwan JR, Hart SL. Inhibition of neointimal hyperplasia in a rabbit vein graft model following non-viral transfection with human iNOS cDNA. Gene Ther 2013;20:979.
[89] Weiss MF, Scivittaro V, Anderson JM. Oxidative stress and increased expression of growth factors in lesions of failed hemodialysis access. Am J Kidney Dis 2001;37:970.
[90] Jones GT, van Rij AM, Packer SG, Walker RJ, Stehbens WE. Venous endothelial changes in therapeutic arteriovenous fistulae. Atherosclerosis 1998;137:149.
[91] Jeremy JY, Shukla N, Angelini GD, Wan S. Endothelin-1 (ET-1) and vein graft failure and the therapeutic potential of ET-1 receptor antagonists. Pharmacol Res 2011;63:483.
[92] Wan S, Yim AP, Johnson JL, et al. The endothelin 1A receptor antagonist BSF 302146 is a potent inhibitor of neointimal and medial thickening in porcine saphenous vein-carotid artery interposition grafts. The J Thorac Cardiovasc Surg 2004;127:1317.
[93] Chang CJ, Ko YS, Ko PJ, et al. Thrombosed arteriovenous fistula for hemodialysis access is characterized by a marked inflammatory activity. Kidney Int 2005;68:1312.
[94] Pascarella L, Lulic D, Penn AH, et al. Mechanisms in experimental venous valve failure and their modification by Daflon 500 mg. Eur J Vasc Endovasc Surg 2008;35:102.
[95] De Marchi S, Falleti E, Giacomello R, et al. Risk factors for vascular disease and arteriovenous fistula dysfunction in hemodialysis patients. J Am Soc Nephrol 1996;7:1169.
[96] Kaygin MA, Halici U, Aydin A, et al. The relationship between arteriovenous fistula success and inflammation. Ren Fail 2013;35:1085.
[97] Tsapenko MV, d'Uscio LV, Grande JP, et al. Increased production of superoxide anion contributes to dysfunction of the arteriovenous fistula. Am J Physiol Renal Physiol 2012; 303:F1601.
[98] Lin CC, Yang WC, Lin SJ, et al. Length polymorphism in heme oxygenase-1 is associated with arteriovenous fistula patency in hemodialysis patients. Kidney Int 2006; 69:165.
[99] Juncos JP, Tracz MJ, Croatt AJ, et al. Genetic deficiency of heme oxygenase-1 impairs functionality and form of an arteriovenous fistula in the mouse. Kidney Int 2008;74: 47.
[100] Faries PL, Marin ML, Veith FJ, et al. Immunolocalization and temporal distribution of cytokine expression during the development of vein graft intimal hyperplasia in an experimental model. J Vasc Surg 1996;24:463.
[101] Nguyen BT, Yu P, Tao M, Hao S, Jiang T, Ozaki CK. Perivascular innate immune events modulate early murine vein graft adaptations. J Vasc Surg 2013;57:486.
[102] Sharony R, Pintucci G, Saunders PC, et al. Matrix metalloproteinase expression in vein grafts: role of inflammatory mediators and extracellular signal-regulated kinases-1 and -2. Am J Physiol Heart Circ Physiol 2006;290: H1651.
[103] Jiang Z, Berceli SA, Pfahnl CL, et al. Wall shear modulation of cytokines in early vein grafts. J Vasc Surg 2004;40:345.
[104] Kauhanen P, Siren V, Carpen O, Vaheri A, Lepantalo M, Lassila R. Plasminogen activator inhibitor-1 in neointima of vein grafts: its role in reduced fibrinolytic potential and graft failure. Circulation 1997;96:1783.
[105] Yet SF, Layne MD, Liu X, et al. Absence of heme oxygenase-1 exacerbates atherosclerotic lesion formation and vascular remodeling. FASEB J 2003;17:1759.
[106] West N, Guzik T, Black E, Channon K. Enhanced superoxide production in experimental venous bypass graft intimal hyperplasia: role of NAD(P)H oxidase. Arterioscler Thromb Vasc Biol 2001;21:189.
[107] Castier Y, Brandes RP, Leseche G, Tedgui A, Lehoux S. p47phox-dependent NADPH oxidase regulates flow-induced vascular remodeling. Circ Res 2005;97:533.
[108] Hagen PO, Davies MG, Schuman RW, Murray JJ. Reduction of vein graft intimal hyperplasia by ex vivo treatment with desferrioxamine manganese. J Vasc Res 1992;29:405.
[109] Hattori K, Yamanouchi D, Banno H, et al. Celiprolol reduces the intimal thickening of autogenous vein grafts via an enhancement of nitric oxide function through an inhibition of superoxide production. J Vasc Surg 2007;46:116.
[110] Kodama A, Komori K, Hattori K, Yamanouchi D, Kajikuri J, Itoh T. Sarpogrelate hydrochloride reduced intimal hyperplasia in experimental rabbit vein graft. J Vasc Surg 2009;49:1272.
[111] Huynh TT, Davies MG, Trovato MJ, Barber L, Safi HJ, Hagen PO. Reduction of lipid peroxidation with intraoperative superoxide dismutase treatment decreases intimal hyperplasia in experimental vein grafts. J Surg Res 1999;84:223.
[112] Lee ES, Shen Q, Pitts RL, et al. Serum metalloproteinases MMP-2, MMP-9, and metalloproteinase tissue inhibitors in patients are associated with arteriovenous fistula maturation. J Vasc Surg 2011;54:454; discussion 9–60.
[113] Southgate KM, Mehta D, Izzat MB, Newby AC, Angelini GD. Increased secretion of basement membrane-degrading metalloproteinases in pig saphenous vein into carotid artery interposition grafts. Arterioscler Thromb Vasc Biol 1999;19:1640.
[114] Lin CC, Yang WC, Chung MY, Lee PC. Functional polymorphisms in matrix metalloproteinases-1, -3, -9 are associated with arteriovenous fistula patency in hemodialysis patients. Clin J Am Soc Nephrol 2010;5:1805.
[115] Misra S, Shergill U, Yang B, Janardhanan R, Misra KD. Increased expression of HIF-1alpha, VEGF-A and its receptors, MMP-2, TIMP-1, and ADAMTS-1 at the venous stenosis of arteriovenous fistula in a mouse model with renal insufficiency. J Vasc Interv Radiol 2010;21:1255.
[116] Jiang Z, Tao M, Omalley KA, Wang D, Ozaki CK, Berceli SA. Established neointimal hyperplasia in vein grafts expands via TGF-beta-mediated progressive fibrosis. Am J Physiol Heart Circ Physiol 2009;297:H1200.
[117] George SJ, Zaltsman AB, Newby AC. Surgical preparative injury and neointima formation increase MMP-9 expression and MMP-2 activation in human saphenous vein. Cardiovasc Res 1997;33:447.
[118] O'Blenes SB, Zaidi SH, Cheah AY, McIntyre B, Kaneda Y, Rabinovitch M. Gene transfer of the serine elastase inhibitor

elafin protects against vein graft degeneration. Circulation 2000;102(19 Suppl 3):III289.
[119] Sun DX, Liu Z, Tan XD, Cui DX, Wang BS, Dai XW. Nanoparticle-mediated local delivery of an antisense TGF-beta1 construct inhibits intimal hyperplasia in autogenous vein grafts in rats. PLoS One 2012;7:e41857.
[120] George SJ, Wan S, Hu J, MacDonald R, Johnson JL, Baker AH. Sustained reduction of vein graft neointima formation by ex vivo TIMP-3 gene therapy. Circulation 2011;124(11 Suppl): S135.
[121] Heine GH, Ulrich C, Sester U, Sester M, Kohler H, Girndt M. Transforming growth factor beta1 genotype polymorphisms determine AV fistula patency in hemodialysis patients. Kidney Int 2003;64:1101.
[122] Wolff RA, Ryomoto M, Stark VE, et al. Antisense to transforming growth factor-beta1 messenger RNA reduces vein graft intimal hyperplasia and monocyte chemotactic protein 1. J Vasc Surg 2005;41:498.
[123] Ikegaya N, Yamamoto T, Takeshita A, et al. Elevated erythropoietin receptor and transforming growth factor-beta1 expression in stenotic arteriovenous fistulae used for hemodialysis. J Am Soc Nephrol 2000;11:928.
[124] Stracke S, Konner K, Kostlin I, et al. Increased expression of TGF-beta1 and IGF-I in inflammatory stenotic lesions of hemodialysis fistulas. Kidney Int 2002;61:1011.
[125] You WJ, Xiao MD, Yuan ZX. Significance of changes in transforming growth factor-beta mRNA levels in autogenous vein grafts. Chin Med J (Engl) 2004;117:1060.
[126] Zhang J, Silva T, Yarovinsky T, et al. VEGF blockade inhibits lymphocyte recruitment and ameliorates immune-mediated vascular remodeling. Circ Res 2010;107: 408.
[127] Yang B, Janardhanan R, Vohra P, et al. Adventitial transduction of lentivirus-shRNA-VEGF-A in arteriovenous fistula reduces venous stenosis formation. Kidney Int 2013; 85:289.
[128] Jadlowiec CC, Feigel A, Yang C, et al. Reduced adult endothelial cell EphB4 function promotes venous remodeling. Am J Physiol Cell Physiol 2013;304:C627.
[129] Hu Y, Zou Y, Dietrich H, Wick G, Xu Q. Inhibition of neointima hyperplasia of mouse vein grafts by locally applied suramin. Circulation 1999;100:861.
[130] Cheng J, Du J. Mechanical stretch simulates proliferation of venous smooth muscle cells through activation of the insulin-like growth factor-1 receptor. Arterioscler Thromb Vasc Biol 2007;27:1744.
[131] Luo Z, Asahara T, Tsurumi Y, Isner JM, Symes JF. Reduction of vein graft intimal hyperplasia and preservation of endothelium-dependent relaxation by topical vascular endothelial growth factor. J Vasc Surg 1998;27:167.
[132] Stark VK, Hoch JR, Warner TF, Hullett DA. Monocyte chemotactic protein-1 expression is associated with the development of vein graft intimal hyperplasia. Arterioscler Thromb Vasc Biol 1997;17:1614.
[133] Schepers A, Eefting D, Bonta PI, et al. Anti-MCP-1 gene therapy inhibits vascular smooth muscle cells proliferation and attenuates vein graft thickening both in vitro and in vivo. Arterioscler Thromb Vasc Biol 2006;26:2063.
[134] Shuhaiber JH, Evans AN, Massad MG, Geha AS. Mechanisms and future directions for prevention of vein graft failure in coronary bypass surgery. Eur J Cardiothorac Surg 2002; 22:387.
[135] Nath KA, Grande JP, Kang L, et al. β-Catenin is markedly induced in a murine model of an arteriovenous fistula: the effect of metalloproteinase inhibition. Am J Physiol Renal Physiol 2010;299:F1270.
[136] Zou Y, Hu Y, Mayr M, Dietrich H, Wick G, Xu Q. Reduced neointima hyperplasia of vein bypass grafts in intercellular adhesion molecule-1-deficient mice. Circ Res 2000;86:434.
[137] Yerdel MA, Kesenci M, Yazicioglu KM, Doseyen Z, Turkcapar AG, Anadol E. Effect of haemodynamic variables on surgically created arteriovenous fistula flow. Nephrol Dial Transplant 1997;12:1684.
[138] Saucy F, Haesler E, Haller C, Deglise S, Teta D, Corpataux JM. Is intra-operative blood flow predictive for early failure of radiocephalic arteriovenous fistula? Nephrol Dial Transplant 2010;25:862.
[139] Owens CD, Wake N, Conte MS, Gerhard-Herman M, Beckman JA. In vivo human lower extremity saphenous vein bypass grafts manifest flow mediated vasodilation. J Vasc Surg 2009;50:1063.
[140] Greenfield JC Jr, Rembert JC, Young WG Jr, Oldham HN Jr, Alexander JA, Sabiston DC Jr. Studies of blood flow in aorta-to-coronary venous bypass grafts in man. J Clin Invest 1972; 51:2724.
[141] Gurne O, Chenu P, Buche M, et al. Adaptive mechanisms of arterial and venous coronary bypass grafts to an increase in flow demand. Heart 1999;82:336.
[142] Walpoth BH, Schmid M, Schwab A, et al. Vascular adaptation of the internal thoracic artery graft early and late after bypass surgery. J Thorac Cardiovasc Surg 2008;136:876.