Published in final edited form as:

Adv Chronic Kidney Dis. 2009 September ; 16(5): 329–338. doi:10.1053/j.ackd.2009.06.009.

Advances and New Frontiers in the Pathophysiology of Venous Neointimal Hyperplasia and Dialysis Access Stenosis

Timmy Lee^{1,2,3} and Prabir Roy-Chaudhury^{1,2,3}

¹Department of Internal Medicine and Division of Nephrology and Hypertension, Cincinnati, OH

²University of Cincinnati, Cincinnati Dialysis Access Program, Cincinnati, OH

³Cincinnati VA Medical Center, Cincinnati, OH

Abstract

Hemodialysis vascular access dysfunction is a major cause of morbidity and mortality in hemodialysis patients. The most common cause of this vascular access dysfunction is venous stenosis as a result of venous neointimal hyperplasia within the peri-anastomotic region (AV fistula) or at the graft-vein anastomosis (PTFE grafts). There have been few effective treatments to-date for venous neointimal hyperplasia in part because of the poor understanding of the pathogenesis of venous neointimal hyperplasia. Therefore, this article will (1) describe the pathology of hemodialysis access stenosis in AV fistulas and grafts, (2) review and describe both current and novel concepts in the pathogenesis of neointimal hyperplasia formation, (3) discuss current and future novel therapies for treating venous neointimal hyperplasia, and (4) suggest future research areas in the field of hemodialysis vascular access dysfunction.

Introduction

Successful dialysis treatments require thrice weekly access to a patient's bloodstream; thus, the vascular access is the *lifeline* for the hemodialysis patient. Vascular access dysfunction, however, remains a major cause of morbidity and hospitalizations at a total cost of over \$1 billion U.S. dollars annually (1). Venous stenosis at the arteriovenous (AV) (Figure 1) or graft-vein anastomosis, leading to thrombosis, is the primary cause of vascular access failure. The histology of this venous stenosis has been well characterized as aggressive neointimal hyperplasia in both AV grafts and fistulas (2–4). However, there have been few effective therapeutic interventions to treat vascular access stenosis largely because of the lack of understanding of the cellular and molecular mechanisms that lead to development of neointimal hyperplasia in chronic kidney disease (CKD) and hemodialysis patients.

© 2009 The National Kidney Foundation, Inc. Published by Elsevier Inc. All rights reserved.

Address for correspondence: Timmy Lee, M.D., M.S.P.H., F.A.C.P., Assistant Professor of Clinical Medicine, Department of Internal Medicine, Division of Nephrology and Hypertension, University of Cincinnati, 231 Albert Sabin Way, M.L.0585, Cincinnati, OH, 45267-0585, timmy.lee@uc.edu, Phone: 513-558-4782, Fax: 513-558-4309.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial Disclosure: Dr. Lee has no financial disclosures. Dr. Roy-Chaudhury is on the advisory board for Pervasis Therapeutics, Inc. and Proteon Therapeutics, a consultant for Angiotech, and receives research support from Mercator MedSystems, Inc. through NIH 1R43DK077552-01A1.

Pathology of Hemodialysis Vascular Access Stenosis

Venous stenosis in both AV grafts and fistulas is primarily due to venous neointimal hyperplasia (Figure 2). In AV grafts, venous stenosis occurs most commonly at the graft-vein and juxta-anastomotic vein segments, although recent data suggests that stenosis at the graft-artery anastomosis occurs more frequently than previously thought (5). Venous stenosis in AV grafts most frequently arises from progressive neointimal hyperplasia, characterized by (a) the presence of alpha smooth muscle actin positive cells, (b) an abundance of extracellular matrix components, (c) angiogenesis (neovascularization) within the neointima and adventitia, (d) a macrophage layer lining the perigraft region and (e) an increased expression of mediators and cytokines such as TGF- β , PDGF, and endothelin within the media, neointima and adventitia (3,6).

While the neointimal hyperplasia in AV fistulas is similar to AV grafts in terms of pathogenesis, the stenosis that develops in AV fistulas is highly influenced by the vasodilatory capacity of the vein and surgical technique; and the location of stenoses differs by type of AV fistula placed. In AV fistulas the two main etiologies of failure are an initial failure to mature and a subsequent (late) venous stenosis. In both cases the site of stenosis depends on the type of AV fistula. Radiocephalic fistulas most commonly fail due to a stenosis within the peri-anastomotic region, while brachiocephalic fistulas often have narrowings at the juxta-anastomosis. More proximal stenoses can also occur in both cases especially in the case of brachiocephalic fistulas (cephalic arch stenosis) (7,8). Similar to AV grafts, venous neointimal hyperplasia in late AV fistula stenosis has been shown to be composed primarily of alpha smooth muscle actin positive cells, together with expression of mediators and cytokines such as TGF- β , PDGF, and endothelin within the media and intima of the vein (6,9). More recently, the lesion of early AV fistula failure (prior to initiation of dialysis) was also described by our group to have significant neointimal hyperplasia (Figure 2) (2).

Our group has been particularly interested in the exact cellular phenotype of the alpha smooth muscle actin positive cells that comprise the majority of the neointimal lesion (both in AV fistulas and AV grafts), and we have recently demonstrated that the vast majority of these cells express markers that characterize them as “myofibroblasts” or “synthetic” phenotype smooth muscle cells. Specifically, these cells express vimentin and alpha smooth muscle actin but not markers such as desmin and smoothelin (Figure 2)(9). It is not known whether these myofibroblasts are transformed fibroblasts migrating from the adventitia that develop a smooth muscle cell actin expression to become myofibroblasts or contractile smooth muscle cells migrating from the media which lose desmin expression and acquire vimentin expression. However, targeting of myofibroblasts, rather than fibroblasts or contractile smooth muscle cells, could serve as future novel therapies for hemodialysis access stenosis. Finally, it needs to be emphasized that lack of dilation of either the downstream or the proximal vein could also play an important role in the magnitude of final venous stenosis, particularly in the context of AV fistula non-maturation. Thus, even a small amount of neointimal hyperplasia in the presence of a lack of dilation could result in a tight stenosis. On the other hand, the presence of significant neointimal hyperplasia may not result in venous stenosis if it occurs in tandem with positive vascular remodeling or dilatation (Figure 3).

Pathogenetic Mechanisms of Neointimal Hyperplasia Formation in Hemodialysis Access Dysfunction

The pathogenesis of venous neointimal hyperplasia in AV graft stenosis and late AV fistula stenosis has been well described and is commonly divided into upstream and down events (10). Upstream events are characterized as the initial events and insults that are responsible for endothelial injury, which lead to a cascade of mediators (downstream events) that regulate

oxidative stress, endothelial dysfunction, and inflammation. Upstream events that are believed to contribute to the pathogenesis of neointimal hyperplasia include (10): (1) surgical trauma at the time of AV surgery, (2) hemodynamic shear stress at the vein-artery or vein-graft anastomosis, (3) bioincompatibility of the AV graft, (4) vessel injury due to dialysis needle punctures, (5) uremia resulting in endothelial dysfunction, and (6) repeated angioplasties causing further endothelial injury. Downstream events represent the response to endothelial (vascular) injury from the upstream events, resulting in the migration of smooth muscle cells from the media to the intima, eventually forming neointimal hyperplasia.

The pathogenesis of early AV fistula failure (non-maturation), in contrast remains poorly understood. At a histological level there is aggressive neointimal hyperplasia in both animal and human models (2,4,11,12), as early as 1 month in animals and 3 months in humans. The underlying factors (upstream events) which may contribute to early AV fistula failure, include (10,13): (1) small diameter sizes in the vein and artery, (2) surgical injury at the time AV fistula placement, (3) previous venipunctures, (4) development of accessory veins after surgery, (5) hemodynamic shear stress at the AV anastomosis, (6) a genetic predisposition to vascular constriction and neointimal hyperplasia, and (7) pre-existing venous neointimal hyperplasia.

The remainder of this section will focus on the downstream events and mechanisms responsible for neointimal hyperplasia such as oxidative stress, inflammation, endothelial dysfunction, and also alternative origins for neointimal cells.

Oxidative Stress

Many of the upstream mechanisms above (particularly hemodynamic shear stress and angioplasty injury) have been documented to result in an increase in the production of free radicals and its downstream products nitrotyrosine and peroxynitrate. The latter is a potent upregulator of the matrix metalloproteinases (MMPs) (14,15). MMPs are key enzymes that cause breakdown of extracellular matrix proteins such as collagen and elastin which facilitate the migration of vascular smooth muscle cells (VSMCs) in neointimal hyperplasia formation (16). Paradoxically, the same mechanisms have also been shown to facilitate a beneficial dilatation of the feeding artery (through a breakdown of the internal elastic laminae) in both rabbit and mouse AV fistula models (17,18). In experimental studies of AV grafts, Misra et al. have demonstrated a differential upregulation of MMP-2 at the graft-vein anastomosis, with early expression (9 days) in the adventitia and a later expression (19 days) within the intima, supporting the concept of cellular migration from the adventitia to the intima (see section on alternative mechanisms below) (19). They have also described linkages between hemodynamic shear stress and the expression of oxidative stress markers and cytokines in a pig model of AV graft stenosis (20). In clinical studies of stenotic and thrombotic AV grafts and AV fistulas requiring revision, Misra et al. have described an upregulation of MMPs (21), while Weiss et al. have documented the co-localization of oxidative stress markers with inflammatory cytokines such as transforming growth factor-beta (TGF- β), and platelet-derived growth factor (PDGF) (6), within the neointima of stenotic AV grafts and fistulas.

Heme-oxygenase-1 (HO-1) is an important enzyme pathway which has been shown to confer protective effects in the vascular endothelium and other organ systems through its anti-inflammatory, antioxidant, or antiproliferative actions and properties (22). At an experimental level, Juncos et al. have described an increase in both the magnitude of arteriovenous stenosis and the frequency of thrombosis following the creation of AV fistulas in HO-1 knock out mice (increased baseline oxidative stress) as compared to wild type animals (23). Furthermore, in the HO-1 knockout mice, there was significant induction of MMP-9 expression in the vein at 1 week compared to wild type mice, suggesting that MMP expression in vascular tissue and its deleterious effects with regard to promoting cellular migration may be in part inhibited by HO-1. In a recent clinical study, Lin et al demonstrated a higher frequency of AV fistula

failure in patients with heme oxygenase-1 (HO-1) gene polymorphisms with long GT repeats (resulting in increased oxidative stress) (24).

In addition, it is important to emphasize, that both CKD and ESRD are characterized by increased baseline levels of oxidative stress which has been implicated in the causation of endothelial dysfunction (see below) and vascular morbidity in these patients (25). Specifically, anti-oxidant therapies have been shown to decrease cardiovascular events in ESRD patients but not in the general population (26). Collectively, these studies demonstrate the urgent need to evaluate antioxidant therapies for the prevention of AV fistula and graft stenosis.

Inflammation

ESRD is associated with a chronic inflammatory state, characterized by the elevation of circulating cytokines (27). This inflammation has been proposed to play a role in the initiation and progression of atherosclerosis in ESRD, but may also play a significant role in vascular access stenosis. Support for this paradigm comes from recent work by Kokubo et al. in which uremic mice developed a 2–3 fold greater magnitude of neointimal hyperplasia at the arteriovenous anastomosis as compared to non-uremic animals in a mouse model of AV fistula stenosis (28).

At the clinical level, a recent study by Liu et al. have described significantly higher levels of inflammatory blood markers such as high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) in hemodialysis patients with AV fistula dysfunction as compared to both incident hemodialysis patients with newly placed AV fistulas and to prevalent hemodialysis patients with no AV fistula dysfunction (29). In addition, Stracke et al. have described possible linkages between the presence of inflammatory cells (macrophages and lymphocytes), cytokines such as TGF- β and insulin-like growth factor-1 (IGF-1) and the magnitude of neointimal hyperplasia and venous stenosis within stenotic AV fistulas (30).

Local bioincompatibility to PTFE graft material could also result in local inflammation. Thus, in vitro studies have demonstrated that conditioned media obtained after the interaction of peripheral blood mononuclear cells (PBMCs) with PTFE graft material resulted in a significant upregulation of smooth muscle cell proliferation as compared to control media. This proliferative response was attenuated by TNF- α inhibitors (31). In addition, we have described the presence of macrophages that line PTFE graft material in both experimental and clinical AV graft stenosis with co-expression of inflammatory cytokines such as basic fibroblast growth factor (bFGF) (9,32) These data suggest that inflammatory cytokines produced by macrophages are likely to play a role in the pathogenesis of neointimal hyperplasia.

Endothelial Dysfunction

The presence of uremia in hemodialysis patients has been shown to exacerbate endothelial dysfunction, possibly through the pathways of inflammation and oxidative stress described above (33,34). In the specific context of dialysis access stenosis, endothelial dysfunction is likely to be responsible for the pre-existing venous neointimal hyperplasia (35), medial hypertrophy (36) and radial artery intima-media thickening (37) that is present even before the creation of AV fistulas in uremic patients. Pre-existing arterial intima-media thickness (greater than 500 microns) has been correlated with future AV fistula dysfunction (38), but there are unfortunately no studies that have assessed the impact of pre-existing venous changes on AV fistula survival.

Asymmetrical dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide (NO) synthase and has been implicated as an important contributor to endothelial dysfunction (39)

(40). ADMA is not excreted in ESRD patients and its levels have been reported to be two to six times higher in this patient population as compared to non-uremic individuals (41). In a recent study by Wu et al, patients with elevated ADMA levels at the time of percutaneous transluminal angioplasty of an initial AV fistula stenosis had a significantly increased risk of a recurrent AV fistula stenosis (42).

Alternative Origins of Neointimal Cells

Although the traditional paradigm for the pathogenesis of neointimal hyperplasia stresses the migration of smooth muscle cells from the media to the intima, a number of groups have reported that following coronary angioplasty or saphenous vein bypass grafting there is also a migration of cells (fibroblasts) from the adventitia, through the media, and into the intima, where these cells transform into “myofibroblasts” (43–45).

More recently, a number of studies in AV grafts have supported the concept of a migration of adventitial cells into the intima where they contribute to final neointimal volume (46,47).

In addition, recent data from some (but not all) experimental AV fistula stenosis models have shown that smooth muscle cells in the neointima, may in part, originate from bone-marrow-derived cells that bind to the site of vascular injury and later differentiate into a smooth muscle cell phenotype in the neointima (48,49)(50).

From a therapeutic standpoint, it is likely that better information about the true source of neointimal cells (bone marrow versus adventitia versus media), will allow us to target the appropriate part of the vessel wall with future novel therapies (see below).

New Frontiers in Treatment and Research

The purpose of this last section is to (a) describe novel therapies for AV fistula and graft stenosis that are currently at the clinical trial stage and (b) explore future avenues for translational research in this area.

Novel Therapies

Two recent large multi-center studies sponsored by the National Institutes of Health (NIH) Dialysis Access Consortium (51,52) have provided us with important new information on the role of anti-platelet agents for the prevention of dialysis access stenosis. The NIH AV fistula study showed that clopidogrel significantly reduced the incidence of AV fistula thrombosis at 6 weeks but did not increase the proportion of AV fistulas that were suitable for hemodialysis between months 4 and 5 following the creation of the AV fistula. Recently, results from the NIH AV graft study has been published and reported a modest, but statistically significant, improvement in primary unassisted patency in the dipyridamole and aspirin group compared to placebo (53). The primary unassisted patency at 1 year was 23% in the placebo group and 28% in the dipyridamole and aspirin arm. This is the first therapy to date shown to be effective in treating dialysis access stenosis, but the results from the AV graft study should be interpreted cautiously as the benefit of long-term dipyridamole and aspirin therapy is unknown and formal cost-effective analyses have yet to be performed. However, these results should stimulate further research in evaluating anti-proliferative therapies on a basic and translational level and developing novel delivery systems of these anti-proliferative therapies.

Both studies, however, have drawn attention to the magnitude of the problem of dialysis access dysfunction in the United States. More importantly, the results from these large multi-center studies suggest that conventional systemic therapies, as described above, may not be successful for the treatment of the aggressive multi-factorial stenosis that characterizes dialysis access dysfunction. Specifically, we believe that local therapies may be the only way to successfully

modulate, in a beneficial manner, the multiple upstream and downstream players involved in the pathology and pathogenesis of dialysis access dysfunction (see above). The following paragraphs will review some of these local therapies with a special focus on local perivascular delivery with drugs, cells, genes and chemicals (Figure 4).

The rationale behind such local approaches are that (a) dialysis access grafts and fistulas could be the ideal clinical model for the use of perivascular therapies since these can be easily applied at the time of surgery (b) perivascular therapies preferentially target the “active” adventitia (see alternative origins section above) (c) studies have demonstrated that lipophilic molecules when placed over the adventitia rapidly diffuse through all the layers of the vessel wall (54) and (d) small amounts of otherwise toxic drugs can be safely delivered to the site of stenosis using the perivascular approach resulting in high local concentrations with minimal systemic toxicity.

- a. *Drug eluting perivascular wraps*: Experimental studies in our laboratory and those of others have previously demonstrated the efficacy of paclitaxel eluting wraps in large animal models of AV graft stenosis, probably as a result of its anti-proliferative effects (55,56). A large multi-center clinical study on the use of paclitaxel wraps, however, was recently suspended following a DSMB review, due to an imbalance in the incidence of infections in one of the arms (either control or treatment). An alternative approach is the use of sirolimus eluting COLL-R® wraps. An initial Phase II study demonstrated primary unassisted AV graft patencies of 75% and 38% at 1 and 2 years respectively with these wraps (57).
- b. *Endothelial cell loaded gel foam wraps*: The rationale behind the use of these wraps is that the endothelial cell (in addition to lining blood vessels) is also a “bioreactor” which produces a large number of beneficial mediators. Initial experimental studies have documented a beneficial effect of endothelial cell loaded gel-foam wraps in porcine models of AV fistula and graft stenosis (58,59). In addition, a recent Phase II study was able to demonstrate technical feasibility and safety in hemodialysis patients who received a “Vascugel®” wrap loaded with treated human aortic endothelial cells at the time of AV fistula or graft placement (60). A multi-center randomized-controlled study using the Vascugel® wraps in human AV grafts is currently being designed.
- c. *Vascular endothelial growth factor D (VEGF-D) gene therapy*: In animal models of angioplasty induced restenosis, the delivery of adenoviral particles encoding for vascular-endothelial growth factor C to the site of vascular injury has been shown to trigger the release nitric oxide and prostacyclin and reduce neointimal hyperplasia (61). Preliminary studies on the use of VEGF-D gene therapy (using a packaged adenoviral vector and a bio-degradable local drug delivery device) in patients receiving PTFE grafts, have been able to document technical feasibility and safety. A pivotal phase III study using this technology is scheduled to open enrollment during the second quarter of 2009.
- d. *Recombinant Elastase PRT-201*: PRT-201 is a recombinant elastase which has been shown to result in both arterial and venous dilation and an increase in AV fistula blood flow in a rabbit model (62). The potential clinical benefit of this approach is that it could enhance AV fistula maturation (through rapid vascular dilation) and so reduce dependency on tunneled dialysis catheters. A phase II study using this novel technology is currently underway in the United States.
- e. *Adventa® catheter*: All of the above technologies require that the identified intervention is applied at the time of AV fistula or AV graft placement. In order to deliver these therapies at a time point distant to surgery (since stenosis does not only

occur in the peri-operative period). Mercator Med has developed the Adventa® endovascular balloon catheter, which has a sheathed micro-needle that pierces the vessel wall when the balloon is inflated. This “perivascular” needle can then be used to deliver the drug, cell, gene or chemical of interest to the site of vascular injury at a time point that is distant from surgical placement of the AV fistula or graft (63).

We believe that all of the above are important studies in that they open the door for the development of novel local delivery systems (drugs, cells, genes and chemicals) that target the key downstream pathways for venous stenosis (oxidative stress, endothelial dysfunction, and neointimal hyperplasia) described in the pathogenesis section of this review.

Future Research Areas

Over the last decade we have learned that both AV fistula maturation failure and AV graft stenosis are characterized by venous neointimal hyperplasia in the setting of inappropriate vasodilatation. In order to advance the field further, we need to better understand and delineate both the clinical and experimental pathways that result in venous neointimal hyperplasia; using advanced technologies in cellular and molecular biology, bioengineering, genomics, proteomics and vascular imaging. In response to this unmet clinical need, the NIH has established the hemodialysis fistula maturation consortium (HFMC) which aims to identify specific clinical and biological predictors of AV fistula maturation.

Finally, in order to better understand the molecular basis for venous neointimal hyperplasia we need to develop a “back to basic science approach” with a focus on the genomic and proteomic analyses of stenotic tissue segments using both animal and human models. Few studies to date have been performed using the novel technologies described above in the setting of dialysis access stenosis (64,65).

Conclusion

The magnitude of dialysis access dysfunction is clearly evident, and will only become magnified in coming years as the prevalent dialysis population increases. Only by launching a “translational” research initiative (“from animal to human”) can recent advances in the understanding of the mechanisms of neointimal hyperplasia formation and vascular stenosis be translated to the development of novel systemic and locally-delivered therapies. Furthermore, AV fistulas and grafts may be the ideal clinical model to test and deliver novel therapies for neointimal hyperplasia, since this pathological entity, occurs not only in the setting of dialysis access dysfunction, but also in other critically important clinical settings such as coronary artery disease, peripheral vascular disease, and post-angioplasty restenosis.

Acknowledgements

Support: Dr Lee is supported by NIH 1K23DK083528-01. Dr. Roy-Chaudhury is supported by NIH 1U01DK082218-0, NIH 2R01EB004527-05, NIH 1R43DK077552-01A, and a VA Merit Review.

References

1. Feldman HI, Kobrin S, Wasserstein A. Hemodialysis vascular access morbidity. *J Am Soc Nephrol* 1996;7:523–535. [PubMed: 8724885]
2. Roy-Chaudhury P, Arend L, Zhang J, et al. Neointimal hyperplasia in early arteriovenous fistula failure. *Am J Kidney Dis* 2007;50:782–790. [PubMed: 17954291]
3. Roy-Chaudhury P, Kelly BS, Miller MA, et al. Venous neointimal hyperplasia in polytetrafluoroethylene dialysis grafts. *Kidney Int* 2001;59:2325–2334. [PubMed: 11380837]

4. Wang Y, Krishnamoorthy M, Banerjee R, et al. Venous stenosis in a pig arteriovenous fistula model--anatomy, mechanisms and cellular phenotypes. *Nephrol Dial Transplant* 2008;23:525–533. [PubMed: 18037619]
5. Asif A, Gadalean FN, Merrill D, et al. Inflow stenosis in arteriovenous fistulas and grafts: a multicenter, prospective study. *Kidney Int* 2005;67:1986–1992. [PubMed: 15840048]
6. 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;37:970–980. [PubMed: 11325679]
7. Beathard GA, Arnold P, Jackson J, Litchfield T. Aggressive treatment of early fistula failure. *Kidney Int* 2003;64:1487–1494. [PubMed: 12969170]
8. Turmel-Rodrigues L, Pengloan J, Baudin S, et al. Treatment of stenosis and thrombosis in haemodialysis fistulas and grafts by interventional radiology. *Nephrol Dial Transplant* 2000;15:2029–2036. [PubMed: 11096150]
9. Roy-Chaudhury P, Wang Y, Krishnamoorthy M, et al. Cellular phenotypes in human stenotic lesions from haemodialysis vascular access. *Nephrol Dial Transplant*. 2009(in press)
10. Roy-Chaudhury P, Sukhatme VP, Cheung AK. Hemodialysis vascular access dysfunction: a cellular and molecular viewpoint. *J Am Soc Nephrol* 2006;17:1112–1127. [PubMed: 16565259]
11. Lin T, Horsfield C, Robson MG. Arteriovenous fistula in the rat tail: a new model of hemodialysis access dysfunction. *Kidney Int* 2008;74:528–531. [PubMed: 18509320]
12. Chi-Jen C, Po-Jen K, Lung-An H, et al. Highly increased cell proliferation activity in the restenotic hemodialysis vascular access after percutaneous transluminal angioplasty: implication in prevention of restenosis. *American journal of kidney diseases: the official journal of the National Kidney Foundation* 2004;43:74–84. [PubMed: 14712430]
13. Roy-Chaudhury PRP, Asif A, Spergel L, Besarab A. Biology of Early AV Fistula Failure. *Journal of Nephrology*. 2006
14. Lehoux S. Redox signalling in vascular responses to shear and stretch. *Cardiovasc Res* 2006;71:269–279. [PubMed: 16780820]
15. Dixon BS. Why don't fistulas mature? *Kidney Int* 2006;70:1413–1422. [PubMed: 16883317]
16. Rotmans JJ, Velema E, Verhagen HJ, et al. Matrix metalloproteinase inhibition reduces intimal hyperplasia in a porcine arteriovenous-graft model. *J Vasc Surg* 2004;39:432–439. [PubMed: 14743149]
17. Castier Y, Brandes RP, Leseche G, Tedgui A, Lehoux S. p47phox-dependent NADPH oxidase regulates flow-induced vascular remodeling. *Circ Res* 2005;97:533–540. [PubMed: 16109921]
18. Tronc F, Mallat Z, Lehoux S, Wassef M, Esposito B, Tedgui A. Role of matrix metalloproteinases in blood flow-induced arterial enlargement: interaction with NO. *Arterioscler Thromb Vasc Biol* 2000;20:E120–E126. [PubMed: 11116076]
19. Misra S, Doherty MG, Woodrum D, et al. Adventitial remodeling with increased matrix metalloproteinase-2 activity in a porcine arteriovenous polytetrafluoroethylene grafts. *Kidney Int* 2005;68:2890–2900. [PubMed: 16316367]
20. Misra S, Fu AA, Puggioni A, et al. Increased shear stress with upregulation of VEGF-A and its receptors and MMP-2, MMP-9, and TIMP-1 in venous stenosis of hemodialysis grafts. *Am J Physiol Heart Circ Physiol* 2008;294:H2219–H2230. [PubMed: 18326810]
21. Misra S, Fu AA, Rajan DK, et al. Expression of hypoxia inducible factor-1 alpha, macrophage migration inhibition factor, matrix metalloproteinase-2 and -9, and their inhibitors in hemodialysis grafts and arteriovenous fistulas. *J Vasc Interv Radiol* 2008;19:252–259. [PubMed: 18341958]
22. Nath KA. Heme oxygenase-1: a provenance for cytoprotective pathways in the kidney and other tissues. *Kidney Int* 2006;70:432–443. [PubMed: 16775600]
23. 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;74:47–51. [PubMed: 18368029]
24. 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;69:165–172. [PubMed: 16374439]
25. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int* 2002;62:1524–1538. [PubMed: 12371953]

26. Tepel M, van der Giet M, Statz M, Jankowski J, Zidek W. The antioxidant acetylcysteine reduces cardiovascular events in patients with end-stage renal failure: a randomized, controlled trial. *Circulation* 2003;107:992–995. [PubMed: 12600912]
27. Sezer S, Ozdemir FN, Arat Z, Turan M, Haberal M. Triad of malnutrition, inflammation, and atherosclerosis in hemodialysis patients. *Nephron* 2002;91:456–462. [PubMed: 12119477]
28. Kokubo T, Ishikawa N, Uchida H, et al. CKD accelerates development of neointimal hyperplasia in arteriovenous fistulas. *J Am Soc Nephrol* 2009;20:1236–1245. [PubMed: 19423694]
29. Liu BC, Li L, Gao M, Wang YL, Yu JR. Microinflammation is involved in the dysfunction of arteriovenous fistula in patients with maintenance hemodialysis. *Chin Med J (Engl)* 2008;121:2157–2161. [PubMed: 19080177]
30. 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;61:1011–1019. [PubMed: 11849456]
31. Mattana J, Effiong C, Kapasi A, Singhal PC. Leukocyte-polytetrafluoroethylene interaction enhances proliferation of vascular smooth muscle cells via tumor necrosis factor-alpha secretion. *Kidney Int* 1997;52:1478–1485. [PubMed: 9407493]
32. Kelly BS, Heffelfinger SC, Whiting JF, et al. Aggressive venous neointimal hyperplasia in a pig model of arteriovenous graft stenosis. *Kidney Int* 2002;62:2272–2280. [PubMed: 12427156]
33. Bolton CH, Downs LG, Victory JG, et al. Endothelial dysfunction in chronic renal failure: roles of lipoprotein oxidation and pro-inflammatory cytokines. *Nephrol Dial Transplant* 2001;16:1189–1197. [PubMed: 11390719]
34. Ghiadoni L, Cupisti A, Huang Y, et al. Endothelial dysfunction and oxidative stress in chronic renal failure. *J Nephrol* 2004;17:512–519. [PubMed: 15372412]
35. Wali MA, Eid RA, Dewan M, Al-Homrany MA. Pre-existing histopathological changes in the cephalic vein of renal failure patients before arterio-venous fistula (AVF) construction. *Ann Thorac Cardiovasc Surg* 2006;12:341–348. [PubMed: 17095976]
36. Feinfeld DA, Batista R, Mir R, Babich D. Changes in venous histology in chronic hemodialysis patients. *Am J Kidney Dis* 1999;34:702–705. [PubMed: 10516352]
37. Ku YM, Kim YO, Kim JI, et al. Ultrasonographic measurement of intima-media thickness of radial artery in pre-dialysis uraemic patients: comparison with histological examination. *Nephrol Dial Transplant* 2006;21:715–720. [PubMed: 16249200]
38. Kim YO, Choi YJ, Kim JI, et al. The impact of intima-media thickness of radial artery on early failure of radiocephalic arteriovenous fistula in hemodialysis patients. *J Korean Med Sci* 2006;21:284–289. [PubMed: 16614515]
39. Zoccali C. Endothelial damage, asymmetric dimethylarginine and cardiovascular risk in end-stage renal disease. *Blood Purif* 2002;20:469–472. [PubMed: 12207095]
40. Kielstein JT, Zoccali C. Asymmetric dimethylarginine: a novel marker of risk and a potential target for therapy in chronic kidney disease. *Curr Opin Nephrol Hypertens* 2008;17:609–615. [PubMed: 18941355]
41. Cooke JP. Does ADMA cause endothelial dysfunction? *Arterioscler Thromb Vasc Biol* 2000;20:2032–2037. [PubMed: 10978245]
42. Wu CC, Wen SC, Yang CW, Pu SY, Tsai KC, Chen JW. Plasma ADMA predicts restenosis of arteriovenous fistula. *J Am Soc Nephrol* 2009;20:213–222. [PubMed: 19118151]
43. Scott NA, Cipolla GD, Ross CE, et al. Identification of a potential role for the adventitia in vascular lesion formation after balloon overstretch injury of porcine coronary arteries. *Circulation* 1996;93:2178–2187. [PubMed: 8925587]
44. Shi Y, O'Brien JE, Fard A, Mannion JD, Wang D, Zalewski A. Adventitial myofibroblasts contribute to neointimal formation in injured porcine coronary arteries. *Circulation* 1996;94:1655–1664. [PubMed: 8840858]
45. Shi Y, O'Brien JE Jr, Mannion JD, et al. Remodeling of autologous saphenous vein grafts. The role of perivascular myofibroblasts. *Circulation* 1997;95:2684–2693. [PubMed: 9193438]
46. Li L, Terry CM, Blumenthal DK, et al. Cellular and morphological changes during neointimal hyperplasia development in a porcine arteriovenous graft model. *Nephrol Dial Transplant* 2007;22:3139–3146. [PubMed: 17602194]

47. Roy-Chaudhury P, McKee L, Miller M, Reaves A, Armstrong J, Duncan H, Munda R, Kelly B, Heffelfinger S. Adventitial fibroblasts contribute to venous neointimal hyperplasia in PTFE grafts. *J Am Soc Nephrol* 2001;12:301A.[Abstract].
48. 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–F475. [PubMed: 17344190]
49. 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;172:839–848. [PubMed: 18276778]
50. Castier Y, Lehoux S, Hu Y, Foteinos G, Tedgui A, Xu Q. Characterization of neointima lesions associated with arteriovenous fistulas in a mouse model. *Kidney Int* 2006;70:315–320. [PubMed: 16760906]
51. 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;299:2164–2171. [PubMed: 18477783]
52. Dixon BS, Beck GJ, Dember LM, et al. Design of the Dialysis Access Consortium (DAC) Aggrenox Prevention Of Access Stenosis Trial. *Clin Trials* 2005;2:400–412. [PubMed: 16317809]
53. Dixon BS, Beck GJ, Vazquez MA, et al. Effect of dipyridamole plus aspirin on hemodialysis graft patency. *N Engl J Med* 2009;360:2191–2201. [PubMed: 19458364]
54. Creel CJ, Lovich MA, Edelman ER. Arterial paclitaxel distribution and deposition. *Circ Res* 2000;86:879–884. [PubMed: 10785510]
55. Kelly B, Melhem M, Zhang J, et al. Perivascular paclitaxel wraps block arteriovenous graft stenosis in a pig model. *Nephrol Dial Transplant* 2006;21:2425–2431. [PubMed: 16822794]
56. Kohler TR, Toleikis P, Gravett DM, Avelar RL. Inhibition of neointimal hyperplasia in a sheep model of dialysis access failure with the bioabsorbable Vascular Wrap Paclitaxel Eluting Mesh. *J Vasc Surg* 2007;45:1029–1038. [PubMed: 17466798]
57. Paulson WD, NK, Kipiani K, Beridze N, DeVita MV, Shenoy S, Iyer SS. Safety and Efficacy of Locally Eluted Sirolimus for Prolonging AV Graft Patency (PTFE Graft Plus Coll-R) First in Man Experience. 2008
58. Nugent HM, Groothuis A, Seifert P, et al. Perivascular endothelial implants inhibit intimal hyperplasia in a model of arteriovenous fistulae: a safety and efficacy study in the pig. *J Vasc Res* 2002;39:524–533. [PubMed: 12566978]
59. Nugent HM, Sjin RT, White D, et al. Adventitial endothelial implants reduce matrix metalloproteinase-2 expression and increase luminal diameter in porcine arteriovenous grafts. *J Vasc Surg* 2007;46:548–556. [PubMed: 17826244]
60. Lawson, JH.; MSC; Marc, Glickman; Earl, Schuman; A. Frederick, Schild; John, Ross; Scott, Berman; Prabir, Roy-Chaudhury. Safety of Vascugel Treatment after the Creation of Arteriovenous Access. Philadelphia: American Society of Nephrology; 2008.
61. Hiltunen MO, Laitinen M, Turunen MP, et al. Intravascular adenovirus-mediated VEGF-C gene transfer reduces neointima formation in balloon-denuded rabbit aorta. *Circulation* 2000;102:2262–2268. [PubMed: 11056103]
62. Burke, SK.; FNF; LaRochelle, Alan; Mendenhall, HV. Local Application of Recombinant Human Type I Pancreatic Elastase (PRT-201) to an Arteriovenous Fistula (AVF) Increases AVF Blood Flow in a Rabbit Model. Philadelphia: American Society of Nephrology; 2008.
63. Roy-Chaudhury P. for The Mercator Study Investigators Perivascular Dexamethasone for PTFE Graft Stenosis: The HAPPI (Hemodialysis Access Patency Extension with Percutaneous Transluminal Infusion of Dexamethasone) Study. *J Am Soc Nephrol* 2007;18:468A.
64. Croatt AJ, Juncos JP, Hernandez MC, et al. Upregulation of Inflammation-Related Genes and Neointima Formation in Arteriovenous Fistula (AVF) Model in the Rat (Abstract). *J Am Soc Nephrol* 2008;19:252A. [PubMed: 18094367]
65. Misra S, Fu AA, Puggioni A, et al. Proteomic profiling in early venous stenosis formation in a porcine model of hemodialysis graft. *J Vasc Interv Radiol* 2009;20:241–251. [PubMed: 19028119]

Fig 1. Perianastomotic stenosis in an AV Fistula

describes the classic picture of early AV fistula failure with two tight **venous** stenoses (lower black arrows) in the venous segment of an AV fistula. These lesions are responsible for a very significant morbidity and economic cost. White arrowhead points to the AV anastomosis (courtesy Dr Asif).

Fig 2. Venous neointimal hyperplasia

Figs 2a–d describe H and E (Fig 2a), SMA (Fig 2b), vimentin (Fig 2c) and desmin (Fig 2d) stains on sequential sections of the venous segment of an AV fistula with maturation failure. Note the very significant degree of neointimal hyperplasia (black double headed arrows in Figs 2a and 2b) with relatively less medial hypertrophy (white double headed arrows in Figs 2a and 2b). Note also that while most of the cells within the region of neointimal hyperplasia appear to be SMA +ve, vimentin +ve, desmin –ve myofibroblasts, there are also some SMA +ve, desmin +ve contractile smooth muscle cells present within the neointima (small black arrows in Fig 2d). +ve = positive; –ve = negative (Adapted from Roy-Chaudhury et al. *Am J Kidney Dis* 2008)

Fig 3. Vascular remodeling versus vessel wall thickening

The top panel in Fig 3 shows a marked increase in lumen size following creation of an AV fistula because of vascular dilatation, despite significant vessel wall thickening/neointimal hyperplasia. In marked contrast the bottom panel documents that even a small amount of vessel wall thickening/neointimal hyperplasia can result in a marked reduction of lumen size if this thickening is accompanied by negative vascular remodeling or vasoconstriction.

Fig 4. Novel local therapies for dialysis access stenosis

Fig 4a shows an endothelial cell loaded gel-foam wrap being placed around the graft-vein anastomosis and proximal venous segment. Fig 4b describes the placement of a paclitaxel eluting wrap around the graft-vein anastomosis. Fig 4c is a diagrammatic representation of the biodegradable reservoir that will be used for VEGF-D gene therapy. Fig 4d is a magnified view of the Adventa® catheter that can deliver therapies to the perivascular region through an endovascular approach.