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Hemodialysis Vascular Access Dysfunction

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1. Introduction

A successful functioning vascular access is the "lifeline" for a hemodialysis patient. Hemodialysis vascular access dysfunction is a major cause of morbidity and mortality in hemodialysis patients[1-3]. Improving vascular access outcomes remains an ongoing challenge for nephrologists, vascular access surgeons, and interventionists. In arteriovenous fistulas (AVF) and grafts (AVG), the most common cause of this vascular access dysfunction is venous stenosis as a result of neointimal hyperplasia within the peri-anastomotic region (AVF) or at the graft-vein anastomosis (AVG) [4,5]. 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. Central venous catheters (CVC) are prone to frequent thrombosis and infection and the treatment of catheter-related bacteremia (CRB) remains on ongoing debate [6-8]. Therefore, this review will: (1) describe the pathology and pathophysiology of hemodialysis access stenosis in AVFs and AVGs, (2) discuss the pathogenesis of CRB and catheter thrombosis (3) discuss current and future novel therapies for treating venous neointimal hyperplasia, (4) discuss current strategies to treat CRB and catheter thrombosis, and (5) suggest future research areas in the field of hemodialysis vascular access dysfunction.

1.1 Types of hemodialysis access

Successful hemodialysis treatment requires access to the bloodstream to deliver a high enough blood flow to achieve an adequate dialysis dose. There are three primary types of hemodialysis vascular access to achieve this goal: (1) arteriovenous fistula, (2) arteriovenous graft, and (3) tunneled central venous catheter. Each type of access has unique advantages and individual problems.

1.1.1 Arteriovenous fistula

AVFs are the preferred vascular access for hemodialysis patients, because once mature and functional, they require fewer interventions to maintain patency and develop fewer infections compared to AVGs [9-13]. However, AVFs have higher rates of nonmaturation and longer maturation times compared to AVGs, which may lead to prolonged periods of CVC dialysis [9,14,15]. Recent reports from the United States have shown that up to 60% of AVFs never mature adequately to be successfully cannulated for dialysis [16] compared to 20-25 years ago where the nonmaturation rates in AVFs was approximately 10% [12].

1.1.2 Arteriovenous graft

Arteriovenous grafts (made from polytetrafluoroethylene, a synthetic fluoropolymer of tetrafluoroethylene) are advantageous because of short maturation time and relative ease to cannulation compared to AVFs [12,17-19]. Until recently, AVGs were the most common access used in hemodialysis patients in the Unites States [20]. However, the main disadvantages of AVGs are development of recurrent venous stenosis, requiring frequent interventions to maintain patency, and graft infection [19,21-24].

1.1.3 Tunneled central venous catheter

Tunneled central venous catheters have the advantage of immediate use, multiple sites for insertion, and the ability to provide access for hemodialysis for a period of months, permitting time for AVF or AVG maturation, in patients who require immediate hemodialysis [19,25-28]. However, the main disadvantages are the high risks of morbidity and mortality caused by infection [7,29-33], catheter thrombosis [19,34-37], and central venous stenosis [37-39].

2. Epidemiology and clinical significance of hemodialysis vascular access dysfunction

2.1 Epidemiology of hemodialysis vascular access

Due to reduced AVF use and increased AVG (70% in 1993 [40]) and catheter use in the United States from the mid-1980's-1990's, the National Kidney Foundation in 1997, in an effort to improve vascular access outcomes, published the first Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines for vascular access to optimize the care of vascular access in hemodialysis patients using evidenced and opinion-based guidelines [41]. Since these initial clinical practice guidelines have been published, we have seen the creation of the Fistula First Breakthrough Initiative (FFBI) [42-45] and two more revised K/DOQI clinical practice guidelines and performance measures for vascular access [19,46], which have clearly impacted and improved hemodialysis vascular access management. The most recent report from the 2009 United States Renal Data System (USRDS) has showed an AVF prevalence of 50% [47], a marked improvement since 2004 (39% AVF prevalence), 2000 (30% AVF prevalence), and 1998 (26% AVF prevalence)[48] in the United States. In contrast, AVF prevalence in Europe and Japan, reported from the Dialysis Outcomes and Practice Patterns Study (DOPPS) has been historically much higher, ranging from 57-91% [20].

While the K/DOQI guidelines and FFBI have clearly played an instrumental role in meeting the initial target goal of 50% AVF prevalence (new goal 66% [19,42]), the prevalence of CVC use continues to remain between 20-30% in the United States [42]. Furthermore, this trend of increased catheter use has also been observed in other countries, such as Spain, France, Belgium, Germany, and Italy [20]. This is likely due to an increase in the number of AVFs that have failed to mature for dialysis use in recent years [14,16].

2.2 Clinical significance and economic implications of hemodialysis vascular access dysfunction

When patients develop vascular access dysfunction, due to an immature AVF or thrombosed AVF or AVG, they are often consigned to CVC use for prolonged periods. Because dialysis with a catheter is associated with increased morbidity and mortality [49-55], CVC use has significant clinical implications such as increased risk of bacteremia which has been reported to occur at a frequency ranging from 2.5 to 5.5 episodes per 1000-catheter

days [6,56], increased risk of 1-year mortality [49], and 60-70% higher risk of subsequent AVF failure [32,57]. The cost of treating one CVC-related bacteremia in the United States has been estimated to be as high as $45,000 per episode with an average of $22,000 per bacteremic episode [58].

3. Pathology and pathophysiologic mechanisms of hemodialysis vascular access dysfunction

3.1 Pathology of Hemodialysis Vascular Access Stenosis in AVF and AVG

Venous stenosis that occurs in both AVFs and AVGs is primarily due to neointimal hyperplasia. Venous stenosis in AVGs most frequently arises from the development of aggressive neointimal hyperplasia, characterized by (a) the presence of alpha smooth muscle actin positive cells myofibroblasts, and microvessels within the neointima, (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 inflammatory cytokines such as TGF-β, PDGF, and endothelin within the media, neointima and adventitia [59-64].

While the neointimal hyperplasia in AVFs is similar to AVGs in regards to pathogenesis, the venous stenosis that develops in AVFs is highly influenced by the capacity of the vein to vasodilitate and vascular injury from surgical technique [65]. In AVFs the two main etiologies of failure are an initial failure to mature (nonmaturation) and a subsequent (late) venous stenosis [4]. Similar to AVGs, venous neointimal hyperplasia in late AVF 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 [60,65]. However, recently, the lesion of AVF nonmaturation at 6 weeks after AVF creation has also been described to have significant neointimal hyperplasia [66].

3.2 Pathophysiologic mechanisms of neointimal hyperplasia formation in hemodialysis access dysfunction

The pathogenesis of venous neointimal hyperplasia in AVG stenosis and late AVF stenosis has been well described and is commonly divided into upstream and downstream events[4]. Upstream events are characterized as the initial events and insults that are responsible for endothelial and smooth muscle cell injury, which leads to a cascade of mediators (downstream events) that regulate oxidative stress, endothelial dysfunction, and inflammation (eventually resulting in venous neointimal hyperplasia). Upstream events that are believed to contribute to the pathogenesis of neointimal hyperplasia include [4,62,67-70]: (1) surgical trauma at the time of AV surgery, (2) hemodynamic shear stress at the vein-artery or vein-graft anastomosis, (3) bioincompatability of the AVG, (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 and eventually the development of neointimal hyperplasia [65].

The pathogenesis in AVFs that fail to mature (early failure) for dialysis, in contrast to AVG and late AVF failure, remains poorly understood. At a histological level early AVF failure is also characterized by aggressive neointimal hyperplasia in both animal and human models, seen as early as 1 month in animals [63,71] and 3 months in humans [64,66]. The underlying factors

(upstream events) which may contribute to early AVF failure, include [4,72-81]: (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 subsequent sections will focus on the downstream events and three main mechanisms responsible for neointimal hyperplasia such as oxidative stress, inflammation, endothelial dysfunction, and alternative origins of neointimal-derived cells.

3.2.1 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 latter (peroxynitrate). The latter is a potent upregulator of the matrix metalloproteinases (MMPs) [82,83]. 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 [84]. MMPs, paradoxically, have also been shown to facilitate a beneficial dilatation of the feeding artery (through degradation of the internal elastic laminae) in both rabbit and mouse AVF models [82,85]. Experimental studies of AVGs 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 [86]. Furthermore, linkages between hemodynamic shear stress and the expression of oxidative stress markers and cytokines have also been described in a porcine model of AVG stenosis [87]. Clinical studies of stenotic and thrombotic AVGs and AVFs have also demonstrated an upregulation of MMPs [88], and 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), within the neointima of both stenotic AVGs and AVFs [60].
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 [89]. Experimental studies in AVFs have described an increase in both the magnitude of arteriovenous stenosis and the frequency of thrombosis following the creation of AVFs in HO-1 knock out mice (increased baseline oxidative stress) as compared to wild type animals [90]. 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 in part be inhibited by HO-1. Clinical studies have demonstrated a higher frequency of AVF failure in patients with heme-oxygenase-1 (HO-1) gene polymorphisms with long GT repeats (resulting in increased oxidative stress) [73].

3.2.2 Inflammation

ESRD is associated with a chronic inflammatory state, characterized by the elevation of circulating cytokines and chemokines [91]. This inflammation has been proposed to play an important 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 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 AVF stenosis [92], and a recent study which showed marked upregulation of monocyte chemoattractant protein-1 (MCP-1) in the venous segment of AVF compared to rats deficient in the MCP-1 gene [93].

In clinical studies, possible linkages have described the presence of inflammatory cells (macrophages and lymphocytes), cytokines such as TGF-ß and insulin-like growth factor-1 (IGF-1) and the magnitude of neointimal hyperplasia and venous stenosis within stenotic AVFs [94].

Local bioincompatability to synthetic polytetrafluoroethylene (PTFE) material in AVGs could also result in local inflammation [95]. 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 [96]. This proliferative response has been shown to be attenuated by tumor necrosis-alpha (TNF-α) inhibitors [96]. Furthermore, the presence of macrophages that line PTFE graft material has been described in both experimental and clinical AVG stenosis with co-expression of inflammatory cytokines such as basic fibroblast growth factor (bFGF) [61,97].

3.2.3 Endothelial dysfunction

An intact and functional endothelium is essential for the vein to properly respond to acute changes in blood flow that occurs after creation of AVFs and AVGs [98]. Nitric oxide (NO) is an important mediator responsible for these transformations [99,100]. 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 [101,102]. In the specific context of vascular access stenosis, endothelial dysfunction is likely to be responsible for the development of pre-existing venous neointimal hyperplasia [77-81], medial hypertrophy [77,81] and radial artery intima-media thickening [103-105] that is present even before the creation of AVFs in uremic patients. Pre-existing arterial intima-media thickness has been correlated with future AVF dysfunction [103]. Recently, pre-existing venous neointimal hyperplasia has been linked to poor AVF maturation in a small clinical study [77].

Asymmetrical dimethylarginine (ADMA) is an endogenous inhibitor of NO synthase and has been implicated as an important contributor to endothelial dysfunction in ESRD patients [106]. 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 [107]. In a recent clinical study in AVFs, patients with elevated ADMA levels at the time of percutaneous transluminal angioplasty of an initial AVF stenosis had a significantly increased risk of a recurrent AVF stenosis [108].

3.2.4 Alternative origins of neointimal cells

Although the traditional paradigm for the pathogenesis of neointimal hyperplasia has emphasized the migration of smooth muscle cells from the media to the intima, where they proliferate and contribute to the final volume of neointimal hyperplasia, a number of studies 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" [109-111]. In dialysis access, a number

of recent studies in AVGs have supported the concept of a migration of adventitial cells into the intima where they contribute to final neointimal volume [59,112]. In addition, recent data from several experimental AVF 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 [82,113,114]. From a therapeutic standpoint, it is likely that better information about the true source of neointimal cells will allow for the development of novel therapeutic interventions targeting specific cell types.

3.3 Hemodynamic and vascular remodeling in hemodialysis access dysfunction

A number of experimental studies have shown that turbulent, low flow, low fluid sheer stress are involved in neointimal hyperplasia development [115-119]. High sheer stress has been associated with vascular dilatation through inhibition of smooth muscle cell proliferation and high levels of nitric oxide release, whereas low sheer stress has been associated with smooth muscle cell proliferation and lack of vasodilatation [120-123]. Poor hemodynamic profiles could be a risk factor for neointimal hyperplasia development and poor venous dilatation, and the degree of luminal stenosis is dependent upon both the magnitude of neointimal hyperplasia and the capacity for vasodilatation or vasocontriction. Therefore, a significant amount of neointimal hyperplasia and medial hypertrophy may not result in luminal stenosis in the presence of adequate vasodilatation, while a small amount of neointimal hyperplasia, but with poor vasodilatation, may result in severe venous stenosis [4,124]. Unfortunately, the factors that are responsible for vascular remodeling are unknown, but adventitial angiogenesis and scar formation are hypothesized to play a significant role[125,126]. Thus, the ideal therapy for vascular stenosis would be an intervention that would prevent vascular constriction (adverse remodeling) and neointimal hyperplasia[4]

4. Central venous dialysis catheters

CVC dysfunction and related-infection remains a common cause of morbidity, mortality, and high economic costs in treating chronic hemodialysis patients. This section will provide a brief overview of catheter dysfunction and catheter-related infections.

4.1 Catheter dysfunction

Catheter dysfunction can occur immediately after placement or in a catheter which has been previously functioning without difficulties, and most commonly manifests with low catheter blood flows during dialysis or negative arterial pressures on the dialysis machine [6]. In more severe cases catheter thrombosis is characterized by the inability to aspirate blood from the dialysis port [6]. Catheter dysfunction which occurs immediately after placement is most likely due to placement problems [6].

Installation of a thrombolytic agent for 30 to 60 minutes is a treatment for catheter dysfunction, followed by a second installation if necessary [6]. Recently published studies have reported varied success rate when treating catheter dysfunction with thrombolytics, ranging anywhere between 60-95% [26,28,35,127,128]. When thrombolytic therapy is unsuccessful in providing adequate blood flow and adequate dialysis, despite repeated installations, then catheter exchange needs to be performed. The current K/DOQI guidelines recommends treatment with thrombolytic agents in all catheters with a persistently low blood flow rate (<300 ml/min) [19].

The current standard of care to prevent catheter thrombosis is installation of an anticoagulant in both dialysis ports at the completion of each dialysis session. In the United States, heparin is most commonly used, while in Europe citrate is the more common anticoagulant [6]. The studies to-date have shown similar efficacy when comparing citrate to heparin for prophylaxis of catheter thrombosis, but with fewer complications of systemic bleeding with citrate [129-132]. A recent multicenter, randomized-controlled trial has reported that use of a thrombolytic, tissue plasminogen activator as a locking solution compared to heparin had reduced incidence of catheter dysfunction [34].

4.2 Catheter-related bacteremia

Currently, a precise definition for diagnosis catheter-related bacteremia is lacking. More rigorous definitions require a positive blood culture obtained from the catheter and a peripheral vein with the quantitative colony count being at minimum four-fold higher from the catheter sample [133]. However, recently, the Infectious Disease Society of America has recognized the challenges in obtaining peripheral blood cultures from hemodialysis patients (e.g. priority for preserving veins and difficult cannulations) and has considered a definition of "possible" catheter-related bacteremia as positive blood culture obtained from the catheter in a symptomatic patient [134].

The two main pathways where organisms can gain entry into the blood stream to initiate catheter-related bacteremia are intraluminal and extraluminal [135]. Organisms gain entrance through the bloodstream extraluminally through contact between the skin surface organisms and the external surface of the catheter at the time of catheter placement or following catheter placement before healing of the exit site or endothelialization of the subcutaneous tunnel [7]. Subsequently, the organisms colonize or migrate through the intracutaneous exterior tract of the catheter to the tip, allowing for hematagenous dispersion of the organisms and leading to catheter-related bacteremia [7]. Intraluminal-derived infections results from the transfer of organisms from hand contact with the catheter, leading to contamination of the internal catheter surfaces [7]. Infection from the extraluminal pathway most commonly occurs immediately after catheter insertion, while infections from the intraluminal pathway occurs throughout the life of the catheter [7]. Irrespective of the route of bacterial entry, the bacteria will either adhere to the CVC or become incorporated into a fibrin sheath. Adherence of the bacterial organisms to the CVC initiates a common pathway of biofilm production. A mature biofilm is a self-sustaining colony of microorganism, guarded by an exopolysaccharide matrix, that is stimulated and secreted by the organism and very difficult to eradicate [7,136-140].

Catheter-related bacteremia can result in devastating complications such as endocarditis, osteomyelitis, thrombophlebitis, septic arthritis, spinal epidural abscess, and large atrial thrombi [30,31,141-149]. The majority of isolated organisms from catheter-related bacteremia are gram-positive organisms (52-84%) with *Staph Aureus* responsible for the majority of these organisms [7,30,31,143,150,151]. Gram-negative are isolated in 27-36% of episodes and fungal isolated are relatively uncommon (<10%) [141-143,149,152]. Therefore, it is important to identify catheter-related bacteremia early so treatment can be initiated immediately.

4.2.1 Treatment of catheter-related bacteremia

Initial empiric antibiotic treatment should include broad-spectrum coverage for gram-positive and gram-negative organisms using knowledge of the common organisms and

sensitivity patterns that are grown at the dialysis center. Due to the high prevalence of methicillin-resistant *Staph Aureus* (MRSA), empiric therapy should include coverage for MRSA. When the specific organism and antibiotic sensitivities are identified, it is important to narrow the antibiotic therapy to prevent the development of drug resistant organisms. While the exact duration of antibiotic treatment for catheter-related bacteremia is uncertain, the Infectious Disease society of America recommends a 2 week course of antibiotics [153], while the K/DOQI guidelines recommends a 3 week course of antibiotics [19]. Other therapies, which have been used in conjunction with systemic antibiotics, to treat catheter-related bacteremia are antibiotic catheter locks. A number of studies have shown that antibiotic locks (which may treat the biofilm layer) used in conjunction with systemic antibiotics, in tunneled dialysis catheters, have documented a 70% cure rate [30,145,154-156].
Recent studies have evaluated pharmacologic therapies to prevent catheter-related bacteremia. Routine application of topical antibiotic ointments at the CVC exit such as mupirocin, povidine-iodine, and polysporin triple ointment has been associated with a 73-93% reduction in the risk of catheter-related bacteremia [7,151,157-159]. Prophylactic antibiotic catheter locks have also recently been evaluated. A marked reduction in catheter-related bacteremia has been reported, ranging from 51-99%, with use of a prophylactic antibiotic catheter locking solution [7,160-164]. However, of concern, a recent study has shown emergence of gentamicin-resistant organisms after 6 months when using a gentamicin-heparin prophylactic catheter lock [165].
The above strategies for treatment of catheter-related bacteremia apply to patients who are clinically stable. However, catheter removal, in addition to antibiotic therapy, should be the treatment of choice when patients: (1) are clinically unstable, (2) have persistent fever for 48 hours, (3) have evidence of tunnel infection, or (4) develop metastatic infectious complications [7].

5. Translating science to therapies in hemodialysis vascular access dysfunction: from the bench to bedside

There are currently few if any effective therapies to treat hemodialysis vascular access stenosis and neointimal hyperplasia. However, the knowledge obtained in recent years regarding the pathology and pathogenesis of vascular access access dysfunction has provided a framework for development of therapies that target neointimal hyperplasia and vascular stenosis. The purpose of the next section is to (1) describe current therapies for AVF and AVG stenosis and (2) novel therapies using localized delivery systems for AVF and AVG.

5.1 Systemic therapies

Systemic therapies, such as dipyridamole, angiotensin-converting enzyme inhibitors, aspirin, and fish oil, from small clinical trials and observational studies have been shown to have the potential to block smooth muscle cell proliferation and migration and to prevent thrombosis in AVFs and AVGs [166-170]. Most recently, two large randomized controlled trials, sponsored by the National Institutes of Health, evaluating anti-platelet agents in AVG and AVF to prevent neointimal hyperplasia were published [16,171]. In the AVG study, dipyridamole and aspirin, modestly reduced the risk of stenosis and improved primary unassisted patency [171]. In the AVF study clopidogrel reduced frequency of early thrombosis but did not improve AVF suitability defined as cannulation with two needles, minimum

dialysis blood flow of 300ml/min, successful use 8/12 dialysis sessions, and use after 120 days from creation [16]. While these two studies have shown some promising results, the clinical significance of these drugs used as standard treatment for hemodialysis access stenosis remains questionable.

Fish oil has been shown to prevent AVG stenosis and thrombosis in one randomized, controlled trial [172]. Currently, another study evaluating fish oil and AVG stenosis and thrombosis is ongoing [173]. Other systemic agents, though not tested in randomized clinical trials, which have shown potential anti-proliferative effects targeting neointimal hyperplasia in CVD or PVD models, include peroxisome proliferation-activated receptor γ agonist [174-176], sirolimus [177], and imatinib mesylate [176,178,179].

5.2 Radiation therapy

Radiation therapy has been hypothesized to be a potential therapy to treat vascular stenosis due to its antiproliferative effects and potential beneficial effects of vascular remodeling[180-183]. In experimental models, both external beam and endovascular radiation therapy has proven effective to reduce neointimal hyperplasia in AVF and AVG [184,185]. However, in clinical studies, a recent randomized-controlled trial of in AVGs 25 patients showed that 42% of the radiated AVGs achieved the target lesion primary patency end point at 6 months as compared to 0% of the control group ($p = 0.015$), but this did not translate into an improvement in secondary patency at either 6 or 12 months [186].

5.3 Far infrared therapy

Infrared radiation is an invisible electromagnetic wave with a longer wavelength than that of visible light. In experimental models, far infrared therapy has been shown to improve skin blood flow and endothelial function in cardiovascular disease [187-189]. The rationale for far infrared therapy to treat dialysis vascular access stenosis is that the dialysis vascular access in patients are located at a superficial site and improving access flow may improve vascular access performance. In the lone clinical study of far infrared in dialysis access in AVFs, patients who received far infrared therapy had improved access flows and longer unassisted patencies [190].

5.4 Local drug delivery systems for hemodialysis access

The rationale behind local delivery of drugs treat hemodialysis vascular access stenosis is that (1) AVFs and AVGs could be the ideal clinical model for the use of perivascular therapies since these can be easily applied at the time of surgery, (2) perivascular therapies preferentially target the "active" adventitia, (3) studies have demonstrated that lipophilic molecules when placed over the adventitia rapidly diffuse through all the layers of the vessel wall, and (4) 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 [4]. The subsequent section will discuss local therapies to treat hemodialysis vascular access stenosis from experimental models and clinical studies.

5.4.1 Drug eluting paclitaxel perivascular wraps

Experimental studies have previously demonstrated the efficacy of paclitaxel eluting wraps in AVG stenosis likely due to anti-proliferative effects [191-193]. In 2007, a large multi-center randomized-controlled study, evaluating the use of paclitaxel-eluting mesh wraps, Vascular

Wrap™, (Angiotech Pharmaceuticals, Inc.; Vancouver, British Columbia, Canada), was initiated to study the effectiveness and safety of this therapy on primary AVG patency compared to a standard AVG. However, this study was recently suspended in 2009 following a data safety monitoring 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 (Covalon Technologies Ltd: Mississauga, Ontario, Canada). An initial Phase II study demonstrated primary unassisted AVG patency of 75% and 38% at 1 and 2 years respectively with these wraps [194].

5.4.2 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 that reduces thrombosis, inflammation, stenosis, and increases lumen diameter. Initial experimental studies have documented a beneficial effect of endothelial cell loaded gel-foam wraps in porcine models of AV fistula and graft stenosis [195-198]. A recent Phase II study ("V-HEALTH") 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 AVF or AVG placement [97]. A phase III multi-center randomized-controlled study using the Vascugel® (Pervasis Therapeutics, Inc., Cambridge, MA) wraps in human AVGs is currently being designed.

5.4.3 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 of nitric oxide and prostacyclin and reduce neointimal hyperplasia [199]. Preliminary studies on the use of VEGF-D gene therapy (using a packaged adenoviral vector and a biodegradable local delivery device (collar) made of collagen wrapped at the venous anastomosis at the time of surgery), "Trinam®" (Ark Therapeutics; London, UK), in patients receiving AVGs, have been able to document technical feasibility and safety. A phase III study using this technology was initiated in 2009 but terminated in 2010 due to poor enrollment.

5.4.4 Recombinant elastase PRT-201

PRT-201 (Proteon Therapeutics; Waltham, MA) is a recombinant pancreatic elastase topically applied at the outflow vein at the time of surgery access creation which has been shown to result in both arterial and venous dilation and an increase in AVF blood flow in experimental models [200]. The clinical benefit of this approach is the potential ability to enhance AVF maturation (through rapid vascular dilation) and prevent venous stenosis in AVGs. A phase II study using this novel technology is ongoing in the United States evaluating this therapy and whether or not it improves primary patency and cumulative survival in AVG and AVF, as well as safety.

5.5 Endovascular stent therapy

Endovascular vascular therapies (angioplasty or angioplasty with stent placement) remains the only true intervention available to treat vascular stenosis. The main advantage of stent therapy after angioplasty is a reduction in adverse remodeling. In dialysis access, placement

of bare metal stents after angioplasty compared to angioplasty [201] alone has been shown to improve primary patency [202,203]. However, bare-metal stents have yielded poor results due to aggressive development of in-stent restenosis. In experimental models of dialysis access in AVGs, drug-eluting stents have shown to reduce neointimal hyperplasia and improve luminal stenosis compared to bare-metal stents [204]. However, there are no clinical studies evaluating drug-eluting stents in dialysis access to date.

Stent grafts (covered stents constructed from the same material of AVGs) have received recent attention as a therapy for prevention of restenosis due to its ability to prevent elastic recoil and inability of the neointimal cells to penetrate the covered barrier. A recently published multicenter, randomized controlled, clinical trial showed stent grafts (Bard Peripheral Vascular, Tempe, AZ), placed after angioplasty, to treat venous stenosis had better primary unassisted patency compared to angioplasty alone [205]. This is the only treatment to date that has shown to be effective to treat vascular access stenosis in a large, randomized, clinical trial.

5.6 Improving hemodynamics

Hemodynamic sheer stresses play a significant role in development of neointimal hyperplasia [87,112,206,207]. Therefore, altering the sheer stress pattern to prevent turbulent, low-flow, and low-sheer stresses could reduce the development of neointimal hyperplasia. Previous clinical data to date to support such an intervention comes from several studies evaluating cuffed AVG grafts ("Venaflo"; Bard Vascular, Tempe Arizona) [208-210]. In a recent randomized control trial evaluating cuffed vs non-cuffed AVG, cuffed AVGs showed better primary patency and cumulative survival [211]. Finally, results from a newly developed anastomotic implant device, "OptiflowTM" (Bioconnect Systems; Ambler, PA), to connect the artery and vein in AVFs and improve hemodynamics by providing a symmetric flow pattern, have shown a primary patency of 83% at 90 days [212]. This primary patency rate was higher compared to other similarly published studies [213].

6. Future perspectives: new frontiers in research

In the last decade our knowledge of vascular access dysfunction has significantly evolved. We now understand that the most common pathologic lesion seen in AVF and AVG dysfunction is aggressive venous neointimal hyperplasia, and biofilms and fibrin sheaths play a major role in CVC infection and dysfunction. In order to advance the field further, we need to further our current understanding of both the clinical and experimental pathways that result in venous neointimal hyperplasia and mechanisms that lead to biofilm and fibrin sheath production in CVCs by using the advanced technologies and tools in cellular and molecular biology, bioengineering, genomics, proteomics, and vascular imaging (ultrasound, computed tomography, and magnetic resonance imaging) [65,124,214]. Finally, small and large animal models of AVF and AVG, which a number of investigators in this field have already developed [61,93,207,215-217], will play an essential role in "translating" our knowledge of pathophysiologic mechanisms in vascular access dysfunction to novel therapies for patients.

7. Conclusion

The magnitude and costs of dialysis access dysfunction is clearly evident, and will only become magnified in the coming years as the prevalent dialysis population continues to

increase. 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 and catheter dysfunction be translated to the development of novel effective therapies for patients.

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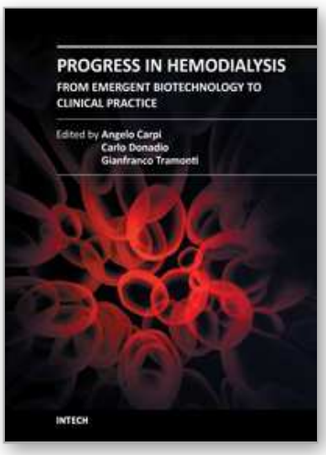

Progress in Hemodialysis - From Emergent Biotechnology to Clinical Practice

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Hemodialysis (HD) represents the first successful long-term substitutive therapy with an artificial organ for severe failure of a vital organ. Because HD was started many decades ago, a book on HD may not appear to be up-to-date. Indeed, HD covers many basic and clinical aspects and this book reflects the rapid expansion of new and controversial aspects either in the biotechnological or in the clinical field. This book revises new technologies and therapeutic options to improve dialysis treatment of uremic patients. This book consists of three parts: modeling, methods and technique, prognosis and complications.

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