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Future research directions to improve fistula maturation and reduce access failure

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Abstract

With the increasing prevalence of end stage renal disease there is a growing need for hemodialysis. Arteriovenous fistulae (AVF) are the preferred type of vascular access for hemodialysis but maturation and failure continue to present significant barriers to successful fistula use. AVF maturation integrates outward remodeling with vessel wall thickening in response to drastic hemodynamic changes, in the setting of uremia, systemic inflammation, oxidative stress and preexistent vascular pathology. AVF can fail due to both failure to mature adequately to support hemodialysis, as well as development of neointimal hyperplasia (NIH) that narrows the AVF lumen, typically near the fistula anastomosis. Failure due to NIH involves vascular cell activation and migration and extracellular matrix remodeling with complex interactions of growth factors, adhesion molecules, inflammatory mediators, and chemokines, all of which result in maladaptive remodeling.

Different strategies have been proposed to prevent and treat AVF failure, based on current understanding of the modes and pathology of access failure; these approaches range from appropriate patient selection and use of alternative surgical strategies for fistula creation, to the use of novel interventional techniques or drugs to treat failing fistulae. Effective treatments to prevent or treat AVF failure requires a multidisciplinary approach involving nephrologists, vascular surgeons and interventional radiologists, allowing careful patient selection and the use of tailored systemic or localized interventions to improve patient-specific outcomes. This review provides

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contemporary information on the underlying mechanisms of AVF maturation and failure and discusses the broad spectrum of options that can be tailored for specific therapy.

Keywords

Arteriovenous fistula; maturation; maturation failure; angioplasty

Introduction

1. The prevalence of ESRD is increasing

Chronic kidney disease (CKD) is increasing in incidence worldwide, and with an estimated prevalence of 8%–16%, contributes significantly to the global burden of disease [1, 2]. The global prevalence of diabetes in adults is 9.1% (415 million people) according to a report published in 2015 by the International Diabetes Federation, rising beyond 10.4% (642 million people) by 2040 [3], largely due to the global increase in type 2 diabetes and obesity, especially in China, India and some developing countries in Africa [4–6]. This increase in the number of people developing diabetes has had a major impact on the development of diabetic kidney disease (DKD). DKD and an aging population have become the two challenges in managing end-stage renal disease (ESRD) worldwide. DKD is the leading cause of ESRD, accounting for approximately 50% of cases in the developed world. Although overall incidence rates for ESRD attributable to DKD have recently stabilized in the USA, these rates continue to rise in high-risk groups such as middle-aged African Americans, Native Americans, and Hispanics. The elderly population constitutes the fastest growing sector of the ESRD population and have unique needs by virtue of their high prevalence of comorbid conditions, slower progression of renal disease, and reduced survival; in the Medicare population alone, DKD-related expenditure among the elderly was nearly $25 billion in 2011 [7, 8]. With the increasing prevalence of ESRD, there is a growing need for renal replacement therapies (RRT).

2. AVF is the preferred form of RRT but is far from optimal

RRTs are the lifeline for ESRD patients. Modes of RRT include peritoneal dialysis (6.4%), renal transplant (29.3%), and hemodialysis (HD) (64.2%) [9, 10]. In 2010, 64.7% of patients in the United States with ESRD were treated with HD with either arteriovenous fistula (AVF), arteriovenous grafts (AVG), or tunneled and non-tunneled central venous catheters [11].

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines and the Fistula First Breakthrough Initiative prefer AVF as the optimal access for HD [12], as they have superior patency rates, fewer complications and lower health care costs [11, 13–15]. Additionally, a recent systematic review and meta-analysis on outcomes of vascular access for hemodialysis remains in support of autogenous access as the best approach when feasible: AVF were associated with the best patency and lowest infection and mortality outcomes, followed by AVG and catheters [16, 17]. AVF have also been recommended in the pediatric population [18].

However, AVF are not immediately available for use as an access for HD as they must mature, e.g. dilate and thicken. Unfortunately, AVF have a high rate of primary maturation failure with up to 60% not suitable for HD by 5 months after creation [19–22]. Furthermore, a recent systematic review and meta-analysis reported that the primary patency rates of AVF were 60% at 1 year and 51% at 2 years, with secondary patency rates of 71% at 1 year and 64% at 2 years, clearly suboptimal for a permanent treatment [23]. Although there are conflicting results regarding sex influence on AVF failure, most studies demonstrated that women have prolonged maturation time and decreased patency rate [17, 24, 25]; early thrombosis was also associated more frequently with women [26]. Controversially, AVF may not be favored for HD access in older patients [27–29]. Olsha et al demonstrated that 88% of their patients who were older than 80 years had vasculature suitable for autogenous access construction, with patency and complications similar to those of their younger counterparts, with adequate preoperative planning and postoperative maintenance [29]. However, elderly patients with ESRD frequently have a high prevalence of comorbidities, short life expectancy, and poor reported quality of life that is associated with lack of AVF maturation and diminished primary and cumulative AVF patency [28]; in these patients AVG placement might be more beneficial [27, 28, 30].

3. Lack of well-established clinical criteria to define AVF maturation or failure

AVF maturation is considered clinically successful if 6 weeks after surgery the fistula supports a flow of 600 mL/min, is located at a maximum of 6 mm from the skin surface and has a diameter of >6 mm [12], but this definition is difficult for clinical use. The North American Vascular Access Consortium definition may be more useful: a fistula is mature if it can be successfully used for dialysis with two-needle cannulation for two-thirds or more of all dialysis runs for 1 month and if it delivers the prescribed dialysis within the prescribed time frame [31].

Although there are some clinical criteria to define successful AVF maturation, the clinical definition of AVF failure is less clear, with frequent confusion between various types and stages of failure. Based on previous criteria and recent multicenter research [12, 26, 31], we have defined the 3 types of AVF failure as: early thrombosis, failure to mature, and late failure (Table 1).

Many variables contribute to successful AVF maturation or AVF failure: patient age, sex, presence of diabetes, obesity, vessel characteristics, surgical technique and surgeon experience, preoperative planning and mapping [32–34]. Successful access surgeons frequently adhere to the dictum that a successful AVF should be performed in the right patient at the right time in the right circumstances based upon comprehensive understanding of the mechanisms contributing to AVF maturation and AVF failure. The goal of this review paper is to give a basic understanding of the adaptive changes of AVF maturation as a framework to understand the mechanisms of AVF failure as well as subsequent treatments.

Mechanisms contributing to AVF maturation and failure

Mechanisms of AVF maturation

1. AVF maturation integrates outward remodeling and wall thickening—After AVF creation, the vein is exposed to a high flow, high shear stress, high pressure, and oxygen-rich arterial environment, leading to "maturation" of both the arterial inflow limb as well as venous outflow limb. Adaptation of the vein to the increased flow and shear stress of the arterial environment requires dilation by outward remodeling of the venous wall, (Poiseuille's law), whereas increases in pressure and tensile stress result in wall thickening, (Laplace's law). During this adaptive remodeling, hemodynamic changes are translated into endothelial and adventitial signaling, inducing structural changes in cells and the extracellular matrix (ECM); inflammation, growth factors and cell adhesion molecules in all three layers of the venous wall are involved with the process inducing remodeling (Figure 1).

1.1 Hemodynamic flow: Blood flow in the cephalic vein is normally approximately 28 ± 14 ml/min [35]. Successful radial-cephalic AVF have flow rates averaging between 600–1000 ml/min with higher peak flows in the larger diameter brachial-cephalic AVF. Dixon et al. reported that 90% of forearm AVF have flows between 500–2000 ml/min, whereas 90% of upper arm AVF have flows between 500–3000 ml/min [36]. Shear stress in the cephalic limb of a brachial-cephalic fistula increases from preoperative venous magnitudes of 5–10 dyne/cm^2 to 24.5 dyne/cm^2 after one week, which then normalizes to 10.4 dyne/cm^2 over 3 months [37]. With these high magnitudes of flow in the AVF, the character of the flow may be disturbed, e.g. non-laminar and disordered, possibly even turbulent [38–41].

1.2 Outward remodeling and wall thickening: AVF maturation is the product of both vessel wall outward remodeling and thickening and is thought to be an adaptive process to the increased pressure, shear stress, and oxygen tension from the arterial inflow that is no longer attenuated by resistive forces of the arterioles and the capillary bed. Different from vein grafts, AVF adapt mainly via outward dilation and wall thickening with less intimal thickening [42]. Schwartz et al. confirmed this behavior using a rabbit model, showing that AVF are exposed to higher flow than vein grafts (AVF: 82 ± 17 ml/min; vein grafts: 16 ± 4 ml/min) as well as increased shear stress (AVF: 71 ± 50 dyne/cm^2; VG: 0.96 ± 0.38 dyne/cm^2). AVF showed increased dilation (AVF: 194%; VG: no change), whereas vein grafts were exposed to higher pressure (VG: 62 ± 3 mmHg; AVF: 6 ± 2 mmHg) and had increased myointimal area (VG: 4.72 ± 0.83 mm^2; AVF: 1.9 ± 0.55 mm^2)[43].

Outward remodeling is thought to be mediated by the venous endothelium and adventitia that sense hemodynamic forces and integrates these forces to allow successful adaption without loss of luminal area and vessel patency [21, 24, 44, 45]. Venous diameter expansion is a critical element of outward remodeling and predicts clinical success for both AVF and vein grafts [46–48]. Several studies examining venous dilation in AVF reported mean diameter increases from 2.3–3.2 to 5.8–6.6 mm by 3 months after fistula creation. These values reflect a 45%–86% increase within the first month and an increase of up to 179% after 3 months, corresponding to an average cross-sectional area of approximately 10–12 mm^2, to normalize the shear stress [49, 50].

Wall thickening is the adaptation of the vessel wall to increased pressure. This process involves expansion of all the vessel layers via both ECM deposition and cell proliferation and migration [44, 45, 51]. Several types of cells are involved in wall thickening, including smooth muscle cells, adventitial fibroblasts, and bone marrow derived progenitor cells [45, 52–54]. The adventitial myofibroblast is critical during venous adaptation to arterial flow and helps maintain venous wall integrity and hemostasis after surgical creation of the AVF [45]. Myofibroblast precursors residing in the venous adventitia sense the abrupt mechanical forces produced by arterial flow to rapidly adjust their genomic expression program to help increase vascular resistance. This adaptive response includes the formation of bundles of contractile microfilaments and extensive cell-to-matrix attachment sites as well as the secretion of MMPs, collagen, and ECM proteins that strengthen the fistula wall [45, 55]. Targeting the adventitia to treat NIH is a newer strategy to prevent AVF venous stenosis [56].

1.3 Endothelial Signaling: Molecular signaling within the maturing AVF is of vital importance to understand and control the normal adaptive response of fistula maturation and the abnormal maladaptive response of fistula failure. The release of chemotactic and inflammatory mediators from the endothelium during surgical manipulation and hemodynamic variation are important during the initial phase of adaptation. Directly after AVF creation, high magnitudes of arterial flow result both in passive vascular distention and nitric oxide (NO) synthesis by endothelial cells with subsequent vascular smooth muscle cell (VSMC) relaxation, resulting in acute vasodilation [57–59]. NO is produced by endothelial nitric oxide synthase (eNOS), and is a potent vasodilator and signaling molecule with anti-inflammatory and anti-platelet properties [51, 59, 60]. eNOS may contribute to adaptive vein wall remodeling both through its anti-inflammatory and anti-thrombotic properties as well as through its anti-proliferative properties. Both eNOS and inducible nitric oxide synthase (iNOS) are upregulated in the AVF and may mediate adaptation; inhibition of eNOS results in increased MCP-1 and IL-8, leading to NIH [54, 61]. 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 NIH in AVF as well as in the plasma of patients with chronic renal failure and hemodialysis; ET-1 may mediate wall thickening in response to localized hemodynamic forces [62–64].

1.4 Matrix remodeling: Venous adaptation of AVF also depends on coordinated synthesis, secretion, and degradation of ECM [42]. The matrix metalloproteinase (MMP) family regulates ECM remodeling and allows cell migration through degradation of collagen and elastin. MMP activity is stimulated by a variety of factors present during vein graft adaptation including flow, stretch, mechanical injury, inflammation, and oxidative stress [65–69]. In AVF, MMP-2 and MMP-9 expression are upregulated, and a high serum ratio of MMP-2 to TIMP predicts AVF maturation [61, 65, 66, 68].

During AVF venous limb maturation, the process of ECM expression, synthesis, secretion, and deposition occurs in distinct temporal phases (Figure 2) [70]. Initial ECM degradation occurs early after AVF creation, coincident with early increased expression of MMP and tissue inhibitor of metalloproteinase 1 (TIMP-1). By day 7 there is increased expression of

many collagen subunits as well as changing patterns of MMP expression. By day 21, a later phase is characterized by reduced MMP expression and increased expression of larger structural and non-collagenous matrix proteins.

Matrix degradation is regulated by MMP whereas matrix deposition is regulated by transforming growth factor-β (TGF-β); TGF-β is produced by a variety of cell types present in the venous wall, including endothelial, smooth muscle, and inflammatory cells, potentially contributing significantly to intimal and medial thickening [63, 71, 72]. 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 [61, 71, 73, 74].

1.5 Adventitia and perivascular cells: With growing recognition of the importance of the adventitia and perivascular cells to vascular remodeling, the role of adventitial fibroblasts has gained attention. Recent data suggests that NIH consists of smooth muscle alpha-actin-positive, vimentin-positive and desmin-negative myofibroblasts that have probably migrated from the adventitial layer [52, 75]. AVF failure is associated with an increased adventitial fibrosis, myofibroblast activation and capillary rarefaction [76].

Molecular signals originating from the adventitia and perivascular cells play essential roles in regulation of vascular development, physiology, vascular wall remodeling, immune surveillance, and vascular disease. The adventitia contains many different interacting cell types including fibroblasts, microvascular endothelium, nerves, resident macrophages, T cells, B cells, mast cells, and dendritic cells; the adventitia is also the home to resident vascular progenitor cells [77]. Perivascular adipose tissue (PVAT) plays multiple roles in vascular physiology and remodeling including production of vasorelaxing and anticontractile factors [78, 79]. One important component of this adipose tissue–derived anticontractile activity is adiponectin. Adiponectin is an adipocyte-derived 244 amino acid long peptide hormone that regulates metabolic processes such as fatty acid oxidation, and also mediates vasorelaxation. Adiponectin receptors on VSMC activate calcium-sensitive potassium channels (BKca) leading to stimulation of eNOS activity and production of NO [80]. A similar pathway exists in endothelial cells. Together, the production of NO from endothelial cells and SMC mediates the anticontractile effects of PVAT-derived adiponectin [79].

Mechanisms of AVF failure

1. Early thrombosis—Blood, flow and the vessel wall, components of Virchow's triad, are traditionally considered to be the three critical components of thrombosis [81]. Patients with ESRD show both a bleeding risk and an increased risk of thrombosis. The bleeding episodes involve platelet dysfunction, impaired platelet–vessel wall interactions and anemia [82–84], in addition to the use of anticoagulants during hemodialysis. Several clinical trials have also shown increased risk of both spontaneous venous and arterial thrombosis along the entire spectrum of CKD, beginning from CKD stage 2 to stage 5 patients [85–87].

ESRD is characterized by a number of metabolic abnormalities that alter the balance of pro- and anti-thrombotic factors that affect both thrombosis and hemostasis [88]. This is likely to be an important contributor to the increased risk of thrombosis in patients with ESRD. Several pro-thrombotic hemostatic mediators are elevated in CKD patients, including

fibrinogen, which directly contributes to a hypercoagulable state [89], soluble thrombomodulin [90], soluble tissue factor (TF), thrombin-anti-thrombin (TAT) [91], von Willebrand factor (vWF) [91], factor VIII and C-reactive protein (CRP) [91, 92]. The generalized inflammatory state, endothelial dysfunction and possibly poor clearance of some of the thrombotic mediators may account for this metabolic derangement [89]. CKD and ESRD patients have a disrupted endothelial glycocalyx, which also contributes to the increased risk of thrombosis [93, 94]. The endothelial cells of uremic patients express elevated levels of tissue factor, a crucial procoagulant activating the extrinsic coagulation cascade [95, 96]. Uremic endothelial cells also release small extracellular vesicles, called microparticles, loaded with TF to augment thrombosis.[96–98].

In addition, hypercoagulable states also predispose to an increased risk of early thrombosis. Factor V Leiden polymorphism has been inconsistently implicated [99, 100]. High levels of phospholipid antibodies, probably due to the uremic state and high levels of low density lipoprotein have similarly shown an association [101, 102].

In the setting of the pro-thrombotic state of ESRD, lack of surgical experience and insufficient preoperative vessel mapping can result in early thrombosis. A study from the Hemodialysis Fistula Maturation Study group showed that factors that contribute to early thrombosis include: female sex, use of forearm AVF, smaller arterial size, draining vein diameter of 2 to 3 mm, and protamine use [26]. Patient selection, sufficient preoperative mapping and an appropriately experienced surgical team are important to prevent early thrombosis.

2. AVF failure to mature

Effects of Hemodynamic Flow and Shear Stress: In response to the hemodynamic changes after AVF creation, an AVF will undergo adaptive remodeling with outward remodeling and increased wall thickness. But in the setting of pre-existent vasculopathy and systemic abnormalities, an AVF will fail to mature either because of aggressive NIH or impaired outward remodeling, or both. Although most research on the pathophysiology of AVF maturation failure focuses on NIH, the role of vascular outward remodeling should be also highlighted [103].

The increased hemodynamics of arterial flow that increases vessel wall shear stress (WSS) is likely to be a critical event after AVF creation that promotes AVF adaptation [104–106]. In a patient-specific side-to-end fistula, image-based computational fluid dynamics studies showed laminar flow within the arterial limbs and a complex multidirectional and reciprocating flow field on the inner side of the swing segment in the proximal venous limb [106]. NIH is predisposed to occur in the inner wall of the venous segment near the anastomosis, and has a strong inverse correlation with magnitudes of shear stress, but is also related to flow patterns [107].

In contrast, disturbed flow, with low and reciprocating WSS, induces selective expression of atherogenic and thrombogenic genes (pro-oxidant, proinflammatory, procoagulant, and proapoptotic) in endothelial cells [108]. Dai et al. compared the effects of two different atheroprone and atheroprotective shear stress patterns in vitro and demonstrated an

important effect of low and oscillating WSS on the EC cytoskeleton, interleukin production, and nuclear translocation of transcription factor NF-κB to enhance expression of adhesion molecules [109]. Disturbed flow promotes an inflammatory and thrombotic phenotype in arterial ECs, increasing binding of monocyte chemotactic protein-1 (MCP-1) to the cysteine-cysteine receptor and stimulating SMC migration and proliferation, all of which may enhance NIH [110, 111].

Using pulsatile computational fluid dynamics simulation with idealized models of AVF, Ene-Iordache et al found that despite the high flow rate after AVF creation, WSS in the areas of the juxta-anastomotic vein was low and oscillating, both in end-to-side and end-to-end anastomosis configurations [39]. Due to the pulsatility of flow during the cardiac cycle, recirculation and reattachment flow with low velocity develops near the wall, inducing disturbed flow with low and reciprocating WSS on the inner surface of the juxta-anastomotic segment and on the distal artery. In a parametric idealized model of end-to-side AVF, Ene-Iordache et al further studied whether the anastomosis angle influences the pattern of disturbed flow. Quantification of these areas showed that the smaller the angle, the smaller the area of low and oscillating WSS, as quantified by the relative residence time. These results suggest that an acute anastomosis angle (30°) should be preferred to minimize the risk of NIH in the juxta-anastomotic vein [112]. They also demonstrated that in hemodialysis patients, the peak shear stress rather than the average shear stress, is the key factor in driving vessel dilatation to increase blood volume flow [113].

Bharat et al. performed a clinical study in patients undergoing radiocephalic AVF comparing three different anastomotic techniques. A novel technique of vascular anastomosis, the piggyback straight-line onlay technique, was characterized by a very small anastomosis angle and resulted in very few juxta-anastomotic stenoses compared to the traditional end-to-side and side-to-side techniques [114]. By using the piggyback straight-line onlay technique, disturbed flow is reduced due to the acute angle and the venous wall injury produced by the traditional torsion of the juxta-anastomotic vein is minimized [114]. Recently, Sadaghianloo et al reported that radial-cephalic fistulae with angles <30° have reduced primary and secondary patency and increased numbers of interventions, suggesting that, if possible, surgeons should avoid an anastomotic angle of <30° when creating radial-cephalic fistulae [115]. Chemla et al reported that AVF created with the VasQ™, an external support device, showed a high unassisted maturation and patency rate, possibly by minimizing flow disturbance around the area of anastomosis [116]. All of these data suggest that research based on anastomotic geometry may optimize the flow state and potentially be used for preoperative surgical planning.

Responses to injury: Endothelial and vascular injury results in the activation, proliferation and migration of fibroblasts, smooth muscle cells, and myofibroblasts from the media and/or adventitia to the intima; complex interactions of adhesion molecules, inflammatory mediators and chemokines results in venous NIH [117]. During this process, inflammation, oxidative stress, cellular phenotype change and migration of vascular cells and ECM remodeling play important roles.

Inflammation: In the inflammatory state of the uremic environment, the injury of AVF creation and local hypoxia is characterized by the presence of CD68-positive macrophages and CD3-positive lymphocytes. This infiltration is more significant in the setting of CKD [118]. Some inflammatory cytokines are upregulated such as IL-6, IL-8, MCP-1, and PAI-1 [61, 63, 119], and these mediators are associated with fistula failure [120]. IL-6 and TNF-α are more highly expressed in thrombosed AVF, and both CRP and fibrinogen are associated with AVF failure [121, 122].

CD68- and CD3- positive cells have been found in increased numbers in stenotic vessels. Macrophage migration inhibitory factor (MMIF) is hypothesized to play an important role in this local inflammatory response, potentiating neointimal thickening by driving inflammatory cells toward the neointima and leading to the proliferation of medial and intimal cells [123, 124]. MMIF has been identified in clinical and experimental models of vascular access. MMIF acts through the CD74 receptor, chemokine receptor 2, and chemokine receptor 4 [123]. These in turn act through extracellular signal-regulated and p38 mitogen-activated protein kinase pathways that up-regulate vascular endothelial growth factor (VEGF)-A, interleukin (IL)-8, and monocyte chemotactic protein-1 (MCP-1) [124].

MCP-1 is a potent chemokine that plays an important role in atherosclerosis and other vascular diseases through promoting chemotaxis of monocytes and macrophages, activation and migration of endothelial cells, proliferation and migration of smooth muscle cells, and induction of procoagulant mediators [125–128]. Expression of MCP-1 increased 1 week after AVF creation in mice, and was localized within the endothelium, smooth muscle cells, and leukocytes in a rodent AVF model. The MCP-1 knockout mouse model showed reduced NIH [129]. Moreover, in the murine model of CKD with AVF, there is an increase in gene expression of arginase-1, a marker for proinflammatory macrophages, followed by an increase in inducible nitric oxide, a marker for reparative macrophages [130]. Thus, MCP-1 appears to be upregulated very early after AVF creation and serves as a mediator for AVF dysfunction and failure.

Oxidative stress: Patients with ESRD have systemic inflammation and oxidative stress; the hemodynamic changes and local injury of the AVF procedure may further increase oxidative stress in the AVF wall. Oxidative stress and injury stimulates synthesis and secretion of ROS that in turn stimulate numerous signaling pathways, regulating diverse processes such as smooth muscle cell migration and proliferation as well as activating latent MMP, potentially mediating many aspects of venous remodeling [64, 131]. For example, superoxide can deplete NO, resulting in disruption of numerous pathways with resultant endothelial cell and general vascular dysfunction.

Recent investigations have shown that heme oxygenase (HO) production is related to AVF function [132–136]. HO is a cytoprotective and rate-limiting enzyme responsible for heme degradation, generating free iron, biliverdin, and carbon monoxide; biliverdin is subsequently converted to bilirubin by biliverdin reductase, and free iron is rapidly sequestered by ferritin [134]. Bilirubin is a free radical scavenger that blocks lipid peroxidation [137]. Carbon monoxide is a physiologically important vasodilator, acting via cyclic guanosine monophosphate (cGMP) [138]. HO exerts antioxidant, anti-inflammatory,

antiapoptotic, and angiogenic functions through its reactive products [134, 137, 138]. HO-1 is the inducible isoform, whereas HO-2 is expressed constitutively. Patients with HO-1 gene polymorphisms characterized by long GT repeats, resulting in less HO-1 production, were more likely to have worse AVF patency [132, 133]. In murine AVF, HO-1 gene expression is markedly induced in the vascular smooth muscle cells; HO-1 knockout mice how reduced patency with thinner vein walls and increased luminal area, as well as increased expression of proinflammatory and pro-oxidant mediators such as MCP-1, MMP-2 and MMP-9 [139]. A functional AVF also requires HO-2 [135]. Shear stress can regulate HO-1 activity, with high flow inducing HO-1 to generate NO and mitochondria-derived hydrogen peroxide; low flow induces lower levels of HO-1 that lead to macrophage infiltration and superoxide production within the vessel wall, suggesting an important role for HO in promoting outward remodeling and preventing NIH [140].

Cellular phenotype change and migration of vascular cells: The development of NIH is a complex process that requires activation, phenotype change and migration of vascular cells; NIH that forms at the venous anastomosis of a dialysis access graft or fistula is comprised primarily of smooth muscle alpha-actin-positive, synthetic VSMC phenotype or vimentin-positive and desmin-negative myofibroblasts that probably migrated from the media or adventitia layers in response to vascular injury [52, 75]. Other studies have suggested that bone marrow–derived cells are capable of differentiation into smooth muscle cells and may be another potential origin of neointimal cells [54, 141]. Interestingly, VSMC from the proximal artery may contribute substantially to venous intimal hyperplasia; in a murine AVF model increased Notch signaling can drive migration of these cells to the venous outflow tract [142].

In addition to increased cell numbers, there is synthesis of new ECM within the intima to form the lesion of NIH [21, 103, 117]. VSMC also become resistant to NO, decreasing SMC relaxation and preventing AVF maturation by reducing the ability to successfully outward remodel [143].

These data show that the entire vessel wall is involved in the processes that lead to access failure, and suggest additional targets for potential therapy; recent studies have demonstrated the potential to target and treat the adventitial space to prevent the adventitial response to injury and prevent AVF failure [56, 144, 145].

Growth Factors and Cell Adhesion Molecules: Numerous growth factors and cytokines play roles during AVF maturation, particularly by regulating pathways that control ECM synthesis, secretion, and degradation, as well as through control of cell proliferation and migration [42].

Local inflammation with monocyte infiltration into the AVF increases expression of TGF-β1 and insulin-like growth factor-1 (IGF-1) [74]. TGF-β1, despite its classically having anti-inflammatory properties, leads to ECM deposition, potentially causing thrombosis [74]. Differences in TGF-β1 polymorphisms, result in differing levels of TGF-β1 production, have been correlated with AVF patency [71]. TGF-β is expressed within stenotic AVF, and correlates with areas of ECM deposition; TGF-β1 also activates the fibroblast transition to

the myofibroblast phenotype [146]; myofibroblasts are the major cellular component found in AVF stenoses, producing ECM proteins and MMP [52]. Sustained TGF-β expression abolishes myofibroblast disappearance and leads to NIH [63]. In toto, increased expression of TGF-β is associated with decreased AVF patency, likely due to increased deposition of ECM [73, 74].

Other growth factors participate in AVF maturation. IGF-1 also induces ECM synthesis, smooth muscle proliferation and migration, and inhibits apoptosis [74]. Platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) also play significant roles in stimulating cell proliferation and migration. Both PDGF-α/β and IGF-1 expression are upregulated in AVF [61, 64]. 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, ECM deposition, and modulation of the inflammatory response. VEGF may also play an inhibitory role in AVF adaptation, since overexpression of VEGF-A contributes to negative remodeling and NIH, whereas inhibition of VEGF-A is associated with increased lumen area and decreased inward remodeling [56].

Selectins facilitate leukocyte adhesion. P-selectin is present on endothelial cells and platelets, and E-selectin is present on endothelial cells; ICAM and VCAM facilitate additional binding and migration [147]. P-selectin and E-selectin expression are both upregulated early after AVF creation, followed by decreased P-selectin expression after 1 month [61]. VCAM-1, but not ICAM-1, is highly expressed in thrombosed and stenotic AVF [121]. β-catenin and c-Myc expression are increased 1 week after AVF creation, correlating with decreased N-cadherin and associated with smooth muscle cell proliferation [148].

ECM remodeling: ECM remodeling involves coordinated synthesis, secretion, and degradation of ECM, which plays an important role both in normal AVF maturation as well as in the development of neointima and AVF failure [20, 21, 149]. ECM degradation occurs early after AVF creation, coincident with early increased expression of MMP and TIMP-1 [70]. Outward remodeling in response to the increased arterial flow requires early expression of MMP-2 and MMP-9 to degrade cell basement membranes and the internal elastic lamina, allowing vessel enlargement [150]. A high serum ratio of MMP-2 to TIMP predicts AVF maturation [65, 66, 68]. 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 [66]. Diminished elastin results in enhanced outward remodeling, suggesting that elastin degradation might be an option to improve AVF maturation [151].

However, the disruption of the elastic lamina and loss of integrity of this structural barrier may allow migration of medial VSMC or adventitial fibroblasts into the intima. Moreover, elastin degradation products can act as chemo-attractants for VSMC. MMP-2 and MMP-9 are also elevated in AVF stenoses and may play a role in thrombosis. Decreased expression of MMP-1, MMP-3, and MMP-9 have been linked to increased AVF failure and stenosis secondary to accumulation of ECM and impaired wall remodeling [152]. Although the role of TIMP is not clear [65–67], an unbalance of MMP and TIMP may contribute to the failure of AVF maturation. ADAMTS-1 is a matrix metalloproteinase that is expressed during AVF

maturation and plays a role similar to MMP-2 and MMP-9; reducing ADAMTS1 expression leads to positive vascular remodeling [144].

3. Late failure in the mature AVF—Although a mature AVF can support HD, in the setting of uremia and other systemic abnormalities, compounded with local injury due to the anastomotic configuration as well as repeated needle puncture, even the mature AVF is predisposed to eventual failure. NIH worsens with time, typically leading to stenosis of the AVF venous limb. This later failure usually requires interventional treatment or surgical revision to maintain the access for functional HD.

3.1 Systemic abnormalities: ESRD patients have systemic abnormalities, such as uremia, systemic inflammation, endothelial dysfunction, lipid abnormalities, hyperparathyroidism, hyperphosphatemia and hypercalcemia [21, 153–155]. These abnormalities may predispose the vessel wall to inward remodeling and stenoses after AVF creation.

Uremia: The inherent uremia of ESRD increases inflammation and oxidative stress [154, 155]. This oxidative stress is further increased by HD, which causes activation of phagocytes, release of oxygen radicals, peroxidation of lipids and ultimately depletion of the patient's antioxidant protectants [154, 156]. Certain cytokines implicated in the formation of NIH, such as IL-6, TGF-β and TNF-α, are elevated in uremia [120]. Uremia adversely affects endothelial function resulting in a prothrombotic state, increasing the tendency for calcific uremic arteriopathy (CUA) [88, 157]. CUA is associated with multiple histologic abnormalities that collectively result in medial calcification, stenoses, fibrosis, proinflammatory and prothrombogenic arterioles that are compatible with a calcific obliterative vasculopathy. The mechanism is thought to be initiated by the interaction of uremic hyperphosphatemia, multiple uremic toxins, and reactive oxygen species (ROS) with decreased local vascular calcification inhibitory proteins such as Matrix Gla protein (MGP) and the systemic globulin: fetuin-A—(a2-Heremans-Schmid glycoprotein) AHSG [158].

Systemic inflammation: Inflammation is a typical prominent feature of ESRD and contributes to the uremic phenotype in advanced stages of CKD [155]. Systemic concentrations of both pro- and anti-inflammatory cytokines are often several fold higher than in healthy individuals.[159, 160]. Persistent inflammation is also a major cause of vascular aging and vascular calcification [159, 161].

Endothelial cell dysfunction: Due to the negative impacts of uremia and oxidative stress on the endothelial cells, flow-mediated, endothelium-dependent vasodilation is markedly reduced in uremic patients compared with normal control patients [162, 163]. The reasons for this endothelial dysfunction include increased oxidative stress, the presence of NO inhibitors such as asymmetric dimethylargine (AMDA) and a reduced number and function of endothelial progenitor cells [164]. AMDA accumulates with progressive CKD, and high levels are associated with aggressive restenosis after angioplasty [165]. AMDA and glycation end products (AGE) lead to decreased NO bioavailability, impairing arterial dilation as well as impairing NO-related signaling [166].

Other abnormalities: Dyslipidemia is a well-established traditional risk factor for atherosclerosis in the general population in addition to patients with CKD and may actively participate in the increased cardiovascular morbidity [153]. Hyperphosphatemia and hypercalcemia, typical features of advanced CKD, are often accompanied by dysregulation of parathyroid hormone (PTH), contributing to the inflammatory state [167]. They also induce vascular calcification and stiffness [161].

3.2 Pre-existent vascular pathology: The role of pre-existent arterial and venous vasculopathy in uremic patients has been gathering increased attention. Vessel morphology and function seen with preoperative duplex ultrasound mapping correlate with AVF maturation and patency [168]. The systemic abnormalities in ESRD patients induce accelerated atherosclerosis, vessel thickening, vascular calcification and stiffness [166, 169]. Whereas atherosclerosis is associated with intimal calcification, calcification of the media occurs independently of atherosclerotic plaque formation and is commonly observed in all-diameter arteries in CKD patients [170]. This arterial vasculopathy impairs the vessels ability to expand upon exposure to high-flow.

The detrimental effects of CKD on the arterial system may affect veins in a similar manner [171]. Marked pre-existing segmental venous disease is frequently present in patients with ESRD prior to vascular access surgery [172, 173]. Lee et al. reported extensive calcification in the intima and media of venous segments that were harvested at the time of vascular access surgery [173]. Venous calcification is likely to reduce venous compliance, as it does in arteries, potentially limiting the ability of the vein to dilate and outward remodel for successful AVF maturation.

Although minimum vein diameter (MVD) has been reported as a unique clinical factor associated with both AVF maturation and long-term patency [174], other studies suggest that forearm venous distensibility is a better predictor of successful AVF maturation [175], which is consistent with the increased outward remodeling of the venous AVF limb compared with the feeding artery [37]. Additional studies are needed to determine the impact of pre-existing venous calcification on AVF maturation failure and whether this is a potentially modifiable factor for clinical treatment [168].

Future Approaches to Treatment

With only 26–58% of arteriovenous fistulae functional at 1 year various therapies have been pursued to treat access failure and improve long-term patency. Many medical treatments using different drugs aimed at decreasing access failure and improving patency have been examined in patients using an AVF or AVG for HD. A recent systematic review and meta-analysis reported the effects of aspirin, ticlopidine, dipyridamole, dipyridamole plus aspirin, warfarin, fish oil, clopidogrel, and sulfinpyrazone. The study showed that three trials compared the platelet aggregation inhibitor ticlopidine versus placebo and favored active treatment (OR 0.45, 95% CI 0.25 to 0.82; p = 0.009); three RCT assessed aspirin versus placebo and did not show a statistical benefit (OR 0.40, 95% CI 0.07–2.25; p = 0.30); two trials compared clopidogrel with placebo and did not favor treatment (OR 0.40, 95% CI 0.13 to 1.19; p = 0.10); two RCT assessed fish oil and did not favor treatment (OR 0.24, 95% CI

0.03–1.95; p = 0.18); and single trials comparing dipyridamole alone, dipyridamole plus aspirin, and sulfinpyrazone against placebo favored active treatment but a meta-analysis could not be undertaken; a single trial of warfarin versus placebo found warfarin resulted in increased bleeding complications and worse patency rates [176]. Despite the overall quality of evidence being low with short follow-up, this systematic review showed that there currently is no adjuvant treatment showing increased AVF or graft long term patency [176].

Table 2 summarizes the most popular current approaches to treatment of the failing AVF, as well as some treatments that may become more popular in the future. Despite surgical revision having traditionally been the most effective treatment of local disease, the current standard treatment for arteriovenous stenosis is percutaneous transluminal angioplasty (PTA) [177] [12]. Although PTA can improve patency and function in some cases of thrombosis and stenosis, PTA is not the optimal treatment for many lesions including resistant or recurrent stenosis [178]. This section of the review focuses on treatment of AVF access failures, broadly dividing them into stimulatory and inhibitory treatments, with further division into endovascular approaches, perivascular approaches and internal/external support devices.

Stimulatory Treatments

Stimulatory treatments recapitulate AVF maturation by promoting dilation and/or wall thickening, encouraging the cells of the intima, media or adventitia to proliferate or differentiate into useful phenotypes that will allow the fistula to mature or become usable after stenosis or occlusion. The two commonly used stimulatory endovascular approaches are currently balloon-assisted maturation (BAM) and angioplasty with stent placement. Cutting balloon angioplasty remains popular as well.

Balloon Assisted Maturation

The BAM technique uses repeated balloon angioplasty to disrupt the venous wall and sequentially dilate the vein to a larger diameter useable fistula; with this technique, it is possible to use even smaller diameter veins for access [179, 180]. However, the concern with this technique lies in its very nature; angioplasty injures the intima and media to produce NIH [181]. Although balloon injury has been described most commonly in the context of arteries, it is likely that veins show a similar response to angioplasty, especially in the uremic environment of renal failure. Diabetes, the most common etiology for renal failure, is also implicated in endothelial dysfunction. The clinical question is how to modulate the NIH response to allow this technique to achieve long term durability and successful use of the access site.

Although there is a relative paucity of randomized data on this technique, there are several positive short term studies. One report of 53 patients showed 85% secondary patency at 1 year; complications did include occlusion, conversion to a graft, and ligation due to steal [179]. Another report of 42 fistulae with maturation failure treated with 1.45 ± 0.57 balloon angioplasties showed a success rate of 46.2% at 1 year; however, there was no significant difference in AVF flow ratio between the successful and failure groups [182]. Miller et al matured 118 out of 122 fistulae requiring 1.5 interventions per access year with a secondary

patency of 75% at 1 year; however 14 patients with upper arm fistulae required stents in the cephalic arch to maintain patency [183]. Gallagher et al performed 185 BAM in 45 patients (mean 3.7 procedures per patient); all cases except one were successfully dilated but 7 patients failed to mature due to cephalic arch and subclavian vein stenosis, with maturation after angioplasty of the venous outflow [184].

Interestingly, BAM is frequently complicated by vessel rupture but rupture does not necessarily cause fistula failure. Derderian et al performed 139 BAM in 30 patients with 74 hematomas post procedure but still noted a statistically significant increase in flow [185]. Although BAM has appeal and early reports suggest that it might be a useful procedure, as yet no blinded randomized clinical trial exists to allow for conclusions on its clinical use.

Cutting Balloon Angioplasty

Cutting balloon angioplasty is used to dilate stenoses, and like BAM, creates trauma to the vessel wall, but attempts to limit the trauma; longitudinal incisions along the stenosis are made in a controlled fashion, at lower pressures than the conventional balloon, potentially also reducing risk of vessel rupture. 3 or 4 blades are mounted longitudinally on a non-compliant balloon that after inflation create incisions and release hoop pressure; the lower pressure and decreased force is thought to reduce the risk of a neoproliferative response and restenosis [186], and may limit dissection [187]. Several studies have reported improved patency at up to 6 months [188–192]. Prospective randomized trials have had heterogeneous data but not conclusively shown long term durability [193–195].

Stenting

Angioplasty with stenting of failing fistulae is another tool to treat resistant stenoses; multiple studies have reported higher primary and secondary patency rates after stent placement, in both fistulae and grafts. One prospective multicenter randomized trial tested self-expanding nitinol stents covered with PTFE and showed a higher 6-month patency rate in the stent graft group compared to balloon angioplasty alone (51% vs. 23%, $p<0.001$); there was also greater freedom from subsequent interventions (32% vs. 16%, $p=0.03$) and less restenosis (28% vs. 78%, $p<0.001$) [196]. A meta-analysis of 10 studies suggested there was improved primary patency at 6 months in those treated with nitinol stents compared to angioplasty; however, bare metal stents showed no significant increase in patency [197]. Covered stents can also be used to treat pseudoaneurysms that develop within the access [198]. Other issues with stents include how to locate sites for needle cannulation of the access in relationship to the stent, as well as the potential for infection of the foreign body.

Elastase Therapy

Elastin within the vessel wall provides elastic recoil and resting vessel tone. In animal AVF models, delivery of recombinant human type 1 pancreatic elastase resulted in vessel dilation, inhibition of NIH and improved patency [199]. These findings suggest that use of elastase in humans could improve AVF dilation and maturation; elastase must be delivered topically over the fistula adventitia as elastase is inactivated in blood.

A randomized, double blinded, placebo controlled dose escalation study suggested improved primary patency at low doses [200]. A second double-blinded, randomized, placebo controlled trial suggested improved unassisted maturation but without increased primary patency [201, 202]. Without meeting the primary efficacy end point, it is not clear whether additional trials will be performed.

Inhibitory Treatments

Inhibitory treatments seek to inhibit NIH. Treatments can be applied primarily to prevent initial access failure and possibly promote maturation, or treatments can be applied secondarily, to directly treat a failed AVF or to prevent secondary restenosis associated with a stimulatory treatment such as angioplasty. Several delivery strategies can be used including direct delivery to the endothelium, delivery to the adventitia, or delivery to the entire vessel wall; mechanical support devices have also been used.

Drug Eluting Angioplasty

Drug eluting angioplasty has shown encouraging results in the management of coronary artery in-stent restenosis and peripheral arterial stenosis; as such there has been recent interest to use this technique to treat failing AVF, with paclitaxel being the most commonly reported drug. Katsanos et al treated 20 patients with failing arteriovenous fistula with paclitaxel coated balloon angioplasty; there was an overall statistically significant improvement in primary patency at 6 months (70% vs 25%); however only 35% had autologous fistulae and in these cases there was a 45% device success rate with patients requiring high-pressure post procedure dilatation [203]. Lai et al treated radiocephalic fistulae with either plain balloon angioplasty or plain balloon angioplasty followed by paclitaxel-coated balloon; there was increased 6-month patency in the paclitaxel group, but not at 12 months [204]. Kitrou et al showed a numerical improvement with paclitaxel coated balloon angioplasty compared to plain angioplasty but there was no statistical significance in outcome; however, there were only 7 patients in each group [205]. A meta-analysis of 6 studies, 2 RCT and 4 cohort studies, reported encouraging 6-month patency with drug eluting balloon angioplasty (70–97% vs. 0–26%), although in these studies the numbers of patients were small and heterogeneous [206]. Infection also remains a concern for paxlitaxel [207].

Dual antiplatelet therapy (DAPT) is beneficial and currently recommended for patients with coronary stenosis after placement of a DES [208], and also beneficial for patients with peripheral arterial diseases to reduce major adverse cardiovascular events and death [209], although a recent meta-analysis reported lack of evidence for DAPT after endovascular arterial procedures [210]. Although some studies used DAPT or clopidogrel after implantation a DES to treat AVF stenosis [203, 211], there is no study of DAPT on the outcome of AVF patency after DES treatment.

Cryoplasty

Cryoplasty uses liquid nitrous oxide to fill the balloon during inflation, cooling the vessel wall to −10 degrees Celsius, with the goal of inducing smooth muscle cell apoptosis. Subzero temperatures induce ice crystal nucleation in the vessel wall extracellular fluid to

produce a hypertonic environment, since ice does not incorporate solutes, resulting in osmotic dehydration; upon removal of the cold source, the extracellular fluid thaws and osmolality returns to normal resulting in rehydration of the smooth muscle cells and induction of apoptosis. Cell survival is dependent on the rate of freezing and thawing cycles, the lowest temperature reached and the length of time at subzero temperature.

In porcine PTFE grafts there was no significant difference in intimal hyperplasia but a significant difference in media to intima thickness ratio at 4 weeks [212]. Rifkin et al treated 5 patients with perianastamotic PTFE graft-vein stenoses after 3 failed balloon angioplasty; 3 patients had no recurrence of stenosis at 12 weeks [213]. Gray et al treated 20 patients (AVG 18 patients; AVF 2 patients), with 80% needing immediate post cryotherapy angioplasty to achieve anatomical success; 3-month patency rates were equivocal at 3 months but only 16 and 25% at 6 months. Cryotherapy was also more painful than angioplasty [214].

Brachytherapy

Endovascular brachytherapy delivers beta radiation to the vessel wall, typically using either high doses over a short period of time or low doses over a long period using beta-particle emitting stents. Brachytherapy decreases vascular smooth muscle cell proliferation and migration [215].

In a canine PTFE graft model, brachytherapy was associated with reduced NIH at up to 9 months [216]. An early study treating 5 patients with restenosis showed only 2 patients with a clinically patent fistula at 6 months [217]. Waksman et al treated 18 grafts with restenosis with 11 sites remaining patent at 44 weeks [218]. The BRAVO 2 trial aimed to randomize patients into brachytherapy or sham treatment after the promising results of the BRAVO pilot, but this trial was halted preliminarily [219, 220].

Adventitial Wraps

The role of adventitial wraps to deliver sirolimus or paclitaxel has been extensively investigated; rat, pig, dog and sheep models using paclitaxel wraps showed decreased NIH [207, 221–224]. A significant concern with perivascular delivery however, is leak of the impregnated drug to surrounding tissues; a clinical trial was stopped early due to a 25% increase in infections [207]. This trial, however, used mesh for delivery to PTFE grafts.

Sanders et al used a non-porous polymer barrier laminated with a drug loaded hydrogel to allow unidirectional release towards the target area. In a porcine model there was no detection of the drug within any surrounding tissues; addition of a polylactide-co-glycolide wrap showed acceptable degradation over time and was undetectable by day 35 [224].

An interesting study described a sirolimus-eluting collagen membrane (Coll-R). In a small clinical trial of 12 patients, there was minimal toxicity and primary patency rates were 76% and 38% at 12 and 24 months respectively [225]. A phase 3 trial is currently in progress.

Mechanical Support Devices

Mechanical support devices can be used to optimize the geometry of the fistula anastomosis to prevent or delay NIH. The Optiflow™ device has been the most studied; in a human pilot study safety and technical success were achieved in 10 patients [226]. A follow up study of 41 patients showed unassisted patency of 78% at 90 days with no device related adverse events [227]. Similarly, the VasQ™ device provides an external support to control the geometry and flow, with a small study reporting maturation rates of 74% at 6 months [116].

Gene Therapy

Gene therapy continues to be of interest, with research directed towards understanding what patient risk factors predispose to access failure and thus might be suitable for appropriate targeted gene therapy. Several polymorphisms have been associated with vascular access thrombosis including methylenetetrahydrofolate (MTHFR), HO-1, factor V, TGFβ-1 and klotho (KL) [71, 133, 177, 228–230]. Polymorphisms of NOS have also been implicated in arterial restenosis [231]. Single nucleotide polymorphisms in the gene for Factor V were significantly associated with increased risk of access failure despite treatment with antiplatelet agents [232].

Gene therapy can alter luminal area and stenosis in large animal PTFE graft models. Rotmans et al used C-Natriuretic Peptide to increase lumen area and the intima/media ratio [233]. Luo et al. showed reduced NIH with beta-adrenergic receptor kinase C-terminus [234].

Gene therapy targeting VEGF-A may be promising. VEGF-A is necessary at low concentrations to promote endothelial cell health, nitric oxide and prostacyclin production, vasodilatation, antithrombosis and suppression of smooth muscle cell proliferation; at high concentrations VEGF-A promotes angiogenesis and vasculogenesis. Systemic VEGF receptor gene transfer in rats decreased carotid artery restenosis, suggesting the utility of targeting this pathway [235]. Increased VEGF expression is associated with early AVF thrombosis in human patients [236], and patients with the VEGF-936C/C gene polymorphism have a 5.54 increased risk of fistula thrombosis [237]. Lentivirus inhibiting adventitial VEGF-A expression decreased cellular proliferation and constrictive remodeling and increased patency in a mouse model [56]. However, a human trial administering VEGF-D was stopped early due to poor recruitment[238].

Future Directions

Successful hemodialysis requires a strong collagen tube that can be punctured repetitively to support the high flows necessary for efficient dialysis exchange. Veins are typically preferred, as arterial use can lead to ischemia and prosthetics have reduced patency and increased infection. However, the thin walled veins must successfully adapt to the arterial environment with a combination of diameter expansion and wall thickening. Failure to mature successfully is an important mechanism of access failure, just as NIH is an important mechanism of late failure. Accordingly, therapy to promote maturation, e.g. diameter expansion and wall thickening, is an important component of providing successful access;

however, promoting wall thickening for strength, without exuberant thickening and NIH, is a current challenge.

The role of hemodynamics such as shear stress in the development of NIH is recognized, especially in the pathogenesis of juxta-anastomotic stenosis that frequently develops along the inner wall of the swing segment. Both pharmacological as well as mechanical approaches may be applicable for therapy. The new RADAR technique to create AVF, e.g. minimizing venous handling and potential for wall ischemia, alters hemodynamics and may be a simple and low-cost method to improve access patency [239].

An interesting alternative that may obviate fistulae is the use of tissue engineered blood vessels. Although still in development and trials, tissue engineered grafts can resist high pressures, providing an endothelial-lined tube that supports dialysis [240, 241]. Continued advances in tissue engineering and 3D printing may show that tissue engineered vessels might replace the current gold standard fistula.

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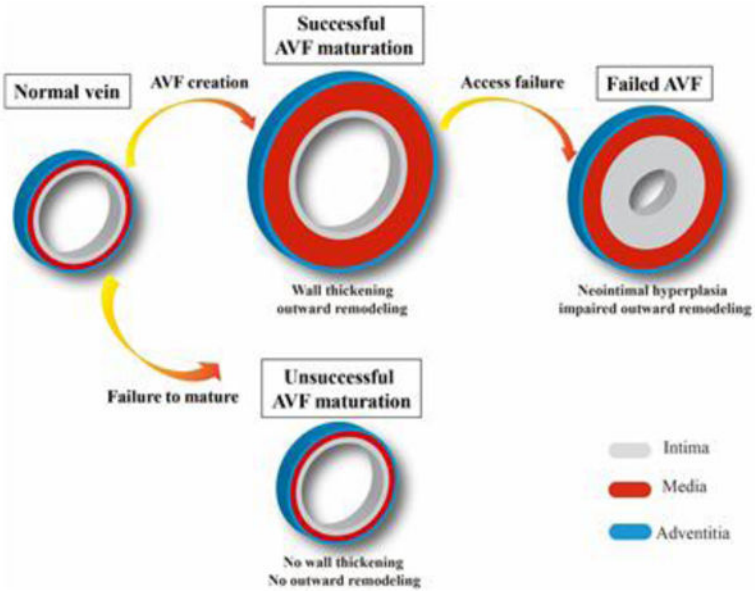

Figure 1.

Schematic representation of the venous wall structural changes that occur after AVF creation. AVF successful maturation integrates wall thickening and outward remodeling. A failed AVF can be due to early failure to mature, with failure to develop outward remodeling or wall thickening, or may be due to later development of neointimal hyperplasia and impaired outward remodeling in a previously functional conduit.

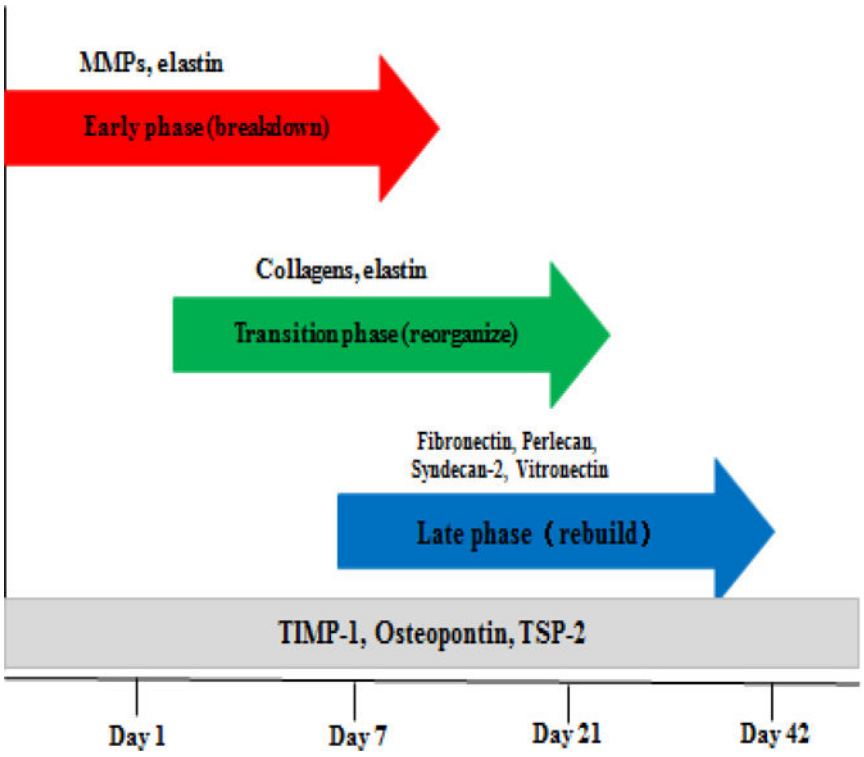

Figure 2.

Diagram depicting the 3 phases of ECM changes during the adaptive process of AVF maturation. There is an early phase of ECM breakdown from MMP degradation. A transition phase follows with collagen and elastin reorganization of the venous scaffold. A later rebuilding phase strengthens the matrix of the AVF with larger non-collagenous and glycoproteins. TIMP-1, osteopontin and thrombospondin-2 (TSP-2) are highly expressed throughout AVF maturation suggesting regulatory roles for these proteins.

Table 1

Types of AVF failure.

AVF failure type	Time	Definition	Pathophysiology
Early thrombosis	< 3 weeks	thrombosis of the access	Hypercoaguability
Failure to mature	< 6 months	Patent access but not suitable for cannulation or high efficiency hemodialysis	Inability to remodel outwardly
Late failure	> 3 months	a mature AVF used for at least 3 months that subsequently develops a problem requiring intervention	Neointimal hyperplasia

Table 2

Current and future approaches to treatment of the failing AVF.

Gold Standard: percutaneous transluminal angioplasty (PTA) or surgical revision		
Stimulatory Approaches: promote dilation and/or wall thickening		
	Application	**Limitation**
Balloon Assisted Maturation	Promotes maturation in an AVF with limited outward remodeling	Injures intima and media, increasing likelihood of NIH and recurrent stenosis; vessel rupture
Cutting Balloon Angioplasty	Dilate stenoses with reduced wall trauma	Some wall trauma; long term durability
Angioplasty with Stent	Dilate stenoses	Optimal stent type and design not established; long term durability
Elastase Therapy	Facilitate vessel dilation	Dose and efficacy not established; requires topical delivery
Inhibitory Approaches: prevent or inhibit NIH		
Drug Eluting Angioplasty	Inhibit VSMC proliferation	Optimal drug and dose not established; single treatment
Cryoplasty	Induce VSMC apoptosis	Variability in cell survival after freeze-thaw; more painful than angioplasty
Brachytherapy	Inhibit VSMC proliferation and migration	Dose and efficacy not established
Adventitial Wraps	Inhibit VSMC proliferation	Wrap design and toxicity; optimal drug and dose not established
Mechanical Support Devices	Optimize AVF geometry	Limited data
Gene Therapy	Identifiable patient risk factors	Optimal targets not established; ethical considerations for human trials

PTA, percutaneous transluminal angioplasty; AVF, arteriovenous fistula; BAM, balloon assisted maturation; NIH, neointimal hyperplasia; VSMC, vascular smooth muscle cell