Unraveling mechanisms of vascular remodeling in arteriovenous fistulas for hemodialysis

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Chapter 2

Arteriovenous access failure: More than just intimal hyperplasia?

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Abstract

Hemodialysis vascular access patency is severely compromised by fistula non-maturation and access stenosis. Intimal hyperplasia (IH) is considered the culprit lesion in failed fistulas, resulting in luminal narrowing and stenosis. This review focuses on the biology and pathophysiology of fistula failure and highlights not only the classically associated intimal hyperplasia but also some relatively neglected but potentially important contributors such as inadequate outward remodeling. In addition, the complex process and fragile balance of successful fistula maturation might be partially hindered by pre-existent chronic kidney disease-mediated vasculopathy. Further unravelling the (patho)physiology of outward remodeling and intimal hyperplasia could contribute to novel therapies and enhance fistula patency.

Introduction

Patients with end-stage renal disease are largely dependent on dialysis as renal replacement therapy. For chronic hemodialysis, an adequately functioning high-flow vascular access is required. Arteriovenous fistulas (AVFs) are the preferred modality in view of the superior patency rates and fewer complications as compared to arteriovenous synthetic grafts[1-3]. Nonetheless, the durability of AVFs is far from optimal with one year primary patency rates ranging from 60-65%[4;5]. In fact, these numbers are too optimistic, as they frequently do not account for fistulas that failed to mature. Maturation failure contributes significantly to the dismal patency rates of AVFs as illustrated by a recent multi-center study which revealed that 60% of the AVFs were not suitable for dialysis between 4-5 months post surgery[6], although, these numbers do vary between different types of AVFs[7]. According to the KDOQI guidelines, an AVF maturation is clinically considered 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 surface and has a diameter greater than 6 mm[2]. The exact underlying mechanisms responsible for maturation failure are however unknown, but impaired outward remodeling as well as intimal hyperplasia (IH) are both considered to contribute.

Thus far, most research on the pathophysiology of AVF failure focuses on IH. In contrast, the role of vascular outward remodeling in the setting of AVFs is often neglected. However, adequate outward remodeling could preserve luminal caliber and may therefore be valuable for successful fistula maturation. We postulate that the balance between outward expansion and potential luminal narrowing due to IH may ultimately determine fistula flow and patency (Fig.1). This review focuses on the pathophysiology of both AVF maturation failure and failure of already matured AVFs, and highlights some potential contributors thus far gaining relatively little attention, such as outward remodeling and the implications of chronic kidney disease (CKD) mediated vascular pathology.

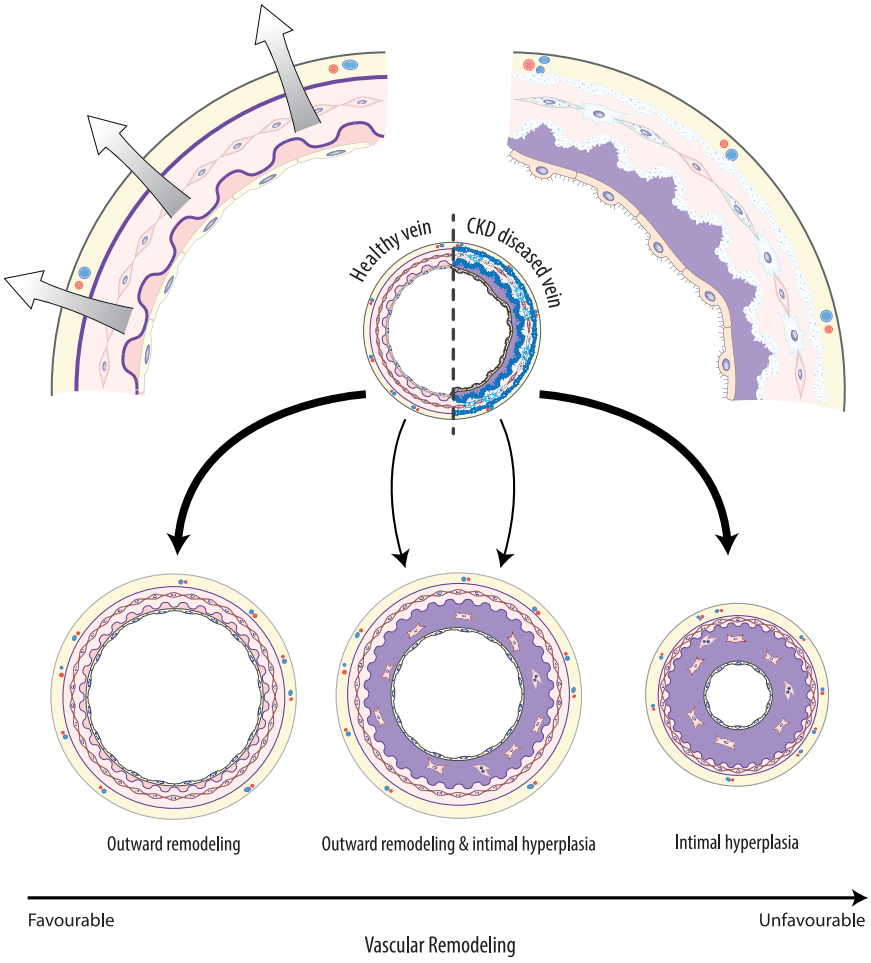

Figure 1. Different modalities of the vascular remodeling response after fistula creation. Whereas a healthy vein has the potential for successful outward remodeling (top left), adequate maturation may be partially hindered by CKD-induced pre-existing vasculopathy such as IH (top right). As shown below, we postulate that the net resultant of IH and outward remodeling may determine ultimate luminal calibre. In case of IH formation, adequate outward remodeling could to a certain extent remain lumen calibre intact, thus providing a patent fistula. However, if IH outbalances outward remodeling this could result in stenosis and fistula failure.

Outward remodeling: an emerging concept in arteriovenous fistulas?

The connection of a low-pressure vein to the high-pressure arterial system results in a chain of vascular events that starts with an immediate increase of blood flow through the both the feeding artery and the draining vein[4;8]. Directly after construction of the AVF, this rapid

increase in flow results in both passive vascular distension and in nitric oxide (NO) synthesis by endothelial cells with subsequent vascular smooth muscle cell (VSMC) relaxatio[n9-11] resulting in acute vasodilation. Concomitantly, the hemodynamic changes following AVF creation initiate a more structural vascular remodeling response leading not only to a further increase in arterial and venous calibre[12-14] but also to thickening of especially the venous wall[15;16]. Increased wall shear stress (WSS) and wall tension are the driving forces. WSS is the frictional force exerted by blood on the vessel wall and is mathematically defined by Poiseuille's formula: $4\eta Q/\pi r^3$ where η = blood viscosity, Q = flow and r = vessel radius. An increase in blood flow will provoke an adaptive response of the vessel in which the luminal diameter increases in attempt to reduce WSS to pre-AVF levels (5-10 dyn/cm^2). Furthermore, due to the pressure increase in the venous outflow tract after fistula creation, the wall tension rises leading to another adaptive response culminating in medial thickening (i.e. venous arterialization). These phenomena are elegantly illustrated in a study of Corpataux et al[12], where hemodynamic changes in the venous part of AVFs in six patients were investigated using echo-tracking and Doppler-ultrasonography. Within the first week after fistula formation the flow increased to 539 mL/min accompanied by an almost threefold increase in WSS to 24.5 dyn/cm^2. The continuous increase in flow resulted in a progressive increment in venous luminal calibre from 2.4 mm preoperative to 6.6 mm after 12 weeks. Since WSS is inversely related to lumen size, the WSS gradually returned to a physiological range (10.4 dyn/cm^2 at 12 weeks). In addition, the venous wall thickness increased, demonstrated by an augmentation of cross sectional wall area. This adaptive response is also applicable for the arterial side of the AVF, where the increment of arterial flow results in an increase of arterial luminal diameter[14], although to a lesser extent than the venous side[12]. This change in diameter does not result in wall thickening but likely rather results in arterial wall remodeling (i.e. an increase in both internal and external diameter without an increase in wall cross sectional area)[14].

On a biological level, these changes in WSS and wall tension are sensed by the endothelial cells, that function as mechanosensors and convert these hemodynamic stimuli to biochemical signals such as vasodilating agents (e.g. NO), growth factors that can control VSMC proliferation and migration and cellular adhesion molecules[10;17-19]. Upregulation of proteases such as matrix metalloproteinases (MMPs) and cathepsins results in matrix degradation and restructuring of the vascular scaffold leading to luminal expansion[15;20-22]. In addition, with an increased circumference of the vessel wall, it seems logical that some VSMC reorganization should occur as well to keep in pace with the expansion, as is also described in arterial setting[23]. However, to date little is known about the role of VSMCs in outward remodeling in AVFs.

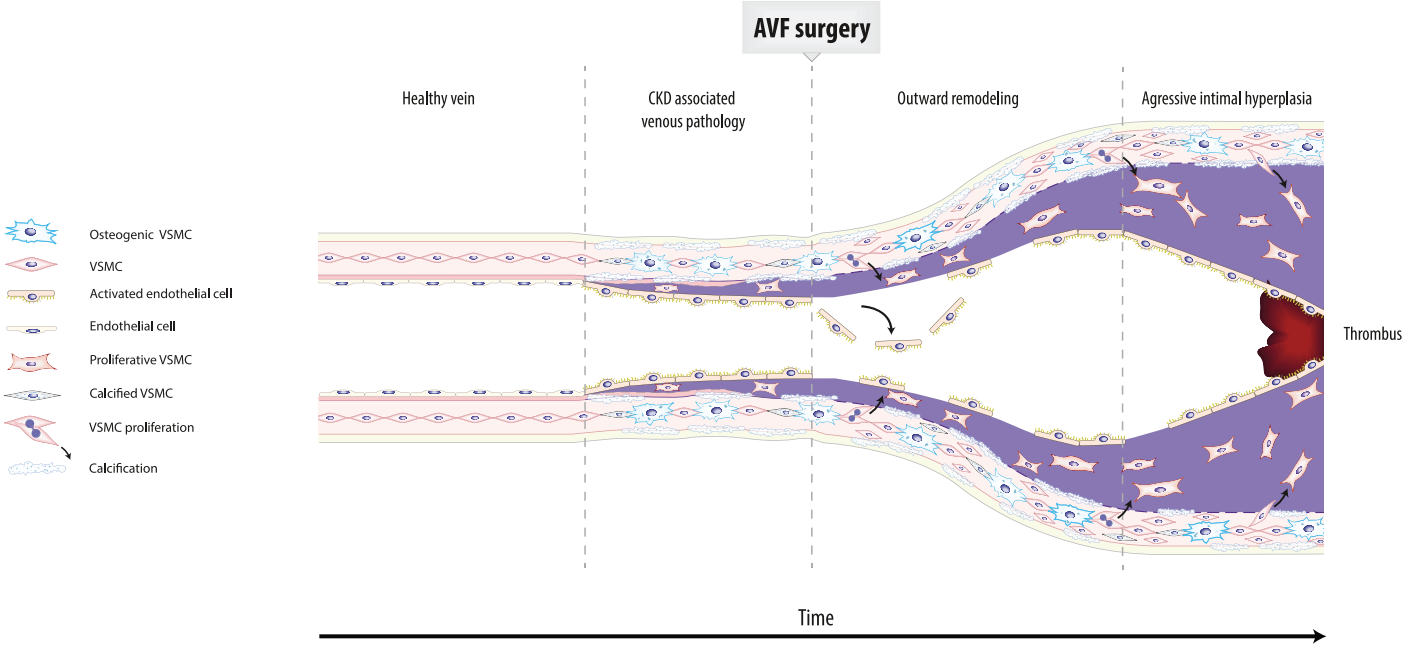

Figure 2. Potential mechanisms of the remodeling response upon fistula creation. Upon fistula creation, in response to the altered hemodynamic environment a plethora of structural changes may occur in the vessel wall; amongst others surgery induced endothelial denudation, matrix reorganization to accommodate outward expansion but possibly also VSMC proliferation and migration contributing to intimal hyperplasia formation. Physiological outward remodeling may to a certain extent compensate for detrimental intimal lesions.

As explained before, the adaptive outward remodeling response occurs both in the feeding artery and in the draining vein of the fistula[12;14]. Nonetheless, the majority of the stenotic lesions in fistulas failing to mature are localized in the venous part, mostly in the juxta-anastomotic region[24;25]. The latter observation could suggest that not only IH but also venous luminal expansion may be important for the preservation of the luminal calibre, thereby allowing the fistula to mature. We postulate that the net resultant of adaptive outward expansion and potential luminal narrowing by IH and thrombosis may ultimately determine luminal calibre, flow and long term AVF patency.

Intimal hyperplasia: adverse vascular response that hampers AVF function

Intimal hyperplasia is the pathologic lesion in AVFs that may result in stenosis and ultimately thrombosis. It is characterized primarily by α-smooth muscle actin (α-SMA) positive cells, extracellular matrix proteins and cytokines such as platelet-derived growth factor, transforming growth factor-β and endothelin within the intima and media of the vein[26-28]. The vast majority of the α-SMA positive cells in the intimal lesions exhibit a myofibroblasts or synthetic VSMC phenotype[29]. These cells could either be differentiated fibroblasts that migrated from the adventitia and acquired α-SMA expression[30], or dedifferentiated medial VSMCs[5]. Furthermore, recent studies of non-AVF models suggest that a proportion of the α-SMA positive cells in IH lesions might originate from multipotent vascular stem cells from the bone marrow[31;3233].

In most physiological conditions, high laminar shear stress triggers endothelial quiescence, endothelial alignment in parallel with the flow and secretion of anti-inflammatory and anti-coagulant substances[17;18;34], thus preventing IH. In contrast, low flow and WSS levels as well as oscillating flow patterns are involved in endothelial cell activation with increased expression of pro-coagulant and pro-inflammatory mediators that predispose for IH[34;35]. Although AVFs merely express high flow profiles, recent studies revealed the coexistence of spot regions with low and oscillating flow and WSS levels in the venous part of the AVF, using a pulsatile computational fluid dynamics simulation[36]. These spot regions corresponded with in previous studies documented IH prone regions in the juxta-anastomotic area of the AVF. Alterations in anastomosis angle could impact the flow rates and patterns, potentially influencing IH formation, with sharper angles (30°) generating favourable outcomes[37]. This was further illustrated by Krishnamoorthy et al[38], demonstrating a correlation between AVF configuration, WSS pattern and the development of IH in a porcine AVF model. Thus, IH in an AVF setting is likely to be associated with an abnormal WSS profile. Nevertheless, IH has also been observed in veins prior to vascular access placement[39] and in saphenous veins[40], suggesting that an abnormal WSS profile is not the sole cause for development of IH. Epidemiological studies have identified diabetes mellitus, race, older age, peripheral vascular disease, female sex and in

some studies also cardiovascular disease as risk factors for maturation failure[41-43]. Furthermore, individual variation in patency outcomes may also in part be explained by genetic susceptibility. Indeed, several single nucleotide polymorphisms are associated with poor functional outcome of vascular access conduits for hemodialysis[44;45].

Most studies on fistula failure focussed on the effect of several parameters on IH, as IH is considered to be the pathognomonical lesion in fistula failure. However, as mentioned above, luminal calibre can be preserved by adequate outward remodeling. Consequently, in addition to IH, impaired outward remodeling may be another important but relatively overlooked contributor to fistula failure. Despite its potential impact on fistula patency, relatively little is known about outward remodeling in AVFs. Future research aiming to gain more insight in the (patho)physiology of outward remodeling in fistulas might therefore contribute to new therapeutic strategies that could improve fistula patency.

Interestingly, some of the elementary factors in outward remodeling are also involved in the process of IH. Whereas outward remodeling in AVFs is related to matrix protease activity such as MMPs and cathepsins[20-22], it is shown that MMPs are also involved in IH formation in AVFs[46;47] and cathepsins in IH formation in balloon-injured artery[48]. The relative contribution of these proteases to expansive remodeling versus IH is not yet established, though the crucial role in outward remodeling suggests a more beneficial than detrimental effect, especially in the initial phase of AVF maturation. The latter suggestion is underscored by a recent report showing increased serum MMP-2 levels in patients with matured fistulas as compared to those with maturation failure[20]. However, as a consequence of elastolytic protease activity the internal elastic lamina is fragmented[21;49]. This disruption of the elastic lamina and loss of integrity of this structural barrier may allow migration of adventitial fibroblasts or medial VSMCs to the intima. Moreover, the elastin degradation products can act as chemo-attractants for VSMCs and fibroblasts and might direct them to the intimal region and support their proliferation[50-52]. Thus, potentially the balance of this partially overlapping beneficial outward remodeling and detrimental IH may affect fistula patency outcomes.

Vascular pathology in chronic kidney disease

Noteworthy, this complex process and fragile balance of successful fistula maturation might be partially hindered by pre-existent vascular abnormalities often present in patients with CKD. Especially in these patients with elevated comorbidity burden, a tailored surgical technique[53;54] and surgical expertise[54] are important in determining fistula patency outcomes. Furthermore, CKD itself is a well-known risk factor for cardiovascular morbidity[55]. The increased prevalence of cardiovascular disease in CKD-patients is only partly explained by traditional risk factors such as hypertension, diabetes, dyslipidemia and increased age. Epidemiological studies revealed

that CKD is an independent risk factor for cardiovascular morbidity[56]. The latter observations implicate a role for additional inimical stimuli in CKD-patients such as chronic inflammation, increased oxidative stress, uremic toxins and endothelial dysfunction, as is reviewed in more detail elsewhere[57-59]. Most studies on CKD mediated vasculopathy concentrate on the arterial system. A functional AVF requires both adequate venous and arterial maturation. Pre-existent arterial vasculopathy may therefore reduce patency. In addition, although not extensively studied, the detrimental effects of CKD on the arterial system may influence veins in a similar manner[60]. Indeed, recent studies elegantly showed marked pre-existing IH in venous segments of patients with end-stage renal disease prior to vascular access surgery[39;61;62]. Another potential contributor to vascular pathology in CKD is vascular calcification. Whereas calcification in the tunica intima is classically associated with atherosclerosis, calcification in the tunica media can occur independently of atherosclerotic plaques and is frequently observed in arteries of any size in CKD-patients[63], resulting in vascular stiffness[64;65]. In arterial setting this is known to impair the vessel's ability to expand upon high flow stimulation[66]. Interestingly, Lee et al[67] recently also demonstrated extensive calcification in the intima and media of venous segments that were harvested at the time of vascular access surgery. This might result, similar to the arterial setting, in reduced venous compliance, thus potentially limiting the utility of AVFs by inhibiting outward remodeling and AVF maturation. Clinical studies already showed that forearm venous distensibility (i.e. increase in luminal diameter upon inflation of an upper arm cuff) rather than baseline venous diameter predicts successful AVF maturation[68]. Although a recent study revealed that medial calcification in the supplying artery of AVFs was not associated with maturation failure[69], future studies should explore the impact of venous calcification prior to access surgery on maturation failure. Indeed, the outward remodeling response is much more pronounced in the venous part of AVFs compared to the feeding artery[12].

Therapeutic strategies to improve vascular access patency

In order to create a proper basis for a successful AVF, pre-operative vein preservation and careful selection of suitable vessels for AVF creation should be performed routinely[2;70]. In case of fistula non-maturation or stenosis a percutaneous transluminal angioplasty (PTA) and/or surgical revision is required[2;70]. To date, there are no adequate therapies improving the remodeling process of the AVF in the intermediary period. Moreover, despite the good results of PTA on the short term, it often induces restenosis on the longer term[71-73]. Therefore there is a strong clinical need for new therapeutic strategies to improve fistula patency.

Possibilities to encourage outward remodeling include the use of elastase, thereby reorganizing the extracellular matrix scaffold of the vessel and promoting rapid dilation. After successful results in an AVF rabbit model[35], the use of recombinant-elastase PRT-201 was recently

clinically evaluated in a randomized controlled trial in human AVFs[74]. Perivascular delivery of PRT-201 appeared to be safe but no effect on primary patency was observed. A larger clinical trial is underway since this first study was not powered to assess efficacy. Given the potential detrimental effects of elastin degradation products on both vascular calcification[75] and VSMC proliferation[51;52], the overall effectiveness of this agent remains to be elucidated.

Potential candidates for targeting IH are agents that inhibit VSMC proliferation, such as paclitaxel and sirolimus, although with data obtained only in AVG setting[76;77] their effect in AVFs remains to be established.

As mentioned above, outward remodeling and IH are two processes that are in part intertwined. Some factors that are involved in outward remodeling such as MMPs may in a later stage also facilitate IH formation. Therefore, the potential of a therapy directed to a factor contributing in both types of remodeling could be influenced by the time of application. Limiting IH in an early stage might also decelerate the outward remodeling response and vice versa. Enhancement of maturation might require a different intervention than prevention of AVF failure once the AVF is successfully used for hemodialysis. Therefore, time dependent delivery might be a suitable approach to tackle fistula failure. Fistulas are ideal targets for such therapy, due to their easy accessibility and the potential to use perivascular delivery methods. However, to create a successful intervention strategy, more insight in the course and (patho)physiology of vascular remodeling is warranted.

Incorporation of other disciplines in the field of vascular access might offer new perspectives. IH is studied extensively in the field of cardiology and vascular surgery and the process of outward remodeling in physiological situations such as pregnancy. Furthermore the technology in slow-release drug delivery systems is rapidly expanding. Another relatively new field with exciting developments is vascular tissue engineering. With vascular tissue engineering it is possible to create a diameter- and length-matched blood vessel free from valves and accessory vessels and has the unique potential to adjust a vessel to patient specific requirements. Importantly, tissue engineered blood vessels are free from pre-existing vascular disease. The potential of a tissue engineered blood vessel (TEBV) as arteriovenous graft was illustrated by the group of l'Heureux and McAllister. Using a so-called sheet-based method, a completely biological TEBV was developed without the use of synthetic material, thereby creating a TEBV that resembles a native vessel in both composition and structure. The TEBV was evaluated as AVG in ten patients resulting in a primary patency rate of 78% and 60% after 1 and 6 months respectively[78]. With spectacular progresses in the field of vascular tissue engineering[79-81], the use of a TEBV might become a realistic alternative in the nearby future.

Conclusion

Upon AVF creation a complex cascade of remodeling events should occur. The net resultant of beneficial outward expansion, potential luminal narrowing by intimal hyperplasia and the possible interference of CKD induced vascular pathology may ultimately determine luminal calibre, flow and long term AVF patency. Due to the potential positive contribution to fistula maturation and its assumed role in luminal calibre preservation, we pledge for more research emphasis on the role of outward remodeling. Further unravelling the complex pathways that mediate both IH and outward remodeling processes after AVF creation could provide new targets and therapies to improve fistula patency.

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