

Arteriovenous access failure: more than just intimal hyperplasia?

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ABSTRACT

Haemodialysis 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 IH but also some relatively neglected but potentially important contributors such as inadequate outward remodelling. 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 remodelling and IH 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 haemodialysis, 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 compared with arteriovenous synthetic grafts [1–3]. Nonetheless, the durability of AVFs is far from optimal with 1-year primary patency rates ranging from 60

to 65% [4, 5]. In fact, these numbers are too optimistic, as they often 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-centre study, which revealed that 60% of the AVFs were not suitable for dialysis between 4 and 5 months after surgery [6], although, these numbers do vary between different types of AVFs [7]. According to the KDOQI guidelines, 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 surface and has a diameter of >6 mm [2]. The exact mechanisms underlying maturation failure are, however, unknown, but impaired outward remodelling 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 remodelling in the setting of AVFs is often neglected. However, adequate outward remodelling could preserve luminal calibre 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 (Figure 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 remodelling and the implications of chronic kidney disease (CKD)-mediated vascular pathology (Figure 2).

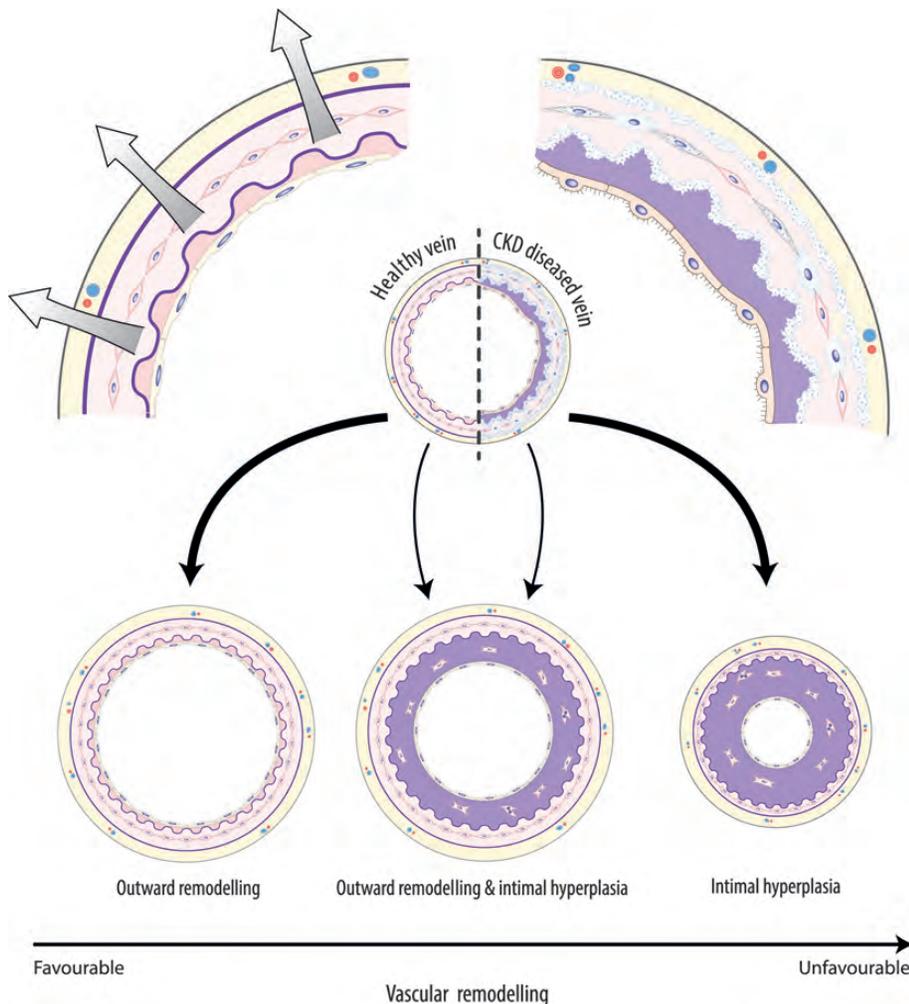


FIGURE 1: Different modalities of the vascular remodelling response after fistula creation. Whereas a healthy vein has the potential for successful outward remodelling (top left), adequate maturation may be partially hindered by CKD-induced pre-existing vasculopathy such as IH (top right). As shown below,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

OUTWARD REMODELLING: AN EMERGING CONCEPT IN AVFs?

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 both the feeding artery and the draining vein [4, 8]. Directly after construction of the AVF, this rapid increase in flow results both in passive vascular distension and in nitric oxide (NO) synthesis by endothelial cells with subsequent vascular smooth muscle cell (VSMC) relaxation [9–11] resulting in acute vasodilation. Concomitantly, the haemodynamic changes following AVF creation initiate a more structural vascular remodelling response leading not only to a further increase in arterial and venous calibre [12–14] but also to thickening especially of 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 an attempt to reduce WSS to pre-AVF levels (5–10 dyn/cm²). 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 haemodynamic 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 3-fold increase in WSS to 24.5 dyn/cm². The continuous increase in flow resulted in a progressive increment in venous luminal calibre from 2.4 mm

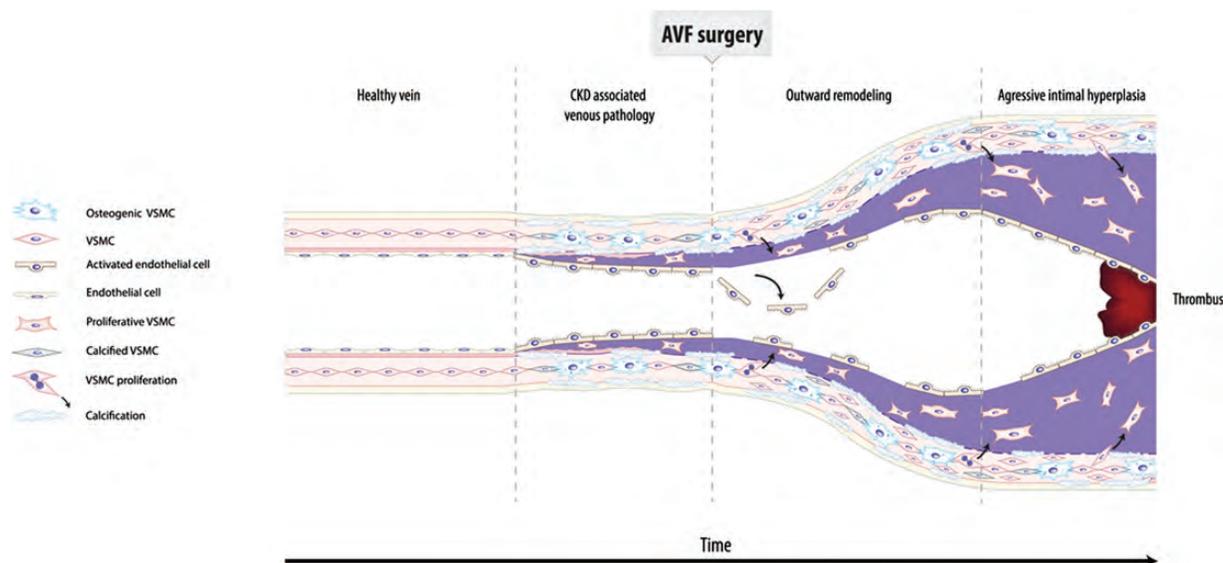


FIGURE 2: Potential mechanisms of the remodelling response upon fistula creation. Upon fistula creation, in response to the altered haemodynamic environment a plethora of structural changes may occur in the vessel wall; among others, surgery induced endothelial denudation, matrix reorganization to accommodate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

pre-operatively 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 to 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 remodelling (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 into 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 remodelling in AVFs.

As explained before, the adaptive outward remodelling 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.

IH: ADVERSE VASCULAR RESPONSE THAT HAMPERS AVF FUNCTION

IH 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 [31–33].

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 to IH [28, 34]. 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 [35]. These spot regions with low and oscillating flow corresponded with in previous studies documented IH prone regions in the juxta-anastomotic area of the AVF. Alterations in anastomosis angle could impact on the flow rates and patterns, potentially influencing IH formation, with sharper angles (30°) generating favourable outcomes [36]. This was further illustrated by Krishnamoorthy *et al.* [37], 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 [38] and in saphenous veins [39], suggesting that an abnormal WSS profile is not the sole cause of 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 [40–42]. 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 outcomes of vascular access conduits for haemodialysis [43, 44].

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

Interestingly, some of the elementary factors in outward remodelling are also involved in the process of IH. Whereas outward remodelling 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 [45, 46] and cathepsins in IH formation in the balloon-injured artery [47]. The relative contribution of these proteases to expansive remodelling versus IH is not yet established, though the crucial role in outward remodelling 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 compared with those with maturation failure [20]. However, as a consequence of elastolytic protease activity, the internal elastic lamina is fragmented [21, 48]. 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 [49–51]. Thus, potentially, the balance of this partially overlapping beneficial outward remodelling and detrimental IH may affect fistula patency outcomes.

VASCULAR PATHOLOGY IN CKD

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 [52, 53] and surgical expertise [53] are important in determining fistula patency outcomes. Furthermore, CKD itself is a well-known risk factor for cardiovascular morbidity [54]. The increased prevalence of cardiovascular disease in CKD-patients is only partly explained by traditional risk factors such as hypertension, diabetes, dyslipidaemia and increased age. Epidemiological studies revealed that CKD is an independent risk factor for cardiovascular morbidity [55]. The latter observations implicate a role for additional inimical stimuli in CKD-patients such as chronic inflammation, increased oxidative stress, uraemic toxins and endothelial dysfunction, as is reviewed in more detail elsewhere [56–58]. Most studies of 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 [59]. Indeed, recent studies elegantly showed marked pre-existing IH in venous segments of patients with end-stage renal disease prior to vascular access surgery [38, 60, 61]. 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 commonly observed in arteries of any size in CKD patients [62], resulting in vascular stiffness [63, 64]. In the arterial setting this is known to impair the vessel's ability to expand upon high-flow stimulation [65]. Interestingly, Lee *et al.* [66] 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 remodelling 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 [67]. Although a recent study revealed that medial calcification in the supplying artery of AVFs was not associated with maturation failure [68],

future studies should explore the impact of venous calcification prior to access surgery on maturation failure. Indeed, the outward remodelling response is much more pronounced in the venous part of AVFs compared with 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, 69]. In case of fistula non-maturation or stenosis, a percutaneous transluminal angioplasty (PTA) and/or surgical revision are/is required [2, 69]. To date, there are no adequate therapies that can improve the remodelling 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 long term [70–72]. Therefore, there is a strong clinical need for new therapeutic strategies to improve fistula patency.

Possibilities to encourage outward remodelling 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 [28], the use of recombinant-elastase PRT-201 was recently clinically evaluated in a randomized controlled trial in human AVFs [73]. Perivascular delivery of PRT-201 appeared to be safe but no effect of 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 both on vascular calcification [74] and on VSMC proliferation [50, 51], the overall effectiveness of this agent remains to be elucidated.

Potential therapeutics that could target IH are agents that inhibit VSMC proliferation, such as paclitaxel and sirolimus, although with data obtained only in the arteriovenous graft (AVG) setting [75, 76] their effect in AVFs remains to be established.

As mentioned above, outward remodelling and IH are two processes that are in part intertwined. Some factors that are involved in outward remodelling 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 remodelling could be influenced by the time of application. Limiting IH in an early stage might also decelerate the outward remodelling response and vice versa. Enhancement of maturation might require an intervention different from prevention of AVF failure once the AVF is successfully used for haemodialysis. Therefore, time-dependent delivery might be a suitable approach to tackling 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 into the course and (patho)physiology of vascular remodelling 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 remodelling 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. Vascular tissue engineering enables creation of 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 (TEBVs) are free from pre-existing vascular disease. The potential of a TEBV as AVG 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 [77]. With spectacular progress in the field of vascular tissue engineering [78–80], the use of a TEBV might become a realistic alternative in the near future.

CONCLUSION

Upon AVF creation, a complex cascade of remodelling events should occur. The net resultant of beneficial outward expansion, potential luminal narrowing by IH 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 remodelling. Further unravelling the complex pathways that mediate both IH and outward remodelling processes after AVF creation could provide new targets and therapies to improve fistula patency.

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CONFLICT OF INTEREST STATEMENT

None declared.

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How important is transfusion avoidance in 2013?

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ABSTRACT

Prior to the advent of recombinant erythropoietin in the late-1980s, blood transfusions were the mainstay of anaemia management in patients with end-stage renal failure, many of whom required “top-up” transfusions every 2 to 4 weeks to relieve the debilitating symptoms of severe anaemia. Erythropoietin therapy, however, allowed for the first time, such patients to achieve a sustained correction of anaemia, and there was a dramatic fall in both the use of red cell transfusions in dialysis units, as well as the associated transfusional iron overload prevalent in dialysis patients. Avoidance of blood transfusions improved access to, and outcomes of, kidney transplantation, due to reduced HLA sensitization. In recent years, however, there have been safety concerns regarding the use of erythropoiesis-stimulating agents (ESAs), and there are signs that the use of blood transfusions is once again increasing. The aim of this review is to reassess how important transfusion avoidance is in 2013, and whether we should still have the same concerns about HLA sensitization that we had 20 years ago.

INTRODUCTION

Prior to the 1990s, blood transfusions were the mainstay of anaemia management in patients with end-stage renal disease, with a large number of patients requiring ‘top-up’ transfusions every 2–4 weeks to relieve a constellation of severe debilitating symptoms, including profound lethargy, shortness of breath on mild exertion and poor physical capacity. The disadvantages and potential harm associated with this practice were well-recognized, and included the risk of transmission of infectious agents, sensitization to HLA antigens and transfusional iron overload [1]. The effects of the blood transfusions were transient, and chronic repeated transfusional support was the norm for many patients. The advent of recombinant human erythropoietin in 1990 transformed this situation, and allowed the vast majority of dialysis patients to achieve a sustained correction of anaemia to levels of haemoglobin that significantly reduced the need for regular transfusions. Three major consequences arose over the next decade or so: (i) there was a steady but progressive rise in haemoglobin concentration from a mean of ~9.5 g/dL to a mean of ~11.5 g/dL [2];