Intimal Hyperplasia and Arteriovenous Fistula Failure: Looking Beyond Size Differences

Roberto I. Vazquez-Padron, Juan C. Duque, Marwan Tabbara, Loay H. Salman, and Laisel Martinez

1 DeWitt Daughtry Family Department of Surgery, Leonard M. Miller School of Medicine, University of Miami, Miami, FL; 2 Katz Family Division of Nephrology, Department of Medicine, Leonard M. Miller School of Medicine, University of Miami, Miami, FL; 3 Division of Nephrology, Albany Medical College, Albany, NY

Correspondence:
Laisel Martinez, PharmD, MS
Division of Vascular Surgery
University of Miami Miller School of Medicine
1600 NW 10th Avenue, RMSB 1011B
Miami, FL 33136

Telephone: 305-243-3582
E-mail: lmartinez6@med.miami.edu
ABSTRACT

The development of venous intimal hyperplasia (IH) has been historically associated with failure of arteriovenous fistulas (AVF) used for hemodialysis. This long-standing assumption, based on histological observations, has been recently challenged by clinical studies indicating that the size of the intima by itself is not enough to explain stenosis or AVF maturation failure. Irrespective of this lack of association, IH is present in most native veins and fistulas, is prominent in many cases, and suggests a role in the vein that may not be reflected by its dimensions. Therefore, the contribution of IH to AVF dysfunction remains controversial. Using only clinical data and avoiding extrapolations from animal models, we critically discuss the biological significance of IH in vein remodeling, vascular access function, and the response of the venous wall to repeated trauma in hemodialysis patients. We address questions and pose new ones such as: What are the factors that contribute to IH in pre-access veins and AVFs? Do cellular phenotypes and composition of the intima influence AVF function? Are there protective roles of the venous intima? This review explores these possibilities, with hopes of rekindling a critical discussion about venous IH that goes beyond thickness and AVF outcomes.
INTRODUCTION

Intimal hyperplasia (IH) is a build-up of myofibroblast-like cells (neointimal cells) and extracellular matrix (ECM) within the tunica intima, the innermost layer of the vein (1). In pre-access veins of chronic kidney disease (CKD) patients, IH manifests as an idiopathic and benign histological feature that does not compromise blood flow (2-6). Following arteriovenous fistula (AVF) creation, expansion of the intima may remain innocuous or aggravate inward remodeling leading to stenosis and access failure (3). The actual contribution of IH in relation to other transformation processes in the wall after AVF creation remains uncertain (7). Importantly, once stenosis becomes a pathology it is not easily treatable, with frequent recurrences after endovascular procedures (8-14). The lack of more effective therapies against stenosis reflects our simplistic view of the processes of intimal expansion and wall remodeling, and our unawareness of the characteristics that distinguish between benign and occlusive IH.

This review critically discusses what we know about IH in human veins and AVFs, what we are missing, and how this knowledge may influence IH-targeted therapies to improve AVF outcomes. We discuss the historical assumption that IH alone causes stenosis and AVF failure and extend our debate beyond IH size, the focus of published research in this area. Finally, we highlight the necessity for innovation, state-of-the-art omics, and single-cell technology to clarify the actual role of IH in venous remodeling.
PRE-EXISTING INTIMAL HYPERPLASIA

Intimal hyperplasia in the pre-access vein: more common than previously thought

The cephalic and basilic veins are the preferred choices for AVF creation (15). These are medium-size veins with the three vascular layers well defined (tunica intima, tunica media, and tunica externa or adventitia) and diameters between 1 and 5 mm (16, 17) (Figures 1-2). The intima is the innermost layer of the vessel and is demarcated by a thin or discontinuous internal elastic lamina on the medial side and a continuous endothelial line that separates it from the lumen. Thin folds of collagen-rich connective tissue covered by endothelium extend from the intima and form the valves at regular intervals along the vein.

The size of the intima layer in pre-access veins ranges from almost inexistent to thick and rich in intimal cells and ECM, with this latter scenario being the norm rather than the exception (2-6, 18-24). Almost 20 years ago, Wali et al. observed generalized IH in cephalic veins from 20 renal failure patients (25, 26). In more recent and larger patient cohorts (N=57-129), maximal intimal thickness (the longest distance between the media and the lumen) ranged from 1 to 660 μm in forearm and upper-arm pre-access veins (Table 1), with higher values in the latter (2, 4, 6). The Hemodialysis Fistula Maturation (HFM) Study confirmed the high prevalence of IH in 365 pre-access veins and quantified it as percent luminal occlusion (5) (Table 1). Twenty-two percent of the patients presented moderate IH (21-40% luminal occlusion) while 35% portrayed severe IH (>41% occlusion). In agreement with Allon et al. (4), percent luminal occlusion was lower in cephalic veins (mean 30.6%) than in upper-arm vessels (mean 40.3%). Martinez et al. expressed IH as intima/media area ratio (I/M ratio) in 110 upper-arm veins (3) to account for morphometric changes in the media such as atrophy or hypertrophy (18, 20, 25, 26). The median
I/M ratio in this cohort was 0.32, in line with previous reports of cephalic and other pre-access veins (18, 19, 24) (Table 1).

Despite its common occurrence in pre-access veins, whether IH development is influenced by CKD remains unknown because experimental animal models do not develop spontaneous IH. Various studies support an increase in IH in the setting of CKD (6, 21, 25-27), but the number of non-CKD upper extremity veins is low (3-15 individuals), which makes it difficult to draw a definite conclusion on this issue. The I/M ratio of the great saphenous vein was also found significantly higher in CKD patients compared to controls, and in end-stage renal disease versus CKD stages 1 and 2 (27), but it is not clear whether these groups were matched with respect to age and baseline characteristics. It is tempting to speculate that IH increases during the course of renal dysfunction secondary to volume/flow overload (anemia, sodium, and water retention) as well as other poorly defined clinical factors. However, frequent IH was observed in cephalic and saphenous veins from elderly patients with normal renal function (28), suggesting that uremia is not the only vascular insult causing intimal thickening. Synergistic insults may include endothelial dysfunction in CKD and vascular injury related to venipuncture or catheterization. On the other hand, the presence of a thick intima in basilic veins (2, 3) as in the superficial cephalic vein (4-6, 19) suggests that mechanisms other than venipuncture-related trauma promote IH. Single-cell sequencing and spatial proteomics may help identify differences in cell and ECM composition (if any) between the CKD and non-CKD pre-access intima. This may, in turn, uncover common and disease-relevant origins of IH.
Composition of the pre-access intima: identifying knowledge gaps

Three types of cells predominate in the intima of pre-access veins: endothelial cells (ECs), smooth muscle cells (SMCs), and myofibroblasts/fibroblasts (1, 2, 5, 18-20, 29). Endothelial cells line the luminal side of the intima, whereas SMCs and myofibroblasts embedded in ECM populate the core of the layer. Endothelial cells play an essential role in preventing thrombosis, but their contribution to controlling IH has not been fully elucidated. While there is wide support for the inhibitory effect of EC-derived nitric oxide in intimal cell proliferation and migration (30), there is also evidence for other endothelial paracrine factor(s) that stimulate venous IH (31). The overall effect of the endothelium on IH is likely dependent on flow and pathophysiological conditions. Along these lines, profound changes in EC and SMC morphology (25, 26, 32) and function (33-39) have been detected in CKD patients.

Using a combination of contractile (smooth muscle myosin heavy chain [SM-MHC], desmin, h-caldesmon, calponin), synthetic (vimentin), and pan SMC markers (alpha smooth muscle actin [αSMA]), various groups have observed a mixture of SMC and/or myofibroblast phenotypes in the intima of pre-access veins (2, 18-20, 29, 40, 41), whose functions remain uncertain. Contractile SMCs are typically associated with low proliferation and migration rates, and low secretion of ECM (42). The opposite behavior is characteristic of “synthetic” or “myofibroblastic” SMCs that have lost expression of contractile markers. Serum from dialysis patients favors the synthetic transformation of cultured human SMCs by promoting epigenetic downregulation of contractile gene expression (27). Interestingly, despite the high number of synthetic SMCs in pre-access veins, they show minimal staining of the proliferation and metabolic markers Ki-67 and PGM-1, respectively, suggesting that intimal cells are relatively quiescent prior to access creation (5, 18). The HFM Study also reported rare apoptotic cells by
cleaved caspase 3 expression in less than 10% of analyzed intimas (4/48) (5). How expression of contractile markers in CKD veins relates to venoconstriction or dilation is unclear. A thick intima likely serves as a barrier for the diffusion of both circulatory vasoactive factors and EC-derived molecules that regulate medial SMC contraction or dilation. This may be an advantageous adaptation to reduce vasoconstrictive responses. On the other hand, studies in saphenous veins proposed that intimal thickness >120 µm is associated with impaired endothelium-dependent vasodilation (43). If there is a signaling cascade of soluble factors from ECs or the lumen that is amplified by intimal myofibroblasts or SMCs remains to be discovered.

In contrast with the abundance of inflammatory cells in the arterial intima with disease, the number of immune cells in pre-access veins is minimal. Approximately 50% of analyzed veins in the HFM Study (25/48) showed only one CD68-expressing macrophage in the intima with approximately 7.7 cells in the whole section (5). Martinez et al. also reported low numbers of CD68\(^+\) macrophages (about 40 cells per cross-section) in 45 basilic veins, mostly located at the edge between the media and the adventitia (44). In terms of T cells, Lee et al. observed minimal CD3\(^+\) staining in the intima (18). Despite the low levels of immune infiltration in pre-access veins, a transcriptomic analysis uncovered expression of myeloid-related inflammatory genes in intimal and medial SMCs and myofibroblasts, suggesting a key role of resident cells in vascular inflammation (44). Five genes (\textit{CSF3R}, \textit{FPR1}, \textit{S100A8}, \textit{S100A9}, and \textit{VNN2}) were associated with AVF maturation failure, and expression of \textit{S100A8} and \textit{S100A9} had a weak correlation with postoperative IH (44). Wasse et al. also found expression of TNF-\(\alpha\), TGF-\(\beta\), and IL-6 in the intima of pre-access veins (24). Immunohistochemistry analyses demonstrate that not all cells in the intima and media are positive for these proteins (24, 44), demonstrating again a
heterogeneity of SMC and myofibroblast phenotypes with potential implications for the inflammatory status of the vessel.

The ECM composition of the intima is an important aspect of remodeling, and perhaps the most neglected characteristic of this layer. The HFM Study observed significant inter-patient variability by histology in the amount and distribution of collagen and proteoglycans in the intima (5). Intimal expansion in earlier reports of 20 cephalic veins was also characterized by marked deposition of fragmented collagen fibers and dispersed elastin (25, 26). Intimal calcification was observed in 2% of the cases in the HFM Study and 15% in Wali et al (5, 25). It is important to note that the proportion and configuration of the ECM and the types of ECM proteins in the intima may play a role in cell proliferation and migration (45-48), vein stiffness (49, 50), and/or compressibility of this layer under high flow conditions (51). Accumulation of collagen is associated with fibrosis, whereas high proteoglycan content may confer resistance to compression and act as a reservoir of cytokines and growth factors that influence cell survival and proliferation (49, 51). Future proteomic studies are needed for a more accurate characterization of the intimal ECM.

**Does pre-existing intimal hyperplasia increase the risk of AVF failure?**

The initial idea that pre-existing IH potentially led to stenosis and poor AVF outcomes has been recently challenged in several independent studies (2-4, 52). Allon et al. studied the association between maximal intimal thickness in the pre-access vein and postoperative AVF stenosis (4). Of the 113 patients included in the analysis, 50% developed a hemodynamically significant stenosis. However, there was no association between IH and the presence of
postoperative stenosis (Table 1). This lack of association remained true when analyzed by type of AVF and location of the stenosis (4). The results of this study were confirmed by the HFM Study in 365 individuals (52). The development of stenosis was evaluated by ultrasound at 1 day, 2 weeks, and 6 weeks after AVF creation. Pre-existing IH (percent luminal occlusion) was not associated with AVF stenosis at any of these time points nor with the internal diameter of the vessel (52).

The relationship between pre-existing IH and maturation failure was analyzed by the HFM Study and Martinez et al. (3, 52). The HFM Study found a significant association between the pre-existing percent of luminal occlusion and venous blood flow rate at 6 weeks after access creation (Table 1). However, the association with unassisted or overall maturation failure did not reach statistical significance (52). Pre-existing I/M ratio also failed to predict non-maturation in 110 patients in Martinez et al (3). Lastly, Tabbara et al. analyzed the association between pre-existing IH and primary unassisted patency in 52 upper-arm fistulas (2). Neither maximal intimal thickness nor I/M area ratio predicted loss of primary patency. While there seems to be no association between pre-existing intimal morphometry and AVF failure, additional studies are needed to assess the effects of intimal cell and ECM composition on postoperative outcomes.

**POSTOPERATIVE INTIMAL HYPERPLASIA**

**Intimal hyperplasia after AVF creation: selective activation of pre-existing cells?**

The transformation of the vein after AVF creation remains one of the least understood processes in vascular biology. The current knowledge emphasizes on the role of ECs in sensing arterial shear stress to release vasodilators that potentially lead to maturation (53, 54). However,
the endothelium is almost certainly severely damaged by surgical trauma secondary to the common use of dilators and saline flushing to expand venous size before anastomosis. This suggests that intimal and medial cells likely play a protagonist’s role as mechanosensors of hemodynamics changes and vascular trauma. The best evidence we have about postoperative remodeling of the intima is from two-stage AVFs, which allow us to collect a biopsy of the remodeled vein (now a fistula) during transposition surgery.

In upper-arm fistulas, maximal intimal thickness increased approximately four folds with respect to the pre-access vein, with values ranging from 0.1 to 2.0 mm in 79 patients who underwent two-stage AVF creation (2) (Table 1). This increase was not associated with the waiting time between AVF creation and transposition surgeries nor with the thickness of the intima in the pre-access vessel. The lack of relationship between pre-existing and postoperative IH agrees with a selective activation of cells in the wall and different responses to surgical or hemodynamic injury between patients. Moreover, the absence of correlation between IH and the time between AVF creation and transposition surgeries suggests that most intimal expansion occurs early during maturation. Medial atrophy is frequently seen in AVFs (Figure 3) possibly as a result of cell death or migration of SMCs into the intima. This SMC loss is either replaced by ECM (fibrosis) or results in thinning of the media. A median I/M area ratio of 0.77 was reported in 115 two-stage AVF cross-sections, significantly higher than in native veins (3) (Table 1). In agreement with maximal intimal thickness, I/M ratio also demonstrated a lack of correlation between pre-existing and postoperative values in pairwise analyses.

In contrast to native veins (5), IH in most upper-arm AVFs is eccentric (Figure 3). Unequal hemodynamic forces along the length of the vein are thought to explain this morphometry. This has been recently imaged in mice (55), although confirmatory studies in
large animal models and humans are needed. It has been proposed that low wall shear stress, pulsatile stretch, and flow turbulence causes injury and elicits proliferation of intimal cells (56-60). However, it is possible that such eccentric appearance may be explained by pockets of increased cell proliferation, migration and/or ECM deposition; and that these pockets are determined, in turn, by the phenotypes of the pre-existing intimal cells.

At the cellular level, the postoperative remodeling process seems to favor the intimal expansion and/or survival of myofibroblasts and synthetic SMCs in the AVF wall. Tabbara et al. observed that the intima of upper-arm AVFs collected at the time of transposition was mostly made up of synthetic SMCs (positive for αSMA, negative for SM-MHC) (2). Other studies also reported a majority of myofibroblasts (αSMA+, vimentin+, desmin-) (40, 41, 61) and reduced expression of SM-MHC and calponin (29) in the intima of stenotic samples collected at the time of AVF revision. In all studies, medial SMCs retained contractile protein expression (2, 29, 40, 41). The proportion and phenotypes of AVF intimal cells that are actively proliferating remains unknown. High intimal levels of the proliferation marker PCNA were observed in stenotic areas of resected AVFs (41, 62), but were contradicted by the more accurate marker Ki-67 (63). High PCNA and cdk2 levels in de Graaf et al. were also accompanied by significantly lower expression of the cell cycle regulator p21Waf1 (62). Future single-cell tracing experiments will help define whether the increase in synthetic SMCs and myofibroblasts in the AVF intima is due to the postoperative dedifferentiation and expansion of contractile SMCs in the wall, or proliferation of a pre-existing synthetic population. This information will be instrumental for the design of targeted therapies.

The role of immune cell infiltration in postoperative IH and AVF dysfunction is not clear at the moment. Increased macrophage and T-cell infiltration was seen in 15 stenotic AVF
sections compared to pre-access veins (64). In contrast, a comparison of 13 non-thrombosed stenotic samples and 23 thrombosed specimens revealed that immune cell infiltration was in fact characteristic of the latter (65). Similar to the localization of pro-inflammatory proteins in intimal SMCs and myofibroblasts in pre-access veins (44), various studies have also demonstrated elevated inflammatory and oxidative markers in resident intimal cells of resected AVF specimens (64, 66). It is important to note that most of the information about immune cell infiltration after AVF creation comes from extrapolation from animal models (67-70) where it is possible to obtain AVF samples early after surgery. Whether inflammation from infiltrated or resident cells plays a role in human AVF maturation or dysfunction will require the analysis of early human AVF samples (within two weeks of surgery), including non-stenotic segments. This may be possible through a multicenter collection of veins from steal syndrome and stenotic accesses that require early surgical revision.

As in pre-access veins, the ECM composition of the AVF intima has been barely studied. Martinez et al. observed various levels and patterns of ECM deposition in the intima of two-stage transposition fistulas (3), although a comparative analysis of the samples was not presented. These patterns included intimas that were mostly cellular (low in ECM), with widespread ECM distribution, or with separate areas for cells and ECM deposition. Such interpatient variability in composition is likely relevant to the occlusive character of the intima, the response of the vein to cannulation injury, and the efficacy of endovascular treatments.
Postoperative intimal hyperplasia and AVF outcomes: let us update the theory

The most important question about IH is whether growth of this layer after AVF creation underlies access failure. Various case reports of AVFs that failed observed the presence of moderate to severe IH but lacked a comparative group of functional fistulas (21, 29, 41, 61). Despite this limitation, these observations reinforced the assumption that a thicker intima was responsible for AVF failure. The analysis of postoperative samples from two-stage upper-arm AVFs has challenged this idea (2, 3, 71).

Tabbara et al. found a lack of association between postoperative IH (measured as maximal intimal thickness and I/M ratio) and maturation failure in a cohort of 79 individuals (2) (Table 1). These analyses were not adjusted for any other clinical characteristics. Martinez et al. also failed to find an association between I/M ratio and maturation failure in 115 individuals after adjusting for sex effects (3). Interestingly, the same study demonstrated that postoperative medial fibrosis was significantly associated with failure. What is more, IH was associated with failure only in those AVFs with medial fibrosis over the median value, and not in the other half of the accesses (3) (Table 1). Given that high medial fibrosis can adversely influence the biomechanical properties and distensibility of AVFs, this study proposed that under highly fibrotic wall conditions high IH is occlusive, but not when the vessel is able to compensate through other biomechanical mechanisms. This underscores the importance of understanding AVF remodeling as a whole and the mechanistic relationships between IH and other wall remodeling processes.

Pairwise comparisons of adjacent stenotic and non-stenotic segments in two-stage upper-arm AVFs further confirmed that IH does not define the true luminal area of the access (71). In a report of stenotic and non-stenotic tissue pairs from 14 AVFs, there were no significant
differences in intima size between both segments (Table 1). Lastly, no significant association
has been found between maximal intimal thickness or I/M ratio and primary unassisted patency
(2). The above postoperative data on maturation failure, focal stenosis, and primary patency are
limited to upper-arm AVFs due to practical limitations. It is possible that postoperative IH has a
larger effect on the outcomes of forearm fistulas.

RESEARCH MODELS, CURRENT CHALLENGES, AND PENDING QUESTIONS

Role of animal models in the study of intimal hyperplasia

Animals are essential to address basic science questions such as the origin and
differentiation of intimal cells, temporal remodeling of the wall, and the effects of local and
circulatory stimuli or treatments (29, 67, 68, 72-79). Research mice and rats have the added
advantage of allowing genetic manipulation (gene knock-ins and knockouts, cell labeling, etc.)
and inclusion of high numbers of animals. Swine and sheep are often used as translational
models to test pharmacological and endovascular interventions, primarily in arteriovenous grafts
(80-83). Arguably, the best animal model for AVF functional studies is the one in sheep due to
the superficial location of peripheral veins, which allows for not only AVF creation but also for
potential cannulation (73).

Most animal models develop a certain form of venous IH within 2-6 weeks after AVF
creation (29, 67, 68, 72, 74-79). However, they have important limitations for the study of the
occlusive role of IH in AVF remodeling and failure. In the case of small animals, there are
profound differences in pre-existing vein morphology (very thin walls and subendothelial space)
and hemodynamic characteristics (low blood flow) with respect to humans (29, 67, 68, 76, 78,
In addition, most models lack an underlying long-term CKD component and a human-equivalent definition of failure. These limitations underscore the necessity of expanding tissue biobanks of human AVFs to all possible forms to promote retro-translational studies, where human findings could be further dissected at the mechanistic level in animal models. Excellent reviews of AVF and CKD animal models have been included in the References (84-87).

**Current challenges in treating AVF stenosis: a call for mechanism-based approaches**

The idea that IH was the main cause of stenosis in AVFs motivated the use of therapies that treat restenosis in coronary circulation to salvage dysfunctional accesses. As a result, percutaneous transluminal angioplasty (PTA) became the first-line treatment for postoperative stenoses (15). Angioplasty mechanically stretches the vein and compresses the intima but may cause significant injury to the vessel. Although efficacious in the short-term, PTA frequently requires reintervention within one or two years after the first angioplasty procedure either due to regrowing of occlusive IH and/or fibrotic scarring of the AVF wall (8-14). Stent placement is the last line of treatment for recurrent and high recoil stenoses due to concerns of vein depletion, stent migration or fracture, and intrastent thrombosis (88, 89). Stent grafts are favored for in-stent restenosis (15, 89), but are prone to “edge stenosis” that occurs close to both ends of the stent and migrates toward the center (90, 91).

In an attempt to improve post-procedure patency, anti-proliferative drugs (mainly paclitaxel) are delivered to the AVF wall by means of drug-eluting balloons (DEB) or stents. Multiple individual studies have shown patency and/or re-intervention benefits of DEB vs. conventional angioplasty (12-14, 92-95). However, meta-analysis studies have yielded variable
conclusions, and patency rates over six months still have much room for improvement (96-99). The observed variability in efficacy with antiproliferative agents and failure to significantly extend long-term patency may indicate insufficient delivery or retention of the drug (100-102), low sensitivity of cells to treatment (103), or a mismatch between the therapeutic effects of the drug and mechanisms of restenosis in AVFs. In vitro data suggest that paclitaxel targets all three presumed processes of restenosis (proliferation, migration, and ECM production) (104, 105). However, it is not clear which of these cellular mechanisms are actually targeted in AVFs in vivo. Of note, the effect of paclitaxel in SMCs is cytostatic and not cytotoxic (106, 107). Therefore, any stenotic mechanisms that remain unaffected may continue happening or possibly worsen after DEB treatment.

Anti-stenotic treatment modalities to improve venous remodeling during maturation include perivascular delivery of sirolimus (108), allogeneic ECs (109, 110), or pancreatic elastase (111, 112), as well as devices (VasQ, Optiflow) that support the ideal angle of arteriovenous anastomosis (113-117). The latest results on the sirolimus implants are pending (108). VasQ resulted in high maturation rates in single-arm and retrospective studies (117-119), but mixed results in short-term primary or secondary patency compared to the control arm (114, 118, 119). The rest are currently not recommended by the KDOQI guidelines due to lack of phase 3 studies (Optiflow) or significant benefits in AVF outcomes (ECs, elastase) (15). Far infrared radiation and external pneumatic compression (Fist Assist) have shown promising results in AVF maturation parameters (120-123) and secondary patency after PTA in specific patient demographics (124), but require further validation in a broader hemodialysis population. These clinical trials illustrate the desire to innovate in the search for preventive and postoperative AVF treatments. However, until we understand how human AVF cells respond to flow
disturbances, repeated cannulations, and endovascular trauma at the molecular level, it is likely that any successes will come after significant trial and error.

**What to look beyond intimal thickness**

Why have we failed to find an association between intima size measurements and AVF outcomes? The answer may be methodological and/or biological in nature. From the methodological point of view, there are many limitations to the way we measure intima size. Two-dimensional (2D) and static histological assessment of IH misses the actual size of the lumen under circulation. In addition, none of the measurements considers the potential compressibility of the intima or distensibility of the vessel. At least one clinical study has reported a lack of association between maximal intimal thickness by histology and internal diameter of the vein (4), illustrating the limitations of 2D morphometry measurements in determining luminal area.

From the biological point of view, intima size only represents a partial measurement of inward remodeling. Looking for associations between intima size and AVF outcomes ignores other macro processes of the wall, such as inward remodeling of the media, outward remodeling of the wall, and changes in the ECM. Importantly, we still do not understand what drives any of these processes. Is it cell death? Changes on SMC phenotypes? SMC- or immune cell-derived inflammation? Are IH and medial fibrosis mechanistically related? From the biomechanical point of view, how compressible is the intima? What characteristics make it more or less compressible? Does vein distensibility change after AVF creation? A better understanding of the role of SMCs and myofibroblasts in intimal expansion and wall remodeling, and where in the
range of their phenotypic transformation they become problematic, will require detailed phenotypic analyses and single-cell omics techniques in clinically relevant human samples.

Lastly, the complexity of AVF remodeling lies in identifying an optimal level of IH and fibrosis that maintains vein integrity under extreme hemodynamic conditions and frequent cannulations, but without causing stenosis. Thus, can we envision protective roles for the intima? Does it prevent excessive immune cell infiltration? Does it protect medial SMCs from the oxidative stress of high $O_2$ pressures? Do synthetic cells confer regenerative capacity for wall healing after cannulation? We must consider all of these possibilities if we truly want to optimize maturation and prevent restenosis after endovascular treatments.

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AUTHOR CONTRIBUTIONS

R Vazquez-Padron: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Writing - original draft; Writing - review and editing

J Duque: Data curation; Formal analysis; Investigation; Methodology; Writing - review and editing

M Tabbara: Conceptualization; Investigation; Methodology; Writing - review and editing

L Salman: Conceptualization; Investigation; Writing - review and editing

L Martinez: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Supervision; Visualization; Writing - original draft; Writing - review and editing
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| Study                     | N<sup>a</sup> | Vein                               | Parameter(s)<sup>b</sup>     | Measurements<sup>e</sup> | Association(s)<sup>d</sup>                                                                 |
|--------------------------|---------------|-----------------------------------|------------------------------|--------------------------|--------------------------------------------------------------------------------------------|
| **PRE-EXISTING INTIMAL HYPERPLASIA** |               |                                   |                              |                          |                                                                                             |
| Feinfeld et al. 1999<sup>23</sup> | 15            | Brachial (n=15)                  | Ave. I Thickness             | 6.0 ± 0.9 µm             | N/A                                                                                         |
| Lee et al. 2011<sup>18</sup>     | 12            | Cephalic (n=6), Axillary (n=3), Antecubital (n=1), Basilic (n=1), Brachial (n=1) | Ave. IM Thickness | 0.34 ± 0.12 mm | Significant association with maturation failure (P=0.03, n=7) N/A                      |
|                            |               |                                   | Max. IM Thickness            | 1.16 ± 0.30 mm          | N/A                                                                                         |
|                            |               |                                   | I/M Area Ratio              | 0.24 ± 0.07             | N/A                                                                                         |
|                            |               |                                   | % Luminal Occlusion         | 46.6 ± 9.3 %            | Lack of association with maturation failure (P=0.085, n=7) N/A                             |
| Wasse et al. 2012<sup>24</sup> | 10            | Cephalic, basilic                 | Ave. I Thickness             | 0.066 ± 0.019 mm        | N/A                                                                                         |
|                            |               |                                   | Max. I Thickness             | 0.166 ± 0.042 mm        | N/A                                                                                         |
|                            |               |                                   | Mean I/M Thickness Ratio     | 0.26 ± 0.07             | N/A                                                                                         |
|                            |               |                                   | Max. I/M Thickness Ratio     | 0.69 ± 0.19             | N/A                                                                                         |
|                            |               |                                   | Intimal Area                | 0.27 ± 0.08 mm<sup>2</sup> | N/A                                                                                         |
|                            |               |                                   | I/M Area Ratio              | 0.24 ± 0.06             | N/A                                                                                         |
| Allon et al. 2013<sup>4</sup> | 113           | Upper Arm (65%), Forearm (35%)   | Max. I Thickness            | 0.022 [0.013-0.045] mm  | Lack of association with postoperative stenosis (P=0.49) N/A                             |
| Lee et al. 2014<sup>21</sup>   | 29            | N/A                               | Mean I/M Thickness Ratio     | 0.43 ± 0.07             | N/A                                                                                         |
|                            |               |                                   | Max. I/M Thickness Ratio     | 0.86 ± 0.07             | N/A                                                                                         |
| Lazich et al. 2015<sup>19</sup> | 18            | Cephalic (n=18)                  | Max. I Thickness            | 0.052-0.81 mm           | N/A                                                                                         |
|                            |               |                                   | Intimal Area                | 0.16-7.70 mm<sup>2</sup> | N/A                                                                                         |
|                            |               |                                   | I/M Area Ratio              | 0.07-1.80               | N/A                                                                                         |
|                            |               |                                   | Mean I/M Thickness Ratio     | 0.07-1.99               | N/A                                                                                         |
|                            |               |                                   | Max. I/M Thickness Ratio     | 0.14-2.44               | N/A                                                                                         |
|                            |               |                                   | % Luminal Stenosis          | 44.9-96.3 %             | N/A                                                                                         |
| Tabbara et al. 57          |               | Basilic (n=54),                   | Max. I Thickness            | 0.18 [0.10-0.20] mm     | Lack of association with primary                                                             |
| Year  | Study Authors | Study Design | Site | Technique | I/M Area Ratio | % Luminal Occlusion | Lack of Association |
|-------|---------------|--------------|------|-----------|----------------|-------------------|-------------------|
| 2016² | Brachial (n=3) | I/M Area Ratio | N/A | unassisted patency (P=0.2, n=52) |
|       | HFM Study²⁵,⁵² | Cephalic (69%), Basilic (29%), Brachial (2%) | % Luminal Occlusion | 28.1 ± 27.2 % (cephalic), 39.5 ± 30.4 % (basilic), 21.2 ± 23.4 % (brachial) | Lack of association with postoperative stenosis at 1 day (P=0.49), 2 weeks (P=0.91), or 6 weeks (P=0.07); lack of association with unassisted (P=0.07) or overall maturation failure (P=0.11) |
|       | Martinez et al. 2018³ | Basilic (n=104), Brachial (n=4), Cephalic (n=2) | I/M Area Ratio | 0.32 [0.22-0.52] | Lack of association with maturation failure (P=0.7) |
|       | Allon et al. 2019⁶ | Upper Arm (65%), Forearm (35%) | Max. I Thickness | 0.037 ± 0.040 mm | N/A |

**POSTOPERATIVE INTIMAL HYPERPLASIA**

| Year  | Study Authors | Study Design | Site | Technique | Mean I/M Thickness Ratio | Max. I/M Thickness Ratio | % Luminal Stenosis | Lack of Association |
|-------|---------------|--------------|------|-----------|--------------------------|--------------------------|-------------------|-------------------|
| Roy-Chaudhury et al. 2007⁴¹ | Cephalic (n=4), all early failures | Mean I/M Thickness Ratio | 3.12 ± 0.43 | N/A |
|       | Max. I/M Thickness Ratio | 7.77 ± 1.49 | N/A |
|       | I/M Area Ratio | 1.67 ± 0.10 | N/A |
|       | % Luminal Stenosis | 85.8 ± 3.4 % | N/A |
| Lee et al. 2014²¹ | Cephalic (n=15), Basilic (n=5); all stenotic segments | Mean I/M Thickness Ratio | 3.84 ± 0.55 | N/A |
|       | Max. I/M Thickness Ratio | 7.78 ± 0.88 | N/A |
| Tabbara et al. 2016² | Basilic (n=74), Brachial (n=5) | Max. I Thickness | 0.62 [0.38-0.86] mm | Lack of association with maturation failure (P=0.3); lack of association with primary unassisted patency (P=0.6) |
|       | I/M Area Ratio | N/A |
| Duque et al. | Basilic (n=12), | I Area | 3.33 [1.94-4.86] mm² in | Lack of association with focal stenosis |
| Year | Type | Patient Details | Intima/Media Area Ratio | Non-Stenotic Mean ± Standard Error | Stenotic Mean ± Standard Error | $P$-Value |
|------|------|-----------------|-------------------------|-----------------------------------|---------------------------------|----------|
| 2017 | Brachial (n=2); all AVFs had stenotic and non-stenotic segments | Min. I Thickness | 0.09 [0.05-0.31] mm in non-stenotic, 0.11 [0.05-0.43] mm in stenotic | | Lack of association with focal stenosis ($P=0.18$) |  |
|      |      | Max. I Thickness | 0.75 [0.54-1.08] mm in non-stenotic, 0.98 [0.78-1.20] mm in stenotic | | Lack of association with focal stenosis ($P=0.22$) |  |
|      |      | Min. IM Thickness | 0.37 [0.17-0.70] mm in non-stenotic, 0.30 [0.23-0.88] mm in stenotic | | Lack of association with focal stenosis ($P=0.22$) |  |
|      |      | Max. IM Thickness | 1.14 [0.84-1.38] mm in non-stenotic, 1.38 [1.30-1.57] mm in stenotic | | Lack of association with focal stenosis ($P=0.13$) |  |
|      |      | I/M Area Ratio | 0.97 [0.63-1.18] in non-stenotic, 1.00 [0.70-1.20] in stenotic | | Lack of association with focal stenosis ($P=0.73$) |  |
| Martinez et al. 2018 | Basilic (n=97), Brachial (n=14), Cephalic (n=4) | I/M Area Ratio | 0.77 [0.48-1.30] | | Lack of association with maturation failure by itself ($P=0.09$, n=115), but significant association in AVFs with high medial fibrosis ($P=0.035$, n=58) |  |

a. Number of veins analyzed after study exclusions
b. I, intima; M, media; IM, intima + media; I/M, intima/media
c. Values presented as mean ± standard error (standard deviation in the HFM Study and Allon et al. 2019), median [interquartile range], or range in Lazich et al.; N/A, not reported or studied
d. N/A, not reported or studied
e. HFM, Human Fistula Maturation. Data obtained from Alpers et al. and Cheung et al.
f. Pairwise comparison of stenotic and adjacent non-stenotic segments in upper-arm AVFs
FIGURE LEGENDS

Figure 1. Upper-extremity veins in trauma donors with normal renal function. A-D) Cross-sections of the cephalic (A-B) and basilic veins (C-D) from a Hispanic 56-year-old male without history of hypertension, diabetes, or coronary artery disease. E-H) Cephalic (E-F) and basilic veins (G-H) from a Hispanic 55-year-old male with history of controlled hypertension (<5 years). Sections were stained with Movat pentachrome stain, with cells showing in brown/red, collagen in yellow, and elastin in black. Boxed areas in A, C, E, and G are magnified in B, D, F, and H, respectively. Arrows in B and H identify the internal elastic lamina. I, intima; M, media; A, adventitia.

Figure 2. Pre-access basilic veins in end-stage renal disease patients. A-C) Cross-sections of basilic veins collected during first-stage surgery of a two-stage brachiobasilic arteriovenous fistula (AVF). Patient A is a 42-year-old Black female with history of hypertension. Patient B is a 68-year-old Black female with hypertension and diabetes; while C is a 65-year-old Hispanic female positive for hypertension, diabetes, and coronary artery disease. All three veins matured successfully after AVF creation. Sections were stained with Movat pentachrome stain, with cells showing in brown/red, collagen in yellow, and elastin in black. Boxed areas in A-C are magnified in D-F, respectively. Arrows in E and F identify the internal elastic lamina. I, intima; M, media; A, adventitia.

Figure 3. Venous cross-sections of arteriovenous fistulas (AVFs) in end-stage renal disease patients. A-C) Cross-sections of juxta-anastomotic AVF segments from two-stage brachiobasilic
fistulas collected during second-stage surgery (77-91 days after AVF creation). Patient A is a 38-year-old Hispanic male with history of hypertension. Patient B is an 80-year-old Black female with hypertension and diabetes, while C is a 40-year-old Black male positive for hypertension and coronary artery disease. All three AVFs failed to mature and underwent a salvage procedure or creation of a new fistula. Sections were stained with Movat pentachrome stain, with cells showing in brown/red, collagen in yellow, proteoglycans in blue, and elastin in black. Boxed areas in A-C are magnified in D-F, respectively. Arrows in D and F identify the internal elastic lamina. I, intima; M, media; A, adventitia.
