



Flow-Induced High-frequency Vascular Wall Vibrations: A New Mechanobiological Stimulus for Vascular Remodeling?

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Abstract

Despite substantial progress in vascular access research, the mechanobiological mechanisms driving adverse remodeling of vascular walls, such as intimal hyperplasia, remain unclear. Native arteriovenous fistula (AVF), the preferred vascular access for hemodialysis, represents an ideal condition to investigate the effect of hemodynamic changes on vascular cells' biological functions. Our recent work provides converging evidence that disturbed venous flow in AVFs not only triggers endothelial dysfunction but also induces high-frequency mechanical vibrations within the vessel wall. These vibrations may directly influence smooth muscle cell proliferation, phenotype, and overall wall remodeling. This review summarizes relevant work in the field and calls for a paradigm shift in future AVF research: moving beyond the role of hemodynamic shear stress on the endothelium and considering the role of vibration-related mechanobiological stimuli in these pathological processes acting throughout the entire vascular wall and involving all vascular cell phenotypes.

Keywords Arteriovenous fistula · Hemodialysis · Transitional flow · Wall vibrations

Introduction

Despite decades of scientific and clinical research, the mechanisms responsible for onset and progression of vascular diseases remain incompletely understood. Pathological vascular changes, such as atherosclerosis and intimal hyperplasia (IH), tend to develop in focal areas of the arterial tree, particularly near bifurcations and branches [1]. In contrast, circulating factors are present throughout the entire vasculature but do not affect most regions. This evidence suggests that local hemodynamic conditions play a key role

in affecting the biology of vascular cells and the development of vascular disease. The interaction between blood flow and the luminal vessel wall surface generates the shear stress, defined as the tangential frictional force per unit area exerted by the flowing blood on the vascular wall. Endothelial cells (ECs) lining the lumen sense and respond to wall shear stress (WSS), whose magnitude and direction depend on the local hemodynamic environment. In straight arterial vessels, blood flow is predominantly laminar, with velocities aligned parallel to the inner surface of the vessel wall. When the flow is laminar, the WSS is unidirectional and pulsatile, with magnitude in the so-called “physiological range” of 10–20 dynes/cm² [2]. Under these conditions, WSS promotes vascular cell quiescence and induces paracrine effects. These include increased production by ECs of nitric oxide (NO), prostaglandins, together with decrease production of endothelin and angiotensin converting enzyme (ACE). In addition, WSS induces antioxidant activities and increased expression of Kruppel-like transcription factor 2 (KLF2), that is involved in gene expression related to all these cellular responses [3]. Secondary flows develop where blood vessels alter their geometry, such as at branches, stenoses, or aneurysms. While pulsatile flow causes temporal variations in WSS throughout the vasculature, secondary flows

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generate complex multidirectional WSS patterns, including regions of oscillatory shear stress, exposing ECs to completely different mechanical stimuli [2]. Since decades ago, it was proposed that WSS oscillating between opposite directions may induce functional changes in ECs [4]. In these conditions, oscillating WSS promotes a prooxidant and proliferating state in the underlying vascular smooth muscle cells (SMCs). This is associated with decreased production of NO and prostaglandins, increased production of endothelin and ACE, EC activation with decreased expression of KLF2, and increased expression of adhesion molecules [5].

It is well known that ECs, beyond lining the vascular lumen and acting as interface between circulating blood and the underlying vessel wall, exert paracrine effects on the vascular SMCs. Changes in blood flow volume are detected by variations in WSS, which regulate the vasomotor response [6]. If blood flow increases in an artery, the rise in WSS sensed by ECs promotes the release of vasoactive compounds such as NO, which induce relaxation of underlying SMCs. If these altered hemodynamic conditions persist over time, ECs signal the underlying SMCs to undergo phenotypic changes and remodeling processes, leading to outward vascular remodeling and an increase vessel inner diameter, thereby restoring the WSS value within the original physiological range [7]. In addition to sensing blood perfusion, arterial vessels also sense blood pressure with similar mechanisms that involve primarily SMCs. Thus, an increase in blood pressure triggers vascular cells to proliferate and to remodel the extracellular matrix to increase vessel wall thickness and restore mechanical stress in the vessel wall near the physiological range [7]. More generally, it is well known that the maintenance of the vessel wall structure requires physiological blood flow and related WSS conditions, which regulate ECs signaling that induces paracrine effects acting on the underlying SMCs [7].

Vascular Access as a Model of Flow-Induced Intimal Hyperplasia

Despite the extensive study of different blood flow conditions, and the related shear and tensile stress states acting on vascular cells, the precise mechanisms that initiate vascular changes remain poorly understood. These mechanisms are responsible for vascular disease development such as atherosclerosis and IH. Relating flow-induced mechanical signals to vascular cell dysfunction is challenging because vascular changes often develop silently and become clinically apparent only at advanced stages. For this reason, it is difficult to investigate the cell signals triggered by local pathological conditions. Native arteriovenous fistulae (AVFs) are surgically created connections between an artery and a vein in the arm of the patients undergoing hemodialysis (HD). They

provide an ideal clinical model for studying vascular cell responses to abrupt changes in blood flow. It has been clearly shown that when an artery in the arm is connected to a vein to increase blood flow as required by extracorporeal circulation during HD, the arterial and venous vascular walls adapt to sustain the increased WSS and pressure. In particular, in the venous side near vessel anastomosis, the vessel wall enlarges to increase the diameter and the vessel wall thickens in the so-called outward remodeling [8, 9]. However, in a large number of patients, these flow conditions, mainly characterized by flow instabilities and secondary flow patterns, promote the development of IH [10]. This process is associated with SMC proliferation and migration, which over a relatively short period—typically months to a few years—gives rise to IH, progressive venous stenosis, reduced blood flow, and ultimately AVF failure [1]. Clinically, this is a major challenge, as patients must undergo the creation of a new vascular access to continue HD treatment. We therefore took advantage of these surgical procedures and the related vessel wall response, to investigate the mechanisms underlying IH development. In this context, the onset of the vascular changes is known, and longitudinal follow-up can directly relate evolving local hemodynamic conditions to subsequent vascular wall remodeling.

Hemodynamic Conditions in the Vascular Access

In order to investigate the changes in blood flow conditions induced by surgically created AVF, we developed a medical image-based computational fluid dynamics (CFD) pipeline [11]. One of our initial observations in AVF hemodynamics was that the massive increase in blood flow generates turbulent-like blood flow conditions at the anastomosis and in the juxta-anastomotic vein. Thus, the arterial, and especially the venous vessel, previously experiencing low and unidirectional WSS, is suddenly exposed to turbulent-like blood flow with very fast WSS variations in time and direction [12, 13]. We then suggested that these unsteady WSS may trigger different biological responses in the ECs, leading to the production of signal molecules that promote the transition of SMCs from a quiescent state to a proliferative and migratory phenotype, thereby contributing to vascular wall remodeling. Notably, we have shown that segments of the vein most affected by IH are precisely those characterized by the presence of unsteady, turbulent-like blood flow conditions [13].

Despite the growing body of knowledge provided by CFD studies performed by our group [13, 19], and others [14, 15], several WSS-related indices have been proposed, often yielding heterogeneous or even conflicting interpretations, and the exact mechanisms underlying AVF failure remain elusive. For this reason, we extended the analysis beyond the fluid domain and investigated

how disturbed AVF flow mechanically excites the vascular wall using preliminary fluid-structure interaction (FSI) simulations [16]. We found that the unsteady flow conditions in the venous segment near the anastomosis also induce fast motion of the vessel wall resembling mechanical vibrations of different frequencies. In particular, we have estimated that these vessel segments exhibit mechanical vibrations with frequency ranging from 50–70 to more than 200 Hz [17]. This new evidence on the effect of unsteady flow on blood vessels, involving not only changes in WSS acting on ECs but also vibration of the entire vessel wall, suggested a new hypothesis about the mechanisms responsible for flow-related vascular changes. We reasoned that, besides the effect of unsteady WSS on ECs, vascular wall vibrations themselves may directly influence the biological response of all vascular cells. Thus, we proposed that it is important to investigate whether vessel wall vibrations are involved in biological changes responsible for vascular diseases. If this is the case, new biological pathways responsible for IH may be identified and eventually new pharmacological treatments may be developed.

Effects of Mechanical Vibrations on Vascular Cells

Although studies on the effects of high-frequency mechanical stimuli on cell biology are limited, the available evidence supports this new hypothesis. Indeed, *in vivo* and *in vitro* investigations consistently show that mechanical vibrations modulate vascular cell phenotype and regulate gene expression [18]. Specifically, vibrations consistently induce morphological and functional alterations in vascular cells, including reorganization of the cytoskeleton, modulation of proliferative activity, and changes in the secretion of key signaling molecules. These cellular responses are associated with vascular dysfunction, disruption of the internal elastic lamina, and activation of inflammatory pathways, processes that together may drive vascular remodeling and ultimately contribute to vessel stenosis and occlusion. Multiple mechanotransduction pathways have been implicated in mediating these effects. Notably, activation of ERK1/2 in SMCs promotes intimal thickening and facilitates the recruitment of inflammatory cells to sites of vascular injury. Additional effectors, including Syn4, VEGF, KLF2, ICAM-1, and NFATc3, have also been identified as vibration-responsive regulators [18]. Beyond vascular signaling, high-frequency mechanical stimulation appears to modulate pathways associated with muscle atrophy, potentially inducing hypertrophic adaptations in skeletal muscle. Together, these responses may provide a mechanistic basis for stenosis development in certain vessels, including AVFs.

High-Resolution FSI Simulation in AVFs

Motivated by the first computational study [17] and supported by biological evidence [18], we addressed the key limitations of our original FSI simulations, aiming to investigate the role of vibrations in vascular remodeling using a more realistic FSI approach. Specifically, we implemented an advanced FSI model incorporating patient-specific and visit-specific pulsatile inlet boundary conditions in place of the previously assumed steady-state flows (see Fig. 1a). The vessel wall material behavior was modeled using a three-term Mooney–Rivlin model, calibrated on experimental data reported in literature. Distinct material properties were assigned to the artery and vein [19]. Moreover, the original FSI approach did not account for the influence of perivascular tissue, a limitation we addressed by implementing Robin boundary conditions acting on the vessel wall. Collectively, these refinements substantially enhanced the physiological relevance of the FSI model [19].

We then applied this advanced FSI model to a particularly informative case: a patient with a native radio-cephalic AVF who developed a stenosis that ultimately led to access failure 1.5 years after surgery, providing a unique opportunity to gain insight into stenosis onset and progression [20]. This AVF was monitored at 5 time points during follow-up using magnetic resonance imaging and ultrasounds to assess the evolution of morphology, hemodynamics, and vascular wall mechanical stresses. The results revealed that flow instabilities induced elevated vibration amplitudes and high-frequency strain in the initial segment of the cephalic vein, corresponding with the region where stenosis subsequently manifested in this patient. These vibrations reached their maximum value at the time point before the formation of stenosis, suggesting a key role of mechanical vibrations in the onset and progression of the pathological vascular remodeling [20].

To extend these results, we performed a one-year longitudinal assessment of six patients with native distal radio-cephalic AVFs using magnetic resonance imaging and Doppler ultrasound [21]. Patients were classified according to AVF outcomes: two maintained adequate patency, whereas four developed complications (two stenoses and two excessive dilatations). We performed high-fidelity FSI simulations at the different time points, using the advanced FSI model previously described, with patient-specific and visit-specific pulsatile inlet boundary conditions, the Mooney–Rivlin model calibrated on literature data, thickness of the artery and vein which increased during AVF maturation modeling, and Robin boundary conditions for the perivascular tissue. AVFs that remained patent showed negligible high-frequency components in both fluid velocity and wall displacement spectrograms throughout the study. In contrast, all AVFs that later developed complications

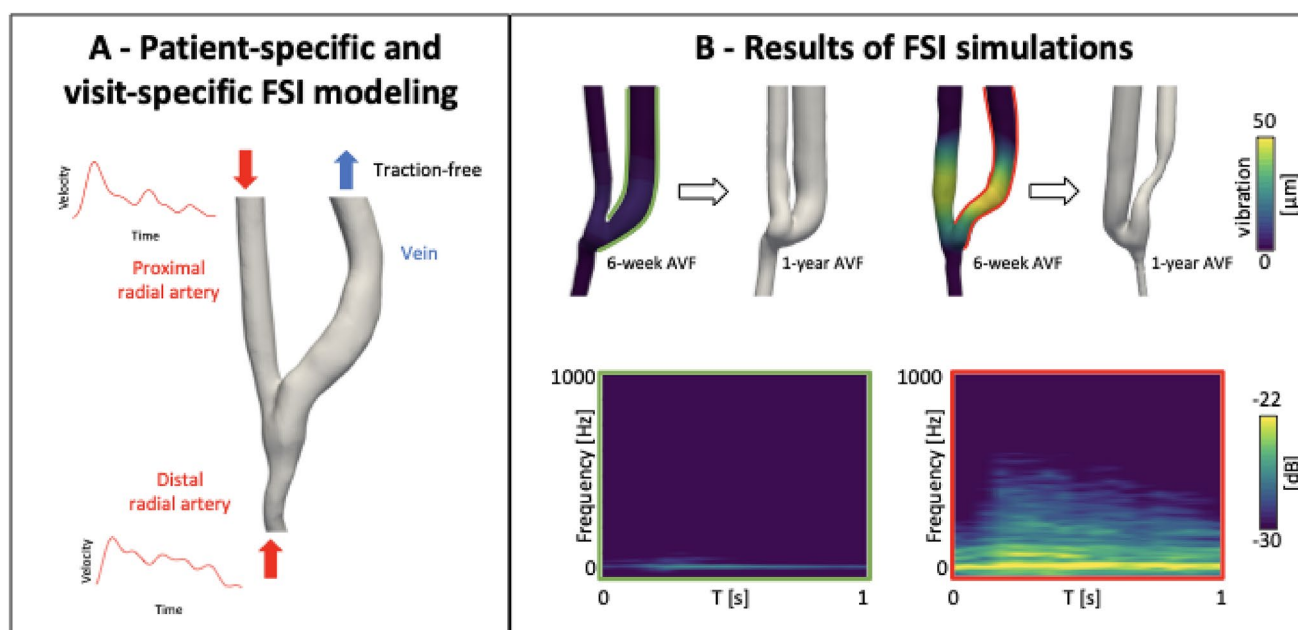


Fig. 1 **a** Representative velocity boundary conditions (left), applied in FSI simulations, and the 3D AVF model (right). **b** Fluid-structure interaction results for a representative patient who experienced optimal maturation and preserved patency and second one who experienced stenosis formation. Three-dimensional representation of high-frequency vascular vibrations at 6 weeks is followed by 1-year 3D model geometry. Green and red colors highlight the portion of the

vein represented in the spectrogram of the wall displacement, which show the presence of negligible vibrations in the patient with preserved patency and high-frequency vibrations in distinct bands in the patient who developed stenosis. *AVF* arteriovenous fistula, *FSI* fluid-structure interaction, *MRI* magnetic resonance imaging, *T* time, *s* second, *Hz* Hertz

exhibited high-frequency vascular wall vibrations, regardless of whether the adverse remodeling manifested as stenosis or excessive dilatation. Notably, these high-frequency signatures were prominent at the timepoint preceding the onset of the pathological remodeling, supporting a potential mechanistic link with pathological vascular adaptation. Moreover, distinct spectral patterns differentiated the two types of complications. Patients who developed IH displayed two narrow, well-defined frequency bands in the wall-displacement spectrogram before stenosis formation. After stenosis onset, these bands shifted to higher frequencies and decreased in amplitude, likely reflecting lumen narrowing and reduced flow. On the contrary, patients who developed excessive venous dilatation exhibited a single, prominent narrow band at a lower frequency prior to outward remodeling. Representative results are shown in Fig. 1b.

In Vitro Response of Vascular Cells to Vibrations

To test the hypothesis of a mechanistic link between specific FSI-derived frequencies and stenosis development, we employed a purpose-designed vibrational-loading device capable of delivering controlled vertical displacements on monolayers of ECs and SMCs [22]. Specifically, vibration bands observed in FSI results at 75 and 150 Hz were

selected as mechanical stimuli for in vitro experiments. ECs and SMCs exposed to 150 Hz vibrations exhibited greater migration, as demonstrated by a significant increase in both cell accumulated distance and velocity over the 6 h monitoring period compared with control cells. Moreover, SMCs subjected to 24 h of vibration showed a significant increase in the percentage of Ki67-positive nuclei relative to total nuclei, indicating enhanced proliferative activity. In addition, SMC proliferation was significantly increased after 24 h of culture with conditioned medium from ECs exposed to 75 Hz and 150 Hz vibrations, indicating that the mechanical stimulus modulates endothelial secretion of soluble factors that promote SMC proliferative behavior [23].

Conclusions

In conclusion, this review highlights the role of mechanical vibrations as a critical yet largely overlooked determinant of AVF remodeling and failure. By integrating computational modeling and mechanobiological experiments, we provide converging evidence that disturbed venous flow in AVFs not only induces EC dysfunction but also generates high-frequency mechanical vibrations within the vessel wall. These vibrations may directly modulate SMC proliferation

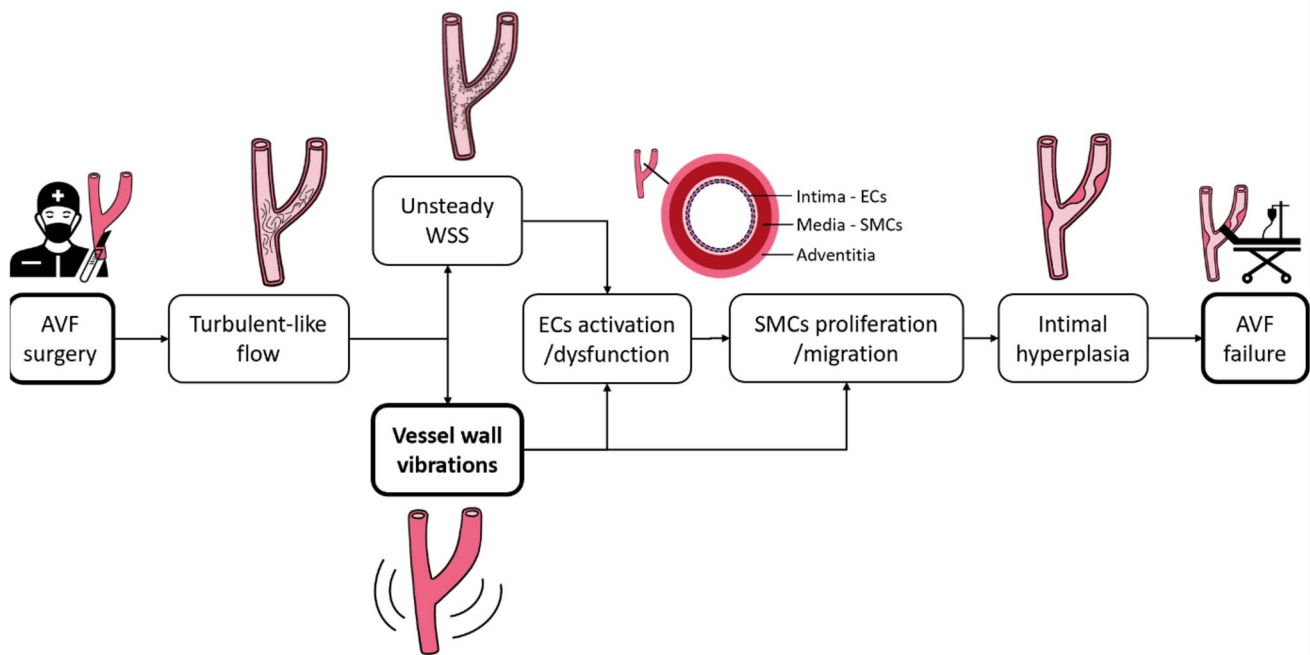


Fig. 2 Schematic representation of the proposed mechanism of IH development in native AVF. AVF surgery is followed by hemodynamic changes that cause turbulent-like flow. This leads to oscillating and reversing WSS and vessel wall vibrations, both contributing

to ECs activation and dysfunction. Vascular wall vibrations and ECs activation directly modulate SMCs proliferation and phenotype, leading to intimal hyperplasia. AVF arteriovenous fistula, EC endothelial cell, SMC smooth muscle cell, WSS wall shear stress

and phenotype, thereby playing a central role in the development of IH (as summarized in Fig. 2), a condition known to be involved also in the initial phase of atherosclerosis [24]. We therefore suggest a paradigm shift in the future research on flow-related vascular remodeling, moving beyond the role of hemodynamic forces on the endothelium and accounting for vibration-related forces acting within the entire vascular wall and affecting all vascular cell phenotypes.

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