RESEARCH LETTER

High-Frequency Vessel Wall Vibrations Associate With Stenosis Formation and Arteriovenous Fistula Failure

To the Editor:

Despite significant computational and experimental efforts and progress made over the past few decades, the mechanobiological mechanism underlying vascular stenosis formation in arteriovenous fistulae (AVF) for hemodialysis (HD) remains mostly unknown.

To investigate potential mechanisms, we presented the case of a 72-year old patient with end-stage kidney disease who experienced the failure of a distal radio-cephalic AVF 1.5 years post-surgery due to stenosis formation. High-fidelity patient-specific fluid-structure interaction simulations were performed at 5 consecutive time points to assess the evolution of hemodynamics and vascular wall mechanical stresses.

The results revealed that flow instabilities induced elevated vibration amplitudes and high-pass 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 just before the formation of stenosis. This suggests that high-frequency vascular wall vibrations and strain may be overlooked mechanobiological stimuli that directly influence vascular cells, potentially contributing to adverse vascular remodeling, and warrant further investigation.

If confirmed in larger cohorts, our findings could potentially pave the way for a rapid, noninvasive, and cost-effective method for monitoring AVF evolution through the quantification of mechanical vibration amplitudes and frequencies.

The AVFs are vital conduits for patients with kidney failure who require kidney replacement therapy through HD; however, 40% fail within the first year after surgery.[1] The primary cause of AVF failure is vascular stenosis resulting from intimal hyperplasia development. Despite numerous efforts to correlate this inward vascular remodeling with altered wall shear stress at the endothelium, a definitive association remains elusive.[2]

Our group has recently shown that transitional flow,[3] from laminar to turbulent, induces high-frequency vibrations in the wall of the AVF vein.[4,5] We hypothesized that vascular wall vibrations, whether complementary to or independent of wall shear stress, could be a trigger that directly impacts the mechanobiology of endothelial and smooth muscle cells, potentially leading to adverse vascular remodeling.

We explored this hypothesis in a particularly interesting patient with a native radio-cephalic AVF who developed stenosis leading to AVF failure 1.5 years after surgery, thus offering the opportunity to gain valuable insights into stenosis progression. This AVF was monitored at 5 time points during follow-up using magnetic resonance imaging (MRI), ultrasounds (US), and computational analysis.

A 72-year male individual with kidney failure due to chronic hypertension received a native radio-cephalic side-to-end AVF in the distal forearm at the Unit of Nephrology and Dialysis of ASST Papa Giovanni XXIII hospital (Bergamo, Italy). No preexisting medical history of vascular pathologies or prothrombotic disorders was reported at the time of the AVF creation. The US-measured preoperative diameter of the radial artery and cephalic vein in the distal forearm were 2.55 mm and 2.65 mm, respectively. Noncontrast-enhanced MRI and Doppler US examinations were performed 3 days after the successful surgical creation of the AVF. Subsequent follow-ups were scheduled at 40 days, 6 months, 1 year, and 1.5 years post-surgery (Fig 1A). The AVF 3D models were reconstructed from MRI acquisitions at each time point (Fig 1B). A detailed description of MRI acquisition and model reconstruction can be found in our previous work.[6] During the first 40 days after surgery, the AVF experienced successful maturation, characterized by the vein's cross-sectional areas increasing by an average of +15.6% and doubling in blood flow rate (268 mL/min vs 567 mL/min). Thus, 43 days after surgery, when the venous limb of the AVF was easily palpable, the patient started HD with a schedule of twice-weekly sessions with buttonhole cannulation. This cannulation technique, not considered standard of care, may have contributed to the altered AVF hemodynamics,[7] and subsequent vascular remodeling.[8] Then, at the 6-month follow-up, the vein's cross-sectional areas had further increased (+19.5% on average) and the blood flow volume tripled relative to its post-surgery value. However, between 6 months and 1-year post-surgery, venous stenosis developed, causing a 63% decrease in lumen cross-sectional area, which became very marked at 1.5 years (−79% in lumen cross-sectional area). Concurrently, the blood flow rate declined, returning to immediate post-surgery levels, being no longer adequate for performing HD (Fig 1B). As a result of this AVF failure, a new vascular access had to be created in a more proximal location.

The MRI-based models were used to perform high-fidelity fluid-structure interaction simulations of the blood flow, vascular wall, and perivascular tissue.[9] Patient-specific flow waveforms derived from Doppler US measurements were imposed on the model at the inlet of the proximal and distal artery. The simulations also accounted for the distinct mechanical properties of the vein and artery, and the stiffening and thickening of the cephalic vein during maturation. A detailed methodological description is provided in the Supplementary Material (Item S1).

The illustration of vortical structures at peak systole (Fig 2A) identifies areas of complex and transitional flow in the juxta-anastomotic vein (JAV). Over time, flow instabilities in the JAV progressively intensified, peaking at 6 months post-surgery before decreasing after the onset of stenosis. The computed vascular wall displacement and strain underwent high-pass filtering with a frequency threshold of 25 Hz to isolate high-frequency vibrations from low-frequency pulsations.[5,10] Complex flow patterns within the JAV induced wall vibrations with amplitudes that consistently increased until 6 months, as both inflow and turbulence reached their maximum values, peaking at

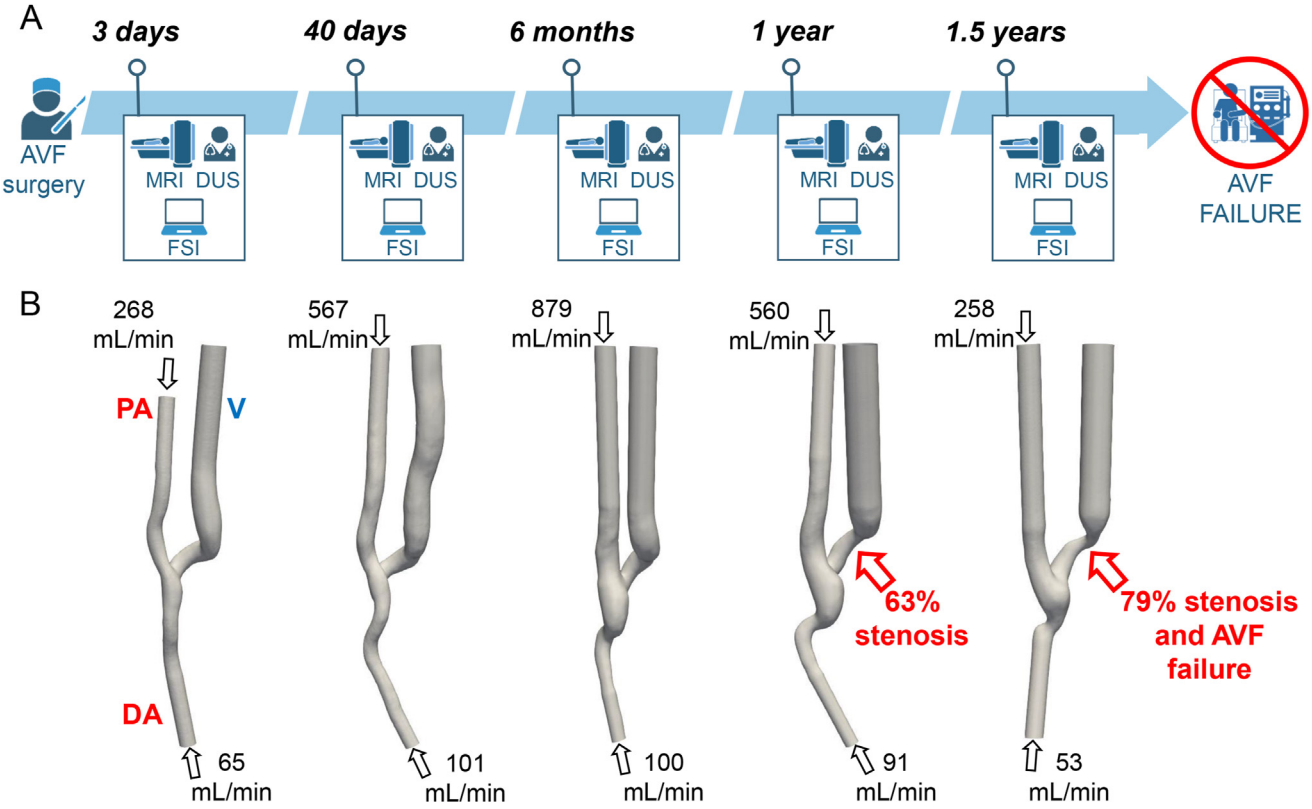

Figure 1. Study timeline and corresponding AVF 3D models and average blood flow volume. (A) study timeline from surgical creation of AVF until failure, highlighting the 5 time points considered in the study. (B) 3D model reconstructions of AVF and related average blood flow volume at the inlet of the proximal and distal artery, at all 5 time points. AVF, arteriovenous fistula; DA, distal artery; DUS, doppler ultrasound; FSI, fluid-structure interaction; MRI, magnetic resonance imaging; PA, proximal artery; V, vein.

33 μm near the bifurcation (Fig 2B). Consistently, the high-pass strain was elevated just before stenosis development, with maximum values occurring at the inner curvature of the vein (Fig 2C).

Spectrograms represent the evolution of high-frequency content within the fluid velocity and wall displacement signals. Fluid velocity in the JAV increased during maturation and peaked in both frequency and amplitude at 6 months, exhibiting high-frequency content up to 400 Hz and amplitudes exceeding −6 dB (Fig 2D). These intensified flow instabilities led to prominent narrow bands in the wall displacement spectrograms (Fig 2E). Furthermore, just before stenosis formation (6 months), 2 bands emerged between 40-55 Hz and 65-80 Hz, with consistent amplitudes exceeding −22 dB. Both fluid velocity and wall displacement frequency contributions progressively decreased parallel with stenosis progression, as a result of blood flow regularization caused by inward remodeling.[6]

Characterization of the vibration modal frequencies, along with the other hemodynamic results, is detailed in the Supplementary Material (Items S2 and S3) and illustrated in Figures S1 and S2.

This study focused on a single patient with AVF, who was monitored for 1.5 years after the surgical creation. To the best of our knowledge, this is the first report to use high-fidelity computational tools to show the impact that vibrations have on AVF adverse remodeling. Notably, these vibrations not only related to a specific spatial location but also occurred in conjunction with the formation of intimal hyperplasia. Indeed, our results showed a consistent increase in vibration amplitudes and frequencies in the wall of the AVF vein over time, peaking at 6 months post-surgery, before stenosis formation. Similarly, high-pass strain values exhibited a similar trend, which was particularly pronounced in the initial segment of the anastomosed vein at 6 months, exactly where the stenosis later developed.

This suggests that transitional flow-induced high-frequency wall vibrations and elevated high-pass strain may specifically stimulate subsequent focal inward vascular remodeling. These findings highlight the novelty of this study, indicating that flow-induced vascular wall vibrations may represent an overlooked mechano-biological stimulus acting on smooth muscle cells to develop stenosis. This hypothesis warrants further investigation, as the impact of high-frequency mechanical stresses on smooth muscle cells has been explored in only a few biological studies.[11]

Notably, our results revealed high-frequency vibrations well before stenosis onset. Although we acknowledge that our findings are based on only a single case,

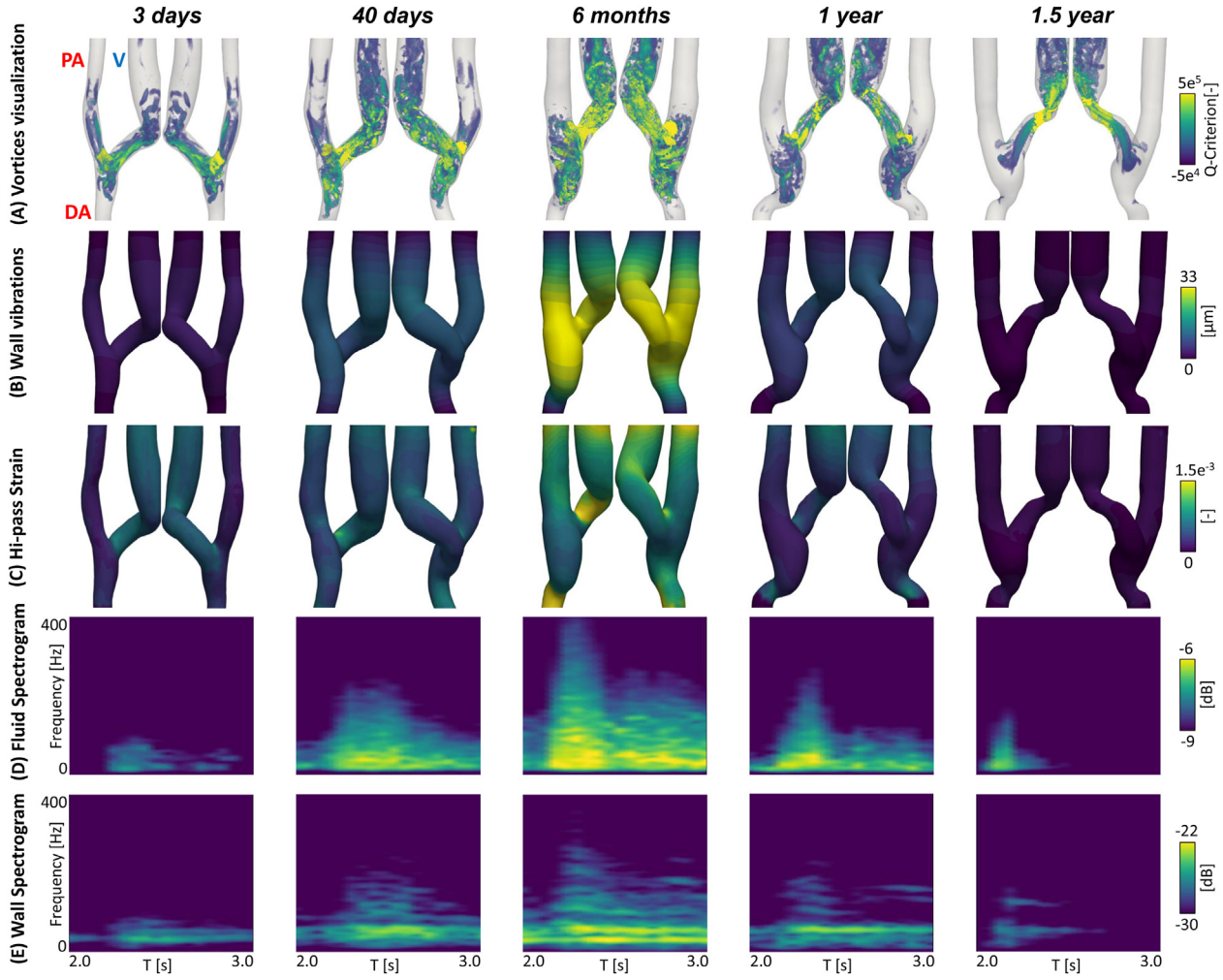

Figure 2. Effect of flow instabilities on deformation metrics and corresponding frequencies. (A) vortices visualization (Q-Criterion) highlighting the flow instabilities within the AVF. (B) wall vibration amplitudes visualization. (C) high-pass strain (ie, the strain contribution for frequencies > 25 Hz) visualization. (D) fluid velocity spectrograms. (E) wall displacement spectrograms. DA, distal artery; PA, proximal artery; V, vein.

and the prognostic value of vibrations remains to be demonstrated, our study suggests that, in this specific patient, wall vibrations could have been used as a predictive factor for intimal hyperplasia development, enabling timely intervention and potentially preventing AVF failure.

Thus, if confirmed in future longitudinal studies with a larger cohort of patients, the influence of high-frequency vibrations on intimal hyperplasia formation and AVF failure might have significant implications that could ultimately enhance routine clinical practice and AVF surveillance. To date, nurses and clinicians typically monitor AVF function based on qualitative assessments of skin vibration, the AVF thrill, and by listening to AVF sounds with a stethoscope.[12] However, these approaches are subjective and dependent on the operator's experience and judgment, highlighting the need for more objective criteria. Thus, the quantitative assessment of AVF vibrations could play a crucial role in addressing this need. Looking ahead, our findings could potentially pave the way for a rapid, noninvasive, and cost-effective device capable of quantifying vessel wall vibration amplitudes and related frequencies, enabling objective and quantitative monitoring of AVF function. Notably, recent research proposed a similar approach using a pulsed radar sensor to analyze vascular wall motion and correlate it with AVF flow rate and functionality,[13] but focused solely on the low-frequency range, whereas our study considered high-frequency wall vibration amplitudes.

Finally, we believe that our results may inspire investigations into alternative anastomotic configurations or vascular devices[14] that could effectively mitigate vibrations, thereby promoting AVF patency.

Luca Soliveri, MS, Sofia Poloni, MS, Paolo Brambilla, MD, Anna Caroli, PhD, Andrea Remuzzi, EngD, Michela Bozzetto, PhD, and Kristian Valen-Sendstad, PhD

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Figure S1: Wall shear stress hemodynamics. (A) time-averaged wall shear stress (TAWSS). (B) oscillatory shear index (OSI). (C) spectral power index (SPI).

Figure S2: AVF vibration modal frequencies, amplitudes and mode shapes. (A) spectrogram of wall displacement, emphasizing the rocking modes (ways of motion of the AVF) of increasing frequency. Subsequent rows in this figure follow the same coloring scheme. (B) spatial 99th percentile value of the vibration amplitude associated with rocking modes and bruit, in μm. (C-G) mode shape representation in the region predominantly influenced by the associated frequencies. The shapes are normalized to the size of the AVF vein so that each mode is shown at the same visual amplitude.

Item S1: Fluid-structure interaction pipeline.

Item S2: Wall shear stress hemodynamics.

Item S3: AVF vibration modal frequencies, amplitudes and mode shapes.

ARTICLE INFORMATION

Authors' Affiliations: Department of Biomedical Engineering, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Bergamo, Italy (LS, AC, MB); Department of Engineering and Applied Sciences, University of Bergamo, Dalmine (BG), Italy (SP); Diagnostic Radiology, ASST Papa Giovanni XXIII Hospital, Bergamo, Italy (PB); School of Medicine, University of Milano-Bicocca, Milan, Italy (PB); Department of Management, Information and Production Engineering, University of Bergamo, Dalmine (BG), Italy (AR); and Department of Computational Physiology, Simula Research Laboratory, Oslo, Norway (KV-S).

Address for Correspondence: Michela Bozzetto, PhD, Medical Imaging Laboratory, Department of Biomedical Engineering, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Via Gian Battista Camozzi, 3, 24020 Ranica Bergamo, Italy. Email: michela.bozzetto@marionegri.it

Authors' Contributions: PB performed all MRI acquisitions. LS and SP performed all FSI simulations and data analysis. KV-S and AR jointly supervised the study. Each author contributed important intellectual content during article drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. Authors MB and KV-S contributed equally to this work.

Support: The simulations were performed on the Saga cluster, with resources provided by UNINETT Sigma2—the National Infrastructure for High Performance Computing and Data Storage in Norway, Grant number nn9249k. Luca Soliveri acknowledges a research fellowship received from Fondazione Dompè.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Patient Protections: The patient was enrolled in a clinical study (Reference number NCT04141852) approved by the Bergamo Ethics Committee (Reg 107/19). The patient consented to his clinical and imaging data being used for research purposes and publication.

Acknowledgements: The authors would like to thank Drs David Bruneau and Kei Yamamoto for fruitful discussions.

Data Sharing: All data are available on the Zenodo platform (www.zenodo.org), following a specific request to the authors.

Peer Review: Received July 8, 2024. Evaluated by 1 external peer reviewer, with direct editorial input from an Associate Editor and the Editor-in-Chief. Accepted in revised form December 16, 2024.

REFERENCES

1. Bozzetto M, Poloni S, Caroli A, et al. The use of AVF.SIM system for the surgical planning of arteriovenous fistulae in routine clinical practice. *J Vasc Access*. 2023:112972982110626. doi:10.1177/11297298211062695
2. Colley E, Simmons A, Varcoe R, Thomas S, Barber T. Arteriovenous fistula maturation and the influence of fluid dynamics. *Proc Inst Mech Eng H*. 2020;234(11):1197-1208. doi:10.1177/0954411920926077
3. Bozzetto M, Ene-Iordache B, Remuzzi A. Transitional flow in the venous side of patient-specific arteriovenous fistulae for hemodialysis. *Ann Biomed Eng*. 2016;44(8):2388-2401. doi:10.1007/s10439-015-1525-y
4. Bozzetto M, Remuzzi A, Valen-Sendstad K. Flow-induced high frequency vascular wall vibrations in an arteriovenous fistula: a specific stimulus for stenosis development? *Phys Eng Sci Med*. 2024;47(1):187-197. doi:10.1007/s13246-023-01355-z
5. Soliveri L, Bruneau DA, Ring J, Bozzetto M, Remuzzi A, Valen-Sendstad K. Toward a physiological model of vascular wall vibrations in the arteriovenous fistula. *Biomech Model Mechanobiol*. 2024;23(5):1741-1755. doi:10.1007/s10237-024-01865-z
6. Soliveri L, Bozzetto M, Brambilla P, Caroli A, Remuzzi A. Hemodynamics in AVF over time: A protective role of vascular remodeling toward flow stabilization. *Int J Artif Organs*. 2023;46(10-11):547-554. doi:10.1177/03913988231191960
7. Fulker D, Simmons A, Kabir K, Kark L, Barber T. The hemodynamic effects of hemodialysis needle rotation and orientation in an idealized computational model. *Artif Organs*. 2016;40(2):185-189. doi:10.1111/aor.12521
8. Parisotto MT, Schoder VU, Miriunis C, et al. Cannulation technique influences arteriovenous fistula and graft survival. *Kidney Int*. 2014;86(4):790-797. doi:10.1038/ki.2014.96
9. Bergersen A, Slyngstad A, Gjertsen S, Souche A, Valen-Sendstad K. TurtleFSI: a robust and monolithic FEniCS-based fluid-structure interaction solver. *JOSS*. 2020;5(50):2089. doi:10.21105/joss.02089
10. Bruneau DA, Steinman DA, Valen-Sendstad K. Understanding intracranial aneurysm sounds via high-fidelity fluid-structure-interaction modelling. *Commun Med (Lond)*. 2023;3(1):163. doi:10.1038/s43856-023-00396-5
11. Carrara E, Soliveri L, Poloni S, Bozzetto M, Campiglio CE. Effects of high-frequency mechanical stimuli on flow related vascular cell biology. *Int J Artif Organs*. 2024;47(8):590-601. doi:10.1177/03913988241268105
12. Lok CE, Huber TS, Lee T, et al. KDOQI Clinical practice guideline for vascular access: 2019 update. *Am J Kidney Dis*. 2020;75(4)(suppl 2):S1-S164. doi:10.1053/j.ajkd.2019.12.001
13. Chen CH, Tao TH, Chou YH, Chuang YW, Chen TB. Arteriovenous fistula flow dysfunction surveillance: early detection using pulse radar sensor and machine learning classification. *Biosensors*. 2021;11(9):297. doi:10.3390/bios11090297
14. Bozzetto M, Soliveri L, Poloni S, et al. Arteriovenous fistula creation with VasQTM device: a feasibility study to reveal hemodynamic implications. *J Vasc Access*. 2024;25(1):60-70. doi:10.1177/11297298221087160