An Interstitial Fluid Circulatory System throughout the Body

Hongyi Li[1,2,*], Bei Li[1,2,3], Jin Cai[1,2,4], Nandu Goswami[5,6,*]

[1] Research Center for Interstitial Fluid Circulation, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China
[2] Department of Cardiology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China
[3] Peking Union Medical College, Beijing, China
[4] Peking University Fifth School of Clinical Medicine, Beijing, China
[5] Gravitational Physiology and Medicine Research Unit, Division of Physiology and Pathophysiology, Otto Loewi Research Center, Medical University of Graz, Graz, Austria
[6] Center for Space and Aviation Medicine, College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates

*__Correspondence:__ Hongyi Li, Research Center for Interstitial Fluid Circulation, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing 100730, China; Department of Cardiology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing 100730, China.
E-Mail: leehongyi@bjhmoh.cn
Nandu Goswami, Gravitational Physiology and Medicine Research Unit, Division of Physiology and Pathophysiology, Otto Loewi Research Center, Medical University of Graz, Graz 8010, Austria; Center for Space and Aviation Medicine, College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai P.O. Box 505055, United Arab Emirates.
E-Mail: nandu.goswami@medunigraz.at

Abstract

Accumulating evidence has shown that interstitial fluid (ISF) can flow along the adventitia of the vasculature and peripheral nerves, and within the skin, in both humans and animals. Recently, we further verified that ISF flows centripetally in the adventitia along the major arteries and veins of the systemic vasculature to the epicardium and myocardium, then flows into the lungs via the pulmonary arteries and returns to the heart via the pulmonary veins. This pathway is neither perivascular tissue nor blood or lymphatic vessels. Unlike conduit-like blood vessels, the channel structures for adventitial ISF flow consist of the interstitial matrix–membranes, including layers of fascia surrounding the vessel wall, extracellular matrix in the adventitia, and the surface of the smooth muscle cells on the inside. The driving mechanism to regulate the ISF flow along the vasculature has been found to be the synergistic movements of the heart and lungs. Under physiological conditions, the adventitial ISF flow velocity was positively correlated with heart rate, increased during breath holding, and became pulsatile during heavy breathing. During the respiratory cycle, each expansion of the lungs during inflation generates a centrifugal flow of adventitial ISF,

Received: 27 May 2026; **Accepted:** 14 October 2026
DOI: 10.15302/HB.2026.0014
© The Author(s) 2026. This article is published by Higher Education Press at journal.hep.com.cn.
This is an open access article distributed under the Creative Commons Attribution License 4.0 (CC BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

while each contraction of the lungs during deflation generates a centripetal adventitial ISF flow. During the cardiac cycle, each atrial or ventricular dilation generates a centripetal flow of adventitial ISF, while each atrial or ventricular contraction generates a centrifugal adventitial ISF flow. It appears that a respiratory movement of the lungs can retard the centripetal flow of adventitial ISF generated by the beating heart. This article will review the current findings about the ISF circulatory system and discuss its future developments and challenges.
Keywords: systemic interstitial fluid circulatory network, tissue fluid, interstitial matrix–membranes network system

Introduction

Since William Harvey discovered blood circulation in 1628 and the Starling hypothesis was proposed in 1896, the movement of extracellular fluid throughout the body has been understood to involve a rapid circulation of blood and lymph, along with a constant flow of interstitial fluid (ISF) through the extracellular matrix (ECM) after it is filtered from the capillary wall[1]. The flow of ISF includes two types: (1) diffusion surrounding cells; (2) localized flow in perivascular spaces (PVS) in specific tissues or organs[2]. However, after nearly two decades of exploration, a more complex ISF flow network in the connective tissues such as the adventitia of large blood vessels, skin, nerves, and fascia in humans and animals, and the physiological regulatory mechanisms of the vascular adventitial ISF flow network have been reported[3–7]. These findings provide a new picture of systemic fluid circulation: in addition to diffusing around cells, ISF can also flow in the interstitial matrix membrane channels (MMCs) network system driven by periodic continuous movements such as heartbeat and respiration to form an "ISF fluid circulatory network" throughout the body. Together with the blood circulation and lymphatic system, the ISF circulatory network realizes functions such as fluid regulation and maintaining homeostasis of the internal environment, and has great biological and medical research value.

The phenomena of ISF flow along blood vessels

With the advancement of microscopy technology and the discovery of various biological dyes, the diffusion and local flow of ISF have received close attention from physiologists. The extracellular fluid in connective tissues is named interstitial fluid/tissue fluid, which refers to the fluid around cells in the tissue interstitial space. The National Committee for the Examination of Scientific and Technological Terms defines ISF as "fluid flowing in the pores of the matrix." It appears that the diffusion of ISF around cells and the local flow in tissues and organs have been known for quite some time now.

PVS

PVS are anatomical cavities formed by the pia mater covering the adventitia of blood vessels and the surface of brain tissue when intracranial blood vessels enter and exit the brain tissue. PVS were first recorded by Durand–Fardel in 1843 and described in detail by Rudolf Virchow in 1851[2]. With the advancement of medical imaging technology and the deepening of understanding of cerebral small vessel diseases, people have found that PVS are distributed along penetrating arteries, small arteries, capillaries, small veins, and larger-diameter veins, constitute a pathway network for brain ISF flow, which is connected to cerebrospinal fluid (CSF) and the lymphatic system, and is related to pathogen spread, tumor metastasis, hydrocephalus, lacunar cerebral infarction, chronic cerebral ischemia, etc.[2,8]. PVS are not only distributed around small blood vessels in the brain, but also in thyroid gland, liver, kidney, spleen, bone, pineal gland and other organs[2,8,9].

However, studies on ISF flow in PVS have so far focused mainly on the intracranial compartment, whereas ISF flow in the vascular adventitia and perivascular connective tissues of arteries and veins has only recently been described.

Interstitial tissue channels

Interstitial tissue channels refer to the water-rich, disordered pathways within the connective tissues which connect capillaries to initial lymphatics. In order to visualize these channels, blood perfusion imaging methods

are commonly adopted such as injection of ink, fluorescein isothiocyanate, or ferrocyanide precipitates. The results showed that tracers circulating in the blood were unevenly distributed in the connective tissues near the blood vessel wall, skeletal muscle and small intestinal wall[10,11]. It is speculated that the tracer is transported in the tissue channels around the capillaries. However, due to the low imaging resolution, the boundary structure of the fluid flow channel cannot be observed. Compared with the definition of ISF, the definition of tissue channels has not progressed much. Its conceptual connotation only further describes the phenomenon of fluid flow in the interstitial space around cells. It neither reveals the flow principles of ISF in tissue channels nor answers important questions such as the anatomical distribution and dynamic mechanism of ISF flow in animals or humans.

Vascular adventitial ISF circulatory network and physiological regulatory mechanisms

The ISF flow network is distributed in the skin, nerves, vascular adventitia, fascia and other parts, but the full picture of the distribution of this ISF flow network in the human body or animal body is not clear. Recently explored in detail in animal experiments was the vascular adventitial ISF flow network.

Vascular adventitial ISF circulatory network

By injecting fluorescent or paramagnetic tracers into perivascular tissues of human body and animal models, the ISF flow was illustrated[5,7]. To further confirm the findings and provide detailed structural insights, hematoxylin and eosin (H & E) staining, as well as combined staining methods like van Gieson and Verhoeff iron-hematoxylin (VG + VIH), were applied to the fluorescently stained adventitial pathway samples[6]. The results showed that it is the vascular adventitia (the outermost connective tissues covering of vessels) that serves as the site of ISF flow along arteries and veins. The ISF flows centripetally in the adventitia along the major arteries and veins of the systemic vasculature to the epicardium and myocardium, then into the lungs via the pulmonary arteries and returns to the heart via the pulmonary veins, comprising an adventitial ISF circulatory network[5–7]. In the process of centripetal flow along the long axis of the blood vessel, ISF in the adventitia passes through the fascia surrounding the vascular adventitia and diffuses into the tissues surrounding the blood vessels[6]. The flow velocity of fluorescein in the adventitial ISF was measured by stereo fluorescence microscopy. The results showed that it was about 3.6–15.6 mm/s in rabbits[6] and about (598.1 ± 107.7) μm/s in rats[7].

Subsequent studies explored myocardial perfusion through adventitial interstitial fluid transport. Using spectral micro-computed tomography (SMCT) to trace the distribution of silver nitrate administered via adventitial infusion and intravenous injection, it was found that compared with myocardial perfusion through blood circulation, the amount of tracer transported through the adventitial ISF of rat lower limb vessels was greater in myocardial tissue, indicating that myocardial tissue perfusion is likely to occur through two pathways: blood perfusion and vascular adventitial ISF transmission[12].

Interstitial MMCs in vascular adventitia

As analyzed by real-time frozen sections, the adventitial pathways for the ISF flow, which were stained by the flow of the FluoNa from the distal, consisted of the outermost layer of fascia and the inner adventitial matrix, covering the media of either arterial or venous vessels. The intrinsic structures of the adventitial pathways were composed of adventitial matrix, within which, the micro-CT found that there were approximately 2,300–2,800 fibers inside the adventitial pathways of the femoral artery and vein, respectively. However, neither fibers nor gel-like substances within adventitial matrix can flow freely along the vessels over a long distance. Hence, the boundary structures for adventitial ISF flow longitudinally along the vessels were the outermost layers of fascia and innermost tunica media of blood vessels. This adventitial ISF flow pathway was named "interstitial MMC"[7].

Several interspatial structures involved in ISF flow were identified within the vascular adventitia[6,7], including: (1) internal channels between the multiple layers of fascia surrounding the adventitia and between the fascia and the adventitial matrix; (2) internal channels on the surface of the fibers within the adventitial matrix; (3) internal channels between the adventitial matrix and the surface

of the tunica media. These internal channels within the adventitial tissue were named MMCs.

The regulatory mechanism of ISF flow modulated by heartbeat and respiration

Using quantitative speckle tracking velocimetry to measure the velocity and direction of the ISF flow in the adventitia along the femoral vein in rats, the effects of physiological parameters such as heart rate, respiratory frequency, tidal volume, and inspiratory–expiratory ratio on ISF flow can be readily investigated. In experiments with rats under physiological conditions[7], the following findings were observed: (1) Heart rate is positively correlated with the flow velocity of the femoral venous adventitial ISF; (2) When a large tidal volume was administered using a ventilator, it induced fluctuating changes in the ISF flow velocity, with the frequency of the fluctuations matching the respiratory rate. The amplitude of the flow velocity fluctuations was positively correlated with the tidal volume. During inspiration, the flow velocity of the venous adventitial ISF decreased, whereas during expiration, it increased. The inspiratory–expiratory ratio provided by the ventilator determined the ratio of the descending and ascending phases of the fluctuating flow velocity changes. Furthermore, in experiments with freshly deceased rats, the following observations were made[7]: (1) repeated chest compressions on the heart induced centripetal flow of the femoral venous adventitial ISF; (2) using a ventilator to cause the lungs to expand and contract repeatedly induced centrifugal flow of the femoral venous adventitial ISF. This indicates that the flow of ISF in the adventitia along large blood vessels is closely related to both heartbeat and respiration.

Comparison with the lymphatic system, perivascular spaces, and adventitial ISF circulatory network

The adventitial ISF circulatory network and the lymphatic system differ in their anatomical structure. The lymphatic system is a conduit-like vessel system. It consists of initial lymphatics, collecting lymphatics, and lymph nodes, and is lined by lymphatic endothelium. In contrast, the adventitial ISF circulatory network is not a conduit-like vessel system. It consists of interstitial MMCs within the vascular adventitia, bounded externally by fascial layers and internally by the surface of the tunica media.

PVS differ from the adventitial ISF circulatory network in their anatomical distribution and structural basis. PVS are perivascular compartments bounded by the pia mater on the arterial side and by the glia limitans along capillaries and veins. They surround penetrating vessels as these enter the brain parenchyma and are distributed along penetrating arteries, capillaries, and veins[2]. In contrast, the adventitial ISF circulatory network flows within the vascular adventitia. Its structural basis is the interstitial MMC in the adventitia. It is distributed along the adventitia of arteries and veins throughout the body.

Perivascular pump

The perivascular pump mechanism is not the direct cause of the ISF flow in the adventitia along large blood vessels. In intracranial PVS studies[13], the driving force behind ISF flow within the PVS is typically considered to be the perivascular pump mechanism, which includes: (1) Pulsating blood flow that impacts the PVS adjacent to intracranial small vessels, causing ISF to flow within the PVS; (2) Mechanical waves generated by cardiac pulsation that propagate along the vascular tree to the walls of intracranial small vessels, driving ISF flow within the PVS. To differentiate the relationship between the ISF flow in the adventitia along large blood vessels and the perivascular pump, a subsequent experimental step was carried out[7]: The apex of freshly deceased rats was excised, allowing the left and right ventricles to communicate with the air. This ensured that repeated heart compressions would not cause systemic blood flow. A laser mechanical vibrometer was used to monitor the mechanical vibrations of the arterial and venous vessel walls on both the left and right sides in real-time. Type I collagenase was used to disrupt the adventitial tissue of the left femoral artery and vein, while the adventitial tissue of the right femoral artery and vein remained intact. After administering fluorescent tracer dye to the left and right ankle regions, repeated heart compressions were applied. The results showed: (1) Mechanical pulsations generated by compressing the heart were detected in the vessel walls of both the left and right femoral arteries and veins; (2) The fluorescent dye from the ankle region

stained the adventitial tissue of right femoral artery and vein, but did not stain the adventitial tissue of femoral artery and vein that had been disrupted by collagenase. This experiment further indicates that the flow of ISF in the adventitial tissue of large blood vessels is a result of repeated mechanical movements of the heart and lungs and is not directly related to the vibrations of the vessel walls. However, the effects of blood flow on shear stress in the vessel walls, among other physiological factors, on the ISF flow still require further experimental verification.

Hypothesis of the driving mechanism of the vascular adventitial ISF circulatory network

The driving mechanism of the vascular adventitial ISF circulatory network consists of two components: the driving force and the MMCs distributed along the vasculature in the adventitia. The understanding of both components is still in its early stages, and further pioneering explorations are needed. Based on the recent observations, the following are proposed:

The matrix pump hypothesis

By measuring the velocity changes in the flow of femoral venous adventitial ISF, we found that contraction of the atria or ventricles generates a "push force" that drives centrifugal flow of the vascular adventitial ISF, while dilation of the atria or ventricles generates a "pull force" that drives centripetal flow of the ISF. Contraction of the lungs generates a "pull force" that drives centripetal flow, while lung expansion generates a "push force" that drives centrifugal flow. Based on these limited experimental observations, we propose a working hypothesis regarding the driving source of ISF circulatory network, aiming to stimulate further exploration: (1) When the heart and lungs repeatedly expand or contract, the interstitial matrix in these organs undergoes periodic compression and deformation, acting as a driving pump, termed the "matrix pump" or "gel pump;" (2) Deformation of the heart or lung matrix pump can generate at least two driving forces: pressure gradients and interfacial interaction forces generated by fluids within the matrix; (3) Pressure gradients generated by the contraction of the atrial or ventricular matrix and expansion of the pulmonary matrix will drive the adventitial ISF along the vasculature, either away from or toward the driving source; (4) Under the mediation of intact adventitial tissue, fluctuations in interfacial interaction force generated by the expansion of the atrial or ventricular matrix and the contraction of the pulmonary matrix will pull the adventitial ISF along the vasculature toward the driving source. In experiments conducted on live rabbits, the "heart matrix pump" drew peripheral ISF from the lower limbs along the vascular adventitial into the heart and into the pericardial cavity. Further in-depth research is required to validate the matrix pump hypothesis.

Active interfacial fluid flow in the MMC

There exist various channels of "interfacial fluid flow" within the adventitial matrix, and between the matrix and surrounding structures. The boundary structure of these interfacial channels is formed by the interfaces created through the contact of the fluid within each channel with the surrounding structures. These interfaces include the liquid–solid interface formed by the fluid contacting and enveloping the multilayered fascia surrounding the vascular adventitia, the liquid–gel interface formed by the fluid contacting the gel-like matrix, the liquid–solid interface within the matrix where the fluid contacts fibrous filaments, and the liquid–solid interface formed by the fluid contacting the smooth muscle of the vascular media, among others. Adjacent interfaces form channels for fluid flow. When fluid enters the interfacial MMCs, in the absence of an external driving force, the ISF diffuses in a disordered manner within the adventitial tissue. The "push force" and "pull force" generated by the periodic deformation of the cardiac and pulmonary matrix pumps, mediated by the intact vascular adventitial tissue, drive the to-and-fro flow of fluid within the various interfacial MMCs. Under the continuous active influence of heartbeat and respiratory movements, a sustained phenomenon of interfacial fluid flow is established within the MMC, which is concisely referred to as matrix flow or interfacial flow.

Opportunities and challenges in establishing and promoting the systemic ISF circulatory network

Biomedicine can be studied and understood from various perspectives and levels, such as molecule,

macromolecule, cell, tissue, organ, organ system, organism, with complex interactions and integrations among them. The ISF circulatory network can be categorized under the tissue and organ levels. Comprehensive research into the physiological and pathophysiological functions of this network can potentially drive advancements in medical diagnostic technologies and therapeutic approaches. This is now discussed.

New methods to regulate the microenvironment of tissues and organs

Traditional physiology holds that ISF constitutes the microenvironment of cells and the internal environment of the body, diffusing between the gaps of microcirculation (capillaries) and cells. By targeting the "adventitial ISF circulatory network," the development of mechanical, acoustic, optical, and electromagnetic stimulation methods could potentially lead to new techniques for directly regulating the microenvironment of visceral organs or tissues.

A novel drug delivery pathway mediated by ISF circulatory network

The adventitial ISF flow in the vascular adventitial ISF flow network can transport drugs into myocardial tissues. In previous research in rats, esmolol was employed to compare drug delivery via the adventitial pathway with intravenous injection. Real-time fluorescent imaging tracked the drug's distribution in myocardial tissues, while liquid chromatography-tandem mass spectrometry (LC-MS/MS) quantified the drug concentration in myocardial tissues. The results showed that adventitial drug delivery of esmolol achieved a more gradual and longer-lasting reduction in heart rate compared to intravenous administration. Moreover, the adventitial approach resulted in a higher drug concentration in myocardial tissues[7]. In-depth study of drug metabolism and delivery characteristics of this special pathway may lead to the development of a new series of drug therapy methods targeting the heart.

Potential relationship with diseases

The physiological and pathological roles of such an ISF circulatory system remain largely undefined, such as what solutes it transports, to what extent it is involved in systemic metabolism, how it perfuses organs or tissues, whether it supplies nutrients to vascular media and how it influences cardiac function, cardiac electrophysiology and myocardial energetics are all open questions. In particular, the metabolism of the blood vessel wall mainly depends on the *vasa vasorum*. However, we and other research teams have found that the ISF in adventitia flowing along the vascular tree can enter the tunica media and diffuse around the smooth muscle cells. Hence, answering questions such as whether this adventitial ISF flow along the arteries and veins is involved in the nutrients supply, metabolic products and pathogens clearance of vascular smooth muscle cells, and its relationship with the *vasa vasorum* will bring new perspectives to vascular physiology[14,15].

Conventional physiological knowledge holds that almost all fluid in the interstitium is entrapped within the tissue gel, with less than one percent in normal tissues being free of the proteoglycan molecules and can flow freely. Our series of studies have verified that under the coordinated actions of heartbeat and breathing, fluid in the adventitia flows along the vasculature to form a flow and circulation network around the heart and lungs. The vascular system is distributed throughout the body. Therefore, free fluid not entrapped by the gel-like extracellular matrix in various tissues and organs

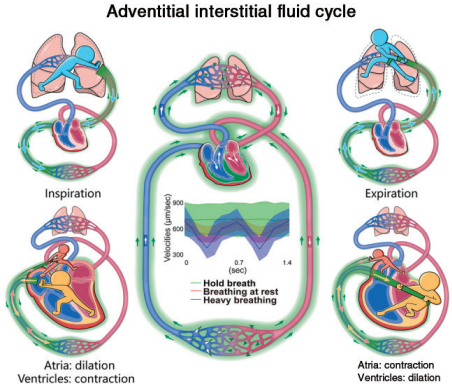

Figure 1: Schematic of the vascular adventitial ISF circulatory network. ISF flows centripetally in the adventitia of the systemic and pulmonary vasculature, driven by the synergistic movements of the heart and lungs. During the cardiac cycle, atrial or ventricular contraction drives centrifugal flow, whereas atrial or ventricular dilation drives centripetal flow. During the respiratory cycle, lung expansion drives centrifugal flow, whereas lung contraction drives centripetal flow. Reproduced from Li et al. (2024), *iScience 27*, 109407[7], under CC BY-NC 4.0.

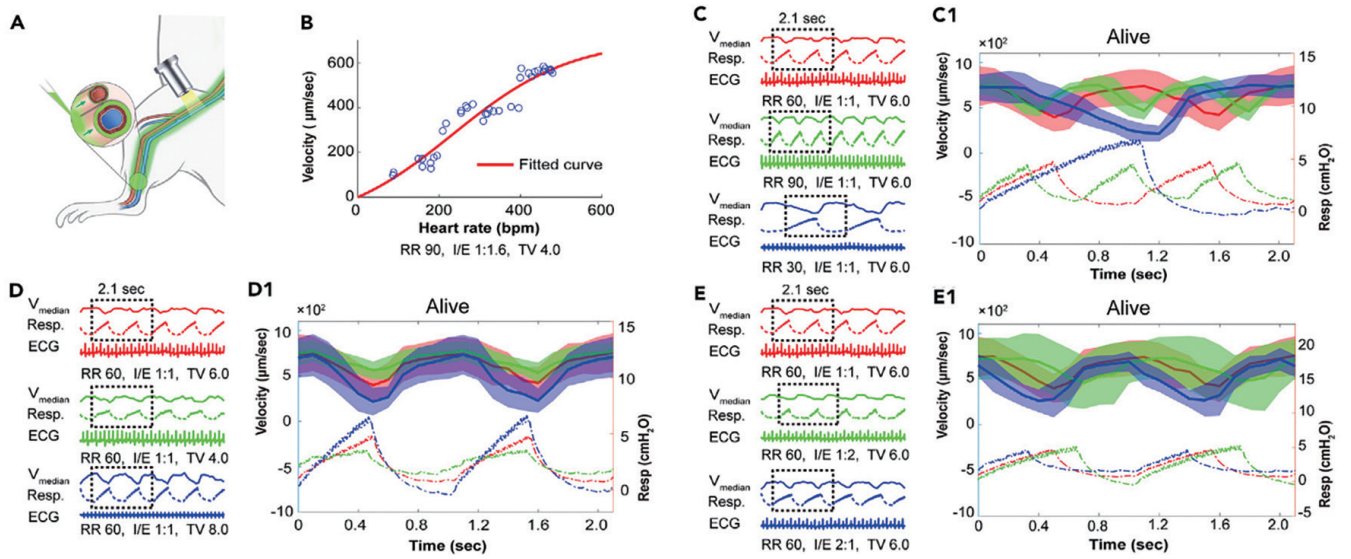

Figure 2: Regulation of adventitial ISF flow along the femoral vein by heart rate and respiration.

(A) Schematic of the observation site for adventitial ISF flow in the venous adventitial pathways of the femoral vessels. (B) Adventitial ISF flow velocity increases with heart rate (HR 150–450 bpm; RR 90 bpm, I/E 1:1, TV 4.0 mL; $n = 1$ rat; sigmoid fit). (C and C1) The frequency of the pulsatile flow matches the respiratory rate. (D and D1) Greater tidal volume increases the pulse amplitude. (E and E1) The inspiratory/expiratory ratio (1:1, 2:1, 1:2) determines the descending and ascending branches of the velocity pulse. Data in C–E are mean ± SEM; $n = 6$ rats per group. Adapted from Li et al. (2024), *iScience 27*, 109407[7], under CC BY-NC 4.0.

is likely to flow into the adventitia of the vascular tree, forming an interstitial fluid circulatory system through all parts of the body. Herein, these findings will expand our understanding of systemic fluid circulation from within vascular vessels to the significantly larger interstitial spaces between tissue cells. Elucidating the functions of ISF circulation, its relationship to diseases, and the development of related medical diagnostic and therapeutic technologies will bring about innovations in medicine.

Author contributions

Hongyi Li and Nandu Goswami conceived the scope and framework of this review and supervised the work. Bei Li and Jin Cai conducted the literature search and contributed to the drafting of the manuscript. Jin Cai prepared the figures. All authors reviewed, edited, and approved the final version of the manuscript and agree to its publication.

Acknowledgments

This work was supported by the National Key R&D Program of China, grant number 2025YFC3507600 and the National High Level Hospital Clinical Research Funding, grant number BJ-2025-120. We express our sincere gratitude to the editor and reviewers for their constructive comments and to the journal and its publisher for their professional support.

Ethics statement

This review article is based on previously published literature and does not involve human participants, human data, or animal experiments. Figure 1 and Figure 2 are adapted from Li et al. (2024), *iScience* 27, 109407, under the CC BY-NC 4.0 license, with appropriate attribution provided in the figure legends.

AI statement

Language editing only: The authors used DeepSeek (online version) as a language-editing tool to improve grammar, clarity, and readability. The AI tool was not used for data analysis, data generation, image processing, or scientific content creation. All outputs were carefully reviewed and verified by the authors, who take full responsibility for the final content.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Levick JR. Flow through interstitium and other fibrous matrices. *Q J Exp Physiol*. 1987;72(4):409-437.
2. Wardlaw JM, Benveniste H, Nedergaard M, et al. Perivascular spaces in the brain: anatomy, physiology and pathology. *Nat Rev Neurol*. 2020;16(3):137-153.
3. Li HY, Chen M, Yang JF, et al. Fluid flow along venous adventitia in rabbits: is it a potential drainage system complementary to vascular circulations? *PLoS One*. 2012;7(7):e41395.
4. Li H, Yang C, Lu K, et al. A long-distance fluid transport pathway within fibrous connective tissues in patients with ankle edema. *Clin Hemorheol Microcirc*. 2016;63(4):411-421.
5. Li H, Yang C, Yin Y, et al. An extravascular fluid transport system based on structural framework of fibrous connective tissues in human body. *Cell Prolif*. 2019;52(5):e12667.
6. Li H, Lyu Y, Chen X, et al. Layers of interstitial fluid flow along a "slit-shaped" vascular adventitia. *J Zhejiang Univ Sci B*. 2021;22(8):647-663.
7. Li H, Li B, Luo W, et al. Regulation of interstitial fluid flow in adventitia along vasculature by heartbeat and respiration. *iScience*. 2024;27(4):109407.
8. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Sci Transl Med*. 2012;4(147):147ra111.
9. Pirri C, Wells RG, De Caro R, Stecco C, Theise ND. What's old is new again: the anatomical studies of Franklin P. Mall and the fascial-interstitial spaces. *Clin Anat*. 2023;36(6):887-895.
10. Casley-Smith JR. Calculations relating to the passage of fluid and protein out of arterial-limb fenestrae, through basement membranes and connective tissue channels, and into venous-limb fenestrae and lymphatics. *Microvasc Res*. 1976;12(1):13-34.
11. Hauck G. The connective tissue space in view of the lymphology. *Experientia*. 1982;38(9):1121-1122.
12. Li B, Yang C, Qi X, et al. Myocardial perfusion by adventitial interstitial fluid transport. *Chin J Cardiovasc Res*. 2023;21(2):138-143.
13. Mestre H, Tithof J, Du T, et al. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. *Nat Commun*. 2018;9(1):4878.
14. Zhao J, Li T, Sun J, et al. Distribution of SARS-CoV-2 spike protein in the epicardium and vascular adventitia of human specimens during the acute phase of infection. *Chin J Virol*. 2025;41(1):33-38.
15. Gursky Z, Khan ZN, Koundal S, et al. Age-dependent brain responses to mechanical stress determine resilience in a chronic lymphatic drainage impairment model. *J Clin Invest*. 2025;135(17):e182555.