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Review

The FLOW Framework: a panvascular-on-a-chip platform to model systemic disease and guide panvascular interventional device suitcordance

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ABSTRACT

Panvascular diseases, encompassing systemic vascular disorders driven by atherosclerosis, represent the leading cause of global mortality, posing significant challenges in modeling due to their prolonged, multi-organ nature and complex device–vessel interactions. Current *in vitro* and *in vivo* models fall short in recapitulating high-fidelity hemodynamics, long-term monitoring, multi-vascular bed heterogeneity, and three-dimensional (3D) dynamic interactions essential for advancing interventional device development. To address these gaps, we introduce the FLOW framework—a novel panvascular-on-a-chip platform leveraging organ-on-a-chip (OoC) technology. This framework integrates four core modules: Fidelity hemodynamic reconstruction (F) for simulation of physiological/pathological blood flow; Longitudinal physiological surveillance (L) for real-time tracking of chronic processes like endothelialization and inflammation; Omni-vascular bed modeling (O) for simulating coexisting lesions across diverse vascular beds and inter-organ crosstalk; and Whole-space 3D interactive work-flow (W) for evaluating device deployment and biomechanical interactions in 3D vascular microenvironments. Guided by the concept of "suitcordance" (defined here as short-term suitability and long-term concordance between devices and vascular tissues), the FLOW platform enables high-fidelity modeling of panvascular pathologies, such as atherosclerosis-induced downstream diseases (e.g., myocardial infarction, stroke, diabetic foot) and thrombosis, while facilitating optimization of interventional devices like stents, valves, and thrombectomy catheters to achieve post-intervention rebalancing of biomechanical, cellular, and physicochemical–immune ecologies. We review macro-construction foundations, including microfluidic technologies, real-time sensing, cell engineering, and hydrogel-based structural designs, and discuss applications in mechanistic studies and device translation. Future prospects include multi-organ integration, AI-driven analytics, long-term culture, and gene editing for personalized medicine, positioning panvascular-on-a-chip as a paradigm-shifting tool to bridge clinical outcomes, enhancing device–vessel harmony and combating humanity's "number one killer".
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1. Introduction

The panvascular system refers to the human vascular network, a complex structure composed of arteries, veins, lymphatic vessels, and other components, which transports oxygen and nutrients to vital organs throughout the body. Panvascular disease, first proposed by our team in China, is a group of systemic vascular disorders characterized by vascular lesions (with 95% involving

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atherosclerosis) as a common pathological feature, primarily affecting critical organs such as the heart, brain, liver, kidney, limbs, and major arteries [1]. In a broader sense, panvascular disease also encompasses small and microvascular disorders, venous conditions, and vascular diseases associated with tumors, diabetes, and immune disorders, positioning it as the "number one killer" of modern humanity [2]. The panvascular theory advocates for multidisciplinary and interdisciplinary integration in research, re-examining the pathogenesis and progression of vascular diseases from a systems biology perspective, thereby providing new insights for the diagnosis, treatment, and study of related conditions.

Interventional devices serve as key weapons in combating this number one killer of humanity: for instance, coronary artery stenting for coronary heart disease [3], inferior vena cava filters for preventing pulmonary embolism [4], transcatheter aortic valve replacement (TAVR) for aortic stenosis [5], coil embolization for intracranial aneurysms [6], occluder devices for atrial septal defects [7], ventricular septal defects [8], patent foramen ovale [9], and prevention of left atrial appendage thrombosis [10]. However, the development, manufacturing, and clinical application of existing devices primarily focus on alleviating acute pathological states, achieving only short-term macroscopic relief of the disease. Taking cardiovascular stents and valves as examples, these can improve hemodynamics in the short term [11,12], partially restoring a compensatory equilibrium (compensilibrium) in vascular biomechanical ecology, cellular ecology, and physicochemical–immune ecology. Nevertheless, over extended time scales, imbalances re-emerge in the device–vessel interactions, including biomechanical ecology (e.g., vascular stress and hemodynamics), cellular ecology (e.g., endothelial cells (ECs), valvular interstitial cells (VICs), smooth muscle cells (SMCs), fibroblasts, and immune cells), and physicochemical–immune ecology (e.g., temperature, pH, lactate concentration, lipid types and levels, immune-related factors (IL-1β, TNF-α), and extracellular matrix components (collagen, non-collagen proteins, elastin, glycosaminoglycans, and proteoglycans)). This can lead to late adverse events, such as in-stent restenosis (ISR) [13], unexpected stent fracture [14], and structural valve deterioration (SVD) [15]. With economic development, the trend toward younger onset of panvascular diseases and extended human life expectancy will further amplify the limitations of current interventional devices.

Therefore, we have proposed the concept of suitcordance (short-term suitability and long-term concordance) [16,17] to guide interventional devices toward achieving short-term compatibility with the vasculature (alleviating acute pathological states) and long-term harmony (reducing late adverse events). This aims to rebalance the biomechanical, cellular, and physicochemical–immune ecologies between the device and vessel, ultimately realizing long-term co-regulation of the device–vessel fate community [18].

However, as a class of systemic diseases characterized by slow onset, prolonged course, and inter-organ pathological mechanisms with mutual crosstalk, panvascular diseases pose significant modeling challenges for in-depth research. Current studies on related interventional devices not only lack dynamic monitoring platforms *in vitro* but also fail to establish mature modeling systems that combine excellent operability, strict experimental controllability, and high physiological relevance. The absence of such critical models severely hinders the elucidation of underlying pathological mechanisms and the development of effective clinical treatment strategies.

With the rapid advancement of microfluidics and tissue engineering technologies, microphysiological models capable of simulating human physiological and pathological states—known as "organ-on-a-chip" (OoC)—have emerged [19]. OoC is a microfluidic cell culture device constructed from optically transparent materials (such as plastics, glass, or flexible polymers like PDMS). Its core feature involves perfused microchannels populated with living cells, reconstructing tissue-level or organ-level structures and functions *in vitro* to recapitulate *in vivo* physiological and pathological characteristics [20]. Since the pioneering work by Huh et al. in 2010 [21], OoC technology has evolved into various organ types. This technology effectively addresses the aforementioned modeling challenges, enabling more precise simulation of human disease models and real-time data monitoring, thereby bridging *in vitro* models with clinical research [22]. In this context, the importance of OoC is increasingly prominent. In April 2025, the FDA issued a statement planning to phase out traditional animal testing and transition to organoids and OoC systems for drug safety testing, which is regarded as a "paradigm shift" in future drug development [23]. Consequently, the demand for more mature OoC platforms will continue to grow in both basic research and interdisciplinary applications, making their development a key focus of current R&D efforts. However, widely used OoC platforms currently support only mechanistic studies of single vascular bed pathophysiology and drug development. For panvascular interventional devices such as vascular stents, valves, occluders, and coils, there is an urgent need to develop targeted OoC platforms. These platforms must specifically address: simulating the physical processes of device insertion/deployment, accurately recapitulating the complex hemodynamic environment at the implantation site (e.g., high shear stress, turbulence, and stent compression), constructing 3D microstructures including device anchoring interfaces (e.g., stent strut–endothelium contact), and enabling real-time dynamic monitoring of tissue responses induced by the device (e.g., endothelialization, thrombosis, inflammation, and intimal hyperplasia). The lack of suitable platforms severely constrains the clinical translation of interventional devices (Fig. 1).

In this article, starting from the core challenges in current mechanistic research and clinical applications of panvascular diseases, we propose and elucidate how the "FLOW" framework, constructed using OoC technology, systematically addresses these challenges. We will review the latest advances in building panvascular chip-based microphysiological systems based on this framework and discuss their applications and broad prospects in future systemic research on panvascular diseases and the suitcordance-guided improvement and development of interventional devices.

2. Why OoC platform suits panvascular disease research?

In previous mechanistic studies of panvascular diseases and the clinical translation of interventional devices, considerable efforts have been devoted to constructing *in vivo* and *in vitro* models, including widely used two-dimensional (2D) cell cultures, animal models, and 3D cell cultures [24–29]. However, these models struggle to accurately simulate the core features of panvascular diseases and the complex interactions with interventional devices. OoC technology, with its unique advantages, offers a breakthrough solution for panvascular research (Fig. 2). Its core strengths can be distilled into the FLOW framework—an advanced platform integrating Fidelity hemodynamic reconstruction (high-fidelity hemodynamic reconstruction), Longitudinal physiological surveillance (longitudinal physiological monitoring), Omni-vascular bed modeling (comprehensive vascular bed modeling), and Whole-space 3D interactive work-flow (whole-space 3D interactive work-flow). This enables the *in vitro* recapitulation of the dynamic flow of real blood through vascular networks (FLOW).

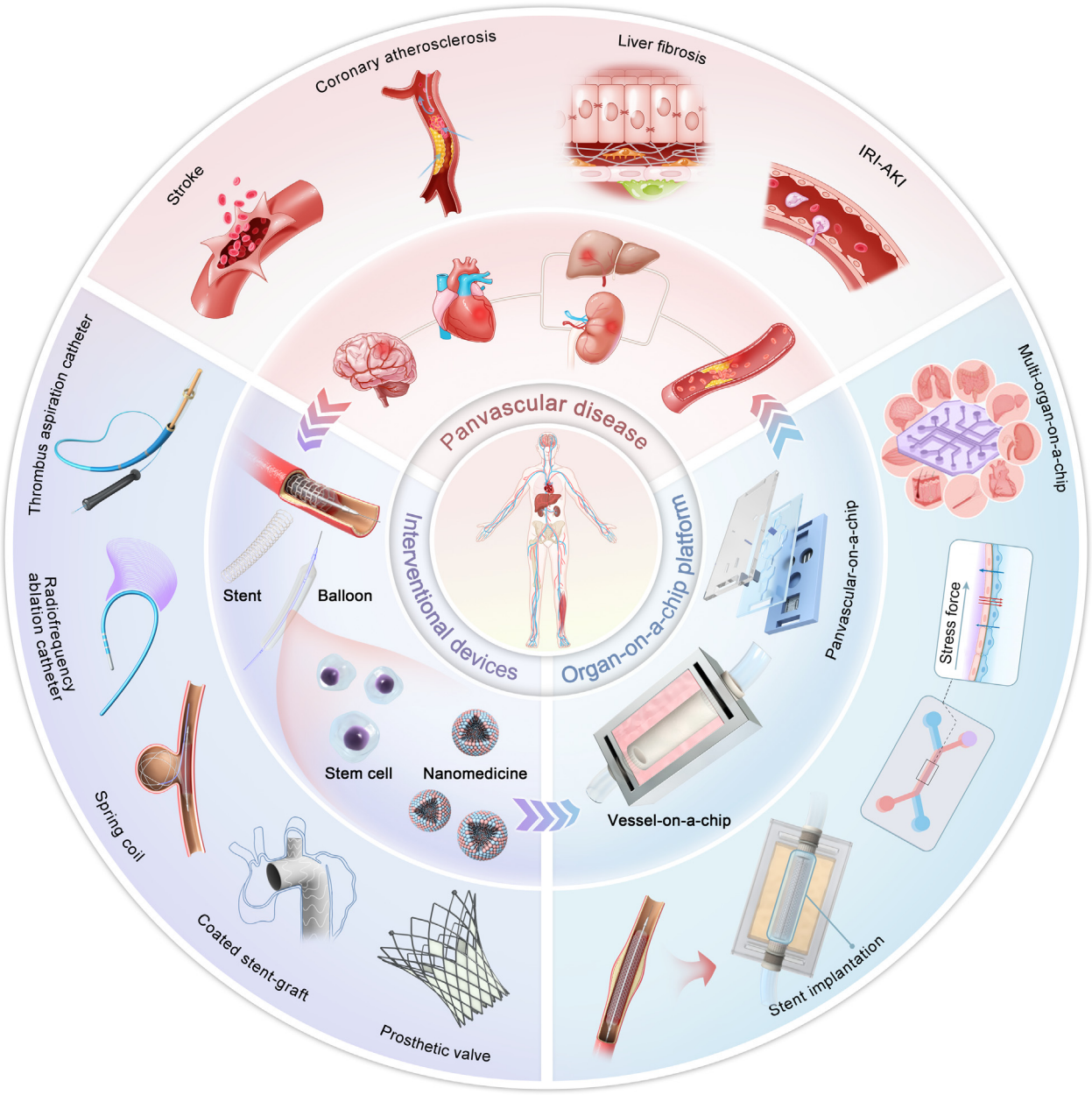


Fig. 1. An integrated paradigm for panvascular disease, intervention, and OoC platforms. This diagram illustrates the ecosystem of panvascular disease, encompassing various pathologies (e.g., stroke, coronary atherosclerosis) and their corresponding interventional devices. The OoC platform is positioned as a central technology connecting these domains by enabling the precise modeling of disease mechanisms. This technology is shown evolving from single-vessel to multi-organ systems, establishing a visualized and biomimetic platform to assess the "suitcordance" of interventional devices with the human vascular microenvironment and revolutionizing the conventional research and treatment paradigm.

2.1. F: Fidelity hemodynamic reconstruction

Hemodynamic fidelity is the foundation of vascular pathophysiology modeling, since abnormal shear stress and pulsatile flow directly drive endothelial dysfunction, plaque formation, and thrombosis.

The performance testing of interventional devices (such as vascular stents, valves, occluders, vena cava filters, and coils) is highly dependent on the accurate simulation of blood flow environments. Traditional 2D cell cultures expose ECs to static media and lack shear gradients, whereas 3D scaffold cultures provide only limited diffusion-based transport without controllable pulsatile forces [30]. Animal models, though dynamic, exhibit discrepancies in hemodynamic parameters (e.g., shear stress, flow velocity, and flow rate) compared to human target vessels [31]. *In vitro* simulated circulatory systems struggle to simultaneously and faithfully reproduce the physiological or pathological blood flow states across multiple interconnected vascular beds (e.g., systemic vascular resistance (SVR) and collateral circulation), limiting the assessment of local and distal hemodynamic changes post-device intervention (e.g., vortices, stagnation zones, and wall shear stress variations).

In contrast, the core microfluidic technology of OoC platforms enables high-fidelity reconstruction of the physiological or pathological hemodynamic flow characteristics in target vascular beds by precisely controlling key parameters such as shear stress and

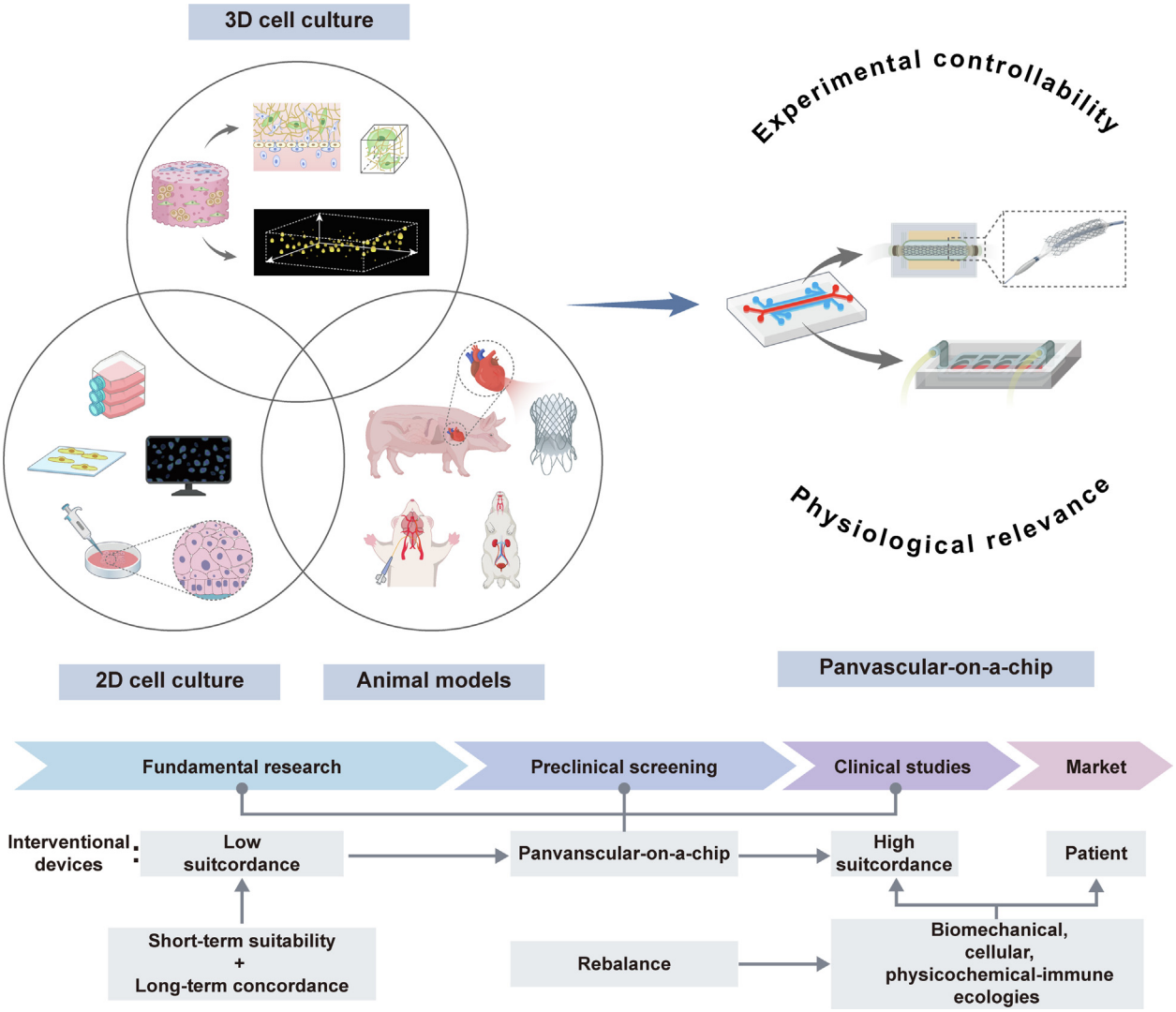


Fig. 2. A comparative framework for models in panvascular research. Compared to traditional 2D/3D cell culture and animal models, panvascular-on-a-chip has higher experimental controllability and physiological relevance. This unique combination makes it a critical platform to connect the entire development continuum for interventional devices, linking fundamental research, preclinical screening, clinical studies, and market application. The use of panvascular-on-a-chip can facilitate the evolution of interventional devices from low suitcordance to high suitcordance throughout the entire process, ultimately achieving the goal of restoring the biomechanical, cellular, and physicochemical–immune ecologies between the device and vessel.

pulsatile flow [32–34]. This provides an unparalleled precise environment for evaluating the impact of interventional devices (e.g., stents, valves, and filters) on local and distal blood flow (e.g., vortices, stagnation zones, and wall shear stress changes), overcoming the distortions in flow simulation inherent to traditional models.

2.2. L: Longitudinal physiological surveillance

Long-term physiological monitoring is indispensable for revealing chronic processes such as endothelialization, inflammation, and vascular remodeling following device implantation. Although animal models can simulate overall physiological environments, they lack the technical means for long-term, *in situ* monitoring of dynamic changes at the interfaces of intravascular interventional devices (e.g., stents, valves, and occluders), making it difficult to assess in real time the key pathophysiological processes at the vessel wall/device interface over years or even decades post-implantation (e.g., endothelialization progression, chronic inflammatory responses, and material degradation kinetics). Conventional 2D and 3D cultures only provide endpoint measurements—immunostaining or biochemical assays—without continuous observation of microenvironmental evolution. They also suffer from limited nutrient exchange and loss of cell viability beyond several weeks, preventing the study of late complications [21]. This results in poor predictability for late complications of interventional procedures (e.g., ISR, late thrombosis, and SVD). Existing *in vitro* models face challenges in maintaining long-term cell viability and precisely controlling and observing dynamic microenvironmental parameters in real time [35].

Recent advances have demonstrated that microfluidic OoC systems can integrate non-invasive microsensors (e.g., electrochemical, impedance, or optical sensors) for continuous *in situ* monitoring of vascular and tissue responses over extended periods while maintaining stable cellular behavior [36,37]. These sensor-integrated designs enable long-term visualization of endothelialization, inflammatory dynamics, and thrombus formation without significant perturbation of the local microenvironment.

Addressing these critical points, OoC platforms integrate microfluidic systems with high controllability and visualization capabilities, supporting the long-term co-culture of human-

derived cells (e.g., ECs and THP-1 macrophages) [19,38]. This enables real-time monitoring of the dynamic evolution of chronic inflammation, endothelialization processes, material degradation, and late complications (e.g., restenosis and thrombosis formation). It improves upon the deficiencies of traditional models in temporal monitoring, providing essential data for evaluating the long-term biocompatibility and performance evolution of devices.

2.3. O: Omni-vascular bed modeling

System-level modeling across multiple vascular beds is crucial for reproducing the heterogeneous and interconnected nature of panvascular disease. Devices are often applied across different vascular beds (e.g., coronary arteries, peripheral vessels, and cerebral vessels). Here, the term "Omni-vascular" does not denote a literal reconstruction of all vascular systems throughout the body, but rather a scalable and integrative modeling concept that allows simultaneous representation of multiple, heterogeneous vascular beds within a unified hemodynamic framework. This concept emphasizes versatility and systemic connectivity rather than overextension. Existing animal models struggle to simulate coexisting pathological states at multiple sites with heterogeneous lesion characteristics (e.g., severe calcified stenosis at one site combined with an aneurysm at another) within the same system, making it impossible to assess the comprehensive performance and systemic impacts of devices across diverse anatomical regions. *In vitro* models (Conventional 2D or 3D cultures) are even less capable of constructing such spatially distributed networks of systemic lesions [19]. Multi-organ interconnected systems built on OoC platforms can integrate simulations of different vascular beds and their coexisting, heterogeneous pathological environments [39], reconstructing key interaction pathways in the panvascular system (e.g., remote crosstalk of inflammatory factors [40]; metabolite-mediated organ dialogues [41]; and neuroimmune axis–mediated artery–brain circuits [42]). At the same time, these platforms enable real-time monitoring of systemic effects triggered by device intervention at a single lesion site via these pathways (e.g., elevated systemic inflammation post-stent implantation exacerbating damage to vulnerable brain regions), addressing the limitations of traditional models in evaluating dynamic "device–multi-organ" interactions.

2.4. W: Whole-space 3D interactive work-flow

3D spatial interaction is the decisive dimension for faithfully evaluating how interventional devices deploy, expand, and mechanically interact with vascular walls. 2D models are entirely incapable of assessing the deployment morphology, apposition, delivery performance, and 3D interactions of devices (e.g., vascular stents, thrombectomy catheters, and valves) with ECs/SMCs in real lumens [43]. Even advanced 3D printed or hydrogel constructs often lack perfusable lumens or physiologically realistic compliance, resulting in static geometry rather than dynamic vascular behavior [44]. Although animal models allow implantation, their vascular dimensions, anatomical configurations (e.g., curvature and bifurcation angles), and tissue mechanical properties (e.g., calcification degree and vessel wall elasticity) differ significantly from humans, leading to distorted evaluations of device delivery, expansion, anchoring effects, and impacts on local hemodynamics, with limited real-time observability [45]. *In vitro* 3D models (e.g., bioprinted vessels) remain immature in precisely simulating lesion morphologies (e.g., severe calcification, irregular stenoses, and aneurysms), multilayered vessel wall structures, and biomechanical responses, and they lack long-term, physiologically relevant dynamic blood flow perfusion [46]. The core of vascular OoC platforms lies in constructing a whole-space 3D dynamic interactive work-flow. This allows interventional devices to be implanted into 3D vascular microenvironments, enabling direct observation of device deployment, apposition, anchoring, and mechanical interactions with endothelial/smooth muscle/immune cell populations under simulated dynamic blood flow. It achieves precise simulation and visual analysis of the 3D dynamic interactions among "device–vessel wall–blood flow," serving as an ideal platform for evaluating device deliverability, suitability, and biomechanical and mechanobiological effects.

In summary, the FLOW framework of OoC—integrating high-fidelity hemodynamic reconstruction (F), longitudinal physiological monitoring (L), comprehensive vascular bed modeling (O), and whole-space 3D interactive work-flow (W)—constructs a highly physiologically mimetic, experimentally controllable, and standardized advanced platform for panvascular disease research. It not only faithfully recapitulates the dynamic flow of blood through vascular networks but also promises a creative leap from panvascular mechanistic studies to device evaluation, breaking down barriers between "basic research" and "clinical application" and driving a paradigm shift from "single-organ isolated perspectives" to "multi-organ systemic integration." This concept aligns closely with our team's research mission—we not only pioneered the panvascular concept to focus on the systemic cascade effects of vascular lesions but are also committed to building a research system for "panvascular interventional complex systems," aiming to enhance device–vessel "suitcordance" to guide the design and optimization of next-generation interventional devices, ultimately benefiting clinical practice and improving patient outcomes. With technological advancements, it holds immense promise in panvascular disease modeling and interventional device translation (Table 1).

3. Macro-construction foundations of vascular chips

To fully leverage the advantages of the vascular chip platform's "FLOW" framework—achieving high-fidelity hemodynamic simulation (F), dynamic regulation and long-term monitoring of pathophysiological microenvironments (L), heterogeneous panvascular tissue modeling (O), and 3D interactive work-flows (W)—its core lies in the refinement and integration of macro-construction technologies. After establishing the foundational framework incorporating key elements such as precise microfluidic manipulation, microenvironment regulation, real-time sensing, cell engineering, multi-organ interconnection, and precision structural design, the subsequent content will focus on the core construction technologies and material selections that underpin the realization of each FLOW module's strengths. This includes how specific material properties, processing techniques, and system designs concretely enable the high fidelity of blood flow in the F module, dynamic microenvironment control and long-term stability in the L module, cellular heterogeneity and functional arrangement in the O module, and whole-space 3D interactive environments in the W module, thereby laying a solid technical foundation for building advanced platforms that truly simulate complex vascular physiological and pathological states as well as device interactions (Fig. 4).

3.1. F module construction (Fidelity hemodynamic reconstruction)

The construction of vascular chips at the technical scale primarily relies on advanced microfluidic technology, which is also key to achieving high-Fidelity hemodynamic reconstruction (F module) in the "FLOW" framework. Microfluidic systems precisely control fluid flow at minute scales (typically 10^{-18}–10^{-9} L) [47] to simulate *in vivo* environments, such as blood flow, oxygen gradients,

Table 1
Comparative assessment of biological models for research applications.

Feature/Model	2D cell culture	3D cell culture	Animal models	Organ-on-a-chip
Physiological relevance	Low (useful for basic molecular studies)	Moderate–high (better tissue-level organization)	Moderate–high (whole-organism, but species differences)	High (organ-level functionality under controlled microenvironment)
Structural complexity	Low	Moderate–high	High	Moderate (engineerable architecture)
Cellular microenvironment	Low	High	High	High (microfluidic shear, gradients, interfaces)
Cost (resource and equipment)	Low (common consumables)	Moderate (high media and maintenance cost)	High (animal housing, ethical cost)	Low–high (low reagent/cell use but higher setup cost)
Throughput	High	Moderate	Low	Moderate (parallelization possible but limited by system complexity)
Ethical issues	Low (minimal ethical concern)	Low–moderate	High (animal welfare concerns)	Low (FDA supports non-animal testing; strong ethical advantage)
Genetic heterogeneity	Low	High (patient-derived options)	Variable (transgenic or inbred lines)	High (iPSC/patient-derived cells)
Experimental controllability	High	Moderate	Low	Moderate–high (precise control but system complexity)
Systemic *in vivo* response	Not applicable/Low	Low–moderate	High (intact physiological system)	Moderate (single-organ limited; multi-organ platforms partially reproduce systemic functions)
Applicable stage	Basic research; high-throughput primary screening	Mechanism studies; drug toxicity/efficacy primary screening	Preclinical safety/efficacy evaluation	Mechanism studies; translational research; precision medicine; toxicity prediction

nutrient delivery, and more refined aspects like shear stress, cyclic mechanical strain, and chemical concentration gradients. This enables scientists to accurately replicate the fluid dynamic environments within biological systems at microscopic scales. Specifically, microfluidics involves manipulating small volumes of fluid in microscale channels (i.e., 1–1000 μm in height or width) [48]. Such microchannels have large relative surface areas, facilitating high mass transfer. Additionally, the smaller fluid volumes (on the order of nL–μL) minimize the use of expensive reagents and human samples, requiring fewer cells for experiments [49]. Other inherent advantages of microfluidic technology include faster mixing rates, better volume control, and rapid reagent reactions [50,51]. Its core function lies in high-fidelity simulation of hemodynamics (e.g., shear stress and pulsatile flow) to recapitulate physiological or pathological blood flow environments. This high-precision blood flow simulation is crucial for assessing local hemodynamic changes post-implantation of interventional devices (e.g., stents, valves, and occluders), predicting the risk of late adverse events, and thereby guiding the optimization of device mechanical properties to enhance interventional device suitcordance.

In practical terms, biomimetic pulsatile flow can be achieved through programmable pneumatic or peristaltic micropumps coupled with compliant channel materials (e.g., PDMS or hydrogel-based membranes), allowing dynamic modulation of pressure and flow waveforms to reproduce cardiac-like pulsatility and wall deformation [52]. Moreover, microfluidic vascular constructs incorporating dual-layer designs—typically ECs and SMCs co-cultures—enable the simulation of fluid–structure interactions (FSI) at the blood–vessel interface, which are essential for reproducing realistic shear–strain coupling under physiological or pathological flow conditions [53]. These approaches collectively enhance the biomimetic fidelity of hemodynamic environments, further supporting the FLOW framework's F module for high-fidelity vascular reconstruction.

However, current microfluidic vascular models still face challenges in maintaining stable pulsatile flow and replicating the full-scale biomechanical feedback of large vessels over extended culture durations [54,55]. Future optimization of pump control precision and long-term elastic material stability is essential to achieve sustained hemodynamic fidelity.

3.2. L module construction (Longitudinal physiological surveillance)

3.2.1. Real-time monitoring systems

The construction of panvascular chip systems also requires the integration of sensing modules for real-time monitoring of metabolic products (e.g., lactate, glucose, oxygen, ROS, cytokines, and collagen fibers) [56–58] and physicochemical parameters (e.g., temperature, pH, and ion concentrations) [59]. Recent advances have demonstrated that these monitoring modules can incorporate optical (e.g., pH and oxygen fluorescence probes), electrical (e.g., impedance-based endothelial barrier sensors), and electrochemical (e.g., amperometric glucose and lactate detectors) modalities within microfluidic architectures to enable continuous, high-sensitivity signal acquisition [60,61]. The function of these sensing modules is to dynamically track chronic inflammation and endothelialization processes, monitor material degradation kinetics and metabolic products, and evaluate the long-term biocompatibility of device–vessel interactions, thereby enabling Longitudinal physiological monitoring (L module) *in vitro*. Real-time, long-term monitoring of physiological parameters holds irreplaceable value for evaluating the biocompatibility, material degradation kinetics, drug release effects, and induced chronic inflammation or endothelialization processes of interventional devices (e.g., drug-eluting stents and covered stents).

Despite significant progress, sensor drift, biofouling, and limited long-term stability remain technical bottlenecks in continuous *in vitro* monitoring. Integrating self-calibrating sensor arrays and antifouling surface coatings may address these issues and extend monitoring durations beyond weeks [62,63].

3.2.2. Microenvironment regulation for long-term perfusion culture

Stable microenvironmental regulation forms the foundation of long-term physiological surveillance, ensuring that vascular-on-a-chip systems can sustain dynamic perfusion and cell viability over extended periods. To precisely recapitulate the complex dynamic interaction networks among cells, matrices, and factors in human tissues, cells must be co-cultured with composite matrices and growth factors. Beyond biochemical signaling and mechanical forces, the microenvironment also encompasses the cellular microecology—comprising ECs, SMCs, fibroblasts, macrophages, and other supporting cells—that collectively maintain vascular

homeostasis and immune–metabolic balance. This multidimensional co-culture system simulates physiological-level biochemical signaling and mechanical stimuli to reconstruct functional crosstalk between cells and between cells and their microenvironments, thereby optimizing the dynamic balance of cell proliferation, differentiation, and function. For efficient application in panvascular disease research, system construction must prioritize the integration of precise regulation technologies for key mechanical stimuli such as oxygen concentration gradients and fluid shear stress/mechanical tensile forces [64,65]. These dynamic controls not only replicate *in vivo* mechanical stimulation but also stabilize the biochemical milieu, thereby sustaining long-term perfusion culture and enabling longitudinal observation of vascular responses. The goal is to optimize cell proliferation, differentiation, and functional maintenance, achieving Longitudinal physiological monitoring (L module). The ability to precisely regulate mechanical and biochemical microenvironments provides a critical platform for simulating *in vitro* the immediate damage to the vessel wall caused by interventional procedures (e.g., balloon dilation and stent implantation) and subsequent repair/inflammatory responses, facilitating research on device–vessel interaction mechanisms and the optimized design of devices.

The major limitations lie in maintaining long-term cell viability under dynamically changing conditions and ensuring uniform distribution of mechanical stimuli throughout the perfused network [66]. Optimization of medium composition, oxygenation systems, and microactuator response is being actively pursued to overcome these constraints. Therefore, microenvironmental regulation serves as the engineering and biological basis of the L module, enabling stable long-term perfusion culture, preservation of multicellular microecology, and continuous physiological surveillance within OoC systems.

3.3. O module construction (Omni-vascular bed modeling)

3.3.1. Cell sources and spatial organization

The construction of panvascular-on-a-chip also requires consideration of acquiring specific organ-functional cells, primarily from three categories: primary cells from patients or cell banks [67], products of adult stem cell differentiation, and human induced pluripotent stem cells (hiPSCs) with multidirectional differentiation potential [68]. Precisely arranging these cells in predefined regions of the chip to simulate target organ functions effectively addresses the scarcity of tissues such as neural or cardiac sources [69]. Its core role lies in resolving issues of scarce tissue sources, simulating target organ functions (e.g., co-culture of ECs, SMCs, VICs, and immune cells), and constructing heterogeneous cellular ecologies, corresponding to Omni-vascular bed modeling (O module). Utilizing patient-derived cells (e.g., hiPSC-differentiated) to build personalized vascular models enables the assessment of interventional device safety and efficacy in specific patient populations (e.g., high bleeding risk (HBR) groups), accelerating the application of precision medicine in the interventional field.

3.3.2. Multi-OoC integration basis

For efficient application in panvascular disease research, the construction of panvascular chip systems must also support the simulation of coexisting lesions across multiple vascular beds (e.g., coronary stenosis + cerebral aneurysm), enabling cascade studies of "vascular stenosis–organ ischemia." This requires microfluidic interconnection interfaces, vascularized organoid serial linkages, and mechanical/metabolic coupling designs, likewise corresponding to Omni-vascular bed modeling (O module). Diseases in various parts of the panvascular system share commonalities while also exhibiting unique characteristics. In response to the distinctive anatomical structures of each organ in the panvascular system, corresponding chips and vascular chips adapted for interventional devices must incorporate differentiated architectures. Such frameworks can simulate coexisting lesions across multiple vascular beds and their cascade effects (e.g., coronary stenosis inducing myocardial ischemia), holding forward-looking significance for testing the comprehensive efficacy and potential systemic impacts of interventional devices in complex pathological environments.

While multi-organ integration greatly enhances systemic modeling capability, it is constrained by nutrient gradient imbalance and inter-organ medium compatibility. Advanced vascularization strategies and optimized universal perfusion media are key to achieving physiologically stable long-term multi-organ co-culture [70].

3.4. W module construction(Whole-space 3D interactive work-flow)

3.4.1. Structural design principles

Accurate structural design is the cornerstone of constructing physiologically relevant vascular models, forming the foundation of the Whole-space 3D interactive work-flow. The aim is not only to geometrically reproduce vascular architecture but also to ensure that the reconstructed systems convey realistic mechanical and biochemical cues to cells and interventional devices.

From a design perspective, the vascular-on-chip system should integrate structural fidelity, mechanical compliance, and functional responsiveness. Elastic and transparent materials such as PDMS [21,71–73] allow precise replication of microvascular geometries, while multilayer architectures composed of compliant substrates and ECM-mimetic matrices reproduce the compliance gradient across vascular layers. These structures enable realistic deformation under pulsatile flow, faithfully translating cyclic strain and shear stress to the cellular microenvironment [74].

Beyond the replication of geometry, the structural layout should be conceived to facilitate spatially resolved interactions between blood flow, vessel walls, and implanted devices. Embedding gradient matrices or compartmentalized regions allows the simulation of heterogeneous mechanical and biochemical microenvironments characteristic of different vascular beds. In this manner, the structural design establishes the functional scaffold upon which fabrication techniques (Section 3.4.2), matrix composition (Section 3.4.3), and intelligent integration (Section 3.4.4) are implemented to achieve a fully interactive panvascular model.

3.4.2. Fabrication techniques

Microfluidic vascular models are primarily fabricated through soft lithography or 3D bioprinting, each offering distinct advantages and limitations.

Soft lithography using PDMS enables rapid prototyping with high optical transparency, elasticity, and micron-scale precision, making it ideal for microchannel replication and real-time observation [21,71]. However, PDMS's hydrophobic surface and limited scalability restrict its ability to construct complex multilayer 3D geometries [72,73].

In contrast, 3D bioprinting allows layer-by-layer fabrication of anatomically realistic vascular networks using cell-laden bioinks [75]. This approach offers high design flexibility and enables the integration of heterogeneous materials, thereby facilitating the reconstruction of multilayer vascular architectures and tissue interfaces [76,77]. Nonetheless, printing resolution, bioink viscosity, and mechanical stability remain technical challenges for maintaining channel fidelity and long-term culture stability.

Hybrid fabrication strategies that combine the structural precision of soft lithography with the biological complexity of bioprinting have recently emerged, providing balanced solutions for

fabricating microvascular systems with both geometrical fidelity and biomimetic functionality [78].

3.4.3. Material selection and matrix composition

Hydrogel materials are commonly used as filling matrices in OoC fabrication, including natural polymers (e.g., collagen, alginate, and gelatin) and synthetic polymers (e.g., poly(lactic acid) (PLA) and poly(lactic-co-glycolic acid) (PLGA)) [79,80]. These hydrogels not only share compositional similarity with extracellular matrices but can also be tuned in their physicochemical properties to meet the unique requirements of different simulated environments [81].

Natural polymers provide inherent bioactivity and promote cell adhesion, migration, and signaling but suffer from batch variability and limited mechanical strength. Synthetic polymers, on the other hand, offer tunable stiffness and degradation profiles but often require surface modification to support cell adhesion and proliferation [81]. Hybrid hydrogel systems that integrate both natural and synthetic components are increasingly used to balance mechanical stability with biological functionality, offering a more physiologically relevant microenvironment for vascular remodeling and device–tissue interaction studies [82].

Processed via technologies such as soft lithography and 3D bioprinting, these materials together provide the 3D ECM-mimetic microenvironment necessary for the implantation, deployment, and interaction of interventional devices (e.g., stents, thrombectomy devices, and balloons) with the vessel wall, thus realizing the construction of Whole-space 3D interactive work-flows (W module) and enabling precise evaluation of structural design, material performance, and operational optimization (Table 2).

Despite progress in hybrid materials, mechanical fatigue, degradation kinetics, and reproducibility remain challenges for long-term culture. Emerging photo-crosslinkable and self-healing hydrogels offer potential solutions for sustaining stable structural integrity during prolonged dynamic experiments [83].

3.4.4. Intelligent analysis and high-throughput integration

Building upon the structural and material foundations described above, the FLOW framework further evolves toward intelligent integration and high-throughput analysis. As OoC technologies become increasingly multiplexed and automated, vast amounts of high-dimensional data are continuously generated from real-time monitoring, mechanical regulation, and multi-organ interactions. The FLOW-based vascular chips, by integrating these multimodal data streams, enable systematic characterization of dynamic vascular microenvironments, device–tissue interactions, and pathophysiological responses at unprecedented spatiotemporal resolution.

To address the bottleneck between data generation and interpretation, artificial intelligence (AI) and machine learning (ML) algorithms are increasingly applied for automated pattern recognition, correlation analysis, and predictive modeling based on chip-derived datasets [84–86]. Such data-driven approaches facilitate the identification of key hemodynamic and biochemical signatures, prediction of disease progression, and evaluation of interventional device performance (e.g., restenosis or thrombosis risk). Moreover, coupling AI-assisted analytics with 3D printing and microfabrication further enhances the precision, reproducibility, and scalability of vascular-chip production [87,88]. Through computer vision–based feedback and generative design algorithms, fabrication errors can be minimized while material performance and flow characteristics are optimized in real time.

By integrating high-throughput experimentation with intelligent analysis, the FLOW framework transitions from a purely reconstructive system to an adaptive, data-driven platform capable of autonomous optimization and predictive simulation. This convergence of experimental and computational capabilities establishes a powerful foundation for next-generation panvascular research—accelerating the discovery, testing, and refinement of interventional devices through real-time, high-throughput, and intelligently guided experimentation. However, despite the promising potential of AI-integrated chip systems, several challenges remain, including data biases, model generalizability, and the lack of standardized datasets for training and validation [89,90]. Future advances in cross-platform data harmonization, cloud-based analysis pipelines, and interpretable AI models are expected to further enhance the reliability and translational value of FLOW-based intelligent systems.

Diseases in various parts of the panvascular system share commonalities while also exhibiting unique characteristics. In response to the distinctive anatomical structures of each organ in the panvascular system, corresponding chips and vascular chips adapted for interventional devices must incorporate differentiated architectures. The specific details of these commonalities and characteristics, along with related designs, will be elaborated in the following sections.

4. OoC platforms in panvascular disease and interventional device development—from pathological states to downstream diseases

4.1. Atherosclerosis and downstream diseases

4.1.1. OoC simulation of atherosclerotic pathological states

Atherosclerosis represents the primary common pathological feature of panvascular diseases. Factors such as abrupt changes in vascular geometry due to branching, sharp bends, or stenoses, which cause local flow disturbances, as well as abnormal elevations in blood components like lipids and inflammatory factors, can all contribute to the formation of atherosclerosis [91]. This may cumulatively affect the cardiovascular, cerebrovascular, and peripheral vascular systems, leading to panvascular diseases such as myocardial infarction, coronary heart disease, stroke, lower limb ischemia, and diabetic foot. Hemodynamic disturbances and immune inflammation are considered two key points for *in vitro* chip-based modeling of atherosclerosis [92].

At arterial bifurcations and branches, blood flow often exhibits abnormally elevated shear stress and turbulent states, which in turn induce endothelial dysfunction and promote atherosclerotic plaque formation [93]. Given the significant spatiotemporal heterogeneity in hemodynamic parameters at lesion sites, microfluidic technology has garnered widespread attention for its outstanding advantages in constructing channel networks with complex geometries and multilevel microstructures, as well as its precise control over fluid environments within chips [94]. Menon et al. [95] designed an atherosclerosis chip featuring 2D and 3D stenotic microchannels with varying constrictive geometries to investigate flow disturbances under different degrees of occlusion and wall shear stress (100–2000 dyne/cm^2), summarizing blood flow-mediated endothelial dysfunction and blood–ECs interactions in atherosclerosis. The mechanisms revealed by this model, whereby flow disturbances lead to endothelial dysfunction and plaque formation, provide key insights for future optimization of stent designs to improve local hemodynamics and reduce restenosis risk. Tovar-Lopez et al. [96] developed an atherosclerosis chip by constructing a series of ridge-like obstacles to simulate flow patterns at arterial bifurcation points and curvatures, facilitating the study of turbulent flow's pathological induction on ECs and revealing that endothelial–immune cell communication is a prerequisite for atherosclerotic plaque formation. This discovery

Table 2
FLOW modular framework for vascular system simulation.

"FLOW" modules	Technical terms	Specific technology/Materials	Functional descriptions
F: Fidelity hemodynamic reconstruction	Microfluidic technology	Precise control of shear stress; pulsatile flow; chemical gradients	High-fidelity simulation of hemodynamics (e.g., shear stress, pulsatile flow); replication of physiological/pathological blood flow
L: Longitudinal physiological surveillance	Real-time monitoring system	Integrated sensing modules: metabolites (lactate, glucose, ROS); cytokines (IL1β, TNFα); physicochemical (pH, temperature, ionic concentration)	Dynamically tracks chronic inflammation/ endothelialization; monitors material degradation kinetics & metabolic products
	Microenvironment regulation	Oxygen gradient control; fluid shear stress/mechanical strain simulation; growth factor addition	Optimizes cell proliferation/differentiation/function maintenance; simulates pathological microenvironments (e.g., inflammation)
O: Omni-vascular bed modeling	Cell source and spatial organization	Primary cells (patient/cell bank); somatic stem cell derivatives; hiPSCs (induced pluripotent stem cells)	Solves scarce tissue sourcing; simulates target organ functions (e.g., ECs, SMCs); constructs heterogeneous cellular ecosystems
	Multi-organ-on-a-chip integration basis	Microfluidic interconnects; vascularized organoid cascades; mechanical/metabolic coupling design	Supports simulation of concurrent vascular pathologies (e.g., coronary stenosis + cerebral aneurysm), enabling cascade modeling of vascular stenosis → organ ischemia
W: Whole-space 3-D interactive work-flow	Structural design	PDMS microfabrication via soft lithography; multilayer hydrogel architecture (collagen, gelatin, PLA, PLGA)	Reconstructs 3D vascular geometry and multilayer vessel wall; reproduces mechanical compliance and ECM microenvironment for realistic device–tissue interaction
	Fabrication techniques	Soft lithography (PDMS); 3D bioprinting (bioinks, multilayer structures); hybrid fabrication combining microprecision and biointegration	Enables accurate microstructure replication and multilayer vascular construction for *in vitro* implantation and device testing
	Material selection and matrix composition	Natural/synthetic/hybrid hydrogels (collagen, gelatin, PLA, PLGA); tunable stiffness and degradation	Provides ECM-like biochemical and mechanical support; balances bioactivity and mechanical integrity for long-term culture stability
	Intelligent analysis and high-throughput integration	AI/ML-assisted design and analytics; vision-guided 3D printing; multi-sensor data fusion	Enables predictive modeling and automated optimization of chip fabrication and performance; enhances throughput and precision in vascular-on-chip systems

directly guides the development of anti-inflammatory coated stents to inhibit immune cell activation.

Hyperlipidemia, hyperglycemia, and inflammatory responses synergistically exacerbate oxidative stress and ECs activation, a pathological process that clinically manifests as atherosclerosis [97]. Su et al. [98] developed a novel arterial wall chip using an improved surface tension-based extracellular matrix (ECM) patterning method to construct a co-culture chip platform with distinct intimal-medial structures, culturing ECs and SMCs in separate ECM layers. By adding inflammatory factors (IL-1β and TNFα) and oxidized low-density lipoprotein (ox-LDL) to the EC channel on the chip, they simulated the early inflammatory and hyperlipidemic environment of atherosclerosis, explaining how inflammatory factors and ox-LDL induce endothelial inflammation (ICAM-1 expression), promote lipoprotein uptake by cells, and facilitate SMCs migration. The mechanisms elucidated by this model, involving inflammatory factors and ox-LDL inducing endothelial inflammation and SMCs migration, point the way for designing drug-eluting stents targeting inflammatory pathways or lipid metabolism.

However, the aforementioned models are limited to single-factor induction of atherosclerotic pathological features and do not fully exploit the high experimental controllability advantages of OoC platforms (L module in the FLOW framework). We believe that future research can build on these models by simultaneously regulating hemodynamic factors along with physicochemical factors such as ox-LDL and inflammatory cytokines (IL-1β, IL-6, TNF-α), as well as incorporating immune cells (e.g., THP-1) and related lipids (e.g., cholesterol, triacylglycerol (52:4), sterol ester (27:1/18:2), and diacylglycerol (18:1_18:2)) into microfluidics to recapitulate the human atherosclerotic pathological microenvironment, including cellular ecology, physicochemical–immune ecology, and biomechanical ecology, enabling systematic and comprehensive analysis of atherosclerotic pathological mechanisms at the microscopic scale.

4.1.2. OoC simulation of downstream diseases caused by atherosclerosis

As atherosclerotic pathological states progress over time, plaques enlarge, potentially leading to vascular lumen stenosis, hemodynamic obstruction, and even acute thrombosis due to plaque rupture, causing ischemia and hypoxia in the corresponding supplied tissues and organs—such as coronary artery occlusion triggering myocardial infarction, cerebral vascular occlusion leading to stroke, lower limb arterial stenosis inducing lower limb ischemia, and diabetic patients being more prone to severe complications like diabetic foot due to superimposed vascular lesions and neural damage [99]. These downstream diseases not only have high disability and mortality rates but also involve multifaceted interactions in their pathological mechanisms, including local blood flow disturbances (coronary ischemia, carotid ischemia, lower limb ischemia) [100–102], abnormal intercellular communication (e.g., cardiac fibroblasts releasing exosomes rich in damaged mitochondria (mtExosomes) that are taken up by macrophages, upregulating NLRP3/Caspase-1/IL-1β and TLR9/NF-κB/IL-6 signaling pathways leading to post-AMI ventricular remodeling [103]; astrocyte low-density lipoprotein receptor-related protein-1 (LRP1) inhibiting ARF1 lactylation to transfer mitochondria to neurons and alleviate cerebral ischemic stroke [104]; lactate produced by inflammatory macrophage glycolysis promoting skin keratinocyte repair function through histone lactylation and angiogenesis [105]), inflammatory responses, and abnormal repair [106–108]. Traditional animal models struggle to precisely simulate human pathological processes due to species differences, while 2D cell cultures cannot recapitulate complex organ microenvironments. Therefore, there is an urgent need to leverage OoC technology to construct models closer to *in vivo* physiological states, enabling analysis of dynamic disease progression mechanisms, screening of targeted therapeutic strategies, and providing more reliable experimental platforms for research and translational medicine in these diseases.

4.1.2.1. Myocardial infarction-on-a-chip. Varying degrees of coronary atherosclerosis-induced coronary occlusion can lead to acute or chronic myocardial ischemia, a direct pathological consequence of panvascular diseases. Partial or complete blockage of coronary blood flow results in hypoxia and nutrient deprivation in the supplied cardiac tissue [109], leading to myocardial infarction (MI) [110]. Veldhuizen et al. [111] simulated myocardial ischemia through 3D co-culture of hiPSC-derived cardiomyocytes (hiPSC-CMs) with human cardiac fibroblasts (hCFs), combined with a hypoxic environment (1% O_2), discovering that hypoxia significantly activates the HIF-1 signaling pathway, inhibits oxidative phosphorylation, and upregulates glycolysis (increased lactate secretion), while inducing fibroblast-to-myofibroblast transition (upregulated α-SMA expression). Hypoxia also caused myocardial contractile rhythm disturbances and downregulated calcium regulatory genes (ATP2A2, RYR2). After reperfusion, although metabolic indicators (e.g., lactate levels) returned to normal, myocardial tissue exhibited persistent contractile dysregulation and a survival rate drop to 75%, indicating metabolic-functional decoupling in reperfusion injury. Notably, the hypoxia-induced fibrotic phenotype (high α-SMA expression) was significant only in the 3D co-culture system, with no response in 2D models, highlighting the necessity of 3D structures for pathological microenvironment simulation. The model's revelations of persistent functional impairment and fibroblast activation post-reperfusion provide important pathological mechanistic insights for developing devices to mitigate reperfusion injury (e.g., stents with anti-fibrotic coatings).

4.1.2.2. Stroke-on-a-chip. Stroke, one of the leading causes of global mortality [112,113], is essentially a terminal event of panvascular diseases, with its occurrence and development closely linked to pathological changes in the systemic vascular system, primarily triggered by cardiac disease and atherosclerosis-induced cerebral vascular occlusion (ischemic stroke) or rupture (hemorrhagic stroke) [114,115]. Interruption of cerebral blood supply leads to severe oxygen and nutrient (glucose) deficiency in tissues, subsequently causing neuronal activity abnormalities, inflammation, necrosis, and other pathological changes in the brain microenvironment [116]. Wevers et al. [117] constructed a more complex neurovascular unit (NVU) on-chip model, with perfused vessels composed of primary human brain ECs grown on collagen I gel and co-cultured with induced pluripotent stem cell-derived astrocytes and neurons, using hypoxic and hypoglycemic environments to induce stroke conditions. Under these simulated conditions, the cell cultures exhibited typical stroke features, such as decreased blood-brain barrier (BBB) integrity, reduced mitochondrial membrane potential, and lowered ATP levels. Additionally, the model can incorporate other cell types like pericytes and microglia, providing a powerful tool for studying mechanisms of cellular ecological balance and imbalance under stroke conditions. The model's confirmation that hypoxia and hypoglycemia lead to BBB integrity disruption and mitochondrial dysfunction directly guides the development of neurointerventional devices designed to protect the blood-brain barrier (e.g., optimized thrombectomy devices to minimize endothelial damage).

4.1.2.3. Diabetic foot-on-a-chip. Diabetic foot, as a typical local pathological phenotype of panvascular diseases, essentially represents the concentrated manifestation of systemic vascular lesions (arterial stenosis/occlusion) in the peripheral circulatory system [118]. Biglari et al. [119] designed a three-channel microfluidic chip incorporating fibroblasts, macrophages, and ECs, constructing a 3D vascular network via Matrigel (a basement membrane matrix) to successfully simulate the wound inflammatory microenvironment and validate the efficacy of anti-inflammatory drugs. This study, through immune cell integration and dynamic microenvironment regulation, holds promise for long-term *in vitro* maintenance of functional microvascular networks and stable operation under high-glucose/inflammatory conditions, serving as a potential platform for future research on cellular–physicochemical–immune ecological balance and imbalance mechanisms in peripheral vascular ischemia complicated by diabetic foot microenvironments, and providing a promising *in vitro* platform for drug screening and pathological mechanism studies. The model's validation of anti-inflammatory drugs' restorative effects on microvascular function offers experimental support for optimizing peripheral vascular interventional devices (e.g., drug-coated balloons to promote endothelial repair).

In summary, current OoC models for downstream atherosclerotic diseases such as myocardial infarction, stroke, and diabetic foot demonstrate significant advantages in simulating disease pathological features: by constructing multi-cellular co-culture systems (e.g., cardiomyocytes with fibroblasts, various NVU cells), they can recapitulate cellular ecological networks under disease states, dynamically capturing core pathological processes like abnormal intercellular communication and local inflammatory activation, providing experimental foundations close to *in vivo* environments for mechanistic analysis.

However, some models lack mature vascularized structures and blood flow perfusion (F module in FLOW), making it difficult to recapitulate the impact of hemodynamic changes on tissue ischemia; simulations of mechanical stimuli and physicochemical–immune microenvironments are insufficiently comprehensive (L module in FLOW). In the future, efforts should focus on promoting integration strategies of "vascular chips + organoids": linking atherosclerotic vascular chips with functional tissue models such as cardiac organoids, brain organoids, and skin organoids to construct full-chain simulation systems from vascular lesions to downstream organ damage [120,121], thereby precisely simulating the entire cascade mechanisms of atherosclerosis-induced downstream panvascular diseases in clinical settings. Existing experiments constructing corresponding microphysiological models have demonstrated the feasibility of this technology [122]. By incorporating key elements such as dynamic blood flow, mechanical feedback, and immune cell recruitment, these systems can recapitulate cascade reactions of "vascular stenosis–tissue ischemia–organ dysfunction," enabling more accurate analysis of panvascular disease progression patterns and providing more reliable technological platforms for multi-target drug screening and personalized treatment development.

4.1.3. Prospects of OoC for improving panvascular interventional devices in related diseases

Ischemic lesions induced by atherosclerosis (AS) heavily rely on vascular stent interventions in clinical treatment. While traditional bare-metal stents (BMS) and drug-eluting stents (DES) are widely used, they are prone to late adverse events such as ISR due to long-term retention [123]. Consequently, bioresorbable stents (BRS) with high "suitcordance" (short-term suitability and long-term concordance) to human vasculature have emerged as a key focus for clinical translation [124,125]. Among them, polylactic acid (PLA) stents have demonstrated nearly complete strut absorption while maintaining lumen patency in 5-year follow-up trials, confirming their safety and efficacy [126].

Beyond PLA, other biodegradable polymer scaffolds, such as polyglycolic acid (PGA), polycaprolactone (PCL), and collagen-based matrices, have also been explored for vascular applications. These materials differ in degradation rates, mechanical properties, and metabolic byproducts, which can distinctly modulate the vascular microenvironment. In addition, biodegradable metals, such as magnesium- and zinc-based stents, offer superior initial

mechanical support but release ions (Mg^{2+}, Zn^{2+}) that can affect vascular remodeling and paracrine signaling [26].

Notably, recent *in vivo* investigations confirm that these compositional differences lead to divergent biological outcomes. For example, degradation products from PGA have been associated with SMCs dedifferentiation and intimal hyperplasia in preclinical arterial models [127]. Conversely, long-term implantation of PCL-based grafts demonstrates excellent patency and structural stability but slower remodeling kinetics consistent with PCL's gradual resorption, with late-stage cellular regression and focal calcification observed after 12–18 months [128]. Collagen-containing scaffolds promote endothelialization and neovascularization in rabbit vascular carotid artery models, exhibiting good structural integrity and mechanical performance comparable to native vessels [129]. Biodegradable magnesium stents in porcine coronary arteries accelerate endothelial recovery and exhibit acceptable short- to mid-term biosafety [130], yet corrosion-associated oxidative stress highlights the need for surface or alloy optimization. Zn–Cu–Mn alloy stents in porcine models achieved rapid endothelialization and near-complete vascular recovery within 12 months, with controlled degradation and no adverse systemic or thrombotic effects, underscoring the biosafety and translational potential of zinc-based scaffolds [131]. Together, these *in vivo* findings underscore that the degradation kinetics and byproducts of different materials critically determine vascular healing and long-term biocompatibility, reinforcing the importance of rational material selection.

A comprehensive assessment therefore requires systematic comparison of (i) degradation kinetics and resulting chemical species, (ii) mechanical behavior over time (loss of radial strength, creep, fatigue), and (iii) physicochemical–immunological consequences (pH change, ion toxicity, reactive oxygen species, and inflammation). The FLOW platform is particularly well suited for this task: the F module reproduces physiological pulsatile loading and flow-wall coupling to test mechanical durability and device–wall interactions under realistic hemodynamics; the L module provides long-term, multimodal *in-situ* sensing to quantify temporal profiles of degradation products (metabolites, ions, pH, ROS) and downstream biological readouts (endothelial integrity, leukocyte recruitment); the O module enables side-by-side modeling of different vascular beds or patient-specific cellular contexts to reveal tissue- and region-dependent susceptibilities; and the W module (3D structural work-flows and material integration) allows testing in anatomically realistic, multilayer constructs that capture the mechanical/ECM context influencing degradation and biological response. Together, these capabilities allow direct comparison across organic and inorganic degradable scaffolds, revealing trade-offs (e.g., faster polymer resorption that raises local acidity vs. metal corrosion producing bioactive ions) and guiding rational choices of polymer composition, alloying, surface coatings, or drug-release strategies to preserve local homeostasis and improve suitcordance.

4.2. Thrombosis

4.2.1. Simulation of thrombotic pathological states

Thrombosis is the terminal outcome of vascular endothelial injury, abnormal blood flow, or hypercoagulable blood states (Virchow's triad), characterized by the formation of blood clots within vessels, leading to hemodynamic disturbances and potentially causing downstream tissue and organ ischemia, endangering systemic blood circulation [132]. Rupture of atherosclerotic plaques readily triggers acute thrombotic diseases [133], which are essentially a class of panvascular diseases characterized by vascular lesions. Traditional animal models are limited by species differences, while *in vitro* 2D cell culture models struggle to integrate complex hemodynamics (e.g., shear stress) and 3D vascular microenvironments, posing challenges to precisely simulating thrombosis formation processes under human physiological/pathological conditions. In contrast, vascular chips can simulate vascular structure and function, including key factors such as ECs, vessel wall cells, and hemodynamics, to study the initial stages of thrombosis, platelet activation and aggregation, the role of coagulation factors, and endothelial regulatory mechanisms [134,135], providing powerful tools for constructing thrombosis models closer to human physiological and pathological states and in-depth investigation of their dynamic processes and mechanisms.

Building upon this foundational capability of vascular chips, the "FLOW" framework provides a systematic and enhanced strategy to deconstruct the complexity of thrombosis. It enables the precise integration of Virchow's triad and supports the long-term dynamic observation essential for unraveling thrombus mechanisms and evaluating therapies. Specifically:

(1) The F module (Fidelity hemodynamic reconstruction) moves beyond simple perfusion to precisely simulate the pathological shear stress flows that are critically involved in platelet activation and thrombogenesis.

(2) The L module (Longitudinal physiological surveillance) allows for non-invasive, real-time tracking of the entire thrombotic process—from initiation and growth to stabilization and dissolution—while simultaneously facilitating the assessment of the pharmacodynamics of antithrombotic drugs.

(3) The O module (Omni-vascular bed modeling) makes it possible to investigate bed-specific thrombotic pathologies (e.g., arterial vs. venous) and patient-specific susceptibilities within a single, standardized platform.

(4) The W module (Whole-space 3D interactive work-flow) supports the construction of anatomically relevant, multi-cellular 3D vascular architectures, providing a highly biomimetic biological context that profoundly influences thrombotic responses.

The following studies exemplify how this integrated FLOW approach is being implemented to advance thrombosis research and device optimization.

Liu et al. [136] developed a microfluidic chip-based thrombosis simulation system by constructing a vascular endothelial layer, perfusing whole blood, and simulating physiological blood flow environments, combined with light-controlled thrombosis technology (focused laser stimulation of specific endothelial regions), achieving precise triggering and regulation of thrombi (controllable thrombus position, volume, and occlusion degree). The study confirmed through dynamic microscopic imaging that thrombus formation is directly related to laser parameters (power, time), and anti-thrombotic drug testing (e.g., heparin, rt-PA) showed that drugs significantly reduce thrombus stability and promote dissolution, consistent with clinical mechanisms. The model's demonstrated capabilities in precise thrombus triggering and drug thrombolytic efficacy evaluation provide important testing platforms and design ideas for improving thrombectomy catheter designs (e.g., incorporating local drug release functions to enhance thrombolytic efficiency). Lam and co-workers [137] developed a novel "thrombo-inflammation chip" model, achieving for the first time long-term dynamic monitoring of microvascular thrombo-inflammation formation and resolution, as well as drug mechanism studies. It systematically analyzed the spatiotemporal evolution patterns of microvascular thrombi, revealed the central role of neutrophils in thrombus resolution, and validated the therapeutic potential of enoxaparin and other drugs. The model's revelation that neutrophils dominate thrombus resolution points to innovative directions for developing novel catheters with both mechanical clearance and immune regulatory functions (e.g., applying anticoagulant or anti-inflammatory coatings) (Fig. 3) (Table 3).

4.2.2. Prospects of OoC for improving panvascular interventional devices in related diseases

In terms of interventional therapy, thrombectomy catheters serve as crucial tools for treating acute thrombotic diseases (e.g., acute myocardial infarction, acute thromboembolic renal artery occlusion) [138,139], yet their clinical application still faces multiple challenges. From a technical perspective, catheters exhibit efficiency limitations when dealing with high-burden or organized thrombi, particularly in tortuous, calcified, or small-branch vessels, where poor navigability and adaptability can lead to incomplete aspiration or procedural failure. Insufficient biocompatibility of catheter materials may cause vascular endothelial injury or in-catheter thrombosis, further compromising safety. As mentioned earlier (4.2.1), vascular chip platforms (e.g., light-controlled thrombosis models and thrombo-inflammation models) provide powerful evaluation tools for improving interventional devices such as thrombectomy catheters. These platforms not only enable real-time monitoring of device operation processes and assessment of novel devices (e.g., with different designs, materials, coatings, or local drug release functions) in terms of thrombus removal efficacy and impact on vascular endothelium but also allow targeted adjustments to structural designs and mechanical parameters (e.g., aspiration force). By simulating diverse vascular anatomies (e.g., curvatures, bifurcations) and thrombus characteristics (e.g., fresh, organized), chip platforms can screen for more efficient, safer, and adaptable device design solutions. The ultimate goal is to guide devices, through chip platforms, toward a leap from mere "mechanical clearance" to "precise repair" (reducing endothelial damage and modulating local inflammatory/coagulative microenvironments), significantly enhancing the safety and thrombus clearance efficiency of interventional procedures.

5. Future application prospects: building panvascular-on-a-chip to achieve a paradigm shift from mechanisms to clinical, from single-organ perspectives to systemic integration

With continuous innovations in manufacturing technologies, an increasing number of disease models can be recapitulated using OoC, providing promising platforms for disease mechanism research and new drug development. However, OoC still faces bottlenecks such as the lack of vascular–organ interactions, insufficient multi-organ system integration, and inability to simulate the entire panvascular system on a single chip—these are critical barriers that must be overcome in panvascular disease research (systemic vascular diseases with whole-body characteristics, such as atherosclerosis affecting multiple vascular beds including cardiac, cerebral, and limb vessels).

Single-organ models remain limited in recapitulating complex inter-organ mechanical force transmission, metabolite exchange, and neuro-endocrine regulatory networks, failing to meet the systemic demands of panvascular disease research [19]. Addressing this limitation, multi-organ integrated chip systems based on microfluidic technology exhibit unique advantages. By precisely regulating fluid shear stress, pressure gradients, and biomechanical stimuli in tissue microenvironments, functional coupling interfaces between vasculature and parenchymal organs can be established. Currently, several multi-OoC models have been successfully applied to systemic disease research: liver-intestine co-chips reveal how intestinally absorbed free fatty acids (FFAs) exacerbate hepatic lipid accumulation via the portal vein, while hepatic metabolites (e.g., bile acids) reflux to affect intestinal vascular barriers [140]; liver-pancreas chips explore associations between sinusoidal blood flow abnormalities and systemic glucose metabolic disorders in the context of insulin resistance [141]. More importantly, such multi-organ vascularized platforms offer unique perspectives for simulating panvascular diseases with "FLOW" characteristics (e.g., systemic atherosclerosis). In the future, cardiovascular-cerebrovascular connection models constructed on chips can dynamically analyze how inflammatory factors, bioactive lipids, microemboli, etc., released from plaque formation or rupture in cardiovascular regions (e.g., coronary arteries) as culprit lesions remotely influence endothelial function in cerebral vessels (non-culprit vessels) through the circulatory system, triggering or accelerating atherosclerotic progression, thereby recapitulating clinically observed cascade phenomena of panvascular disease lesions *in vitro* [142].

These advancements provide inspiration for comprehensively revealing disease pathogenesis, systemic impacts, therapeutic effects of novel interventional devices, and their interaction mechanisms across multiple vascular beds within the complex panvascular interventional system framework. In the future, breakthroughs in 3D bioprinting, organ-specific ECM hydrogels, and organoid co-culture technologies will enable the construction of novel multi-OoC—panvascular-on-a-chip—with vascularized connection networks closer to physiological states, dynamically analyzing molecular events such as inter-organ immune cell migration [143] and metabolite communication [67].

By fully leveraging panvascular-on-a-chip, the cascade amplification mechanisms of tissue-level and organ-level lesions at the vascular system level will be further elucidated. Through further integration of biosensing technologies and patient-specific models, this technology holds promise for driving a paradigm shift in panvascular disease treatment from "single-organ isolated systems" to "multi-organ systemic networks," laying the foundation for multi-target combination therapeutic strategies in the era of precision medicine.

At the same time, the suitcordance of novel interventional devices such as covered stents, intracranial stents, artificial heart valves, and occluders can be further quantified via this platform: At the level of device interactions with complex hemodynamic environments, subtle changes in mechanical environments may trigger cross-scale, global responses and reconstructions from molecular-cellular to tissue-organ levels in physiological systems, thereby inducing new vascular system diseases (e.g., clinically common ISR, neointimal damage, and device-related strokes). Can novel interventional devices successfully adapt to specific fluid environments and restore biomechanical ecological balance? At the level of interactions between interventional materials and vascular cells, does material degradation properly guide benign cellular responses and trigger related reparative signaling transduction mechanisms to restore cellular ecological balance? At the level of physicochemical–immune interactions between interventional devices and vascular microenvironments, do concentration changes in specific microenvironment components caused by material degradation (e.g., Zn^{2+} from Zn-based stent degradation, lactate from polylactic acid artificial valve degradation) positively regulate local immune responses (e.g., affecting macrophage polarization, neutrophil activity), and synergize with physicochemical factors (e.g., pH, ion concentrations, cytokine levels) to collectively promote functional reconstruction and repair of vessels, ultimately restoring the physicochemical–immune ecological balance of damaged vessels?

Novel panvascular-on-a-chip are reshaping the research paradigm of panvascular diseases from multiple dimensions—decon structing multi-organ and multi-vascular bed interaction networks at the systemic level, analyzing whole-body and whole-flow-domain dynamic pathological signals at the molecular level, and achieving comprehensive suitcordance evaluations of interventional devices on high-biomechanical and mechanobiological simulation platforms, ultimately realizing value translation from basic research outcomes to clinical applications.

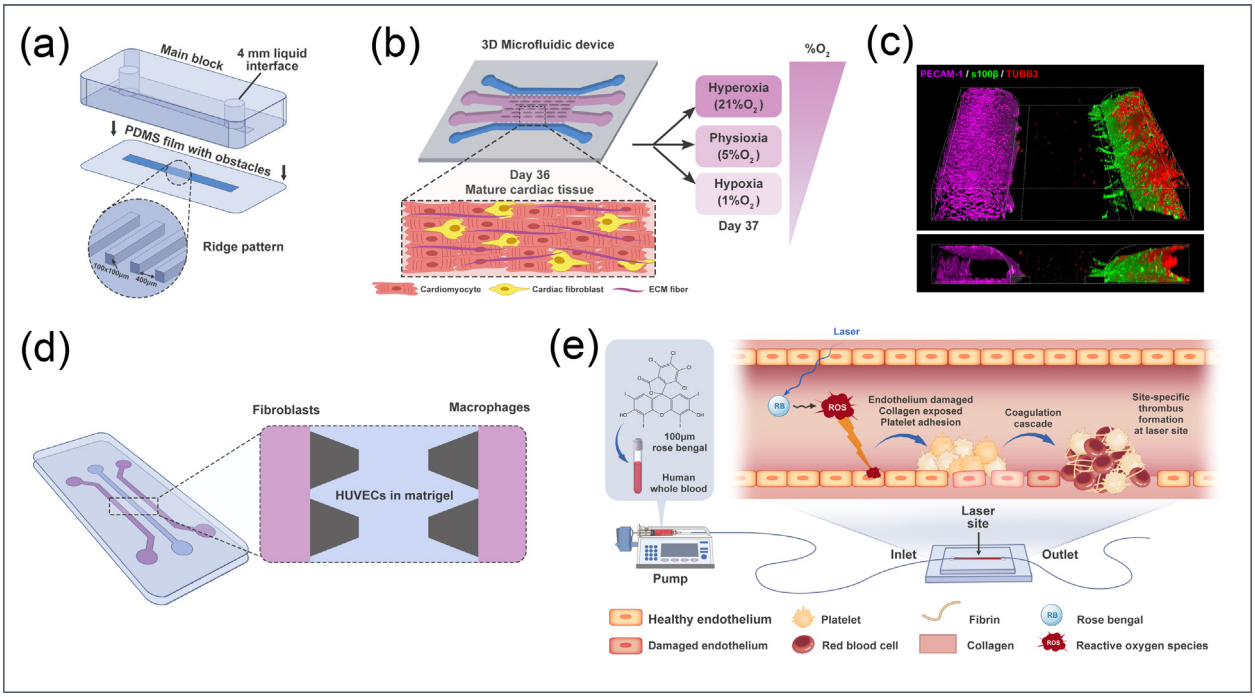


Fig. 3. Specific applications of OoC platforms in panvascular disease research. (a) Vessel-on-a-chip with integrated ridged obstacles for modeling atherosclerosis, reproduced from Ref. [96]. (b) Heart-on-a-chip model of myocardial ischemia induced by low oxygen concentration, reproduced with permission from Ref. [111]; Copyright © 2022, Elsevier. (c) Neurovascular-unit-on-a-chip model reconstructs human brain endothelial vessels (PECAM-1, magenta) grown on extracellular matrix gel in co-culture with astrocyte networks (s100β, green) and neurons (TUBB3, red), Reproduced from Ref. [117]. (d) Wound-on-a-chip device cultures fibroblasts in left microchannels and macrophages in right microchannels with a central channel containing HUVEC-embedded Matrigel ECM, Reproduced with permission from Ref. [119]; Copyright © 2018, John Wiley and Sons. (e) Photothrombosis-on-a-chip modeling thrombosis formation; reproduced with permission from Ref. [136]; Copyright © 2024, Royal Society of Chemistry.

6. Summary and outlook

In summary, panvascular diseases, as systemic vascular lesions, have long been limited in in-depth research by the deficiencies of traditional models in simulating 3D dynamic interactions, long-term biocompatibility, and heterogeneous multi-vascular bed environments. Vessel-on-a-chip (VoC) technology, with its FLOW framework—precise microfluidic regulation (F module in FLOW), 3D bioprinted structures (W module in FLOW), multi-cellular long-term co-cultures (L/O module in FLOW), and multi-organ integration potential (O module in FLOW)—brings a paradigm breakthrough to panvascular research: successfully constructing highly mimetic models to simulate pathological states such as atherosclerosis and thrombosis, along with their true flow (FLOW) states; poised to enable real-time dynamic evaluation of interventional device performance, quantifying multi-dimensional short-term suitability and long-term concordance between devices and vessels in mechanics, cellular, and physicochemical–immune aspects under the guidance of the "suitcordance" concept via the FLOW platform, ultimately advancing the long-term vision of device–vessel fate co-regulation.

Currently, research on OoC still faces multiple limitations, such as high manufacturing costs and complex processes; chip platform culture durations are generally limited to 14–21 d, making it difficult to simulate the long-term evolutionary processes of panvascular diseases [94]; and different OoC systems have varying layouts and interfaces, rendering them unable to be easily connected, interchanged, or compared [144]. Moreover, reproducibility across laboratories remains limited due to manual fabrication and operation steps, while cell source variability—including differences in donor genetics, maturity, and passage—introduces experimental inconsistency. Current OoC models also lack system-level regulation and full physiological feedback, such as neurohumoral and immune–metabolic coupling, which restricts their ability to fully recapitulate human vascular homeostasis. In addition, maintaining long-term stability, sterility, and dynamic perfusion balance remains technically challenging, especially under high-throughput or multi-organ interconnected conditions. Addressing these challenges requires progress in automated microfabrication, scalable material design, vascularization strategies, and standardized benchmarking protocols, laying the groundwork for translating panvascular-on-a-chip platforms from experimental models to robust, reproducible, and clinically relevant systems [19,145,146].

With the future trend of multidisciplinary integration, these pain points in current OoC research will be addressed, propelling panvascular chip platform studies to new heights:

Long-term culture and spatiotemporal compression: on one hand, significantly extending tissue viability to several months allows simulation of long-term chronic disease progression and evaluation of distant effects of interventional devices (e.g., endothelialization, late thrombosis); on the other hand, innovatively compressing disease timelines, using controllable pathological stimuli to recapitulate key lesions that would take years (e.g., atherosclerosis, ISR) within weeks. This "one day in heaven, one year on Earth"—like spatiotemporal manipulation capability enables in-depth analysis of long-term interactions between interventional devices and vascular tissues within controllable cycles, powerfully positioning panvascular-on-chips as the new gold standard for evaluating the safety and efficacy of interventional devices.

Standardization and automation: establishing international standards for chip manufacturing, operation, and data analysis, along with developing automated high-throughput platforms, can reduce costs, promote large-scale applications, and enhance

Table 3
Disease-specific OoC models for vascular pathologies.

Disease type	Chip type	Materials & fabrication techniques	Simulated physiological structures	Mechanistic findings	Future directions for device research and development	Reference
Atherosclerosis	Stenotic lesion model (Menon et al.)	PDMS microchannels; 2D/3D constricted geometric structures	Stenotic blood vessels with different occlusion degrees, wall shear stress (100–2000 dyne/cm^2)	Blood flow disturbances lead to endothelial dysfunction, promoting plaque formation	Optimize stent design to improve local hemodynamics and reduce restenosis risk	[95]
	Branch point flow disturbance model (Tovar-Lopez et al.)	PDMS ridge-shaped obstacles	Flow disturbance patterns at arterial branches/bends	Endothelial–immune cell communication is a necessary condition for plaque formation	Develop anti-inflammatory coated stents to inhibit immune cell activation	[96]
	Inflammatory/hyperlipidemic pathological model (Su et al.)	ECM-patterned co-culture chip (collagen matrix)	Clear intima-media structure (ECs/SMCs layered culture)	Inflammatory factors (IL-1β/TNFα) and ox-LDL induce endothelial inflammation (ICAM-1↑) and SMCs migration	Design drug-eluting stents targeting inflammatory pathways or lipid metabolism	[98]
Myocardial ischemic	Ischemic model (Veldhuizen et al.)	hiPSC-CMs + hCFs 3D co-culture; Hypoxic environment (1% O_2)	Hypoxic microenvironment of cardiac tissue	Hypoxia activates the HIF-1 pathway → Inhibits oxidative phosphorylation, upregulates glycolysis; Fibroblasts transform into myofibroblasts (α-SMA↑)	Develop devices to improve reperfusion injury (e.g., anti-fibrotic coated stents)	[111]
Stroke	NVU model (Wevers et al.)	Primary brain ECs + hiPSC astrocytes/neurons; collagen I	Neurovascular unit (BBB structure) + hypoxia induction	Hypoxia and hypoglycemia lead to decreased BBB integrity and impaired mitochondrial function	Design neurointerventional devices that protect the blood-brain barrier (e.g., thrombectomy devices to reduce endothelial damage)	[117]
Diabetes foot	Wound inflammation model (Biglari et al.)	Three-channel microfluidics (fibroblasts/macrophages/ECs); Matrigel 3D vascular network	Microvascular network + inflammatory environment	Verify the repair effect of anti-inflammatory drugs on microvascular function	Optimize peripheral vascular interventional devices (e.g., drug-coated balloons to promote endothelial repair)	[119]
Thrombosis	Light-controlled thrombosis model (Liu et al.)	Endothelial layer + whole blood perfusion; laser precision-triggered thrombosis	Thrombosis at specific endothelial injury sites	Thrombus volume/occlusion degree is related to laser parameters; Heparin/rt-PA can dissolve thrombus	Improve the design of thrombus aspiration catheters (e.g., combining local drug release to enhance thrombolysis efficiency)	[136]
	Thromboinflammatory model (Lam et al.)	Microvascular thrombosis model; long-term dynamic monitoring	Spatiotemporal evolution of microvascular thrombosis	Neutrophils dominate thrombus resolution; enoxaparin promotes dissolution	Develop new catheters with both mechanical clearance and immunomodulatory functions (e.g., anticoagulant coatings)	[137]

efficiency in drug/device development, thereby lowering the production costs of panvascular-on-a-chip and facilitating serial studies across different vascular bed organ chips.

Integration with gene editing and patient-specific modeling for clinical translation and precision medicine: gene editing technologies have already been widely combined with OoC for mechanistic studies of corresponding diseases [147]. In the future, within ethically permissible scopes, integrating iPSC-derived cells from panvascular disease patients with gene editing will lay the foundation for constructing truly patient-specific vascular models.

Building on this, such individualized VoC systems embedded within the FLOW framework can directly accelerate the clinical translation of personalized vascular interventions. By generating microphysiological chips that recapitulate each patient's unique genetic and inflammatory profile, these models can be used to predict differential responses to stent implantation, antithrombotic therapy, or vascular graft materials prior to clinical procedures.

In this way, the FLOW framework not only provides a multidimensional simulation platform for vascular physiology but also serves as a preclinical "precision trial" environment, bridging laboratory innovation and patient-tailored clinical decision-making. The combination of iPSC technology, gene editing, and dynamic FLOW-based perfusion may thus enable "patient-on-a-chip" studies that refine trial design, reduce clinical risks, and accelerate the realization of individualized vascular therapeutics (Fig. 4).

Overall, panvascular-on-a-chip is driving a revolutionary paradigm shift in research from "single-organ isolated analysis" to "multi-organ systemic integration." With the deep interdisciplinary fusion of big data and artificial intelligence, cell biology and materials science, as well as the establishment of the foundation and development of China's National Basic Science Center for panvascular interventional complex systems, they will play a central role in elucidating disease mechanisms, empowering precision medicine, innovating interventional devices, and accelerating new drug development, providing robust systemic solutions and clinical translation bridges for ultimately conquering humanity's "number one killer"—panvascular diseases.

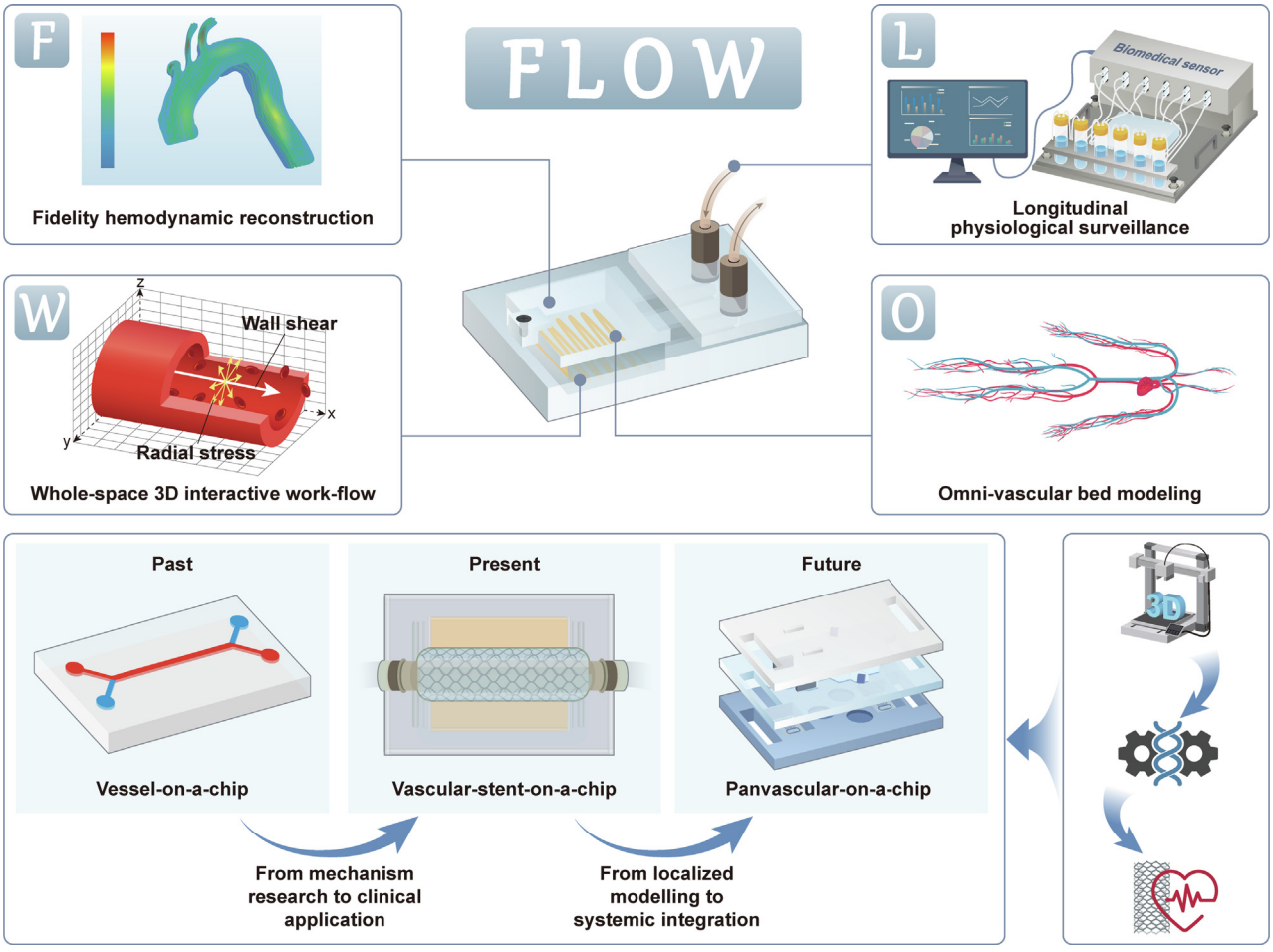


Fig. 4. The FLOW framework guiding the evolution of OoC for systemic panvascular research and high-suitcordance device design. The "FLOW" framework drives the multi-scale integration of four key modules: Fidelity hemodynamic reconstruction, Longitudinal physiological surveillance, Omni-vascular bed modeling, and Whole-space 3D interactive work-flow. This synergy enables the *in vitro* recapitulation of dynamic blood flow within vascular networks. This conceptual framework will guide the iterative evolution of chip technology along the "Vessel-on-a-chip (Past)–Vascular-stent-on-a-chip (Present)–Panvascular-on-a-chip (Future)" trajectory. Through deep integration with technologies like 3D printing and gene editing, this approach will facilitate the leap from localized vascular modeling to systemic integration, ultimately creating a closed-loop translational pathway from the laboratory bench to clinical application.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

Lingsen You, Yuheng Chen, Zeyang Zhang, Yu Wang, Zhongze Gu, Li Shen, and Junbo Ge jointly conceived and planned this literature. Lingsen You, Yuheng Chen, and Zeyang Zhang extracted the thematic content and wrote the main manuscript text, to which Yu Wang provided critical feedback and shaped the final manuscript. Zhongze Gu, Li Shen, and Junbo Ge revised the manuscript text. All authors reviewed the manuscript.

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