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Recent Progress of Organ-on-a-chip Towards Cardiovascular Diseases: Advanced Design, Fabrication, and Applications

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Abstract

Cardiovascular diseases (CVDs) are a major cause of death worldwide, leading to increased medical care costs. To turn the scale, it is essential to acquire a more in-depth and comprehensive understanding of CVDs and thus formulate more efficient and reliable treatments. Over the last decade, tremendous effort has been made to develop microfluidic systems to recapitulate native cardiovascular environments because of their unique advantages over conventional 2D culture systems and animal models such as high reproductivity, physiological relevance, and good controllability. These novel microfluidic systems could be extensively adopted for natural organ simulation, disease modeling, drug screening, disease diagnosis and therapy. Here, a brief review of the innovative designs of microfluidic devices for CVDs research is presented, with specific discussions on material selection, critical physiological and physical considerations. In addition, we elaborate on various biomedical applications of these microfluidic systems such as blood-vessel-on-a-chip and heart-on-a-chip, which are conducive to the investigation of the underlying mechanisms of CVDs. This review also provides systematic guidance on the construction of next-generation microfluidic systems for the diagnosis and treatment of CVDs. Finally, the challenges and future directions in this field are highlighted and discussed.

Key Words: cardiovascular diseases; microfluidics; organ-on-a-chip; blood-vessel-on-a-chip; heart-on-a-chip

Introduction

CVDs such as coronary heart disease, peripheral arterial disease, and rheumatic heart disease usually have a long incubation period but a short outbreak time, and thus have become the prime causes of death worldwide, accounting for about 32% of the total global deaths. [1-3] However, the direct study of the complex microenvironment of blood vessels in the human body faces many difficulties including uncontrolled variables, such as the actual operation being impractical, and the deep influencing factors of vascular lesions is poorly understood. [4, 5] Therefore, the creation of a high-biomimetic and multi-functional vascular research model in vitro is necessary to advance the mechanisms of study, diagnosis, and treatment of CVDs.

At present, there are many technologies for constructing in vitro cardiovascular models such as microfluidics, 3D printing, and self-assembly. [6-11] In general, tissue-engineered blood vessels generally use specific cells and biocompatible materials to prepare, reconstruct and regenerate vascular replacement materials. [12-18] However, it is difficult to simulate dynamic, three-dimensional blood vessels out of the body. [19] Traditional two-dimensional cell culture conditions do not allow for the composition of complex vascular microenvironments. [20, 21] In addition, the establishment of in vitro cardiac models is important. The two traditional methods for cardiac models are 2D cell culture in dishes and animal models. [22-25] Nevertheless, the complex physiological functions of the heart cannot be represented in a 2D cell culture system and it is even more difficult to accurately predict human responses in animal models. [26] The three-

dimensional structure of the microfluidic chips can bring longer viability to cells and better maintain their contractile activity, and the microfluidic devices have the advantage of high-throughput drug screening, drug-carrier production and modeling, etc. which is helpful for the treatment of CVDs. [27, 28] Therefore, people gradually realize that organ-on-a-chip (OOC) such as blood-vessel-on-a-chip (VOC) and heart-on-a-chip (HOC) can be used as in vitro models to replace the complex natural functions of organs, structures and microenvironments to simulate pathological conditions and conduct a series of related studies. [29] In order to further improve the performance of microfluidic devices, biocoating technology, electrospinning and other methods are gradually introduced. [30, 31]

Microfluidic devices were used to research on CVDs (**Figure. 1**) includes pathogenesis modeling, rapid disease diagnosis, therapeutic device development, effective drug screening, and therapeutic carrier production. Pathogenic mechanisms can provide physiological and pathological data for basic CVDs research and drive diagnosis and treatment. [32-35] Biomarkers are the most used diagnostic indicators [36, 37] to assess the physiological, pathogenic, and pharmacological processes of CVDs as the understanding of their pathogenesis continues to grow. For example, C-reactive protein (CRP) and cardiac troponin I (cTnI) are representative biomarkers of heart attacks that can help with diagnosis and prognosis evaluation. [38-40] Currently, drugs are mostly used to treat CVDs. [41] As VOC and HOC can accurately simulate the physiological and pathological environment of cardiovascular tissues in vitro, they can achieve high-throughput drug screening arrays by integrating multiple parallel channels and docking structures. [42, 43] In addition, these

devices can be used to prepare advanced drug carriers such as nanoparticles, microneedles, and microcapsulesto enhance the performance of cardiovascular drugs. [44-46] For instance, microfluidics can endow carriers with uniform morphology, size, and controllable drug delivery capabilities, which significantly improve the safety and effect of treatment.

The onset and progression of CVDs is a complicated process involving a variety of pathogenic factors, which are regulated by a variety of mechanisms. [47-49] The discovery of the underlying pathogenesis is the foundation for the development of diagnostic and treatment methods. The use of transparent and high light transmittance material for the construction of microfluidic devices can provide not only a clear interior structure of the microchannels for observation but a three-dimensional structure for simulating the natural tissue architecture. Additionally, these devices make it possible to imitate the hemodynamics of cardiovascular blood flow by carefully regulating the flow parameters of trace fluid in the microchannel. Furthermore, the surface properties of microchannels can also be changed to mimic complex cardiovascular biophysical interactions. [50-51] Thus, microfluidics can be used to create in vitro models that simulate the activities, mechanics, and even the physiological responses of the cardiovascular system, such as the atherosclerosis-on-a-chip (AOC) [52-56].

In this review, we overview the development of microfluidic devices used in CVDs research with a special focus on the VOC and HOC. We principally collected and organized materials, physical and biological factors that should be considered during design and fabrication of microfluidic

devices for CVDs. In addition, we summarize the diverse biomedical applications of microfluidic biomimetic vessels for disease diagnosis and treatment. Finally, the current challenges and future perspectives of microfluidic technology in CVD research are proposed and discussed.

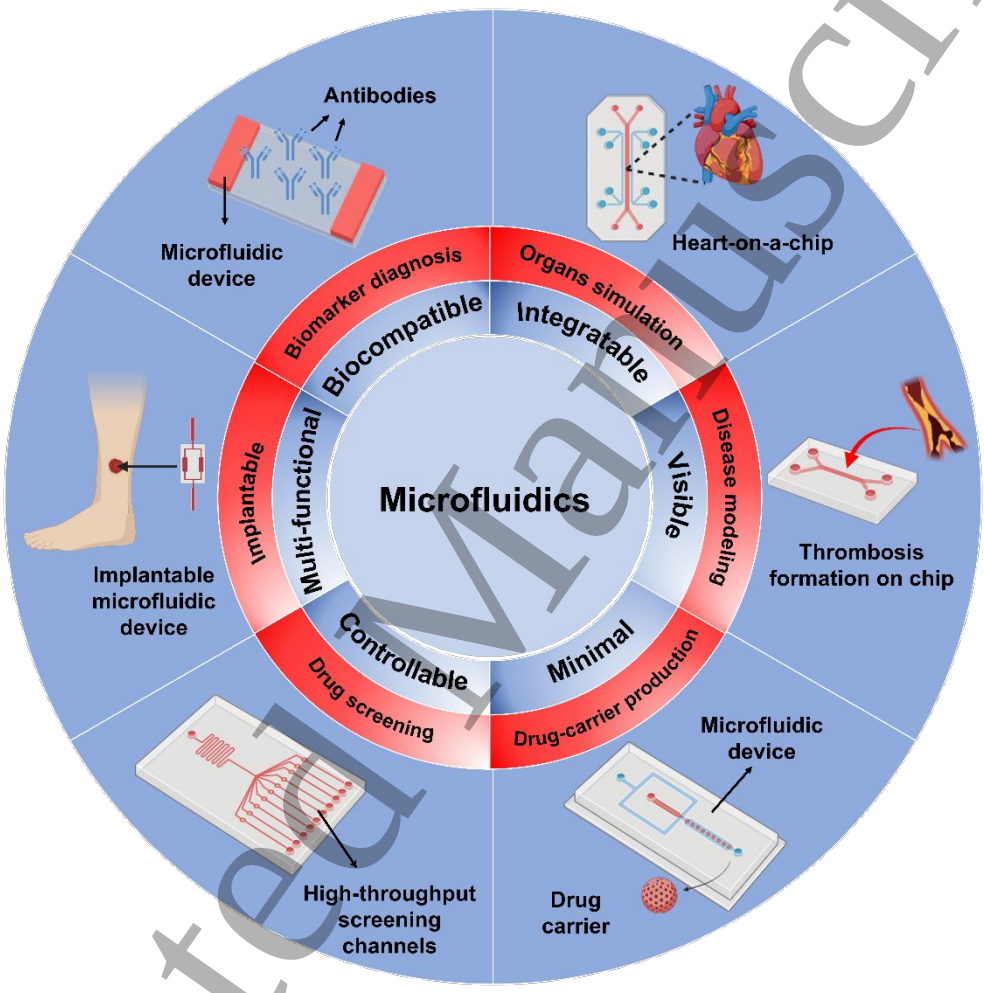

Figure. 1 Applications and properties of microfluidic devices based on CVDs.

2. The brief history of microfluidic devices for cardiovascular diseases

Since the 21st century, microfluidics has been widely used in mechanical engineering, biomedical engineering, materials engineering, and other fields, such as organ mimic devices, high-throughput

screening, and the preparation of new biological materials. [57-59] Therefore, microfluidic devices play a significant role in CVDs research. Herein, we briefly review the history and development of microfluidic devices related to CVDs research as shown in **Figure. 2**.

Even if microfluidics has a short history, it is still one of the popular technologies for producing CVDs in vitro. Since the advent of micro-electromechanical systems (MEMS) technology, it has been keen to design miniaturized components and systems. Weinberg and Bell developed the first artificial blood vessel model in 1986 to study the interactions of vascular cells, extracellular matrix components and rheological forces. This model consists of a 3D multi-layer polyester mesh-integrated collagen scaffold that mimics the multi-layer structure of blood vessels. Vascular smooth muscle cells (VSMCs) were seeded on the scaffold for study. [60] We studied the cardiovascular microenvironment and disease mechanisms using these in vitro models. The fabrication of early micro-components was almost achieved by photolithography, but it is difficult to apply them to non-semiconductor materials such as glass and polymers. [61, 62] If lithography has opened the door to the world of microfluidics, the emergence of soft lithography has laid the foundation for the rise of microfluidic blood vessels. Soft lithography, a technology that overcomes almost all the flaws of lithography while remaining inexpensive, was developed in the late 1980s. This new technology can directly pattern a variety of materials and use elastic molds instead of rigid photomasks to transfer patterns (organic and biomolecules, polymers, etc.). [63] As a consequence of the disadvantages of being expensive, opaque, and having poor air permeability, early microfluidic devices, typically made of silicon and glass cannot be used in biological research.

Microfluidic devices made of polydimethylsiloxane (PDMS) are optically transparent, easy-to-process, flexible, and inexpensive alternative compounds that were developed for applications in cell biology research in the 1990s. [64, 65] Faced with the opportunities and challenges of tissue engineering, particularly the need for blood perfusion of cell scaffolds and engineered in vitro tissues, researchers began to use micromachining methods to cultivate human cells and engineered human tissues at the end of the last century and the beginning of this century. OOC was invented in 2010 and has been utilized as a tissue and organ model for drug development, pathophysiology, and biological process research. The OOC can replicate complicated activities of organs swiftly and can be grouped to be a "human" which activated as a whole system. Microfluidic devices have also been considered well-suited to cardiovascular system modeling because of their high efficiency, low cost, and precise control. HOC as a sort of OOC was designed in 2011 and published in the famous journal "Lab on a Chip" [66]. One year later, VOC was first created. [67] The VOC not only simulates the blood vessels and controls the flow, but it can also be used to dynamically reshape the vascular system in the body by adding cells, growth factors, and other biological elements. After nearly ten years of development, VOCs have been widely used in CVDs studies, including the multifunctional vascular scaffold, and the microvascular-on-a-chip for deep study of tiny blood vessels, which was introduced in 2018. [68-71] Roger D. Kamm and his team created a model in 2021 that outperformed standard Transwell detection. This model allows the quantitative assessment of vessel sprouting in 3D vascular structures and may be employed more effectively and with real-time assessment capabilities than animal models. In addition, this model could potentially be used to screen different pro-angiogenic elements for therapeutic purposes.

[72]

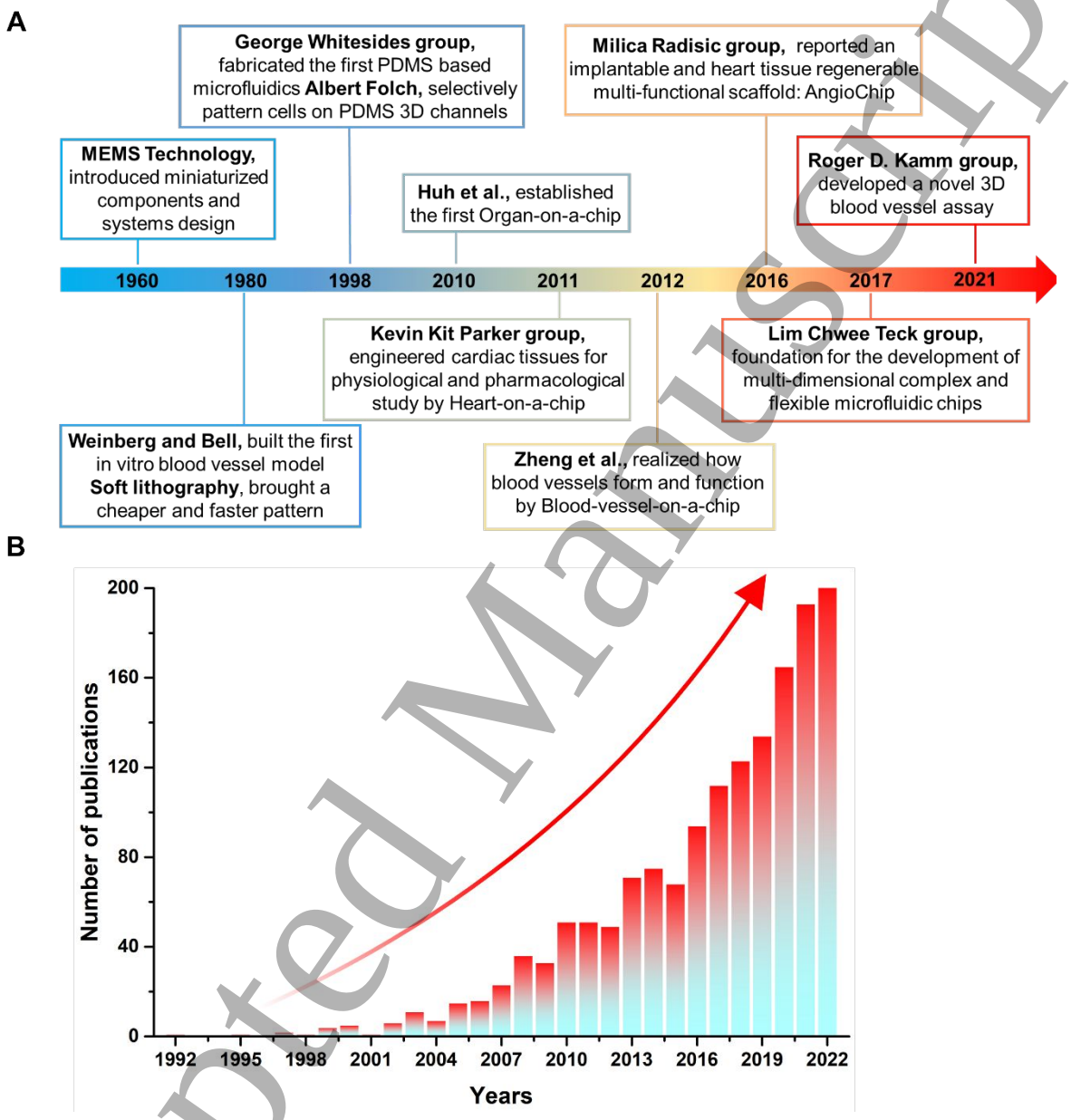

Figure. 2 Brief history and development of microfluidic devices. (A) Representative development of microfluidics for applications in CVDs research to date. (B) Publications of OOC in recent years. (Data from Web of Science by searching the key word of "chip" and "cardiovascular diseases" from 1992 to 2022)

3. The principle of microfluidic devices

Microfluidic devices for CVDs work on the same premise as OOC: an in vitro organ was created with physiological features by duplicating the key structure and functions of the corresponding organ in the body. [73, 74] In these microfluidic devices, the experimental fluid is mostly liquid, and the laminar flow phenomenon accompanied by a low Reynolds number often occurs in the experiment. The study of the fluid motion is of great significance for better design.

The physiological function of blood vessel-mimicking microfluidic devices is reproduced in normal blood vessels in vitro, and disease modeling is carried out on the basis of regeneration. [75-77] As shown in **Figure. 3A**, in a healthy vessel (top), the blood flow exhibited stable laminar flow with a constant velocity profile. However, when atherosclerotic plaque forms (middle) or narrows due to external compression and insertion (bottom), disruption of blood flow, platelet aggregation, wall shearing, and shear rate changes. Force and stress changes can be predicted by computational fluid dynamics (CFD) simulation methods [78-79], and then the simulation values and prediction results are used to improve the design of the microfluidic device. (**Figure. 3B**). Whole blood perfusion was performed in the enhanced microfluidic device under a microscope, and the pathogenesis of the diseases was compared and analyzed based on the simulation prediction results (**Figure. 3C**).

Cardiac bionic microfluidic chips are typically used to simulate the microcirculation of nutrients

and waste transport in the body, thereby testing the effectiveness of drugs for treating CVDs. [80] The principle is the same as that of VOC, both of which are used to imitate the physiological functions of the organ. The design of the HOC mostly needs to consider the natural tissue structure in the ventricular wall (**Figure. 3D**) and anisotropic mechanical stretching, etc. [81-84] The flow velocity in the device (**Figure. 3E**), the diffusion of nutrients [85] such as oxygen (**Figure. 3F**), and even the diffusion of drugs is predicted under simulation to calculate parameters at key locations. [86, 87] For better design, high-throughput detection of drug-induced cardiotoxicity, electrical stimulation, electrophysiological detection, optical recording, etc., must be considered. [88-90]

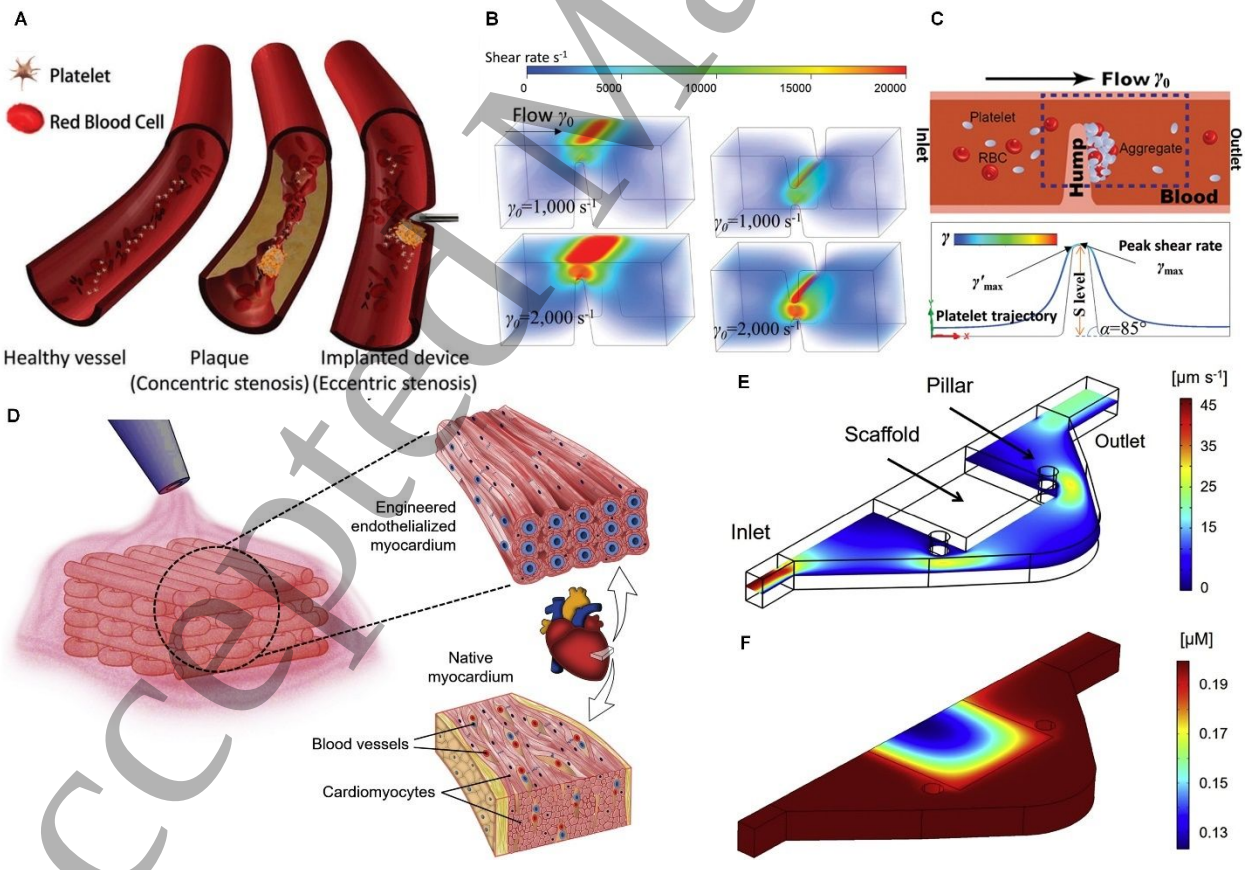

Figure. 3 Principle of microfluidic devices about cardiovascular modeling. (A) Blood flow in a

healthy vessel (top), a vessel with concentric stenosis due to atherosclerotic plaque (middle), and a vessel with eccentric stenosis due to foreign body insertion (bottom). (B) CFD contour plots in eccentric (left) and concentric (right) narrow microfluidic channels. Note that the color on the wall represents the wall shear distribution; the representative streamlines of the platelet trajectories show the shear rate distribution. (C) Differential interference contrast microscopy image of biomechanical platelet aggregation in an eccentric stenosis microfluidic channel after whole blood perfusion at γ_0, mimicking the physiological shear rate in arteries and arterioles. (D) Schematic illustration of the process of fabricating endothelialized myocardium using 3D bioprinting technology. (E) Simulation results of flow velocity distribution after combining 3D bio-printed scaffolds with bio-reactive microfluidic devices. (F) Simulation results of oxygen distribution after combining 3D bio-printed scaffolds with bio-reactive microfluidic devices. (A-C) Reproduced with permission.[76] Copyright 2021, Tech science press. (D-F) Reproduced with permission.[85] Copyright 2016, Elsevier.

4. Materials and factors consideration for designing microfluidic devices

VOC and HOC have several factors that should be considered in design as a result of ongoing physiological inspiration, from the realization of the endothelialization of artificial blood vessels in vitro to the fabrication of three-dimensional vascularized tissues. [91-94] These factors include materials for fabrication, design of structures, manufacturing methods, physiological conditions during organ mimic and the pathological status for disease modeling. [95-98] Therefore, this

review summarized the factors considered in designing OOC in recent years and classified them into three major sections. The selection of materials and processing methods for preparing microfluidic devices are important factors affecting their bionic performance [99], which will be discussed in the first section. The current VOC and HOC are mainly divided into single-layer and multilayer structures. Based on different applications, the design of microchannels needs to consider specific physiological factors such as stretch, blood flow rate, shear rate and shear stress. These belong to physical factors. Furthermore, some conditions for constructing pathological conditions such as the endothelial barrier are mainly determined by cells. It determines whether the blood vessel wall is intact. [100, 101] The cells, growth factors, and chemokines used in OOC are related to the biological factors. OOC is rapidly shifting to translational research to verify the results of genomic research and provide better models for drug testing, paving the way for personalized medicine. The use of OOC in conjunction with gene editing and induced pluripotent stem cell (iPSC) technology to better manipulate the genetic background is emerging as a novel and appealing approach for studying circulatory system function. [102, 103]

4.1 Materials and design for microfluidic devices related to cardiovascular research

The material as an influencing factor affects the performance and applications of microfluidic devices. We summarize the materials used in the fabrication of microfluidic devices, such as PDMS, hydrogels, and other materials. PDMS is currently one of the major materials used in microfluidic devices. [104] However, the biocompatibility of hydrogels has resulted in a gradual increase in manufacturing. [105, 106] In addition to these two materials, some polymers [107-109]

such as thiolene based polymers, cyclic olefin polymers and other elastomers have been used to fabricate microfluidic devices. In this section, the relationship between material traits and performance is discussed.

4.1.1 PDMS-based microfluidic devices

PDMS has many advantages such as quick and easy integration with glass, transparency which allows real-time monitoring and the ability to replicate structures at the nanometer level. In addition, PDMS has good biocompatibility, permeability, and low autofluorescence, which have broad application prospects in microfluidic devices. As an important material for producing microfluidic devices in vitro, the advantage of PDMS lies in its structure. In terms of mechanical properties and compliance of physiological blood vessels, deformable channels can be used to simulate the structure of physiological blood vessels in vitro. Cells such as endothelial cells [110] can grow and move into the PDMS channels with additional growth factors.

Herein, we introduce two methods for fabricating PDMS-based VOC and HOC. Normally, microfluidic devices are obtained by the PDMS poured mold and then directly bonded with glass after plasma treatment. [111, 112] To make the three-dimensional structures (**Figure. 4A-B)**, it is necessary to combine them with other tools (such as needles of different sizes [113]), and even biological factors need to be added for construction. [114] In 2018, Jain et al. proposed a customizable device for evaluating hemostasis and thrombosis in patients with thrombosis (**Figure. 4C**). They intend to obtain tissue and blood from patients and co-culture them into a

microfluidic device via induced pluripotent stem cell (iPSC) technology. Therefore, different patients receive individualized treatment plans based on thrombosis assessment results, making treatment more efficient. [115] In addition to disease modeling, drug evaluation can be implemented on microfluidic chips. Zhang et al. [85] conducted a HOC (**Figure. 4D i-iv**) to evaluate the effectiveness of different doses of doxorubicin on myocardial tissue.

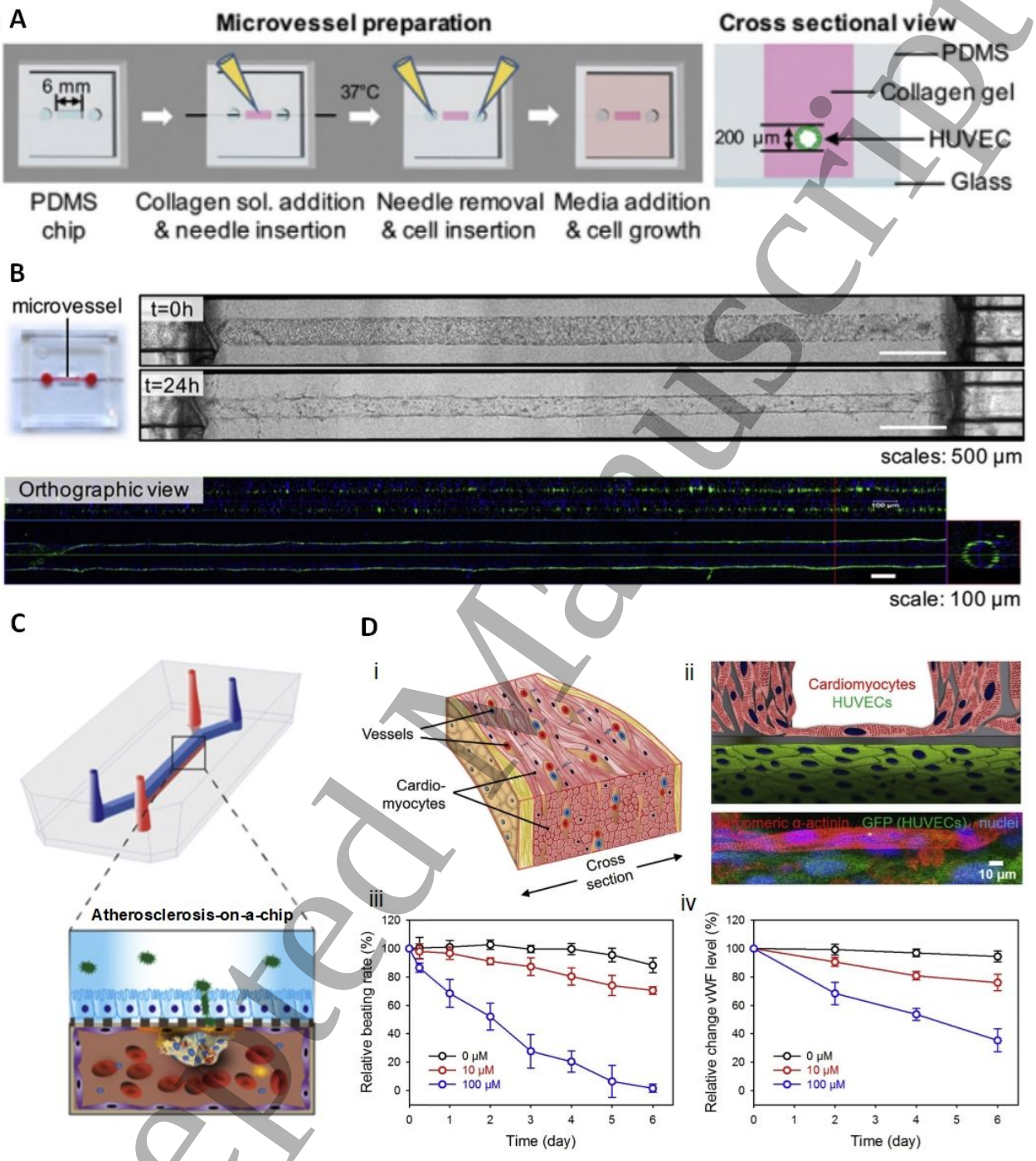

Figure. 4 Representative research of PDMS-based microfluidic devices. (A) Schematic diagram of the fabrication method of the 3D VOC. (B) Phase-contrast and confocal images of the microfluidic device. The orthographic view shows the lumen (green: actin cytoskeleton, blue: nucleus). (C) An application of VOC in atherosclerosis modeling. Reproduced with permission.

[107] Copyright 2018, Elsevier. (D i) Schematic diagram of native myocardium and blood vessels. (D ii) Schematic and confocal images of HOC. (D iii) Relative beating of myocardial tissue after treatment with different doses of doxorubicin. (D iv) Expression levels of von Willebrand factor in myocardial tissue after treatment with different doses of doxorubicin. (A-B) Reproduced with permission.[114] Copyright 2017, Elsevier. (C) Reproduced with permission. [115] Copyright 2018, Elsevier. (D) Reproduced with permission. [85] Copyright 2016, Elsevier.

4.1.2 Hydrogel-based microfluidic devices

Hydrogels exhibit excellent biocompatibility and degradability. As a novel material that gradually replaces PDMS for microfluidic devices, hydrogels have unprecedented properties for integration with various cellular sources, construction of extracellular matrix (ECM)-mimicking environments, molecular diffusion, and gradient generation. [116-118] In recent years, hydrogels have been used as host materials for biomimetic models. However, their properties generally depend on the type, gelation method, and fabrication technique.

Cho et al. created a VOC [119-120] with an adjustable size and shape through 3D printing (**Figure. 5A-B**). This method eliminates the bonding process and ensures the stability of the whole equipment as much as possible. During inflammatory diseases, blood vessels often undergo pathological changes, such as loss of anti-adhesion ability and disruption of the endothelial barrier. These changes can lead to disease progression and complications such as atherosclerosis. Therefore, it is particularly important to study the pathogenic changes in VOC

and HOC fabricated using biocompatible materials. Gao et al. modeled inflammation on hydrogel-based VOC and observed disruption of the endothelial barrier (**Figure. 5C**). [121] Hydrogel-based microfluidic devices enable the flow of nutrients, gases, and metabolic wastes between cells and cell-ECM. Long-term survival and effective maintenance of vascularized tissues require adequate oxygen and food supply as well as microenvironmental regulation. [122, 123]

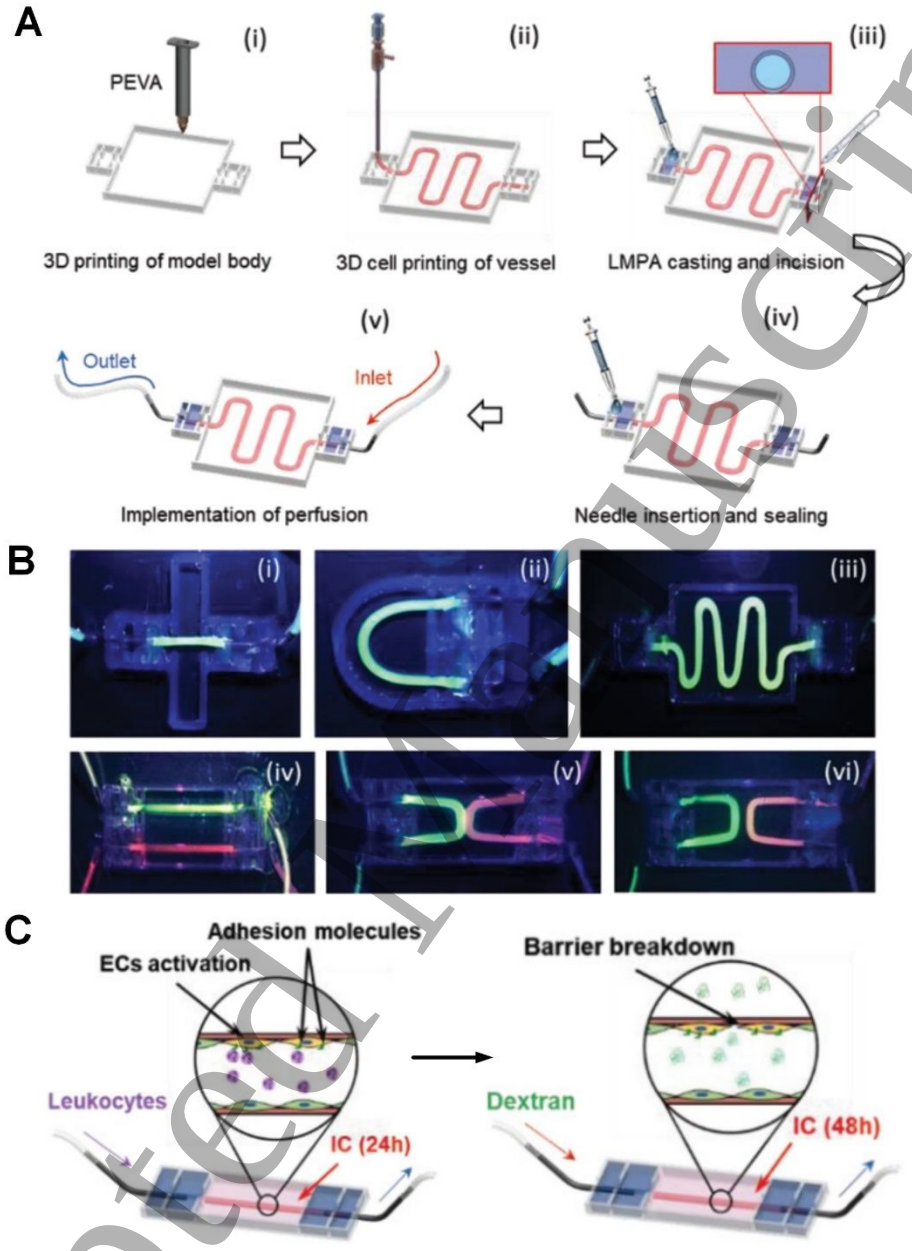

Figure. 5 Representative research of hydrogel-based microfluidic devices. (A) Schematic diagram of VOC fabrication. (B) Perfusion of differently shaped channels. (C) Prolonged inflammatory treatment leads to a model of endothelial barrier disruption. (A-C) Reproduced with permission. [121] Copyright 2018, John Wiley and Songs.

4.1.3 Other materials-based microfluidic devices

Elastomers, such as poly (ester amide)s can be used to fabricate microfluidic devices. Wang et al. created a polymer called poly (1,3-diamino-2-hydroxypropane-co-polyol sebacate)s (APS) [124], which is part of a new class of biodegradable elastomeric poly (ester amide)s. It has been developed as a replacement for traditional crosslinked aliphatic polyesters has been routinely utilized in biomedical systems and is safe and inexpensive. The low Young's modulus of the matrix and variable biodegradation half-life allow it to replicate ECM mechanical qualities while also being compatible with dynamic mechanical settings. [125] The engagement of the polymer in hydrogen bonding also allows for further conjugation, cell seeding, and adhesion.

Based on the materials discussed in this section, the PDMS and hydrogel are the mainstream materials for OOC. PDMS-based microfluidic devices can endow the encapsulated channels with strong mechanical strength through direct mechanical combination or chemical treatment. For VOCs and HOCs, the physiological conditions such as flow force and shear stress for CVDs are more appropriate to be modeled by PDMS-based OOC. However, the cell-loaded property of hydrogel allows the integration of cells and diffusion of small molecules. More importantly, hydrogels are compatible with 3D printing, and they can be cross-linked twice. Traditional templates for pattern demolding can be replaced by hydrogel-based OOC. Related to the specific application, the other materials for OOC such as PMMA and elastomers were introduced to replace the hydrogels with low hardness and the PDMS with insufficient biocompatibility. Great

biocompatibility, easy fabrication, disease modeling without external support are the ideal properties for CVDs related OOCs. Ultimately, to achieve these properties, we need to design the OOC regarding to novel materials with these properties, combined with other technologies such as electrospinning, or 3D printing, etc.

4.2 Physical and biological factors for microfluidic devices

Endothelial cells (ECs) in arteries are constantly exposed to two hemodynamic forces: fluid shear stress (FSS) and cyclic stretch (CS), both of which are caused by blood flow and blood pressure. [126, 127] Mechanical forces at the physiological level are required for the formation and maintenance of an appropriate blood vessel structure and function. Normal FSS (1.5–7.0 Pa) can trigger ECs to generate bioactive molecules, such as nitric oxide (NO) and endothelin, which can maintain blood vessel stress within a particular range while inhibiting platelet adherence to the intima and VSMCs proliferation. Mechanical forces that are out of whack have a big influence on the onset and progression of atherosclerosis. For example, hypertension stimulates inflammatory responses in VSMCs by activating various signaling pathways. Low FSS (1.0–1.2 Pa) has been shown to impair the protective effect of NO and increase the permeability, absorbance, and production of oxidized low-density lipoprotein (ox-LDL) in ECs, potentially leading to atherosclerosis. A low FSS can also cause the production of reactive oxygen species (ROS), enhance inflammatory cell adherence and infiltration to the vascular wall, and cause inflammation underneath the intima. [128] Tachycardia, or an abnormally fast heartbeat rate, can increase the

amount and frequency of tensile stress imposed on the artery wall and prolong EC exposure to a low and oscillatory FSS, causing structural and functional alterations in ECs in atherosclerosis-prone areas. [129]

OOC are tiny cell culture devices used to imitate the functional units of human organs outside the body. In addition, OOCs can be seamlessly coupled to create a "human-on-a-chip" that can simulate the interactions and physiological reactions of multiple organs as a system. [130] To build the microenvironment of OOC, the first step is to understand the anatomical structures of the target organ and regenerate the basic framework for physiological activity. The next step is to construct the physiological composition, including cell types, specific biochemical and physical factors. Physical factors are mostly related to force and electricity. Biological factors often involve the source of cells and additives, such as ECM mimicking biomaterials and growth hormones (**Figure. 6**). [131, 133] Multiple individually addressable flow-through microchambers are typically included in the device to nurture several cells while adjusting the culture environment related to cell types.

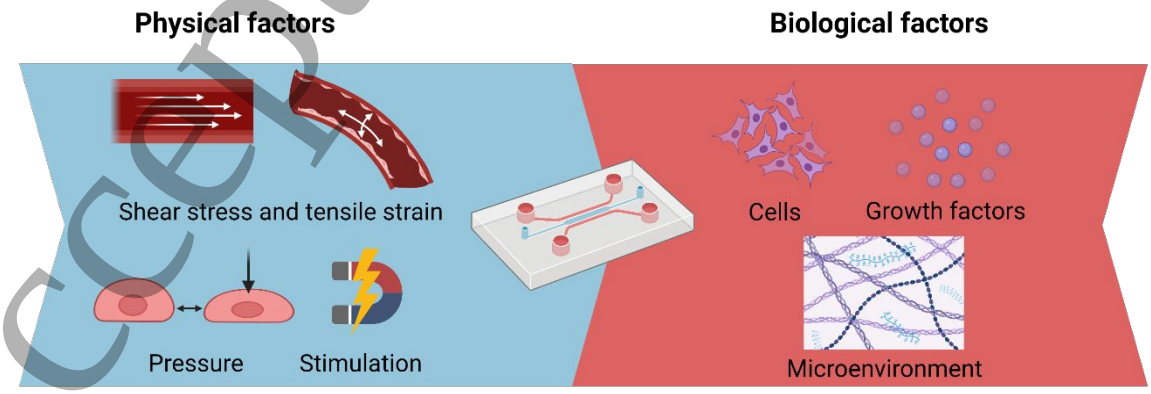

Figure. 6 Physical and biological factors considered in microfluidic device design. Created with

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4.2.1 Physical factors for microfluidic devices

Mechanical changes play a vital role in pathological, high-shear platelet aggregation (thrombosis). [134-136] Platelets aggregate when the pathological shear rate exceeds 4000 s^{-1}, and the average physiological range is estimated to be 500-1500 s^{-1}. Craig R. Forest et al. devised a microfluidic device [137, 138] to evaluate the shear rate of platelet aggregation in whole pig blood under healthy and pathological flow conditions (500-13000 s^{-1}). The structure of the vessel wall was employed to withstand and convey the forces of blood flow and pressure to the surrounding tissue. The stretching cyclic force operating radially and longitudinally on the artery wall was measured using the blood pressure (P). Peripheral (or hoop) stresses in the vessel wall are caused by compression-induced radial tensile forces. Shear stress is also created by the blood flow parallel to the vessel lumen. The physiological parameters, physiological forces, and associated stresses present in the vessel wall are summarized in **Figure. 7A i-ii.** They also discovered that the amount of blood needed to generate an occlusive thrombus varied dramatically depending on the shear rate. [139-141] Huang et al. created a sensor-integrated VOC [142] that could be stretched (**Figure. 7B i**). Depending on the vacuum-induced elastic deformation of the stretchable sensor and adherent cell layer, and real-time monitoring, this device perfectly replicated similar physiological and pathological situations in vivo (**Figure. 7B ii-iii**) and also overcame the limitation of not being able to detect in vitro reconstructed tissue in situ.

Blood travels through the heart chambers from the start of the heartbeat, and this physical stimulation influences cardiomyocyte proliferation [143]. Therefore, to design a HOC, consideration of specific external stimulation and real-time monitoring of the dynamic electrophysiology and contractile response of heart tissue in situ is required. In the natural microenvironment, shear stress parallel to the vessel wall was caused by the blood flow (**Figure. 7C**). Changing the blood flow during each systolic-diastolic cycle increased the strain encountered by cardiomyocytes in addition to shear stress. This force is known as the mechanical load, and it changes depending on the blood viscosity, which is mostly determined by the red blood cell content. The blood is in direct contact with the endocardium inside the heart, exerting shear pressure that causes cyclic strain on the three layers of the heart. The pericardial fluid produces shear stress on the epicardium and pericardium, as well as tension on the entire heart and outside of the heart. [144] Cardiomyocyte and heart shape are influenced by blood flow and myocardial contractility. This process involves mechanotransduction, therefore, electrophysiology is also an important factor to consider when designing HOC. Huang et al. created a HOC (**Figure. 7D i-ii**) that allows for in-situ electrical stimulation and heart monitoring. Platinum wire electrodes for external electrical stimulation and gold electrode arrays for the real-time collection of cardiac electrophysiological signals were successfully combined on the platform. The HOC (**Figure. 7D iii**) was assessed through optical monitoring, and the beating behavior of the heart tissue was analyzed. Verapamil and isoproterenol stimulation were used to validate the drug detection capabilities of the HOC. [145, 146] Verapamil mainly inhibits L-type Ca^{2+} channels to block calcium transients in the cardiac tissue, which determines the beating frequency of the heart. [147,

148] Isoproterenol, a synthetic catecholamine, restores cardiomyocyte beating by inducing positive inotropic and chronotropic responses. [149-150] Furthermore, they discovered that cells cultivated under electrical stimulation had synchronized contraction behavior and a faster rate of beating (**Figure. 7D iv**) than the group without electrical stimulation. Other studies have also shown that electrical stimulation stimulates cardiomyocyte development and leads to the development of functioning heart tissue in devices. [151]

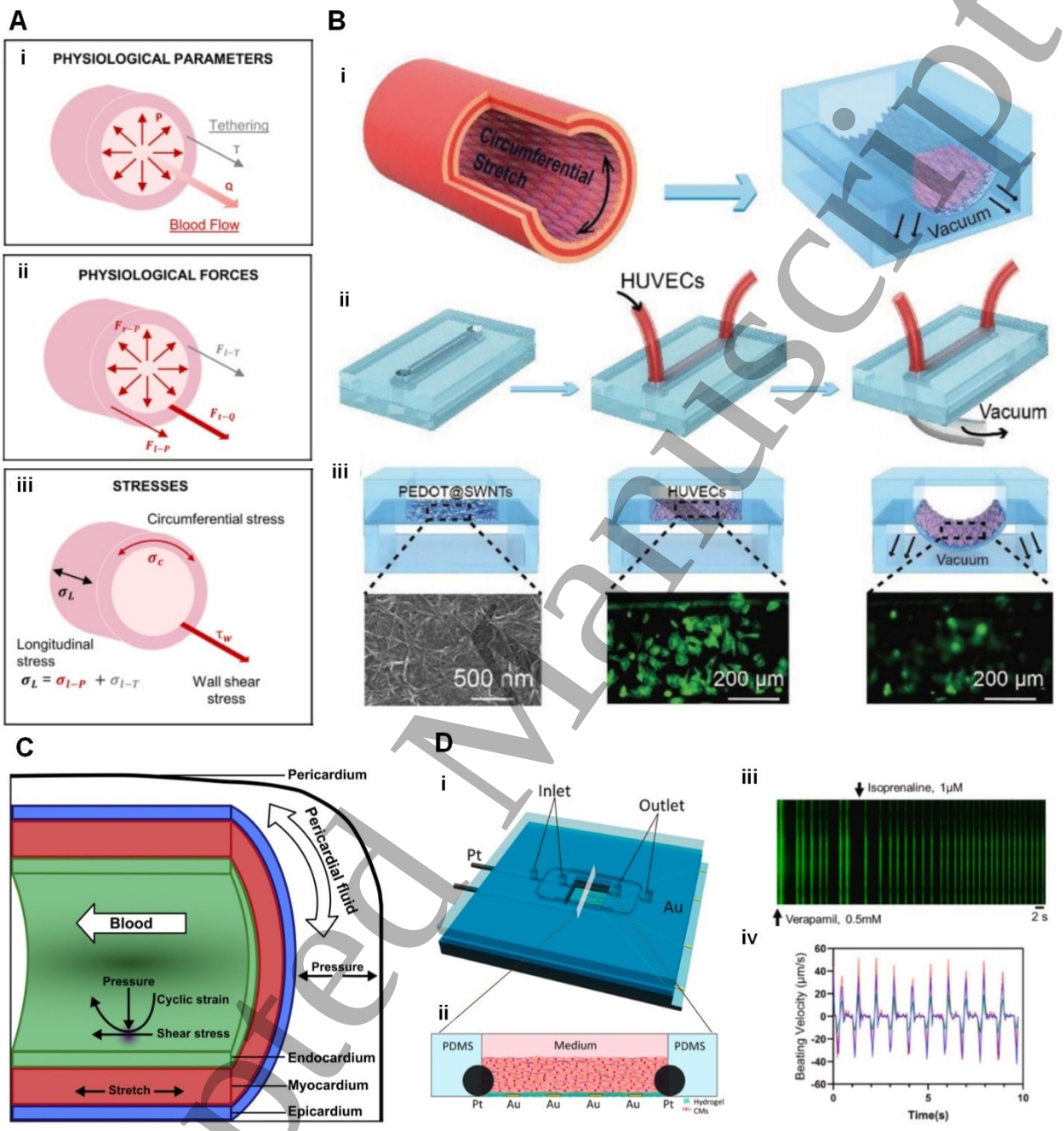

Figure. 7 Physical factors should be considered during the design of VOC and HOC. (A i) Physiological parameters related to forces and stresses acting on native vessel walls. Pressure (P), Volumetric Flow (Q), and Longitudinal Tissue Restraint (T). (A ii) Physiological forces acting on blood vessels are generated by blood flow, blood pressure, and surrounding tissues: radial (F_{r-P}) and longitudinal forces (F_{l-P}) due to blood pressure, tangential forces (F_{t-P}) due to blood flow, and

longitudinal forces (F_{l-T}) due to restraint. (A iii) Physiological forces induce stress in the vessel wall: circumferential stress (σ_C), longitudinal stress (σ_L), and shear stress (τ_w). Longitudinal stress consists of stress due to compression (σ_{l-P}) and restraint (σ_{l-T}). (B i) Schematic diagram of a simulated VOC for circumferential stretching of blood vessels. (B ii) Schematic illustration of cell seeding and vacuum-induced circumferential stretching. (B iii) Sectional view and Scanning electron microscope (SEM) graph of electrode material in biomimetic microfluidic vascular model. Microscopic images of Human umbilical vein endothelial cells (HUVECs) with or without (cells become blurred when they are out of focus) circumferential stretch at an airflow. (C) The inset shows a portion of the heart wall. Arrows represent physiological force vectors such as pressure, shear stress, tensile force, etc. (D i) Overall schematic diagram of the HOC. (D ii) Cross-sectional view showing the distribution of cardiac tissue within the chamber. (D iii) Representative fluorescence recording of Ca^{2+} transients on electrically stimulated tissues after sequential treatment with verapamil and isoprenaline. (D iv) Recording of cardiac tissue beating velocity under electrical stimulation. (A) Reproduced with permission. [139] Copyright 2021, Elsevier. (B) Reproduced with permission. [142] Copyright 2019, John Wiley and Sons. (C) Reproduced with permission. [144] Copyright 2016, Elsevier. (D) Reproduced with permission. [151] Copyright 2021, Elsevier.

4.2.2 Biological factors for microfluidic devices

To mimic the microenvironment of an organ, biological factors such as cells and growth factors are inseparable during the design of HOC and VOC for CVDs. Gu et al. reported a foam cell

formation device for atherosclerosis research. [152] A three PDMS layers co-culture system consisting of VSMCs, ECs, and human leukemia monocytic cell line (THP-1) was developed for the structural features of the vascular wall, which constitutes the intima (endothelium), media (smooth muscle layer), and adventitia. The improvement of this device is that it simulates both the multi-cell system and the triple-layer properties of blood vessels. This microfluidic device not only has a biomechanical microenvironment such as tensile and shear stress, but it can also directly model diseases based on the microenvironment of blood vessels. However, a limitation of this system is that it cannot simulate the dynamic formation of atherosclerosis, and the vascular geometry and metabolic mechanisms that contribute to the development of atherosclerosis were not considered. Because of the physiological and pathological differences between humans and animals, animal models are insufficient to simulate the human myocardium, resulting in a low rate of clinical translation of drugs. [153, 154] Pinar Zorlutuna et al. created a HOC (**Figure. 8A i**) in which iPSC-derived cardiomyocytes and iPSC-derived ECs were co-cultured (**Figure. 8A ii**) to better mimic the human myocardium and surrounding microvasculature. HOC enables drugs or small molecules to diffuse into the simulated myocardial tissue through microvascular channels owing to spatial 3D co-culture. In addition, the device can be used to study the specific genes responsible for CVDs risk factors. [155]

After determining the cells required for the corresponding device, it is important to consider specific cytokines and drugs to build a disease model. Su et al. developed a novel microfluidic ECs–VSMCs 3D co-culture platform that mimics the structural and biological trials of the human

artery wall to simulate early atherosclerosis. [156, 157] They used the modified surface tension-based ECM patterning method to create a well-defined intima–media-like structure and identified an ECM composition that keeps the VSMCs in a quiescent and aligned state as seen in a healthy artery. Stimulation of ECs with cytokines Interleukin-1 (IL-1), Tumor Necrosis Factor-α (TNF-α) and oxLDL was used to investigate early atherosclerosis (**Figure. 8B**). Furthermore, Wang et al. created a myocardial hypoxia model using the oxygen consumption blocker carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone (FCCP). [158, 159] Cardiomyocytes and skeletal myoblasts were seeded in different chambers and then used to create an environment of myocardial hypoxia. After hypoxia-induced myocardial damage, the chamber between cells was opened to allow co-culture. Finally, they discovered that cell-to-cell interactions allowed cardiomyocytes to be repaired.

In addition to cells and growth factors, new blood vessel formation is an important biological process. Angiogenesis marks the emergence of new blood vessels that contain in vivo physiological conditions such as cellular crosstalk effects and complex microenvironments. When designing microfluidic devices, angiogenesis will undoubtedly enable a more intuitive and comprehensive analysis of fabricated models. [160, 161] Based on previous research, the Valeria V. Orlova team improved the design and developed the VOC. iPSC-derived vascular cells self-organized and created stable microvascular networks in this device. These vascular networks were stable for up to 3 weeks (**Figure. 8C**). At the same time, vascular networks also exhibit the morphology and function of natural blood vessels. This VOC will aid in the research and

quantification of changes in vascular structure and function due to pharmacological therapy or during vascular development. [162, 163]

Except the cell types, angiogenesis included in the design, the mechanism and decision of drugs used for CVDs is also an important part of biological factors when design the OOC. Due to the diffenrences between animals and human beings, iPSCs were used to CVDs modeling and drug screening. [164, 165] Mills et al. produced a microfluidic chip for CVDs drug screening. [166] This chip avoided the false positive results effectively that is tested in traditional 2D culture and forecasted the potential side effects for heart tissue. (**Figure. 8D**) The most importantly, they investigated the potential healing targets with the minimum toxicity for heart in the chip and indicated the mechanism was related to mevalonate pathway. Fang et al. [167] enumerated the small molecules that can block the ferroptosis pathway for CVDs treatment such as Ferrostatin 1, liproxstatin 1 and antioxidants. They also indicated that common heart medicines might present the novel anti-ferroptosis activity. Recently, Marracino et al. [168] demonstrated the potential therapeutic methods based on "Notch" signal pathway (**Figure. 8E**) for CVDs diagnosis and treatment. Activated "Notch" prevented the apoptosis of myocardial cell and endothelium cells. [169, 170] Therefore, they suggested that activate the "Notch" in these cells with MiRNA based drug. [171] and high-throughput screening in microfluidic chips may be a novel method for selection of the most effective drugs for CVDs treatment.

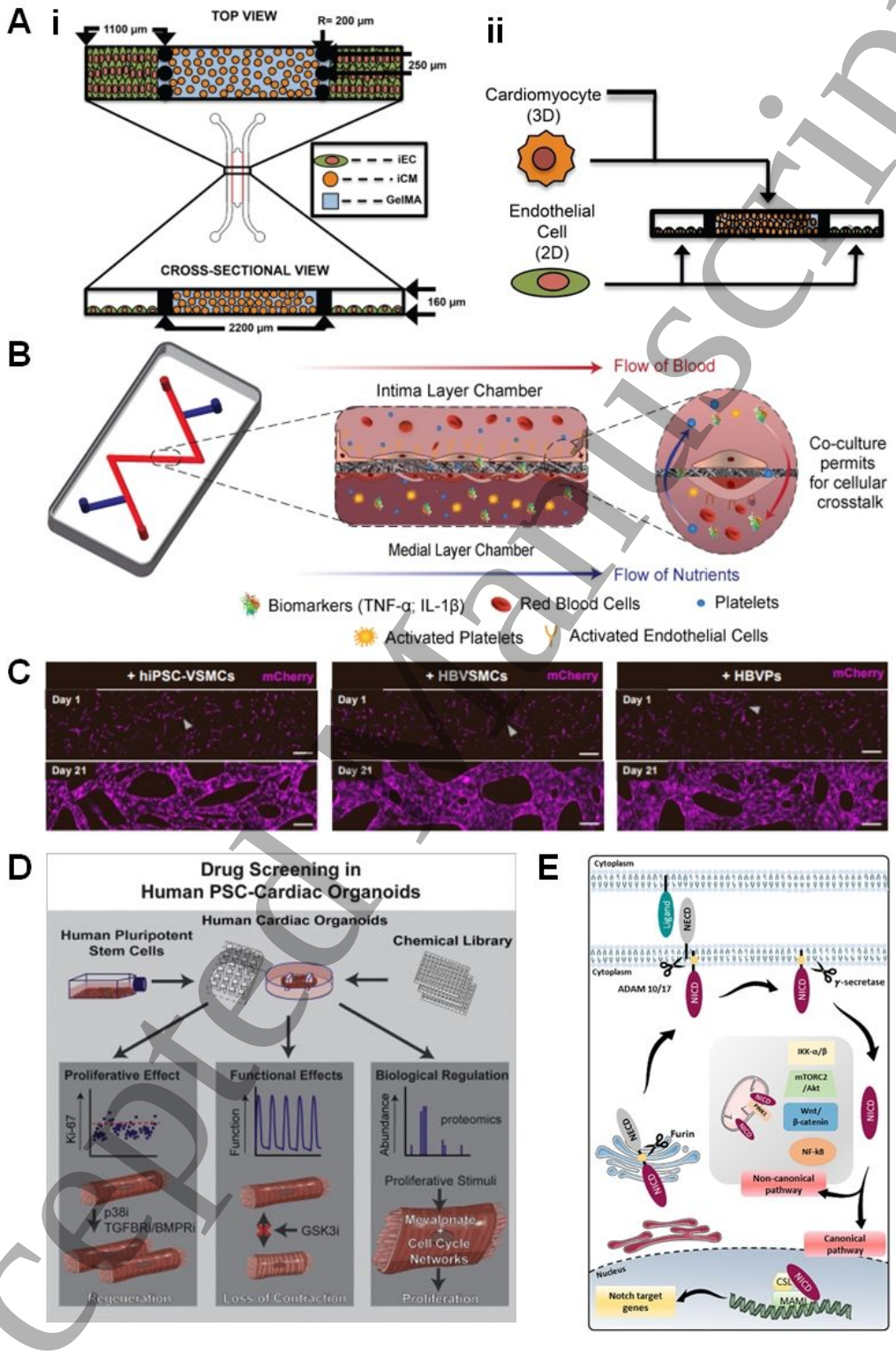

Figure. 8 Biological factors should be considered during the design of VOC and HOC. (A i) Schematic illustration of cardiomyocytes encapsulated in UV-activated hydrogels and seeded into

myocardial channels, followed by seeding with iECs. (A ii) Schematic diagram of co-culture of cardiomyocytes and endothelial cells. (B) Schematic diagram of the construction of a VOC for simulating CVDs. (C) Self-organization, angiogenesis, and vascular remodeling of vascular cells for 21 days; white arrows show vacuole formation. (D) A strategy for CVDs drug screening on microfluidic chip. (E) Notch pathway related to pathophysiology of CVDs. (A) Reproduced with permission. [155] Copyright 2017, AIP Publishing. (B) Reproduced with permission. [158] Copyright 2019, Elsevier. (C) Reproduced with permission. [162] Copyright 2021, Elsevier. (D) Reproduced with permission. [166] Copyright 2019, Elsevier. (E) Reproduced with permission. [168] Copyright 2021, frontiers.

5. Applications of microfluidic devices on cardiovascular diseases

Microfluidics can be used to create visible channels with a simulated vascular network structure, as well as to precisely control the flow conditions of trace fluids in microchannels to simulate cardiovascular blood flow. [172-174] Therefore, microfluidic devices related to CVDs can be customized for specific applications such as VOC for pathogenesis studied, HOC for drug screening, and microfluidic scaffolds for implantation. With the advancement of OOC, more complex devices based on cardiovascular pathology research, such as AOC will be discussed in this section. The progress of CVDs research will be aided by these small, multifunctional in vitro devices.

5.1 Blood-vessel-on-a-chip

Arterial endothelial dysfunction, sclerosis, and atherosclerotic lesions for the basis of CVDs. In recent years, many OOCs have been proven to be able to summarize the basic aspects of the human cardiovascular system and have been used in CVDs-related research. Generally, the types of blood vessels that may be involved in CVDs are arteries, arterioles, venules and capillaries. [175-177] VOCs as a type of OOC can be divided into two categories based on their functions. VOCs that simulate vascular morphology are mainly dedicated to the high bionics of blood vessels outside the body, such as implantable vascular scaffolds and the different size of blood vessels. Another type of VOC focuses on pathological conditions, which are mainly used to study the different pathological mechanisms of CVDs. The AOC is an example of this type of VOC. Here, we summarize the parameters of the novel VOC design in **Table. 1**.

Table. 1 Parameters for designing the novel blood-vessel-on-a-chip.

Materials	Structure	Physical factors	Biological factors	Comments	Ref.
PDMS	lumen	sheer stresses	iPSC and VEGF	The 3D vascular network.	[178]
	lumen	flow stress	HUVEC and VEGF	Determination of angiogenesis in vitro.	[179]

	complex blood vessels	flow stress	blood cells	A VOC with both major vessels and capillary structures.	[180]
	microgrooves	shear stress and cyclic stretch	rat mesenchymal stem cells and HUVEC	For studying vascular biomechanics.	[133]
	channels	cyclic stretch	aortic smooth muscle cells	For aortic valve disease research	[181]
PDMS + glass	lumen and channels	flow and shear stresses	HUVEC and VEGF	Demonstrate the drainage in angiogenesis.	[182]
	lumen	flow and shear stresses	HUVEC+THP-1 and TNF-α	Angiogenesis without support.	[183]
	channel	flow and shear stresses	blood outgrowth endothelial cells	Modeling based on patient-specific levels.	[184]
	channel	flow stress	HUVEC+TNF-α	Study venous pathophysiology	[185]
PDMS + Hydrogel	blood vessel	flow stress	fibroblast cell, HUVEC, and	Restored the three-layer structure of	[186]

			VSMCs	blood vessels.	
Hydrogel	customizable channel	shear stresses	HUVEC and TNF-α	Multilayer and in vitro model of endothelial barrier disruption.	[187]

Using silicone molds and collagen casting gels, Zheng et al. produced the first VOC that imitated the characteristics of angiogenesis. [67, 188] In the past, collagen gels were utilized for this purpose, but previous devices never achieved the same level of endothelial functionality or permitted real-time observation using this method. The microvessels were lined with continuous endothelium and they also sprouted additional branches and recruited pre-seeded mural cells when stimulated with proper biochemical signals. Liu et al. recently used VOCs to examine angiogenic sprouting and functional vessel development (**Figure. 9A**). They discovered that vascular endothelial growth factor (VEGF) is a determinant of the initiation of vascular sprouting, and this device is suitable for studying the effects of angiogenic factors or medications during angiogenesis. [189]

Apart from regenerating the healthy conditions of organs, the pathogenesis of CVDs also can be explored using visible microfluidic devices. In 2016, Zheng et al. proposed the first microfluidic model for the reconstruction of early atherosclerosis. [129] (details in **Figure. 9B i & ii**) They

simulated aberrant mechanical stresses as well as early atherosclerotic metabolic and inflammatory conditions in the setting of a physiological hemodynamic environment. All processes avoid time-consuming, expensive, and ethically problematic animal trials. Under the same hyperlipidemia (high cholesterol) and inflammation (TNF-α) activation conditions, the levels of vascular endothelial cadherin (VE-cadherin) in the model cells were much lower than those in the culture dishes. [190] They disclosed the cells in the early atherosclerosis model were more sensitive to biochemical stimulation than those in traditional culture dishes.

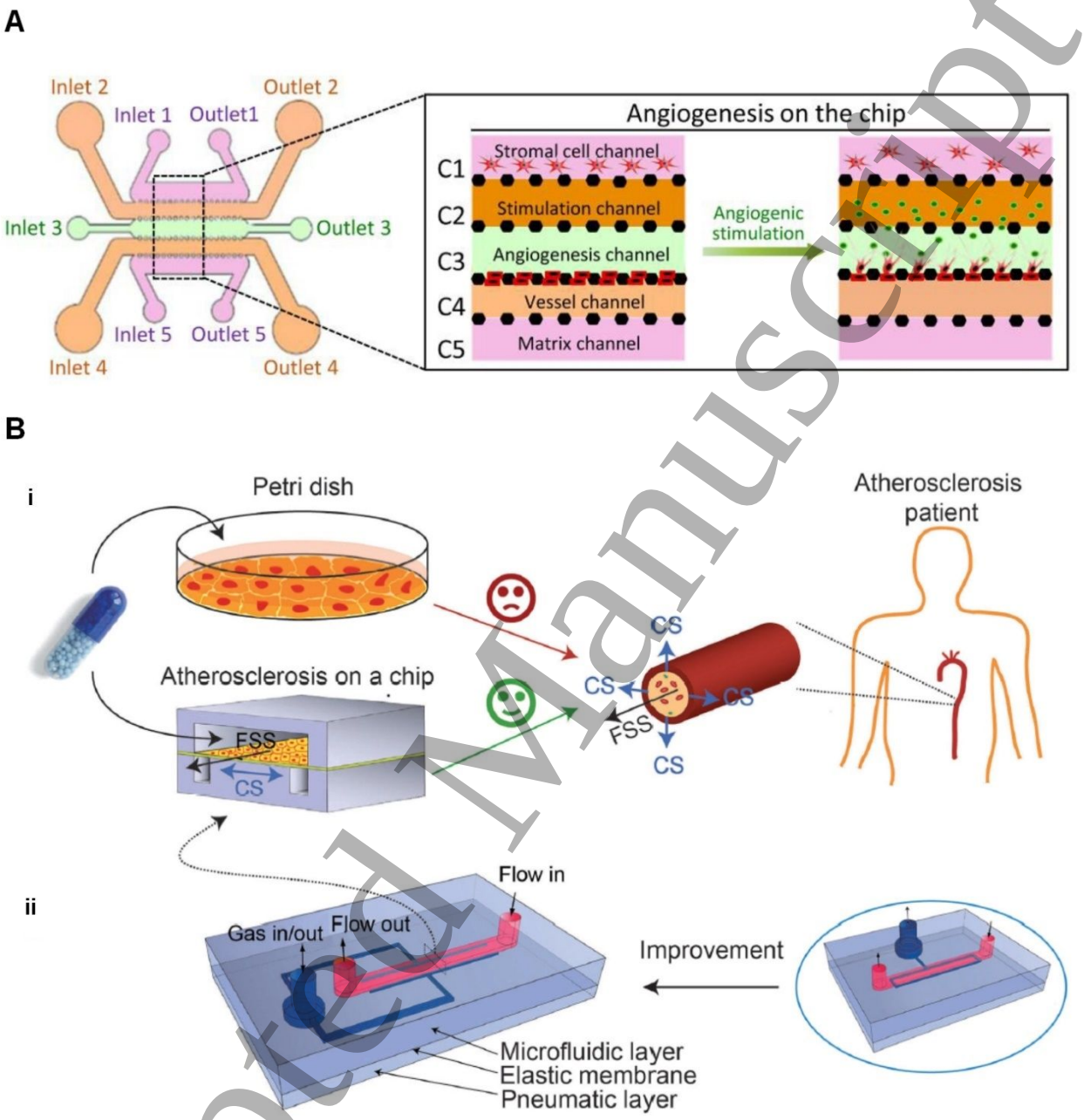

Figure. 9 Angiogenesis and disease modeling by blood-vessel-on-a-chip. (A) Schematic of the angiogenic microfluidic device (left) and the corresponding channels setup (right). (B i) Atherosclerosis model based on microfluidics better recapitulates the physiological and pathological conditions of arteries in vivo than models established with traditional petri dishes. (B ii) Microfluidic device for early atherosclerosis modeling. (A) Reproduced with permission. [189]

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5.2 Heart-on-a-chip

The HOC was created for the construction of biomimetic heart function and disease modeling, [191] similar to VOC. However, a complicated microenvironment leads to complex compositions and processes particularly electromechanical stimulation and real-time monitoring. Based on different CVDs models, different HOCs have been developed for cardiac ischemia [192], cardiac fibrosis [193], and cardiotoxicity [194]. The parameters and comments for designing the novel HOC are summerized in **Table. 2**.

Table. 2 Parameters for designing the novel heart-on-a-chip.

Materials	Structure	Physical factors	Biological factors	Comments	Ref.
PDMS + glass	micropost	contraction	iPSC and basic fibroblast growth factor (bFGF)	Establishment of a cardiac ischemia model.	[195, 196]
PDMS	microchannel, chamber, diaphragm,	contraction	iPSC+bFGF, VEGF and bone morphogenetic protein	Can be used for drug discovery and	[197]

	and push bar		4 (BMP4)	cardiotoxicity testing.	
	walls	mechanical stimulation	Neonatal cardiomyocyte+cardiac fibroblasts and cell-ECM	High-throughput study of cardiac hypertrophy.	[198]
Hydrogel	vertical arrangement of tri-layer	contraction	iPSC	In situ quantification of real-time shrinkage stress measurements.	[199]
	complex heart	contraction	iPSC	Build a 3D structure that replicates the heart.	[200]
	Post and channels	contraction	neonatal cardiac fibroblasts + Transforming growth	A cardiac scar model was developed.	[201]

factor beta 1(TGFβ1)

As an important CVDs modeling tool, HOCs have a more complex design based on specific pathological conditions. Mehdi Nikkhah et al. updated the HOC they designed [195] and used it to model myocardial ischemia [196]. As shown in **Figure. 10A**, iPSC-derived cardiomyocytes were co-cultured with cardiac fibroblasts and encased in collagen. The encapsulated cells were injected into the HOC and conditions were set up (1% hypoxia, 5% physioxia, and 21% hyperoxia). Since ischemia leads to myofibroblast differentiation in the native myocardium [202, 203], in each image acquisition, they recognized the matching expressed protein α-smooth muscle actin (αSMA) and then normalized the integrated density of αSMA to the integrated density of actin. (**Figure. 10B i-iii**). They found a significant increase in the fibrotic response within the tissue under hypoxic conditions compared with physiological and hyperoxic conditions. Additionally, myocardial ischemia can lead to irregular contraction patterns due to factors such as the development of tissue fibrosis [204, 205]. Therefore, they measured the spontaneous beat rate (**Figure. 10C**) and inter-beat variability of the cardiac tissue (**Figure. 10D**) at different oxygen concentrations. The inter-beat interval variability was significantly increased under hypoxic conditions and they successfully established a heart disease model in the HOC.

HOCs have been designed for high-throughput drug screening based on minimal and controllable traits. Sun et al. constructed a HOC that could be easily fabricated. [206] This HOC can test various drug doses and therapeutic candidates to create a high-throughput drug screening

platform for cardiotoxicity (**Figure. 10E**). They investigated the dose-dependent cardiotoxicity using clinically approved doxorubicin (DOX), cyclophosphamide (CP), ivabradine (IVA) and carbachol (CAR) (**Figure. 10F**). Eventually, they demonstrated the versatility and high efficiency of HOC in studying the cardiotoxicity and cardioprotective efficacy of drugs.

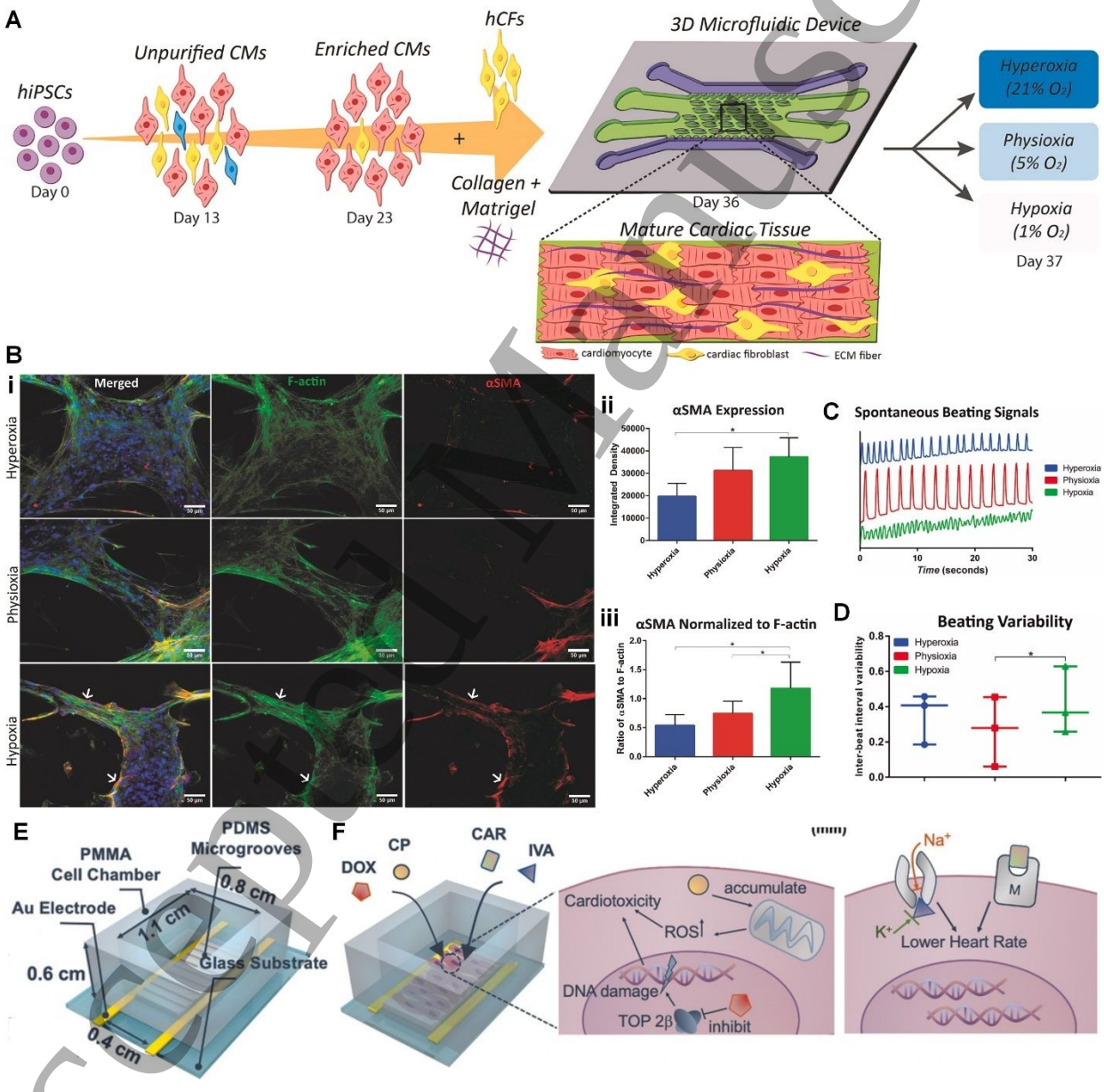

Figure. 10 Heart disease modeling and drug screening by heart-on-a-chip. (A) Flow chart for reproducing myocardial ischemia model in HOC. (B i) Immunostaining of cardiac tissue after

exposure to the different oxygen levels of F-actin (green) and αSMA (red), with white arrows indicating co-localization of F-actin and αSMA. (B ii) Comprehensive staining density of αSMA. (B iii) Comprehensive density of αSMA stain normalized to the integrated density of F-actin fibers. (C) Representative spontaneous beating signals at three oxygen concentrations. (D) Inter-beat variability in cardiac tissue exposed to three oxygen concentrations. (E) Schematic diagram of the HOC for high-throughput drug screening. (F) Screening and evaluation of drug-induced cardiotoxicity and cardioprotective efficacy in the device. (A-D) Reproduced with permission. [196] Copyright 2022, Elsevier. (E-F) Reproduced with permission. [206] Copyright 2020, John Wiley and Sons.

5.3 Polymer scaffolds

Polymer scaffolds are often used for tissue reconstruction. For the cardiovascular system, the current grafts of artificial blood vessels and cardiac patches have been fabricated using expanded polytetrafluoroethylene (ePTFE), polyester (PET), polyurethane (PU), or other materials. [207-210] Currently, a major limiting issue for achieving in vitro cultivation of solid organs with polymer scaffolds is whether an efficient vascular network system can be built inside. [211] Based on the controllable, integrative and biocompatible properties, microfluidic devices can be manufactured as mini scaffolds that avoid secondary injury of CVDs or provide support. Microfluidics-based scaffolds are usually co-fabricated by electrospinning [212], 3D printing [213], etc. The results are shown (**Table. 3**) which summarizes the parameters and comments for the design of polymer scaffolds.

Table. 3 Summary of microfluidics-based polymer scaffolds of design.

Materials	Structure	Physical factors	Biological factors	Comments	Ref.
PoMaC	branched, 3D microchannel network	flow and shear stresses	human embryonic stem cell (hESC)	Implantable and tissue regeneration.	[214]
	microwells	Contraction and electrical stimuli	iPSC	Generate composite heart tissue containing atrial and ventricular regions	[191]
PCL, PLGA, PDMS	three-layer tubes	crimp stress	HUVEC, VSMC, fibroblast	Long-term implantable, biodegradable.	[212]
Hydrogel	sphere	shear forces and fluid pressures	iPSC+ dermal fibroblasts and ECM coating	A new method for making heart micro-tissues proposed	[215]

At present, the Milica Radisic team uses biological 3D printing to print microvascular networks with good porosity and a high degree of simulation directly and they named it “AngioChip” [214]. They used a biodegradable, flexible, UV polymerizable, and rapid prototyping polymer [poly (octamethylene maleate (anhydride) citrate)] (POMaC). Therefore, these microstructures can

quickly complete vascularization and endothelialization. The AngioChip has thin and flexible walls and sufficient mechanical strength to support the perfusion vasculature in the contracted tissue. Vessel walls contain micro- and nano-scale pores that facilitate molecular exchange and cell migration. They demonstrated the successful vascularization and inflammatory response of the AngioChip. In addition, they successfully prepared functional and vascularized heart tissues based on the AngioChip which showed the expected positive chronotropic response to epinephrine [216, 217]. Except for the organ simulation, the AngioChip can be implanted directly into the hind limb of adult mice for blood circulation between the arteries-arteries and the arterial-venous vessels during surgical anastomosis. This study provides an effective method for tissue regeneration, which can directly and quickly realize conversion from in vitro to in vivo.

Furthermore, they have been designed the "Biowire II" was designed to reconstruct cardiac tissue and CVDs modeling. [218-221] Biowire II is an update of the previous version and the new generation can realize the separation or co-culture of atrial and ventricular tissues on a microfluidic device (**Figure. 11A**) and the device can also be used for heart disease modeling and disease gene screening. The development of cardiac tissue is influenced by ECM, soluble factors, mechanical and electrical stimulation. [222, 223] Therefore, they cultured the atrial and ventricular tissues in the devices that exhibited different functional responses following electrical manipulation by comparing the force-frequency relationship of the adult atrial myocardium (**Figure. 11B-E**). iPSC-derived cardiomyocytes from the patient were subjected to a lengthy electrical conditioning procedure to imitate left ventricular hypertrophy. The active force was decreased in the mimicked

tissue during the first 6 weeks and after 8 months of cultivation (**Figure. 11F-H**) and had a high level of expression of genes related to hypertrophy (**Figure. 11I**)

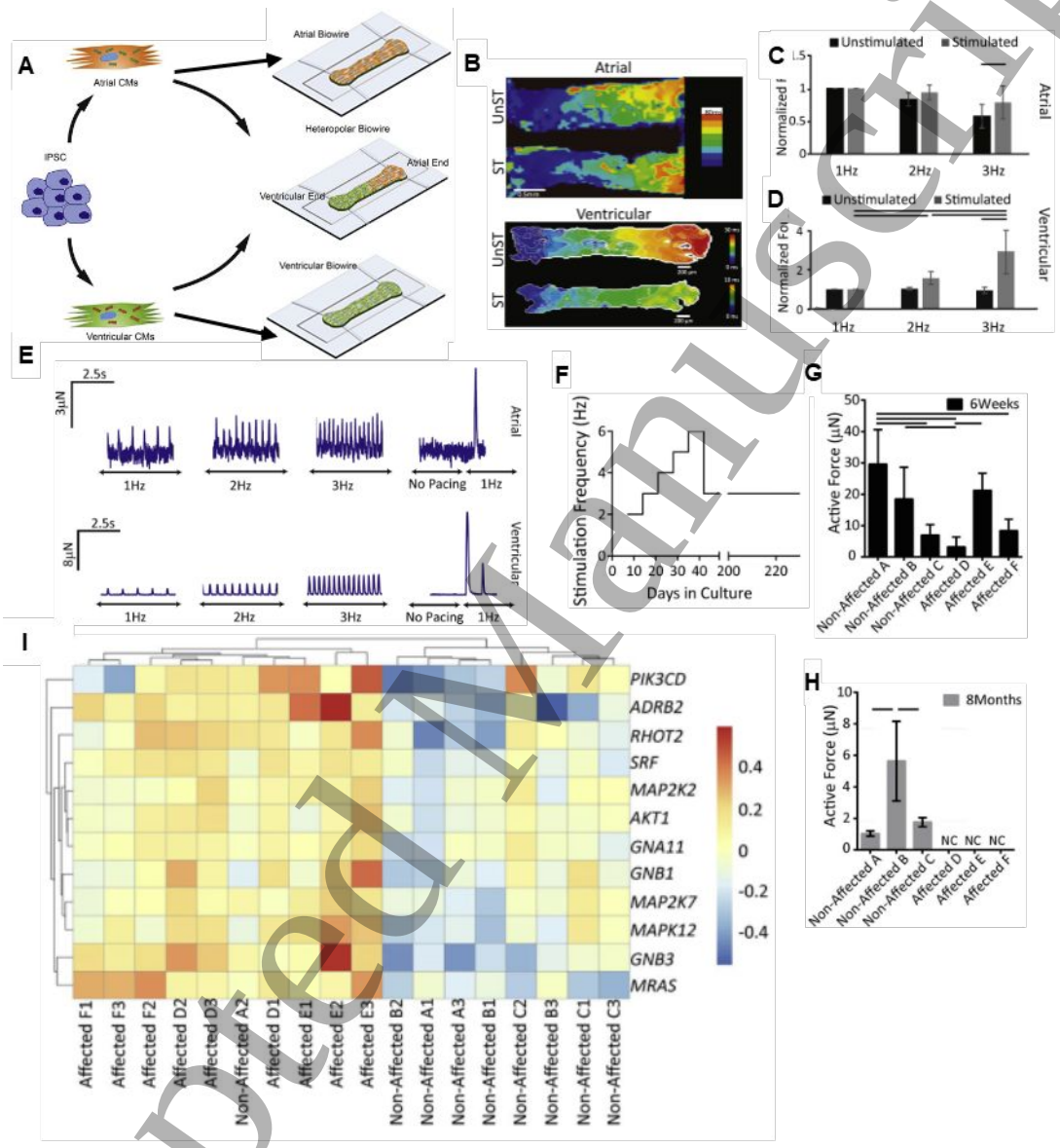

Figure. 11 Polymer scaffolds for cardiac tissue generation and disease modeling. (A) Schematic diagram of a HOC constructed from patient-derived iPSCs with atria, ventricles, and atrium-ventricle. (B) Conduction velocity maps of atrial and ventricular tissue on the constructed device. (C) The atrial device and (D) The ventricular devices with and without electrical regulation. (E) Representative force traces of atrial and ventricular tissue. (F) A chronic electrical modulation

protocol mimicking the chronic increase in cardiac load induced by hypertension. (G) The systolic function of iPSC-derived ventricular tissue after six weeks of culture in participants with/without ventricular hypertrophy. (H) Contractile function of ventricular tissue derived from iPSCs obtained in participants with and without ventricular hypertrophy after eight months of long-term culture. (I) Heatmap showing subsets of genes associated with cardiac hypertrophy. (A-I) Reproduced with permission. [220] Copyright 2019, Elsevier.

6. Conclusion and outlook

The concept of microfluidics has been proposed for more than a decade. It is considered an in vitro model that can transform traditional 2D cell culture systems or even replace animal experiments and has been applied in many fields. Currently, microfluidics is widely used in CVDs research including the establishment of normal organ and CVDs models, high-throughput drug screening, drug carrier preparation, and development of diagnostic and therapeutic devices. Functional products are being gradually developed and commercialized based on the gradual maturity of microfluidics. Therefore, both the market and demand for basic research have shown clear growth trends.

PDMS remains still a major material for microfluidic device fabrication. PDMS-based microfluidic devices are mostly based on supporting structures such as chambers and flow channels. However, cross-linkable and biocompatible hydrogels progressively reveal benefits in

the fabrication of OOC. Hydrogel-based microfluidic devices can be fabricated without support. In addition to selecting materials related to the application, the biological and physical factors of the microenvironment also need to be considered. The complex structure of the blood vessel, physiological force, the stress in the blood vessel, types of cells, and cytokines must be considered. Additional pathological mechanisms of CVDs have been explored based on advanced functional cardiovascular models.

Nevertheless, microfluidic devices have limitations. There are no standards for the design, production, and evaluation of microfluidic devices. Owing to the advantages of rapid fabrication, relatively uniform preparation, and biocompatibility, the introduction of hydrogels may gradually overcome this problem. However, more research is needed on the microstructural processing methods that support hydrogels. In addition, the poor mechanical properties, inadequate deformability, and toxicity of crosslinking agents still need to be addressed for hydrogels. Furthermore, traditional valves and pumps are difficult to integrate into microfluidic chips, and it is also difficult to control the liquid in channels precisely. The shape memory polymer with dual magnetic and optical responses can realize flow channel deformation under the synergy of magnetic field and near-infrared laser. Meanwhile, adjusting the Laplace pressure through the magnetic field and irradiation of near-infrared laser can accurately control the flow rate and angle of twist. During the deformation of shape memory polymers caused by external stimulation such as voice, they can spontaneously achieve the necessary tensile force and stress conditions for cardiovascular disease modeling. The precise control for cardiovascular drug screening and

testing can be achieved by pH sensitive shape memory polymers-based chip based on physiological pH variation. With the shape memory property, these polymers can also combine with 3D printing technology to realize 4D printing for manufacturing. Simultaneously, some shape memory polymers with dual responses such as ethylene-vinyl acetate copolymer have also been confirmed to be biocompatible, showing great potential in biomedical application.

In summary, microfluidic devices have developed rapidly since their application in CVDs research. High-fidelity cardiovascular models have been produced and applied in pathological research, drug development, and disease detection. However, microfluidic devices based on shape memory materials have rarely been reported. It is believed that the introduction of shape memory materials will improve from fabrication to application, and the existing problems discussed will gradually be overcome. This review contributes to the development of novel microfluidic devices and provides important assistance for the prevention and treatment of CVDs.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

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