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Microfluidic organ-on-a-chip models of human lungs and heart: A review

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Abstract

A micro-physiological system is another term for an organ-on-a-chip. Due to the idea's widespread use in drug discovery, precision medicine, and drug screening, interest in it has increased recently. The primary message of this article is to illustrate how artificial drug proof can closely imitate the human body in every regard. Important work for a biomimetic system of physiological organs based on a microfluidic chip using cell biology, engineering, and biomaterials technology. In addition, the use and effectiveness of the gut-on-a-chip, liver-on-a-chip, lung-on-a-chip, and heart-on-a-chip are examined. We have discussed the current status of this project, OOC prospects for the future, and opportunities for microfluidic devices and organs on a chip in this section.

Keywords: OOC- organ-on-a-chip; ECM- Extracellular matrix; PDMS- polydimethylsiloxane; PMMA- polymethylmethacrylate; cardiomyocytes; PILC- perfusion-incubator-liver-chip; interleukins; LOC- lab-on-a-chip

1. Introduction

The Organ-on-a-Chip (OOC) is a 3D multichannel integrated circuit, microfluidic cell culture that performs the same physiological responses and activities as whole organs or organ systems, also known as artificial organs. Optimizing such a system can be a long process. Organ-on-a-chip designs vary from researcher to researcher. Organs simulated by microfluidic devices include the brain, lung, heart, liver, kidney, bone, skin, cartilage, prostate, etc. The ability of organs-on-chips (OOCs), often referred to as micro-physiological systems or "tissue chips" (the terms are interchangeable), to provide useful information at various phases of the drug discovery and development process has sparked a great deal of interest in recent years. These cutting-edge tools might offer insights into healthy organ function and disease pathology and more precisely forecast the efficacy and safety of experimental medications in humans [1].

Organ-on-a-chip system is specifically designed to in vitro perform the shape and function of multicellular human organs on a microfluidic chip. Biological organ functions as well as the biochemical, bioelectrical, and biomechanical characteristics of cellular microenvironments and extracellular matrix (ECM) are examples of such devices [2]. Organ-on-a-chip systems, which may closely resemble in vivo tissues and serve as platforms for drug delivery assays and biological cell characterisation, have recently been shown to be feasible. In this review, particular examples of devices on a chip are given, including lungs, hearts, guts, and livers. The prospects for organs-on-a-chip are highlighted in addition to the shortcomings of current systems and fundamental manufacturing techniques for microfluidic devices.

1.1. Microfluidic Device

The Microfluidic Device is a chip used to study microchannels. Organ-on-a-chip is a microfluidic cell culture device fabricated by the microarray fabrication method, which contains continuously flushed chambers filled with living cells arranged to simulate tissue- and organ-level physiology. It also enables real-time high-resolution imaging and in vitro analysis of living cells' biochemical, genetic, and metabolic activities in the functional context of tissues and organs [3].

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It is of particular value in investigating molecular mechanisms of action, prioritizing lead candidates, testing toxicity, and identifying biomarkers. The basic design of the microfluidics device is given in Fig. 1[3]

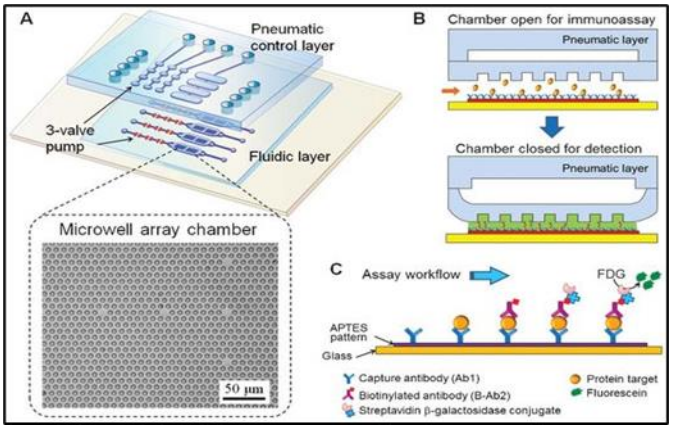

Figure 1 Design of the microfluidic device[3]

1.2. Design Concepts

The culture system requires control of the external and internal cellular environment. Combining micromachining and cell biology, organ-on-a-chip can control external parameters and accurately simulate physiological environments. Dynamic mechanical stress, on-chip shear, and concentration gradients are required [3]. Cellular patterning should also be implemented in ways that fully reflect physiological processes.

1.3. Microfluidics shear force

Force enables dynamic cell culture with perfusion micropumps that facilitate nutrient delivery and timely waste disposal. The dynamic environment in which cells reside is more comparable to in vivo environmental conditions than static culture. Furthermore, shear stress induces organ polarity. Importantly, organ-on-a-chip exerts the physical pressure necessary for the normal biological function of endothelial cells by activating signalling associated with cell surface molecules [3]. Similarly, the incorporation of liquids into organ-on-chip devices enables biological assessment at the individual body level.

1.4. Concentration gradients

At the microscale, fluids act predominantly as laminar flow, resulting in stable gradients of biochemical molecules that are spatially and temporally controlled. Several biochemical signals are controlled by concentration gradient biological phenomena such as angiogenesis, invasion, and migration. Microfluidics simulates complex physiological processes in the human body by using microvalves [3] and micropumps to alter flow rates and channel geometries to achieve stable three-dimensional (3D) biochemical concentration gradients to do.

1.5. Dynamic Mechanical Load

Normal daily organ pressures include blood, lung, and bone pressure. These pressures play an important role in sustaining mechanically stressed tissues such as skeletal muscle, bone, cartilage, and blood vessels [3]. In microfluidics, elastic porous membranes can be used to generate cyclic mechanical stress. This mechanical stimulation is considered a key factor in the differentiation of physiological processes.

1.6. Cellular Organizations

Human tissues require complex and ordered arrangements of multiple cells to form functional systemic interactions. Microfluidic patterning of control cells to build in vitro physiological models of complex geometries. Surface treatments, stencils, and 3D printing help structure the cells on the chip. The 3D printing process enables multi-level cellular structuring to form hydrogel scaffolds [3] with complex channels.

2. Organ-on-a-chip technologies

2.1. LUNG-ON-A-CHIP

2.1.1. Introduction of lungs

Lungs are the major organ of the respiratory system of humans and most other animals, including some snails and a few fish [19]. In mammals and most other vertebrates, two lungs are located near the spine on either side of the heart. Their function in the respiratory system is to extract oxygen from the air and transport it to the bloodstream, releasing carbon dioxide from the bloodstream into the atmosphere in the process of gas exchange. The overview of these lung diseases is shown in Fig. 1

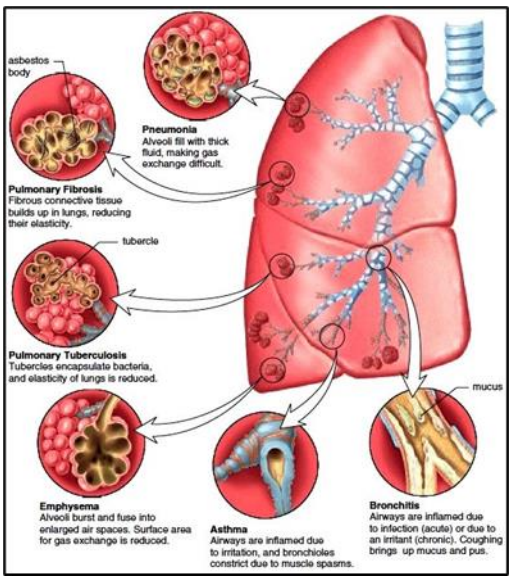

Figure 2 Diseases of the lungs

2.1.2. *Different techniques are used for the fabrication of lung-on-a-chip models*

Lithography-based microfabrication technology

Huh, et al. first designed a lung-on-a-chip model, polymer polydimethylsiloxane (PDMS), using soft lithography-based microfabrication techniques [5]. this model Consists of separate top and bottom microchannels Thin (10 mm) which are shown by fig no.2 (A, B), flexible, microporous, extracellular Matrix (ECM) coated membranes. The top of the ECM (fibronectin or collagen) coated porous membrane was made of human material alveolar epithelial cells and the underside contained human pulmonary capillary endothelial cells. time Alveolar cells are confluent, The upper channel was aspirated to produce an air-liquid Interface to alveolar cells. lower vessel Channel maintained continuous culture medium flow. Applying a cyclic vacuum to the two hollow chambers causes periodic mechanical stretching. Flexible PDMS sidewalls. A central porous membrane with an attached layer of cells was also stretched, mimicking physiological breathing movements[4]. Sellgren et al. designed another microfluidic lung model involving epithelial airways cell [7]. These are cultured at the air-liquid interface, lung fibroblasts, and microvascular endothelial cells in 3 vertically stacked compartments each, Each is separated by a nano-porous membrane given in fig no. 2 (D). Stucki et al. To mimic this, we created a reversibly connected alveolar-on-a-chip model Lung parenchymal microenvironment. To simulate the diaphragm in vivo, we used a micro diaphragm to stretch the alveolar barrier.

2.2. Thermoplastic methodology

A thermoplastic lung airway-on-a-chip model was created by Humayun et al [6]. utilizing solvent bonding and micro-milling techniques as shown in fig no. 2 (C). The chip replicated the interactions between smooth muscle cells (SMCs), epithelial cells (ECs), and supporting ECM as well as the lung airway microenvironment (Collagen, Matrigel, or a combination of both). The chip included media reservoirs for SMC culture in the upper, middle, and lower chambers, a suspended hydrogel layer in place of the membrane, and epithelial cells cultivated in the air-liquid interface, middle chamber, and lower chamber, respectively. The apparatus can be disassembled to collect the suspended hydrogel for

additional examination, which will help research how the SMC, EC, and cellular matrix interact to form chronic lung diseases (CLDs).

2.3. Bioprinting of 3D cells

Park et al. created an airway-on-a-chip model with a vascular network utilizing 3D cell bioprinting [20]. They created a vascular platform using polycaprolactone (PCL), lung fibroblasts (LFs) bio-ink, endothelial cells bio-ink, and PDMS. The VP, which had two side reservoirs for EC bio-ink and one for LF bio-ink reservoirs, was immediately 3D printed utilizing a cell-filled decellularized extracellular matrix (dECM) bio-ink. Microchannels for media flow and a location for PDMS bonding to the upper PDMS chip were used to separate.

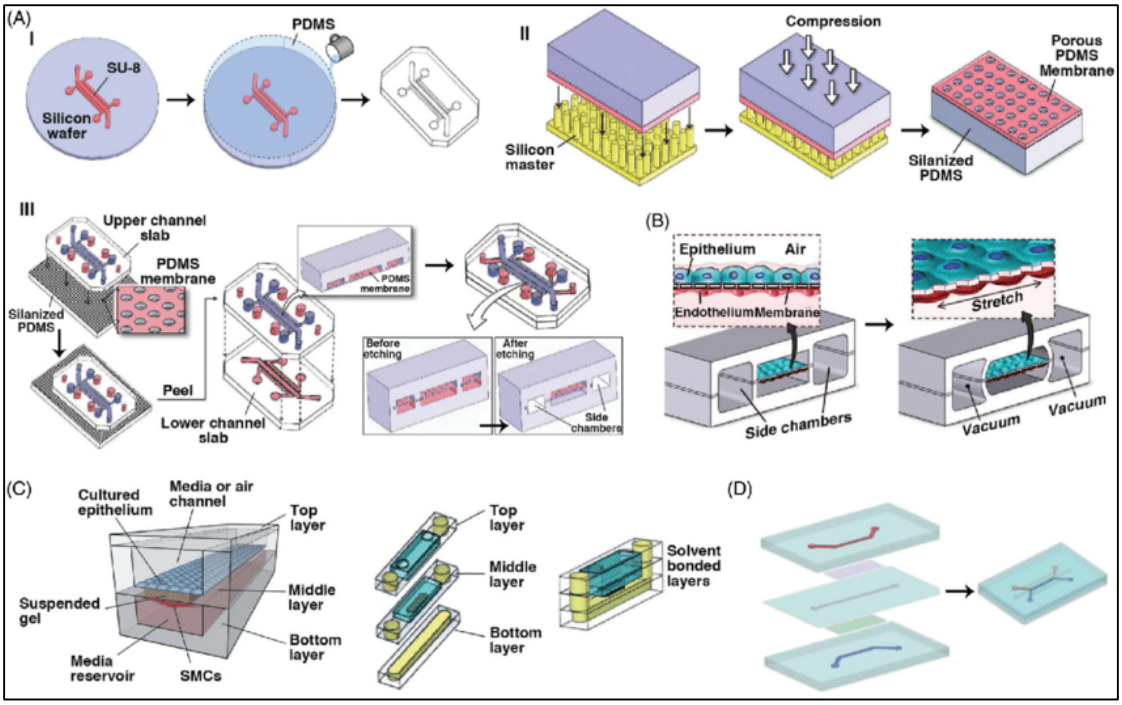

Figure 3 Development of a chip with a working lung[20]

2.3.1. Different studies using lung on a chip model

Lung on a chip is used to study the following aspects:

- Lung physiological studies
- Toxicological study
- Disease modeling

Lung physiological studies

According to the experimental criteria for simulating physiological activities within chips, researchers have created a range of models. According to Huh et al., the addition of air to the epithelial chamber allowed cells to survive for longer periods (>2 weeks) [5]. This also increased the production of pulmonary surfactants, which is significant because they are essential for maintaining alveolar-capillary contact. The Sellgren et al. model showed primary human tracheobronchial epithelial cells that were well-differentiated at the air-liquid interface

and duplicated physiological processes [7]. According to Stucki's study, repeated mechanical stretching has a big impact on how permeable the epithelial barrier is. Furthermore, compared to static mode culture, dynamic mode culture significantly increased the metabolic activity of the cultivated alveolar cells [21].

Toxicological studies

Organs-on-chip models are expected to be used in toxicity assessment shortly, perhaps replacing or at least minimizing the requirement for animal experiments. By moving nanoparticles through the membrane from the alveolar to the

vascular channel, the lung-on-a-chip mimicked the movement of particles over the alveolar-capillary interface [21]. This study demonstrated the importance of mechanical movements in the function of the lungs by showing how nanoparticle exposure and physiological breathing motions caused and accelerated harmful effects on the lung. These results are comparable to those of a study using an in vivo lung ventilation-perfusion model in mice.

Disease modeling

With the successful creation of disease models, the potential for using lung-on-a-chip models to research the pathophysiological mechanisms of many lung illnesses has increased. Table no.-1 lists respiratory conditions examined using lung-on-a-chip.

Table 1 Respiratory conditions examined using lung-on-a-chip

Disease	Studies using lung-on-a-chip	References
COPD	M-CSF was identified as a potential novel biomarker and therapy by reproducing COPD's characteristics.	[8]
ASTHMA	Reproduced asthmatic musculature response to viral infections, characteristics of asthma, and acute severe asthma exacerbation.	[8-9]
PULMONARY EDEMA	Identification of the pathophysiology of IL-2-induced pulmonary edema, the effects of natural breathing, and new pharmaceutical medicines.	[12]
PULMONARY THROMBOSIS	Pulmonary thrombosis pathophysiology Parmodulin-2 is a new antithrombotic drug (PM2).	[13]
LUNG CANCER	Physiological breathing motions' effects on the growth, invasion, and treatment resistance of cancer cells.	[14]
RESPIRATORY DISTRESS SYNDROME	Identification of liquid plug flows in the lung clinical surfactant drug's effects.	[11]
PULMONARY FIBROSIS	Exposure to gastric contents caused alveolar damage and pulmonary fibrosis to develop.	[10]

Applications of the lung on a chip are described in Fig no.-3

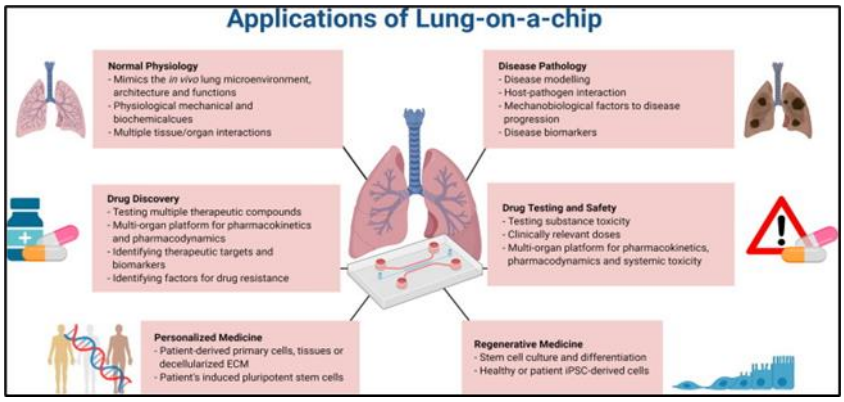

Figure 4 Applications of the lung on a chip

2.4. Heart-on-a-chip

One of the most crucial parts of the human body is the heart. It gives blood circulation the necessary capacity to nourish and oxygenate organs while also removing metabolic waste. Heart diseases have recently surpassed all other causes of death worldwide due to changes in eating habits and rising blood pressure. Establishing disease (or normal) models is necessary to investigate the pathophysiology of heart disorders and find viable treatments. Cell cultures and animal

models are often the two techniques that are employed the most. The animal model's physiological circumstances and organ functioning are dissimilar from those of a human. The responses and/or functionalities [22] of humans may not be precisely predicted by the outcomes of animal research. cardiovascular diseases are described in fig no.-4

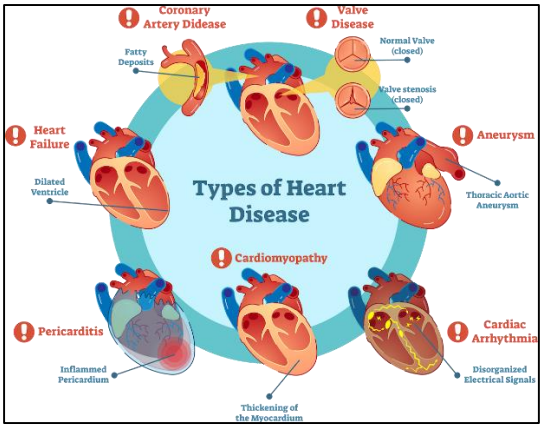

Figure 5 Cardiovascular diseases

2.4.1. The structures of heart-on-a-chip

One of the most crucial parts of the human body is the heart. Based on a survey of the literature, we suggest that a highly integrated heart-on-a-chip contains four components: a microfluidic chip, cells and microtissues, microactuators for physical and chemical stimuli, and microsensors for cell status monitoring. A heart-on-a-chip may not contain all four of these components in actual research, but the microfluidic chip and cells/microtissues are essential. Microactuators and microsensors have been incorporated into heart-on-a-chip in recent years thanks to improvements in manufacturing technology (such as 3D bioprinting). Microsensors are used to determine the condition of the cells, whereas microactuators are used to encourage the maturation and functionalization of cardiac cells. These four components are introduced in the following:

Microfluidic chips

One of the most crucial parts of the human body is the heart. In terms of soft lithography, PDMS is placed onto a ready-made mould [15]. The PDMS slab is then adhered to the glass substrate after being hardened and pulled off from the mould. The production of microstructures in polymers is possible due to laser etching. The high temperature of the laser causes materials to sublimate, and the laser's intensity can be used to control the depth of microstructures. In hot embossing, thermoplastic materials, such as PMMA, are pushed against the heated mould. PMMA is capable of acquiring microstructures when subjected to high pressure and temperatures. This method is simple to use and effective for mass production. However, the high temperature could lead to the deformation of microfluidic chips.

Microtissues

The microtissues are the heart-on-a-second chip's component. Microtissue can be classified as 2D microtissue or 3D microtissue depending on the dimension. A possible method for creating 3D microtissues is 3D bioprinting. The nozzle of a 3D printer is used to manufacture the cell-filled bioinks. For the 3D bioprinting of microtissues, bioinks are crucial. Hydrogels are currently the most widely utilized bioinks. Similar structures, ECM, porous characteristics, and excellent biomolecule transport are all present in hydrogels. They are therefore excellent options for creating microtissues and simulating the milieu in which heart cells thrive when used in vivo. After alteration, they have good biocompatibility and tunable stiffness. The creation of microtissues has proved to have considerable potential when using hydrogel-based 3D bioprinting. Hydrogel-based microtissues offer the best microenvironments for cell development and proliferation because of their high biocompatibility [18].

Microactuators

The microactuators, which are used to provide external stimuli to cells and microtissues, are the heart-on-a-third chip's component. The microactuator's primary job in a heart-on-a-chip is to stimulate the cells and microtissues and encourage their maturation. Cardiomyocytes are known to respond to electrophysiological stimulation. Cell synchronization and calcium processing can both benefit from electrical stimulation, which can also enhance the proportion of cells that beat spontaneously [15]. Electrical stimulation in a heart-on-a-chip typically takes place through

electrodes in contact with cells. CMs exhibit synchronous contraction in normal cardiac tissues via intercellular electrical transmission, producing a potent contraction force. It has been discovered that adding conductive materials, such as carbon nanotubes (CNTs), to cell culture scaffolds can facilitate electrical communication and the maturation of cardiac tissues.

Microsensors

The fourth component of a heart-on-a-chip is a microsensor. The purpose is to keep track of the health of the heart-on-a-cells chips and microtissues. In the beginning, cells were stained to define their condition and functions using various biochemical reagents. Recently, some scientists have started to include microsensors into heart-on-a-chip to non-invasively monitor the physiological status of cardiac cells. The fabrication of an elastic component in a heart-on-a-chip is one often employed technique. The CMs cultivated on the elastic component would result in the component's obvious deformation [15]. A microscope can see and record the deformation caused by the elastic component being bent by the contraction force of CMs. After that, image processing can calculate the contraction force. The whole fabrication procedure of heart-on-a-chip is described in fig no.-5[15]

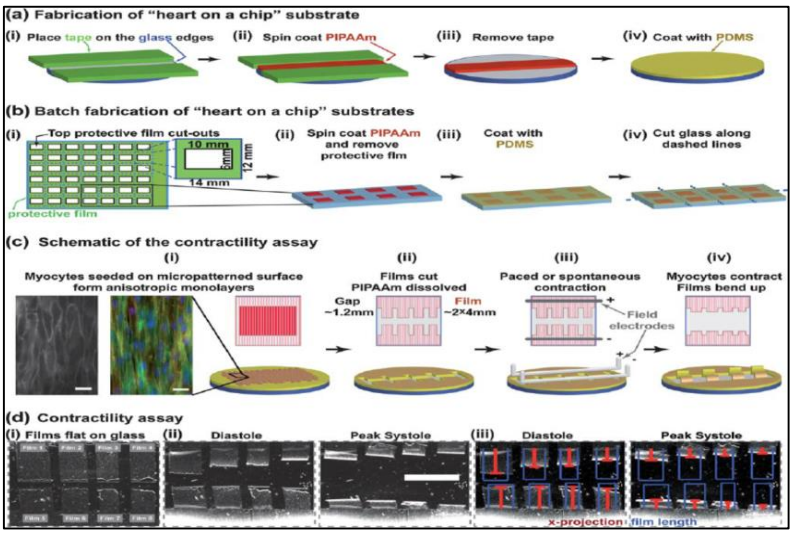

Figure 6 Fabrication procedure of heart-on-a-chip

2.5. Biomedical applications of heart-on-a-chip

Applications for heart-on-a-chip include physiological research, disease modeling, and medication screening. Heart-on-a-chip can more accurately imitate cellular microenvironments and supports the growth of microtissues when compared to conventional approaches. Heart-on-a-chip also makes it possible to track the condition of cells and microtissues in real-time. In this section, we go over the uses of heart-on-a-chip for studying physiology, modeling diseases, and screening drugs.

- **Physiological study**

A biowire framework was used to create a heart on a chip by some researchers. Glue is used to join two stretchy poly (octamethylene maleate (anhydride) citrate) (POMaC) polymer strands [15]. The chip was utilized to investigate how immature CMs responded to electrical stimulation. Electrical stimulation has been shown to modify electrophysiology and calcium transients, enhance electrical conductance, and increase myofibrillar microstructure. The heart and an intricate system of blood vessels make up the human circulatory system. With the use of a cardiac chip, blood pressure, a serious circulation issue, can be researched. The development of a chip by Sethu et al. that can precisely imitate hemodynamic stress led to the discovery that stress can aid in the maturation of CMs.

- **Disease modeling**

Disease modeling is a crucial step in understanding the causes of diseases and creating medications to treat them. The stenosis or obstruction of the arterial lumen brought on by coronary atherosclerosis is referred to as coronary heart disease. Myocardial infarction can develop as a result of coronary heart disease. To analyze the myocardial damage brought on by hypoxia, Wang et al. created a heart-on-a-chip with well-controlled oxygen levels. This allowed them to

better comprehend coronary heart disease and explore potential remedies. Heart failure may result from the accumulation of many fibrosis scar tissues caused by cardiac fibrosis. By adjusting the number of fibroblasts and collagen concentration in the created microtissues, Heart-on-a-Chip may replicate the cardiac fibrosis model [15].

These heart-on-a-chip models can be utilized to research the pathology of cardiac fibrosis, which paves the way for investigating the most efficient treatments. Arrhythmia, also known as altered heartbeat rhythm brought on by aberrant cardiac electrical activity, is another factor in heart failure. Arrhythmia and associated cardiovascular disorders have been model using the Heart-on-a-Chip technology. By using a heart-on-a-chip, Healy et al. created a 3D in vitro arrhythmia model. They looked at arrhythmia-related electrophysiological signals and contraction force. The reaction to a particular class of medications was also studied using the chip. Heart-on-a-chip research has also been used to simulate other cardiovascular disorders such as hypertension, hypotension, and hypertrophy [15].

- **Drug screening**

One of the most significant uses for heart-on-a-chip is drug screening. Heart damage or even heart failure may occur as a side effect of various medications. Therefore, research into drug-induced cardiotoxicity is necessary. Cardiotoxicity can be assessed using the efficient and precise in vitro model known as the heart-on-a-chip. According to Parker et al research employing heart-on-a-chip, isopropyl-noradrenaline has a beneficial effect on the contraction force of CMs [16]. A heart-on-a-chip was created by Ren et al. for high-throughput drug screening [17]. They selected doxorubicin and cyclophosphamide, which are clinically approved, as model medications to study dose-dependent cardiotoxicity, and ivabradine and carbachol as potential treatments to lessen cardiotoxicity. A 3D microtissue heart-on-a-chip was created by Wan et al. and used to study the cardiotoxicity of various medicines (antibiotics, antidiabetic drugs, and anticancer drugs).

- **Current challenges and future prospectives**

Despite the development of numerous organ-on-a-chip systems in recent years that can functionally imitate many tissues and organs, there is still considerable work to be done to produce these systems. In general, an organ-on-a-chip system's ultimate goal is to create human-on-a-chip systems employing human cells and tissues, which can eventually replace animal testing. To do this, organ-on-a-chip systems' viability, dependability, controllability, and observability must be increased so that they may serve as full platforms for drug toxicological and metabolic testing. The long-term stability of organ-on-a-chip systems needs to be confirmed for reliability. It might not cause any undesirable alterations to the properties of cells or the integrity of their genes or act as a possible inducer of cell cancer. Additionally, these systems must preserve structural integrity even after prolonged contact with chemicals and biological materials and solutions. To increase chemical resistance while maintaining high compatibility with soft lithography processes and biological cells, widely used PDMS materials must be modified or replaced. Organ-on-a-chip fabrication and screening automation both need to be standardized and improved for controllability. It is necessary to introduce bio-computer-aided design and manufacturing (Bio-CAD and Bio-CAM) to quicken the design process for organ-on-a-chip systems. Additionally, novel interconnection techniques to connect many organs-on-a-chip devices and approaches to better imitate an organ's inherent functionalities at various levels are highly wanted for simulating drug metabolism. The adoption of modularized methodology—a technique for quickly building highly dependable systems with a variety of needed functions—will be necessary for the designs of human-on-a-chip systems in the future. Various prebuilt components will be combined to create a workable system.

Abbreviations

- OOC- organ-on-a-chip
- 3D- Three dimensional
- ECM- Extracellular matrix
- PDMS- polydimethylsiloxane
- SMC- smooth muscle cells
- ECs- epithelial cells
- CLD- chronic lung diseases
- PMMA- polymethylmethacrylate
- CM- cardiomyocytes
- 2D- Two dimensional
- PILC- perfusion-incubator-liver-chip
- ILs- interleukins

- LOC- lab-on-a-chip
- POC- point-of-care

3. Conclusion

Microfluidics and tissue engineering have seamlessly combined to create OOC platforms, which use building blocks of human organs on biochips to mimic organ physiology and recapitulate organ functionality in vitro. These platforms have been created in conjunction with advancements in microtechnologies and the development of LOC devices in life science, particularly for POC applications. To bring this technology to the POC, effective and intimate collaboration between scientists, physicians, and engineers is required. To be adopted by clinicians and the pharmaceutical industry and to speed up patient treatment, we believe that future OOC devices for POC applications must be multi-organ platforms that are personalized and use patient-derived cells or tissue biopsies to recapitulate the complexity of each patient on a biochip.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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