

Progress of 3D bioprinting of heart tissue

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Abstract: In recent years, the rapid development of bio-3D printing technology has brought great changes and breakthroughs to the medical field. Biological materials and cells can be assembled in an orderly manner according to a specific structure and composition through bio-3D printing technology, so as to achieve the manufacture of highly customized artificial organs and tissues. The emergence of this technology not only provides a new treatment for patients with tissue and organ damage, but also provides a new experimental model for the development of medical research and biological science. The heart is one of the most important organs in the human body, which is of great significance for the simulation and drug development of heart diseases. Over the past three decades, there have been significant advances in bioprinting research and applications for the heart. Through a deep understanding of the structure and function of the heart, combined with the advantages of bioprinting technology, in vitro simulation of the heart can be achieved. The purpose of this paper is to review the research and application of bio-3D printed heart in the past 30 years, in order to provide reference for related.

Keywords: The development of 3D organ printing technology, Artificial organ, Material development for printing organs

1. Introduction

3D printing technology was born in the 1980s, and is now known as "one of the important symbols of the third industrial revolution", and its related research has set off a new development boom at home and abroad. At present, 3D printing technology has become increasingly mature in many aspects of the medical field, but bioprinting is the forefront of the current research of 3D printing technology, and it is also the most dynamic and promising direction of 3D printing technology [1]. 3D bioprinting technology (under the control of computers, through computer-aided design (CAD) and computer-aided manufacturing (CAM), the seed cells, biomaterials and biomolecules are precisely arranged in space to form bioactive tissues or organ substitutes that are close to, the same as, or even more functional than the target tissues or biological organs [2]. This new technology has attracted much attention by solving the bottleneck problem in traditional medical problems, greatly improving the level of medical development, and becoming a remarkable life science frontier. This paper mainly summarizes the principle of 3D bioprinting technology, the methods and characteristics of 3D bioprinting technology, the application technology of 3D bioprinting technology, the research and application of 3d printed heart parts, and the challenges of 3d bioprinting organs in clinical application.

2. Biological 3d printing technology principle

Bioprinting is an innovative way to build three-dimensional structures using biological materials and biological cells. The core principle is to slice the three-dimensional model of the target organ in layers through computer-aided design software,[3] and then stack biological materials and cells layer by layer through the print head, and finally achieve the construction of the entire organ.

In 3D bioprinting, it is first necessary to obtain a three-dimensional model of the target organ. This can be done by obtaining patient organ data through medical imaging technology (such as CT, MRI, etc.), [4] or by virtual modeling through computer-aided design software. The three-dimensional model is then sliced into two-dimensional layers with a certain thickness to facilitate stacking layer by layer. Secondly, the appropriate biomaterials and cells are selected for printing. A biomaterial is usually a biocompatible material, such as bioceramics, natural polymers or synthetic polymers. Cells are a key component of organ construction and can be stem cells, adult cells or cell lines.

During the printing process, the printhead stacks biological materials and cells layer by layer in a predetermined layer and structural manner. Some printing technologies use droplet inkjet methods to control the position of materials and cells by controlling the movement and temperature of the nozzle. Other printing technologies use lasers or light-cured resins to achieve interlayer bonding.

After the printing is completed, with proper treatment and culture, the biological material and cells can gradually fuse and differentiate to form a complete organ with biological functions. This process can take a while, depending on the complexity of the organ and the characteristics of the cells.

The principle and operation process of bioprinting technology can be adjusted and optimized according to different printing equipment and materials. The application of this technology in the field of life science is increasingly extensive, and has become one of the most promising frontier technologies in the 21st century.

3. Biological 3d printing technology classification

In recent years, bioprinting technology has developed rapidly, bringing many innovations and breakthroughs to the biomedical field. According to different application requirements and printing principles, 3D bioprinting technology can be classified into the following types.

3.1. Inkjet printing technology

Inkjet printing technology is a more common technology in bioprinting, which draws on the working principle of inkjet printers. The technology works by injecting biological material into tiny nozzles and then squirting the material layer by layer to a specific location by controlling the nozzle's movement trajectory and jet speed, ultimately forming the desired organ structure. This technology has the advantages of low cost, simple operation, but the resolution is low, can not achieve more fine structure printing, more limited to its development is that the inkjet bioprinting technology of biological materials must be liquid.

3.2. Light curing printing technology

Photocuring printing technology is a kind of fine printing technology through the photocuring of photosensitive materials. This technology uses a light source of a specific wavelength, such as ultraviolet or blue light, to irradiate a photosensitive material and cause it to undergo a polymerization reaction and cure. By controlling the position and intensity of the light source, higher resolution printing can be achieved. This technique is widely used in fields such as making miniature organs and cell culture models.

3.3. Bio-jet printing technology

Bio-jet printing is a technology that jets biological materials directly to a specific location in liquid or semi-solid form. The technology uses high-pressure air streams or mechanical forces to spray biological material to a target location to form the desired structure. This technique is suitable for applications such as printing complex structures and thin-film structures[5].

3.4. Biomelt deposition printing technology

Biomelt deposition printing technology is a kind of printing technology by heating and melting biological materials in a solid form. The technology works by heating the biological material in the nozzle, melting it, and depositing the melted material layer by layer to the target location by controlling the trajectory of the nozzle's motion. This technique is suitable for printing large-sized organs and tissues, but requires more fine-grained control due to the effect of the high-temperature environment on the cells.

The classification of 3D bioprinting technology described above is only part of it, and new classifications will continue to emerge as the technology continues to evolve. For different application needs, it is very important to choose the right printing technology, which will directly affect the quality and functional performance of the printed organ structure. Therefore, an in-depth understanding of the characteristics and scope of application of various printing technologies is of great significance to promote the development of bioprinting technology.

4. Biological 3d printing technology application field

4.1. 3D printed blood vessel

Nowadays, with the increase of cardiovascular and cerebrovascular diseases, the clinical demand for vascular grafts is becoming increasingly prominent. As early as the 1950s, artificial blood vessels were successfully manufactured and widely used in the replacement of large artery vessels. However, traditional artificial blood vessels have not made breakthrough progress in the manufacture of veins with a diameter less than 6mm. Today, the capillaries created by 3D bioprinting technology use mesenchymal stem cells and endothelial cells collected from patients as a source of "ink." LEE and his colleagues overcame the difficulty of small blood vessels and capillaries transplantation by directly producing blood vessel tissue with a diameter of 1mm using a printer. KANG et al. [6] removed about 5g of fat from the rhesus monkey body, extracted adipose mesenchymal stem cells to make the "ink" required for 3D bioprinting, and then printed blood vessels with special equipment, and replaced a section of about 2cm abdominal aorta in the monkey body, and the printed blood vessels were integrated with the Rhesus monkey's own abdominal aorta 1 month after surgery. In addition, patients who transplant traditional artificial blood vessels need to use anticoagulants for life, and 3D printed blood vessels reduce this time to 5 days after surgery, after which no drug treatment is required.

4.2. 3D printed skin

Due to the limitations of current medical technology, many burn patients cannot return to normal skin after treatment. At the same time, autologous transplantation is often used for traditional skin transplantation, which is limited to minor skin injuries and requires patients to undergo a second surgical procedure. The principle of printing skin: First select a piece of healthy skin, use 3D bioprinting technology to induce the proliferation and differentiation of pluripotent stem cells, and then let these cells as "ink" through the 3D bioprinter to print out a bioactive skin. Since the pluripotent stem cells that induce regeneration come from the patients themselves, they can effectively avoid immune rejection.

At present, the Laboratory of Regenerative Medicine at Wake Forest University in the United States has developed a method of using 3D bioprinting technology to directly print skin cells on the injury wound, which is not only suitable for a large area of skin injury, but also allows patients to avoid the pain of second surgery. First, a laser built into the 3D bioprinter takes measurements of the shape and size of the wound, and then precisely prints specific skin cells at the site of the injury. The results of experiments using this method in mice have shown that repairing damaged areas through 3D bioprinting can make them heal quickly and safely.

4.3. 3D printing is used to repair bone damage

The process of 3D bio-printing in repairing bone tissue injury is generally to print bionic scaffold materials first, then plant seed cells on scaffold materials to form cell-scaffold material complex, and finally implant the cell-scaffold material complex into the bone defect site. While the biomaterials are gradually degraded, the implanted bone cells are constantly proliferating. So as to achieve the purpose of repairing bone tissue defects. PATI et al. printed scaffolds using PCL/PLGA/ β -TCP as raw materials, implanted human bone marrow mesenchymal stem cells into the scaffold material, and then implanted the cell-scaffold material complex into the bone defect site of mice. [7]After a period of time, a large number of bone-like tissues were generated at the site where the cell-scaffold material complex was implanted, and the defect site was almost completely repaired. However, at present, after the 3D printed scaffold materials and seed cells are implanted in the defect site, they can eventually have effects but also rely on the blood circulation system to transport nutrients and take away waste, and the failure of the blood supply establishment in the defect site will not only make the transplanted cell-scaffold material complex ineffective, but will become a foreign body attacked by the body's immune system. Therefore, whether blood vessels can be induced after the cell-scaffold material complex is a necessary condition for the successful repair of bone tissue injury. The study of Che Pengcheng et al. showed that the composite scaffold material made of PVA and carrageenan by physical blending technology and repeated freezing-thawing method was easy to induce vascularization at the injured site, and this study provided a new idea for the exploration of materials for 3D bioprinting to repair bone injury.

4.4. 3D printed organs

4.4.1. Early bioprinted organ research

In the past three decades, 3D bioprinting technology has received extensive attention and in-depth research in the field of organ regeneration. Early bioprinted organ research has focused on exploring printable biomaterials and the feasibility of printing technologies.

In terms of biological materials, early research mainly used natural biological materials such as gelatin, sodium alginate, etc., as printing materials. These materials have good biocompatibility and biodegradability, and can provide suitable growth environment for cells. However, due to the mechanical properties and low printing accuracy of these materials, the accurate reproduction and functional expression of organs are limited.

On the other hand, the early bio-3D printing technology mainly uses traditional printing methods such as inkjet printing and filament textile printing. These methods, while simple and easy to implement, face challenges when printing highly complex organ structures. The complex shapes and fine details of organs are difficult to print accurately, which is difficult to achieve the reproduction of organ structure and function.

Although there are some limitations and challenges in early bio-3D printed organ research, they have played an important role in promoting subsequent research[8]. The early research laid the foundation for the later development of bio-3D printing technology, and provided important experience and guidance for the further realization of printing complex organs.

All in all, early bioprinted organ research has focused on exploring suitable biomaterials and printing methods to achieve accurate organ replication and functional expression. Despite some limitations and challenges, the early research has played a crucial role in the subsequent development of bioprinting technology. With the continuous advancement of technology, the research of bio-3D printed organs has developed by leaps and bounds in recent decades, providing many cutting-edge and innovative solutions for the medical field.

4.4.2. Technological advances in 3d bioprinted organs

The technological progress of 3d biopharmaceutical printing organs is an important development direction in the field of 3d biopharmaceutical printing in the past three decades[9]. With the continuous innovation and improvement of technology, the preparation method of bioprinted organs has been continuously improved.

In the technological advancement of 3d bioprinted organs, material selection is an important aspect. With the deepening of research, scientists continue to explore new materials for the preparation of bioprinted organs. Currently commonly used materials include biodegradable polymers, extracellular matrix and bioceramics. These materials have good biocompatibility and bioactivity, and can provide an ideal extracellular environment to promote cell growth and tissue regeneration.

In addition, the preparation technology of bioprinted organs is also constantly innovating. Traditional 3d printing technology is mainly based on the Additive Layer Manufacturing (ALM) principle, by stacking materials layer by layer to build the structure of the organ. In recent years, with the development of multi-component printing technology, scientists are able to print multiple materials at the same time, achieving more complex and fine organ structures. For example, the use of cell printing technology can directly inject cells during the 3d printing process, making the constructed organs more biocompatible and bioactive.

In addition, tissue engineering methods and biological guidance have also been widely used in the preparation of bioprinted organs. By utilizing the principles of tissue engineering, scientists can control the directed differentiation of cells and tissue growth to achieve a natural simulation of the shape and function of organs during growth and development. At the same time, the guidance of biology can help scientists better understand the growth and development mechanism of organs, so as to guide the preparation and application of organs.

To sum up, the technological progress of bioprinted 3d printing organs in the past three decades has achieved remarkable results. Major breakthroughs have been made in material selection, preparation technology and clinical applications, bringing great potential and opportunities for the development of the biomedical field. With the continuous improvement and perfection of the technology, it is believed that the application of bioprinting organs will play an increasingly important

role in future development.

4.4.3. The application of 3D printed organs

In recent years, China has become the world's second largest organ transplant country after the United States in terms of the average annual number of organ transplants, and China can successfully complete more than 2,000 liver transplants and 5,000 kidney transplants every year. However, the demand for liver transplants is increasing by more than 4,000 cases per year, and the demand for kidney transplants is increasing by more than 10,000 cases per year. At the same time, patients who have undergone allogeneic organ transplantation have to take immunosuppressants for a long time, and the quality of life of patients after surgery has also been seriously affected[10]. The emergence of 3D bioprinting technology makes organ reconstruction possible.

Organovo, an American company, recently used 3D bioprinting technology to print 20 layers of liver parenchymal cells and liver stellate cells, two main types of liver cells, to make a miniature liver organ. The miniature liver organ produced by 3D printing technology, although only 4mm wide and 0.5mm deep, has many functions of a natural liver, which can filter blood, transport nutrients and metabolism, and can synthesize albumin, cytochrome P450 and cholesterol[11]. However, the natural liver has a complex blood vessel system, and the artificial liver's complex blood vessel system cannot be completely printed through 3D bioprinting technology. Therefore, how to improve the accuracy of 3D printing has become an urgent problem for researchers to solve. In addition, GAETANI et al. successfully produced a patch for repairing myocardial infarction by mixing cardiac progenitor cells and hyaluronan/hydrogel with 3D bioprinting technology.

5. Research and application of 3d printed heart parts

5.1. Research status of bio-3D printing technology for heart parts

The heart is one of the most important organs in the human body, and heart disease is one of the leading causes of death worldwide. Traditional heart disease treatments include medication, surgery and heart transplantation, but these methods have certain limitations and risks. In recent years, the emergence of bio-3D printing technology has brought new possibilities for the treatment of heart disease.

The research on bioprinting of heart parts aims to replace diseased heart tissue by creating artificial heart parts that match the patient's own heart. This customized treatment provides better biocompatibility and physiological function, reducing the risk of rejection and surgical complications.

In the current study, the bioprinting technology mainly uses cellular biomaterials and biological scaffolds to manufacture heart parts. First, cellular biomaterials are custom manufactured with specific shapes and structures through 3D printing technology. These cellular biomaterials can be stem cells, fibroblasts, or other heart-related cells.

In addition, the selection of biological scaffolds is also a key step. Biological scaffolds are biodegradable materials used to support and guide cell growth and tissue regeneration.[12] The biological scaffold can be made of natural materials such as collagen and gelatin, or synthetic materials such as polylactic acid casein. These biological scaffolds can provide support structures for cells to attach and grow, and gradually degrade after tissue recovery is complete, providing a better environment for new tissue.

In recent years, studies have shown that 3D bioprinting technology has made some important advances in the study of heart parts. For example, researchers have successfully used 3D printing technology to manufacture parts such as heart valves[13], heart muscle tissue, and heart vessels. These bioprinted heart parts have good biocompatibility and physiological function, and can provide effective cardiac support and treatment in vivo.

However, although 3D bioprinting technology has made some progress in the research of heart parts, there are still some challenges. First of all, how to choose the appropriate cell biomaterials and biological scaffold materials is still a problem that puzzles researchers. Different materials have different properties, and it is necessary to consider their mechanical properties, biocompatibility and degradation characteristics.

In addition, the technology for bioprinting heart parts also needs to be further optimized. Current bioprinting technologies still face some manufacturing challenges, such as resolution, material

tunability, and cell localization. These technological challenges require more research and development to address.

In general, 3D bioprinting technology has made some progress in the research of the heart part, providing new opportunities for heart disease treatment. Future research should continue to strive to improve the bioprinting technology to improve the manufacturing efficiency and quality of heart parts and further expand its prospects for clinical applications.

5.2. The prospect of 3d bioprinting of heart parts in clinical applications (emphasizing functions and applications, supplementing specific cases)

The prospect of 3D bioprinting technology in clinical application is very broad, and the 3D bioprinting technology of heart part also has great potential and prospect. As heart disease continues to increase and the need for heart transplant surgery becomes increasingly urgent, 3D printing technology provides new treatments and solutions for heart patients.

First, 3D bioprinting of the heart can provide a customized solution. Everyone's heart is not the same shape and structure, so traditional standardized prosthetics may not be fully adapted to each patient's needs. Through bioprinting technology, it is possible to customize the printing of prosthetics or stents suitable for the structure and function of the heart according to the specific conditions of the patient. This personalized treatment can improve the outcome of surgery and reduce the risks and complications of surgery.

Secondly, the bio-3D printing technology of the heart part is of great significance in improving heart transplant surgery. At present, heart transplantation is the final option for treating severe heart disease, but many patients cannot get a heart transplant in time due to the shortage of donor hearts and rejection. Through bioprinting technology, heart organs similar to the patient's own tissue can be printed, solving the problem of traditional donor hearts. This synthetic heart organ could provide longer lasting treatment and avoid rejection.

In addition, the bioprinting technology of the heart part can also be used to simulate cardiac pathologic processes and evaluate the efficacy of drugs. By simulating the printing of the patient's heart organs, it is possible to better understand the mechanism of the occurrence of heart lesions and evaluate the effectiveness of different drugs in cardiac treatment. This simulated organ could provide clinicians with more accurate and real-time treatment options, thereby improving the precision and effectiveness of treatment.

However, the bio-3D printing technology of the heart part still faces some challenges and problems in clinical application. First of all, the current bioprinting technology still has certain limitations, such as the selection of printing materials and biocompatibility issues. In addition, the printing of heart organs requires higher accuracy and stability, which also puts higher requirements on 3D printing equipment and technology. Therefore, further research and improvements are needed to overcome these technical limitations.

In short, the bioprinting of heart parts has a wide range of prospects in clinical applications. Through the application of personalized treatment methods, [14]improved heart transplant surgery and simulated cardiac pathologic processes, bioprinting technology provides new treatment options and solutions for patients with heart disease. However, further research and efforts are still needed to advance the development and application of this field.

5.3. Cardiac bioprinting in heart disease treatment

In terms of the research status of 3D bioprinting technology for heart parts, many researchers have made certain progress in using different types of biomaterials and cells to print heart-related tissues. For example, 3D bioprinting can be used to print structures similar to heart vessels, cardiomyocytes and heart valves. These printed heart tissues can form functional tissues through self-assembly of biomaterials and cells, with potential applications in transplantation and alternative therapies (Table 1).

In terms of the prospects of biological 3D printing technology in clinical applications of the heart, researchers have conducted some clinical trials to verify the safety and effectiveness of biological 3D printing of heart tissue[15]. These experiments indicate that bio 3D printed heart tissue can be regenerated smoothly in vivo and has good biocompatibility and functional recovery ability. This provides a new option for applying biological 3D printing technology to the treatment of heart diseases.

Table 1: Some questions about heart research

Serial number	Expound	Sum up
1	Heart disease is one of the most common disabling and fatal diseases worldwide	Heart disease is disabling and fatal.
2	Conventional cardiac therapies have limitations, such as limited transplant sources and biocompatibility issues with stents	Traditional treatments have limitations
3	3D bioprinting could be used to treat heart disease.	3D bioprinting technology for heart disease treatment.
4	Many researchers are using 3D bioprinting to study heart-related tissues.	Researchers are using 3D bioprinting to study heart-related tissue.
5	3D bioprinted heart tissue has potential applications for transplantation and alternative therapies	3D bioprinted heart tissue has a promising application.
6	Several clinical trials have shown the safety and effectiveness of 3D bioprinted heart tissue.	Clinical trials have shown that 3D bioprinted heart tissue is safe and effective.
7	Current bioprinting techniques are still unable to fully replicate the structure and function of natural heart tissue.	3D bioprinting can't replicate natural heart tissue exactly.
8	The selection of biomaterials and cells and the optimization of printing parameters require further research.	Research on biomaterials, cell selection and printing parameters.
9	The long-term effects and safety of 3D bioprinted heart tissue require a more rigorous and comprehensive evaluation	Evaluation of the long-term efficacy and safety of 3D bioprinted cardiac tissue.
10	3D bioprinting of heart parts has great potential in the treatment of heart disease.	3D bioprinting has potential in the treatment of heart disease.
11	Further research is needed to overcome current technical challenges and ensure the successful application of 3D bioprinting in clinical practice.	Further research is needed to overcome technical challenges and successfully apply to clinical practice.

However, 3D bioprinting of heart parts still faces some challenges in the treatment of heart disease. First, current bioprinting technologies are not yet able to fully replicate the structure and function of natural heart tissue. Secondly, the selection of biomaterials and cells and the optimization of printing parameters still require further research. In addition, the long-term effects and safety of bioprinted heart tissue also need to be evaluated more rigorously and comprehensively.

In short, the bioprinting technology of the heart part has great potential in the treatment of heart disease. Through continuous research and development, we are expected to achieve the use of 3D bioprinting technology to prepare highly complex and functional heart tissue, providing better treatment options for patients with heart disease. However, further research is needed to overcome the current technical challenges and ensure the successful application of 3D bioprinting in clinical practice.

6. Challenges and opportunities in bioprinting

Seizing the new round of development opportunity of bioprinting, the research of developing China's bioprinting technology into the international advanced level has a very broad development prospect. At present, the biological 3D printing technology, opportunities and challenges coexist, such as: single cell, multiple cells, cell clusters of controlled three-dimensional space transport, accurate positioning, arrangement and assembly, as well as the biological manufacturing process on the cell damage and biological function of the impact. Due to the diversity of complex organ structure and function of the human body, the particularity of cells and biological materials, the manufacturing process is more complex, involving the selection of a variety of materials and the adjustment of printing parameters. The current technology is still unable to fully realize the complex structure and function of real organs; The biocompatibility and functional stability of 3d bioprinted organs is also a challenge. Since the printing process involves the interaction of cells and biological materials, it is necessary to ensure the survival and function of cells. In addition, the long-term stability of biological

organs is also a problem that needs to be solved, because after implantation, biological organs need to maintain their structure and function for a long time; The cooperation of multiple interdisciplinary disciplines such as materials science, manufacturing science, biology and the application of multi-nozzle bio-3D printing equipment will become the trend and mainstream of the future development of the discipline, and is also the core of the realization of complex organ manufacturing. In addition, there are ethical and legal challenges in clinical application. The implantation of bioprinted organs into human body involves a series of ethical and legal issues, such as the legality of organ sources and the informed consent of patients. These problems need to be properly solved in parallel with the development of technology.

In the near future, with the continuous deepening of research, the integration and breakthrough of various disciplines, and the breakthrough of many scientific problems, bio-3D printing will become a very simple, easy and rapid medical technology, and will also become the most accurate, fast and effective means of repair in clinical practice, and ultimately be efficiently applied in clinical practice to benefit patients.

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