3D Printing and Bioprinting for Cardiovascular Tissue Engineering

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Recent decades have seen a plethora of regenerating new tissues in order to treat a multitude of cardiovascular diseases. Autografts, xenografts and bioengineered extracellular matrices have been employed in this endeavor. However, current limitations of xenografts and exogenous scaffolds to acquire sustainable cell viability, anti-inflammatory and non-cytotoxic effects with anti-thrombogenic properties underline the requirement for alternative bioengineered scaffolds. Herein, we sought to encompass the methods of biofabricated scaffolds via 3D printing and bioprinting, the biomaterials and bioinks recruited to create biomimicked tissues of cardiac valves and vascular networks. Experimental and computational designing approaches have also been included. Moreover, the in vivo applications of the latest studies on the treatment of cardiovascular diseases have been compiled and rigorously discussed.

cardiovascular disease | tissue engineering | 3D bioprinting | cell therapy

1. Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally; according to World Health Organization (WHO) more than 17.9 million people die from such causes every year—an estimated 31% of all deaths worldwide [1]. Simultaneously, the estimated healthcare cost for cardiovascular disease in Europe reaches to 169 billion € [2]. It is well established that more than 80% of CVD deaths occur in low-and middle-income countries compared to high-income countries [3][4]. Therefore, the need to reduce the economic burden is not debatable. CVD includes a wide group of complex disorders, namely peripheral arterial disease (PAD), coronary heart disease (CHD), cerebrovascular disease and rheumatic heart disease [2].

Current high-cost therapies include conventional tissue engineering, cell therapy and medical approaches [5][6]. In valve repairment, autografts are widely used by harvesting from autologous cell sources, namely parts of a patient's body with the advent of low risk of thromboembolism and prosthetic valve infection [7]. The end stage heart failure is treated by allografting a heart from a donor, while some valve replacement surgeries employ bovine or porcine heart valves. Xenografts, though, impute other undesirable properties, including cytotoxicity and calcification [8]. Conclusively, the aforementioned grafts have their set of drawbacks, including shortage of donor organs, mechanical mismatches, anticoagulation therapy and immune rejection [9]. Synthetic valves and vascular grafts can also be implanted to treat CVD; however, the high structural durability and low rate of re-operation is outweighed by the increased risk of anticoagulation complications in patients with long life expectancy [10]. Small-diameter vascular grafts (SDVGs) constructed from synthetic polymers and decellularized matrices are promising

in the field of reconstructive surgery; however, further evaluation and in vivo implementations are mandatory in order to be applied to therapeutic approaches in CVD [2].

Therefore, one showcasing solution will be the overarching focus on identifying alternative tissue treatments that preserve natural tissue without deleterious side effects.

The increased demand on recovery of damaged cardiovascular tissues in combination with the demand for low-cost but effective constructions, heralds new methods in tissue engineering [11]. Three-dimensional (3D) printing and bioprinting are the recent promising methods that successfully regenerate various organs, scaffolds and blood vessels, which can be used for replacing partly or thoroughly natural organs in the human body [12][13]. With the advent of additive manufacturing, 3D bioprinting technology employs a layer-by-layer approach which enables precise control over multiple compositions (biomaterials) and spatial distributions (cells) resulting in architectural construction accuracy [14]. Biomaterials that have been employed in 3D printing for cardiovascular tissue engineering are major natural or synthetic hydrogels, or decellularized matrices in order to mimic the dense vascular network that supports the cardiac tissue, by providing an interconnected porous network that enables cells to migrate, proliferate and receive vital nutrients and adequate oxygen supply [2][11][15][16]. This takes into consideration the survival distance limitation for cells which is no further than 100 ÷ 200 μm away from blood vessels [17]. Alginate and collagen are the most commonly used hydrogels in bioprinting following gelatin methacrylate, fibrinogen and gelatin [18]. Cell viability, proliferation and morphology after printing are crucially affected by characteristics of the selected bioink [19]. The challenge of bioink design is the improvement of printability without detracting cell viability [20]. Biomaterial-based hydrogels are capable of cell encapsulation. The major cell types that integrate the cardiac tissue are cardiomyocytes, endothelial cells, smooth muscle cells and fibroblasts. Furthermore, computational simulation with a patient's anatomical data and features is compulsory for an integrated patient-specific bioprinted construct.

2. From 3D Printing to the New Era of 3D Bioprinting

2.1. Three-Dimensional Printing—Additive Manufacturing

The terms "3D printing" and "additive manufacturing" are usually confused. According to the American Society for Testing and Materials (ASTM), additive manufacturing is the process of joining materials using 3D model data layer by layer in contrast to subtractive manufacturing methodologies, such as traditional machining [21][22], whereas "3D printing" is defined as object fabrication through the deposition of a material with the help of a print head, nozzle or another printer technology [21]. The two terms are often used synonymously, especially considering they are low end in price and/or overall capability [21].

Moroni et al. tried to define "3D printing" based on the appearance of the printing process with cell-laden inks [23]. According to them, in this additive manufacturing technology a jet of binder is directed at a powder bed to define a pattern. A slice of solid material is formed after the binding of the solvent to the powder. A new layer of powder is set and by repeating this process the scaffold is build layer by layer. This definition was based on the first patent for

3D printing of Sachs et al., in which a binder solution was deposited in a powder bed according to a Computer Aided Design (CAD) model [24]. However, in the recent research of Marti et al., 3D printing is referred as the process of additive production of 3D objects, which starts from a 3D digital model [25]. Thus, the term 3D printing is still used instead of additive manufacturing for the sake of simplicity.

Computational Stage—Preparation of 3D Printing

Computational methods are widely used to study tissue engineered constructs. However, the entrance of computer designing is essential in the field of tissue bioengineering due to personalized medicine. The main idea is to produce a specialized human part for each specific patient, thus contributing to a more efficient and low-cost tissue engineering [26]. The main purpose of this strategy is to create a tissue engineered scaffold with similar mechanical and biological properties concerning the defective tissue [20]. This procedure includes the following steps.

The tissue defect is digitally visualized using imaging machines, particularly CT scan (Computer Tomography scan), MRI (Magnetic Resonance Imaging) and ultrasound scan. The next step is to create a scaffold that readily supports the formation of the new tissue. The architecture of the scaffold can be meticulously designed using Computer Aided Design (CAD), a feasible way to manipulate the design parameters of tissue porosity, dimensions and biological-related properties. The scaffold can now be integrated into the 3D model of the defective tissue. Subsequently, bioink will be fabricated by assessing the proper materials, the cell types and bioactive molecules, and the location and requirements of the injured area of the patient. Eventually, using bioprinting technology the cell seeded construct can be manufactured and then placed in a cell culture or implanted directly into the patient [27].

Three-dimensional printing enables the precise fabrication of computationally designed scaffolds with increased accuracy, flexibility and reproducibility. These methods allow scientists to conduct low-cost parametric studies in order to create the most functional construct for the addressed medical issue. The structural design and the mechanical behavior under different conditions of the small diameter composite vascular grafts can easily be optimized by using computational methods.

Computational methods integrate the 3D printing methods and provide the following advantages:

- more accurate techniques to model the scaffolds (e.g., image-based modelling using micro-CT), as an extra feature to reinforce the personalised medicine
- more detailed mechanobiological models to simulate different types of tissues
- more similar to in vivo conditions simulations of the scaffold’s properties and behavior under different conditions
- minimized size effect during scaffold modelling
- reduced experimental expenses (elimination of trial-and-error techniques to find the suitable scaffold)

- simultaneous estimation of the scaffold degradation and tissue regeneration in the time-dependent simulations [28][29].

2.2. Bioprinting

Three-dimensional bioprinting has emerged as an advanced and novel process in the field of tissue engineering and regenerative medicine. Notably, researchers' interest in bioprinting is also evident in their efforts to define the term. According to Groll et al., Moroni et al. and Lee et al., bioprinting could be defined as the production of bio-engineered structures through computer-aided transfer processes in order to pattern and assemble living and non-living materials with a prescribed 2D or 3D organization [30][31][32].

Currently, the use of biomaterials in regenerative medicine and cardiovascular engineering faces challenges, including host inflammatory responses, immunogenicity, biomaterial degradation and toxicity of degradation products, that may affect the long-term function of the engineered tissue construct [33][34][35]. Therefore, the innovative biomaterial-free method of bioprinting is gaining attention in the scientific society.

Three-dimensional bioprinting has been expected to be a promising method in tissue engineering because of the ability to control precisely the geometry and the amount of biomaterials during construct fabrication [35]. More specifically, this technique can fully incorporate cells into hydrogels that satisfactorily mimic the microenvironment of the extracellular matrix (ECM) and directly print onto the targeted host location [36]. In cardiovascular engineering there are multilateral problems that need to be overcome in order to achieve an integrated 3D bioprinted model [37][38].

Cell viability and vascularization of printed tissues are key factors which determine the effectiveness of bioprinted tissues. Another impediment that needs to be overcome is the promotion of mass transfer of nutrients and oxygen into bioprinted scaffolds, including adhesion molecules and factors that induce angiogenesis [39]. The vascular tissues need substitutes with specific physical characteristics. For example, high stiffness is not favourable like in the cases of bone and cartilage tissues. On the contrary, vascular substitutes must be malleable enough to be shaped correctly in order to regenerate vessels [18]. A schematic representation of the bioprinting process and most recruited bioprinters is illustrated in **Figure 1**.

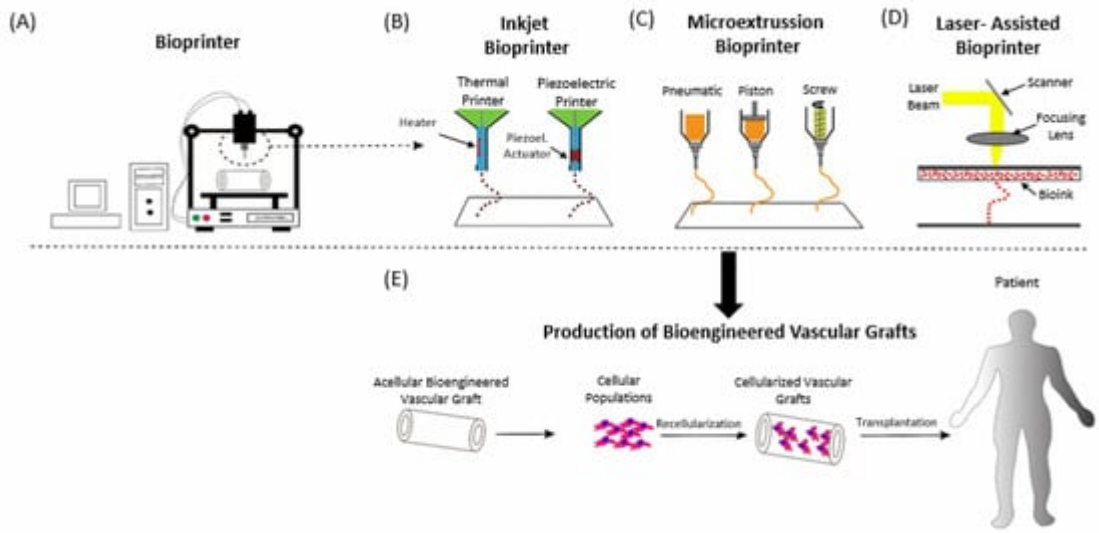

Figure 1. Schematic representation of bioprinters. (**A**) Development of bioengineered vascular grafts with computer assisted software. Different types of bioprinters (**B**), microextrusion bioprinter (**C**) and laser-assisted bioprinter (**D**). (**E**) Production and transplantation of bioengineered vascular grafts. Piezoel: Piezoelectric.

3. In Vivo Applications of 3D Bioprinting in CVD

The main aim of 3D bioprinting is to design functional tissues or parts of organs in situ for in vivo applications. The pivotal problem in terms of in vivo application is the compliance of cells and hydrogels, where cells need to precisely assemble themselves together exactly after printing, to achieve an adequate cell viability and vascularization of printed tissues. Cell–cell interaction for oxygen and nutrient interchange is mandatory to promote paracrine activity and homeostasis [40].

3.1. Cell Viability and Biocompatibility

Adequate cell viability is more than debatable in printed scaffolds due to high shear stresses on the cells delivered from extremely small diameter needle tips [41]. Cell viability decreases as the wall shear stress increases and the nozzle diameter of the deposition 3D bioprinting system decreases [42]. Overall, researchers should carefully select the cell density, the alginate concentration and dispensing pressure, and the coaxial nozzle size to obtain optimum cell viability on 3D bioprinted constructs [43].

Moreover, the estimation of cell viability is of paramount importance in order to decipher the interactions and stimulations between bioinks and cells, in a way that cells will satisfactorily adhere and survive [44]. Available methods for the evaluation of cell viability in 3D printed constructs are the common assays of trypan blue, release of LDH (lactate dehydrogenase), early apoptosis detection (Annexin V), Tetrazolium dye (MTT), study of DNA damage at the chromosome level (micronucleus assay) and other similar methods [45]. The optimum method to estimate cell viability, though, is fluorescent-based probes in the form of live/dead cells. Liu et al. utilized an improved in situ microscope method, where 3D constructs were split in order to investigate layer by layer the fluorescent number of cells and categorize live/dead cells [46].

Regarding in vivo studies, Bejleri et al. used bioprinted cardiac patches composed of native decellularized ECM and human cardiac progenitor cells (hCPCs). This specific combination of bioinks achieved cell viability of over approximately 75% [47]. Moreover, patches were retained on rat hearts and show vascularization over 14 days in vivo, indicating that the patches integrate well with the native myocardium inducing nutrient exchange with implanted cells.

Ong et al. suggested that in vivo implantation promoted vascularization of 3D bioprinted cardiac patches with engraftment into native rat myocardium [48]. In this study, multicellular cardiospheres consisted of human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs), human adult ventricular cardiac fibroblasts (FBs) and human umbilical vein endothelial cells (ECs) assembled using a 3D bioprinter, and simultaneously the cell viability, in this patch, surpassed 90%.

Biocompatibility and circumvented cell cytotoxicity are mandatory in the field of 3D bioprinting materials as mentioned before. The in vivo study of Maxson et al. supports the potential use of a collagen-based bioink as an alternative for a tissue engineered heart valve implant [49]. Results of this study showed increased host cellularization potential, biocompatibility and biomechanical behavior results. The bioink was successfully printed with MSCs and showed remodeling.

3.2. Microarchitecture and Composition of 3D Construct Vascular Network

Three-dimensional bioprinting technology aims to combine different cell types and biomaterials heading to an enhanced cell repopulation within a 3D structure. An integrated vascular network is necessary to achieve cell viability in cardiovascular 3D printed tissues. Via that network, the influx and outflow of nutrients, metabolites and regulatory molecules are achieved. Large blood vessels ensure the flow in remote distances, whereas molecular diffusion occurs between capillaries and the surrounding tissue. In addition, the size of pores of 3D bioprinted constructs plays a major role for host cell recruitment. A pore size scaffolding >1 mm enables diffusion of nutrients until sufficient vascularization is achieved [50]. In the study of Shao et al., large scale constructs with mesoscale pore networks (100 μm to 1 mm) were successfully printed and the encapsulated vein endothelial cells were spread more efficiently compared toconstructs without mesoscale pore networks [50]. In hydrogel-based scaffolding the preferable pore size of 1–150 μm provided structural support and adequate nutrient diffusion; specifically, in the study of Zhang et al., 120–150 μm pore size resolution encouraged cells to gradually migrate into the microfibers to form a layer of confluent endothelium [51].

In the study of Maiullari et al. hydrogels and cells were printed layer by layer, thus emulating the native tissue architecture. Specifically, heterotypic human umbilical vein endothelial cells (HUVECs) and induced pluripotent cell-derived cardiomyocytes (iPSC-CMs) were transplanted hypodermically in mice and the bioprinted engineered tissue effectively merged with the host vasculature by providing enriched vascular networks [52].

Angiogenic factors play a pivotal role in the neovascularization of bioprinted cardiac tissues [53]. Notably, the tissue-engineered constructs need blood vessel development in the core. The Vascular Endothelial Growth Factor (VEGF) is used as such a regulator. VEGF regulates the vascular development and its therapeutic overexpression

by the cells loaded into the construct. In this way, blood vessels sustainably grow directly into the core of the bio-engineered graft. Poldervaart et al. underlined the VEGF secretion from gelatin microparticles into the 3D constructs and the following vascularization was widely examined [53]. Further in vivo studies, regarding the effectiveness of 3D bioprinted materials, need to be implemented in order to overcome the challenge of VEGF overexpression with the intertwined side effect of vascular tumor growth (angioma) in the myocardium and other tissues [54].

3.3. Improved 3D Prined Grafts in Animal Models

Three-dimensional bioprinted cardiovascular grafts require robust control over a range of physical and mechanical properties that will enable bioink tailoring to a specific clinical application [41]. Overall, the greatest post-implantation challenge of 3D construct in cardiovascular tissue engineering is to maintain integrity and durability over time. Therefore, studies with animal models are necessary to improve the sustainability of 3D bioprinted cardiovascular grafts.

In the study of Melchiorri et al., 3D fabricated poly (propylene fumarate) PPF graft maintained mechanical properties, long-term mechanical support and physical parameters of graft (inner diameter and wall thickness) post six months of implantation in the venous system of the mice-selected animal model, while no thrombosis, aneurysm or stenosis were obtained [55]. In a rat animal model, 3D printed polyvinyl alcohol (PVA) mimicking 3D vascular grafts showed increased postoperative endothelialization during 30 days with significant decreased thrombogenesis [56]. Another study regarding a porcine animal model, utilized tissue engineered vascular graft (TEVG) with optimum anatomically fit and hemodynamic properties and adequate physical properties in a low-pressure venous system within one month [57].

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