3D Bio Printing in Cardiac Surgery

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Introduction:

Background:

Humankind has always been intrigued by the prospect of prolonging our lives. This intrigue has led to the rapid progression of technology in medicine throughout the world. With 3D printing technology becoming more accessible and reaching consumer markets, we are beginning to see its incorporation into medical practice.

The goals of this study are to explore new advancements in 3D bio printing and apply those advancements to three major cardiac procedures. These procedures will include cardiac transplantation, valve replacement and congenital cardiac surgery.

Literature review:

Throughout medical history we have seen significant advancements in the treatment of cardiac pathologies. According to the US department of Health and Human Services (2022), 3817 cardiac transplants were performed in the United States in 2021. While important, these numbers are dwarfed by the number of cardiac valves replacements in the United States. Approximately 182,000 valve replacements are performed each year in the United States (IData Research, 2020). Congenital cardiac defects effect approximately 40,000 newborns each year and around ¼ of these defects require surgical intervention and hospitalizations. The interventions associated with these defects account for approximately $5.6 billion in hospital costs (CDC, 2022). All of the above procedures can be limited by either a lack of available resources or limitations of

anatomical imaging. The purpose of this study will be to look at how advancements in 3D bio printing can provide these necessary resources and guide cardiac procedures. The study will analyze new advancements in 3D bio printing and attempt to apply them to the cardiac procedures mentioned above.

Early 3D bio printing in health care was utilized mainly for the creation of prosthetic limbs, surgical implants and equipment (Bartlett, 2013). New research is now indicating that bio printing of entire organs, tissue patches, and on-demand bio-implants could also be feasible (Bartlett, 2013; Lee, 2016; Schubert, Langeveld & Donoso, 2013). This is due to new techniques being developed for bio printing including laser-based bio printing, droplet-based bio printing, extrusion-based bio printing, and stereolithographic-based bio printing (Vikram Singh et al., 2019). These advancements could take significant pressure off the transplant sector and increase patient access to lifesaving procedures. They could also decrease patient wait times when specific implants or tissues are required. This literature review aims to apply these advancements in 3D bio printing to the field of cardiology. This review will specifically focus on cardiac transplantation, valve replacement and congenital cardiac surgery while outlining the potential benefits of 3D bio printing through increasing available resources and guiding procedures in cardiology. Cardiology is an area of medicine that could benefit significantly from these new advancements in bio printing. Cardiac valve replacements are a common procedure for aging adults in North America. New bio printing processes could allow for the on-demand generation of a biological valve from the patient's own tissues as well as the rapid generation of synthetic valves with perfect dimensions. Through the use of echocardiographic imaging, 3D models of the patient's heart can be generated, allowing for exact measurements and pre-procedure adjustments to be made (Vashistha et al., 2019; Tuncay and van Ooijen, 2019). Congenital surgeries could also receive benefit through procedural planning using 3D printed models of the

patient's heart before surgery (Vukicevic et al., 2017; Anwar et al., 2018). Finally, bio printing cardiac tissue could allow for the generation of perfect HLA-antigen matched heart transplants without the need for a deceased donor or immunosuppressive medications (Wang et al, 2021).

Methods:

Study Design:

This study will cover the history of 3D bioprinting, descriptions of previous and new methods for 3D bioprinting, use in transplantation in adults and children, use in valve replacement in adults and children, use in congenital cardiac surgery in adults and children, use in education, and current challenges in 3D bioprinting.

Keywords:

3D Bio Printing, Cardiac Transplants, Cardiac Valve Replacements, Congenital Cardiac Surgery

Search Strategies Utilized:

Databases searched will include Sage Journals Online, BMJ Journals Online, and AccessMedicine. Articles published in English from 2010 – present will be reviewed. Selected articles will be screened through reviewing titles and abstracts. More key words will be added when required to increase available data. Duplicates will be removed as required. Articles that will be reviewed include articles that report on new methods in 3D bio printing and their applications for cardiac transplants, valve replacements and congenital cardiac surgery. Articles that provide information on the availability of cardiac transplants, the availability biologic cardiac valves and limitations of current imaging techniques for congenital cardiac surgery will be included as well. These articles can include prospective cohort studies, case reports, case series, textbooks, systematic reviews and randomized controlled trials

Discussion:

History of the technique

First invented in the 1980's by Charles Hull, 3D printing is becoming more commercially accessible and affordable (Schubert, van Langeveld & Donoso, 2013). Forms of 3D printing were initially used for custom-creating prototypes and spare parts for various industries using materials like plastic, metal and rubber (Bartlett, 2013). These initial applications used a process called stereolithography. Stereolithography is a process where successive layers of material are printed on top of each other to create 3D objects. These objects are typically built using Computer Aided Design (CAD) and can be distributed to other users. Using stereolithography, the creator can specify certain criteria for the object such as thickness, color and texture (Schubert, van Langeveld & Donoso, 2013).

The year 2013 saw some early integration of 3D bio printing into health care when researchers at Cornell University used the technology to create an artificial ear. Later that same year, doctors at the University of Michigan successfully printed and implanted a precisely modelled bioresorbable tracheal splint onto a baby's left bronchial tube after it began suffering from tracheobronchomalacia (Bartlett, 2013).

With assistance from doctors, engineers and scientists, new printing techniques have been developed. These techniques are generally classified under seven categories including: vat photopolymerization, material extrusion, material jetting, powder bed fusion, binder jetting, sheet lamination, and energy deposition (Jin et al., 2021). In terms of health care, vat

photopolymerization, material extrusion and material jetting are currently the most commonly used techniques in 3D printing of organ models.

Many of these techniques are capable of using bioink for biofabrication. Bioinks are soft materials that contain living cells that are essential for bioprinting. A very common type of bioink is known as the hydrogel because it is a highly hydrated polymer network capable of providing a tissue-like environment for cells. Current materials being used to generate hydrogels include gelatin, methylcellulose and Pluronic polymers (Fu, Angeline, & Sun, 2021).

These advancements in 3D printing technology have increased its adoption into many hospitals around the world. The Ottawa Hospital was the first in Canada to open an integrated 3D printing program that has been used for education, surgical planning and further research. The Hospital General Universitario Gregorio Maranon in Madrid, Spain, has a special laboratory designed to accelerate the development of 3D printing technology within the hospital. Sawai Man Singh Hospital in Jaipur, India has already used 3D printing technology for over 22 surgeries (Abdullah & Reed, 2018).

Description of the Techniques:

Vat Photopolymerization:

Vat photopolymerization uses photosensitive polymer liquid materials that are cured layer by layer using a specific light to form an object. The materials used are often called photopolymers. These materials will change their state from liquid to solid when exposed to specific light sources like UV light (Fonseca et al., 2020; Jin et al., 2021). These photopolymers will often be epoxy based or hybrid materials with increased temperature resistance, higher moisture absorption and increased shrinkage compared to acrylate based materials. Some newer techniques for vat photopolymerization include digital light processing (DLP),

microstereolithography (MSL), continuous liquid interface production (CLIP) and computed axial lithography (CAL). Vat photopolymerization methods have higher manufacturing accuracy compared to other techniques but materials needed can be more expensive (Jin et al., 2021; (Sharma & Goel, 2018).

Material Jetting:

Material jetting, also known as inkjet printing, is another technique based on liquid curing. This process involves liquid material being ejected through a print nozzle as a droplet or liquid jet. Droplets are deposited in layers from the bottom-up and rapidly cured by a curing device. This curing device will often be UV light (Jin et al., 2021). Different variations of this process exist including continuous streaming, drop-on-demand and acoustic or microvalve printing. Continuous streaming involves a continuous jet of material that breaks into a stream of droplets while forming the object. Drop-on-demand removes the stream and only places droplets at desired coordinates as they are required. Acoustic and microvalve methods that use acoustic waves or solenoid pumps to eject droplets rather than piezoelectric or thermal actuators (Fonseca et al., 2020; (Sharma & Goel, 2018).

Material Extrusion:

Material extrusion is similar to jetting in that they both require a nozzle to extrude filamentous materials to construct a structure. The materials used for this process include thermoplastics such as polylactic acid. These materials are initially solid but are heated to a molten state within 3D printer before being released from the nozzle. As the materials cool, they harden back into a solid and form the 3D printed object. Advancements in material extrusion are working toward utilizing softer materials in printing and reducing heat (Jin et al., 2021; (Sharma & Goel, 2018). Pneumatic and displacement-based printers use precise pressure to extrude materials rather than

heat. Among the extrusion-based 3D printers, these are typically preferred for bio printing because precise pressure control is necessary for maintaining cell viability (Fu, Angeline, & Sun, 2021).

Powder Bed Fusion:

Powder bed fusion is based on powder-based materials that are bound together using high powered lasers or electron beams. The powders are melted and bound together to create a solid object. The most common method for this process is known as laser sintering. Powdered materials include metal, ceramics, plastics, glass and granular materials. This process is very quick and stable when compared with other methods for printing. However, the accuracy and finish can be reduced. This can be mitigated slightly by decreasing powder size. Due to deficiencies with accuracy and finish, this process is generally reserved for creating organ models or molds (Jin et al., 2021; Sharma & Goel, 2018).

Binder Jetting:

Binder jetting uses both powder-based materials and a jetting head but does not use lasers. Instead, it uses binder substances to bring together the powdered materials (Sharma & Goel, 2018). A common binding material is gypsum. Binder jetting has a high printing speed and most binder jet printers are small, quiet and low cost. A major downside to this method is that the glues used are often toxic. This reserves binder jetting primarily for organ models or molds (Jin et al., 2021).

Sheet Lamination and Directed Energy Deposition:

Sheet lamination uses metal or paper sheets that are glued together and cut into a final shape. The sheets are then joined together by ultrasound welding to generate an object. Directed energy deposition uses metal or wire powder that is deposited with the help of a robotic arm with a

nozzle. The material is then hardened using a laser, electronic beam melting or plasma arc. Neither of these processes are currently seeing much use in bio printing but may in the future (Sharma and Goel, 2018).

Need for Transplantation in Adults:

In 2021, the Health Resources and Service Administration reported that 45,354 organ transplants were performed in the United States. This represented a 5.9% increase in transplants over the previous year, suggesting that the need for organ transplants is still present. Approximately 17 people die per day while awaiting lifesaving transplants. Of these transplants, 3,817 were cardiac while 3,502 individuals remained on the waiting list (HRSA, 2021).

The ACC/AHA guidelines for cardiac transplantation in adults include refractory cardiogenic shock requiring intra-aortic balloon pump counterpulsation or left ventricular assist device (LVAD); Cardiogenic shock requiring continuous intravenous inotropic therapy (i.e., dobutamine, milrinone, etc.); Peak VO_2 (VO_{2max}) less than 10 mL/kg per min; NYHA class of III or IV despite maximized medical and resynchronization therapy; Recurrent life-threatening left ventricular arrhythmias despite an implantable cardiac defibrillator, antiarrhythmic therapy, or catheter-based ablation; End-stage congenital HF with no evidence of pulmonary hypertension; Refractory angina without potential medical or surgical therapeutic options (Alraies & Eckman, 2014).

According to the Health Resources and Service Administration, in 2020, approximately 1700 children received organ transplantation. Despite this number, approximately 1900 children under the age of 18 remain on the US national transplant waiting list (HRSA, 2021). The unfortunate reality is that some patients are required to wait months to years for life changing organ transplantation due to a lack of availability. For patients requiring cardiac transplantation, this

can be devastating. Pediatric cardiac transplantation represents approximately 14% of all cardiac transplants (Schweiger et al., 2015). The differences in anatomy and physiology between patients make cardiac transplants uniquely challenging as younger pediatric patients generally require smaller transplants (HRSA, 2021).

Pediatric cardiac transplants are generally reserved for pediatric patients suffering from end-stage heart failure. This typically develops due to the presence of congenital ventricular dysfunction or cardiomyopathy. Initially, these patients can be managed with medication but will require transplantation in the near future as heart failure progresses. After transplantation occurs, these patients are required to remain on post-operative immunosuppressive therapy (Schweiger et al., 2015).

Developments in Bioprinting of Organ Transplants:

This increasing demand for organ transplantation combined with a deficiency of organ donors has led to significant advancements in 3D bio printing. Many of these advancements involve the generation of biodegradable scaffolds. These scaffolds are designed to provide shape, mechanical support and microarchitecture for cellular growth and reorganization. This is accomplished by manipulating available oxygen, nutrients and biomolecules for promoting cell growth and differentiation in various areas of the scaffold (Wang et al., 2017). However, no control method is currently available that ensures an optimal microenvironment throughout the scaffold at all times. One of the major challenges of these scaffolds is that once cell density reaches a certain point, optimal cell growth is no longer possible. Current solutions include the use of 3D printed auxetic metamaterials that are able to change their volume and porosity. These changes can promote the flow of increased culture medium toward the cells and waste away

from cells as cell density increases. These scaffolds are printed using the hydrogels mentioned previously (Wang et al., 2017).

The three most well-established techniques for bio printing of organ transplants include laser-induced forward transfer, inject bio printing and robotic dispensing. LIFT involves depositing cells onto a receiving substrate through the use of a laser pulsed beam that is applied to a donor slide or ribbon containing source inks. These inks can include hydrogels and cells. By controlling the movement of the substrate, 3D constructs can be built layer by layer (Wang et al., 2017). Michael et al (2013) utilized the LIFT technique to construct a fully cellularized skin substrate by adding fibroblasts and keratinocytes on top of an acellular dermal substrate. In vivo experiments involving this cellularized construct showed that the printed cells survived well and neovascularization was observed (Michael et al, 2013).

Inkjet bioprinting combines cells with calcium chloride to form bioinks that are injected into an alginate-collagen solution. Upon being injected into the solution, the bioinks form calcium-alginate complexes and solifidy (Wang et al., 2017). Xu et al (2013) was able to fabricate a pie-shaped 3D construct consisting of stem cells, smooth muscle cells and endothelial cells using a thermal inkjet printer. The results on in-vivo experiments indicated that the cells were able to survive, proliferate and maintain cellular function on this 3D construct. Even more impressive was that the stem and endothelial cells were capable of differentiating into bone and blood vessels after respective implantation into mice. The major challenges of inkjet bioprinting include decreased cell viability and frequent nozzle clogging. Decreased cell viability can occur due to critical shear stress that is generated as bioinks pass through the nozzle. While passing through the nozzle, cells within the bioinks can adhere and aggregate within the nozzle leading to clogging (Wang et al., 2017).

Robotic dispensing was inspired by the strong performances of LIFT and inject bioprinting as robotic bioprinting methods are typically easier to use and have good compatibility with various bioinks (Wang et al., 2017). Liu et al (2017) developed a printer with the ability to individually and simultaneously eject seven types of bioink. This printer was designed to overcome the limitation of previous printers that were only able to eject one type of bioink for each printing process (Liu et al, 2017).

Use in Valve Replacement:

Valvular heart disease (VHD) is associated with significant mortality in aged populations. VHD can be associated with aortic regurgitation, mitral regurgitation, mitral stenosis, tricuspid regurgitation, tricuspid stenosis along with coronary artery disease, rheumatic fever and bacterial endocarditis. When VHD occurs, the heart valves become either too contracted to open-up entirely or incapable to close effectively (Vashistha et al., 2019). These pathologies can cause blood to flow in the reverse direction (regurgitation) or prevent blood from effectively leaving the heart chamber (stenosis). Initially, the heart is able to compensate for these changes through hypertrophy of muscle, dilation of heart chambers or both. However, these changes may result in hypoxic conditions leading to myocardial infarction. Prosthetic valve replacement is the only exclusive solution available to compensate for the original valve in these circumstances (Vashistha et al., 2019).

Aortic valve replacements have been performed since the 1950's. The use of biologic prosthesis is increasing in surgical aortic valve replacement (SAVR). Two main options currently exist for replacement including biologic valves and mechanical valves (Head et al., 2017). Use of both options is possible at any age of adulthood. However, current guidelines suggest the use of mechanical valves in patients less than 60 years of age while biologic valves are generally seen

in patients above 60 years. Mechanical valves are generally preferred in younger patients due to less structural valve deterioration over time. This deterioration often leads to required reoperation for patients with bioprosthetic valves. However, patients with mechanical valves require long term anticoagulation while bioprosthetic do not (Head et al., 2017; Isaacs et al., 2015). These risks associated with anticoagulation are the reason for hesitancy regarding mechanical valves in patients greater than 60. The risk for bleeding and reduced chance that reoperation will be required make mechanical valves the less optimal choice for older patients (Head et al., 2017).

In terms of bioprosthetic valves, multiple options are currently available for replacement. The most commonly used bioprosthetic valves are xenografts. These xenografts are usually bovine or porcine in origin and have been pretreated with fixatives and detergents to improve durability and reduce immunogenicity (Kostyunin et al., 2020). These xenografts can be surgically implantable or transcatheter heart valves (THV). THV's are delivered through minimally invasive surgery using the femoral artery, radial artery or through a small insertion between the ribs and then unfold inside the affected valve. Homografts from cadavers or obtained during transplantation are rarely used due to limited availability and difficult implantation. Autografts are more commonly seen in pediatric patients with congenital heart malformations (Kostyunin et al., 2020). The Ross Autograft Procedure involves moving the patient's own pulmonary valve to the aortic position and placing a homograft or xenograft into the pulmonary position. This procedure is difficult to perform with multiple perioperative risks. Structural valve degeneration generally occurs around 7 to 8 years after bioprosthetic valve implantation but varies depending on the patient's individual risk factors. These factors can include the hypertension, hyperparathyroidism, diabetes mellitus, end-stage renal disease and prosthesis-patient mismatch (Kostyunin et al., 2020).

Advances in 3D bioprinting have allowed for the possibility of printing a structurally and functionally identical heart valve. The most promising methods for bioprinting of heart valves involve inkjet printing and laser bioprinting with bioinks. The optimal dimensions for the valve can be modeled using CT and MRI images combined with computer software (Zhang & Wang, 2019). Figure 1 depicts a flow diagram for the process involved in 3D bioprinting a heart valve. Hockaday et al. (2012) presented a novel simultaneous 3D printing and cross linking technique for engineering complex aortic valve scaffolds. These were printed with polyethylene glycol-diacrylate hydrogels supplemented with alginate. Porcine aortic valve interstitial cell seeded scaffolds maintained near 100% cell viability over a 21 day period. Duan et al. (2013) fabricated living alginate/gelatin hydrogel valve conduits with anatomic architecture and incorporation of dual cell types. These cell types included aortic root sinus smooth muscle cells and aortic valve leaflet interstitial cells. The cells maintained viability over a tested 7 day period. However, the hydrogel exhibited slightly reduced modulus, strength and peak strain over the same time frame (Duan et al., 2012).

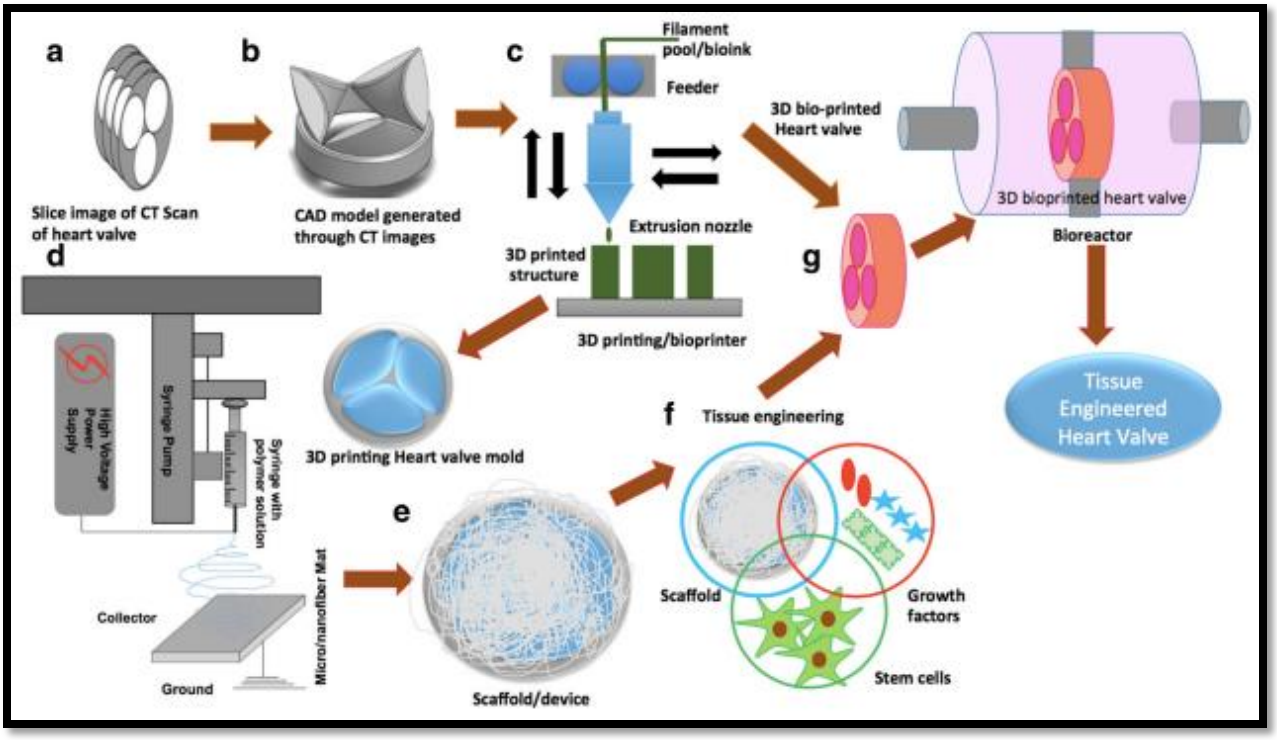

Figure 1: A proposed general overview and schematic representation of the process for 3D bioprinting a heart valve. The use of perfusion bioreactors can rapidly increase cell growth by providing the optimal environment for cellular development. Image adapted from Vashistha et al., 2019.

Use in Surgery of Congenital Heart Disease in Adults:

Congenital heart disease refers to a complex pathology characterized by malformations in the heart and major vessels. It is the most common birth defect among newborns and appears in approximately 9 out of every 1000 live births worldwide (Lau & Sun, 2018). Having a comprehensive understanding of the dimensional and spatial relationship of the inter-cardiac anatomical structures is extremely important for treatment.

Medical imaging technologies advanced dramatically with the inception of CT and MRI. These techniques allow for the rapid generation of high-resolution 3D images. 3D images remain limited by the use of flat screens for visualization and requires the observer to interpret and imagine the depth of the cardiac structures. The ability to add these images to computer aided

design (CAD) and 3D print medical phantom organs and structures could allow for better visualization of congenital heart defects (Wang et al., 2017). Once the defects are visualized, the phantoms can be used for surgical planning, educational training and patient education as well.

Traditionally, medical phantoms were produced using casing and molding processes. These conventional manufacturing processes can be time consuming and expensive, leading to individual medical phantoms rarely being fabricated. Most of these conventional medical phantoms were mass-produced, population averaged, and idealized models for educational purposes. Individualized medical phantoms through 3D bioprinting can imitate the properties of biological tissue and provide more clinically realistic specimens (Wang et al., 2017). They allow for direct manipulation and comprehensive understanding of the individual patient's anatomy prior to congenital cardiac surgeries. For these reasons, in conjunction with traditional imaging techniques, patient specific 3D printed structures can greatly assist with the diagnosis of conditions as well (Wang et al., 2017).

Figure 2: 3D-printed physiological phantoms of an aortic root are shown. The calcifications and the fibers are printed with black materials for better illustration. Image adapted from Wang et al., 2017.

Qian et al (2017), demonstrated that physiological patient specific medical phantoms to plan trans-catheter aortic valve replacement (TAVR) procedures. In this study, medical phantoms were used to predict the occurrence, severity and location of any post-TAVR paravalvular leaks.

They found that the predictions of the location of the dominant paravalvular leak matched well with actual paravalvular leak occurrence with an accuracy of 75% in 12 patients (Qian et al., 2017).

Another pertinent example of 3D printing in cardiac surgery involved Dr. Frank Ing at the Children's Hospital of Los Angeles. Dr. Ing was able to modify an existing stent using a patient specific 3D printed model to repair an artery in a pediatric patient. Dr. Ing reported that the 3D printed model helped him design and adjust the size of the stent during this interventional procedure (Abdullah & Reed, 2018).

Lau and Sun (2018) reviewed 28 articles on patient-specific 3D printed heart models created using human imaging data. Nearly 60% of these articles focused on applications of 3D printed heart models in preoperative planning and simulation. They found that graspable 3D printed models enhanced the perception of distances, dimensions and spatial information of complex cardiac morphology. The 3D printed models were also reported to help surgeons in deciding the best surgical treatment when the optimum surgical approach could not be finalized using traditional diagnostic tools. Additionally, 4 of the studies showed that intra-operative time was shortened with improved surgical outcomes. However, a few of the studies suggested that 3D printed models should be used to complement current diagnostic imaging and not as stand-alone tools for preoperative planning (Lau and Sun, 2018).

Use in Education:

Traditional techniques for educating students, nurses and medical clinicians on cardiac surgeries include reading text, and reviewing pictorial images, diagrams, echocardiograms and cardiac specimens. Unfortunately, these techniques require significant financial cost to generate or

learners to perceive spatial information. Models that are 3D printed can allow for students to manipulate cardiac structures in 3D space and can be used adjunctively with traditional techniques for education. Lau and Sun (2018) reviewed 5 studies where 3D printed cardiac models were used in teaching and training of medical staff and students. Three of these studies reported that the use of 3D printed models improved acquisition of pathological knowledge in pediatric residents and students. Resident's confidence level when managing congestive heart disease patients improved as well. Additionally, 2 more studies reported positive results when incorporating 3D printed models in medical staff training (Lau and Sun, 2018).

Patient education is another potential application for 3D bioprinting. Patient specific models can be generated prior to surgical consults. These models can be used to show the patient the precise pathology within their heart and the tools used for repair.

Challenges for 3D Bioprinting:

Many of the challenges associated with different 3D printing techniques have been mentioned above. Materials for 3D bioprinting must be usable in a 3D printer, have appropriate mechanical properties, be biocompatible, exhibit tissue biomimicry, form safe degradation byproducts and have good degradation kinetics (Kalaskar, 2017). These criteria limit the materials available and can work against one another. An example of this would be bone tissue which benefits from hard materials for osteoblast development, load bearing and bone regeneration but will cause temporary components to degrade slower than necessary (Kalaskar, 2017).

For 3D bioprinting to become commonplace in clinical practice, accessibility to bioprinting technology needs to improve as well. Protocols for image acquisition, automated processing and the creation of files compatible with multiple types of 3D printing technology need to be defined.

The 3D printers themselves also need to become more affordable and easy to repair as the technology progresses (Kalaskar, 2017).

The cost of 3D printing is considered as one of the hurdles limiting its application into routine clinical practice. Depending on the size and materials used, 3D printed models can cost over $400 USD. Biglino et al (2015), were able to reduce the price of individually printed models to approximately $55 per model by using cheaper materials like white nylon. Costs can also be reduced by scaling down the size of models. However, this reduces the models effectiveness in being used for surgical planning (Lau and Sun, 2018).

Image segmentation is another challenge for 3D bioprinting. Image segmentation involves isolating a congenitally malformed heart from its surrounding tissues using threshold techniques (Lau and Sun, 2018). However, current methods for image segmentation use gray values that can be very similar between heart muscle and surrounding soft tissue. This can lead to operators selecting incorrect anatomy for 3D printing. Better automated segmentation algorithms are needed to produce more accurate results (Lau and Sun, 2018)https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6119737/

Difficulties with incorporating vascularization are another current problem for 3D bioprinting. Most organs needed for transplantation are thick and complex. This means that these organs cannot maintain their metabolic functions through diffusion alone and vascularization is a requirement. Collaboration from multiple institutions has been ongoing to develop functional and perfusable capillary networks that can be applied to 3D bioprinted organs and tissues (Ventola, 2014).

Determination of acceptable standards of safety for the use of replicated biological material is still occurring. The major issue with bioprinting from a safety standpoint is that all major risks

associated have not be identified due to the technology not being commonplace yet. Many unforeseen risks still exist and will likely not be identified until 3D bioprinting is more established in medicine (Georgios Tsoulfas et al., 2020). Risks with 3D bioprinting are currently being divided into 2 major groups. These include safety of the replicated biological material itself and safety in the functioning of the new transplants in the receiver's organism. Safety of the replicated biological material involves maintaining the health of the bioprinted material along with the general populace that could come in contact with the material (Georgios Tsoulfas et al., 2020). Safety of the functioning of the new transplant involves the transplant working effectively within the new host and without major complications. Because these transplants cannot currently be tested within the same environment prior to implantation, unforeseen complications are possible (Georgios Tsoulfas et al., 2020).

Outside of complications, access to bioprinting could be another challenge for low income patients. These costs would include the bioprinting process, associated surgery and post-operative care necessary for full recovery. Current costs can be estimated for surgical procedures and post-operative care but costs associated with 3D bioprinting are still unknown. How insurances will handle costs associated with 3D bioprinting are also unknown at this point. With this in mind, access to 3D bioprinted health care services may be limited for those patients with low income (Kalaskar, 2017).

Future Perspectives:

Throughout this review, we have presented information on the advancements and current state of 3D bioprinting. Despite its current limitations, 3D bioprinting continues to progress. New innovations in 3D printing have allowed for the possibility of 4D bioprinting to take place (Kalaskar, 2017). The major difference between the two processes is that 4D bioprinted objects

will evolve in a predefined manner under the influence of external stimuli over time. These stimuli can include heat, pH, light or magnetic fields. These innovations are important because they could overcome difficulties with 3D bioprinted organs lacking vascular networks. Vascular networks could be encouraged to grow and controlled with the use of external stimuli (Kalaskar, 2017).

Conclusion:

Throughout history, medical technology has continued to advance. Many of these advancements have positively impacted the way that we perform cardiac surgeries. Three-dimensional bioprinting has the potential to advance the treatment of cardiac pathologies even further. In this review, we covered recent advancements in 3D bioprinting. We also evaluated the applications for 3D bioprinting in cardiac transplantation, valve replacement, congenital cardiac surgery and medical education.

The most commonly used techniques for 3D bioprinting in health care include vat photopolymerization, material extrusion and material jetting. Vat photopolymerization uses photosensitive polymer liquid materials. These materials change their state from liquid to solid when exposed to specific light sources like UV light (Fonseca et al., 2020; Jin et al., 2021). Material Jetting involves liquid material being ejected through a print nozzle as a droplet or liquid jet. Droplets are deposited in layers from the bottom-up and rapidly cured by a curing device similar to the one used by vat photopolymerization (Jin et al., 2021). Material extrusion is similar to jetting in that they both require a nozzle to extrude filamentous materials to construct a structure. Pneumatic and displacement-based printers use precise pressure to extrude materials rather than heat and are more promising for bioprinting because precise pressure control is necessary for maintaining cell viability (Fu, Angeline, & Sun, 2021).

The three most well-established techniques for bio printing of organ transplants include laser-induced forward transfer, inject bio printing and robotic dispensing. Robotic dispensing is currently the most promising of the three methods (Wang et al., 2017). Liu et al (2017) developed a printer with the ability to individually and simultaneously eject seven types of bioink. This printer was designed to overcome the limitation of previous printers that were only able to eject one type of bioink for each printing process (Liu et al, 2017).

The most promising methods for bioprinting of heart valves involve inkjet printing and laser bioprinting with bioinks. Duan et al. (2013) fabricated living alginate/gelatin hydrogel valve conduits with anatomic architecture and incorporation of dual cell types. These cell types included aortic root sinus smooth muscle cells and aortic valve leaflet interstitial cells. The cells maintained viability over a tested 7 day period. However, the hydrogel exhibited slightly reduced modulus, strength and peak strain over the same time frame (Duan et al., 2013).

The ability to 3D bioprint medical phantom organs and structures could allow for better visualization of congenital heart defects. Once the defects are visualized, the phantoms can be used for surgical planning, educational training and patient education as well (Wang et al., 2017). Lau and Sun (2018) found that graspable 3D printed models enhanced the perception of distances, dimensions and spatial information of complex cardiac morphology. A few of the studies suggested that 3D printed models should be used to complement current diagnostic imaging and not as stand-alone tools for preoperative planning (Lau and Sun, 2018).

Models that are 3D printed can allow for students to manipulate cardiac structures in 3D space and can be used adjunctively with traditional techniques for education. Lau and Sun (2018) found that 3D printed models improved acquisition of pathological knowledge in pediatric

residents and students. Resident's confidence level when managing congestive heart disease patients improved as well (Lau and Sun, 2018).

Some of the challenges to overcome for 3D bioprinting include accessibility to 3D printing technology, costs associated with printing, improving image segmentation and accuracy, incorporating vascular networks into bioprinted organs and structures, along with ethical and safety concerns (Kalaskar, 2017; Georgios Tsoulfas et al., 2020).

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