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# BIOPRINTING: DEVELOPMENT OF PATIENT - SPECIFIC THREE-DIMENSIONAL PEDIATRIC MODELS

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**ABSTRACT** Undoubtedly one of the greatest achievements of medical science is the transplant of tissues and organs. However, a matter of deep concern is the lack of balance between supply and demand of organs, particularly with regard to the pediatric population. The need to overcome this problem has led to the invention and manufacture of additive manufacturing through the latest technology of 3D printing.

**KEYWORDS :** 3D printing, bioprinters, transplants, pediatrics

## INTRODUCTION

3D printing is a process in which images and models are transformed into three-dimensional tangible objects, by the method of sequentially adding layers of material. The 3D printers used in medicine and dentistry are called bioprinters and they are of 3 types: simple, "inkjet" printers and six-axis printers.

The procedure followed is briefly the following: the desired tissue or organ is selected, then designed by the operator on the computer and the special bioink is made from cells. Layers are created with the water-based hydrogel and cells are layered between these layers until the tissue is built. Sometimes gaps are created in the tissue or a scaffold (support) needs to be created, which are done with hydrogel or collagen. Finally, the cells are put into an incubation furnace, where they fuse until they take their final form.

## APPLICATIONS OF 3D-PRINTING AND BIOPRINTING IN THE PEDIATRIC POPULATION

### Construction Of Prosthetic Limbs

The most widely known application of 3d-printing in the pediatric population concerns the so-called "Project Daniel". This project was started by the company "Not Impossible", which used 3d printers to make prosthetic upper limbs for war-mutilated children in South Sudan. The first hand was placed on sixteen-year-old Daniel in November 2013, who managed to eat on his own, something he had been unable to do for two years. The company, founded and headed by Mick Ebeling, set up the first 3d-printing prosthetic limb lab in the war zone of Sudan, training and enlisting local residents to continue making prosthetic limbs for child victims of war (Ni LABS, 2013 ).

### Model Construction

A large part of 3d-printing applications in the pediatric population concerns the construction of models for the study of targeted surgical interventions or specific pharmaceutical therapeutic methods. Already these models find good application in the study of cerebrovascular disease, craniofacial anomalies, tumors of the central nervous system and pelvic injuries. At the research level, the construction of models for the study of congenital heart diseases and other respiratory and otorhinolaryngological diseases is also attempted, while some of these efforts will be mentioned below. These models enhance diagnostic accuracy and serve in preoperative planning, while improving the ability to educate and inform both physicians and patients or their relatives (Nocker et all, 2006).

The modeling technique very briefly involves taking images taken from the patient by CT or MRI of the area or organ of interest, converting them into DICOM (Digital Imaging and Communications in Medicine) digital files, and then printing 3D models through the use of inkjet 3d printers. The models are printed in cross-sections that are joined sequentially, while materials such as amyloid powders, polymers, elastomers, silicone, resins, bonding solutions, etc. are used. (Sodian et al, 2008).

### Cardiology And Cardiac Surgery

The construction of heart models occupies a special place among the applications of 3d-printing in the pediatric population, mainly due to congenital heart diseases and accompanying operations. In 2006 a team of scientists from Cleveland published the results of their efforts to construct 3D flexible biomodels of a child's heart and great vessels for the purpose of precise preoperative PediPump implantation planning. This pump is a tiny device that supports the ventricular function of the heart in children with congenital heart disease and can even be implanted in newborns.

However, due to the small anatomical size of the neonatal and pediatric structures, it was deemed necessary to pre-design the placement of the pump on an accurate biomodel of the actual dimensions of the heart of the patients themselves (aged 2 days to 13 years). Twelve flexible polymer heart models were eventually constructed that enhanced the understanding of the spatial arrangement of complex cardiac structures, with a view to ideal implantation of the assistive device (Nocker et all, 2006).

In addition, a group of scientists from Munich proceeded to create heart models for two patients with a single ventricle (2 and 14 years old), in whom gradual rehabilitation with various operations had failed. These patients were candidates for heart transplantation, however, due to multiple preexisting reconstructive surgeries, transplantation was considered a complex and risky procedure, and accurate imaging of the structures of the transplant candidate patients was required. Therefore, the models helped in the choice of surgical strategy, intraoperative precise orientation and avoidance of excessive tissue scarring, as well as preoperative information to patients and their parents (Sodian et all, 2008).

### Surgery

In the field of craniofacial surgery, the manufacture of cranial models through 3d-printing techniques is an established procedure. In addition, these models are widely used for the manufacture of personalized devices and implants (for skull reconstruction, dental etc.).

The team of scientists from Munich constructed through 3d powder printing cranial models of nine patients (17-20 years old) with syndromic craniosynostosis, in order to pre-operatively plan a mesofacial osteotomy operation (Le Fort III operation) and osteosynthesis in multiple directions. The cranial models were used to create a prefabricated osteosynthesis device, in order to apply it directly and individually intraoperatively to each patient. The results of the technique were encouraging, facilitating the intraoperative application of the device in less time and the correct alignment of the osteosynthesis process, while the 3d-printing technique applied was considered "routine", high precision and low cost (Klammert et all, 2009).

In addition, scientists from Great Britain constructed a scapula model of a six-year-old girl with hereditary multiple ossification, which showed a very large scapular osteochondroma, the exclusion of which was particularly difficult. The model was constructed layer by layer, from plaster, modeled after a CT scan of the child, while it was particularly helpful in approaching and ensuring the success of the operation (Tam et all, 2012).

### Neonatology

This time a group of scientists in Bern, Switzerland, engaged in the construction of the PrINT model, with the aim of creating the first suitable in vitro model of the nose and larynx of a premature neonate to study the distribution in the bronchial tree of treatment with nebulized substances, which are known how they are largely deposited in the upper airways, without reaching their target. Trials that can be performed in this model attempt to demonstrate the effectiveness of inhaled therapy in severe neonatal respiratory conditions such as respiratory distress syndrome.

It is a cast of photopolymer resin (transparent, rigid material) that is an anatomically accurate copy of the upper airways of a premature newborn at 32 weeks' gestation. The comparison between the neonatal MRI and CT of the cast indicated a high degree of anatomical accuracy, making the model suitable for in vitro testing of inhaled drugs in neonates, where corresponding in vivo testing is impossible to perform (Minocchieri et all, 2008). .

**Education**

A 2014 publication by a team of scientists in Toronto, Canada reports that a pediatric pelvic plasty simulator was built as an educational tool using 3d-printing technology. The purpose of creating the simulator is the training of Pediatric Urologists and their acquisition of technical skills in the field of pelvic surgery and, by extension, pediatric laparoscopic surgery. As far as this particular attempt is concerned, it is a silicone rubber model, which depicts the anatomy of a kidney, the distended renal pelvis, the obstructed pelviureteric junction, the ureteric symphysis, and the peritoneum covering these organs, in the proportions of an infant about ten months. Pediatric urologists were asked in this study to perform a pelvic-ureteral obstruction repair operation on the simulator model and then evaluate the model.

By the majority of scientists who tested it, the model was found to be easy to use, realistic and gave the right feel of living tissue. Furthermore, the tool was validated with very good results. It was also considered low-cost (it cost only 100 dollars), in relation to the training methods available so far for surgeons (virtual reality, experimental animals, etc.). This group sees great promise in the use of 3d-printing for the construction of training simulators for a variety of surgical procedures and attempts to add perfusion, improved texture and differentiated echomorphology to the engineered tissues. In addition, the constructed models can be used for training by more than one person, as the members that the learners intervene on are replaced with new ones (Cheung et all, 2014).

Applications in the field of Cardiology and Cardiac Surgery Heart valve diseases, congenital and acquired, are a serious and widespread health problem in the adult as well as in the pediatric population. Valvular diseases are sometimes treated with surgical repair, however in the majority of cases replacing the valves with prosthetics is the only option for patients. In the field of prosthetic valves, mechanical valves have been manufactured, with the risk of clot formation on their surfaces and as a result the need for lifelong anticoagulation, and bioprosthetic valves, which however do not have a long lifespan and are not used in pediatric patients. For the pediatric population, the construction of bioprosthetic valves, capable of being integrated into the recipient's tissue and participating in the growth of normal tissue, is necessary, and this construction is one of the goals of tissue engineering.

A team of scientists from New York claims that 3d-printing technology can be used to make mechanically strong living tricuspid heart valves, incorporating many kinds of valve cell populations. This group constructed living aortic valve conduits with anatomical architecture and a peripherally restricted dual cell population. Using micro-CT images of porcine aortic valves, they constructed a draft of the anatomy of the cusps and root of the aortic valve to be constructed. Then through 3d-printing, on a suitably designed hydrogel substrate of alginate and gelatin, they printed smooth muscle cells of the aortic root cavity (SMC) and interstitial cells of the aortic valve cusps (VIC). Alginic acid salt is a low-cost and non-toxic natural anionic polymer with excellent biotissue compatibility and biomolecular binding capacity.

Their results were encouraging, with encapsulated SMC and VIC cells remaining viable within the hydrogel trays in culture for over seven days. The engineered aortic valve conduit with SMC and VIC cells printed on the valve root and cusps, respectively, exhibited geometry comparable to the prototype valve, while key anatomical structures were faithfully reproduced. Also, the cells expressed structural proteins, such as α-actin and vimentin. According to the researchers, these results confirm the possibility of 3d-printing clinical-sized tricuspid heart valves with heterogeneous cell populations. In the future, the improvement of the mechanical and cellular heterogeneity of the manufactured valves is critical, while additional additions of molecules and culture of the valves in hemodynamic bioreactors are required before the first attempt to implant them in laboratory animals (Duan et all, 2013).

**Applications In The Field Of Otorhinolaryngology**

At the University of Michigan, a team of scientists manufactured a bioabsorbable airway splint, through 3d-printing technology, which they implanted in an infant with tracheobronchiomalacia. The infant presented with severe airway obstruction and respiratory failure, to the extent that even endotracheal intubation and mechanical ventilation could not ensure a stable respiratory status.

The researchers obtained a precise image of the infant's pathological left main bronchus through a CT scan and then, after electronic processing of the image, manufactured with the help of a laser 3d printer the customized polycaprolactone splint for the infant. This splint was surgically placed distal to the pathological bronchus and fixed with sutures. This splint caused dilation of the bronchus resulting in air entering the left lung. The splint can also undergo flexion and extension, while keeping the main bronchus dilated, allowing normal air passage through it, and participating in the normal growth of the bronchus. One year later, imaging and bronchoscopy show patency of the airway, with no unforeseen problems, and the splint is expected to be fully absorbed by the bronchus approximately three years after surgery.

After this attempt, researchers believe that the combination of high-resolution imaging, computer-aided design and 3d-printing of biomaterials can lead to the creation of personalized implantable devices (Duan et all, 2013).

Their attempt was repeated for a 16-month-old boy with tracheomalacia, but as they say, the biggest problem they face and cannot proceed with applying their method to other patients is that they have not received approval from the US Food and Drug Administration. FDA and furthermore find it difficult to convince insurance funds to cover the costs of these incidents (Stein, 2014).

**Applications In The Field Of Osteogenesis**

There is great interest in the literature regarding the reconstruction of craniofacial anomalies in the pediatric population. Until now, autogenous and alloplastic implants have been used in their restoration, which carry the risk of infections or rejection. In the newest efforts, the promotion of osteogenesis at the points of deficits is attempted, with the use of BMP-2 proteins (Bone Morphogenetic Proteins), which are growth factors that stimulate the construction of bone and cartilage even in the most hostile environment. These proteins have already been used with encouraging results in cleft repair and cranial vault reconstruction. However, the research so far shows that large doses of these proteins are required, while their effect on osteogenesis is uncontrolled and depends on their direct contact with the osteoprogenitor cells of the bone surface, where we want to stimulate osteogenesis.

In an effort to improve the application of BMP-2, scientists from Pittsburgh, USA. printed BMP-2 proteins as bioinks onto an acellular skin substrate, which they placed in bone defects they created in the parietal bones of rats. The substrates were placed in such a way that the BMP-2 proteins were in direct contact with the dura mater of the brain, which is a source of osteoprogenitor cells. The result of osteogenesis was satisfactory. The researchers believe that by using this solid phase (substrate), printed with BMP-2 bioink at specific locations customized to the patient's anatomy, they can modulate the osteogenesis induced at the specific contact sites between BMP-2 and osteoprogenitor cells, with lower doses of BMP-2. This method is considered promising and is considered to be able to construct complex and detailed three-dimensional bone sections at the points of craniofacial deficits (Smith et all, 2012).

**Limitations - Future Trends**

Despite the leaps and bounds in technology, many challenges still remain to be overcome in order to create viable organs from a person's own cells. First, success in producing functional human organs depends heavily on advances in the isolation, propagation, and processing of stem cells. But the main obstacle is the creation of a vascular network, so that the cells can maintain their metabolic functions. Different cell types also need to be spatially organized and tissues matured before they are placed into the organism, in order to efficiently interact with the new environment. The most important factor that can make things a little more difficult is, of course, cost.

However, despite the aforementioned reasons, the world of bioprinting remains very ambitious. Printed organs could be used more extensively in drug or vaccine testing, while miniature organs would be a smooth transition to fully functional human organs. Another trend is in-situ printing, where viable organs can be printed on the human body during surgery, while the goal remains to create low-cost do-it-yourself solutions for widespread use (Ozbolat et al. , 2013).

MIT scientists even argue that an achievement of the not-so-distant future will be 4d-printing, where objects will now be able to change shape over time, adapting to changes in the environment (Rieland et all, 2014).

In conclusion, we hope that at the center of the thoughts and actions of the scientific community, and not only, the Man will remain and that the application of all kinds of bioprinters will be done with moderation, prudence and always with the common good in mind.

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