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Personalized development of human organs using 3D printing technology

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ABSTRACT

3D printing is a technique of fabricating physical models from a 3D volumetric digital image. The image is sliced and printed using a specific material into thin layers, and successive layering of the material produces a 3D model. It has already been used for printing surgical models for preoperative planning and in constructing personalized prostheses for patients. The ultimate goal is to achieve the development of functional human organs and tissues, to overcome limitations of organ transplantation created by the lack of organ donors and life-long immunosuppression.

We hypothesized a precision medicine approach to human organ fabrication using 3D printed technology, in which the digital volumetric data would be collected by imaging of a patient, i.e. CT or MRI images followed by mathematical modeling to create a digital 3D image. Then a suitable biocompatible material, with an optimal resolution for cells seeding and maintenance of cell viability during the printing process, would be printed with a compatible printer type and finally implanted into the patient.

Life-saving operations with 3D printed implants were already performed in patients. However, several issues need to be addressed before translational application of 3D printing into clinical medicine. These are vascularization, innervation, and financial cost of 3D printing and safety of biomaterials used for the construct.

Introduction & background

Three-dimensional (3D) printing was first described more than 30 years ago and since then it has found invaluable applications in automotive industry, military services, archaeology, electrical device engineering and science. It is essentially a concept of converting a 2D volumetric digital image into a 3D printed model by printing successive thin layers of a material, the greater number of layers, the higher the resolution. Therefore, it is often referred to as "additive manufacturing". Because it enables rapid prototyping, it is already used for printing truthful replicas of human organs to allow preoperative surgical planning of high-risk operations [1]. It is also used for printing of 3D surgical models in medical education and training, and guiding the construction of medical implants [2]. However, its ultimate medical application that could convert what we have previously regarded as science fiction into reality would be in a 3D printing of human organs.

We are facing with the ageing population, increasing number of failing organs and organ shortage [3]. The paucity of suitable organ donors, the high cost of transplantation and morbidity and mortality of consequent life-long immunosuppression, bring this problem into the focus of the scientific community. Certain reconstructions cannot yet be performed with a transplant. Despite the enormous effort of surgeons and clinical team to carry out groundbreaking transplantations and after years of waiting for a suitable donor, sometimes the allogeneic transplant may not match the biochemical biocompatibility or the exact anatomy of the recipient. This was the case in the world's first human scalp transplant in Texas, the USA earlier this year. Recipient's calvarium was much thinner than the transplant, as seen on the postoperative patient computerized tomography (CT) scan, which led to aesthetic problems and poor healing [4]. What if the skull was designed and the 3D printed based on patient-specific information?

Several types of printers are available including cheaper ink-jet printers with small droplet size and viscosity, more expensive but

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slower microextrusion printers with continuous release of material, and finally the most expensive laser-assisted printers with highest resolution [5]. Additional diversity is achieved by the use of both biological materials like collagen, hyaluronic acid, alginate, chitosan and thermoplastic synthetic polymers like polyurethane and poly(lactic-co-glycolic acid) [3].

Personalized 3D printing could transform plastic and reconstructive surgery, particularly with patients with rare malformations. Moreover, the introduction of 3D printed blood vessels instead of transplanted vascular grafts could change our approach to cardiovascular pathologies.

Hypothesis

In this paper we suggest the idea of 3D printing of human hollow organs with lower architectural complexity, such as arteries, trachea, larynx, urethra, bile duct and facial reconstruction of ears and nose, using detailed patient information acquired by medical imaging, 3D printing and appropriate cell type. The procedure would allow a novel precision medicine approach in surgery (Fig. 1).

Evaluation of the hypothesis

Tissue engineering is one of the most exciting fields of medicine. It involves the use of a biocompatible scaffold loaded with proper cell types include stem cells (capable of self-renewal and differentiation into multiple lineages), differentiated mature cells, or a mixture of differentiated cells in a bioreactor. As the interaction between cells and a scaffold determines the procedure outcome, finding a suitable scaffold is as important as cell source. First tissue-engineered in human airway transplant grasped the enormous attention of the public in 2008 and was described as “the end of the beginning for tissue engineering”. However, it was not an easily reproducible procedure as a decellularized cadaveric trachea was used to provide mechanical support of the graft. Scientists quickly realized that only the development of easily manufactured scaffolds would enable off-shelf availability of human organs [6]. Fuelled by this idea, researchers went on to develop synthetic or biological scaffolds for tissue-engineering resulting in several revolutionary operations performed as

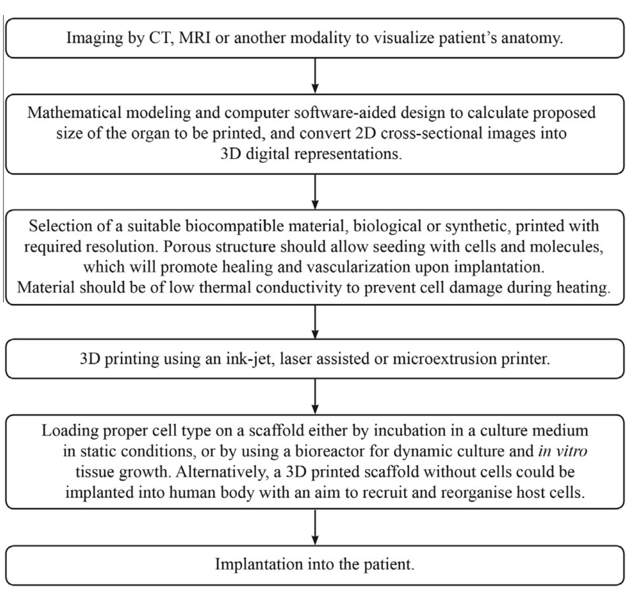

Fig. 1. The procedure of 3D printing human organs.

compassionate cases (Fig. 2), including world’s first synthetic trachea [7] using nanocomposite manufactured in our lab, and world’s first lacrimal duct with our collaborators from Switzerland [8] (Dr. Karal Chaloupka, Department of Ophthalmology, University Hospital Zurich). Despite these few successes researchers have been unable to establish this technique as an available clinical treatment, partially because finding the optimal scaffold manufacturer protocol is a very challenging task. 3D printing could revolutionize tissue engineering and allow full exploitation of its potential in regenerative medicine, due to the superior physical properties of 3D printed scaffolds. Printed scaffolds could mimic the characteristics of the desired tissue and have the same anatomical geometry [9]. They could also abolish the issues of manual cell seeding, and have an easily reproducible and standardized pore size that facilitates cell proliferation and aggregation. By combining biological and synthetic bioresorbable materials, 3D printed scaffold could have enhanced load-bearing properties than original human tissues. A potential difficulty would be to prevent cell death during heating and printing of the scaffold, but several researchers have reported that sufficient cell viability can be restored by incubation in a suitable medium after 3D printing [10].

Various human tissues have already been successfully printed including skin, liver, neuronal tissue, muscle–tendon units and cartilage. Human nasal chondrocytes were seeded on a highly aqueous biohydrogel mimicking extracellular matrix made of nanocellulose and alginate, and cartilage was successfully printed on small constructs and maintained viability [11]. 3D printing of neuronal tissue using rat embryonic neural stem cells, in a collagen hydrogel composite, proved that delicate scaffold structure fabricated by 3D printing could allow incorporation of two different cell types, neurons and astrocytes respectively [12]. Similarly, formation of epidermis and dermis was achieved after bioprinting keratinocytes and fibroblasts using laser-printing technology [13]. Because of their low toxicity and similarity to extracellular matrix, biological materials were more commonly used. However, synthetic thermoplastic materials are getting increased attention as multiple different polymers can be combined to fabricate mechanically stable constructs, as demonstrated in 3D printed muscle–tendon units [14]. Although perfectly suitable for musculo-skeletal organs, hard thermoplastic polymers currently used for 3D printing may not be ideal for soft tissue engineering.

Nevertheless, printing of 3D structures poses new challenges that need to be overcome, mainly the issue of vascularization of the graft. Specific circumstances could allow the graft to be put in a close proximity to existing blood vessels. It could then be connected to them by microvascular surgery and designed with an open inner structure to facilitate supply of nutrients to embedded cells. 3D printing of cartilaginous structures could have a translational application first, as cartilage is histologically simple and avascular tissue, and currently there is no clinical treatment for cartilage destruction. On the other hand, more futuristic and perplexed approach would be 3D printing of the entire vascular network of the organ with branched artificial blood vessels, and 3D printed small-diameter vascular grafts with both horizontal and vertical branches have already been fabricated using bioprinting techniques [15]. This October Chinese company Revotek Co. claimed to develop the world’s first vessel bioprinter, which can print stem cells while they are differentiating into mature cells and produce a 10 cm-long blood vessel in just 2 min. This exciting breakthrough undoubtedly has the potential to revolutionize healthcare, but it is still too early to draw conclusions as the technique is at the stage of prototyping and validation [16].

Although still in its infancy, 3D printing has already had several exceptional applications in the clinics, so why be skeptical about its novel medical use? Living heart valves were fabricated using this bioprinting technology [17]. 3D printed proximal neck of the

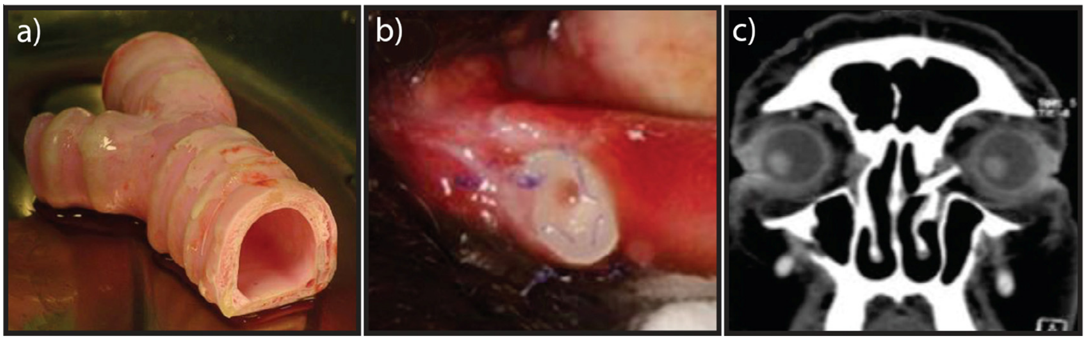

Fig. 2. Laboratory-developed organs already implanted into patients: (a) World's first synthetic trachea implanted into a patient using nanocomposite material [7], (b) and (c) implantation of the first in-human synthetic lacrimal duct [8].

aorta with fenestrations for proximal branches designed uniquely based on individual patient anatomy is currently waiting Food and Drug Administration (FDA) approval for a minimally invasive treatment of abdominal aortic aneurysms. 3D printed aortic sleeve has already been used in a clinical setting instead of a commercial endovascular graft. In that particular case, it took 9 h to print 6.3 cm long and 2 mm thick graft at a reduced cost than standard stents [18]. Researchers from the University of Michigan, USA have successfully implanted a bioresorbable 3D printed tracheal splint fabricated using microextrusion bioprinting in a child with severe tracheobronchomalacia [19]. Due to variable anatomical malformations that often accompany this condition, without personalized splint design, this operation is extremely difficult to perform. Thus children often remain with life-long respiratory support and frequent hospitalizations. Custom-made facial bones manufactured by ink-jet 3D printing are becoming a standard of care in maxillo-facial surgery in Japan, for patients with mandibular hypoplasia, micrognathia or microsomia [20]. Total jaw and skull reconstruction have been performed in Netherlands, using tailor-made 3D printed implants fabricated by the Dutch company Xiloc Medical B.V. The company produces commercially available patient-specific implants that can be sold to patients with permission of their surgeon (Fig. 3) [21]. Life-saving cervical spine reconstruction using a 3D printed vertebral body C2, axis, developed from CT scan digital data was recently implanted into a 12-year-old boy after the surgical removal of a rare musculo-skeletal malignant neoplasm Ewing's sarcoma [22]. Although, still not in widespread use, case reports of life-saving operations using 3D printing technology certainly support our hypothesis of personalized precision medicine in surgery.

Many clinicians believe that 3D printing will firstly become invaluable in plastic surgery due to its potential to fabricate custom-made prosthesis, but only for aesthetic reasons as these would lack any functionality, due to insufficient vascularization and innervation. However, the word "impossible" should be used with caution when it comes to 3D printing technologies. After 3D printing reproducible tissue-engineered human ear [23], 3D printed bionic ears have been fabricated in cybernetic experiments while working to develop devices or organs with similar or enhanced human capabilities [24]. Besides possessing viable

Fig. 3. 3D printed custom-made skull implant produced by Xiloc B.V, treating a left-skull deformity acquired after multiple surgeries and resorption of transplanted bones [21].

cartilage tissue on an auricle construct, electronic silver nanoparticles were infused to allow electrical characterization of sound waves by the printed ear. If medicine keeps up with the advances in a high-technology field, we could have synthetic 3D printed ears that hear and a nose with a sharp sense of smell.

Our current project is the development of tissue-engineered auricles using 3D printing techniques for scaffold processing based on patient specific data together with collaborators in Mumbai, India. At the moment, our 3D printed ears are in pre-clinical trials for patients with microtia and we are working on patient profiling and data collection. In near future, these 3D printed constructs could be used for aesthetic external ear reconstruction, to reduce the stigma and burden of multiple surgeries, associated with this condition.

It is still arguable whether the financial cost of aforementioned procedures will ever be sufficiently low to provide cost-effectiveness and availability to a large group of patients. The cost of 3D printed skull replicas is only $3.85 [25], and 3D printing is likely to be used in surgical planning and medical education. While one tracheal splint would cost $100 [14] and still have a very feasible large-scale application, about $40,000 would be needed for an artificial nose [26]. The one-off expense of hardware and software to set up the facility would increase the total cost by additional $ 13,000–$30,000, depending on the printer type [27]. Bioprinting of live cells using biological materials is, on the other hand, significantly more expensive with prices starting from $280,000 to $300,000. Nevertheless, organ transplantations with subsequent life-long immunosuppression and co-morbidities present a huge financial burden on healthcare systems across the world, so allow sufficient room for development of novel 3D printing techniques.

Perspective

This is a multi-disciplinary team field, and in order to move forward scientists, engineers, software developers and physicians would need to join forces and work on it together. Advances in technology should lower the cost of 3D printing, and make them more affordable to researchers across the world. More experiments are required to investigate human reactions to materials used for printing and demonstrate safety before implanting them into patients. Further tests should also allow standardization of optimal material and type of printer used, as well as suitable time and conditions for maturation of tissues in the fabricated construct, for each approved clinical application. Lastly, scientists and engineers must restore some organ functionality and solve the problem of vascularization to enable 3D printing of more complex organs.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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