

## Is Human Heart Bioprintable?

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### Editorial

Bioprinting commonly refers to the technology which manufactures an organ or a tissue in a layer-by-layer method for the purpose of replacing or healing abnormal organs or tissues [1]. Recently, it has been regarded as one of the most promising and powerful tool of tissue engineering [2]. Due to the shortage of human organs (e.g. heart, kidney, liver) and the huge demands for organ transplantation, bioprinting human organs appear to be a fascinating solution to the problem.

Heart failure, a disease characterized by decreased cardiac output and insufficient perfusion of peripheral tissues and organs, is prevalent in around 2% of adult population in the United States, with nearly 680,000 new cases diagnosed each year [3]. Many insufficiently treated heart failure patients will eventually progress to advanced heart failure when heart transplantation is required for a relatively high proportion of them.

Bioprinting is likely to contribute to the solution by allowing the patient-specific fabrication of human heart. Some seminal studies have investigated the fabrication of human heart valves and human heart constructs, yet the fabrication of whole human heart seems unapproachable [4-6]. One of the most basic questions on the bioprinting of human heart is that: Is human heart really bioprintable?

Bioprinting has been described as a technology that rapidly and additively manufactures an organ or a tissue. This process is so different from the time-consuming prenatal development of human heart which begins with the formation of two endocardial tubes that subsequently fuse into primitive heart tube in the twenty-first day. The primitive heart tube loops and separates into truncus arteriosus, bulbus cordis, primitive ventricle, primitive atrium, and the sinus venosus. Many complex and incompletely understood signalling pathways such as hippo pathway are also involved in the development of human heart [7,8]. It is doubtful if the "rapidly" and "additively" fabrication of human heart can fulfil all these tough conditions of human organ development.

Currently, many cell patterning techniques have been developed to precisely control the placement of cells, such as solid scaffold-based biofabrication, embedding and molding technology, cell sheet technology and so on [9]. Nevertheless, the bioprinting of human heart may not be only about cell patterning, although cell patterning is the first step towards the fabrication of a whole heart. The more important issue is how we can maintain the functionalities of a bioprinted organ. Oxygen consumption is one of the most basic needs of a viable organ which undertakes a specific function. Since human heart is much more dependent on oxygen and nutrient supplies than other organs, oxygen supply is critical to a normally functional human heart, but currently, the vascularization of a bioprinted construct has become a major bottleneck in this field [10].

Furthermore, human heart is a network of cardiomyocytes connected to each other by intercalated discs that enables rapid electrical conduction from atrial syncytium to ventricular syncytium. It remains unknown if a bioprinted human heart is capable of forming electrical

atrial and ventricular syncytia. Are intercalated discs bioprinted, or formed during the subsequent organ culture? The simultaneous printing of multiple cells is another critical hurdle because human heart is not just a muscular but also vascular and innervated organ. For example, the distributions of endothelial cells and nerve cells are important to the normal functions of a human heart. Otherwise, the misplacement of endothelial cells is likely to lead to cardiac ischemia that is like coronary artery disease, while the misplacement of nerve cells probably leads to arrhythmias.

Cardiac bioprinting is a highly interdisciplinary topic that requires the long-term joint efforts of cardiologists, engineers, and biologists. Although the fabrication of human heart encounters lots of issues nowadays, we still hold confidence on it since it may serve as the ultimate choice for advanced heart failure patients.

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