BIOPRINTED TISSUE ENGINEERED VASCULAR GRAFTS WITH STEM CELLS – PROMISING TREATMENT FOR PEDIATRIC CONGENITAL HEART DEFECTS

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ABSTRACT

Surgical treatment of congenital heart abnormalities in children often involves the use of valves, patches, or vascular conduits to establish anatomical continuity. Pediatric patients require a distinct approach from adults due to differences in cardiovascular anatomy, necessitating individualized surgical procedures. Grafts used in these procedures must be precisely designed to ensure long-term performance, given their sensitivity to local hemodynamics. Although tissue-engineered vascular grafts (TEVGs) have made significant progress in the last decade, creating patient- and procedure-specific grafts remains challenging. Combining stem cells with biomaterial scaffolds offers a promising strategy for tissue engineering in both in vitro and in vivo applications. This innovative approach reduces the risk of host rejection, adapts to a child's growth, potentially reducing the need for multiple surgeries, and minimizing immunogenic complications, offering promising prospects for addressing valve defects in congenital heart disease (CHD) patients.

INTRODUCTION

Congenital heart defects (CHDs) affect approximately 6 in 1000 live births in the United States, often necessitating surgical intervention to prevent complications. While procedures like the Fontan operation can address some CHDs, finding suitable grafts for all patients remains challenging. Synthetic grafts have growth limitations in children, potentially requiring revision surgeries. Tissue grafts like cryopreserved allografts and autologous saphenous grafts also have limitations. Tissue-engineered vascular grafts (TEVGs) hold promise in pediatric CHD treatments, but creating patient-specific grafts is challenging due to individual anatomical variations. Bio-printing TEVGs, combined with stem cells, offers a potential solution to tailor grafts to each patient's unique needs, reducing complications.

MATERIALS & METHODS

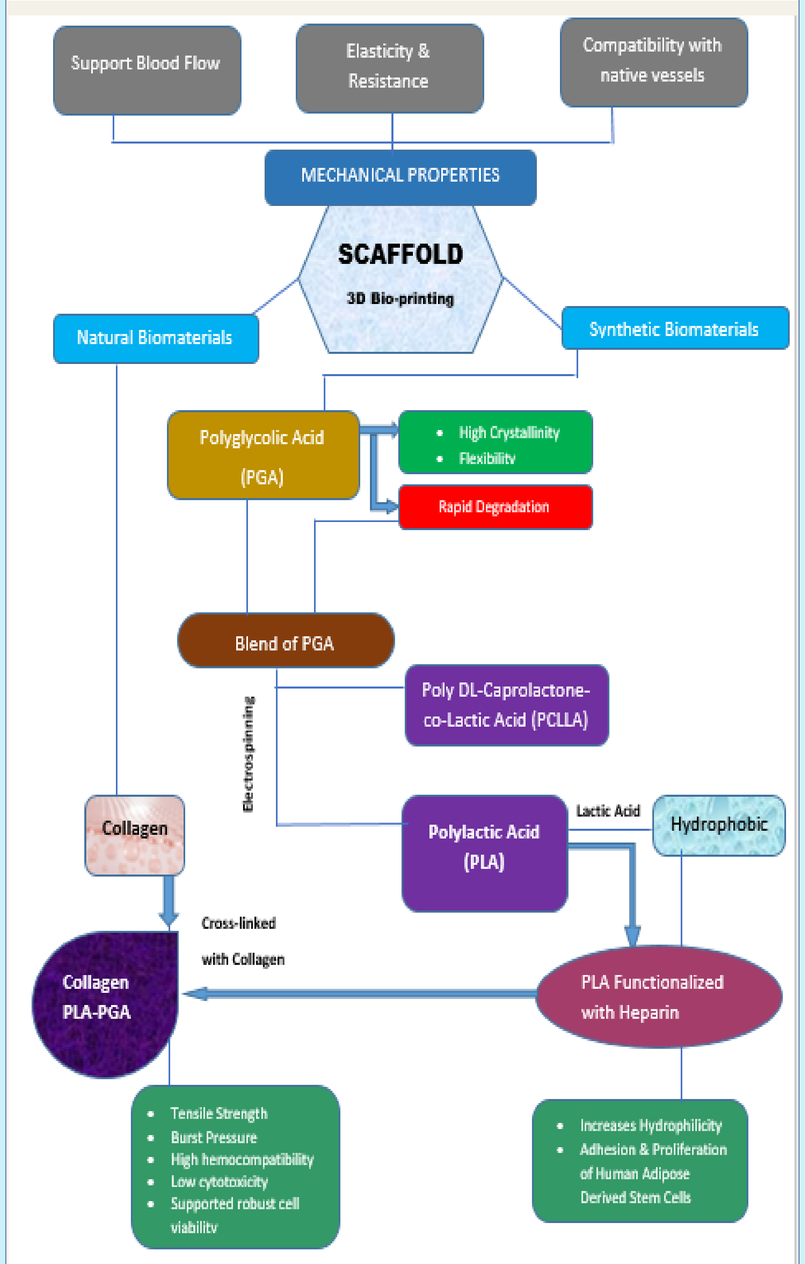

Fig: 1 Flow Chart of Scaffold Biomaterials

STEM CELL DERIVATION

Stem cells, particularly Mesenchymal Stem Cells (MSCs) and Induced Pluripotent Stem Cells (iPSCs), play a crucial role in regenerative medicine, specifically in creating cardiac scaffolds. These cells can differentiate into cardio myocytes, the heart's contractile cells. The process involves obtaining stem cells from sources like bone marrow or adipose tissue for MSCs or reprogramming adult cells into iPSCs. Controlled environments and differentiation protocols guide their transformation into cardio myocytes, closely resembling native heart cells.

Post-differentiation, cardio myocytes are seeded into a 3D-printed scaffold that mimics native cardiac tissue's structure and function. This scaffold supports cell growth and organization. After incubation and rigorous biological testing, including viability and functionality assessments, the engineered tissue is evaluated for implantation suitability. When all conditions are met, the tissue becomes a potential candidate for transplantation, offering hope to patients with heart-related issues and advancing regenerative medicine and cardiac care.

VARIOUS METHODS TO ENGINEER CARDIAC VALVES

Scaffold/Bioink	Bioprinting technique	Seeded cell	Cardiac response
Alginate-Gelatin hydrogel	Inkjet bioprinting	Aortic root sinus SMCs and aortic valve leaflets interstitial cells	Cellular growth and viability within the 3D printed constructs maintained upto 10 days. SMCs showed contractile morphology and expression of elevated alpha-smooth muscle actin and VICs expressed elevated levels of protein vimentin
Methacrylated hyaluronic acid (MeHA) and methacrylated gelatin	Extrusion based bioprinting	HAVIC	High cellular viability of HAVIC and remodeling of the initial matrix with collagen and glycosaminoglycans was observed.
poly (ethylene glycol)-diacarylate (PEG-DA)/alginate hydrogels/	Laer based bioprinting	PAVIC	The scaffolds had significantly high elastic modulus, shape fidelity and cellular growth and viability.
Photocrosslinkable hydrogels, a rigid one (75 kPa) for the root and soft (5kPa) for the leaflet	Laser based bioprinting	PAVIC	Cellular viability upto 4 weeks

Table: 1 Methods to engineer valves

PROPOSED WORKFLOW OF PATIENT-SPECIFIC TEVG FABRICATION

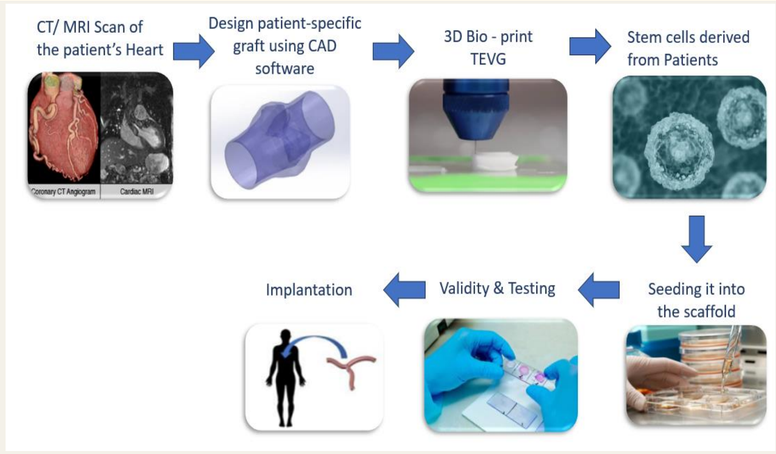

Fig: 2 Flow Chart of TEVG Fabrication

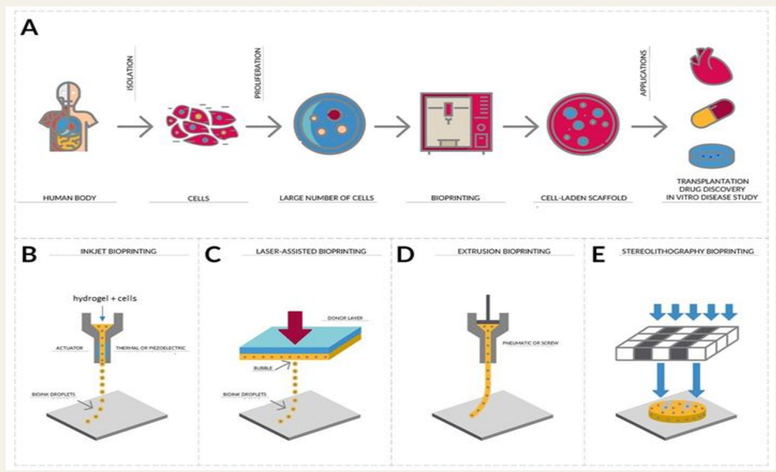

Fig: 3 Bio-printing stem cells

CLINICAL TRIALS AND RESULT

The current clinical requirements for tissue-engineered vascular grafts (TEVGs) include non-thrombogenicity, autologous compatibility, long-term patency, and mechanical properties comparable to native tissue.

In a landmark 1999 case, Shinoka et al. successfully implanted a TEVG in a 4-year-old patient with a congenital heart defect. This TEVG, constructed from a specific polymer blend, remained patent for 7 months after being seeded with the patient's own vascular cells. Building on this success, the team conducted a clinical trial between 2001 and 2004 involving 42 pediatric patients with congenital heart defects. During the initial 16-month follow-up, there were no complications related to the grafts. In a later study with a mean follow-up of 5.8 years, some patients experienced graft stenosis, but the majority recovered without major issues. Importantly, TEVGs demonstrated practicality and immune compatibility, eliminating the need for immunosuppressive medications due to the use of autologous cells. The mechanism behind graft stenosis requires further investigation.

CONCLUSION

In tissue reconstruction, significant strides have been made in addressing unique challenges in both adults and children. 3-D bioprinting stands out as a promising avenue, offering the potential to create customized vascular conduits tailored to each patient's anatomy. The use of hydrogel materials like collagen, fibrin, PEG, alginate, gelatin, and hyaluronic acid has expanded possibilities for soft tissue engineering. However, these bio-printed constructs may face durability limitations under certain conditions. To tackle these challenges, ongoing research explores the functionalization of synthetic biomaterials with stem cells. This approach holds great promise for developing robust vascular conduits that can enhance patient outcomes in tissue reconstruction. Dedication to innovation in this field fuels optimism for the future of personalized and effective tissue engineering solutions for both adults and children.

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