Review on the Current Limitations to the Treatment of Ischemic Heart Disease Through Cardiovascular Tissue Engineering Applications

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Abstract:

Ischemic heart disease is the most prevalent cardiovascular disease in the world. Current treatments primarily rely on organ transplantations; however, issues including lifelong medication to prevent immune rejection, trauma to the cardiovascular system, and the lack of organ donations are yet to be addressed. With the development of current cardiovascular tissue engineering technologies, namely artificial valves, vascular grafts, synthetic scaffolds, and computational approaches, this field has the potential to provide alternative treatment options for ischemic heart disease. This review article aims to cover the effects of ischemic heart disease on the heart and the circulatory system and explore the process, benefits, and limitations of the current approaches to the treatment of ischemic heart disease.

Introduction:

17.9 million people died of Cardiovascular Diseases (CVDs) in 2019 alone [1]. Of which, there are approximately 382,820 registered Ischemic Heart Disease (CHD) deaths annually in the United States [2]. If in-situ heart resurrection fails, heart transplants are most commonly used to treat CHDs. Nevertheless, the rising demand for transplants led people with CHDs to seek alternative treatments.

There are challenges and limitations, including the lack of organ donors, immune rejection, damage to myocardium cells when conducting the transplantation, and trauma to the patient. Consequently, there is a growing need for improved technologies in stem cell cultivation, 3D-Bioprinting, and vascular grafting. The application of these cutting-edge technologies is in growing demand to ultimately design a functioning heart via in-lab culturing, which can produce promising results in saving lives. With recent advancements in cardiovascular tissue engineering, the quality of life may be improved, and the mortality rate may be decreased.

Even though the heart is about the size of a fist for adult humans, it is a cross-center between systemic and pulmonary circulation. With so many demands placed on the heart, it becomes susceptible to disease. On the anatomic level, a heart is a four-chambered system. Precisely, the heart is divided into four separate chambers, each with a unique purpose. To start off, unoxygenated blood with waste products is pumped from the body through the superior and inferior vena cava into the upper right chamber, called the right atrium. Patients affected by CHDs will have reduced blood flow from the vena cava to the right atrium.

After the blood travels through the right ventricles to the lungs, the highly oxygenated blood then enters the left heart to renew the oxygen supply of the body [3]. For CHD patients, blood which returns to the heart is inadequate to provide sufficient oxygen and nutrients to the heart. This may weaken the heart, creating a negative feedback loop to the heart's efficiency [4].

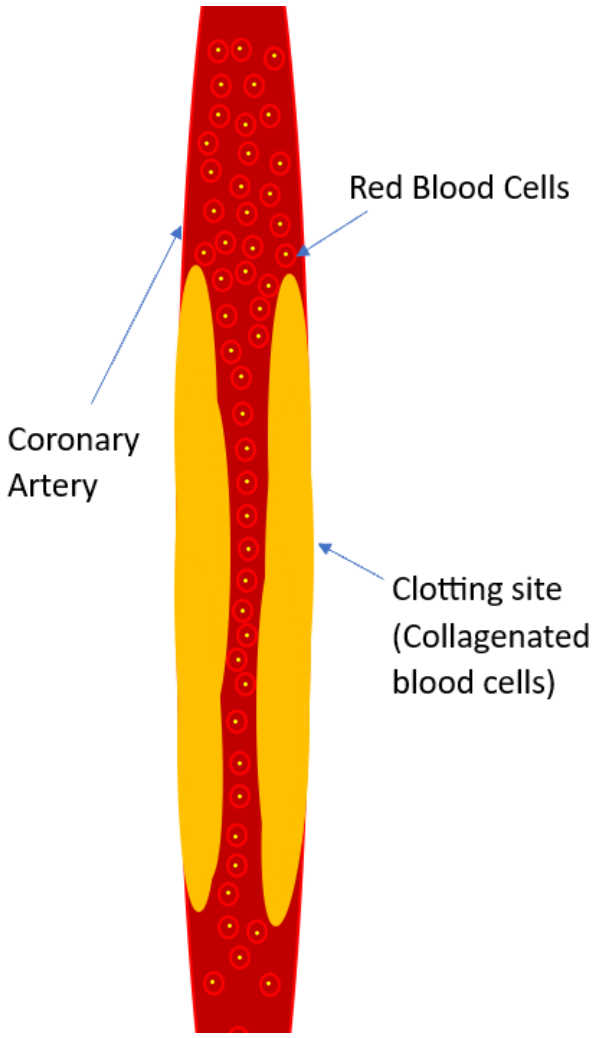

Figure 1: A model of a blocked coronary artery caused by ischemic heart disease. Red blood cells passing through the artery are substantially slowed down, decreasing blood flow to the heart.

Due to the importance of this renewal of oxygen and the transfer of nutrients, not only does the myocardium tissue population but also the artery size is essential for the effectiveness of the systematic and constant cardiovascular system during systole and diastole torsional motion. Hence, any clogging, such as ischaemic heart disease (CHD) may lead to thrombosis, arrhythmia, and left ventricular hypertrophy [5].

On average, there are roughly 5 liters of blood in the human body. 10-15% of that blood is within the arteries at any given moment. 75% of the blood is in the veins. The rest are in the capillaries. Blood travels through blood vessels after every heartbeat, circulating and maintaining the body's oxygen, nutrients, and waste disposal. Blood vessels and the heart alike, are essential for the proper function of the human body, yet they are delicate and distinct [6].

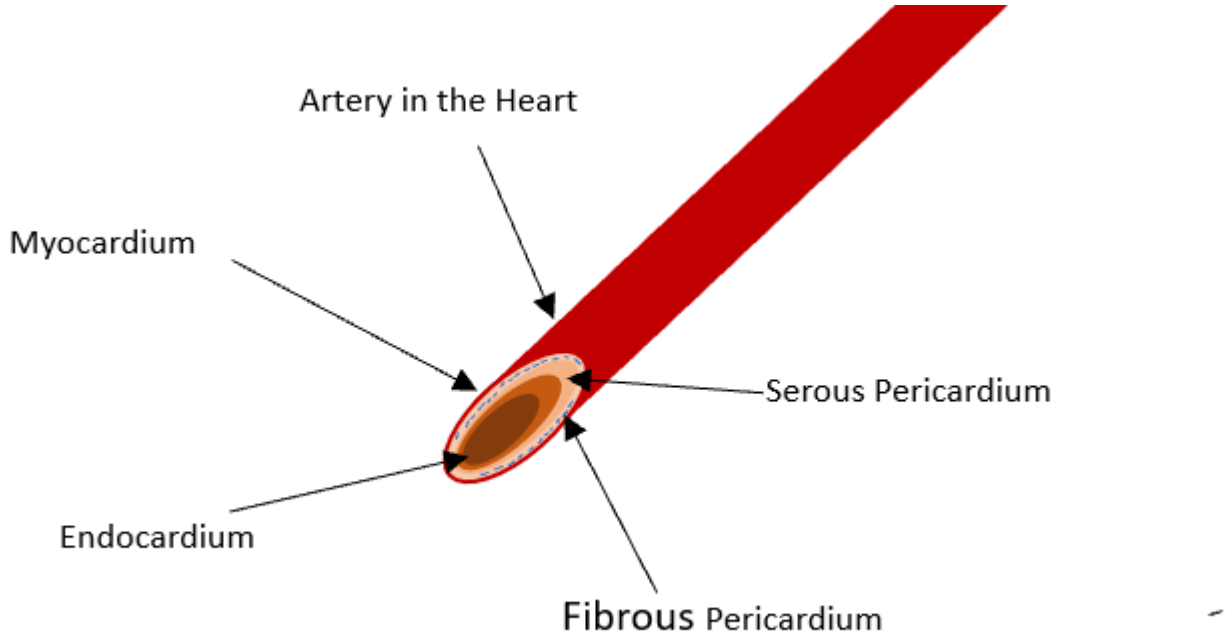

Figure 2: A model of an artery and its four distinct layers. The outmost layer is called the Fibrous Pericardium. The next layer is called the Serous Pericardium. The layer after that is the Myocardium. The last layer is called the Endocardium.

There are 4 distinct layers of an artery. The outmost layer is called the fibrous pericardium layer. It consists of fibroblasts which secure the heart's anatomical position. The next layer consists of the serous pericardium. It secretes lubrication to ensure that the force of the myocardium is functioning properly and prevents any damage or clogging of blood. The third layer consists of the Myocardium, which generates the contractile forces of the heart in order to allow blood to circulate. CHD patients may experience decreased contractile force function as well as the loss of myocardium tissue due to the lack of nutrient and oxygen supply [7]. Finally, the fourth layer is called the endocardium, which has tiny endothelial trabeculae used to increase pump force and contact area [8].

Epithelial Tubular Grafts:

Cell adhesion in artificial valves can cause blood clots, often leading to death. Valve grafts may solve this. Additionally, valve grafts are substantially cheaper than heart transplants and also can be used in cases that cannot be addressed through regenerative medicine.

Currently, there is a significant issue with cell adhesion in artificial valves. It could lead to the formation of blood clots due to the body's innate response to foreign objects, which may be fatal. This calls for the need for valve grafts as they can be clinically used to save those who cannot use regenerative medicine or afford heart transplants. A recent breakthrough on epithelial cell sheets originally used in treatment of patients with burns inspired the application of a new approach to vascular tissue engineering. This approach solely relied on human cells to engineer blood vessels without using exogenous scaffolds.

In one set of experiments, blood cells were initially separated and cultured (30 days) before being mechanically peeled from the culture substrate and subsequently rolled onto a mandrel. The resulting configuration allowed for the production of media and adventitia (connective tissue in the outermost layer of the blood vessel) equivalents. Subsequently, through an 8-week process, a blood vessel exhibiting native functions (three layered; intima, media, and adventitia) will be produced after endothelialization of the lumen side of the tubular graft.

In order to prevent blood clotting, there is an enhancement to the lumen endothelium, which through adding a layer between the intima and media, is able to mimic the internal elasticity of the lamina in a native blood vessel. Furthermore, an experiment on dogs conducted over the period of 7 days yielded results which show that the vascular graft exhibits native-like functions, a higher burst pressure of the vascular graft to become stronger than 2000mmHg (stronger than regular vascular grafts), and adhesion strength, which all together prevents blood clotting. Also, this tubular graft has similar extracellular-matrix (ECM) proteins composed of chondroitin sulphates, collagen types I, III, and IV, laminin, and fibronectin, which too causes the graft to manifest native-like functions.

There is a drawback to this study. Since native-like properties of the tubular graft is dependent on the cell type, there is a lengthy production period. More specifically, during maturation, the graft is prone to tears or damage when peeling the graft off of the culture flask, especially if not done with caution.

This drawback may be addressed through the usage of Temperature-Responsive poly (N-Isopropylacrylamide) biomaterials. When at 37°C, these materials are able to undergo changes through acute adjustments to the temperature due to their hydrophobic and hydrophilic

properties [9]. By manipulating the changes of the biomaterial's properties, it allows peeling the graft to be smoother, hence preventing tears.

Fabrin Glue Grafts:

In a different study, a vascular graft exhibiting native-like functions is demonstrated announced by Syedian et al. (2016). Composed of fabrin glue, the graft is created through fibroblasts that are decellularized to create a tubed-structure, which are then implanted into lambs and are observed. Results show that the host is able to fully adapt with the graft, being able to form elastic connective tissue, collagen, and somatic cells inside of the decellularized graft as well as having full endothelialization. These results indicate that unlike typical vascular grafts which are patent for up to 7 years, it may constitute as a permanent graft for patients after further clinical trials (on pediatric and adolescent patients) [10].

This study may serve as a solution to the current concern of vascular grafts not exhibiting native-like functions such as stiffness, efficiency, and strength. However, the current method of production requires simplification to the culturing process along with tubular formation to improve production and efficiency.

Biodegradable Synthetic Grafts:

The final phase of somatic growth for adolescent and pediatric patients is problematic, needing new interventions for the fabrication of synthetic scaffolds. Shin'oka et al and Hoerstrup et al seeded biodegradable synthetic polymer tubes with autologous cells in a set of experiments. Results show promising increases in graft growth and remodeling. This study is currently in clinical trials. Efforts put into further specialized tasking to expand the growth of synthetic scaffolds would decrease the issue for routined clinical practices which may improve the efficiency in the fabrication of synthetic scaffolds [11].

Braided Tube-Reinforced Silk Fibroin Grafts:

An occurrence where grafts are ineffectual or laggish in adapting to the surrounding tissue's growth rate may lead to the immune system terminating the graft. This lack of biomechanical compatibility with native blood vessels, in turn, will cause neointima formation, activating the immune system and resulting in graft failure.

A study done by Li et al yielded promising results. The graft, which is made of braided tube-reinforced with silk fibroin, was observed to have no signs of damage nor degradation during the test where the graft was placed into an in vitro biomimetic environment.

Though the study does show promising results, the study contains only short-term data for degradation and damage. Without long-term data, nuanced and factual conclusions cannot be drawn [12].

Decellularized ECM Bioinks and Extrusion-Based Bioprinted Heart Valves:

There are three distinct methodologies to reduce cardiac hypertrophy and fibrosis; however all three ways follow the procedure of dual stem cell bioprinting, which can be done with precision.

Decellularized ECM bioinks are used for micro-trauma bioprinting of fully-functional grafts in mice-models for Ischemic heart disease treatment. It can improve cardiac regeneration, cell differentiation, and cell communication. Doing so increases muscle growth in grafted areas, improves heart function, increases vascularization, and reduces fibrosis and hypotrophy. This dual stem cell bioprinting method is capable of rapidly producing ECMs with high cell density, exhibiting native-like functions which are (which are crucial as it decreases the likelihood of tears to the graft and improves stiffness and efficiency) sufficient for clinical use.

On the other hand, the production process is gradual, has variable cell viability, and high pressures at the nozzle, which may damage cells as the bioprinting process is undergone. Additionally, there are limited options in the bio-inks used for this bioprinting method; particularly, materials that have low viscosity are unable to be used.

In contrast, Van der Valk et al conducted a study on extrusion-based bioprinting of heart valves through fabricating a CAVD (Calcific aortic valve disease) model, yielding results that expands on the current knowledge of vascular mechanobiology and show the effective ability of the method to bioprint precise and complex heart valves. Methacrylated gelatin (GelMA), methacrylated hyaluronic acid hydrogels (HAMA), and valvular interstitial cells were used to bioprint the CAVD model in 3D form, which has shown native biomechanic functions.

Similarly, Duan et al used aortic VICs in leaflets and aortic root sinus SMC valve roots to bioprint aortic valve conduits. Results show increased levels of alpha-smooth muscle actin in SMC valve conduits and increased levels of vimentin for VIC valve conduits. These valves have increased viability compared to acellular hydrogels (83.2 ± 4.0% for VIC and 81.4 ± 3.4% for SMC) [13].

SMC and VIC valve conduits increase do allow for precise bioprinting with increased viability. Nevertheless, a deeper understanding of the current knowledge of vascular mechanobiology and more work is needed to fully investigate the affect of SMC and VIC valve conduits regarding the design, biomechanics, and properties of aortic valves.

Computed ECM:

Grafts that are unable to adapt to blood pressures of humans may change blood viscosity and stenosis of the host, which may lead to negative effects such as further worsening of CHD, hyperplasia, and thrombosis. Furdella et al conducted a study using computational approaches to design an ECM that mimics native tissue properties including diameter, thickness of tissue walls, and target tissue appliance. These properties of the ECM improve tissue flexibility, mechanical strength, and cellular function. In turn, it is able to adapt well to in vivo blood pressures. On the other hand, though the ECM does mimic native properties and improve function, more work to adapt to hemodynamic blood pressures and adjustments to the biomechanical response ECM would further enhance its functions [10].

Overall Limitations:

In summary, current approaches to CHD are attempting to bridge the gap of understanding to the immune system and the ability to prevent immune rejection as well as mimicking native functions and properties. Of the six interventions identified above, interventions which tackle cell adhesion, somatic growth, fibrosis and hypertrophy, and the pace of adaption of a vascular graft to a host are the result of dealing with immune rejection. Interventions resolving blood pressures and mimicking native biomechanical properties and functions arise from the concern of biocompatibility.

Further development of current technologies in cardiovascular tissue engineering is needed. In addition, deepening the current understanding of immune rejection and biocompatibility is necessary.

Conclusion:

The heart is a complex structure which is naturally prone for disease. There have been many approaches to the treatment of these diseases such as heart transplantation, regenertive medicine, and therapy. However, from the plenty of recent advancements to the field of tissue engineering and its applications to the treatment of ischemic heart disease, it is undoubtedly a field which contains great potential.

Currently, treatments to ischemic heart disease through cardiovascular tissue engineering approaches focus on the development of artificial valves, vascular grafts (through decellularization and recellularization, and ECMs, bioprinting, and biomaterials including silk fibroin), synthetic scaffolds, and computational approaches. However, due to the limitations of the current technology in treatment and the understanding of CHD, much work is needed to be done.

Advancements may be made if graft biomaterials are more biocompatible and show native-like functions such as stiffness, efficiency, and strength. This would likely increase graft life expectancy, potency, and decrease the likelihood of immune rejection, thereby improving current designs.

Improvements to the complexity of multicellular ECM models would increase efficiency and further mimic native functions.

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