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The future of artificial hearts

Hearts breakthroughs in becoming biomimetic

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INTRODUCTION

Heart failure and donor shortage

The human heart is a remarkable organ that pumps blood through the body with each beat. It has four chambers; the left and right atrium and the left and right ventricle. By pumping the blood, oxygen and nutrients are distributed to all organs, while metabolic waste and carbon dioxide are carried away. Despite the heart's primary function is simple - to pump blood - , its anatomy and physiology are incredibly complex. The right side of the heart pumps oxygen-poor blood to the lungs to receive oxygen, while the left side pumps oxygen-rich blood to every organ in the body. The heart ensures that the blood flow in both circulations remains balanced. In addition, the heart has extreme strength and durability, as it pumps over 3 billion times throughout a lifetime.

Heart failure is characterized by a severely impaired pumping function of the heart. In the Netherlands, approximately 2% of the adult population, or 240.000 people, are affected by heart failure^{1,2}. Each year, 7.500 people in the Netherlands die as a result of this condition². As the global population continues to age, the prevalence of heart failure is expected to rise. It is anticipated that the annual prevalence of people with heart failure in the Netherlands will increase with 72% by the end of 2040³. Heart transplantation is currently considered the gold standard treatment for end-stage heart failure. However, a tremendous shortage of donor hearts exists worldwide. In the Netherlands, approximately 40 heart transplants are conducted each year, while approximately 140 people are on the waiting list to receive a donor heart⁴. Because the majority of patients have no prospect of recovery, there is an urgent need for destination therapies for (biventricular) end-stage heart disease.

Mechanical devices to overcome the shortage in donor hearts

To address the shortage in donor hearts, mechanical devices have been increasingly implanted in the last two decades as alternative therapies to support the failing heart. These devices include left ventricular assist devices (LVADs) and total artificial hearts (TAHs). In the Netherlands, approximately 80 LVADs are implanted each year⁵, while only one TAH has been implanted thus far⁶. While LVADs provide a treatment option for patients with left ventricular failure, they are not suitable for individuals with severe biventricular failure or other conditions that restrict their use⁷. Moreover, it is important to note that LVAD support can lead to a reduced quality of life and carries a significant risk of complications, such as thromboembolic events, bleeding, and driveline infections⁸⁻¹¹.

A TAH is a surgically implanted pump that provides blood circulation through the lungs and body¹². It is implanted in the chest after removal of the native heart, and thus replaces both the left and right ventricles. A TAH provides either pulsatile or continuous blood flow, depending on its working mechanism. TAHs that provide pulsatile blood flow typically consist of two artificial ventricles and four artificial heart valves. Each artificial ventricle is equipped with a membrane that separates the blood collection chamber from the actuation

system, where the actuation principle can be pneumatic, hydraulic, or mechanical. The blood contacting surfaces of pulsatile TAHs consist of the artificial heart valves and the inner surface of the artificial ventricles. In addition, a TAH typically has two vascular grafts and two atrial cuffs that form a connection between the tissue of the patient and the TAH. During surgical implantation, the vascular grafts and atrial cuffs connected to the TAH are sutured to the remnants of the native atria and to the ascending aorta and pulmonary artery.

There are several existing challenges in the development of TAH devices that must be addressed. The device must be of an appropriate size and weight to fit in the pericardial space of the patient. It must be reliable and durable, while beating approximately 35 million times a year. Additionally, the device should be able to respond to changing hemodynamic conditions and to provide a balanced output of the left and right ventricles. Moreover, electrical power must be transferred to the artificial heart, preferably without the use of percutaneous cables. Finally, the TAH must be biocompatible, with a low risk for thromboembolic complications.

To date, the successful development of a TAH device that meets all the necessary requirements has proven challenging. The current clinically available TAHs are characterized by their bulky design, poor biocompatibility and the presence of large percutaneous hoses. Consequently, these factors increase the risk of thrombotic events, infection, and impair the overall quality of life for patients. As a result, TAHs are currently very sparsely implanted¹³. Therefore, it is imperative to seek for a new wave of innovation by using novel technologies to create a new generation of TAH devices that can overcome these limitations and enhance clinical outcomes.

Soft robotic technology

In the past decade, the field of soft robotics has rapidly developed with the goal of creating versatile systems that can safely interact with the human body and tissues¹⁴⁻¹⁶. As the name implies, soft robots are made entirely of soft materials. This new technology has resulted in a wide range of applications and prototypes, such as soft robotic grippers^{17,18}, exoskeletons¹⁹, soft robotic gloves^{20,21}, and minimally invasive surgery tools²²⁻²⁴. Soft robots are lightweight, flexible and can achieve range of motions that emulate biology¹⁶. Soft robotic technology may potentially be well-suited for blood-contacting devices due to its potential ability to minimize harm to blood cells compared to their rigid counterparts²⁵. As a result, there is growing interest in using this technology for developing novel soft robotic cardiac assist devices²⁶ and soft robotic TAHs^{25,27}.

Biocompatibility of TAH devices

Biocompatibility is a term used to describe the ability of a material to perform with an appropriate host response in a specific situation²⁸. In the context of TAH and LVAD development, biocompatibility entails achieving physiological blood flow during ejection, combined with utilizing biocompatible blood contacting surfaces. Obtaining biocompatibility is a significant challenge for the current rigid TAHs and LVADs. The rigid inner parts of rotors used in LVADs and continuous flow TAHs, damage the blood cells and eject blood in a non-physiological way, thereby increasing the risk for thrombosis²⁹. Additionally, the artificial materials used for valves and ventricles of TAHs can induce thrombosis³⁰. To mitigate the risk of thromboembolic complications, all patients with a TAH currently receive antithrombotic medication, which increases the risk of bleeding complications. Furthermore, high fluid flow shear stress produced in the blood pumps, can lead to acquired Von Willebrand disease and also to bleeding complications. Bleeding and thromboembolic complications are the most frequently reported causes of death in the current generation of mechanical circulatory support devices¹¹.

For soft robotic TAHs to become successful, the blood contacting surfaces must be biocompatible and the ejection of blood should mimic nature. The blood contacting surfaces entail the innermost layers of the artificial ventricles and the four artificial heart valves. To enhance the biocompatibility of TAHs, the use of supramolecular biomaterials has been suggested. Supramolecular biomaterials have earlier been used for a wide range of applications, including cardiac patches³¹, vascular grafts^{32,33} and heart valves^{34,35}. This technology could also be highly relevant for developing biocompatible blood chambers and valves for TAHs. The main advantage of using these supramolecular biomaterials is the modularity to create a functional surface with desired properties for any application. A supramolecular structure provides a dynamic environment that resembles the natural extracellular matrix³⁶⁻³⁸, which is normally present around cells. Depending on the fabrication method and the addition of various peptides and other extracellular matrix derived molecules, these biomaterials can have various functions. For instance, they can be fabricated as a highly anti-thrombogenic surface when used as a coating, or they can be used to fabricate scaffolds that attract cells for in situ tissue engineering purposes. In situ tissue engineering relies on endogenous colonization of a scaffold by host cells, followed by in situ tissue formation and remodelling of the implanted scaffolds, while the synthetic scaffold is gradually resorbed. For soft robotic TAH applications, in situ tissue engineering may be useful for the development of valves, vessels, and for the innermost layer of the artificial ventricles. In order to mimic physiological blood flow effectively, a soft robotic TAH should ideally feature biomimetic contraction of the soft artificial muscle, closely resembling the pump function of the human heart. This biomimicry is crucial for reducing the shear stress imposed on blood cells, minimizing potential damage, and ultimately improving biocompatibility. The soft and pliable materials typically used for building soft

artificial muscles offer an ideal platform to achieve this biomimicry, standing in stark contrast to the rigid rotor blades typically used in traditional mechanical circulatory support devices²⁹.

Transcutaneous energy transfer

All LVADs and TAHs are mechanical devices that require electrical power to operate. Currently, percutaneous cables are used to transfer electrical power to the implanted devices. Due to the continuous high-power requirements of at least 5-12 Watts for LVADs and TAHs^{39,40}, implantable battery packs (that are widely used for pacemakers) are not sufficient. The percutaneous cables impair the quality of life of the patient and are associated with a high risk for infections^{40,41}.

A promising solution to this problem is the use of a transcutaneous energy transfer (TET) system. This wireless power delivery system uses magnetic fields to transfer power from an external coil across the skin to an implanted coil, while leaving the skin intact. Internally, the power is used by the implanted controller and the TAH device and/or stored in implanted batteries. The external components other than the external coil include battery packs and a control box that can be carried by the patient in a bag. The challenge to use TET systems for TAHs is that high power levels are demanded, which have to be transferred through the skin. High power levels increase the heat dissipated by the TET coils. Therefore, the skin may be exposed to high temperatures what might result in tissue damage⁴⁰. In order to facilitate transcutaneous powering of TAH devices in the future, it is crucial to achieve high efficiencies in both the TAH as well as the TET system. Once successful, a patient receiving a wireless TAH will have more freedom of movement, a better quality of life, and a significant reduction in the risk for infection.

Objective

Despite decades of research, a viable alternative therapy to heart transplantation for patients with end-stage heart failure has not yet been accomplished. The integration of cutting-edge technologies is required to develop a durable and biocompatible TAH that can overcome the challenges in the field. The Hybrid Heart project represents a collaboration of experts from diverse fields, including robotic engineers, biomaterial scientists, chemists, electrical engineers and clinicians, who have set out to develop a biocompatible soft robotic TAH. Within the scope of the Hybrid Heart project, the aim of this thesis was (1) to provide a better understanding of the challenges related to TAH development and (2) to develop a novel TAH (the Hybrid Heart) using soft robotic technology, biocompatible materials, tissue engineered heart valves, and a TET system (Figure 1).

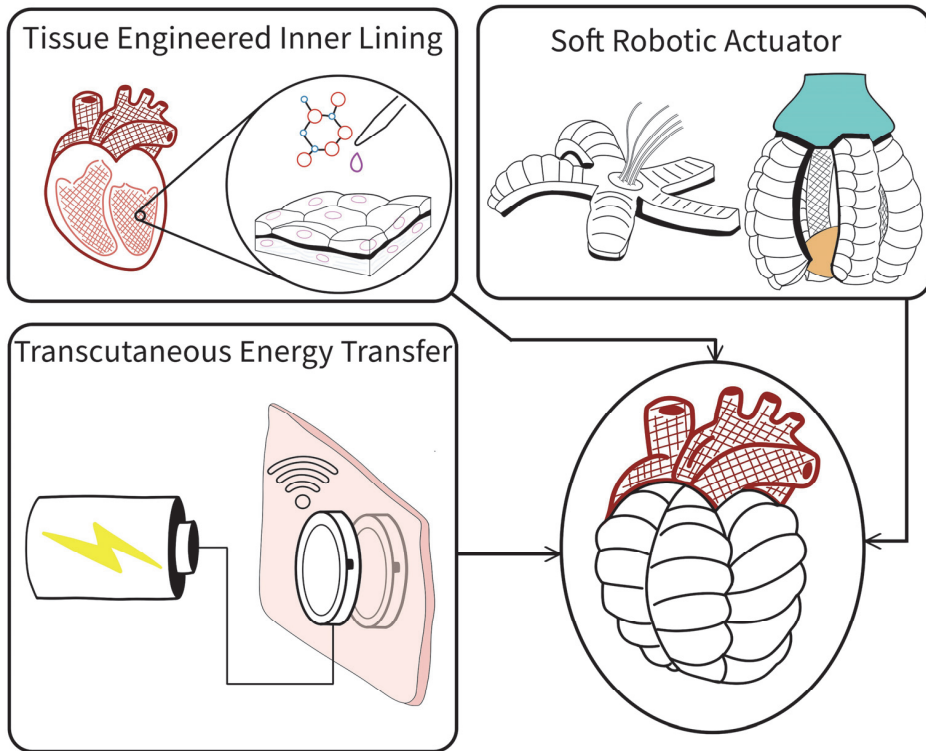


Figure 1. The Hybrid Heart concept. The pumping function of the Hybrid Heart is established by using soft robotic actuators. The blood contacting surfaces (the inner lining of the ventricles and the artificial heart valves) are made biocompatible, by means of in situ tissue engineering techniques. The energy supply to the artificial heart is provided via a transcutaneous energy transfer system. Image from: Arfaee M, Vis A, Kluin J. Future technologies in total artificial heart development: can a robot become as good as a donor heart? *Eur Heart J.* 2022;43(48):4970-4972.

Thesis outline

The development of TAHs can be traced back to the 1960s, and since then, numerous prototypes have been developed and tested. While a few have been successfully implemented into clinical use, most ideas and prototypes have been abandoned for various reasons. Before embarking on the development of our own soft robotic TAH prototype, it is valuable to learn from the successes and failures of the past. Therefore, we conducted a comprehensive literature review of all TAH devices from the past to 2022, as reported in **Chapter 2**. In this chapter, we identify the main challenges in TAH development. Through our research, we gained insight into the difficulty of obtaining biocompatibility and maintaining balanced ventricular outputs of TAHs. To delve deeper into the latter, we conducted a separate literature review on this topic that is reported in **Chapter 3**.

Chapter 4 focusses on the main topic of this thesis, which is the development of the Hybrid Heart, a novel soft robotic artificial heart developed by our consortium. This chapter demonstrates the successful application of soft robotic technology for TAH development, resulting in a working prototype that has been implanted in an animal trial. In **Chapter 5**, we continued our research by developing biocompatible coatings for the innermost layer of the Hybrid Heart's ventricles, specifically making it anti-thrombogenic. **Chapter 6 and 7** describe the long-term in vivo testing of in situ tissue-engineered aortic heart valves implanted in the aortic position in sheep. These in situ tissue-engineered heart valves hold great promise, as they possess the potential to become biocompatible and durable artificial valves that can be integrated into future Hybrid Heart prototypes. In **Chapter 8**, we report on the in-house development of a TET system to power the Hybrid Heart.

Chapter 9 provides a comprehensive discussion of the research findings and their implications, and **Chapter 10** provides a summary of the thesis.

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