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The future of artificial hearts

Hearts breakthroughs in becoming biomimetic

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GENERAL DISCUSSION

Discussion

The incidence of heart failure is on the rise, and so is the number of patients waiting for a donor heart. In recent years, efforts have been made to address the gap between the high number of patients suffering from end-stage heart disease and the limited availability of donor hearts. These include strategies to expand the donor heart pool, such as ex vivo cardiac perfusion¹ and xenotransplantation². However, while ex vivo cardiac perfusion has shown promise, this strategy still relies on the availability of human donor hearts and is unlikely to have a significant impact on increasing the number of heart transplantations. The use of xenotransplantation is still in its early stages, and it remains unclear whether it will become a viable option in the future. An attempt to bioengineer a whole living heart (of a rat) documented visible contractions of the cardiac muscles³. However, the pump function of the engineered heart was limited to about 2% of normal contraction³. These findings underline that these alternative strategies to overcome the donor heart shortage will not be successful soon (if ever). It is evident that other potential strategies to treat end-stage heart disease should be sought after.

Since the 1960s, researchers have been striving to develop a mechanical replacement for failing hearts⁴. However, despite the more than 60 years of research, a durable and biocompatible mechanical replacement for the human heart has yet to be found. Chapter 2 provides an extensive overview of all the total artificial heart (TAH) devices developed thus far, emphasizing the challenges and pitfalls that researchers have faced. The fact that only a few TAH devices are still in use or under further development underscores the difficulties in mimicking the complex functions of the native human heart. It is therefore of utmost importance to learn from past successes and failures when starting to develop a novel TAH.

History of TAH development; lessons learned from the past

A significant challenge encountered in the development of TAHs is the incorporation of preload sensitivity and maintenance of balanced ventricular outputs (Chapters 2 & 3). Severe clinical complications arise when there is an imbalance in the output of the left and right artificial ventricles, primarily resulting in respiratory failure due to fluid accumulation in the lungs. This is supported by a significant mortality rate resulting from respiratory failures observed during animal trials of several TAH devices⁵⁻⁸. In Chapter 3, we conducted an in-depth investigation of the challenges associated with providing balance between the right and left ventricular outputs of TAHs. We discovered that for pneumatic TAHs, passive preload sensitivity could be achieved due to the compressible nature of air. This implies that no sensors or active control mechanisms are required, which reduces the likelihood of component failure. For mechanically actuated TAHs, we observed that passive preload sensitivity systems are not effective. In addition, we found that TAHs with separately actuated left and right ventricles exhibited the most successful preload sensitivity.

Therefore, in terms of achieving preload sensitivity and balanced ventricular outputs, we recommend researchers to focus on developing pneumatic TAHs with separate actuators for each ventricle. If researchers choose to develop a TAH with a single actuation mechanism for both ventricles, it is crucial to be aware of the potential implications and to carefully consider incorporating additional mechanisms that can respond to changes in preload.

Chapter 2 highlights another significant challenge in TAH development, which is the general poor biocompatibility of the devices. Since all TAHs have direct contact with blood, there is a high risk for thromboembolic events. This is reflected by the high number of thrombotic complications observed in animal studies with TAH devices^{5,9,10}. In recent years, considerable progress has been made in developing biocompatible materials. For example, the newest clinically available TAH, the Carmat, has implemented bovine pericardial surfaces to reduce thrombotic incidents, although the use of anticoagulants is still required¹¹. It can be argued that the combination of non-physiological flow during ejection and the use of conventional non-living materials in TAH devices, such as bovine pericardium, mechanical valves and bioprosthetic valves, contribute to the high risk of thrombotic complications. Consequently, it is imperative to investigate alternative materials to address this issue. We believe that the development of biomaterials and tissue engineering approaches that aim to grow a layer of the patient's own cells on the blood-contacting surfaces represents a promising avenue for addressing these challenges.

The findings presented in Chapter 2 and 3 have provided valuable insights into the main challenges in the development of TAH devices (including biocompatibility and balanced ventricular outputs). However, it was incredibly difficult to find information on device failures, reasons why the development of a certain TAH was discontinued, as well as the outcomes of animal experiments. In particular, we observed that essential information regarding animal studies, such as the number of animals involved, complications during follow-up, reasons for death, and the duration of follow-up, were often not reported. Despite not specifically scoring for it, we found that adherence to the ARRIVE guidelines¹², which provides a framework for reporting animal research, was poor for the TAH studies we examined. Essential details such as the species, strain, sex, and weight of the animals were frequently absent. Typically, only the longest surviving animal was reported, while the outcomes of the other animals were not described. Researchers also lacked transparency in reporting the reasons for death or complications during follow-up, which is vital information that should be shared with new TAH researchers to facilitate learning from past experiences. The lack of transparency regarding complications during follow-up and reasons for death resulted in various forms of bias in these articles, including selection and reporting bias. Consequently, the data reported in the papers may present an overly optimistic portrayal of TAH performance. Authors should recognize that the use of animals entails

significant ethical considerations that can only be justified by reporting all aspects of the animal study. Researchers conducting animal studies must always bear in mind the purpose of the ARRIVE guidelines and adhere to them. Journal editors and reviewers also play a crucial role in ensuring compliance with these guidelines by requiring authors to incorporate all essential ARRIVE criteria into their manuscripts before they can be approved for publication. The generally poor quality of reporting in TAH research has left us with a critical question regarding TAH devices that are no longer under development: what were the failures that led to their discontinuation? Despite analysing over twenty TAH devices that stopped their development, we discovered that not a single study reported the reasons for termination. This information is indispensable for advancing the field, and authors should prioritize sharing both their failures and successes to contribute to the progress of TAH device development.

Recent progress and prospects for TAH development

This thesis presents the development of a novel soft robotic TAH, known as the Hybrid Heart, as outlined in Chapter 4. The utilization of soft robotic technology in TAH development is a recent advancement and offers potential advantages, including a biomimetic contraction, which is argued to be less traumatic to the blood cells¹³. Moreover, soft robots are designed to interact safely with their surroundings and may be controlled without the need for electronic components¹⁴. Soft TAHs are lightweight, can be made fully implantable when combined with a transcutaneous energy transfer (TET) system (Chapter 8).

Mimicking nature

The Hybrid Heart is a novel TAH made from soft materials, including fabric and nylon coated with thermoplastic polyurethane (nylon-TPU). The design closely mimics the anatomy of the human heart, featuring two ventricles and a septum. The septum actuates the Hybrid Heart by means of pneumatic pressure and wires. With the development of a soft robotic TAH, we aimed to replicate the contractile motion of the native human heart, mimicking a physiological way of ejecting blood. Our ultimate goal is to prevent trauma to blood cells and reducing the risk for thrombotic events in patients with a TAH. We hypothesized that the use of soft materials on itself would cause less harm to blood cells compared to rigid metal rotor blades that are commonly used in continuous flow LVADs and TAHs. During laparoscopic tests, we observed the formation of folds inside the ventricles of the Hybrid Heart during ejection, occurring in similar fashion for each heartbeat. Additionally, we noted that the lumen diameter of the ventricles decreased during each heartbeat, and increased during relaxation. In our preliminary experiments involving 4D flow magnetic resonance imaging (MRI) of the Hybrid Heart in a mock circulation, we found laminar flow during the filling and ejection phases of the ventricles. Both these findings suggest that the Hybrid Heart potentially mimics the contractile motion of the human heart, although further

research is necessary to confirm this statement. Moreover, at present, we cannot draw definitive conclusions regarding whether this bio-inspired motion effectively reduces thrombotic complications. One critical unanswered question is whether there are any regions inside the Hybrid Heart's ventricles that experience blood stasis. Future work should therefore focus on optimizing 4D flow MRI tests, particularly to simulate physiological test conditions. Specific 4D flow MRI tests should be conducted to study the flow patterns inside the artificial ventricles, aiming to identify any regions where undesired stagnant blood flow occurs. If such regions are identified, adjustments to the contractile motion of the Hybrid Heart should be made to prevent this.

The precise anatomy of the heart muscle has been a subject of investigation for more than four centuries, yet there is no consensus reached on the exact organization of the myocardium. Some anatomical studies suggested that the muscle fibres of the human heart form a helix, starting from the outer layer and proceeding inward in a clockwise direction before reversing and moving outward in a counter clockwise direction. This organization of muscle fibres has been observed as a continuous "rope" or "band"^{15,16}. However, there is limited anatomical support for this statement¹⁷. Alternative interpretations include the idea that the ventricular walls are formed out of "sheets" or "layers"¹⁸, but this has not been confirmed with histology¹⁷. A more recent theory speculates that the cardiomyocytes are aggregated together as a three-dimensional mesh within a matrix of fibrous tissues¹⁷. Although there is no consensus reached on the exact organization of the myocardium, it is clear that the alignment and angulation of the myocytes play an important role in establishing such a strong contractile force of the ventricles^{15,17}. During contraction, the heart undergoes a twisting movement that significantly contributes to its ejection fraction. This is underlined by the fact that the shortening of individual myocytes during contraction is not more than 15-20%, whereas the ventricle as a whole achieves an ejection fraction of 60%^{15,17}.

Therefore, to further optimize the bio-inspired motion of contraction of the Hybrid Heart ventricles, we can learn valuable lessons from nature and implement them in future prototypes. This may result in improved ejection fraction and a more physiological blood flow. Currently, the design of the Hybrid Heart ventricles only exhibits contraction and dilation in the transverse plane, which we know from nature is not very efficient. The incorporation of a twisting movement during contraction of the artificial ventricles is an interesting concept that warrants further exploration in future prototypes. For the Hybrid Heart, we can organize the wires in a spiral shape or potentially a double helix shape around the ventricles. These tests can be conducted through in vitro experiments in mock circulations. However, since investigating all possible wire arrangements is time consuming, conducting initial in silico experiments using computational modelling may prove more efficient.

Soft but non-stretchable materials

Soft and stretchable materials, such as silicones, have been used in previous preclinical cardiac assist devices, such as the cardiac sleeve by Roche et al.¹⁹, and TAHs like the Zurich Heart¹³. However, it is known that the durability of the stretchable materials used for these applications is limited. For instance, the Zurich Heart demonstrates a durability of only 110,000 cycles, roughly equivalent to a single day of pumping¹³. To overcome the poor durability associated with commonly used stretchable materials in the field of soft robotics, we opted to construct our Hybrid Heart prototype using soft but non-stretchable materials. We selected nylon-TPU as base material for our prototypes, which has frequently been employed in other soft robotic applications, such as rehabilitation gloves²⁰, ankle sleeves²¹ and elbow sleeves²². Additionally, the use of nylon-TPU has been used for a soft robotic cardiac compression device²³ and aortic sleeve²⁴. The main benefits of using nylon-TPU for the fabrication of artificial muscles is its strength (six times greater than mammalian skeletal muscle²⁵) and its potential for chemical modifications to tailor its properties for a wide range of applications. However, it should be noted that non-stretchable nylon-TPU has not been previously used in other TAH applications, and there is a lack of literature evidence suggesting its improved durability compared to stretchable materials.

A notable benefit of using stretchable, and thus compliant materials, is the ability to achieve passive preload sensitivity, which holds significant clinical benefit. However, previous studies with utilizing stretchable and compliant materials for TAHs have indeed demonstrated high preload sensitivity, but this was accompanied by undesirable high afterload sensitivity²⁶. Namely, afterload sensitive TAHs show a quick decline in cardiac output when afterload (mean blood pressure) increases. In the case of the Hybrid Heart (Chapter 4), despite using non-stretchable materials, we also observed preload sensitivity. This can be attributed to the fact that under normal preloads, the ventricles were not completely filled, allowing some buffer capacity to accommodate for preload increases. It is unclear yet, if this effect is sufficient or whether an additional passive mechanism that allows for stroke volume changes is necessary in future Hybrid Heart designs. The Hybrid Heart is a pneumatic TAH, which is convenient for implementing balancing mechanisms due to the compressible nature of air. Possible additional passive mechanisms could involve incorporating a system with an extra pneumatic compartment in the ventricles (air cushion) that can be compressed during high preloads, resulting in higher end diastolic volumes. Moreover, the use of origami folding techniques have been described to implement compression and expansion properties of textiles^{27,28}. One could think that the use of origami folding in the Hybrid Heart ventricle would allow for expansion, and thus an end-diastolic volume increase, by a rise in preload. However, the potential effect of such folds on biocompatible coatings and cell adherence should be watched closely. Furthermore, the inclusion of separate actuators for the left and right ventricles, as seen in Syncardia and Carmat systems, offers benefits in regulating the balance between ventricular outputs. It

may be worthwhile to consider implementing such an approach in upcoming Hybrid Heart prototypes.

Although the development of soft TAHs offers clear advantages, such as the possibility of resuscitation through chest compressions during acute emergencies, some possible disadvantages can also be observed. One notable drawback is the absence of a rigid outer shell, making them more susceptible to external influences and their surrounding environment. Within the pericardial space, there are inherent constraints in terms of size and adjacent structures such as lungs, sternum, ribs and the thoracic wall. Moreover, the pressure inside the thorax fluctuates during the respiratory cycle, further complicating the dynamic environment. Shortly after surgery, the pressure inside the pericardial space may also be altered due to the presence of blood or fluid in the pericardium and/or lungs. Similar to the human heart, soft TAHs may experience significant impairments in function that may result in a cardiac tamponade. During the *in vitro* tests, the Hybrid Heart prototype was placed free in the open air allowing unrestricted movement in all directions. However, during the acute animal trial, where we implanted the Hybrid Heart within the pericardial space of the goat, its pumping function may have been compromised due to surrounding anatomical structures. We noted that the achieved cardiac output during the animal trial was only half of what was observed in the *in vitro* studies. To address this issue, it may be beneficial to develop an *in vitro* environment that accurately mimics the available pericardial space.

Pneumatic versus hydraulic actuation systems

The pneumatic actuation system used for actuation of the Hybrid Heart, offers several advantages in terms of easy prototyping and convenience during *in vitro* testing. Similar pneumatic actuation techniques have been successfully employed in clinically available cardiac assist devices, such as the Syncardia TAH, first generation LVADs (such as HeartMate 1000 IP²⁹), and intra-aortic balloon pumps³⁰, which underscores the safety and efficacy of this actuation technique. However, potential disadvantages can be seen when using pneumatic driving systems for fully implantable TAH devices. These include a potential risk of air leakage, which is especially dangerous in case of leakage in the blood stream. Furthermore, pneumatic systems often require a compliance chamber, which is an extra component that takes up space in the pleural or abdominal cavity of the patient and contains highly pressurized air. Theoretically, the same Hybrid Heart prototype can also be actuated by means of a hydraulic actuation system. Within the scope of this project, this has not been investigated yet, but it holds promise for future endeavours. Hydraulic actuation system may be more suitable when developing a fully implantable TAH. This is underlined by the Carmat TAH, which has a hydraulic actuation system in which the pump is also located inside the body. The use of a hydraulic actuation system may offer advantages in terms of reduced risk in the event of a small leak into the bloodstream, as

well as eliminating the need for compliance chambers, and the possibility of noise reduction. However, it is important to note that hydraulic systems may face challenges in obtaining passive preload sensitivity. Literature reports on mechanisms, such as a hydraulic shunt (Chapter 3), that provide potential solutions for this issue in hydraulic actuated TAHs. Future research should be conducted on this topic to investigate whether a shift to a hydraulic actuation system for the Hybrid Heart comes with benefits.

In situ tissue engineering for TAHs

In recent years, the *in situ* tissue engineering approach has gained significant attention as a promising solution for enhancing biocompatibility of various blood-contacting surfaces, including heart valves and vessels. This technique involves implanting cell-free biodegradable scaffolds in the targeted areas, which attract host cells to form new tissue while the synthetic scaffold is resorbed. This results in the formation of a new valve or vessel within the host, using the patient's own cells to achieve optimal biocompatibility. This concept holds also great potential for TAH applications, which also require durable and biocompatible substitutes for heart valves and blood contacting surfaces.

This thesis presents an initial investigation into the use of *in situ* tissue engineering techniques for the blood contacting surfaces of TAHs, which is an innovative approach that has not been explored before. In Chapter 5, we found that the biocompatibility of the nylon-TPU material, used for the fabrication of the Hybrid Hearts ventricles, could be improved by adding supramolecular coatings in combination with heparin functionalization. These results form a good foundation for the potential use of *in situ* tissue engineering in TAH development, with the prospect of further enhancing this coating in future research to attain bioactivity and facilitate cell recruitment. However, it is essential to conduct further research with longer follow-up times on this topic, to examine the benefit of heparin functionalization, especially because it is known that the body quickly eliminates free circulating heparin. Additionally, the slowly biodegradable nature of the supramolecular base coating has to be further assessed. Further *in vivo* studies are needed to assess the incorporation of VEGF and growth factors into the supramolecular coating to grow an autologous endothelial layer on the nylon-TPU material, and to study whether the degradation of the supramolecular coating is in pace with the formation of the endothelial layer.

In Chapter 6, we investigated the use of tissue engineered heart valves in the aortic position, where they were exposed to a high-pressure environment. Throughout the 12-month follow-up period, most of the valves remained functional. Typically, these functional valves remained free from any cells. However, some other valves showed maladaptive remodelling, resulting in cusp retraction, cusp thickening and holes in the leaflets. Despite implanting the same type of valves in the same type of sheep (same sex, age and strain)

that received equal treatment, we observed interval and interleaflet variability in outcomes related to cell influx, tissue remodelling and scaffold degradation. This outcome heterogeneity is also seen in previous studies on in situ tissue engineered heart valves in pulmonary position^{31,32}. Given that the remodelling of the valves depends on the host's inflammatory response, it must be considered that there may be patient- or animal-specific responses to the implanted scaffold. The current reality is that many aspects of the tissue remodelling in in situ tissue engineering techniques remains incompletely understood and therefore unpredictable.

Taking this a step further to clinical translation, the outcomes of in situ tissue engineering is expected to become more prone to variability due to potential differences in host response between patient groups. Although there is still limited knowledge on this topic, research suggests that macrophage and fibroblast behaviour is affected by patient's age, sex and comorbidities³³. Given that tissue remodelling heavily relies on the host's inflammatory response, patients with immune disease (e.g., rheumatoid arthritis) may exhibit a different response to the tissue engineered implants. Therefore, a one-size-fits-all design may not be sufficient when proceeding towards the clinical application of in situ tissue engineered cardiovascular implants. Besides patient specific variations, this thesis also revealed that the hemodynamic environment to which the implant is exposed is of large influence to the cell colonization and tissue remodelling. Chapter 6 presents the first study where in situ tissue engineered heart valves were exposed to the high-pressure circulation. Compared to earlier studies with similar valves that were implanted in the low-pressure environment (as pulmonary valves)^{31,32}, we found that our valves exposed to the high-pressure circulation had limited influx of cells, limited neo-tissue deposition and limited resorption of the scaffold fibres. These differences in outcomes may potentially be attributed to the challenging and harsh nature of the hemodynamic environment, caused by high shear stress and high pressures in the systemic circulation, which may have contributed to the limited cell infiltration. These results suggest the substantial impact of the implant site, highlighting that findings derived from tissue engineered implants in low-pressure circulation cannot be directly extrapolated to the high-pressure circulation. Certainly, both the patient specific response as well as the differences caused by implant site, have implications for the clinical translation of tissue engineered heart valves, necessitating further understanding. Moreover, these influences should also be taken into account when considering further steps in applying in situ tissue engineering techniques to TAH development.

Interestingly, Chapter 6 showed that the best performing tissue engineered aortic valves were largely unpopulated by any cells, while the deteriorated valves were mostly infiltrated by many cells. These findings raise intriguing questions about the necessity of living heart valves and the role of hemodynamic conditions in the tissue formation process. It is possible

that the presence of an endothelial lining alone could be sufficient to reduce the thrombogenic risk associated with current heart valve prostheses, while an acellular heart valve body provides the required durability. However, it is important to note that this approach would limit the growth potential that biodegradable tissue engineered heart valves are suggested to possess. Since TAHs do not require growth potential, it can be suggested that for the integration of in situ tissue engineered heart valves into TAH prototypes, the same non-degradable material used for the artificial ventricles may also be used as base material for the valves and vessels. Supramolecular coatings (Chapter 5) can be applied to the non-degradable materials used for the valves, vessels and blood contacting surfaces to attract circulation host cells and to grow an endothelial layer.

Conclusion

We are on the brink of a new era in which soft robotic technologies are making significant advancements in TAH development. This thesis presents first evidence that soft robotic techniques can be successfully utilized to create a TAH capable of delivering adequate cardiac output under physiological hemodynamic conditions, and can be successfully implanted and actuated in acute animal models. Moreover, this thesis has introduced innovative approaches to enhance the biocompatibility of soft robotic TAHs, including a bio-inspired mode of contraction, the use of bioresorbable scaffolds for the valves and vessels, as well as the application of anti-thrombotic or bioactive coatings to promote the formation of an endothelial layer on the blood-contacting surfaces of the artificial ventricles. The integration of a transcutaneous energy system will allow for a fully implantable system, eliminating the need for percutaneous cables. These breakthroughs propel the field of TAH research forward, bringing us closer to a viable alternative treatment for patients suffering from end-stage heart disease, as an alternative to donor hearts.

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