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Title:

ANATOMIC FITTING OF TOTAL ARTIFICIAL HEARTS FOR IN-VIVO EVALUATION

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Running Title

TAH In-Vivo Anatomic Fitting

Abstract

Successful anatomic fitting of a total artificial heart (TAH) is vital to achieve optimal pump haemodynamics after device implantation. While many anatomic fitting studies have been completed in humans prior to clinical trials, few reports exist which detail the experience in animals for in-vivo device evaluation. Optimal haemodynamics are crucial throughout the in-vivo phase to direct design iterations and ultimately validate device performance prior to pivotal human trials. In-vivo evaluation in a sheep model allows a realistically sized representation of a smaller patient, for which smaller third generation TAHs have the potential to treat. Our study aimed to assess the anatomic fit of a single device rotary TAH in sheep prior to animal trials, and to use the data to develop a three dimensional, CAD operated anatomic fitting tool for future TAH development. Following excision of the native ventricles above the atrio-ventricular groove, a prototype TAH was inserted within the chest cavity of six sheep (28 – 40 Kg). Adjustable rods representing inlet and outlet conduits were orientated towards the centre of each atrial chamber and the great vessels, with conduit lengths and angles recorded for future analysis. A three dimensional, CAD operated anatomic fitting tool was then developed, based on the results of this study, and used to determine the inflow and outflow conduit orientation of the TAH. The mean diameters of the sheep left atrium, right atrium, aorta and pulmonary artery were 39, 33, 12 and 11 mm respectively. The center to center distance and outer to outer edge distance between the atria, found to be 39 ± 9 mm and 72 ± 17 mm in this study, were identified as the most critical geometries for successful TAH connection. This geometric constraint restricts the maximum separation allowable between left and right inlet ports of a TAH to ensure successful alignment within the available atrial circumference.

Keywords

Total artificial heart, anatomic fit, cardiac surgery, heart failure

Introduction

Total artificial hearts (TAH) may be used to completely support the circulation of patients with global left and right heart failure due to an international shortage of donor hearts. Since initial human implantation of TAHs [1], the development of these devices has focused primarily on first generation, positive displacement blood pumps to replace the systemic and pulmonary circulation [2, 3]. However, their inherent size restricts device use to larger patients, whilst contacting components and multiple moving parts within these devices create contact wear which subsequently limits device reliability and thus lifetime [4]. Development of third generation rotary devices, which employ magnetic and / or hydrodynamic levitation and rotation strategies, is currently underway. These devices present a long-term, more reliable therapy with the potential for implantation in smaller patients such as women and children [5, 6]. Meanwhile, the use of dual rotary ventricular assist devices (VADs) to provide complete circulatory support following removal of the native ventricles has been used with promising results [7].

Unlike the implantation of a VAD, currently available TAHs require removal of the ventricles, which creates space for device placement. However, this is not always sufficient for the large first generation devices, which are recommended only for patients with a body surface area (BSA) over 1.7 m^2 [3, 8, 9]. While a large study of patients who received a coronary artery bypass graft reported that only 10% of adults were below this critical BSA [10], a large proportion of children are ineligible for TAH therapy. For example, Reinhartz et al. [11] reported that less than 20% of patients implanted with an LVAD between the ages of seven and seventeen had a BSA over 1.7 m^2 , hence it is vital that these smaller, rotary TAHs rapidly progress to clinical trials. Meanwhile, connection of the pump inflows and outflows to the corresponding atrium or artery requires accurate alignment to prevent kinking or compression of the atrial cuffs or outflow grafts and the surrounding vessels which may hinder the device support capacity [12]. Therefore, anatomic fitting studies are a vital requirement throughout the pump development stage.

Fitting trials for adult human implantation have been completed using non-invasive medical imaging [13-15], cadavers [15] and orthotopic cardiac recipients [15-17]. Dowling et al. [14] developed computer software, based on computed tomography (CT) scans, for use as an anatomic fitting tool for the AbioCor TAH. Each patient was required to undergo a CT scan which, when imported into the software, provided an approximation of whether the AbioCor TAH would fit within the cavity and impinge on any surrounding vessels. The authors reported that the use of this virtual fitting tool was of substantial benefit and has been relied upon for AbioCor TAH patient selection.

While cadaveric specimens are not a perfect model for fitting trials as the rigidity of the tissues does not approximate that of the clinical scenario [15], orthotopic cardiac recipients present an ideal opportunity for such studies. McCarthy et al. [15] used the cardiac transplant opportunity to evaluate the anatomic fit of Cleveland Clinic-Nimbus TAH in six patients. While this study didn't report the detailed anatomic data, the results of the first two fitting studies resulted in an alteration of the left pump outflow port orientation which proved satisfactory in the remaining studies. Shiono et al. [17] and Fukamachi et al. [16] reported detailed results of the intrathoracic dimensions from fitting studies in 26 and 33 adult transplant recipients respectively, providing an excellent platform for TAH anatomic design for adult human implantation.

Although human fitting trials are an obvious requirement for the later stages of TAH development, the key device refinement stage occurs throughout in-vivo evaluation. It is here that excellent haemodynamic results are required for progression to the pivotal human trials. Therefore, the anatomic fit of the device must be enhanced prior to in-vivo experiments to ensure optimal haemodynamics are produced upon TAH implantation. Mambrito et al. [18] used a three-dimensional computerized anatomic model, based on the cardiac measurements of a single calf, to design the shape of a prototype TAH. Two calves were used for a fitting study by Takatani et al. [19], where a prototype device was sutured in place and showed good anatomic fit. The small sample size of these studies limits the significance of the results while no detailed anatomic data were presented.

The smaller cardiac anatomy of a sheep model provides a suitable representation of the smaller patient population, for which these smaller rotary TAHs are capable of supporting. Our research group has previously used a sheep model for VAD and TAH evaluation [20], an environment also used for VAD evaluation by other groups [21, 22]. Therefore, the aim of this paper is to present an anatomic fitting study, with detailed anatomic data, in a sheep model representative of smaller sized patients. The results of this study provide an anatomic fitting tool, which can be used to initiate the in-vivo development stage of any TAH. The tool was then applied to initiate the port orientation design of a single device rotary TAH.

Methods

A prototype TAH was used for the fitting study and development of the anatomic fitting tool. The prototype design was loosely based on a double sided centrifugal impeller pump [5], which aims to provide mechanical circulatory support for small ($BSA < 1.7m^2$) and large patients. The model was made using a rapid prototyper (Object Alaris 30) and was cylindrical in shape measuring 71 mm in length with a 76 mm diameter with a total displacement volume of 320 mL. Inlet ports protruded 12 mm from each end of the cylinder while outlet ports protruded 10 mm from a tangent of the cylinder surface. Adjustable inlets and outlets, made of flexible steel wire, were added to each protruding section which could be modified in length and orientation.

Surgical Procedure

Six healthy sheep, with an average weight of 40.3 ± 8.6 kg (range 28 to 55 kg), were used for the fitting study. All animals were sourced from other studies where the end-point was euthanasia. Ethics approvals were obtained from Queensland University of Technology Research Ethics Unit.

The chest was opened through a median sternotomy and the pericardium incised to expose the heart. The ventricles were removed directly above the atrio-ventricular level. The aorta and pulmonary artery were sectioned immediately distal to the valve. Approximate lengths between the centers of the

left atrium, right atrium, aorta and pulmonary artery were measured using a tape measure to assist with inflow and outflow port orientation. The diameter of each vessel was also measured as a guide for graft size selection.

The prototype pump was then inserted within the chest cavity. Rods which represented the outlet conduits were orientated to point to the centre of the incised aorta and pulmonary artery while rods which represented the inlet ports were orientated towards the centre of each atrium. Once all rods were orientated correctly, the device was removed from the chest cavity and the lengths and angles of each port were recorded for development of the anatomic fitting tool.

Anatomic Fitting Tool

The angles and lengths of the inflow and outflow rods were plotted in 3D using SolidWorks software (Concord, MA, USA) to produce accurate 3D reference geometry for the cardiac dimensions for each sheep. The distance between the plotted points for each vessel was then accurately measured within the software.

A general TAH model, based on the mean anatomic data of all five fitting studies, was then created in SolidWorks as a 3D fitting tool for TAH design. The average distance between the vessels was calculated and these averages were plotted independently to form the basis of the general model developed. This general model indicated the average position of the atria and arteries with respect to the centre of the fitting prototype. The data was then used to design a new TAH prototype with inflow and outflow conduits orientated to the average position of each artery.

The modified TAH prototype with adjusted inlet and outlet ports was manufactured using a rapid prototyper (Object Alaris 30) and evaluated for suitable anatomic fit in the sixth fitting trial. This final study was completed in the largest sheep (55 kg) using the same surgical procedure described above. In this larger animal, an end-to-end anastomosis was used to attach 18 mm diameter Gelweave grafts (Terumo Vascutek, Renfrewshire, Scotland, UK) to the aorta and pulmonary artery. Using several

running sutures, 38 mm diameter Gelweave grafts (Terumo Vascutek, Renfrewshire, Scotland, UK) were attached to the left and right atria. The prototype was inserted within the cavity before all grafts were cut to length. Each graft was attached to the respective inlet or outlet port and the assembly was inspected for kinks.

Results

Results were taken directly from the fitting study to create the 3D fitting model and thus a guide for TAH anatomic fitting in small sheep. The mean distance between the centre of the left and right atria was 39 ± 9 mm with a range between 30 and 50 mm. The mean distance between the centers of the incised aorta and pulmonary artery was 28 ± 3 mm (range of 25 to 30 mm). As is the case with human anatomy, the aorta was situated next to the right atrium, while the pulmonary artery was next to the left atrium. Therefore, the left and right pump outflow grafts must cross over one another when implanting a TAH with this configuration.

Atrial chamber and great vessel diameters were recorded to provide a guide for inflow graft/cuff and outflow graft size selection. The mean diameter of the left atrium was 39 ± 9 mm with a range between 30 and 50 mm. The right atrium was generally smaller than the left, with a mean diameter of 33 ± 6 mm and a range of 25 to 40 mm. The mean diameter of the ascending aorta and pulmonary artery were 12 ± 4 mm (range of 9 to 18 mm) and 11 ± 5 mm (range of 7 to 18 mm) respectively.

The location of the atria and the great vessels for each fitting study was successfully plotted in SolidWorks to assist with inflow and outflow port orientation (Figure 1). The combination of these lengths and orientations resulted in a mean location for each atrium and artery which could be defined with respect to the centre of the prototype pump (Figure 1c). In reference to the axis shown in Figure 1c and expressed as the x, y and z coordinates respectively, the mean left atrial position was 44, 56 and 26 mm from the centre of the pump. The right atrial position was 36, 55 and -32 mm from the

pump centre while the aorta and pulmonary artery positions were -13, 55 and 0 mm and 18, 76 and 6 mm from the pump centre respectively.

The modified TAH prototype, based on the results of this study and the anatomic fitting tool, proved an appropriate fit in the final fitting study. The modified design, shown in Figure 2a, included protruding left and right pump outlets for graft attachment. The protruding outlets were each angled 15 degrees toward one another to allow sufficient space for the overlapping connections to the aorta and pulmonary artery without kinking. Left and right pump inlets were included within the pump casing while additional sections were attached to reduce the inlet separation. The resulting separation between the centre of left and right pump inlets was 39 mm which allowed for connection to the corresponding atria without significantly bending or kinking the grafts.

Discussion

Small rotary blood pumps in the form of single device TAHs or dual LVADs are being investigated as an alternative to the larger first generation TAH devices [5-7]. The anatomic fit of these devices is of vital importance to achieve high pump flows and prevent complications such as thrombus formation in the inflow/outflow conduits [12, 23]. Anatomic fitting studies for TAH implantation have been completed for adult humans in the past [13, 15]. However, a crucial stage in the development of these devices is the in-vivo investigation, where optimal haemodynamics are required to warrant progression to clinical trials. The use of small sheep for TAH evaluation presents an ideal opportunity to assess these devices in a closer representation of smaller patients, for which these latest generation rotary TAHs have the potential to support. Our study showed the variability in anatomic fit of a prototype heart in a sheep model and how vital these fitting studies are prior to in-vivo evaluation.

While the data presented by Shiono et al. [17] after a human TAH anatomic fitting study was less variable than that seen in our study, the results demonstrated the difference in atrial size between the pathological adult human anatomy and that of a healthy sheep. For instance, Shiono et al. reported left

and right atrial diameters of 52.9 ± 1.6 mm and 54.2 ± 2.2 mm respectively which were much larger than the respective 39 ± 9 mm and 33 ± 6 mm diameters found in our study. This is unsurprising given that smaller sheep were used in our study to better represent a population with a much smaller chest size. Furthermore, the large weight range of the animals accounts for the greater variability between measured geometries.

To account for these atrial geometric variations between animals, a modifiable custom made atrial cuff, or a selection of graft sizes (eg. 25 to 50 mm), would be advisable. However in their absence, a short 38 mm diameter graft was found to be a suitable compromise due to the compliance of the atria. Therefore, for our fitting studies, this graft was used for inlet connections to provide device inflow to reduced pressure drop and eliminate graft kinking.

Larger aortas and pulmonary arteries were also noted in humans compared to the animals in our study, while the variation in size between animals was significant. While a small difference between vessel and graft size is acceptable for TAH outflow graft anastomosis, our experience has shown the aorta and pulmonary artery are not sufficiently compliant to compensate for large discrepancies. Therefore, a range of graft sizes (eg. 7 to 18 mm) may be made available for TAH outflow graft anastomosis.

To prevent unwanted reductions in pump flow, optimizing the separation and orientation of the TAH outlet ports is of importance. The high pressure in the left outflow graft of approximately 100 mmHg assists in keeping the graft open and thus preserving pump flow. In our trials, the cross-over between the outflow grafts was achieved by passing the lower pressure right outflow graft directly to the pulmonary artery to prevent graft kinking and reduce right pump outflow resistance. Therefore, the left outflow graft could be passed over the right outflow graft with a reduced risk of kinking complications due to the higher pressure within the graft. The modified TAH prototype with the outlets angled toward, and overlapping, one another assisted with the graft cross-over and prevented graft kinking.

From this study, we found that one of the most critical dimensions for a single device TAH is the match of device inlet separation and atrial to atrial distance to ensure successful anatomic fit and achieving optimal haemodynamics. Unlike the left outlet graft, the low pressure inlets are unable to stent themselves open and are thus prone to kinking, thus reducing pump flow. Our fitting studies, for the purposes of device hemodynamic evaluation, showed that the flexible inlet grafts can cope with some variability in inlet separation. To prevent significant graft kinking, however, the inlet ports must fit within the circumference of the atria and, ideally, have a center to center distance approximately 39 mm apart. Others have reported easier implantation procedures when the inlet separation is reduced [24], while techniques to separate the atria have also been described [25].

The small atrial separation noted in our study prompted the addition of specially shaped inlet sections to the modified prototype TAH, which reduced the inlet separation from 60 mm to 39 mm. However, these sections added an additional 30 mm to the device size in the y axis, thus limiting its ability to fit within the anteroposterior plane. This plane has been identified as the most critical for human fitting of a TAH, with previous devices requiring a distance of 100 mm [26], and as such device size in this plane should be limited. Modified inlet and / or outlet components may also prove beneficial when implanting dual rotary LVADs for TAH support, particularly for smaller patients. While inlet attachment of these smaller rotary devices may be relatively simple, pump outlets would be required to bend up to 90 degrees for centrifugal impeller devices and 180 degrees for the axial impeller devices [27, 28], thus demonstrating the benefit of devices designed specifically for TAH support.

As an example of the usefulness of the recommendations and fitting tool developed in this study, they were subsequently used to determine the initial port orientation of a single device rotary TAH in preparation for functional ovine and bovine animal studies (Figure 2B). In order to reduce the device size in the anteroposterior plane, the larger inlet sections were abolished and replaced with simpler sections that added a gentle 15 degree alteration of inflow port orientation, to effectively reduce the inlet port separation to 55 mm. Whilst this distance does not match the 39 mm recommended in this study, an adequate fit is still expected. That is, the distance between the outer circumference of the left

and right inflow ports would still effectively align within the outer circumference of the left and right atria (72 ± 17 mm). Two custom PTFE cuffs attached to the inlet sections could then be cut to size to enable atrial connection.

Anatomic fitting tools for TAHs have been previously used with success on a case-by-case basis for adult humans [14], yet smaller patients are usually excluded and fitting tools for in-vivo trials are uncommon. While Mambrito et al. [18] created a fitting tool for in-vivo TAH trials, it was based on a single animal and, therefore, did not account for the variability in cardiac anatomy between animals. Our study showed the requirement for multiple fitting studies prior to development of an anatomic fitting tool for TAH implantation. The data from six animals produced a fitting tool that was sufficient for the development of customized inflow and outflow conduits for our in-vivo TAH trials. Meanwhile, the TAH fitting tool developed in this study could be used to assess the anatomic fit of other TAH / dual LVAD systems without the need for additional extensive animal fitting trials.

The locations of TAH inflow and outflow conduits presented in this study were based on an approximate placement of the prototype device within the chest cavity. While all efforts were made for consistent device placement, slight alterations were expected due to small changes in each animal's cardiac anatomy. This ultimately resulted in variations of the distance between the prototype pump and the vessels; however these results should only be taken as a guide for TAH anatomical fit in sheep and not a direct comparison with the pediatric human population. Meanwhile, the influence of closing the chest or inflating the lungs was not accounted for in our study, and may have had a slight influence on TAH anatomic fit.

Conclusion

Assessment of the anatomic fit of a single device TAH in six cadaveric sheep revealed a high degree of variability in the cardiac anatomy. Average vessel diameters and locations with respect to the TAH were determined using a modifiable prototype device. The size of, and distances between, the left

atrium, right atrium, aorta and pulmonary artery were found in the sheep cadavers to determine TAH conduit orientation. These results confirmed that the most critical feature to enable successful connection is the atrial and thus device inflow conduit separation. This is particularly important for single device TAHs which have a fixed inflow port separation. This study clearly demonstrated the importance of in-vivo anatomic fitting studies to achieve optimal haemodynamic results before progressing to clinical trials. The results of this study were then implemented to form a three dimensional anatomic fitting tool to reduce the requirement for in-vivo fitting trials in this early stage. Finally, the fitting tool was successfully used to determine the inflow and outflow conduit orientation of a single device TAH prototype to prevent graft kinking and subsequent pump flow reductions, thus demonstrating its successful use in assessing TAH anatomic fit prior to functional in-vivo trials.

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Figure 1 - Development of the anatomic fitting tool including (a) results from animal #3, (b) combined results from all animals and (c) the prototype with vectors connecting the centre of the pump to the mean location of each vessel. LA - left atrium, RA - right atrium, Ao - aorta, PA - pulmonary artery.

Figure 2 - TAH prototypes including (a) the modified TAH prototype used for the final fitting study and (b) the final prototype design for in-vivo trials.

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