

Early Experience of Implantation of a New Pulsatile Total Artificial Heart (TAH) in the Pig

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Abstract

The shortage of donor hearts and the physiological impact of pulsatile perfusion have driven technical innovation research efforts to create a positive displacement total artificial heart that can produce pulsatile flow and has a reasonable size for long-term assist in chronic heart failure. Such a product is the Scandinavian Real Heart 8 (SRH8); a new pulsatile total artificial heart. We here describe the basic principles of the surgical and anesthesiologic techniques we have developed for implantation of the latest prototype of this device.

Introduction

Patients with terminal heart failure, despite optimal medical treatment, have a poor prognosis. Heart transplantation is the gold standard for treatment of this medical condition. However, due to the lack of donor organs only a limited number of patients can be offered a heart transplant. An alternative to heart transplantation is a ventricular assist device (VAD) or total artificial heart (TAH) either as bridge to transplantation or as destination therapy.

Problems related to these devices still remain, such as thromboembolism, bleeding due to anticoagulation, infection, and technical dysfunction that limit their usage. Furthermore, the quality of life after implantation of a mechanical assist device is not as good as after heart transplantation. Most current devices are axial or centrifugal pumps delivering non-pulsatile blood flow. Baric et al. studied the advantages of pulsatile flow concluding that this seems to be of crucial importance from the physiologic point of view [1].

The concept of a total artificial heart (TAH) replacing the native heart has been an ambition for many decades. Dr. Denton Cooley in 1969 wrote a research paper on the experimental implantation of a total artificial heart, and such a device was first implanted in a human in 1969 [2]. Now, more than four decades later, there is still only one commercially available device (SynCardia®).

The Scandinavian Real Heart 8 (SRH8) is a new positive displacement artificial heart. SRH8 has two atria and two ventricles separated by AV (atrioventricular) valves as in the natural heart. Mechanic energy is transferred to the AV plane by a system driven by an electric motor. The pump uses the Lundbäck [3] principle to deliver pulsatile flow by AV plane movement.

We performed experimental implantation of the SRH8 in a pig to develop and test the optimal surgical and anesthesiologic techniques for this purpose. Emphasis in this observational descriptive study was on the development of surgical and anesthesiologic techniques that

provide the best results, including de-airing of the device and weaning the experimental animal from cardiopulmonary bypass. It was also our aim to see if the SRH8 generates a physiologic pulsatile arterial pressure curve in the right carotid artery, and to detect any modifications necessary when developing the next SRH prototype.

Materials and Methods

The total artificial heart (TAH) SRH8

The design of SRH8 described in this article mimics the anatomy of the natural heart. It is comprised of two separate pumps, left and right, working as one unit to simultaneously pump blood to the systemic and pulmonary circulation respectively. Each pump has an inlet chamber (artificial atrium) and an outlet chamber (artificial ventricle). The left pump and the right pump are identical and the valves within correspond to the mitral valve on the left side and the tricuspid valve on the right side.

The artificial atrium and ventricle of each pump are separated by a mobile cylindrical construction housing the valve plane mechanism. This valve plane cylinder has an outside wall of hard material and an inside cylinder that houses a silicone bellows construction connecting the chambers. The inner diameter of the silicone construction is the same as the diameter of the mechanical valve inside.

The valve plane cylinder is comparable to the atrioventricular (AV) plane of the natural heart.

The valve plane cylinder is connected to a driving unit that causes movement of the valve plane cylinder upwards and downwards between the artificial atrium and ventricle respectively. When the plane moves towards artificial atrium the valve is open enabling blood to flow to the artificial ventricle side. The downward stroke towards artificial ventricle causes the valve to shut and blood is ejected from the ventricle. The SRH8 has an external control unit that enables the cycle to be fixed at between 1 and 100 strokes per minute. The stroke volume

from each chamber depends on the stroke distance of the valve plane cylinder and may be fixed between 1 and 55 ml. The cardiac output thus lies between 1 and 5500 ml per minute depending on the pump frequency and stroke distance of the valve plane cylinder.

Results

The anesthesia, extracorporeal circulation, and the customized surgical technique are presented under this heading as their development was the aim of the study.

Anesthetic technique

The experimental animal was first allowed to rest in a quiet room for approximately 20 minutes, and thereafter premedicated with 3 ml intramuscular Zoletil®-Dexdomitor® (Zoletil® Virbac France, containing tiletamine 25 mg/ml, zolazepam 25 mg/ml, and Dexdomitor®, Orion Pharma, 0.5 mg dexmedetomidinehydrochloride, corresponding to 0.42 mg/ml dexmedetomidine).

After approximately 20 minutes the animal was deeply sedated with no reaction to pinching of the hind limb. A peripheral 17 G × 4.5 mm (BD venflon® Europe, 17G × 45 mm) venous catheter was inserted in the right ear vein before intubation.

We intubated the animal with a Portex 8.0 mm internal diameter cuffed tracheal tube (Smiths Medical, Dublin, OH, USA). The animal was ventilated throughout the experiment with FiO₂ 21% using a Siemens Servo ventilator 900 D (Siemens, Siemens Healthcare, Stockholm, Sweden). The respiratory frequency was set at 16/minute and the tidal volume at 208 ml. The peak pressure in the airways was 21 mmHg throughout the experiment. ZEEP (zero end expiratory pressure) was used. No muscle relaxant was required. We monitored the end tidal CO₂ and arterial oxygen saturation measured at the mouth, all data being shown on a Surgivet V9212® monitor (Smiths Medical, USA). Anesthesia was maintained throughout the experiment by an intravenous infusion of a mixture of fentanyl 25 µg/ml and thiopental 30mg/ml at a rate of 15 ml/h. Adequate analgesia was checked every 30 minutes by pinching the hind limb. A thermal ceiling was used to maintain a constant physiologic body temperature of around 39°C except during cardiopulmonary bypass where light hypothermia (36-37°C) was employed. A central venous line was inserted surgically into the right internal jugular vein (Secalon-T® 16G × 130 mm, Argon Critical Care Systems, Singapore), and an arterial catheter (Secalon-T® 18G × 90 mm, Argon Critical Care Systems, Singapore) was surgically inserted into the right carotid artery.

The arterial cannula was coupled through a pressure transducer coupled to the Surgivet V9212® monitor (Smiths Medical, USA) to enable arterial curve registration. As the peripheral resistance was low during the experiment, a noradrenalin 40 µg/ml infusion (Abcur AB, Helsingborg, Sweden) 5-30 ml/hour was required to maintain a reasonable mean arterial pressure (50-60 mmHg).

Extracorporeal circulation was established in a standard way. We used the Sorin Inspire 8F oxygenator primed with 1100 ml Acetated Ringer solution (Fresenius Kabi, Uppsala Sweden) and 200 ml

mannitol 150 mg/ml (Fresenius Kabi, Uppsala Sweden). The target arterial flow was 2,6 l/m². Online measurement of arterial and venous saturation and hematocrit was possible during CPB. Heparin 3 mg/kg (LEO Pharmaceutical Products Ballerup, Copenhagen, Denmark) was given intravenously prior to CPB when the surgeon inserted the purse-string sutures, and thereafter 40 mg heparin every 40 minutes to assure adequate anticoagulation. During the first 20 minutes of the experiment, the position of the vena cava cannula was not optimal and a flow of only 1.5-2.5 l/min was delivered by the heart lung machine. Following adjustment of the position of the cannula, the flow could be increased to the targeted 2.6 l/m². We used 2 litres of hydroxyethyl starch (Voluven® Fresenius Kabi Uppsala, Sweden) when weaning from CPB in order to reach optimal filling pressures.

Surgical technique

The thorax was opened through a median sternotomy. Purse string sutures (3-0 Prolene Ethicon, LLC® blue monofil) were inserted around both the aorta and the vena cavae. The aorta was cannulated with a 20 Fr straight armed aortic cannula and the vena cavae with 26 Fr/26Fr armed vein cannulae. Metoprolol 1 mg was injected prior to and during cannulation to prevent atrial fibrillation. Snares were placed around both vena cavae, the aorta and the pulmonary artery (PA). CPB was initiated and the aorta and PA were clamped. A body temperature of between 36°C and 37°C was maintained during CPB. The right atrium was incised and the heart mobilised by incisions through both atria preserving their bases including the vena cavae and pulmonary vein. The aorta and PA were divided and the heart removed. The inflow cuffs of the SRH8 pump were sutured to the base of the left and right atrium respectively. The PA and aorta were then sutured to separate grafts that were then sutured to the outflow cuffs of the pump. Gradual de-airing of the right and left chambers of the pump was performed by inserting a needle into the de-airing silicon membrane in the ventricle walls of the pump. This maneuver enabled slow filling of the SRH8 pump ventricles from both atria. The SRH8 pump valve plane cylinders were then started at the lowest speed and amplitude during continued de-airing via the silicon membrane in the uppermost part of the atria of the pump.

When the SRH8 pump was functioning with an optimal stroke volume and frequency the arterial and venous cannulae were removed and the animal filled with the blood from the heart-lung machine.

Device function

The pump and the pump implanted in an animal are presented in Figure 1. The right carotid arterial pressure curve was entirely physiological as illustrated in Figure 2. The mechanical heart cycle was 0.8 seconds with systole 0.2 seconds and diastole 0.6 seconds. The device generated an upstroke of 1000 mmHg/sec in systole and a down stroke of 1550 mmHg/sec in diastole. When the device was started the right carotid arterial pressure was about 50/20 mmHg (Figure 2). The shape of the curve was comparable to the physiological curve generated by the normal heart (Figure 2).



Figure 1: The SRH8 design (left panel) and the prototype implanted in a pig (right panel).

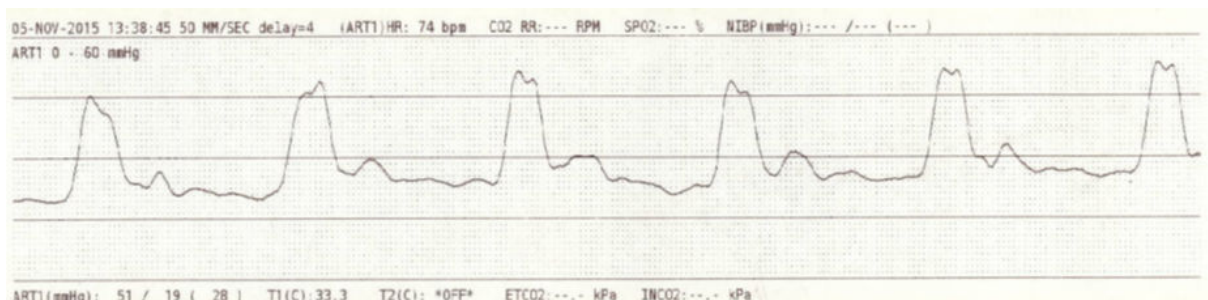


Figure 2: Representative pulsatile flow arterial curve in the right carotid artery while on the SRH8 total artificial heart.

The set pump frequencies and stroke volumes during the 30 minute test period were controlled by the pump's electronic unit, the data are presented in Table 1.

| Pulse Frequency delivered by SRH8® beats/minute | Stroke volume (SV) of the SRH8® mL |
|-------------------------------------------------|------------------------------------|
| 40 start of SRH8 | 20 Start of SRH8 |
| 55 | 25 |
| 60 | 25 |
| 70 | 25 |
| 75 | 25 |
| 75 | 30 |
| 80 | 35 |
| 80 | 40 |
| 80 | 40 |
| 75 | 45 |

Table 1: SRH8 pulse frequencies and stroke volumes during weaning from CPB and during the 30-minute test.

Discussion

As Chon et al. [4] described in their review: "A practical artificial heart has been sought for >50 years. An increasing number of people succumb to heart disease each year, but the number of hearts available for transplantation remains small. Early total artificial hearts mimicked the pumping action of the native heart. These positive-displacement pumps could provide adequate hemodynamic support and maintain the human circulation for short periods, but large size and limited durability adversely affected the recipient's quality of life. The importance of pulsatile circulation remains unclear. Future research is, therefore, needed into positive-displacement and rotary total artificial hearts."

The only commercially available TAH in Europe and the US is the SynCardia® (SynCardia Systems, Inc., Tuscon, AZ, US) that was originally designed by Dr Robert Jarvik and first implanted in August 1985 as a bridge to transplantation over a period of nine days. This TAH became CE marked 1999 and approved by the FDA in 2004 for bridging prior to transplantation in patients with end-stage biventricular heart failure. It has now been implanted in more than 1500 patients and the system includes a portable driver. More than 100 centers around the world have implanted this device, and many others pumps are in the pipeline. The longest support time has been almost 4 years. A pivotal study for use of the system as destination therapy has recently been approved by the FDA. Another TAH system, AbioCor® (AbioMed, Inc., MA, US) was tested in 15 patients, 14 of them during a clinical trial and one after FDA approval. However, due to insufficient

evidence of its efficacy and disappointing results, AbioMed abandoned further promotion of the product after almost three decades of development. This indicates the profound difficulties associated with the establishment of a well-functioning and reliable device without major inherent problems and consequently adverse clinical events.

The present results show that the surgical technique of mobilizing the heart before suturing the atria and arterial grafts to the SRH8 seems to be the most optimal way to manage weaning from the bypass, both anesthesiologically and surgically (we tested several other ways not described here).

Hemodynamic instability was easily resolved and the SRH8 pump delivered a pulsatile flow with a pressure curve similar to that produced by the normal heart. The systole/diastole time ratio was 1:3 with an upstroke (systole) producing 1000 mmHg/sec and a downstroke (diastole) 1550 mmHg/sec. The hematocrit during CPB was 23% falling to 12% after infusion of 2 L colloid just prior to weaning. This implies that transfusion may be necessary at this point in the procedure when the device is tested in future experimental and clinical trials.

The SRH8 device has been redesigned several times. The new TAH prototype functions well but the shape must be redesigned to fit the chest better. A battery powered device must also be developed. Following these improvements, the SRH8 will possibly offer a new solution for patients waiting for heart transplantation as the implantation of the SRH8 pump may also be used as destination therapy. The main target group intended are patients with progressive heart failure who are for some reason deemed unsuitable for heart transplantation.

However further comprehensive experimental and as well survival testing before introducing the device into clinical practice.

Conclusion

A new total artificial heart prototype (Real Heart®) that delivers pulsatile perfusion by AV plane displacement was tested in our animal

lab. The physiologic principle and the pressure curve created indicate the potential of this TAH for further development, with comprehensive long-term animal experiments being the next step.

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Conflict of Interest

-Zoltán Szabó, Jonas Holm and Henrik Ahn have no conflict of interest.

-Göran Hellers is Chairman of the Board in the Scandinavian Real Heart and is shareholder in the Scandinavian Real Heart AB.

-Azad Najar is the main owner with 30% ownership and Board member in the Scandinavian Real Heart AB.

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