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Moderate hypothermia technique for chronic implantation of a total artificial heart in calves

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Abstract

The benefit of whole-body hypothermia in preventing ischemic injury during cardiac surgical operations is well documented. However, application of hypothermia during *in vivo* total artificial heart implantation has not become widespread because of limited understanding of the proper techniques and restrictions implied by constitutional and physiological characteristics specific to each animal model. Similarly, the literature on hypothermic set-up in total artificial heart implantation has also been limited. Herein we present our experience using hypothermia in bovine models implanted with the Cleveland Clinic continuous-flow total artificial heart.

Keywords

Assisted circulation; Heart-assist devices; Hypothermia; Experimental surgery

Introduction

Cleveland Clinic has developed a unique single-piece, valveless, continuous-flow total artificial heart (CFTAH) that achieves passive, sensorless autoregulation of pump flows and filling pressures by varying relative left and right pump efficiencies [1]. The development program included chronic *in vivo* biocompatibility testing of the CFTAH in calves [2]. The operative management and implantation techniques are key factors in achieving optimal surgical outcomes and therefore have undergone several improvements. One major change adopted during this biocompatibility testing was our attempt to create a biological milieu in which the test animal's organs are better protected against ischemia and reperfusion injury.

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Conflict of Interest

The technology was licensed to Cleveland Heart, Inc., a Cleveland Clinic spin-off company. If the total artificial heart is successful, the inventors and Cleveland Clinic may benefit.

The purpose of this study was to evaluate our temperature management used for organ protection when initiating a chronic CFTAH implant.

Materials and Methods

The study was approved by Cleveland Clinic's Institutional Animal Care and Use Committee, and all animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, National Academy Press, Washington, DC, 2011) and institutional guidelines. Male Jersey calves ($n = 4$) with weight range of 79.1–87.0 kg were used.

Administration of premedication and anesthesia followed a standard protocol, as previously described [2]. Surgical access for the CFTAH implantation was through a median sternotomy [3]. The animal's oral and rectal temperatures were measured in addition to the temperature sensors on the cardiopulmonary bypass machine.

Special care was taken for placement of the calf and for temperature management in preparation for and during surgery. Two to three heat mattresses (Gaymar/Stryker, Kalamazoo, MI) were used to warm the posterior surface of the animal's body (lower mattress) and the entire abdominal area (upper mattress) (Fig. 1). Surface cooling (32° C) was initiated once the animal was positioned supine on the operating table and secured. The chest area was properly centered and oriented upwards for the median sternotomy incision. The Olympic Vac-Pac® (Natus Medical Inc., Pleasanton, CA) fixation bag was vacuum sealed and secured. Afterwards, an additional mattress (small size) was used for lower limb coverage as needed. The animal's limbs were covered with a dedicated plastic cover, taped and gently secured to the operating table to eliminate the risk of limb ischemia. The neck and groin areas were covered with a cloth to eliminate large air spaces between the operating table and the mattress so as to ensure an adequate surface heat exchange.

The surgical incision was made and the heart exposed, followed by systemic administration of heparin (300 U/kg). Cannulation for cardiopulmonary bypass (CPB) was established by an arterial line placed into the carotid artery and by bicaval venous cannulation. The animal's core temperature started to decrease gradually to 32°C after CPB was initiated. The native ventricles were removed under CPB and aortic cross-clamping. The atrial cuffs of the CFTAH were sutured to the corresponding stumps of the native heart. The left and right outflow grafts were anastomosed to the aorta and pulmonary artery, respectively, and the pump was connected. During completion of the last vascular anastomosis, rewarming of the animal through CPB was initiated.

Results

The technique of inducing moderate hypothermia (32° C) with complete animal body wrapping for device implantation has been used successfully in chronic bovine models. All animals treated with this hypothermia technique ($n = 4$) recovered well after the operation and showed no neurological deficits (brain or spinal cord injury); their actions – eating and drinking, with restoration of spontaneous respiration, bowel function, diuresis, self-support

(standing and sitting), and general alertness and interest in food and response to human contact – all were normal. We observed no signs of central or peripheral nervous reperfusion injury or of abdominal ischemia. All animals were followed in the operating room after CFTAH implantation, transferred to the chronic care unit, and extubated early after surgery (within 1–3 hours). Detailed operative data and postoperative survival duration are shown in Table 1. One animal had to be terminated early (2nd postoperative day) due to a controller chip failure in the CFTAH. The latter three were terminated at the intended durations of 30 days (one calf) and 90 days (two calves).

Discussion

With improvements in artificial heart technology, anesthesia management, surgical techniques, and postoperative care, experimental animals survive longer, and it has become possible to better evaluate the function of an implanted artificial heart [4]. The outcomes in artificial heart surgery can be affected by a myriad of pump-related parameters and, similarly, multiple pathophysiological factors encountered in the perioperative period. Some factors often overlap, thus making intraoperative judgments difficult and puzzling. In our continuing efforts to achieve better animal recovery post CFTAH implant and to improve outcomes, our group had tailored various techniques, widely used in human surgical practice, to animal operations. In our institution, we have adopted moderate hypothermia as our method of choice.

Kawai et al. [4] first described a so-called “surface cooling,” decreasing the surface temperature, to eliminate the discrepancy between internal organs cooled via CPB, which had become quite cold, and the skin and muscles, which remained warm. That group’s technique consisted of submerging calves (range, 64–94 kg) into ice water, then placing them on the operating table when the rectal temperature reached 24° C. Additional ice bags were placed on the calf’s head, neck, groin, and along the body to continue cooling down to 22° C (range, 18.5°–23.5° C) after chest opening. After the operation, the animals were placed in a 40° C bathtub for rewarming (4). All the cases reported by this group recovered after surgery and appeared to have no neurological damage. The team’s method of operating at low temperatures was technically cumbersome. Also, an important factor to consider is that blood tends to change its viscosity at low temperatures and to become coagulopathic [5]; thus, long-duration surgery at extremely low temperatures may not favor the outcomes of a mechanical blood pump implant.

The moderate hypothermia technique that we have adopted using heat mattresses in addition to cooling via CPB provides simultaneous surface and core cooling of the animal, with special focus on cooling down the abdominal area, which represents a significant portion of the animal’s body. The bovine body parts, such as limbs may not fully represent the immediate temperature changes; similarly, the central part of the body, particularly the abdominal portion, is quite massive and temperature control may be challenging. The food is almost always present inside the gut, which could add more complexity for effective cold and heat dissipation. We did not observe any increase in abdominal circumference, noticeable in normothermic cases, when hypothermia was used. Moderate hypothermia at 32° C can be achieved quickly and does not require any manipulation of the animal prior to

or during surgery. It is equally vital to reduce or increase the core temperature gradually and to ensure adequate temperature distribution throughout the body, both surface and core. The same consideration may be applicable to post-surgical warming. Animal warming using heat lamps and/or blankets is not fully sufficient to maintain and control the core temperature, which makes these techniques to be relatively effective [6]. Therefore, proper planning of each stage of the surgery, duration of CPB, and CPB weaning times should receive careful attention.

This report appears to be the first describing moderate hypothermia obtained through a combination of surface cooling measures and CPB prior to placement of an artificial heart in calves. Using this technique, we provided more gradual and consistent distribution of cooling and rewarming after cardiopulmonary bypass, which was not used in previous cases. The protective effects of moderate hypothermia to manage CFTAH implantation need further evaluation in larger studies where specific proposed benefits can be more meticulously evaluated.

This early observational experience has several limitations. The hypothermia technique was used in four cases. Blood samples specific to tissue ischemia during temperature adjustments, liver enzymes and kidney function were not collected. Future studies focusing on the microcirculation will be necessary to elucidate the potential changes occurring at different phases during hypothermic maintenance and rewarming when implanting a heart-assist/-replacement device.

Conclusion

Our early experience using moderate hypothermia in large animals has proved to be an effective measure for adequate animal cooling and warming, perioperative protection of internal organs, and prevention of postsurgical shivering and bowel dysfunction attributable to internal organ ischemia and highly metabolic gut flora. The massive gastrointestinal tract in bovine animal models requires dedicated measures in long-duration cardiac surgical cases. Every additional measure to reduce the adverse effects of ischemia time during CPB and tissue oxygen demand may favor the protection of internal organs and improve animal recovery post implant.

Acknowledgments

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Fig. 1.
Schematic representation of animal set-up at the operating table. Position is shown for full median sternotomy incision in a calf.

Table 1.

Hypothermia Induced for CFTAH Implantation in Calves: Operative and Survival Data

Variables	Case 14	Case 15	Case 16	Case 17
Anesthesia, duration (hours:minutes)	8:40	7:16	7:40	6:45
Surgery, duration (hours:minutes)	6:51	6:16	6:16	5:39
CPB time(hours:minutes)	3:08	2:17	2:35	2:07
Cross-clamp time (hours:minutes)	2:46	2:12	2:18	2:00
Skin closure to CCU time (hours:minutes)	0:37	1:03	1:00	1:45
Extubation time post-surgery (hours:minutes)	2:57	1:05	1:05	1:05
Survival, duration (days)	2 *	30 **	90 **	90 **

CFTAH, continuous-flow total artificial heart; CPB, cardiopulmonary bypass; CCU, chronic care unit.

* Early termination due to CFTAH controller chip failure

** Planned duration