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BRIEF COMMUNICATION

Artificial Heart (Basic)

Continuous-flow total artificial heart: hemodynamic and pump-related changes associated with posture in a chronic calf model

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Abstract

This study aimed to evaluate the effects of posture (sitting [lying down]/standing) on hemodynamic and pump-related parameters in calves implanted with our institution's continuous-flow total artificial heart (CFTAH). These parameters were analyzed with posture information in four calves that had achieved the intended 14-, 30-, or 90-day durations of implantation. In each animal, postoperative hourly data gathered throughout the study were used to compare average values with the animal sitting vs. standing. Pump flow became significantly higher in the standing than sitting position at the same pump speed (standing 7.9 ± 0.8, sitting 7.4 ± 1.0 L/min, $p = 0.028$). Systemic vascular resistance (SVR) and aortic pressure (AoP) were significantly lower in the standing than sitting position (SVR standing 779 ± 145, sitting 929 ± 206 dyne s/cm^5, $p = 0.027$; AoP standing 93 ± 7, sitting 103 ± 7 mm Hg, $p < 0.001$). No substantial change occurred in pulmonary vascular resistance (PVR) or pulmonary arterial pressure (PAP) with posture (PVR standing 161 ± 39, sitting 164 ± 48 dyne s/cm^5, $p = 0.639$; PAP standing 32 ± 3, sitting 33 ± 4 mm Hg, $p = 0.340$). Posture affected some hemodynamic and pump-related parameters in calves with CFTAH, with implications for patients with implanted pumps.

Keywords Blood flow physiology · Mechanical circulatory support · Heart-assist devices · Cardiac output · Equipment design · Animal model

Introduction

Development of a successful total artificial heart (TAH) must overcome many technical hurdles and imposes multiple requirements for the device, as in the case of the Cleveland Clinic continuous-flow total artificial heart (CFTAH), with its unique architecture and novel self-regulation features [1, 2]. Multiple aspects of the interaction of the pump within the body are still unclear and need to be explored to bring this technology closer to successful use in patients. One aspect is how the CFTAH performs in a living body, especially during various phases of activity, animal positioning, and intensity of animal activity.

Discovering the effects of a TAH in vivo is essential, since the number of patients needing the device is increasing. We conducted a series of chronic studies to evaluate biocompatibility and pump performance in a long-term calf model implanted with the CFTAH [1]. Additionally, we evaluated the effects of postural changes on hemodynamics and pump flow to investigate the CFTAH in vivo. We continuously monitored the hemodynamics of the CFTAH-implanted animals (recorded hourly data points) and evaluated hemodynamic changes observed with postural changes (sitting vs. standing) in our series ($n = 4$) that had achieved the intended 14-, 30-, or 90-day durations.

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Subjects and methods

The study protocol was approved by Cleveland Clinic Institutional Animal Care and Use Committee, and the animals received humane care in compliance with the Guide for the Care and Use of Laboratory Animals and institutional guidelines.

The CFTAH has been implanted through a sternotomy or right thoracotomy in 17 calves (Jersey calves; weight range 77.0–93.9 kg) including four (weight range 79.5–89.5 kg) that had achieved the intended duration of CFTAH implantation (14, 30, or 90 days).

Pre-, intra-, and postoperative management guidelines were standardized in all chronic studies. Cardiopulmonary bypass was instituted using carotid arterial and bicaval venous cannulation and the CFTAH was implanted as per our standard techniques [1]. After surgery, animals were transferred to a chronic care unit and remained monitoring until termination.

Pressures were recorded from fluid-filled lines in the carotid artery (aortic pressure = AoP), right outflow graft (pulmonary artery pressure = PAP), left inlet cuff (left atrial pressure = LAP), and right inlet cuff (right atrial pressure = RAP). These pressure lines are connected to transducers (Model DTX Plus, Becton Dickenson and Company, Franklin Lakes, NJ) that have an error of 2% of the reading (but not less than ± 1 mm Hg) that were amplified through a Gould rack before entering the data acquisition system. A pressure line filled with mineral oil was connected to an additional transducer on one end, and the other end was left open to room air and fixed to the highest point of the back on the harness. The relative pressure at the open end of the fluid-filled pressure line is higher when standing than when it is sitting, thus producing higher pressure on the transducer. When the calf sits, the open end is lower, thus producing less pressure on the transducer. This difference is very significant, and allows for triggering of an alarm operated through the data acquisition system to indicate that the animal monitor should raise or lower the transducer rack to one of the two predetermined locations on the intravenous pole stand set at the beginning of the study to be at the heart height, while standing and sitting. While the animals could lay on the right, left, or center of the torso, errors related to the height difference of the heart in these positions were considered to be insignificant. Because of graft length limitations, flow probes are difficult to use in vivo, but pump flow could be calculated based on equations determined prior to implantation on our in vitro test loop. Systemic and pulmonary vascular resistance (SVR/PVR) was calculated as follows:

$$\mathrm{SVR} = (80 \times (\mathrm{AoP} - \mathrm{RAP}))/\mathrm{flow},$$

$$\mathrm{PVR} = (80 \times (\mathrm{PAP} - \mathrm{LAP}))/\mathrm{flow}.$$

Hemodynamic and pump-related parameters were collected with averaged data on posture in the four calves. Differences in the hemodynamic parameters depending on posture were analyzed by comparing two postures in each calf. All continuous variables are expressed as mean ± standard deviation. Statistical significant differences between the four sets of animal data were assessed using a 2-tailed, paired *t* test. A p value < 0.05 was considered as statistically significant.

Results

All four animals achieved the intended durations of 14 ($n = 1$), 30 ($n = 1$), or 90 days ($n = 2$). The hemodynamic parameters during each position are shown in Table 1. At the same pump speed, pump flow was significantly higher when calves stood than sat (sitting 7.4 ± 1.0 L/min, standing 7.9 ± 0.8 L/min, $p = 0.028$). AoP and RAP were significantly higher when calves sat than stood (AoP; sitting; 103 ± 7 mm Hg, standing; 93 ± 7 mm Hg, $p < 0.001$; RAP; sitting; 20 ± 1 mm Hg, standing; 18 ± 1 mm Hg, $p = 0.027$). No statistically significant difference was found on PAP or LAP between the two postures. Notably, SVR was significantly higher in the sitting than standing position,

Table 1 Pump and hemodynamic parameters in each position

	Pump speed (rpm)	Pump flow (L/min)	AoP (mm Hg)	PAP (mm Hg)	LAP (mm Hg)	RAP (mm Hg)	SVR (dyne s/cm^5)	PVR (dyne s/cm^5)
All data	3028 ± 44	7.6 ± 0.8	99 ± 7	33 ± 3	18 ± 1	19 ± 1	856 ± 160	163 ± 44
Sitting	3022 ± 46	7.4 ± 1.0	103 ± 7	33 ± 4	19 ± 1	20 ± 1	929 ± 206	164 ± 48
Standing	3027 ± 45	7.9 ± 0.8	93 ± 7	32 ± 3	16 ± 1	18 ± 1	779 ± 145	161 ± 39
p value	0.287	0.028	< 0.001	0.340	0.054	0.022	0.027	0.639

Data are expressed as mean ± standard deviation

AoP aortic pressure, *PAP* pulmonary arterial pressure, *LAP* left atrial pressure, *RAP* right atrial pressure, *SVR* systemic vascular resistance, *PVR* pulmonary vascular resistance

although PVR was not different between the two (SVR sitting; 929 ± 206 dyne s/cm^5, standing; 779 ± 145 dyne s/cm^5, $p = 0.027$; PVR sitting; 164 ± 48 dyne s/cm^5, standing; 161 ± 39 dyne s/cm^5, $p = 0.639$). These patterns remained throughout the observation periods (Fig. 1a: pump flow, b: SVR and PVR, c: AoP, PAP, LAP, and RAP).

Discussion

Our studies in these chronic calf models showed that: (1) pump flow was significantly higher at the same pump speed in the standing position; (2) SVR was higher in the sitting position but PVR showed no statistically significant change; (3) AoP and RAP were significantly higher in the sitting position; and (4) these patterns were observed throughout the study durations.

With a natural heart, changes in posture affect hemodynamics [3–6]. When a human changes posture from supine to standing, blood is pooled in the lower part of its body, venous return to the heart decreases, cardiac output is reduced, and blood pressure decreases [3, 7]. Cardiac output (stroke volume) reaches 12–14 ml/beat/min when standing [3, 4]. A similar mechanism can be observed with postural change from supine to sitting position for the same reasons [4]. Thus, after changing position from supine to standing, the native heart must increase pulse rate and contraction force to avoid organ damage from reduced cardiac output. Of note, in this study, the pump speed of the CFTAH was kept constant throughout. Moreover, it was remarkable that such patterns, in which AoP, RAP, and SVR are higher in the sitting than standing position, could have been shown even though the dominant posture in a day changed as the animals recovered. The hemodynamic parameters in this study showed the expected physiological response except for heart.

The change from sitting to standing in calves is different from human's postural change from supine to standing, since the direction of the body changes from horizontal to vertical in a human being and is a more complex mechanism vs. the body lift up from originally horizontal position to upward

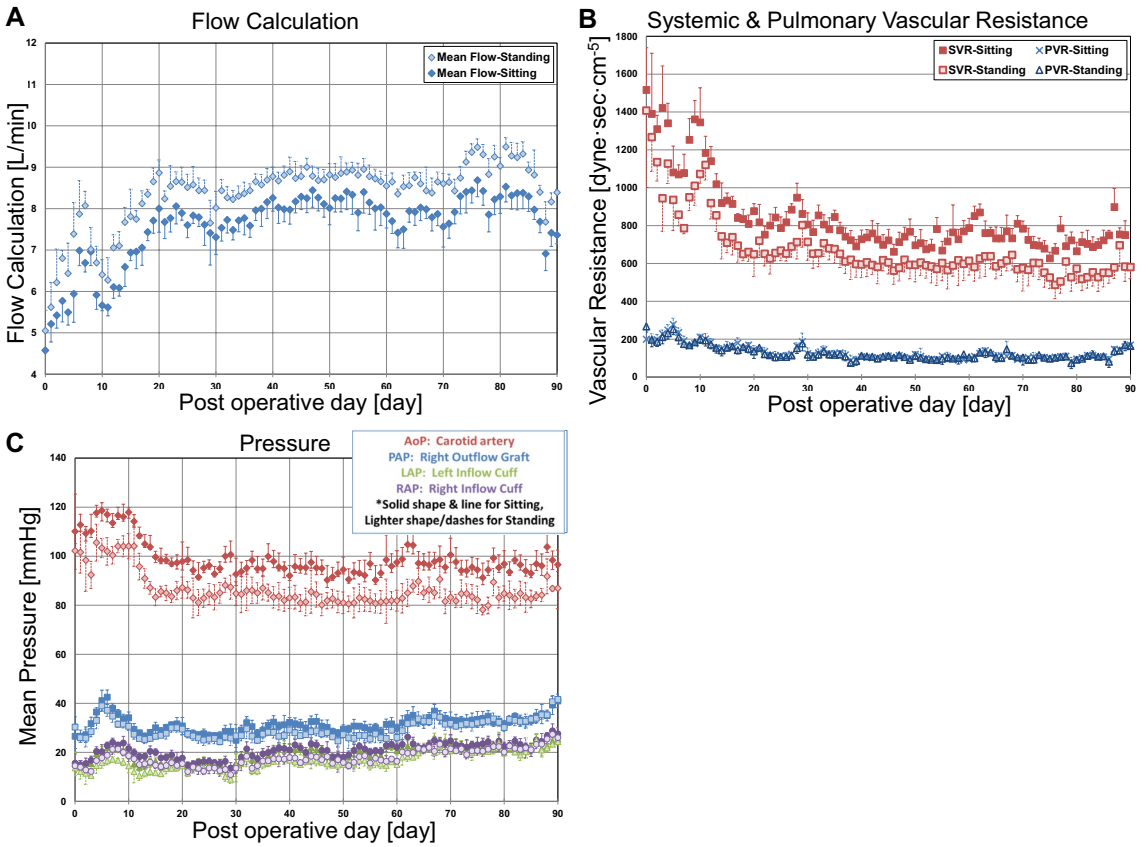

Fig. 1 **a** Mean flow for each postoperative day. The averages of 24 hourly recorded data points as calculated using pump speed and power output in the data acquisition system are shown. Data are expressed as mean ± standard deviation in error bars. **b** Systemic and pulmonary vascular resistance values for each postoperative day in the Critical Care Unit. This is the average of 24 hourly recorded data points as calculated using pressure in the CCU. Data are expressed as mean ± standard deviation in error bars. **c** Mean pressures for each postoperative day. This is the average of 24 hourly recorded data points as displayed in the CCU. Data are expressed as mean ± standard deviation in error bars

horizontal in calves. However, it is obvious that the postural changes cause several hemodynamic changes, related to reduced venous return, after TAH implantation in human as well as in calves when it comes to hemodynamic shifts attributable to body position.

In these series, pump flow was significantly higher when the calf was standing than sitting, at the same pump speed. This difference was due to significantly lower SVR and AoP when standing than sitting, as pump flow is sensitive to pressure differences. PAP and LAP were slightly lower when standing than sitting, but there was no change in PVR or PAP with postural shifts.

We previously showed that posture affects hemodynamics in chronic calves with a pulsatile TAH [8]. In the current study, because we did not change pump speed, the hemodynamic parameters that we recorded were influenced only by the animal's native system, and therefore, the outcome was shown as adequately reflecting a natural physiological response.

The four calves were more likely to be active in the standing position, although the cages were narrow, with little space for them to move. While the calves stood, they were eating or moving; whereas when sitting, they were resting or sleeping. All four gained body weight at the normal rate of 0.5 kg/day with good appetite postoperatively; there was no sign that perfusion was insufficient for them to live or that postural change contributed to inadequate pump flow.

Aside from the small number of animals so far, there were several other limitations to this study. (1) The calves' activity levels during the day were not recorded. Only the animal's two positions in the cage were taken as data, although the calves could eat, sleep, or rest while sitting and eat or drink while standing. We also did not study the effects of circadian rhythm on animal hemodynamics; we plan to record these metrics in future studies. (2) We have to consider the influence on hemodynamics due to passive reaction of the calf's body. Hemodynamics is controlled not only by the TAH but also by temperature or capillary resistance inside the body. (3) Errors present in the flow calculation, and therefore SVR and PVR values, are assumed to be minimal but not unlikely since the calculated flow values are as accurate as the data obtained with ultrasonic flow probes during pre-implant device testing on our in vitro test loop. Further investigations are needed to eliminate or reduce these effects.

Conclusion

Our findings suggest that postural changes affect hemodynamics and pump-related parameters in animals implanted with the CFTAH. In this study series, with similar pump-speed parameters, pump flow was significantly higher in the standing position, and SVR, AoP, and RAP were significantly higher in the sitting position.

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Compliance with ethical standards

Conflict of interest David J. Horvath and Barry D. Kuban are co-inventors of the device. The technology was licensed to Cleveland Heart, Inc., a Cleveland Clinic spin-off company. All other authors have nothing to disclose with regard to commercial support.

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