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Large animal models to test mechanical circulatory support devices

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Mechanical circulatory support (MCS) devices are widely used to treat patients with heart failure. Animal studies have been essential to the development of MCS devices. A number of factors must be considered to ensure good results from these experiments. In this review, we discuss current debates on what might be the ideal surgical approach to evaluating MCS devices in large animals, the hemodynamic and laboratory differences between large animals and humans, heart failure models using large animals, and study designs for developing new long-term MCS devices.

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Introduction

Mechanical circulatory support (MCS) devices are widely used to treat patients with heart failure (HF). Researchers have conducted various types of animal studies to test MCS devices and develop new devices, evaluating hemodynamic effects of MCS, and establishing new surgical methods or strategies. To apply results of animal experiments to the clinical situation, the experimental design should reflect the clinical environment. Large animals such as dogs, pigs, sheep, goats, and calves are the preferred species, but these species differ markedly in anatomy, hemodynamics, and laboratory results from humans. We need to establish normal values of hemodynamic parameters and laboratory tests of these animal models and carefully consider differences between animals and humans. In this review, we discuss the potentially ideal surgical approach to evaluating MCS devices in large animals, hemodynamic and laboratory differences between large animals and humans, HF models using large animals, study design for developing new long-term MCS devices, and management of large animals and several complications encountered in preclinical studies.

Controversy about the ideal surgical approach to implanting MCS devices

Although most left ventricular assist devices (LVADs) are implanted in patients *via* a median sternotomy with an outflow graft anastomosed to the ascending aorta, in animal experiments, LVADs are usually implanted via a thoracotomy with an outflow graft anastomosed to the descending aorta. One rationale for this latter surgical approach in animals is the length of the ascending aorta. Bonchek et al. [1] reported that the brachiocephalic artery arises from the ascending

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aorta within 5–8 cm from the aortic valve in the calf. This report seems to overestimate the length of the ascending aorta in the calf. We reported an *in vivo* case with an extremely short (1–2 cm) ascending aorta (Fig. 1) [2]. Tuzun et al. [3] also reported that the ascending aorta bifurcates within 1–2 cm of the aortic valve in the calf. That group also assessed the effects of outflow-graft location on regional myocardial blood flow in calves with a continuous-flow LVAD. They showed that regional myocardial blood flow was not adversely affected by the location of the outflow-graft anastomosis in healthy calves implanted with a continuous-flow LVAD. Litwak et al. [4] examined the effects of outflow location of LVAD on aortic flow in calves. The investigators reported a significant decrease in mean aortic arch blood flow when the outflow graft was directed to the descending aorta. This approach also may relate to the degree of retrograde flow, aortic valve leak, and left ventricular unloading.

Another reason for choosing thoracotomy is that the risk of wound infection or dehiscence is higher in a median sternotomy than a thoracotomy, because the animal's normal resting position is on its sternum. However, we demonstrated in chronic studies of the continuous-flow total artificial heart in calves that successful sternal fixation was achieved in all animals with a median sternotomy incision, without wound infection or dehiscence [5]. A full median sternotomy provided the additional advantage of larger viewing angles at the anastomotic suture lines after device connection. Kikugawa et al. [6] described their experience with MCS implantation experiments in sheep. They had to cut two ribs to put the two connection tubes through the chest wall. This procedure was considered to be a cause of postoperative respiratory failure. Frazier et al. [7] stated that the left thoracotomy is an ideal approach for total heart replacement with dual centrifugal ventricular assist devices (VADs) in the ovine model. The atria, pulmonary artery, and aorta are easily accessible with this approach. So the ''ideal'' is still controversial, and surgical investigators need to decide on their approach cognizant of these factors.

Hemodynamics and laboratory data; anticoagulation

It is important to know the normal values of hemodynamics and laboratory data. Some reports, including one from us, have shown the normal values of hemodynamics of animals and the influence of anesthesia in an acute study [8–10]. In some studies, the anesthetic agent (e.g., Isoflurane) depressed left and right ventricular contractility while reducing left ventricular (LV) afterload, but increasing right ventricular (RV) afterload [11]. Koenig et al. [12] compared human and animal hemodynamic parameters. The authors found that the vascular stiffness of calves and pigs was strikingly lower than that of humans, with either a normal or low ejection fraction (EF) (e.g., impedance impacts flow and waveforms to the periphery).

The pressure-volume (PV) loop can evaluate dynamic, volume (load)-independent cardiac function under both systolic and diastolic conditions. To analyze the PV loop reliably, it is mandatory to measure the instantaneous LV volume correctly. In addition, to evaluate LV contractility or compliance, multiple PV loops with different loading conditions are necessary. Currently, there are several types of measurement methods; among them are the conductance system [13], admittance-based system [14], three-dimensional echocardiography [15],

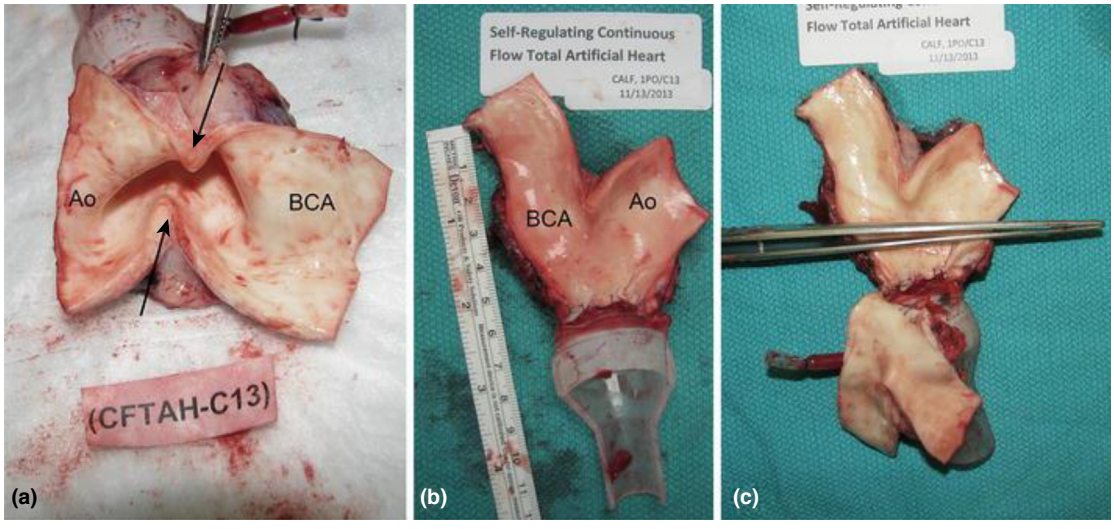

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Fig. 1. Test implantation of Cleveland Clinic continuous-flow total artificial heart—ascending aorta (Ao) and brachiocephalic artery (BCA) of a calf at necropsy. (a) The Ao was extremely short in relation to the sharp angulation (*black arrows*) of the BCA's site of origin. (b) The ``butterflied'' Ao and BCA show the relationship and scale. (c) Forceps indicate the relationship of the aortic cross-clamping site to the anastomotic line and BCA–Ao angle. From Karimov et al., Fig. 1 [2]; reproduced with permission.

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