Partial Support with a Centrifugal Left Ventricular Assist Device Reduces Myocardial Oxygen Consumption in Chronic, Ischemic Heart Failure

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ABSTRACT

Background: Left ventricular assist devices (LVAD) are increasingly used for heart failure (CHF); however, the level of optimal support has not been elucidated. We hypothesize that partial LVAD support in an ovine model of microinfarction-induced CHF significantly reduces left ventricular myocardial oxygen consumption ($LVVO_2$).

Methods and Results: Microembolization of the circumflex coronary artery was used to induce CHF in 5 sheep (ejection fraction 28 ± 2%). Four months later, animals underwent implantation of a centrifugal LVAD. LVAD flow was incrementally increased from 0% (baseline) to 25%, 50%, and 75% support of the LV. $LVVO_2$ and stroke work (SW) were calculated at each increment. At baseline, $LVVO_2$ (μL/100 g LV/beat) measured 43.2 ± 3.4. $LVVO_2$ decreased to 26.5 ± 8.2,* 20.3 ± 8.9,* and 12.6 ± 6.3* at 25%, 50%, and 75% support (*$P < .05$). SW (mm Hg/mL) measured 1933.0 ± 275.7 at baseline and decreased to 1588.0 ± 204.1, 1181.0 ± 157.2,* and 764.5 ± 171.7* at 25%, 50%, and 75% support. Cardiac output, heart rate, and left main coronary artery blood flow were unaffected with partial support.

Conclusion: Complete support with a centrifugal LVAD is not necessary for achieving significant reductions in $LVVO_2$. Partial support of as little as 25% significantly reduces $LVVO_2$ in CHF through comparatively minor reductions in cardiac work. This is the first study to examine partial LVAD support in a CHF model.

Key Words: Mechanical assistance, animal model, myocardial oxygen consumption, chronic heart failure.

Mechanical circulatory support systems provide, in the absence of available donor hearts, temporary respite for the failing heart until transplantation or device weaning can be attained.[1,2] The benefits of mechanical support are known: ventricular assistance promotes myocardial recovery by reducing oxygen consumption of the left ventricle (LV)[3,4]; reversing contractile dysfunction[5]; reversing or promoting structural, molecular, and genetic remodeling[6–9]; reversing metabolic dysfunction[10]; and providing coronary and systemic perfusion.[4] Because LV myocardial oxygen consumption ($LVVO_2$) represents energy utilization based on the availability of oxygen, $LVVO_2$ reductions secondary to ventricular unloading serve as an indicator of myocardial workload reductions. Reducing $LVVO_2$ of the already marginal myocardial tissue, particularly near the border zones of infarcts, may therefore attenuate further ischemia and restore the metabolic requirements of reversibly injured myocytes to promote functional recovery.

The amount of ventricular assistance required to achieve beneficial effects on the failing heart has not been determined. Intuition suggests that complete support would provide for optimal rest and recovery as the device assumes the entire workload of the ventricle. It is unknown whether this is ultimately beneficial to the recovery process. Complete support of the LV may not only be unnecessary, but excessive therapy in chronic heart failure (CHF), having been attributed to aortic valve stasis,[11,12] myocardial atrophy,[13] and the impairment of right ventricular (RV) function

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resulting from geometric or hemodynamic alterations associated with LV decompression.[14–18] Partial support, in which only a portion of the cardiac output is contributed by a left ventricular assist device (LVAD), may avoid these complications while reducing LV energy requirements and encouraging some animation of the myocardium and aortic valve.

Published reports have examined the effects of partial LV support with mechanical assistance, but these studies used healthy animals or animals with acute ischemic injury.[19–22] The effects of mechanical assistance in a *chronically failing* animal model remain unknown. Our laboratory therefore developed an ovine model of chronic, ischemic cardiomyopathy to use as a platform for our investigations.[23] We hypothesize that complete LV unloading with a centrifugal LVAD is not necessary for achieving significant reductions in $LVVO_2$ and that partial support can significantly reduce $LVVO_2$ in CHF while minimizing potentially detrimental complications associated with complete LV decompression. This is the first study to investigate partial LVAD support in an animal model of CHF.

Methods

All animals used in this study were housed in a facility in accordance with the Association for Assessment and Accreditation of Laboratory Animal Care and the Institutional Laboratory Animal Care and Use Committee at The Ohio State University. This investigation conforms to the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

LVAD Implantation

Sheep underwent selective microembolization of the circumflex coronary artery to induce CHF (LV ejection fraction (EF) <35% for 2 consecutive weeks as measured via transthoracic echocardiography), as described previously.[23] Four months after the establishment of CHF, we implanted a centrifugal LVAD (AB-180 iVAD, CardiacAssist, Inc., Pittsburgh, Pennsylvania).[22] Under general anesthesia, a left lateral thoracotomy (fourth intercostal space) was performed. The pericardium was opened anterior to the phrenic nerve. The hemiazygos vein was isolated and ligated from the coronary sinus and a short section of polyethylene tubing was passed into the proximal end and secured for coronary sinus blood sampling. A 16-mm probe and a 4-mm or 6-mm flow probe (Transonic Systems Inc., Ithaca, New York) were placed around the pulmonary artery (PA) and left main coronary artery, respectively. A 10-mm clamp-on flow probe was secured around the 40Fr inlet cannula (Bard, Billerica, Massachusetts) of the LVAD. Our laboratory verified calibration of the inlet cannula flow probe before these procedures by timed, graduated cylinder runs using a mock circulation loop with a 37°C glycerol/saline mixture to mimic the viscosity of blood (data not shown).[22] Flow measurements were obtained using a T206 flow meter (Transonic). Heparin (3000 units) was administered and the descending aorta was clamped with a partial occluding clamp. The pump outflow graft (10-mm ring-reinforced Gore-Tex polypropylene, Gore, Flagstaff, Arizona) was anastomosed end-to-side to the descending thoracic aorta using running polypropylene suture. The partial occluding clamp on the descending aorta was gently released to allow the pump to prime with blood. The outflow graft was clamped and the inlet cannula was passed through a small stab wound into the left atrial (LA) appendage. After being primed and de-aired, the pump was secured outside of the chest to the operating field.

Data Collection

Data collection was performed as described previously.[23] LV hemodynamics and stroke work (SW) were obtained using a 7Fr micromanometer-tipped conductance catheter (SPC-570, Millar Instruments, Houston, Texas) passed through a carotid artery introducer and into the LV. Volume conductance measurements from the catheter were collected by a Sigma 5 DF signal conditioner processor and recorded using Conduct-PC software (processor and software, CD Leycom/Cardiodynamics BV, Zoetermeer, The Netherlands). Pulmonary artery hemodynamics were obtained via a thermodilution catheter passed through a jugular vein introducer. Cardiac output (CO) was determined by either thermodilution or pulmonary artery blood flow (Q_{PA}) where appropriate. Thermodilution and Q_{PA} were evaluated before LVAD support and found to be identical (data not shown). Zero percent support (baseline), defined as no LVAD assistance, began with the outflow graft of the pump clamped. After a 20- to 30-minute stabilization period, hemodynamic data were acquired and arterial and coronary sinus blood gas samples were drawn simultaneously for the calculation of $LVVO_2$. These samples were drawn carefully to avoid arterialization of the blood. The outflow graft was unclamped, and pump motor speed was increased to deliver flows in a stepwise manner of 25%, 50%, and 75% of baseline Q_{PA}, with 20- to 30-minute stabilization periods between each increment. Percent LVAD support was calculated as LVAD flow divided by Q_{PA} (×100) at each increment of support. Data collection was repeated at each increment of bypass. Pharmacologic support was not used during the study. After conclusion of the study, the animals were euthanized under general anesthesia. The hearts were harvested and the LV was excised from the rest of the heart. $LVVO_2$, calculated by multiplying the LV arterial-venous (A-V) O_2 content difference by left main coronary artery blood flow, was normalized for LV wet weight and heart rate.[22] Oxygen content of the arterial and coronary sinus blood was calculated as the product of oxygen saturation, hemoglobin concentration, and the oxyhemoglobin coefficient (1.35 mL/GHb for sheep blood at 37°C).[22]

Statistical Analyses

Statistical analyses were performed using GraphPad Prism v.3.02 (GraphPad Software, Inc., San Diego, California). Where appropriate, data are presented as the mean ± standard error of the mean. After normality testing, data underwent repeated measures analysis of variance followed by Dunnett's post test. $P < .05$ is considered significant. Linear correlation analysis using a Pearson's test was used to assess $LVVO_2$ in relation to hemodynamic and blood gas parameters.

Results

Seven CHF sheep (43.7 ± 4.7 kg) underwent acute LVAD implantation. Two were subsequently excluded from the study: 1 required heavy inotropic support at the time of LVAD implantation; 1 had situs inversus and was excluded