

Exercise Capacity in Patients with The Total Artificial Heart

Canada et al: Exercise in the TAH

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Abstract

There is a dearth of information regarding the functional abilities of patients with the total artificial heart (TAH). Increased utilization of the TAH and patient discharge to home with the portable unit necessitates a shift in focus to quality of life, which includes quantifying and ultimately optimizing functional capacity. To date only single patient case studies have described the exercise response of the TAH patient. Fourteen patients with the TAH underwent cardiopulmonary exercise testing (CPX) with concurrent analysis of TAH device function. All device settings remained fixed during testing. Peak oxygen consumption (VO_2) [0.872 L·min (IQR = 0.828-1.100 L·min)], %-predicted peak VO_2 [36% (IQR = 32-42%)], and ventilatory anaerobic threshold (VAT) [0.695 L·min (IQR = 0.542-0.845 L·min)] were markedly reduced in the TAH compared with predicted normal values. Determinants of VO_2 using device-generated hemodynamics revealed a blunted cardiac output (CO) (+9% increase) and exaggerated oxygen extraction with exercise. Peak VO_2 strongly correlated with resting ($R=+0.548$, $P=0.045$), VAT ($R=+0.780$, $P=0.001$), and peak exercise CO ($R=+0.672$, $P=0.008$). Patients with the TAH have significantly impaired exercise performance. The limitations to CPX performance appear to be related to limited ability of the pump to modulate output for activity and reduced oxygen carrying capacity.

Introduction

Advanced heart failure (HF) therapies are available for patients with end-stage disease who are refractory to conventional medical management. These include the use of inotropic agents, heart transplantation, and mechanical circulatory support devices (MCS).¹To date, the majority of MCS devices implanted are left-ventricular assist devices (LVAD), which unload the native heart's left ventricle and improve survival and quality of life.²However, there are a subset of patients with advanced HF that are not ideal candidates for LVAD therapy due to concomitant right-sided HF or anatomical contraindications.³For this subset of HF patients, the total artificial heart (TAH) is an effective treatment therapy as a bridge to heart transplant.⁴Unlike the LVAD, the TAH (CardioWest, Syncardia Systems, Tucson, AZ, USA) consists of two pneumatically driven pumps that orthotopically replace the failing hearts native ventricles. The device is set at a fixed pump rate and increases in cardiac output (CO) rely solely on fill-volume reserve to accommodate for activity and exercise.³

While studies describing exercise in LVAD patients have been previously published, there is paucity of information regarding the exercise response of the TAH patient. We previously reported on the flat blood pressure (BP) response observed in 37 TAH patients during submaximal exercise; other reports have been limited to case studies on submaximal functional status.⁴⁻⁸To date, to the best of our knowledge, there have been only single patient case studies describing the maximal exercise response of the TAH patient.^{7,9}

The increased utilization of the TAH and the introduction of a portable driver necessitate a shift in focus to quality of life in the TAH patient, which includes quantifying and ultimately optimizing functional capacity. Given the current knowledge gaps, the purpose of this study was to evaluate the cardiopulmonary exercise testing (CPX) response in patients receiving a TAH.

Methodology

This was a single center cross-sectional study analyzing CPX data obtained from 14 consecutive TAH patients at Virginia Commonwealth University Medical Center. Data were prospectively collected and retrospectively analyzed. Institutional Review board approval was granted prior to data analysis (HM#14197). Medical history and pertinent clinical data for all patients included in this study were abstracted from the medical record.

TAH Device Parameters

The following TAH device parameters were recorded at rest via the driver console computer-processing unit: ejection rate (HR), left & right drive pressure, and systolic ejection time. Additionally, the following device-generated hemodynamics was recorded at rest & systematically throughout CPX: left & right CO, left and right fill-volumes (FV). Visual qualitative analysis was performed with the TAH hospital driver console graphical display to assess for waveform changes with exercise. All device settings remained fixed during testing.

Exercise Testing Protocol

The TAH patients underwent CPX to evaluate aerobic exercise performance and develop a cardiac rehabilitation exercise prescription. Contraindications to exercise testing were based on established American College of Cardiology/ American Heart Association Guidelines for exercise testing.¹⁰ Patients were considered appropriate for CPX once they were deemed medically stable by the attending physician and felt to be sufficiently ambulatory per cardiac rehabilitation staff. Sufficient ambulatory status was arbitrarily defined as able to tolerate motorized treadmill walking of at least 1.0 mph for at least 5 minutes' duration without a rest break. All tests were symptom-limited, physician supervised, and administered by a clinical exercise physiologist.

The treadmill protocol utilized was a conservative incremental ramping protocol wherein the speed and grade increased by approximately 0.6 estimated metabolic equivalents (METs) every 30 seconds. Ventilatory gas-analysis was performed using a VMax Encore metabolic cart (Carefusion, Yorba Linda, CA) with a standard mouthpiece and nose-clip. The metabolic cart was calibrated for volume and gas-concentration prior to every test. Ventilatory gas-analysis measurements were obtained for at least 3 minutes in the seated position before the start of exercise and continuously throughout exercise. Blood pressure was monitored with an automated exercise BP system (Suntech Medical, Morrisville, NC).

Exercise Variables Assessed

The following CPX variables were analyzed: peak oxygen consumption ($\dot{V}O_2$), percent-predicted peak $\dot{V}O_2$, ventilatory anaerobic threshold (VAT), respiratory exchange ratio (RER), the minute ventilation/carbon dioxide production (VE/VCO_2) slope, oxygen uptake efficiency slope (OUES), oxygen (O_2) pulse, and the partial pressure of end-tidal CO_2 ($P_{ET}CO_2$) at rest, VAT, and peak exercise.

Peak $\dot{V}O_2$ was defined as the highest 30-second interval average obtained from breath by breath measurements of $\dot{V}O_2$ during peak exercise. Percent of predicted (% pred) normal values was reported using the reference values of Wasserman et al.¹¹ VAT was defined using the ventilatory equivalents method.¹² Peak RER was the ratio of $VCO_2/\dot{V}O_2$ corresponding to the peak $\dot{V}O_2$ at the end of exercise. The VE/VCO_2 slope was the linear regression value ($y = mx + b$ where $m = \text{slope}$) of the relationship between VE and VCO_2 using 10-second interval averages for VE and VCO_2 throughout the entire exercise period. The OUES was determined from the linear relation of $\dot{V}O_2$ versus the logarithmic transformation of VE during exercise, that is, $\dot{V}O_2 = a \log_{10} VE + b$, where 'a' is the OUES and 'b' is the intercept. OUES analysis was based

upon 10-second interval averages for VE and absolute $\dot{V}O_2$ (Liters per minute; $L \cdot \text{min}^{-1}$) throughout the entire exercise period. Resting $P_{ET}CO_2$ measurements were based on the average value of at least two minutes of pre-exercise data. Exercise $P_{ET}CO_2$ measurements were recorded at the VAT and at peak exercise.

Hemodynamic Variables Assessed

Arteriovenous oxygen content ($a-\bar{v}O_2$) difference was calculated through re-arrangement of the Fick equation, wherein $\dot{V}O_2 = CO \times a-\bar{v}O_2$ difference. Arterial oxygen content (CaO_2) was calculated assuming a PaO_2 of 90mmHg using the following equation [$CaO_2 = (\text{Hemoglobin} \times 1.34 \times SpO_2) + (0.003 \times PaO_2)$]. Total peripheral resistance (TPR) was determined as mean arterial pressure (MAP) divided by CO and expressed in arbitrary units as $\text{mmHg} / L \cdot \text{min}^{-1}$. Oxygen extraction ratio (OER) was calculated as $a-\bar{v}O_2$ difference divided by CaO_2 . Normal values for exercise and hemodynamic responses were calculated as a reference from standard values for age/gender-matched healthy individuals.^{11,13}

Statistical Analysis

Descriptive statistics were described using median and interquartile range (IQR; 25-75%). Categorical variables were assessed using Chi-square analysis. Spearman correlation coefficients were assessed to examine the relationship between CPX and TAH device-specific variables. A nonparametric independent samples Kruskal-Wallis test was used to assess for differences between device driver-types and hemodynamic changes from rest to peak exercise. A p-value of < 0.05 was used for significance. SPSS software (Version 22, IBM, Armonk, NY) was utilized for statistical analysis.

Results

The clinical characteristics of the patients and TAH device parameters are displayed in **Tables I** and **II**. The TAH patients had reduced hemoglobin (Hgb) [7.7 g/dL (IQR=7.1-8.4 g/dL)] concentrations compared with normal reference values.¹⁴ Since the TAH patients were post-ventriculectomy, they were treated with less HF specific therapies including beta-blockers.

TAH Device-Related Variables

Most of the CPX's were performed with the patient attached to the hospital driver [n=10 (71%)]. Cardiac output increased significantly with exercise; left CO change (Δ) = 0.55 L·min⁻¹ (IQR=0.10-0.95 L·min⁻¹, P=0.013) and right CO Δ = 0.90 L·min⁻¹ (IQR=0.18-1.33 L·min⁻¹, P=0.021), respectively. Similarly, there was a significant increase in left and right fill volumes from rest to peak exercise; LFV Δ = 4.0 mL·beat⁻¹ (IQR=0.95-7.50 mL·beat⁻¹, P=0.013) and RFV Δ = 10.5 mL·beat⁻¹ (IQR=5.50-11.75 mL·beat⁻¹, P=0.002), respectively. However, this amounted to only a 9% increase in CO with exercise derived from changes in fill-volume.

Table III shows the correlation between the TAH device specific variables and peak $\dot{V}O_2$. Peak $\dot{V}O_2$ correlated with resting (R=+0.548, P=0.045), VAT (R=+0.780, P=0.001), and peak exercise left CO (R=+0.672, P=0.008), respectively. There was no significant association between peak $\dot{V}O_2$ and ejection rate, drive pressures, % systole, or right-sided hemodynamics (all R values <0.20 and p-values >0.08). Furthermore, there was no significant difference between any CPX variable or TAH exercise hemodynamic response when comparing different driver types (all p-values >0.08).

Exercise Capacity

Figure I is a graphical representation illustrating the TAH response to normal values for selected CPX and hemodynamic variables. CPX functional variables are presented in **Table IV** with TAH patients exhibiting a decreased maximal aerobic capacity compared with predicted

values. Peak $\dot{V}O_2$ was $0.828 \text{ L}\cdot\text{min}^{-1}$ (IQR = $0.828\text{-}1.100 \text{ L}\cdot\text{min}^{-1}$) for absolute values or $10.5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (IQR = $9.6\text{-}12.1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) relative to bodyweight, absolute %-predicted $\dot{V}O_2$ was 36% (IQR = 32-42%), and VAT was $0.695 \text{ L}\cdot\text{min}^{-1}$ (IQR = $0.542\text{-}0.845 \text{ L}\cdot\text{min}^{-1}$) or $7.1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (IQR = $6.6\text{-}10.1 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Similarly, there was a consistently elevated VE/VCO_2 slope, reduced OUES, and a flat $P_{ET}CO_2$ response to exercise compared with expected normal values.

The complete cardiovascular, gas-exchange, and ventilatory variables are presented in **Table V**. All exercise tests were symptom-limited and the primary reason for termination was lower extremity fatigue. Maximal cardiopulmonary effort was evidenced in all tests commensurate with a peak RER of 1.34 (IQR = 1.22-1.38). At maximal exercise, the TAH patients had a fixed HR and flat BP response. Lastly, there were no adverse events warranting initiation of emergency procedures during any CPX.

Fick derived a- $\bar{v}O_2$ Difference

Resting a- $\bar{v}O_2$ diff was 5.33 mL/dL (IQR= $4.61\text{-}6.04 \text{ mL/dL}$), which increased to 10.36 mL/dL (IQR= $8.68\text{-}11.62 \text{ mL/dL}$) at the VAT, and reached 12.91 mL/dL (IQR= $12.23\text{-}15.06 \text{ mL/dL}$) at peak exercise. This amounts to a 142% or 2.4-fold increase in a- $\bar{v}O_2$ diff with peak exercise above resting values. Resting ($R=+0.556$, $P=0.039$), VAT ($R=+0.666$, $P=0.009$), and peak a- $\bar{v}O_2$ diff ($R=+0.657$, $P=0.011$) positively correlated with peak $\dot{V}O_2$. Using the estimated CaO_2 , this equates to an OER of 50% at rest, 97% at the VAT, and 125% at peak exercise.

Figure II is a flowchart illustrating the impact of TAH-related factors on Fick equation derived components of peak $\dot{V}O_2$.

Discussion

The present study is the first to report on the response to maximal aerobic exercise testing in a cohort of patients with a TAH. Our results indicate exercise capacity is abnormal in TAH patients. Specifically, peak $\dot{V}O_2$, %pred. peak $\dot{V}O_2$, and VAT are reduced in the TAH patient. This is accompanied by a blunted CO response to exercise and reduced oxygen carrying capacity of the blood.

The TAH has the ability to deliver a CO of >9 liters/min at its maximal stroke volume of 70 ml.⁴The Fick equation ($\dot{V}O_2 = CO \times a-\bar{v}O_2 \text{ diff}$) demonstrates that $\dot{V}O_2$ is largely dependent upon increases in CO [CO = HR x Stroke Volume (SV)]. It is generally accepted that maximal CO is the major determinant of peak $\dot{V}O_2$ during exercise, while additional factors that determine $\dot{V}O_2$ with exercise include: 1) pulmonary diffusing capacity; 2) oxygen carrying capacity of the blood; and 3) tissue extraction of O₂ mainly due to skeletal muscle characteristics.¹⁵

Previous work in LVAD patients has shown that the device is responsible for the majority of the CO increase seen during exercise.^{16,17}Despite restoration of normal to supra-normal resting CO, TAH patients; however, exhibit very low peak $\dot{V}O_2$ values which are comparable to patients with advanced HF.^{18,19}Peak $\dot{V}O_2$ values for TAH patients increased only approximately three-fold above resting metabolism [METS = 2.95 (2.70-3.43)], which is the upper limit with maximal oxygen extraction alone and without any increase in CO during exercise.¹¹In normal healthy adults, CO increases from a resting value of approximately 5 L·min⁻¹ to a maximum of about 20 L·min⁻¹ representing a 300% increase over baseline.²⁰However, the TAH pump has the theoretical ability to maximally increase CO only up to approximately 9.1 L·min⁻¹ during exercise representing a 2.7 L·min⁻¹ or 42% increase using the current study resting values. In the present study, CO increased 0.55 L·min⁻¹ or 9% in the TAH patient, reflecting a negligible change with exercise.

The design of the TAH limits its ability to increase CO and thus constrains performance during exercise. First of all, the TAH has a fixed ejection rate (i.e. HR) that is not responsive to increased venous return or patient motion/activity. Thus, with exercise, the only augmentation of CO is derived via increased SV, through enhanced venous return by the skeletal muscle blood pump during exercise and compensatory venoconstriction.^{5,21} However, during normal operation the reserve volumes in each pump are a fraction of the pump chambers capacity. The left and right pumps each thus have a limited ability to accommodate increases in venous return and may reach “full-fill” with high venous return states (e.g. exercise). In the present study, 9/10 patients’ TAH demonstrated graphical evidence of full-filling (maximum SV) at peak exercise (**Table 3 - Qualitative Waveform Analysis**). These patients with fixed ejection rates had no further SV reserve, thus could not further increase CO. Physiologic control algorithms that allow for modulation of pump parameters in response to patient activity or venous return would seemingly better address the increased metabolic demands of exercise.

Rheological factors may also explain the observations in this study, as the ability to increase CO decreases; the $a-\bar{v}O_2$ difference has a greater influence on the $\dot{V}O_2$ response to exercise. In healthy individuals, $a-\bar{v}O_2$ difference is approximately 5ml/100mL blood at rest (OER = ~30%) and can increase to approximately 15 ml/100mL blood (OER = ~75%) at maximum exercise.¹¹ Efficient delivery and extraction of O_2 are dependent on the O_2 carrying capacity of the blood. In the present study, the estimated CaO_2 was approximately half of normal values due to the severe anemia of the TAH patient. This resulted in an elevated OER at rest (48%) that approached 100% early into exercise at the VAT and exceeded CaO_2 values at peak exercise. Obviously, O_2 extraction cannot exceed available O_2 content, but illustrates the reliance on $a-\bar{v}O_2$ difference to increase $\dot{V}O_2$ with exercise in the context of a blunted CO response and

reduced O₂ carrying capacity (e.g. low Hgb). Agostoni and colleagues evaluated the relationship between Hgb and peak $\dot{V}O_2$ in HF patients.²² They found anemic HF patients had lower peak $\dot{V}O_2$, lower $\dot{V}O_2$ at VAT, and a higher VE/VCO₂ slope than non-anemic HF patients.

Patients implanted with the TAH develop a severe anemia related to surgical bleeding, chronic hemolysis from the four mechanical tilting disk valves, reduced erythropoiesis, and systemic inflammation.²³ Mankad et al. found that implantation of a TAH was associated with significant persistent anemia that was not resolved until device explantation and subsequent heart transplant. In our study, patients with the TAH were severely anemic with Hgb values approximating 60% of normal.

In the study by Agostoni et al., the linear regression slope demonstrated that each gram of Hgb accounted for a 109 ml.min⁻¹ change in $\dot{V}O_2$ (0.97 mL·kg⁻¹·min⁻¹).²² Using this assumption, the TAH group in the present study could potentially increase peak $\dot{V}O_2$ by 67% (0.56 L·min⁻¹) if the Hgb was increased to normal values. In other words, improving anemia by improving pump design (i.e. changing valves), rheological parameters, or modulating TAH parameters (i.e. minimizing ejection pressure) could potentially improve exercise capacity.

A lower Hgb reduces the O₂ transport capacity of the blood, which results in a reduced ability to meet the demands of exercise through aerobic metabolism. This leads to an early increasing reliance on anaerobic glycolysis for energy with a resulting elevated rate of lactic acid production. The observed lower $\dot{V}O_2$ at VAT observed indicates an early shift towards anaerobic metabolism.

Furthermore, this resulting acidosis leads to an increase in ventilation to maintain blood pH. The elevated VE/VCO₂ observed in HF patients is partially attributed to this early metabolic acidosis. In addition, the VE/VCO₂ slope is elevated when there is a ventilation-perfusion (VQ)

mismatch. In the present study, an inability to further augment CO with increasing exercise would lead to a VQ mismatch thus explaining the abnormal ventilatory parameters.

The blunted BP response noted in the TAH group is like that previously reported by Kohli and colleagues.⁸The present study differs in that these MAP values were obtained with maximal exercise versus a submaximal exercise session. This confirms that the BP response previously observed is potentially related to the limitations of the TAH device and not exercise intensity. Blood pressure is the product of CO and TPR where $BP = CO \times TPR$. Exercise BP would thus decrease in a situation of limited ability to augment CO with exercise. Furthermore, in this study an attenuated TPR response was noted in the TAH patient likely as a compensatory mechanism to maintain systemic perfusion.

Limitations

It is important to note when evaluating exercise responses; chronic heart failure and patients with MCS devices (i.e. LVAD, TAH) do not respond like normal individuals'. A significant proportion of the original cohort was not available for CPX (n=6, 30%) during the study period. Of the six patients for which CPX data was not available: one died in the intensive care unit, two were transplanted early (<45 days after TAH implant), two were too sick (unstable) to participate in exercise testing, and one patient refused CPX. To date, this was only a cross-sectional study examining the exercise capacity of TAH patients relatively early after device implantation. The postoperative date of CPX was smaller than that recommended for optimal functional results in the post-MCS patient. DeJonge and others have observed optimal timing for CPX was at least 12 weeks post-MCS implant.^{24,25}The $a-\bar{v}O_2$ difference or O_2 extraction values in this study were based upon a device-generated CO, non-steady state VO_2 conditions, and we used an estimate of the CaO_2 all of which could be prone to error.

Summary/Conclusions

This is the first study to directly measure maximal aerobic exercise capacity in a cohort of HF patients supported with the TAH. Based on these findings, symptom-limited exercise testing can be safely performed in the TAH patient. This study provides a baseline for expected functional ability and exercise responses in this unique patient population. It will help inform discussions of activity guidelines for those entering the community using a portable driver. Furthermore, it may provide an objective reference for future technology improvements.

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References

1. Hunt SA, American College of Cardiology, American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the american college of cardiology/american heart association task force on practice guidelines (writing committee to update the 2001 guidelines for the evaluation and management of heart failure). *J Am Coll Cardiol.* 2005;46(6):e1-82.
2. Kirklin JK, Naftel DC, Kormos RL, et al. Third INTERMACS annual report: The evolution of destination therapy in the united states. *J Heart Lung Transplant.* 2011;30(2):115-123.
3. Shah KB, Tang DG, Cooke RH, et al. Implantable mechanical circulatory support: Demystifying patients with ventricular assist devices and artificial hearts. *Clin Cardiol.* 2011;34(3):147-152.
4. Copeland JG, Smith RG, Arabia FA, et al. Cardiac replacement with a total artificial heart as a bridge to transplantation. *N Engl J Med.* 2004;351(9):859-867.
5. Everett J, Murray K, Brown V, et al. The effect of graded exercise on cardiac output of the jarvik-7-70 total artificial heart in humans. *ASAIO Trans.* 1989;35(3):231-234.

6. Nicholson C, Paz JC. Total artificial heart and physical therapy management. *Cardiopulm Phys Ther J*. 2010;21(2):13-21.
7. Bellotto F, Compostella L, Agostoni P, et al. Peripheral adaptation mechanisms in physical training and cardiac rehabilitation: The case of a patient supported by a CardioWest total artificial heart. *J Card Fail*. 2011;17(8):670-675.
8. Kohli HS, Canada J, Arena R, et al. Exercise blood pressure response during assisted circulatory support: Comparison of the total artificial heart with a left ventricular assist device during rehabilitation. *J Heart Lung Transplant*. 2011.
9. Tarzia V, Braccioni F, Bortolussi G, et al. Cardiopulmonary exercise testing responses to different external portable drivers in a patient with a CardioWest total artificial heart. *J Artif Organs*. 2015.
10. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA guidelines for exercise testing. A report of the american college of cardiology/american heart association task force on practice guidelines (committee on exercise testing). *J Am Coll Cardiol*. 1997;30(1):260-311.
11. Wasserman K, Principles of exercise testing & interpretation. *Principles of exercise testing and interpretation : Including pathophysiology and clinical applications*. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2005:585.
12. Wasserman K, Beaver WL, Whipp BJ. Gas exchange theory and the lactic acidosis (anaerobic) threshold. *Circulation*. 1990;81(1 Suppl):II14-30.

13. *ACSM's guidelines for exercise testing and prescription*. 9th ed. ed. Philadelphia: Philadelphia : Wolters Kluwer/Lippincott Williams & Wilkins Health; 2014.
14. Nutritional anaemias. report of a WHO scientific group. *World Health Organ Tech Rep Ser*. 1968;405:5-37.
15. Bassett DR,Jr, Howley ET. Limiting factors for maximum oxygen uptake and determinants of endurance performance. *Med Sci Sports Exerc*. 2000;32(1):70-84.
16. Jaski BE, Branch KR, Adamson R, et al. Exercise hemodynamics during long-term implantation of a left ventricular assist device in patients awaiting heart transplantation. *J Am Coll Cardiol*. 1993;22(6):1574-1580.
17. Branch KR, Dembitsky WP, Peterson KL, et al. Physiology of the native heart and thermo cardiosystems left ventricular assist device complex at rest and during exercise: Implications for chronic support. *J Heart Lung Transplant*. 1994;13(4):641-50; discussion 651.
18. Mehra MR, Kobashigawa J, Starling R, et al. Listing criteria for heart transplantation: International society for heart and lung transplantation guidelines for the care of cardiac transplant Candidates—2006. *The Journal of Heart and Lung Transplantation*. 2006;25(9):1024-1042.
19. Myers J, Gullestad L, Vagelos R, et al. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. *Ann Intern Med*. 1998;129(4):286-293.

20. Ehrman, Jonathan K., American College of Sports Medicine.,. *ACSM's resource manual for guidelines for exercise testing and prescription*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2010.
21. Izzo JL, Jr, Taylor AA. The sympathetic nervous system and baroreflexes in hypertension and hypotension. *Curr Hypertens Rep*. 1999;1(3):254-263.
22. Agostoni P, Salvioni E, Debenedetti C, et al. Relationship of resting hemoglobin concentration to peak oxygen uptake in heart failure patients. *Am J Hematol*. 2010;85(6):414-417.
23. Mankad AK, Tang DG, Clark WB, et al. Persistent anemia after implantation of the total artificial heart. *J Card Fail*. 2012;18(6):433-438.
24. de Jonge N, Kirkels H, Lahpor JR, et al. Exercise performance in patients with end-stage heart failure after implantation of a left ventricular assist device and after heart transplantation: An outlook for permanent assisting? *J Am Coll Cardiol*. 2001;37(7):1794-1799.
25. Pruijsten RV, de Jonge N, Kirkels JH, et al. Left ventricular assist device: A functional comparison with heart transplantation. *Neth Heart J*. 2008;16(2):41-46.

Figure Legends

Figure I. Graphical comparison of TAH Responses to Normal Physiologic Values. A box-whisker plot represents the entire TAH cohort. The dashed lines represent normal physiologic ranges. Abbreviations: $\text{L}\cdot\text{min}^{-1}$ = liters per minute, VO_2 = oxygen consumption, mmHg = millimeters of mercury, bpm = beats per minute, $\text{mL}\cdot\text{beat}^{-1}$ = milliliters per beat.

Figure II. Physiological Factors Related to Decreased peak VO_2 in the TAH Patient.

Abbreviations: TAH = total artificial heart, VO_2 = oxygen consumption, $a-\bar{v}\text{O}_2$ = arteriovenous oxygen difference, CaO_2 = arterial oxygen content of blood.