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IMPACT OF ISCHEMIC TIME ON FUNCTIONAL EXERCISE CAPACITY AFTER ORTHOTOPIC HEART TRANSPLANTATION

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IMPACT OF ISCHEMIC TIME ON FUNCTIONAL EXERCISE CAPACITY AFTER ORTHOTOPIC HEART TRANSPLANTATION

by

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Abstract

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Purpose: Ischemic time (IT) is an independent risk factor for poor functional exercise capacity (FEC) following orthotopic heart transplantation (OHT). The OHT recipient's post-transplant FEC (peak $VO_{2)}$ is directly associated with improved quality of life. However, there is debate in the literature about the deleterious impact of extended IT on FEC following OHT.

Methods: Fifteen OHT recipients (14 men and 1 woman; < 3 months from OHT) performed a symptom-limited graded CPET where peak VO_2 was measured in an outpatient cardiac rehabilitation. IT was obtained from the anesthesia post-operative note. VO_2 and IT values were dichotomized based on previous literature; high, ≥14 mL/kg/min (or ≥12 mL/kg/min if taking a beta blocker), and low, <14 mL/kg/min (or <12 mL/kg/min if taking a beta blocker), and short, <180 min and long, ≥180 min, respectively. A Fisher's Exact Test was used to determine if extended IT is associated with decreased FEC**.**

Results: The median (IQR) recipient and donor characteristics are presented in Table 3. The Fisher's Exact Test yielded a *p* value of 0.62.

Conclusions: Extended IT was not associated with decreased FEC in the months following OHT in those recipients who survived to discharge with stamina sufficient to engage in outpatient cardiac rehabilitation. The wider IQR of peak VO_2 in recipients with extended IT, despite the higher number of recipients, suggests that while properly selected allografts are able to tolerate a longer IT without compromising intermediate term FEC, this is not a homogenous correlation and other peri-transplant factors may modify FEC.

Chapter 1

Introduction and Background

Orthotopic Heart Transplantation (OHT)

As the battle against the nation's leading cause of death, heart disease, continues to expand, orthotopic heart transplantation (OHT) remains a feasible option for the treatment of end-stage heart failure (HF). OHT is the current gold standard for the treatment of HF due to its potential to extend the life of the recipient, improve the recipient's quality of life (QOL), and functional capacity.[1] Furthermore, OHT has been more effective in decreasing mortality and improving QOL in comparison to alternative HF treatments such as Left Ventricular Assist Device (LVAD) or medical management.[2] More than 70,000 OHTs have been performed since 1988[3] and, due to advancements in technology, the number per year is steadily increasing.[4]

Transplant Donor Guidelines and Organ Procurement

As more patients require OHT, the demand for suitable donor hearts is likely to increase and currently outweighs the supply of available donor organs. In order to accommodate the need for eligible donor hearts, many institutions are working to expand the criteria for what constitutes an acceptable donor heart. Since OHT outcomes are complex and multifaceted, multiple donor qualities and organ procurement and preservation techniques have been reexamined in the hopes of improving the accessibility of OHT. Donor characteristics, such as age and previous health status, have been a growing topic of interest for years, ultimately allowing for an expansion in the donor pool. For example, in the late 1980's, donor hearts were only deemed transplantable if the donor was younger than 35 years of age for men and 40 years of age for women.[5] Recently, however, research has explored the implications of transplanting older donor hearts and older recipients but no age limit has been established.[6, 7]

In addition to donor specific qualities, investigation into donor heart preservation and procurement guidelines has allowed for potential change in the previous donor organ requirements. For example, OHT clinicians have suggested that by increasing the time allowable for a donor heart to reach its destination, donor hearts may become accessible to people in more remote locations (or the most ill nationwide/worldwide). However, more distant destinations may require the donor heart to remain under-perfused for longer periods of time. This characteristic of donor heart preservation, called ischemic time (IT), is currently under investigation. Longer IT may allow for increased availability of donor hearts, but the implications of extended IT are not fully understood.

Heart Ischemic Time (IT)

Heart IT is defined as "the time that an organ is outside the body when the heart is not beating and/or supplied with oxygen by the coronary arteries."[8] According to traditional research and guidelines, is ideal when IT is less than 240 minutes.[5,7] However, some institutions remain more conservative with idealistic IT of 180 minutes or less.[9] While some studies have found that IT is an independent risk factor for mortality and poor prognosis following OHT,[10,11] other studies suggest that extended IT has no impact on long term survival.[12] Moreover, several case studies have investigated donor IT of up to six hours (360 minutes) with no difference in mortality up to 36 months post-transplant.[13] In regards to post-surgical complications and resource allocation, one study suggested that there is no difference in the risk for primary graft dysfunction, length of hospital stay, need for inotropic or ventilatory support or rejection associated with donor IT of less than 4 hours and 4 to 5 hours, but the risk begins to increase after 5 hours.[10] Although there are interventions being explored to minimize the ischemic damage of donor hearts with prolonged IT[14], there is still ongoing discussion as to what constitutes a suitable IT for OHT.

Ischemic Time and Functional Exercise Capacity (FEC)

As there is ongoing debate in the literature regarding long-term impact of prolonged IT on patients with OHT, it is imperative to understand the impact IT has on the donor heart's capacity to do work after OHT. It has been suggested that patients experience a decreased exercise capacity following OHT when compared to healthy individuals,[14,15] which impacts the overall functional exercise capacity (FEC) of the OHT recipient. FEC is a significant component in an individual's ability to perform activities of daily living, participate in recreational and occupational ventures and is associated with QOL after OHT.[2] Low QOL has been associated with increased symptoms of depression and anxiety in OHT recipients[16], which makes it imperative for healthcare professionals to understand the impact prolonged IT may have on the recipient's prognosis.

Given that increased IT may impact cardiac functioning following adult OHT, the impact of IT on FEC should warrants further investigation in order to further understand the implications of using donor hearts with extended IT. In one landmark study, shorter IT was related to increased FEC in OHT recipients two months post-transplant, but this study was not sensitive to the variable needs of the OHT patient population.[16] This particular study estimated the patients' FEC merely by the number of metabolic equivalents (METs) they were able to achieve, without the use of metabolic-cart gas analysis, on a Bruce treadmill protocol. Although, this study provides valuable information; it is not inclusive of the many OHT recipients that may be unable to perform this test due to orthopedic limitations, severe deconditioning observed with end-stage heart failure, and the large increase in speed and incline with each progressive stage.

Therefore, in order to create a more inclusive and specific investigation into the impact of prolonged IT on FEC, a symptom-limited, cardiopulmonary exercise test (CPET) should be used involving a modality and protocol best suited for the individual patient.

Purpose

The purpose of this study was to investigate the effect that donor IT has on FEC, measured by peak volume of oxygen consumption (VO_2), in adults after OHT.

Chapter 2

Methods

Study Design

A prospective, observational study was performed on 15 OHT recipients between January 2019 and October 2019 who were enrolled at the Walter I. Berman Cardiovascular Rehabilitation (CR) and Prevention Center at Baylor Scott and White Heart and Vascular Hospital in Dallas, Texas. All subjects enrolled were hemodynamically stable adult outpatients who underwent OHT fewer than 90 days before enrollment in the study.

Inclusion and Exclusion Criteria *Table 1* provides the inclusionary and exclusionary criteria for the study.

Table 1. Inclusion and Exclusion Criteria for Patient Enrollment

Inclusion Criteria	***Exclusion Criteria***
Male or female	Orthopedic, neurologic or other limitations that prevent exercise testing on a treadmill or cycle ergometer
Hemodynamically stable	Requiring supplemental oxygen
Outpatient enrolled in cardiac rehabilitation	Current permanent tracheostomies
Recipient of OHT within three months from enrollment date	Patients discharged to a long-term acute care facility; skilled nursing facility or with palliative/hospice care
18 to 80 years of age	Inmates
Able to read and understand an informed consent	Pregnant women

Subject Identification

Potential subjects were identified upon admission to the CR program by use of a screening tool illustrating inclusion and exclusion criteria. Patients who met the inclusion criteria were offered participation in the study and if agreeable, were taken through the informed consent process during their first day of CR.

Cardiopulmonary Exercise Testing (CPET)

An order requesting a CPET was signed and dated by the subject's cardiothoracic transplant surgeon, cardiologist, appropriately licensed advanced practice healthcare provider with heart transplant expertise, or primary care physician. Upon admission to the CR program, subjects were scheduled to perform a CPET on either an upright cycle ergometer or treadmill depending on level of comfort and fall risk assessment performed by a registered nurse on the day of testing. Subjects were fitted for metabolic testing (Quark CPET, COSMED, Concord, CA or similar) equipment according to factory requirements and a lead II ECG monitor was attached to the subject (ScottCare VersaCare Telemetry Monitoring System, Cleveland, Ohio or similar) to monitor for arrythmias. Each subject was asked to perform the CPET to the best of their abilities. The modified Borg Rating of Perceived Exertion (RPE-CR10) scale was used during the testing.[17] The RPE-CR10 (1 to 10) scale is a common method for determining exercise intensity levels, where “0” = nothing at all and “10” = very, very hard. The traditional

Borg scale (6-20) was not used due to the disassociation between level of difficulty and heart rate seen in a denervated heart. Continuous blood pressure (BP) measurements were taken to ensure hemodynamic stability and lead II ECG was monitored continuously by telemetry staff.

Termination Criteria

The CPET was terminated if any of the following occurred: (a) subject became symptomatic; (b) increased pain reported; (c) subject asked to terminate test; (d) dangerous arrhythmias reported on ECG; (e) unsafe drop in BP or over 250/120 mmHg reported; or (f) subject reported a "10" on RPE-CR10 scale, indicating maximal effort. Other termination of the test was reserved for the clinical judgment of research staff to ensure safety of the subject. After termination of the test, subject was instructed to perform a cool-down of 3 to 5 minutes. The CPET was performed in an area with immediate access to a "crash cart", a supervising physician, and clinical staff trained in advanced cardiac life support. Donor organ-specific data was gathered through the UNOS Donor Infection ID and Match Run and matched with the corresponding printed CPET report after completion of the test.

Statistical Analysis

The main exposure of this study was duration of IT. The overall median inter quartile range (IQR) of IT were calculated according to standard methods. IT was further dichotomized into longer and shorter IT using cutoff of 180 minutes.[9,18] The main outcome of this study was the subject's FEC, measured by peak VO_2, which was dichotomized into lower and higher FEC using a pre-specified cutoff of 14 mL/kg/min and a pre-specified supplemental analysis was performed using a dichotomous cutoff of 12 mL/kg/min. These two cut-offs were selected as they represent the standard thresholds below which transplant is most typically justified in an ambulatory, non-inodilator-dependent subject (14 mL/kg/min for pre-transplant patients without current beta blocker use and 12 mL/kg/min with beta blocker use).[9,17] Data are shown as percentages or *n* for categorical variables and compared between subjects with lower FEC and those with higher FEC using a Fisher's Exact Test; medians IQR for continuous variables were calculated according to standard methods. Data were analyzed using NCSS 11 (NCSS, LLC - Kaysville, UT).

Chapter 3

Results

Patient Characteristics

The patient demographics and characteristics information for this cohort can be depicted in *Table 2* below.

Table 2. Patient Characteristics Demographics

Characteristics/Demographics	***Median (IQR) or %***
Age (years)	58 (10.7)
Height (cm)	175.26 (7.37)
Body weight (kg)	83.46 (16.92)
Resting HR (bpm)	112 (10)
Asian	6.67%
Black	20.00%
Hawaiian	6.67%
White	66.67%
Hispanic	6.67%
Fall Risk	46.6%
Modified “Slow” USAFSAM	53.33%
Beta Blocker Use	6.67%

Comparison of IT and FEC

The comparison between the long IT and short IT groups as well as the High FEC and Low FEC groups is detailed in *Table 3* and visualized in *Figure 1*. The results of the Fisher's Exact Tests yielded a p value of 0.62.

Table 3. Median (IQR) Donor and Recipient Characteristics Comparing IT and FEC

	Long IT	***Short IT***	***Total***
Donor age (years)	45 (31)	38 (13)	42 (26)
Recipient age (years)	60 (14)	65 (12)	60 (10)
IT (minutes)	249 (46)	115 (52)	224 (148)
VO2 (mL/kg/min)	14.4 (7.0)	14.0 (3.6)	14.4 (4)
High FEC	n= 6	n= 3	15.8 (3.3)
Low FEC	n= 3	n= 3	11.3 (2.7)

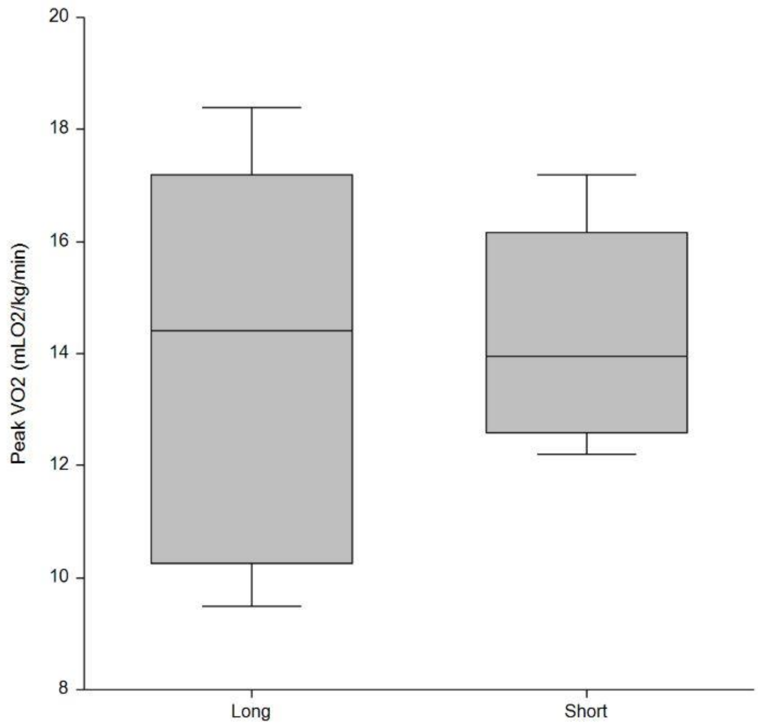

Figure 1. Box Plot of Median Peak VO2 in Long and Short Ischemic Time Categories

Chapter 4

Conclusions and Implications

Interpretation of Results

According to the analysis performed in this cohort, extended IT (>180 minutes) was not associated with decreased FEC (<14 mL/kg/min or <12 mL/kg/min with beta blocker use) in the months following OHT in recipients who survived to discharge with stamina sufficient to engage in an outpatient CR program. The wider IQR of peak VO_2 in OHT recipients with extended IT, despite the higher number of recipients, suggests that while properly selected allografts can tolerate a longer IT without compromising intermediate term FEC, this is not a homogenous correlation and other peri-transplant factors may modify FEC.

Comparison of Results to the Literature

These results do not support the findings of Buendia-Fuentes *et. al.*, regarding donor and recipient specific qualities that impact functional recovery in the 2 months following transplant.[16] This discrepancy may be in part due to the method used to test and evaluate OHT recipients. Those investigators, used the Bruce treadmill protocol, which utilizes steep incline and speed increases each progressing stage. Functional capacity was also estimated using METs, which are not representative of this population due to an abnormal response to exercise.[15,18] Since breath-by-breath gas analysis and a more individualized testing modality were used in the present study, this may more accurately reflect their actual peak VO_2. For subjects that did not present as a fall risk, a modified USAFSAM treadmill protocol (for CHF patients) was used and for those who were deemed unsafe to perform a CPET on a treadmill, a 10 W ramp cycle ergometer protocol was used.[19] Future studies, might need to analyze differences that may exist between cycle ergometry and treadmill outcomes in this clinic population, as we know that VO_2 may be underestimated in cycle ergometry testing.[20]

Limitations

Although the results of the present study provide valuable insight into the relationship between donor IT and the ability of the transplanted heart to do work in the 3 months immediately following surgery, it is not without limitations, particularly due to the small size. Due to the United Network for Organ Sharing's revision to the adult heart allocation policy in October 2018, an increased percentage of OHT recipients required placement post-discharge from the acute-care setting and consequently were ineligible to participate in the study.[21] The increasing accessibility of extracorporeal membrane oxygenation and temporary mechanical circulatory support devices (Impella, intra-aortic balloon pump, etc.), allowing the most critical patients to survive until transplant, resulted in additional orthopedic and neurologic limitations that restricted exercise testing.

Future Recommendations

The investigation into the effect extended IT has on FEC after OHT could be strengthened by a larger sample, across multiple transplant centers, with a longitudinal analysis to account for effect of IT on long-term functional allograft recovery. Due to the variation in results in the literature surrounding the possible impact of increasing IT on the immediate and long-term allograft function post OHT, in addition to the association between FEC and QOL, further investigation is warranted exploring the impact of longer IT.

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Biosketch

Katelyn D. Brown has been working as an Exercise Physiologist at Baylor Scott and White Heart and Vascular Hospital since earning her Bachelors of Science in Kinesiology from The University of Texas at Arlington in 2014. In 2016, she began her studies at the University of Texas at Tyler Graduate School pursuing a MS in Kinesiology. She then completed a thesis, guided by Dr. Arturo A. Arce-Esquivel, Dr. Cheryl Cooper and Dr. Jenny Adams. This thesis served as a joint effort between Baylor Health System and the University to further the research regarding transplant sciences. Thank you for this opportunity.