Cardiopulmonary Exercise Testing—A Valuable Tool, Not Gatekeeper When Referring Patients With ACHD for Transplant Evaluation

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Abstract

Introduction: Treatment of patients with adult congenital heart disease (ACHD) with advanced therapies including heart transplant (HT) is often delayed due to paucity of objective prognostic markers for the severity of heart failure (HF). While the utility of Cardiopulmonary Exercise Testing (CPET) in non-ACHD patients has been well-defined as it relates to prognosis, CPET for this purpose in ACHD is still under investigation.

Methods: We performed a retrospective cohort study of 20 consecutive patients with ACHD who underwent HT between March 2010 and February 2016. Only 12 of 20 patients underwent CPET prior to transplantation. Demographics, standard measures of CPET interpretation, and 30-day and 1-year post transplantation outcomes were collected.

Results: Patient Characteristics. Twenty patients with ACHD were transplanted at a median of 40 years of age (range: 23-57 years). Of the 12 patients who underwent CPET, 4 had undergone Fontan procedures, 4 had tetralogy of Fallot, 3 had d-transposition of the great arteries, and 1 had Ebstein anomaly. Thirty-day and one-year survival was 100%. All tests included in the analysis had a peak respiratory quotient _1.0. The median peak oxygen consumption per unit time (_VO2) for all diagnoses was 18.2 mL/kg/min (46% predicted), ranging from 12.2 to 22.6.

Conclusion: There is a paucity of data to support best practices for patients with ACHD requiring transplantation. While it cannot be proven based on available data, it could be inferred that outcomes would have been worse or perhaps life sustaining options unavailable if providers delayed referral because of the lack of attainment of CPET-specific thresholds.

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Introduction

With a growing population of patients with adult congenital heart disease (ACHD) progressing to advanced heart failure (HF), the number of these patients requiring evaluation for heart transplantation (HT) is similarly on the rise.[1-3] Despite continued improvement in outcomes, treatment of these patients with advanced therapies including HT is often delayed due to a paucity of objective prognostic markers for the severity of HF.[4-6] This absence of data often forces providers to make treatment decisions based on data extrapolated from the existing noncongenital HF literature and guidelines; however, these data may not always be applicable to the patient with ACHD.

One such prognostic tool is cardiopulmonary exercise testing (CPET). While the utility of CPET in non-ACHD patients has been well-defined as it relates to prognosis, CPET for this purpose in ACHD is still under investigation. Fundamental differences in cardiovascular anatomy and physiology such as the variety of anatomical lesions and levels of cyanosis separate ACHD from non-ACHD HF. In addition, patients with ACHD are younger than most non-ACHD transplant candidates and may appear more robust despite very advanced and severe cardiac disease. As such, established CPET thresholds that apply to non-ACHD patients may delay timing of referral for transplantation, potentially leading to worse outcomes for patients with ACHD. At tertiary referral centers, it is not uncommon to hear that patients are not appropriate for HT evaluation yet because "their CPET results do not meet the criteria."

We have previously described favorable outcomes associated with a multidisciplinary approach to HT evaluation in patients with ACHD at the Hospital of the University of Pennsylvania.[5] Herein, we discuss the CPET findings available in a subset of these patients who underwent HT. The aim is to demonstrate the following:

1.   There is a clear role for CPET in evaluating patients with ACHD with HF undergoing HT evaluation; however, the "window of opportunity" for transplantation can be missed if providers await the thresholds established in non-ACHD populations.

2.   Lack of a CPET should not limit a patient's ability to proceed with transplant evaluation, listing, or transplantation.

3.   Currently, CPET is a tool in the armamentarium in caring for HF in patients with ACHD but needs to be evaluated in combination with additional metrics.

Methods

We performed a retrospective cohort study of 20 consecutive patients with ACHD who underwent HT between March 2010 and February 2016. A multidisciplinary team of adult

and pediatric subspecialists evaluated patients. Only 12 of 20 patients underwent CPET prior to transplantation. Demographics, standard measures of CPET interpretation, and 30-day and one-year posttransplantation outcomes were collected.

Institutional Review Board

The institutional review board of the Hospital of the University of Pennsylvania reviewed and approved the study, and individual patient consent was obtained.

Results

Patient Characteristics

Twenty patients with ACHD underwent heart transplantation at the Hospital of the University of Pennsylvania between March 2010 and February 2016, at a median age of 40 years (range 23 - 57 years). Thirty-five percent were male and 75% were Caucasian. Original diagnoses included single ventricle palliated with Fontan (n = 8), d-transposition of the great arteries (d-TGA) after atrial switch (n = 4), tetralogy of Fallot (n = 4), pulmonary atresia (n = 1), Ebstein anomaly (n = 1), unrepaired ventricular septal defect (n = 1), and Noonan syndrome with coarctation of the aorta (n = 1). Nine patients underwent heart/liver transplantation and three underwent heart/lung transplantation. Of the 12 patients who underwent CPET, 4 had undergone Fontan procedures, 4 had tetralogy of Fallot, 3 had d-TGA, and 1 had Ebstein anomaly. Thirty-day and one-year survival was 100% as previously described.[5]

Cardiopulmonary Exercise Testing Data Pretransplantation

All tests included in the analysis had a peak respiratory quotient 1.0 (Table 1). The median peak oxygen consumption per unit time ($\dot{V}o_2$) for all diagnoses was 18.2 mL/kg/min (46% predicted), ranging from 12.2 to 22.6. The median peak $\dot{V}o_2$ was 19.7 mL/kg/min for Fontan, 17.0 mL/kg/min for tetralogy, and 18.7 mL/kg/min for d-TGA. The median peak heart rate as a percentage of predicted was 71% (range: 55%-82%). Median ventilation equivalent of carbondioxide ($\dot{V}_E / VCO_2$) was 31. It should be noted that O_2 pulse may have limited utility in this population due to chronotropic incompetence, hypoxia, or polycythemia. In fact, 4 of 12 had <70% predicted heart rate response and 3 of 12 had respiratory disease based on breathing reserve that contributed to decreased exercise performance.

Of the eight patients who underwent transplantation without prior CPET, three patients had combined heart/lung transplantation. Two of the patients transferred from outside facilities for emergent transplant evaluation prior to testing. The remaining three did not have a documented explanation for not having undergone CPET.

Of the nine patients who underwent combined heart/liver transplant, three of these did not undergo CPET. Three of these patients had protein losing enteropathy (PLE); however, they were transplanted in the setting of worsening congestion and exercise intolerance in line with those without PLE. None of the patients underwent transplantation in the setting of overt liver failure as the primary driver of the decision.

During the evaluation process, five additional patients were listed for transplantation. Two Fontan patients were delisted due to clinical improvement. Three patients died while awaiting transplantation. One patient with Fontan and one d-TGA after Mustard suffered cardiac arrest and died despite being emergently placed on extracorporeal membrane oxygenation. The last, a patient with Shone complex died from overwhelming infection while awaiting transplant.

Discussion

In our cohort of 20 transplanted patients with ACHD, 12 underwent CPET with 1 of 12 meeting the standard, non-ACHD, criteria for transplantation. The analysis demonstrates that within this complicated group of patients, the overall clinical evaluation and expert opinion must influence the decision to pursue advanced therapies such as transplantation. The CPET results must be evaluated within disease-specific or even patient-specific frameworks to avoid inappropriate delays in transplantation evaluation. In addition, our goal was to formally make the statement that transplant is an option for patients with ACHD—even when they do not undergo the standard testing or reach specific thresholds expected of non-ACHD patients.

While several parameters including declining New York Heart Asssociation(NYHA) class, progressive ventricular dysfunction, and elevated serum Brain Natriuretic peptide(BNP)[7,8] have each been associated with increased mortality in patients with ACHD with HF, the specific thresholds to drive decisions regarding timing of advanced therapies are lacking. Cardiopulmonary exercise testing is one assessment often used in acquired non-CHD HF patients to guide transplant listing. In 1991, the ground breaking work by Mancini et al established a peak $\dot{V}o_2$ cutoff of   14 mL/kg/min[9] (12 mL/kg/min in patients taking β-blockers[10]) as a criteria for those in which one-year survival was significantly lower than that achieved through transplantation. Those with $\dot{V}o_2 > 14$ mL/kg/min had 6% one-year mortality, which suggested that transplantation could be safely deferred.

However, the heart transplant guidelines unfortunately do not provide much evidence for patients who do not meet the peak $\dot{V}o_2$ standards. In young patients (<50 years), it is reasonable to consider using alternate standards in conjunction with peak $\dot{V}o_2$ to guide listing, including percentage of predicted (50%) peak $\dot{V}o_2$. In the presence of a submaximal cardiopulmonary exercise test, use of ventilation equivalent of carbon dioxide ($\dot{V}_E / VCO_2$) slope of >35 as a determinant in listing for transplantation may be considered. These are class IIa (level of evidence: B) and class IIb (level of evidence: C), respectively.[11]

According to the most recent ACHD HF guidelines "in patients with ACHD, CPET can be useful for baseline functional assessment and serial testing." And "although specific criteria for timing of referral for transplantation are desirable, universal recommendations cannot be made based on current data".[12] However, specific values do not hold the same prognostic value in patients with ACHD as they do in noncongenital patients due to the broad spectrum of disease within the ACHD population. This is related to both anatomic and physiologic

factors that include cyanotic and acyanotic lesions, single ventricle and biventricular circulations, congenital or acquired chronotropic impairment, and respiratory disease. Thus, conventional non-ACHD CPET results cannot be interpreted with the normative values derived from adult non-CHD patients due to the risk of misguiding clinical interpretation and assessment of HF severity and prognosis. In fact, transplantation programs have become less reliant on CPET as the number of ACHD, hypertrophic cardiomyopathy, and restrictive cardiomyopathy patients has grown.

Recognition of failing patients with ACHD in need of advanced therapies is quite complicated in large part because patients frequently underreport exercise symptoms. One study of greater than 4,000 patients with ACHD showed that 63% of patients reported NYHA class I status.[13] Forty percent of those with Fontan physiology reported class I symptoms. In addition, peak $\dot{V}_{O_2}$ was reduced in patients with ACHD who were asymptomatic compared to healthy patients of similar age.[14]

In patients with HF, CPET requires careful measurement of ventilatory and O_2 uptake patterns in order to quantify severity and prognosticate for patients.[15] The complicated and unique anatomical lesions all impact an ACHD patient's exercise response differently, which makes evaluation challenging. Plus, patients with ACHD frequently have pulmonary, musculoskeletal, and metabolic system abnormalities which impact the normal physiological response to exercise and may make interpretation of CPET challenging.[16]

Furthermore, which components of CPET to use and which anatomy they apply to remain nebulous in patients with ACHD. Kempny et al reviewed data from greater than 4,000 patients with ACHD to identify reference values for $\dot{V}_{O_2}$ peak and $\dot{V}_E / V_{CO_2}$.[17] They found mean peak $\dot{V}_{O_2}$ in patients with ACHD ranged from 31.9 ± 9.2 mL/kg/min in patients with a history of arterial switch for d-TGA to a low of 12.2 ± 3.8 mL/kg/min in those with Eisenmenger syndrome. The $\dot{V}_E / V_{CO_2}$ is significantly dependent on diagnosis with values that ranged from 29.8 ± 4.7 in those postarterial switch to 52.0 ± 19.5 and 71.8 ± 55.0 in those with complex ACHD and Eisenmenger syndrome. Fontan patients have been shown to have an elevated slope due to excessive ventilation explained by either increased dead space or changes in the chemoreceptor set point for Pa_{CO_2}.[18]

Paridon et al demonstrated that the mean peak $\dot{V}_{O_2}$ for a Fontan patient is 27 mL/kg/min.[19] However, while this again highlights differences that exist, these data must be used carefully as age and sex of the patient must also be used to evaluate within a specific physiology. Furthermore, the anaerobic threshold percentage of $\dot{V}_{O_2}$ is higher than typical, because beyond this point the pulmonary vasculature restricts pulmonary blood flow and thus, ventricular preload.

In patients with ACHD, the markers of mortality vary as well. Some studies support using peak oxygen uptake (peak $\dot{V}_{O_2}$), while others argue that $\dot{V}_E / V_{CO_2}$ are also independent predictors of mortality in patients with ACHD.[20,21] A study of 1,375 patients with ACHD showed the highest predictor for the 117 deaths over a median follow-up period of 5.8 years

was a combination of $\dot{V}o_2$ peak and heart rate reserve.[13] Interesting, the prognostic value was diminished by the fact that many patients had a respiratory exchange ratio less than 1.0 —demonstrating a submaximal test.

Dimopoulos et al argued that the ventilatory response to exercise ($\dot{V}_E / VCO_2$ slope) was the strongest predictor of mortality in a cohort of 560 patients with ACHD.[22] Other studies have shown that heart rate reserve predicts mortality independent of functional class and $\dot{V}o_2$ peak.[14] Fernandes et al found that Fontan patients with peak $\dot{V}o_2 < 16.6$ mL/kg/min were at high risk of death or cardiovascular hospitalization.[23] However, Diller et al believe that $\dot{V}o_2$ was predictive only of hospitalization but not of death or need for cardiac transplantation.[24]

Currently, the field lacks prospective studies in patients with ACHD to define cutoffs for predicting one-year mortality. It has been shown recently that change in peak $\dot{V}o_2$ between sequential CPETs, in Fontan patients, is predictive of transplant-free survival beyond the risk that is predicted by a single peak $\dot{V}o_2$.[25] However, this was a small group of patients in whom not all deaths were cardiovascular in nature. This observation has not been replicated in non-Fontan patients and does not provide clear guidance regarding timing of transplantation.

Our data demonstrate a few key points using a group of 20 consecutive patients with ACHD who underwent successful transplantation. First, the peak $\dot{V}o_2$ and peak Heart Rate(HR) may be lower than matched pairs based on age, but they are above the cutoff for which non-ACHD patients are evaluated for transplant. Second, a lack of $\dot{V}o_2$ data did not prevent the evaluation and subsequent successful cardiac transplant. Lastly, clinical evaluation in patients with ACHD is complicated, but the recognition of other markers of failure should be the impetus for referral for advanced therapy evaluation.

Limitations

This is a small single-center retrospective analysis with incomplete data. The data do not allow us to draw conclusions regarding patient outcomes without transplantation.

Conclusion

There is a paucity of data to support best practices for patients with ACHD requiring transplantation. We found that the median peak $\dot{V}o_2$ in this cohort of 20 consecutive patients with ACHD was greater than 14 mL/kg/min, which is a traditional threshold criterion for transplant listing in non-CHD patients. While it cannot be proven based on available data, it could be inferred that outcomes would have been worse or perhaps life-sustaining options unavailable if providers delayed referral because of the lack of attainment of CPET-specific thresholds.

We propose that CPET results should be evaluated within disease-specific and patient-specific frameworks to prevent inappropriate delays in transplantation evaluation.

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Furthermore, team-based approaches are beneficial in the identification of appropriate candidates and timing for successful transplantation.

Acknowledgments

Abbreviations and Acronyms

ACHD	adult congenital heart disease
CPET	cardiopulmonary exercise testing
dTGA	d-transposition of the great arteries
HF	heart failure
HT	heart transplantation
PLE	Protein losing enteropathy
$\dot{V}o_2$	oxygen consumption per unit time

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Table 1.

Patient Cardiopulmonary Exercise Test Results.

Age	Sex	Height (cm)	Weight (kg)	Diagnosis	Organ	Protocol	β-Blocker	Time	Heart Rate		O₂ Pulse	Peak V̇O₂		V̇E / VCO₂	RQ
									Peak	% Predicted	mL/beat	mL/kg/min	% Predicted		
28	M	180	63	Tetralogy of Fallot—after Fontan	Heart/liver	Naughton	No	8:36	130	71	9.9	20.3	46	31	1.18
45	F	163	73	Dextro-transposition of the great arteries	Heart	Naughton	Yes	9:00	128	76	11.1	19.6	63	30	1.11
33	F	152	41	Double inlet left ventricle—after Fontan	Heart/liver	Bruce	No	10:46	109	57	7.4	19.7	53	36	1.14
42	F	157	86	Dextro-transposition of the great arteries	Heart	Naughton	Yes	10:24	121	70	14.1	18.7	57	34	1.02
55	M	163	68	Tetralogy of Fallot	Heart/liver	Naughton	Yes	7:48	102	63	10.7	17.0	56	31	1.11
40	F	168	83	Dextro-transposition of the great arteries	Heart	Naughton	Yes	10:10	129	75	12.0	18.5	55	29	1.05
23	F	163	94	Tetralogy of Fallot/pulmonary atresia	Heart	Naughton	Yes	8:23	140	76	12.3	18.2	45	31	1.03
29	F	155	63	Double-outlet right ventricle—after Fontan	Heart/liver	Cycle Ergometer	Yes	11:24	153	79	8.2	18.0	53	30	1.37
28	F	152	58	Tetralogy of Fallot	Heart	Naughton	Yes	7:34	148	82	6.5	16.2	43	38	1.05
39	M	196	107	Double-inlet left ventricle/TGA—after Fontan	Heart/liver	Cycle Ergometer	Yes	8:50	150	82	14.7	22.6	45	28	1.20
57	F	165	69	Ebstein anomaly/ASD	Heart	Naughton	Yes	7:27	110	68	7.6	12.2	45	38	1.00
33	F	157	89	Double inlet left ventricle/TGA—after Fontan	Heart/liver	Bruce	No	1:31	98	55	14.6	16.1	45	34	1.01

Abbreviations: ASD, Atrial septal defect; F, female; M, male; RQ, respiratory quotient; TGA, transposition of the great arteries; V̇O₂, oxygen consumption per unit time; V̇E / VCO₂, ventilation equivalent of carbon dioxide.