Relation Between New York Heart Association Functional Class and Objective Measures of Cardiopulmonary Exercise in Adults With Congenital Heart Disease

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We aimed to compare New York Heart Association (NYHA) functional class in adult congenital heart disease (ACHD) patients with objectively measured cardiopulmonary exercise testing (CPET) parameters. This study included retrospective review of ACHD patients who underwent a CPET between August 2014 and April 2018 at our center. Patients were grouped according to severity of CHD, and NYHA class as recorded in their medical record or estimated from the clinical narrative. A total of 175 ACHD patients (mean age 30 ± 11 years) with NYHA class I-III enrolled in the study. The NYHA functional class was II or III in most complex CHD. There was a strong inverse relation between NYHA class and peak oxygen consumption, oxygen uptake efficiency slope, and the double product at peak exercise (product of heart rate and systolic blood pressure) ($p<0.0001$). There was no relation between NYHA class and ventilation efficiency slope ($p = 0.37$). In conclusion, NYHA functional class correlates with objective measures of CPET, however there is wide variability in measured exercise capacity in each NYHA classification. Therefore, whereas NYHA class of patients is a simple measure for assessment of functional status, CPET is an important tool to identify the source of exercise limitation in ACHD patients. **(Am J Cardiol 2019;123:1868−1873)**

The New York Heart Association (NYHA) functional class and peak oxygen consumption (pVO_2) are often used to classify severity of heart failure and survival in adults.[1] The comparison between NYHA functional class and pVO_2 and other cardiopulmonary exercise test (CPET) parameters in the assessment of functional status in adult congenital heart disease (ACHD) patients has not been well studied. We aimed to compare NYHA functional class in ACHD patients with objectively measured CPET parameters.

Methods

We retrospectively analyzed CPET in ACHD patients between August 2014 and April 2017 who were cared for at our ACHD Center, and this study was approved by Institutional Review Board of Memorial Healthcare System. A principal diagnosis was determined for every patient and classified according to the thirty-second Bethesda conference.[2] The NYHA class was determined for each patient by physician assessment of patients' self-reported symptoms before the exercise test or estimated from patient narrative from the medical record. Only patients with NYHA class I to III were enrolled in the study, as they were able to participate in CPET. Patients were dichotomized by peak VO_2 < 20 ml/kg/min versus ≥ 20 ml/kg/min (Weber criteria for no limitation in exercise capacity).[3] Similarly, patients were divided into 2 groups based on ventilation efficiency (V_E/VCO_2) slope cutoff of 34 (a prognostic tool of heart failure in adults).[4]

Standard spirometry was available in all patients.[5] Oxygen saturation was measured through a fingertip oximetry with the Masimo SET Radial-7 pulse oximeter (Irvine, California). Symptom limited CPET was performed on all patients using treadmill according to a modified Bruce protocol (97% of patients) or cycle ergometer ramping protocol (3% of patients).[6−7] The commercial gas exchange-measurement system (Ultima2, MedGraphics, St. Paul, Minnesota) was used to calculate respiratory gas exchange: VO_2, carbon dioxide output (VCO_2), minute ventilation (V_E) and related variables on a breath-by-breath basis. Peak heart rate and blood pressure were taken at the maximum exercise. CPET data were calculated as 30 seconds averages, which were updated every 10 seconds. Peak $VO_2$was taken as the highest 30-second average during exercise. VO_2 value was adjusted per ideal body weight.[8] The V_E/VCO_2 nadir was taken as the lowest 30-second average during exercise. The ventilatory threshold was measured using the V-slope method.[9-10] A CPET was considered maximal when respiratory exchange ratio (RER) of ≥ 1.1 was reached.[11] Submaximal O_2 uptake measurements included VO_2 at the ventilatory threshold and O_2 uptake efficient

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slope (OUES), which is the relationship between VO_2 and log VE throughout exercise.[12] The myocardial oxygen uptake, defined as the amount of oxygen consumed by the myocardium during exercise, was estimated by the product of heart rate and systolic blood pressure (double product, [DP]).[13] For convenience of clinical application and based on previously published data, we identified a cut-off value for the OUES 2,000 and for the maximum DP 20,000, as an optimal prognosticator for our study.[14–15]

Results are expressed as mean ± SD for continuous variables or as percent for categorical variables. Comparisons between groups were made with 1-Way ANOVA with Tukey post hoc test or the chi-square test as appropriate. Correlations between NYHA functional class components and CPET parameters were assessed using Spearman's rank correlation coefficient. For all analysis, a value of $p<0.05$ was considered significant. The main analysis was performed using Graph Pad Prism 7 (Graph Pad Software Inc., La Jolla, California).

Results

In total, 175 ACHD patients were enrolled in the study. Mean age at the time of CPET was 30 ± 11years, 78 (44.5%) were women. The most common diagnosis was repaired tetralogy of Fallot (n = 46, 26.2%), followed by Fontan patients (n = 34, 19.4%), repaired valvar diseases (aortic stenosis, pulmonary stenosis, and pulmonary regurgitation) (n = 29, 16.5%), repaired coarctation of aorta (n = 19, 10.8%), transposition of great arteries (TGA) s/p atrial switch (Mustard/Sening procedure) (n = 18, 10.2%), TGA s/p arterial switch (n = 13, 7.4%) and others (repaired atrial septal defect, ventricular septal defect, and Ebstein anomaly, and unrepaired congenitally corrected TGA) (n = 16, 9.1%) (Table 1). A known genetic abnormality was present in 9 (5.1%) patients (Di George syndrome (n = 4), Noonan syndrome (n = 3), Ehlers Danlos syndrome (n = 1), and Down syndrome (n = 1). Seven patients (4%) had implanted (dual chamber) pacemakers and 2 patients (1.14%) had implantable cardioverter defibrillators. The body mass index was ≥ 30 kg/m^2 in 45 patients (25.7%), diabetes mellitus and hypercholesterolemia each in 9patients (5.1%), hypothyroidism in 7 patients (4%), psychological disorders (anxiety, depression, attention deficit and hyperactivity, and obsessive compulsive disorder) in 18 patients (10.2%), deep vein thrombosis in 3 patients (1.7%), osteoporosis in 2 (1.14%) and chronic respiratory diseases (asthma, bronchitis) in 9 patients (5.1%). Patients were divided into NYHA Class I, n = 115 (65.7%); class II, n = 48 (27.4%); and Class III, n = 12 (6.8%) based on their subjective symptoms (**Table 2**).

Table 2
Selected CPET parameters according to NYHA functional class for the whole group of ACHD patients

	NYHA class		
CPET parameters	I	II	III
Peak VO_2	26.6 ± 6.1	21.1 ± 5.5	16.8 ± 4.5
VE/VCO_2 slope	30.8 ± 4.5	32.9 ± 5.8	35.5 ± 8.5
OUES	2,758 ± 849	2,285 ± 638	1,822 ± 462
Double product	27,966 ± 6,257	24,260 ± 5098.6	22,289 ± 4305

Peak VO_2 in the overall study population was 26.4 ± 9.8 ml/kg/min or 72.7 ± 22.3% of predicted. There was a progressive decline in pVO_2 with increasing severity of CHD ($p = 0.001$) (Table 1). There was a strong negative correlation between functional class and pVO_2, with a progressive decline from functional Class I to III ($r = -0.48$; $p < 0.0001$) (Figure 1A). About one-fourth of patients had pVO_2 <20ml/kg/min (Figure 1B) and there was an overlap in pVO_2 in each NYHA functional class. However, 75% of NYHA class III had pVO_2 <20 ml/kg/min compared with 10% in NYHA class I (Figure 1C). Patients in functional class III had a markedly reduced pVO_2 of 16.8 ± 4.5ml/kg/min compared with 26.6 ± 6.1 ml/kg/min in class I ($p = 0.0002$). There was no significant difference in pVO_2 between NYHA class II and III ($p = 0.09$), whereas the

Table 1
Summary of all ACHD patients according to the Bethesda classification

Variables	All	Bethesda 1	Bethesda 2	Bethesda 3	p value
	(n = 175)	(n = 31)	(n = 66)	(n = 78)	
Age (years)	30 ± 11	32 ± 15	30 ± 12	29 ± 9	0.435
Female	77 (44%)	13 (42%)	30 (45%)	34 (44%)	0.944
BMI (kg/m^2)	27 ± 7	27 ± 7	27 ± 7	26.8 ± 6.9	0.938
NYHA class					
I	115 (66%)	22 (71%)	53 (80%)	40 (51%)	0.006
II	48 (27%)	9 (29%)	10 (15%)	29 (37%)	0.105
III	12 (7%)	0 (0 %)	3 (5%)	9 (12%)	0.019
CPET parameters					
Peak VO_2	24.4 ± 6.6	26.6 ± 7.7	25.7 ± 7.1	22.4 ± 5.1	0.001
Predicted peak VO_2 (%)	64.2 ± 15.0	72.8 ± 17.6	66.8 ± 13.9	58.5 ± 12.4	<0.0001
Peak HR	159 ± 22	162± 19	162 ± 24	156 ± 21	0.204
Predicted HR (%)	81 ± 11	84 ± 11	82 ± 11	80 ± 11	0.125
Peak RER	1.11 ± 0.1	1.11 ± 0.1	1.12 ± 0.1	1.11 ± 0.1	0.814
V_E/VCO_2 slope	31.7 ± 5.4	31.4 ± 4.3	29.1 ± 4.1	34.1 ± 5.8	<0.0001
Predicted V_E/VCO_2 slope	114.8 ± 31.7	104.6 ± 24.3	104.8 ± 25.2	127.3 ± 34.8	<0.0001
OUES	2,564 ± 824	2,832 ± 930	2,751 ± 873	2,300 ± 654	<0.001
Double product	26,602 ± 6126	27,005 ± 5481	27,910 ± 6879	25,334 ± 5477	0.038

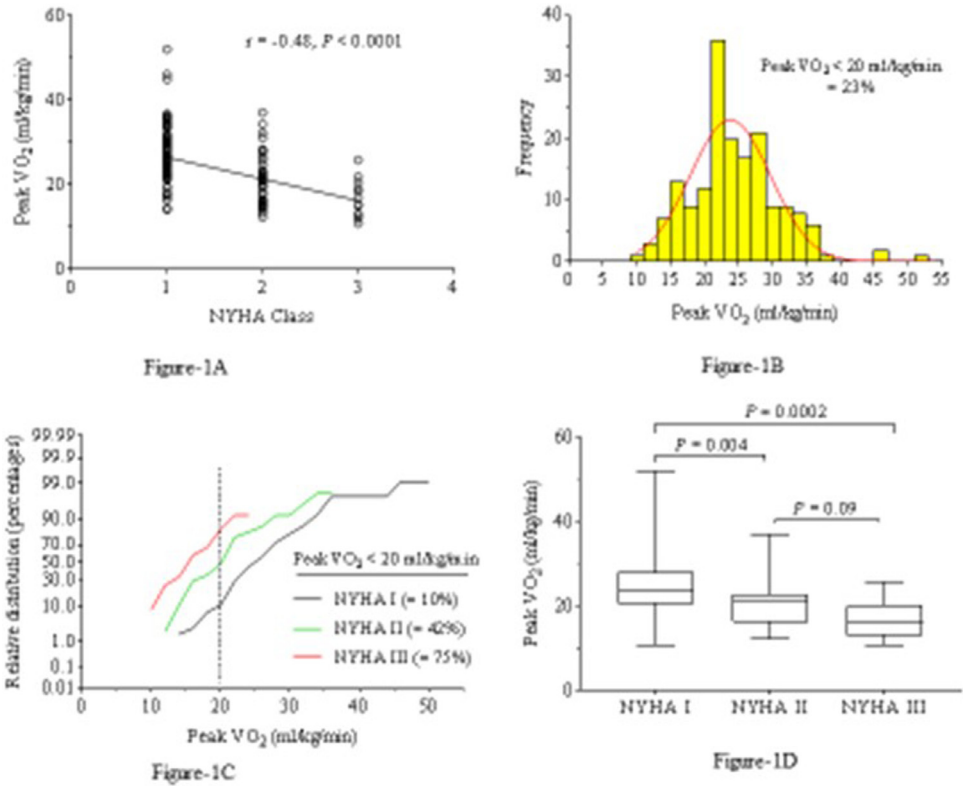

Figure 1. Relation between Peak VO_2 and NYHA class. (A) Spearman correlation between pVO_2 and NYHA class, (B) frequency of distribution of pVO_2, (C) Relative distribution with a cut-off value of pVO_2 20 ml/kg/min, and (D) Box and whisker-plot demonstrating median and quartiles of pVO_2 by NYHA class. NYHA = New York Heart Association.

difference between NYHA class I and II and Class I and III are significant ($p < 0.004$ and $p < 0.00002$ respectively; Figure 1D).

The V_E/VCO_2 slope in the overall study population was 31.7 ± 5.4. Patients in functional class III had the higher V_E/VCO_2 slopes compared with class I and II, but there was no significant correlation between NYHA class and V_E/VCO_2 slope ($r = 0.14$, $p = 0.37$; Figure 2A). The distribution of V_E/VCO_2 slope was within upper normal limits in functional class I patients, but one-fifth of these asymptomatic patients (20%) had an abnormal slope > 34 (Figure 2B). Almost one half of patients in NYHA class II (42%) and III (50%) had a V_E/VCO_2 slope > 34 (Figure 2C). There was no significant difference between NYHA class I and II ($p = 0.071$), or between Class II and III ($p = 0.263$), whereas V_E/VCO_2 was significantly different between Class I and III ($p = 0.011$; Figure 2D).

The OUES in the overall study population was 2,565 ± 825. There was a progressive decline in OUES with increasing severity of NYHA class ($r = -0.35$, $p < 0.0001$; Figure 3A). Majority of ACHD patients had OUES > 2000 (Figure 3B and C). There was no significant difference in OUES between NYHA class II and III ($p = 0.158$), whereas the difference between NYHA class I and II and Class I and III were significant ($p < 0.001$; Figure 3D).

The maximum DP in the overall study population was 26,602 ± 6,127. There was a progressive decline in maximum DP with increasing NYHA functional class ($r = -0.31$, $p < 0.0001$; Figure 4A). Majority of patients had DP > 20,000 (Figure 4B and C). There was no significant difference in maximum DP between NYHA class II and III ($p = 0.749$), whereas the difference between NYHA class I and II and Class I and III were significant ($p < 0.001$ and $p < 0.05$ respectively; Figure 4D).

Discussion

CPET can provide objective and reproducible assessment of the cardiovascular, respiratory, and muscular systems.[16] Also, it has been shown that CPET has prognostic value in patients with a wide variety of ACHD conditions.[17–20] Not all medical centers have the resources to conduct CPET, which is the preferred method of evaluation for functional capacity.[16] If CPET cannot be performed, stratification using NYHA class is an acceptable alternative.[21]

In this retrospective study of ACHD patients assessed by CPET, we found that 3 of its parameters (pVO_2, OUES, and maximum DP) overall correlate well with NYHA functional class especially between NYHA functional class I and III. There was not, however, a significant difference in pVO_2, OUES, and maximum DP between functional class II and III patients. In addition, we found that there is significant overlap of pVO_2, VE/VCO_2 slope, OUES, and maximum DP in each NYHA functional class. Similarly, there is a large variability in NYHA class for any given CPET parameter. This may be the result of patients underestimating their degree of limitations due to being chronically ill and adapting their lifestyle to their functional capability.[17] Therefore they are likely not functional class I.

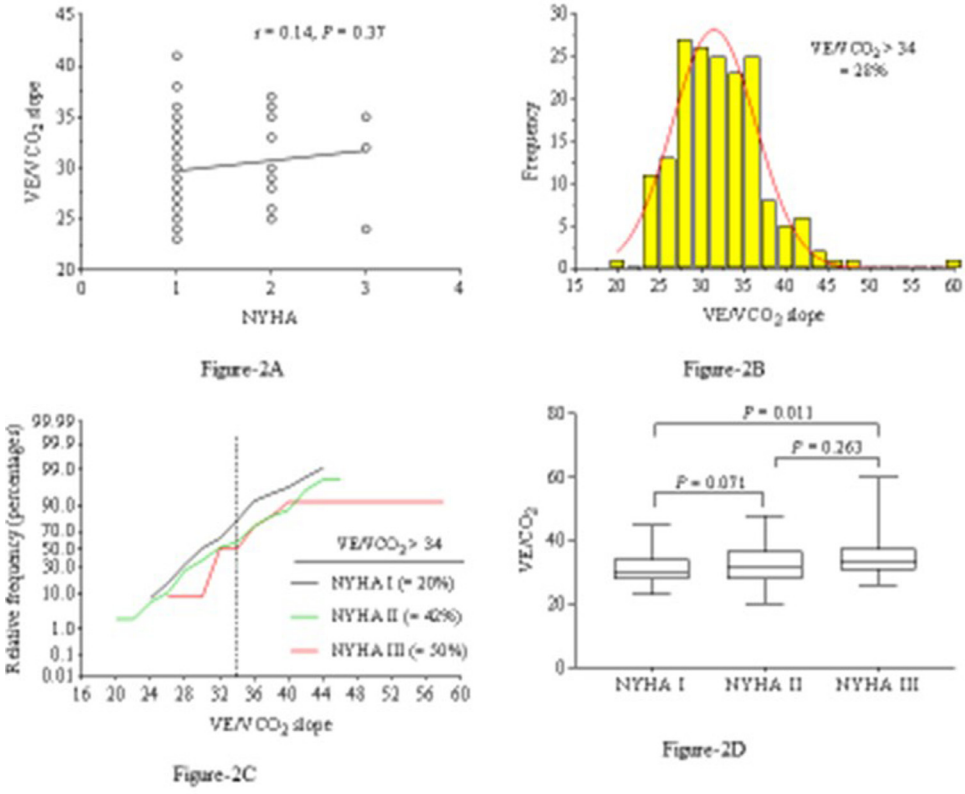

Figure 2. Relation between V_E/VCO_2 slope and NYHA class. (A) Spearman correlation between V_E/VCO_2 and NYHA class, (B) frequency of distribution of V_E/VCO_2, (C) Relative distribution with a cut-off value of V_E/VCO_2 34, and (D) Box and whisker-plot demonstrating median and quartiles of V_E/VCO_2 by NYHA class. NYHA = New York Heart Association.

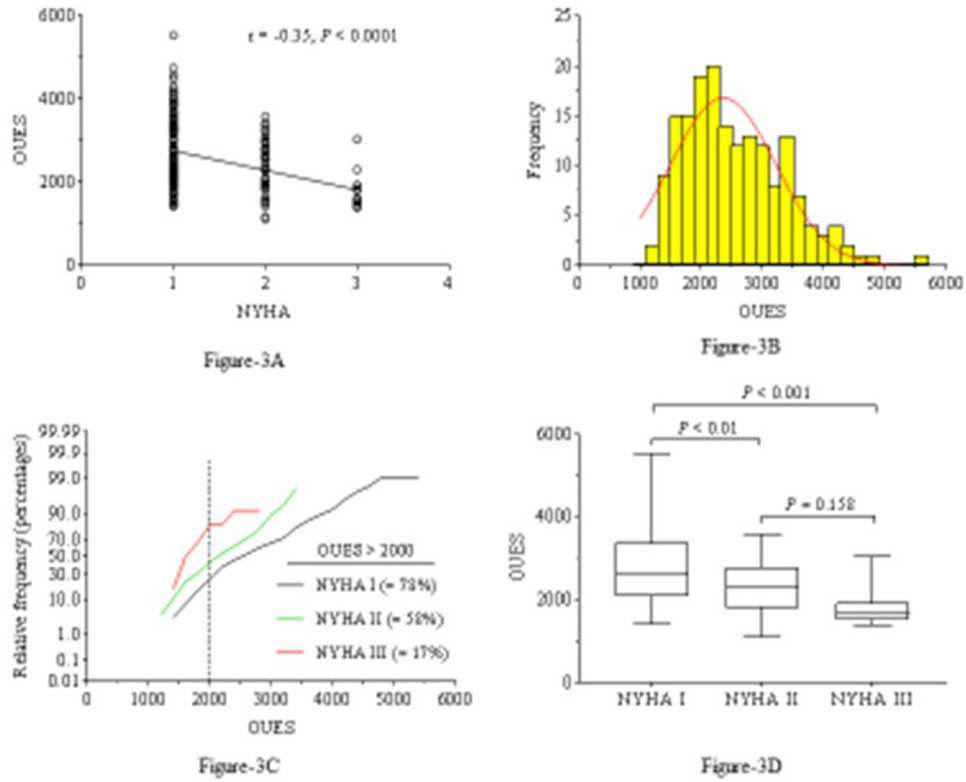

Figure 3. Relation between OUES slope and NYHA class. (A) Spearman correlation between OUES and NYHA class, (B) frequency of distribution of OUES, (C) Relative distribution with a cut-off value of OUES 2,000, and (D) Box and whisker-plot demonstrating median and quartiles of OUES by NYHA class. NYHA = New York Heart Association; OUES = O_2 uptake efficient slope.

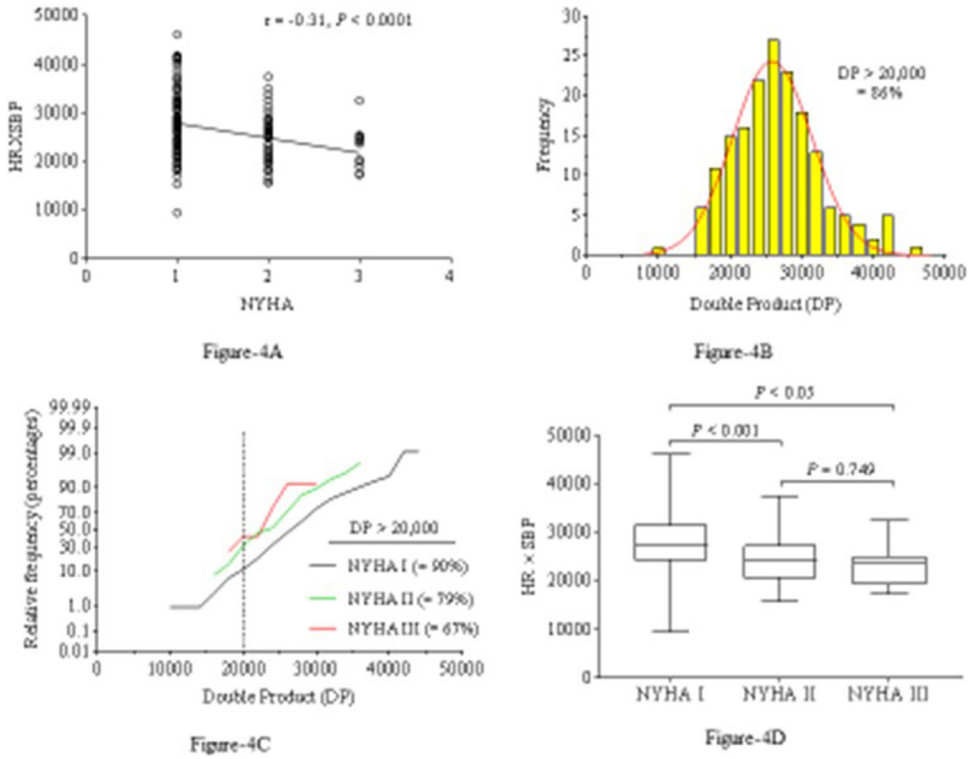

Figure 4. Relation between maximum double product and NYHA class. (A) Spearman correlation between double product (DP) and NYHA class, (B) frequency of distribution of DP, (C) Relative distribution with a cut-off value of DP 20,000, and (D) Box and whisker-plot demonstrating median and quartiles of DP by NYHA class. NYHA = New York Heart Association; OUES = O_2 uptake efficient slope.

There is an extensive body of data demonstrating the role of V_E/VCO_2 slope predicting mortality in adult heart failure patients, independent of pVO_2.[22] In our study, we did not find significant correlation between NYHA class and V_E/VCO_2 slope. Perhaps this is the result of a relatively large cohort of single ventricle patients who do not have a subpulmonary ventricle and frequently have intrinsic abnormalities of their ventilation and pulmonary circulations. However, this could also be due to small total sample size in our study. Future large scale studies are needed to validate prognostic role of V_E/VCO_2 slope in ACHD patients.

Since OUES does not require maximal effort, it is considered a useful measure to stratify functional reserve.[23] Similarly, the maximum DP during peak exercise is an indirect measure of myocardial oxygen uptake, that is, the amount of oxygen consumed by the heart muscle per se.[24] However, unlike pVO_2 and V_E/VCO_2 slope, there is no consensus whether the absolute value or a % predicted value for OUES and maximum DP are useful to functionally classify ACHD patients.

This is a single-center retrospective study but, nevertheless, representative of patients followed in any other accredited ACHD centers. While inclusion of NYHA class IV in the analysis of intervention would have been interesting, this study focused on patients who had undergone a CPET and, thus, patients with functional class IV were excluded as in most cases they were unable to perform the study.

NYHA functional class correlates with objective measures of CPET, however there is wide variability in measured exercise capacity in each NYHA classification. Therefore, whereas NYHA class of patients is a simple measure for assessment of functional status, CPET remains an important tool to identify the source of exercise limitation in ACHD patients.

Disclosures

All authors declare no relationships relevant to the contents of this study to disclose.

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1. Lim FY, Yap J, Gao F, Teo LL, Lam CSP, Yeo KK. Correlation of the New York Heart Association classification and the cardiopulmonary exercise test: a systematic review. *Int J Cardiol* 2018;263:88–93.
2. Webb GD, Williams RG. Care of the adult with congenital heart disease: introduction. *J Am Coll Cardiol* 2001;37:1166.
3. Weber K, Kinasewitz G, Janicki J, Fisherman A. Oxygen utilization and ventilation during exercise in patients with chronic congestive heart failure. *Circulation* 1982;65:1213–1223.
4. Gitt AK, Wasserman K, Kilkowski C, Kleemann T, Kilkowski A, Bangert M, Sneider S, Schwarz A, Senges J. Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. *Circulation* 2002;106:3079–3084.
5. American Thoracic Society. Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med* 1995;152:1107–1136.

6. Myers J, Buchanan N, Walsh D, Kraemer M, McAuley P, Hamilton-Wessler M, Froelicher VF. Comparison of the ramp versus standard exercise protocols. *J Am Coll Cardiol* 1991;17:1334–1342.
7. Edvardsen E, Hansen BH, Holme IM, Dyrstad SM, Anderssen SA. Reference values for cardiorespiratory response and fitness on the treadmill in a 20-to 85-year-old population. *Chest* 2013;144:241–248.
8. Buskirk E, Taylor HL. Maximal oxygen intake and its relation to body composition, with special reference to chronic physical activity and obesity. *J Appl Physiology* 1957. https://doi.org/10.1152/jappl.a957.11.1.72. July 1.
9. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. *Principles of Exercise Testing and Interpretation*. 4th ed. Philadelphia. PA: Lippincott Williams and Wilkins; 2005.
10. Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, Froelicher VF, Leon AS, Pina IL, Rodeny R, Simon-Morton DA, Williams MA, Bazzarre T. Exercise standards for testing and training: a statement for healthcare professionals from American Heart Association. *Circulation* 2001;104:1694–1740.
11. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, Forman D, Franklin B, Guazzi M, Keteyian SJ, Lavie CJ, Macko R, Mancini D, Milani RV. Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. *Circulation* 2010;122:191–225.
12. Baba R, Nagashima M, Goto M, Nagano Y, Tauchi N, Mishibata K. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol* 1996;28:1567–1572.
13. Nelson RR, Gobel FL, Jorgensen CR, Wang K, Taylor HL. Hemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. *Circulation* 1974;50:1179–1189.
14. Sadrzadek AH, Dwey FE, Sungar GW, Ashley AE, Hadly D, Myers J, Froelicher VF. Age and double product (systolic x heart rate) reserve-adjusted modifications of the Duke treadmill score score, Nomogram in Men. *Am J Cardiol* 2008;102:1407–1412.
15. Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol* 2000;36:194–201.
16. Stout KK, Daniel CJ, Aboulhousn JA, Biykem Bozkurt, Craig S. Broberg, Jack M. Colman, Stephen R. Crumb, Joseph A. Dearani, Stephanie Fuller, Michelle Gurvitz, Paul Khairy, Michael J. Landzberg, Saidi Arwa, Anne Marie Valente, George F. Van Hare. 2018AHA/ACC guidelines for the management of adults with congenital heart disease. *J Am Col Cardiol* 2018. https://doi.org/10.1016/j.jacc.2018.08.1029. E-pub ahead of print.
17. Diller GP, Dimopopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation* 2005;112:828–835.
18. Inuzuka R, Diller GP, Borgia F, Benson L, Tay EL, Alonso-Gonzalez R, Silva M, Charalambides M, Swan L, Dimopoulos K, Gatzoulis MA. Comprehensive use of cardiopulmonary exercisetesting identifies adults with congenital heart disease at increased mortality risk in the medium term. *Circulation* 2012;125:250–259.
19. Kempny A, Dimopoulos K, Uebing A, Moceri P, Swan L, Gatzoulis MA, Diller GP. Reference values for exercise limitations among adults with congenital heart disease. Relation to activities of daily life-single center experience and review of published data. *Eur Heart J* 2012;33:1386–1396.
20. Mantegazza V, Apostolo A, Hager A. Cardiopulmonary exercise testing in adult congenital heart disease. *Ann Am Thorac Soc* 2017;14:S93–S101.
21. Bredy C, Ministeri M, Kempny A, Alonso-Gonzalez R, Swan Lorna uebing A, Diller GH, Gatzoulis MA, Dimpopoulos K. NYHA classification in adults with congenital heart disease: relation to objective measures of exercise and outcome. *Eur J Heart* 2018;5:51–58.
22. Dimopoulos K, Okoknko DO, Diller GP, Broberg CS, Salukhe TV, Babu-Narayan SV, Li W, Uebing A, Bayne S, Wensel R, Piepoli MF, Poole-Wilson PA, Francis DP, Gatzoulis MA. Abnormal ventilatory response to exercise in adults with congenital heart disease relates to cyanosis and predicts survival. *Circulation* 2006;113:2796–2802.
23. Chaitman BR. Exercise testing. In: Bonow RO, Mann DL, Zipes DP, Libby P, eds. *Braunwald's Heart Disease: A Text Book Cardiovascular Medicine*, 9th ed, Philadelphia: Saunders Elsevier; 2012:168–200.
24. Giadini A, Specchia S, Garguilos G, Oicchio FM. Accuracy of oxygen uptake efficiency slope in adults with congenital heart disease. *Am J Cardiology* 2009;20:74–79.