Algorithm for Predicting Disease Likelihood From a Submaximal Exercise Test

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Clinical Medicine Insights: Circulatory, Respiratory and Pulmonary Medicine
Volume 11: 1–7

DOI: 10.1177/1179548417719248

ABSTRACT: We developed a simplified automated algorithm to interpret noninvasive gas exchange in healthy subjects and patients with heart failure (HF, n = 12), pulmonary arterial hypertension (PAH, n = 11), chronic obstructive lung disease (OLD, n = 16), and restrictive lung disease (RLD, n = 12). They underwent spirometry and thereafter an incremental 3-minute step test where heart rate and SpO_2 respiratory gas exchange were obtained. A custom-developed algorithm for each disease pathology was used to interpret outcomes. Each algorithm for HF, PAH, OLD, and RLD was capable of differentiating disease groups ($P < .05$) as well as healthy cohorts (n = 19, $P < .05$). In addition, this algorithm identified referral pathology and coexisting disease. Our primary finding was that the ranking algorithm worked well to identify the primary referral pathology; however, coexisting disease in many of these pathologies in some cases equally contributed to the cardiorespiratory abnormalities. Automated algorithms will help guide decision making and simplify a traditionally complex and often time-consuming process.

KEYWORDS: cardiopulmonary, respiratory patterns, decision making, disease likelihood

RECEIVED: February 15, 2017. **ACCEPTED:** June 4, 2017.

PEER REVIEW: Three peer reviewers contributed to the peer review report. Reviewers' reports totaled 718 words, excluding any confidential comments to the academic editor.

TYPE: Original Research

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was funded by Shape Medical Systems Inc.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Noninvasive cardiorespiratory gas exchange during exercise has been a commonly used clinical test to help guide clinical judgment regarding exercise intolerance (typically fatigue or dyspnea) and assess functional capacity, general clinical status, and response to therapy for a number of disease pathologies.[1] However, many of the currently available commercial systems produce a large array of breath-by-breath measures over the course of a test leaving interpretation to a relatively complicated review by individuals with significant expertise. In addition, the testing is typically performed by pushing individuals to their maximum, requiring significant safety measures and available trained personnel in case of emergent issues.[2,3] However, for most disease pathologies, many cardiorespiratory abnormalities and symptoms become evident with submaximal exercise, and for simple screening purposes, tracking of clinical health status or response to therapy, maximal testing is not necessary.[4]

Thus, we have proposed a simplified approach to testing using a submaximal step test and more recently have developed an automated algorithmic approach to differentiate patients into various disease likelihood bins or silos. Our hypothesis was that this automated algorithm would differentiate patients according to their primary disease pathology with only submaximal exercise. An advantage, as well, of this type of algorithm was that most patients have associated comorbidities with multiple pathologies influencing their respiratory gas exchange, and thus, the ranking algorithm weighted not only the primary limitation or abnormality but also the comorbidities as well.

Methods

For this study, patients with known primary pathologies in heart failure (HF, n = 12), pulmonary arterial hypertension (PAH, n = 11), chronic obstructive lung disease (OLD, n = 16), and restrictive lung disease (RLD, n = 12) and a healthy cohort (n = 19) were recruited. Table 1 illustrates the subject characteristics. Subjects were recruited from our outpatient cardiology practice over the course of approximately 6 months.

Prior to participating in the study, the subjects were informed about the sequence of the study protocol and completed informed consent. Thereafter, they underwent simplified spirometry (pulmonary function tests) at rest and underwent an incremental submaximal exercise test. The exercise mode was a 6-minute test and it consisted of 2-minute rest, 3-minute submaximal exercise using a 5.75-inch step with a metronome used to guide the step frequency followed by1-minute recovery. During submaximal exercise, the step frequency was increased every minute targeting 60, 80, and 100 steps or foot movements per minute (equal to 15, 20, and 25 actual steps up per minute). During exercise, heart rate (HR) and SpO_2 were assessed via pulse oximetry, and breathing pattern and respiratory gas exchange were obtained via breath-by-breath respiratory analysis system (Shape Medical Systems Inc., St. Paul, MN, USA). This study was approved by Mayo Clinic Institutional Review Board.

For this study, we present our primary metrics for the algorithm used and display how these variables compare for each of the disease silos of interest, including cardiac disease, pulmonary vascular disease, OLD, and RLD. This includes essentially incorporating previously published cardiorespiratory normative

Table 1. Subject characteristics.

	HF (N = 12)	PAH (N = 11)	OLD (N = 16)	RLD (N = 12)	HEALTHY (N = 19)
Gender, female/male	8/4	8/3	10/6	2/10	2/17
Age, y	61 ± 13	58 ± 12	55 ± 12	68 ± 10	52 ± 11
Height, cm	169.2 ± 9.5	165.6 ± 8.5	169.1 ± 7.4	175.6 ± 6.6	176.3 ± 5.4
Weight, kg	84.4 ± 15.9	85.9 ± 11.1	85.0 ± 14.4	91.7 ± 14.7	83.6 ± 12.3
BMI, kg/m^2	29.6 ± 6.0	31.6 ± 5.1	29.7 ± 4.0	29.8 ± 4.9	26.9 ± 3.8

Abbreviations: BMI, body mass index; HF, heart failure; OLD, obstructive lung disease; PAH, pulmonary arterial hypertension; RLD, restrictive lung disease.
All values are reported by mean and standard deviation.

values and abnormalities obtained during exercise from the literature, creating normative and disease severity ranges and ranking disease likelihood accordingly. From the literature and our previous work, key variables were selected for each disease category and illustrated as disease silos. For the HF silo, ventilatory efficiency (VE/VCO_2) slope,[5,6] oxygen pulse to oxygen consumption (O_2p/VO_2) slope,[7] oxygen uptake efficiency slope (OUES),[8,9] circulatory equivalent VO_2 ($CircEqVO_2$),[10] and HR recovery[11] were selected, whereas VE/VCO_2 slope, a noninvasive measure of pulmonary capacitance (GxCap),[12] a previously reported multiparameter index for pulmonary hypertension (MPIph)[13–15] and oxygen saturation (SpO_2) at peak[16] were selected for the PAH silo. In addition, oxygen desaturation, forced expiratory volume in the first second of expiration (FEV_1),[17,18] breathing reserve (where minute ventilation near peak relative of the FEV_1*35 – index of the maximal voluntary ventilation),[16] and mixed expired pressure of CO_2 to end tidal CO_2 ($PECO_2/PETCO_2$)[19] were selected for the OLD silo, and SpO_2, forced vital capacity (FVC),[18] maximal tidal volume to tidal volume at rest ($VT_{max/rest}$),[20] and lung stiffness (the linear slope of breathing frequency to VCO_2)[21] were chosen for the RLD silo. Table 2 illustrates the selective key variables following each disease category.

Table 3 is an example of the scoring technique for the algorithm explaining how a score was derived. Each disease category has 3 Limits (risk cutoff values) based on the severity of abnormality or how far a value deviated from normal. The outcome which is less or greater (depending on variables) than the value of Limit 1 was the normal range, and thereafter as the Limit increased, the score increased (Normal: 0 point, Limit 1: 1 point, Limit 2: 2 points, and Limit 3: 3 points). After obtaining all points from each variable, all points were averaged to obtain the final score. In the results, a higher score was associated with a more severe pathology or as we refer to as the likelihood for more severe pathology. To determine the capability of key variables for differentiating disease pathology and the sensitivity of silos, nonparametric analyses of variance (ANOVAs) were conducted. Subsequently, post hoc analysis was performed to demonstrate the differences between disease groups. The significance was set at .05.

Results

When compared with the healthy group, the HF group demonstrated significantly impaired VE/VCO_2, OUES, $CircEqVO_2$, and HR recovery ($P < .05$); however, the O_2p/VO_2 ratio was not different ($P > .05$). For the PAH group, they demonstrated significantly impaired VE/VCO_2, GxCap, and MPIph ($P < .05$) and greater desaturation at peak exercise ($P < .05$), but SpO_2 was not statistically different from the healthy group ($P > .05$). The OLD group demonstrated an impaired FEV_1, breathing reserve, and a $PECO_2/PETCO_2$ ratio ($P < .05$) when comparing with the healthy group; however, desaturation at peak level was not different ($P > .05$). Finally, the RLD showed a significantly lower FVC and greater desaturation than the healthy group ($P < .05$) but no significant difference in $VT_{max/rest}$ or in our exercise index of lung stiffness ($P > .05$). Table 4 illustrates the comparison of variables between disease groups and the healthy subjects.

In the HF silo (Figure 1), HF demonstrated the highest score and was significantly different from OLD, RLD, and healthy groups ($P < .05$) except PAH ($P > .05$). In the PAH silo (Figure 1B), PAH showed the highest score and was significantly different from HF, OLD, and healthy groups ($P < .05$) but not RLD ($P > .05$). In addition, in the RLD silo, RLD demonstrated the highest score and was significantly different from PAH, OLD, and healthy groups ($P < .05$; Figure 1D) but not different from HF ($P > .05$). Based on ANOVA, there was no significant difference across groups in the OLD silo ($P > .05$), despite the higher score in the OLD group relative to the other primary disease entities. However, if we compared one group at a time with the OLD silo, we do note that when performing independent *t* tests, the OLD group was different from PAH and RLD, but not HF.

Discussion

We recruited patients based on clinical diagnoses in each of the 4 primary disease categories to determine how well a simple, novel algorithm tracked these disease entities with cardiorespiratory measures from a simplified submaximal exercise test. A challenge of such a test is the fact that rarely does a single chronic disease entity exists without comorbidities, but in

Table 2. Algorithm following disease categories and cutoff values based on disease severity.

VARIABLE NAME	LIMIT 1	LIMIT 2	LIMIT 3
HF			
VE/VCO_2 slope	30	36	45
O_2p/VO_2 slope	3.5	3	1.8
OUES	1.5	1.22	1.05
$CircEqVO_2$ % pred.	90	80	60
HR recovery, bpm	18	12	8
PAH			
VE/VCO_2 slope	40	56	65
MPIph	–1	1	3
Peak GxCap	500	400	300
Rest SpO_2, %	94	90	86
Desaturation at peak, %	3	5	7
OLD			
FEV_1 % pred.	80	69	30
Breathing reserve %	30	20	5
Desaturation at peak, %	5	7	10
$PECO_2/PETCO_2$ rest/ex.	0.85	0.75	0.6
RLD			
FVC % pred.	79	65	50
Desaturation at peak, %	5	7	10
$VT_{max/rest}$	2	1.5	1
Lung stiffness slope	8.5	15	30

Abbreviations: $CircEqVO_2$ % pred., circulatory equivalent oxygen consumption; FEV_1, forced expiratory volume in the first second of expiration; FVC % pred., % predicted of forced vital capacity; GxCap, pulmonary capacitance: oxygen pulse × the partial pressure of end tidal CO_2; HF, heart failure; HR, heart rate; MPIph, multiparameter index for pulmonary hypertension; O_2p, oxygen pulse: oxygen consumption/heart rate; OLD, obstructive lung disease; OUES, oxygen uptake efficiency slope; PAH, pulmonary arterial hypertension; $PECO_2$, the partial pressure of mean expired CO_2; $PETCO_2$, the partial pressure of end tidal CO_2; RLD, restrictive lung disease; SpO_2, oxygen saturation; VE/VCO_2, ventilatory efficiency; VO_2, oxygen consumption.

Table 3. An example of scoring process in algorithm.

VARIABLE NAME	LIMIT 1	LIMIT 2	LIMIT 3	OUTCOME VALUE	SCORE
HF					
VE/VCO_2 slope	30	36	45	33	1.5
O_2p/O_2 slope	3.5	3	1.8	5.7	0
OUES	1.5	1.2	1.05	1.17	2
$CircEqVO_2$ % pred.	90	80	60	116	0
HR recovery, bpm	18	12	8	71	0
Total score					3.5

Abbreviations: $CircEqVO_2$ % pred., circulatory equivalent oxygen consumption; HF, heart failure; HR, heart rate; O_2p, oxygen pulse: oxygen consumption/heart rate; OLD, obstructive lung disease; OUES, oxygen uptake efficiency slope; PAH, pulmonary arterial hypertension; RLD, restrictive lung disease; VE/VCO_2, ventilatory efficiency; VO_2, oxygen consumption.
This is an example of scoring technique. Each variable has 3 Limits based on severity of abnormalities. The total score was obtained from sum of each variable. If outcome of VE/VCO_2 slope is 33 (between Limits 1 and 2), the score is 1.5 (the outcome if is in middle of Limits 1 and 2, so add 0.5 point to lower Limit score and thus the score would be 1.5). The outcome of O_2p/O_2 slope is 5.7 (>Limit 1) and thus the score is 0. The outcome of OUES is 1.17 (between Limits 2 and 3) and thus the score is 2. The outcome of $CircEqVO_2$ % pred. is 116 (>Limit 1) and thus the score is 0. The outcome of HR recovery is 71 (>Limit 1) and thus the score is 0. Therefore, the sum of the score is 3.5.

Table 4. Each disease patient vs healthy subjects.

	VE/VCO_2[a]	O_2P/VO_2 SLOPE[a]	OUES[a]	$CirEqVO_2$[a]	HR RECOVERY[a]
HF silo					
HF	**30.2±9.9**	9.7±1.4	**1.5±0.4**	**76.0±16.0**	**−20.9±7.5**
PAH	30.9±6.3	8.2±1.3[b]	1.8±0.5	71.1±12.2	−21.5±11.1
OLD	21.6±3.8[b]	8.1±1.4[b]	2.1±0.6[b]	80.4±12.3	−30.7±13.3[b]
RLD	24.8±3.6[b]	8.7±0.9	1.9±0.6	67.1±18.3	−23.2±12.2
Healthy	20.3±7.0[b]	8.8±1.2	2.8±0.7[b]	100.5±16.1[b]	−38.7±11.6[b]
	VE/VCO_2[a]	GxCap[a]	MPIph[a]	REST SP_2[a]	DESATURATION[a]
PAH silo					
HF	30.2±9.9	523±133	−0.89±2.03	96.0±2.2	3.0±2.2[b]
PAH	**30.9±6.3**	**457±182**	**−0.26±1.60**	95.6±3.0	**6.1±5.1**
OLD	21.6±3.8[b]	638±166[b]	−3.49±1.08[b]	94.2±3.4	3.4±2.3[b]
RLD	24.8±3.6[b]	554±175	−1.93±1.51[b]	94.6±2.2	6.4±3.5
Healthy	20.3±7.0[b]	941±193[b]	−3.60±2.00[b]	97.1±1.4	2.9±1.6[b]
	DESATURATION[a]	FEV_1[a]	BREATHING RESERVE[a]	$PECO_2$/ $PETCO_2$[a]	
OLD silo					
HF	3.0±2.2	75.2±19.0	49.6±20.1	1.01±0.07	
PAH	6.1±5.1[b]	48.6±40.5[b]	27.7±24.6[b]	0.96±0.06	
OLD	3.4±2.3	**77.9±21.1**	**56.2±20.8**	**0.99±0.05**	
RLD	6.4±3.5[b]	76.0±12.6	53.7±13.0	0.91±0.06[b]	
Healthy	2.9±1.6	97.0±14.7[b]	73.0±7.2[b]	0.94±0.08[b]	
	FVC[a]	DESATURATION[a]	$VT_{MAX/REST}$[a]	LUNG STIFFNESS[a]	
RLD silo					
HF	73.9±18.1	3.0±2.2[b]	1.91±0.45	19.0±14.0[b]	
PAH	48.1±38.9[b]	6.1±5.1	2.08±0.52	11.3±7.5	
OLD	82.2±12.6[b]	3.4±2.3[b]	1.87±0.28	10.0±6.1	
RLD	**65.6±10.7**	**6.4±3.5**	2.15±0.50	7.6±7.5	
Healthy	94.9±11.3[b]	2.9±1.6[b]	2.16±0.58	6.3±7.0	

Abbreviations: $CircEqVO_2$ % pred., circulatory equivalent oxygen consumption; GxCap, pulmonary capacitance: oxygen pulse × the partial pressure of end tidal CO_2; FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; HF, heart failure; HR, heart rate; MPIph, multiparameter index for pulmonary hypertension; O_2p, oxygen pulse: oxygen consumption/heart rate; OLD, obstructive lung disease; OUES, oxygen uptake efficiency slope; PAH, pulmonary arterial hypertension; RLD, restrictive lung disease; VE/VCO_2, ventilatory efficiency; VO_2, oxygen consumption.
Bold values denote significant difference from healthy group. All values are reported by mean and standard deviation.
[a]Significant difference between groups.
[b]Significantly different values when comparing with each disease silo.

general, we have found that the disease likelihood algorithm score ranked the primary disease pathology the highest in most categories. However, it is clear that chronic cardiorespiratory disease has pathology that typically affects both the heart and lungs, and although this makes it challenging to identify a primary disease pathology or exercise limitation, the algorithm developed allows a method to weight and display multiple disease entities and therefore better visualize and understand contributors to exercise intolerance.

In clinical practice, noninvasive measures of respiratory gas exchange, breathing pattern, and other variables (eg, SpO_2) during exercise have been used to determine disease severity for

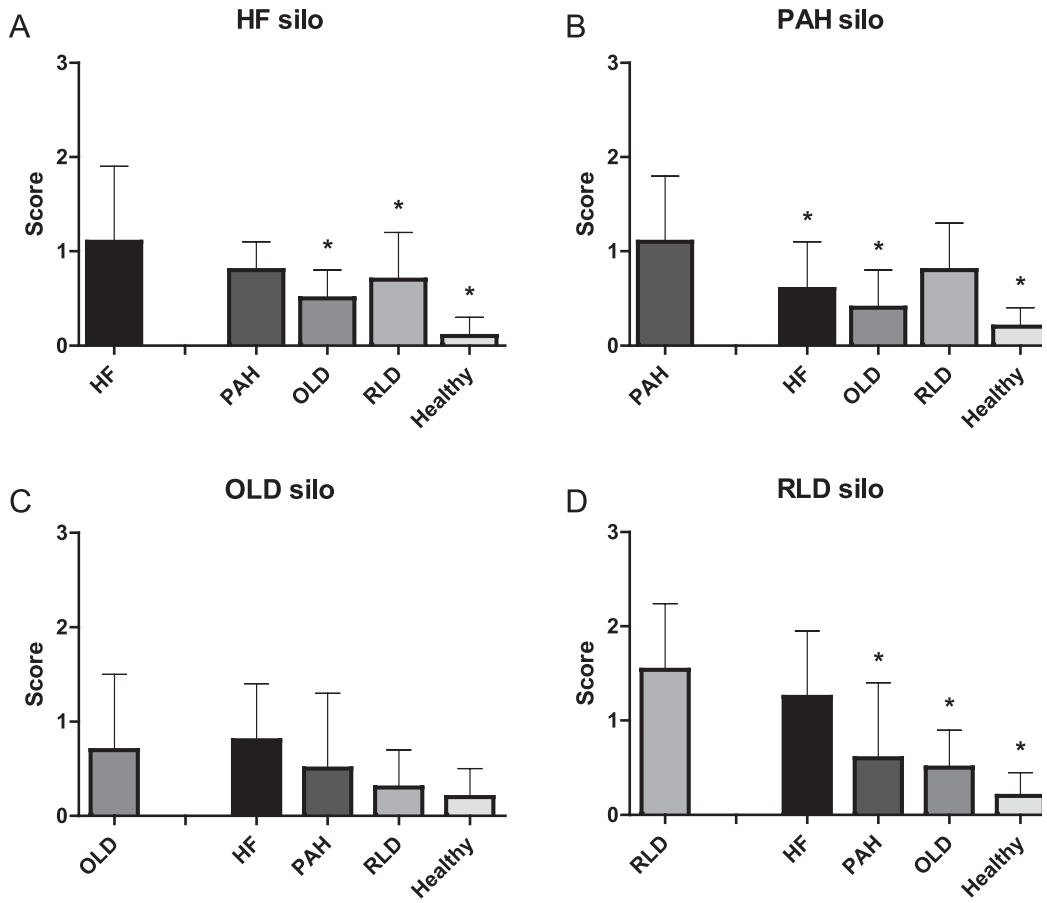

Figure 1. Silo score distribution. (A) Heart failure (HF) silo: * denotes a significant difference from HF. (B) Pulmonary arterial hypertension (PAH): * denotes a significant difference from PAH. (C) Obstructive lung disease (OLD): * denotes a significant difference from OLD. (D) Restrictive lung disease (RLD): * denotes a significant difference from RLD.

specific populations. However, interpreting the data is relatively complicated due to the large array of breath-by-breath measures and variability in disease pathology. Hence, there is need for systematic monitoring with appropriate criteria for implying or guiding the primary disease pathophysiology. The algorithm developed in this study used different key variables following disease silos (HF, PAH, OLD, and RLD) that were selected intuitively from our previous work and published literature. Oxygen uptake efficiency slope, the change in oxygen consumption over the log of VE or ventilation during submaximal exercise, is an objective indicator of general cardiopulmonary performance and disease severity so that it has been used to essentially replace maximal oxygen consumption.[8,9,22] Heart rate recovery is commonly associated with cardiac disease or more severe deconditioning.[11] These variables are clearly impaired in HF when compared with healthy subjects, but clearly, deconditioning may become an important part of the pathophysiology of most chronic diseases. Breathing efficiency (VE/VCO_2), typically linked to high dead space ventilation caused mainly by a rapid shallow breathing pattern and/or hyperventilation,[5,23–25] was more elevated in HF and PAH than other diseases or relative to healthy subjects. A poor breathing efficiency is often associated with changes in $PETCO_2$, and thus, our other more complex measures, GxCap and MPIph, which have been associated with primarily elevated pulmonary vascular pressures were also more impaired in PAH than the other groups.[12,26] Oxygen saturation at peak exercise was also decreased more in PAH and RLD than the other groups. When considering these results, it is challenging to track disease severity and/or differing pathophysiology of diseases with single variables. Therefore, the comprehensive and categorized algorithm with multiple variables is helpful to improve the disease likelihood capture and to reduce potential for errors of single measures. Previously, we have developed scoring systems to interpret comprehensively multiple respiratory gas exchange variables, breathing pattern, and other variables for different disease pathophysiology,[26,27] and these previous works provided a potential utilization of noninvasive respiratory gas exchange in evaluating pathophysiology and severity.

In this study, the disease likelihood scoring per primary disease entity ranked the primary referral disease the highest in most silos, and this may suggest that the algorithm was capable of differentiating disease. However, each disease silo demonstrated coexistent disease pathologies. Given the intimate relationship of the heart and lungs, it is no surprise that when evaluating these seemingly diverse groups, multiple silos also

register or "light up" other than the primary one. For example, it is well known that many patients with HF develop pulmonary hypertension, obstructive, and restrictive pulmonary disorders, and subjects are often overweight, further contributing to their restrictive lung presentation. Furthermore, patients with PAH may be cardiac limited due to the high pulmonary vascular resistance and also often develop restrictive lung changes. Obstructive lung disease is also a complex disease that includes not only airway obstruction but also degradation of the pulmonary vasculature, areas of hypoxic pulmonary vasoconstriction, and mixed or a restrictive component to their disease. In our own data, it was clear that these comorbidities exist together, and even with our attempts to find subjects with a "primary" disease entity, it was clear that these rarely exist on their own. Thus, although an attempt was made to develop an algorithm to weight a particular disease state, it is clear in reality that many of these patients have coexistent issues that contribute to gas exchange abnormalities as well as to exercise intolerance.

Although this study demonstrated the capability of a simplified automated algorithm to identify primary disease pathology, a relatively smaller sample size limits the ability to address the findings. A larger number of subjects per group would have strengthened the study and help confirm the preliminary outcomes.

Conclusions

We have attempted to create an approach to clinical exercise testing that could greatly simplify testing and reduce complexities around interpretation. To do this, we developed an automated algorithm based on classic measures of breathing pattern, respiratory gas exchange, pulse oximetry, as well as use of simplified spirometry. This algorithm, for the most part, appeared to isolate patient groups relative to their primary pathology. In addition, it demonstrated that chronic cardiorespiratory disease does not typically exist alone but rather tends to coexist with other pathologies of the heart and lungs. Future studies will need to determine the utility of this type of submaximal testing and algorithm relative to traditional clinical expert test interpretation.

Acknowledgements

The authors appreciate the volunteer participation of our subjects.

Author Contributions

C-HK, JEH, DJM, and BDJ conceived and designed the experiments; analyzed the data; contributed to the writing of the manuscript; agree with manuscript results and conclusions; made critical revisions; and approved the final version. C-HK and BDJ wrote the first draft of the manuscript. JEH and DJM jointly developed the structure and arguments for the paper. All authors reviewed and approved the final manuscript.

Disclosures and Ethics

As a requirement of publication, authors have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and protection of human subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

REFERENCES

1. Wasserman K, Hansen J, Sue D, Casaburi R, Whipp B. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. New York, NY: Lippincott Williams & Wilkins; 1999.
2. Johnson BD, Whipp B, Zeballos R, et al. Conceptual and physiological basis of cardiopulmonary exercise testing measurement. In the ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Resp Crit Care*. 2003;167:211–277.
3. Milani RV, Lavie CJ, Mehra MR, Ventura HO. Understanding the basics of cardiopulmonary exercise testing. *Mayo Clin Proc*. 2006;81:1603–1611.
4. Hansen JE, Sun X-G, Yasunobu Y, et al. Reproducibility of cardiopulmonary exercise measurements in patients with pulmonary arterial hypertension. *Chest*. 2004;126:816–824.
5. Arena R, Myers J, Abella J, et al. Development of a ventilatory classification system in patients with heart failure. *Circulation*. 2007;115:2410–2417.
6. Kim C-H, Olson LJ, Shen WK, Cha Y-M, Johnson BD. Ventilatory gas exchange and early response to cardiac resynchronization therapy. *J Heart Lung Transplant*. 2015;34:1430–1435.
7. Wasserman K, Hansen J, Sue D, Stringer W, Whipp B. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. Philadelphia. PA: Lippincott, Williams & Wilkins; 2005.
8. Davies LC, Wensel R, Georgiadou P, et al. Enhanced prognostic value from cardiopulmonary exercise testing in chronic heart failure by non-linear analysis: oxygen uptake efficiency slope. *Eur Heart J*. 2006;27:684–690.
9. 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.
10. Sun X-G, Hansen JE, Stringer WW. Oxygen uptake efficiency plateau best predicts early death in heart failure. *Chest*. 2012;141:1284–1294.
11. Kubrychtova V, Olson TP, Bailey KR, Thapa P, Allison TG, Johnson BD. Heart rate recovery and prognosis in heart failure patients. *Eur J Appl Physiol*. 2009;105:37–45.
12. Taylor BJ, Olson TP, Chul-Ho-Kim DM, Johnson BD. Use of noninvasive gas exchange to track pulmonary vascular responses to exercise in heart failure. *Clin Med Insights Circ Respir Pulm Med*. 2013;7:53.
13. Matsumoto A, Itoh H, Eto Y, et al. End-tidal CO2 pressure decreases during exercise in cardiac patients: association with severity of heart failure and cardiac output reserve. *J Am Coll Cardiol*. 2000;36:242–249.
14. Ramos RP, Alencar MCN, Treptow E, Arbex F, Ferreira E, Neder JA. Clinical usefulness of response profiles to rapidly incremental cardiopulmonary exercise testing. *Pulm Med*. 2013;2013:359021.
15. Sun X-G, Hansen JE, Oudiz RJ, Wasserman K. Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. *Circulation*. 2002;105:54–60.
16. Forman DE, Myers J, Lavie CJ, Guazzi M, Celli B, Arena R. Cardiopulmonary exercise testing: relevant but underused. *Postgrad Med*. 2010;122:68–86.
17. Brusasco EV, Crapo R, Viegi G, et al. Series "ATS/ERS task force: standardisation of lung function testing." *Eur Respir J*. 2005;26:319–338.
18. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Resp Crit Care*. 1999;159:179–187.
19. Hansen JE, Ulubay G, Chow BF, Sun X-G, Wasserman K. Mixed-expired and end-tidal CO2 distinguish between ventilation and perfusion defects during exercise testing in patients with lung and heart diseases. *Chest*. 2007;132:977–983.
20. Olson TP, Johnson BD. Influence of cardiomegaly on disordered breathing during exercise in chronic heart failure. *Eur J Heart Fail*. 2011;13:311–318.

21. Agostoni P, Pellegrino R, Conca C, Rodarte JR, Brusasco V. Exercise hyperpnea in chronic heart failure: relationships to lung stiffness and expiratory flow limitation. *J Appl Physiol*. 2002;92:1409–1416.
22. Arena R, Myers J, Abella J, et al. Prognostic significance of the oxygen uptake efficiency slope: percent-predicted versus actual value. *Am J Cardiol*. 2010;105:757.
23. Johnson BD, Beck KC, Olson LJ, et al. Ventilatory constraints during exercise in patients with chronic heart failure. *Chest*. 2000;117:321–332.
24. Woods PR, Bailey KR, Wood CM, Johnson BD. Submaximal exercise gas exchange is an important prognostic tool to predict adverse outcomes in heart failure. *Eur J Heart Fail*. 2011;13:303–310.
25. Woods PR, Frantz RP, Taylor BJ, Olson TP, Johnson BD. The usefulness of submaximal exercise gas exchange to define pulmonary arterial hypertension. *J Heart Lung Transplant*. 2011;30:1133–1142.
26. Kim CH, Anderson S, Maccarter D, Johnson B. A multivariable index for grading exercise gas exchange severity in patients with pulmonary arterial hypertension and heart failure. *Pulm Med*. 2012;2012:962598.
27. Woods PR, Taylor BJ, Frantz RP, Johnson BD. A pulmonary hypertension gas exchange severity (PH-GXS) score to assist with the assessment and monitoring of pulmonary arterial hypertension. *Am J Cardiol*. 2012;109:1066–1072.