JACC: CARDIOONCOLOGY VOL. 4, NO. 2, 2022

EDITORIAL COMMENT

Exercise Testing in Those Treated for Breast Cancer

Can One Forecast Peak Oxygen Consumption?*

Carl J. Ade, PhD,[a,b,c] Ryan Broxterman, PhD,[d,e] W. Gregory Hundley, MD[f]

Over the past several years, mounting evidence has established that assessment of cardiorespiratory fitness in the oncology setting provides an important means for short- and long-term cardiovascular and cancer risk stratification. Importantly, low cardiorespiratory fitness in patients following cancer diagnosis is associated with worse quality of life[1] and higher risk for cancer and cardiovascular disease mortality.[2] However, despite these associations, its routine assessment across the cancer continuum from diagnosis through survivorship remains a significant challenge in clinical practice.

Although multiple indexes of cardiorespiratory fitness exist, the sentinel parameter for its assessment is peak oxygen uptake (V_{O_2}peak). Accurate clinical quantification is best achieved via cardiopulmonary exercise testing with ventilatory expired gas analysis, but this requires specialized instrumentation and trained personnel who often are not readily available. Thus, many practitioners must estimate V_{O_2}peak using prediction equations based on attained treadmill speed, grade, and duration or cycle ergometer work load from standardized exercise protocols, which can introduce significant error in risk prediction and stratification. In this issue of *JACC: CardioOncology*, Michalski et al[3] reveal the challenges of estimating V_{O_2}peak in the oncology setting using such prediction equations. In a large single-center study, 170 patients (mean age 59 ± 10 years) with histories of primary breast cancer (stages I-III), V_{O_2}peak was measured via ventilatory expired gas analysis during incremental treadmill exercise. Established criteria for acceptable attainment of V_{O_2}peak were used. An important experimental consideration is that treadmill exercise may not be feasible in all patients, so the study conclusions may not extend to other exercise modalities. At the time of exercise testing, all patients were ≥1 to <5 years since completion of primary adjuvant therapy (3.1 ± 1.2 years). The measured V_{O_2}peak was then compared with multiple estimates of V_{O_2}peak. Three established prediction equations, using the obtained achieved speed and grade from incremental treadmill exercise, were investigated: the American College of Sports Medicine (ACSM), the Fitness Registry and the Importance of Exercise National Database (FRIEND), which were derived from healthy cohorts, and heart failure-specific prediction equations.

Confirming the investigators' hypothesis, estimated V_{O_2}peak by the ACSM and FRIEND equations was substantially different compared with measured V_{O_2}. The ACSM prediction equation overestimated V_{O_2}peak by 7.0 $mL \cdot kg^{-1} \cdot min^{-1}$ and the FRIEND equation by 3.9 $mL \cdot kg^{-1} \cdot min^{-1}$. These are clinically significant differences; in a large study of patients with histories of cancer, a 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ decrease in V_{O_2}peak was associated with a 14% to 25% increased risk for cardiovascular- or cancer-related

*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

From the [a]Department of Kinesiology, College of Health and Human Sciences, Kansas State University, Manhattan, Kansas, USA; [b]Physician Associate Studies, College of Health and Human Sciences, Kansas State University, Manhattan, Kansas, USA; [c]Johnson Cancer Center, Kansas State University, Manhattan, Kansas, USA; [d]Geriatric Research, Education, and Clinical Center, Salt Lake City Veterans Affairs Medical Center, Salt Lake City, Utah, USA; [e]Department of Internal Medicine, University of Utah, Salt Lake City, Utah, USA; and the [f]Division of Cardiology, Department of Internal Medicine, VCU Pauley Heart Center, Virginia Commonwealth University, Richmond, Virginia, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2022.05.005

death. Interestingly, the investigators reveal that the heart failure–specific equation provided an estimated V_{O_2}peak within 0.21 mL·kg^{-1}·min^{-1} of the measured value. However, given that multiple factors may contribute to alterations in V_{O_2}peak in the oncology setting, the investigators also proposed an oncology-specific model. Starting with 17 variables that include information related to treatment history, treadmill speed and grade, and body composition, cross-validated stepwise logistic regression revealed a final equation using patient age, body mass index, measured peak heart rate, and treadmill speed and grade. The developed model predicted V_{O_2}peak within 0.02 mL·kg^{-1}·min^{-1}. Collectively, their findings suggest (although confirmation in subsequent studies is needed) that an oncology- or heart failure–specific method to predict V_{O_2}peak results in a substantial reduction in prediction error compared with non-oncology-based equations. This in total supports the investigators' hypothesis that oncology-specific equations provide an accurate method of cardiorespiratory assessment in patients with histories of cancer. Of note, cancer stage and time since treatment were not included in the models, and these factors may significantly affect an individual's V_{O_2}peak.

What clinical implications from the work of Michalski et al[3] can be gained, particularly when placed in the context of prior work demonstrating the benefit of V_{O_2}peak in risk prediction and stratification? First, the cumulative direct effect of disease pathophysiology and anticancer therapies, coupled with "indirect" perturbations secondary to treatment (eg, inactivity, weight gain), can damage key components of oxygen transport, with potential for significant reductions in cardiorespiratory fitness.[4-7] Cancer pathology and certain treatment regimens are associated with decreases in cardiac and vascular function, hemoglobin concentration, muscle blood flow, and oxygenation, all steps in the O_2 transport cascade that determine a patient's cardiorespiratory fitness.[4,5,8-13] In additional, structural changes associated with cardiac and skeletal muscle atrophy, coupled with increases in intramuscular fat, have been implicated as determinants of exercise capacity with cancer.[14] Thus, assessment of cardiorespiratory fitness provides an integrative approach to evaluate the structural and functional changes in the pulmonary, hematologic, cardiovascular, and musculoskeletal systems across the cancer treatment continuum.

In addition, evidence supports optimizing cardiorespiratory fitness prior to (ie, "prehabilitation") and following cancer treatment to improve patient outcomes. In a recent meta-analysis, Scott et al[15] reported that exercise therapy was associated with an increase in V_{O_2}peak of +2.8 mL·kg^{-1}·min^{-1}. Although this increase is clinically significant, it concomitantly demonstrates that any assessment of V_{O_2}peak must not only be sensitive enough quantify the physiological effects of cancer and its treatment but also track any intervention improvements achieved with exercise interventions. This raises the first experimental consideration of the present work. Although the oncology- and heart failure–specific predictions were similar to direct measures, future work will be required to determine if these methods can accurately predict the small, but clinically relevant, changes in V_{O_2}peak longitudinally in individual patients.

A strength of the proposed oncology-specific prediction equation for V_{O_2}peak is the inclusion of variables specific to cancer treatment history. This is an important point given adverse physiological effects that occur with radiation and chemotherapy within the O_2 transport cascade. However, this also presents a challenge given the rapid development of new treatment paradigms. An important consideration is that different anticancer therapies (ie, anthracyclines, antimetabolites, immune checkpoint inhibitors, and angiogenesis inhibitors) will have variable effects on O_2 transport and will therefore likely alter their relationship with V_{O_2}peak. Moreover, the effects of these treatments will vary across the treatment continuum, with different short- vs long-term effects. As such, future work will need to establish the validity of the proposed oncology-specific prediction across specific treatment paradigms and in patients actively receiving treatment.

Notwithstanding these important considerations and the need for validation in other cancer cohorts beyond primary breast cancer (eg, colorectal, prostate, lymphoma), with different racial/ethnic and demographic compositions, the work by Michalski et al[3] provides a fundamental step forward in the assessment of cardiorespiratory fitness. This cannot

be understated given the challenge of direct $\dot{V}O_2$ peak assessment in many oncology settings coupled with the clinical implications gained by its assessment. In conclusion, Michalski et al have initiated an important refinement in the assessment of cardiorespiratory fitness across the cancer continuum from diagnosis through survivorship in clinical practice that will serve to enhance short- and long-term cardiovascular and cancer risk classification in these patients.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Carl J. Ade, Clinical Integrative Physiology Laboratory, Kansas State University, Manhattan, Kansas 66506, USA. E-mail: cade@ksu.edu.

REFERENCES

1. Herrero F, Balmer J, San Juan AF, et al. Is cardiorespiratory fitness related to quality of life in survivors of breast cancer? *J Strength Cond Res*. 2006;20:535–540.

2. Groarke JD, Payne DL, Claggett B, et al. Association of post-diagnosis cardiorespiratory fitness with cause-specific mortality in cancer. *Eur Heart J Qual Care Clin Outcomes*. 2020;6:315–322.

3. Michalski M, Rowed K, Lavery JA, et al. Validity of estimated cardiorespiratory fitness in patients with primary breast cancer. *J Am Coll Cardiol CardioOnc*. 2022;4(2):210–219.

4. Brubaker P, Jensen A, Jordan J, et al. Exercise capacity is reduced in cancer survivors previously treated with anthracycline-based chemotherapy despite a preserved cardiac output response. *J Am Coll Cardiol Img*. 2019;12:2267–2269.

5. Cramer L, Hildebrandt B, Kung T, et al. Cardiovascular function and predictors of exercise capacity in patients with colorectal cancer. *J Am Coll Cardiol*. 2014;64:1310–1319.

6. Peel AB, Barlow CE, Leonard D, DeFina LF, Jones LW, Lakoski SG. Cardiorespiratory fitness in survivors of cervical, endometrial, and ovarian cancers: the Cooper Center Longitudinal Study. *Gynecol Oncol*. 2015;138:394–397.

7. Canada JM, Trankle CR, Carbone S, et al. Determinants of cardiorespiratory fitness following thoracic radiotherapy in lung or breast cancer survivors. *Am J Cardiol*. 2020;125:988–996.

8. Sutterfield SL, Caldwell JT, Post HK, Lovoy GM, Banister HR, Ade CJ. Lower cutaneous microvascular reactivity in adult cancer patients receiving chemotherapy. *J Appl Physiol*. 2018;125:1141–1149.

9. Jordan JH, Castellino SM, Melendez GC, et al. Left ventricular mass change after anthracycline chemotherapy. *Circ Heart Fail*. 2018;11:e004560.

10. Bonsignore A, Marwick TH, Adams SC, et al. Clinical, echocardiographic, and biomarker associations with impaired cardiorespiratory fitness early after HER2-targeted breast cancer therapy. *J Am Coll Cardiol CardioOnc*. 2021;3:678–691.

11. Grotto HZ. Anaemia of cancer: an overview of mechanisms involved in its pathogenesis. *Med Oncol*. 2008;25:12–21.

12. Didier KD, Ederer AK, Reiter LK, et al. Altered blood flow response to small muscle mass exercise in cancer survivors treated with adjuvant therapy. *J Am Heart Assoc*. 2017;6:e004784.

13. Ederer AK, Didier KD, Reiter LK, et al. Influence of adjuvant therapy in cancer survivors on endothelial function and skeletal muscle deoxygenation. *PLoS ONE*. 2016;11:e0147691.

14. Reding KW, Brubaker P, D'Agostino R Jr, et al. Increased skeletal intermuscular fat is associated with reduced exercise capacity in cancer survivors: a cross-sectional study. *Cardiooncology*. 2019;5:3.

15. Scott JM, Thomas SM, Peppercorn JM, et al. Effects of exercise therapy dosing schedule on impaired cardiorespiratory fitness in patients with primary breast cancer: a randomized controlled trial. *Circulation*. 2020;141:560–570.

KEY WORDS breast cancer, cardiorespiratory, exercise, fitness