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EDITORIAL COMMENT

The Need for an Early Biomarker of Cardiovascular Disease in Survivors of Hodgkin Lymphoma*

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This issue of *JACC: CardioOncology* includes an interesting and important paper by Rizwan et al (1) that describes the association between percent predicted peak oxygen uptake (ppV$o_2$peak), and cardiovascular events in 64 long-term (>10 years) survivors of Hodgkin lymphoma (HL) who were exposed to chest radiation, with or without chemotherapy, during treatment for their disease (1). Key findings include an association between ppV$o_2$peak and new-onset cardiovascular events, an increased risk for low ppV$o_2$peak among female patients, and an estimated mean decline in ppV$o_2$peak of 7.5% for every 10 years since radiotherapy exposure. In this single-institution cohort, female sex, lower body mass index, time since radiotherapy exposure, and reduced pulmonary function were associated with ppV$o_2$peak ≤85%, which in turn was associated with incident cardiovascular events. These data, along with previous data describing associations between ppV$o_2$peak and mortality in cancer survivors (2,3), indicate that there is potential for use of cardiopulmonary exercise testing (CPET) for early identification of subsequent cardiovascular compromise in this high-risk population.

Curiously, even though 6 of 19 (compared with 1 of 6) cardiovascular events among those with ppV$o_2$peak ≤85% were heart failure, neither left ventricular ejection fraction (LVEF) nor anthracycline exposure was associated with ppV$o_2$peak ≤85% in this study. Given the strong evidence for an association between anthracyclines and heart failure in cancer survivors (4,5), this lack of an association deserves some speculation. In pediatric survivor populations, 3 studies have reported that anthracyclines are associated with ppV$o_2$peak, resting LVEF, and global longitudinal strain in a dose-response fashion (3,6,7). The studies that captured these associations had larger sample sizes, included survivors treated at a younger age, and survivors not exposed to chest radiation. Thus, it is possible that the current study did not have adequate power to detect the association, that treatment with anthracyclines at an older age is not as toxic to the heart as it is in children, or that radiation exposure masked any effects of anthracycline exposure. However, it is also possible that standard resting measures of cardiac function, like LVEF, do not detect early subclinical cardiac disease, because they do not stress the system enough. Foulkes et al (8) reported no association between resting measures of cardiac function and VO2 peak in a small (N = 20) group of pediatric survivors (ages 8 to 20 years), but there were robust associations between cardiac magnetic resonance imaging values of stroke volume index, and cardiac index and VO2peak assessed during exercise. Early detection of impending cardiovascular disease may require measures of cardiac function during exercise.

This retrospective study by Rizwan et al (1) did not include a measure of muscle health. CPET results reflect not only abilities of the respiratory system to take in oxygen and expel carbon dioxide, and the cardiovascular system to deliver oxygen to the periphery, but also the ability of muscle to extract and use oxygen to drive function. Enhancing future

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analyses with measures of muscle health is necessary to completely describe results of CPET in this population; however, as a potential surrogate, the authors (1) did report an association between lower body mass index and ppV$o_2$peak. Cancer cachexia is common during treatment and persists in cancer survivors, affecting both muscle strength and cardiorespiratory function (9). Replacement of skeletal muscle tissue with intramuscular fat (lighter than muscle) is associated with peak VO_2 in several studies. Reding et al (10) and Beaudry et al (11) reported associations between intramuscular fat to skeletal muscle ratio and peak VO_2 in 14 cancer survivors 12 months after anthracycline-based chemotherapy, and in 16 breast cancer survivors with a history of anthracycline exposures, respectively. In the study by Beaudry et al (11), intramuscular fat to skeletal muscle ratio was inversely related to muscle oxygen extraction in the lower leg during plantar flexion exercise. Studies that use CPET to potentially estimate risk for future cardiac events should account for muscle health.

Participant exercise/physical activity status was not available for evaluation in this study. Physical activity levels are lower in cancer survivors than in peers, and importantly are related to both cardiovascular disease morbidity and mortality (12). Participation in physical activity may be difficult for survivors because, as mentioned previously, unresolved cachexia is possible, but also because some survivors have abnormal cardiac autonomic responses to exercise. Adequate muscle strength and adequate autonomic responses to exercise make it possible to engage in activity and for the body to adapt so that exercise is eventually enjoyable. Several parameters of autonomic dysfunction were presented in this paper, including higher resting heart rate and blunted heart rate recovery after exercise. These results are consistent with previous publications describing these parameters (3,13). However, neither this study nor the other 2 cited papers were specifically designed to evaluate autonomic dysfunction in a cancer survivor population. HL survivors treated with chest radiation are vulnerable to sleep disturbances (14,15), which although not well described in the literature in this population, may be attributable to autonomic dysfunction and contribute to an increased risk for death (16). Future research that more thoroughly describes autonomic dysfunction in cancer survivors is needed to provide foundational information for interventions that use exercise to improve overall health and fitness.

This study (1) has several limitations, most described well by the authors, including the small sample size, the potential for selection bias related to the nature of the testing, the lack of information available on physical activity levels, and the lack of detailed radiation dosing metrics. Another limitation of this study (1) is its retrospective nature and associated incomplete longitudinal information on all members of the cohort. Thus, the estimate of mean decline in ppV$o_2$peak using time since last radiation exposure as the time scale is not a true longitudinal analysis. Ideally, individuals with HL would be enrolled prospectively and exercise capacity evaluated serially. This would allow for examination of the onset of impaired exercise tolerance and characterization of the true trajectory of decline. The authors (1) provide here excellent preliminary information to guide clinical care and point to the need for additional work to study this outcome so intervention can be developed.

The clinical take-home message from this paper (1) is that, at-risk survivors of HL who do not participate in exercise on a regular basis, or survivors who report symptoms of discomfort when they exercise should be referred for CPET and other appropriate cardiac, pulmonary, musculoskeletal, and autonomic testing so that they can receive appropriate intervention that accommodates any impairments and allows them to exercise successfully.

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