JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 13, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.07.949

EDITORIAL COMMENT

# Unravelling the Causes of Reduced Peak Oxygen Consumption in Patients With Cancer

## Complex, Timely, and Necessary*

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There are an estimated 14.5 million cancer survivors in the United States, a number that is expected to reach 19 million by 2024 (1). Because of continued improvements in cancer-specific mortality, cancer survivors are at an increased risk of competing causes of morbidity and mortality, particularly, cardiovascular toxicity. As such, there is a growing need to define and understand the chronic and late cardiovascular effects of cancer and its therapeutic approaches.

Following a cancer diagnosis, and dependent on the selected treatment course, patients are subjected to a series of direct or indirect pathological perturbations that can damage 1 or more of the components of the pulmonary, cardiovascular, hematological, and musculoskeletal systems (**Figure 1**). The gold standard assessment of the maximal efficiency of these systems to integratively transport oxygen ($O_2$) from the atmosphere into metabolically active mitochondria (termed the $O_2$ cascade) is maximal ($VO_{2max}$) or peak ($VO_{2peak}$) oxygen consumption. Therefore, marked impairments in $VO_{2peak}$ may be a cardinal feature of patients diagnosed with cancer. The importance of this cannot be understated. Poor $VO_{2peak}$ is a robust, independent predictor of cardiovascular and all-cause mortality, and it provides powerful risk stratification and/or clinical decision-making information in numerous clinical settings (2,3). Thus, characterizing the magnitude of exercise intolerance in patients diagnosed with cancer and why cancer patients exhibit marked impairments in $VO_{2peak}$ is timely and important. Such endeavors elucidate how cancer and anticancer therapies affect the underlying determinants of $VO_{2peak}$.

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In this issue of the *Journal*, Cramer et al. (4) evaluate the level of exercise intolerance and factors associated with the magnitude of intolerance in a cross-sectional cohort of 50 patients with colorectal cancer (CRC), 51 patients with heart failure, and 51 healthy control subjects. Exercise tolerance was assessed using a treadmill protocol to symptom limitation with metabolic gas exchange measurement to assess $VO_{2peak}$. Intriguingly, the investigators found that, on average, CRC patients had a mean $VO_{2peak}$ of 21.8 ml/kg/min, equivalent to 23% below that of the age-matched control subjects (mean 28.0 ml/kg/min), and that $VO_{2peak}$ was only approximately 17% higher than that of the heart failure patients in the study. The marked impairment in $VO_{2peak}$ corroborates work by other investigators who showed that patients with various solid or hematological malignancies have marked reductions in $VO_{2peak}$ (5,6). This is an intriguing finding, because it can be anticipated that exercise tolerance is relatively normal since CRC patients do not receive anticancer therapies that are traditionally expected to significantly impair 1 or

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

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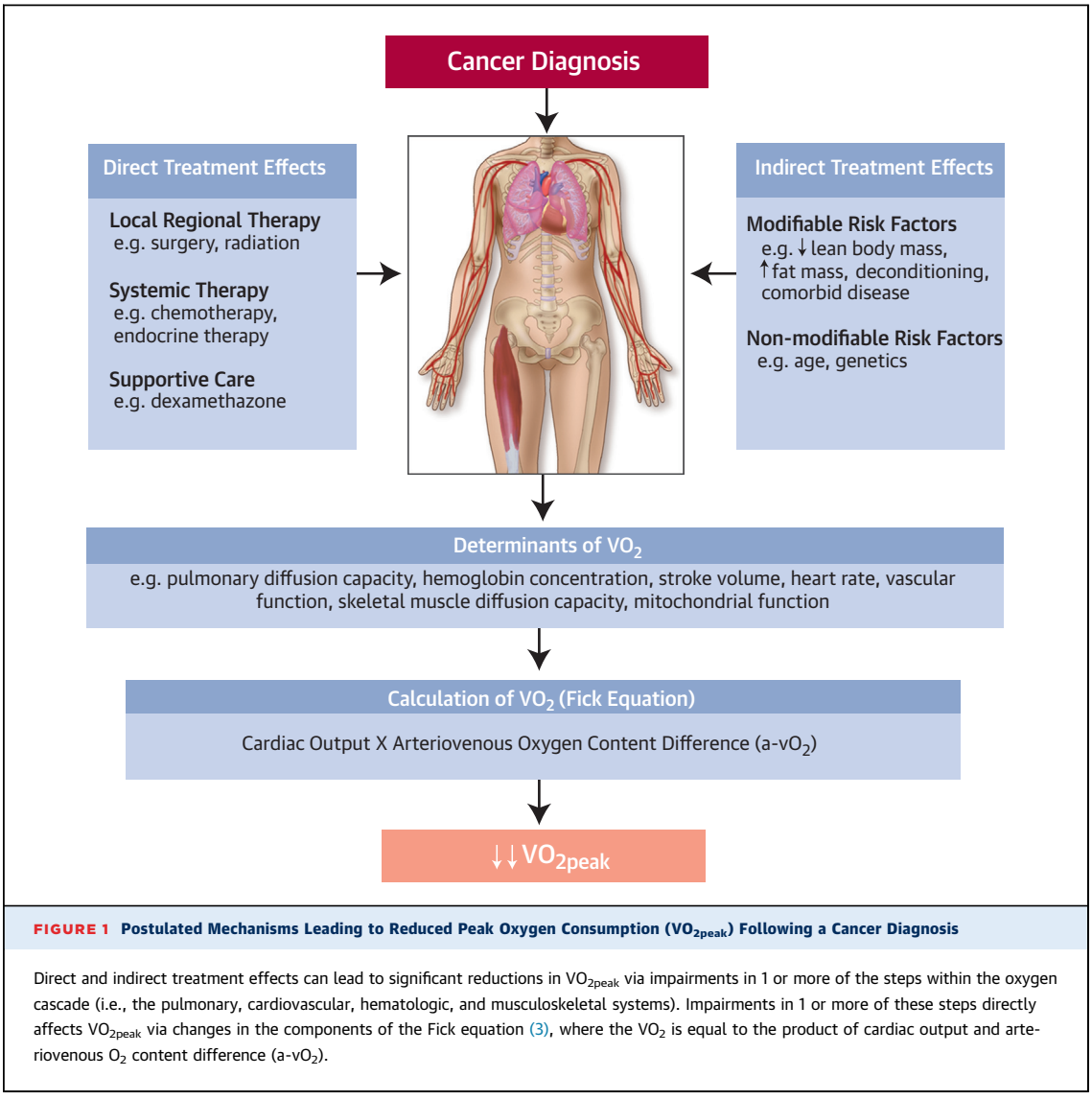


**FIGURE 1 Postulated Mechanisms Leading to Reduced Peak Oxygen Consumption ($VO_{2peak}$) Following a Cancer Diagnosis**

Direct and indirect treatment effects can lead to significant reductions in $VO_{2peak}$ via impairments in 1 or more of the steps within the oxygen cascade (i.e., the pulmonary, cardiovascular, hematologic, and musculoskeletal systems). Impairments in 1 or more of these steps directly affects $VO_{2peak}$ via changes in the components of the Fick equation (3), where the $VO_2$ is equal to the product of cardiac output and arteriovenous $O_2$ content difference (a-$vO_2$).

more of the components of the $O_2$ cascade (e.g., impaired pulmonary diffusion associated with thoracic surgery, cardiotoxicity associated with anthracyclines or human epidermal growth factor receptor (HER2) targeted therapies, skeletal muscle myopathy caused by androgen deprivation therapy). To provide insight into the potential underlying causes of the observed impairments in $VO_{2peak}$, Cramer et al. (4) explored a total of 18 medical and physiological predictors. Of these, hemoglobin, lean mass (leg and whole body), maximal heart rate on exercise, heart rate variability, and the blood biomarker, endothelium-derived C-terminal-pro-endothelin-1, were significant predictors of $VO_{2peak}$. These findings provide new insight into factors that may affect the integrative reserve of the $O_2$ cascade that contributes to the observed reductions in exercise tolerance. However, how some of these factors contribute to impairments in the major determinants of $VO_{2peak}$ remains to be elucidated. Specifically, $VO_2$ is determined by the Fick equation, where the $VO_2$ is equal to the product of cardiac output and the arteriovenous $O_2$ content difference (a-$vO_2$) (3). Impairments in 1 or more of the steps within the $O_2$ cascade that lead to a reduction in either cardiac output and/or a-$vO_2$ will predictably and proportionally reduce $VO_{2peak}$ (3). Although Cramer et al. (4) unfortunately did not specifically measure cardiac output or a-$vO_2$, the assessment of parameters such as hemoglobin concentration (an important component of the $O_2$ cascade) were performed. Reductions in hemoglobin would directly affect convective $O_2$ delivery by a proportional

reduction in the content of arterial $O_2$ deliverable to the active muscle, which leads to impaired $VO_{2peak}$.

Based on the findings of Cramer et al. (4), the critical next step of investigation is to understand how CRC and its associated therapies affect cardiac output and/or a-$vO_2$, as well as steps in the $O_2$ cascade that lead to impairments in $VO_{2peak}$. As in other clinical populations, the causes of exercise intolerance in CRC patients is likely multifactorial, with no single organ component being the cause of limitation (3). This particularly may be the case in the study by Cramer et al. (4), because the patient cohort was heterogeneous with regard to disease stage, treatment status, and type of previous and current anticancer therapy. As previously reviewed by our group (7), the direct effects of surgery, combination chemotherapy, radiotherapy, and antiangiogenic therapy, combined with the effects secondary to treatment (aging, deconditioning), may all affect the convective and diffusive steps in the $O_2$ cascade to varying degrees. Although challenging to conduct, recruitment of cancer cohorts that are homogenous in terms of disease stage and treatment exposure(s), as well as other confounding factors, are optimal to fully elucidate the effect of a given anticancer therapy on $VO_{2peak}$ and its primary underlying mechanism of action. Such efforts, in turn, will inform the design of limitation-driven therapeutic strategies to prevent and/or recover poor $VO_{2peak}$.

Aerobic training is arguably the most effective strategy to improve $VO_{2peak}$ because it improves the integrative reserve of the cardiovascular and musculoskeletal systems (8). Randomized trials have demonstrated that aerobic training is associated with significant improvements in $VO_{2peak}$ in patients with early-stage cancer with minimal adverse events (9). The adaptations associated with aerobic training are well established in healthy individuals (3). However, whether aerobic training causes similar adaptations or how aerobic training affects the sequential steps within the $O_2$ cascade in patients with cancer has not been investigated. This is a major research gap, because elucidation of these complexities are essential to optimize the safety and efficacy of exercise prescriptions in the oncology setting. Furthermore, by elucidating the limitations to exercise in cancer, prescriptions can be optimized that focus on reversing and/or mitigating the specific perturbations caused by cancer and its associated therapy.

The findings of Cramer et al. (4) highlight a key opportunity in the emerging field of cardio-oncology. To date, the majority of work in this field has focused exclusively on the cardio-centric toxicity associated with cancer therapy. It is clear, however, that reduced $VO_{2peak}$ may be a new hallmark of both the cancer itself and the cancer therapy-associated toxicity that is the result of the acute and late effects of therapy. Such impairment is apparent even in the absence of impaired cardiac function (at least when measured by conventional parameters such as left ventricular ejection fraction), suggesting that cardio-oncology specialists may need to think more broadly and consider incorporation of techniques such as cardiopulmonary exercise testing, which provides information that extends beyond the heart when characterizing, monitoring, and managing cancer therapy late effects. Such considerations may facilitate treatment stratification, mortality risk prediction, and surveillance of therapy-induced toxicity and/or recovery across the cancer survivorship continuum.

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**KEY WORDS** cancer, cardio-oncology, determinants, exercise intolerance, peak oxygen consumption, survivorship