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## STATE-OF-THE-ART REVIEW

# Cancer Therapy and Exercise Intolerance: The Heart Is But a Part



## JACC: CardioOncology State-of-the-Art Review

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### ABSTRACT

The landscape of cancer therapeutics is continually evolving, with successes in improved survivorship and reduced disease progression for many patients with cancer. Improved cancer outcomes expose competing comorbidities, some of which may be exacerbated by cancer therapies. The leading cause of disability and death for many early-stage cancers is cardiovascular disease (CVD), which is often attributed to direct or indirect cardiac injury from cancer therapy. In this review, the authors propose that toxicities related to conventional and novel cancer therapeutics should be considered beyond the heart. The authors provide a framework using the oxygen pathway to understand the impact of cancer treatment on peak oxygen uptake, a marker of integrative cardiopulmonary function and CVD risk. Peripheral toxicities and the impact on oxygen transport are discussed. Consideration for the broad effects of cancer therapies will improve the prediction and identification of cancer survivors at risk for CVD, functional disability, and premature mortality and those who would benefit from therapeutic intervention, ultimately improving patient outcomes. (JACC CardioOncol 2024;6:496-513) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Improved understanding of cancer biology and the discovery of novel therapeutic targets have led to remarkable progressions in cancer therapy efficacy in recent decades.<sup>1</sup> The discovery of targeted agents and immunotherapies has facilitated a paradigm shift in cancer management and contributed to a steady increase in survivorship.<sup>2</sup> Five-year survival

rates are rising, and projections forecast that cancer survivor prevalence will grow to 22.5 million by 2032 in the United States alone.<sup>3</sup> This improved survival, however, is associated with a 37% greater risk for cardiovascular disease (CVD),<sup>4</sup> posing a threat to quality of life and longevity in this vulnerable population.

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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](#).

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## HIGHLIGHTS

- CVD is a major contributor to morbidity and mortality in cancer survivors.
- Peripheral toxicities contribute to CVD risk via their effect on exercise tolerance.
- The oxygen pathway can help understand the effect of cancer treatments.

Among cancer survivors, excess CVD risk has been largely ascribed to cancer therapy-induced damage to the heart (ie, cardiotoxicity), giving rise to the medical subspecialty of “cardio-oncology.” In line with this cardiocentric focus, the primary means for diagnosis and risk stratification of cancer survivors with suspected cardiotoxicity are resting cardiac imaging measurements of left ventricular systolic function, primarily left ventricular ejection fraction and global longitudinal strain.<sup>5,6</sup> However, there is growing recognition that resting left ventricular ejection fraction is a less robust predictor of adverse CVD outcomes in cancer survivors,<sup>7</sup> and it does not correlate with objective measures of exercise intolerance,<sup>8</sup> a hallmark feature of CVD. Indeed, it is increasingly apparent that the adverse consequences of cancer therapeutics often extend beyond the heart to affect all components of the oxygen cascade (ie, lungs, blood, vasculature, and skeletal muscle). Therefore, current monitoring strategies, which are intended primarily to quantify cardiac dysfunction as a marker of cancer therapy-related toxicity and CVD risk, do not fully capture the breadth of toxicities that affect the oxygen transport system. We propose that integrative measures of global cardiovascular and skeletal muscle function that are highly adaptive and sensitive, such as peak oxygen consumption ( $V_{O_2\text{peak}}$ ), provide additional insight into CVD prognosis for cancer survivors.  $V_{O_2\text{peak}}$  encapsulates the interaction between both central (ie, cardiac output and pulmonary gas diffusion) and peripheral (ie, blood oxygen-carrying capacity, vascular function, and skeletal muscle function) components of the oxygen cascade and is a powerful independent predictor of mortality from CVD (HR: 0.41; 95% CI: 0.16-1.05), cancer (HR: 0.16; 95% CI: 0.09-0.28), and all causes (HR: 0.17; 95% CI: 0.11-0.27) in post-treatment patients with adult-onset cancers (for high vs low cardiorespiratory fitness, respectively).<sup>9</sup> Furthermore, limitations in  $V_{O_2\text{peak}}$  can affect one’s ability to perform activities of daily living, thereby also serving as an indicator of functional independence and quality of life.<sup>10</sup> Notably,  $V_{O_2\text{peak}}$  is reduced in many

cancer survivors and is not entirely explained by declines in cardiac function.<sup>9-12</sup>

In this review, we use the oxygen cascade as a framework to systematically highlight the peripheral toxicities of conventional (ie, chemotherapy and radiation therapy) and novel cancer therapies (ie, hematopoietic cell transplantation [HCT], immune therapy, targeted therapy, and hormone therapy) and their subsequent impact on  $V_{O_2\text{peak}}$  and CVD risk. We focus primarily on evidence from commonly prescribed cancer therapies such as chemotherapies (eg, anthracyclines, alkylating agents, antimetabolites, taxanes) and radiation therapy given their widespread use and large evidence base. Where possible, we highlight emerging evidence relating to novel targeted agents. The focus on targeted and immune therapies is important as their use is rapidly increasing because of expanding treatment indications, as well as growing data on their efficacy, and cost-benefit analyses. For example, the proportion of U.S.-based patients with cancer eligible for immune checkpoint inhibitors (ICIs) increased from 1.54% in 2011 to 43.63% in 2018,<sup>13</sup> and similar trends have been seen for tyrosine kinase inhibitors (TKIs), monoclonal antibodies (mAbs), and vascular endothelial growth factor receptor (VEGFR) inhibitors.<sup>14-16</sup> The review also draws upon evidence from preclinical and clinical studies to provide an overview of underpinning mechanisms and clinical implications. We propose that phenotyping the effects of cancer therapy beyond the heart (ie, peripheral toxicities) will more accurately identify cancer survivors at risk for CVD, functional disability, and premature mortality who might benefit from therapeutic intervention, ultimately improving patient outcomes.

## OVERVIEW OF THE OXYGEN TRANSPORT CASCADE

The oxygen transport cascade describes the physiological steps involved in transporting oxygen from the atmosphere to muscle mitochondria where the efficient production of energy in addition to numerous other enzymatic reactions that require molecular oxygen occur. During aerobic exercise, the increase in metabolic demand requires more oxygen uptake through convective and diffusive processes coupled with mitochondrial respiration to meet the adenosine triphosphate requirement of the exercising muscles. The convective steps involve the movement of oxygen into the lungs (alveolar ventilation) and transport from the lungs into the periphery via the

## ABBREVIATIONS AND ACRONYMS

- CVD** = cardiovascular disease
- DMO<sub>2</sub>** = muscle oxygen diffusive conductance
- HCT** = hematopoietic cell transplantation
- ICI** = immune checkpoint inhibitor
- mAb** = monoclonal antibody
- SMD** = standardized mean difference
- TKI** = tyrosine kinase inhibitor
- VEGF** = vascular endothelial growth factor
- VEGFR** = vascular endothelial growth factor receptor
- $V_{O_2\text{peak}}$**  = peak oxygen consumption
- V/Q** = ventilation/perfusion

circulatory system (hemoglobin and cardiac output). The diffusive steps occur as oxygen moves across the alveolar-pulmonary capillary membrane in the lung and during the unloading of oxygen from hemoglobin into capillaries, where cells use oxygen for a variety of biological functions. Importantly, most of the oxygen is consumed by mitochondria to generate adenosine triphosphate via oxidative phosphorylation. Although prior reviews focused on cardiac-specific toxicities,<sup>5-17</sup> we focus on the impact cancer therapies have on the factors peripheral to the heart (lungs, blood, vasculature, and skeletal muscle) and subsequently  $V_{O_2}$ peak as organized by the noncardiac components of the oxygen cascade (**Table 1**).

### DIFFUSIVE OXYGEN LOADING

The pulmonary system performs 2 important roles in the oxygen cascade: ventilation, allowing the movement of air molecules from the atmosphere into the alveoli, and gas exchange, which includes the diffusion of oxygen from the alveoli to the pulmonary capillaries. Ventilation increases in response to exercise to enable greater movement of oxygen into the alveoli, where oxygen diffuses into the pulmonary capillary membrane and binds to hemoglobin. Impairment in the efficiency of gas exchange (alveolar to arterial  $P_{O_2}$  difference) can occur during exercise when there is a mismatch in the ventilation/perfusion (V/Q) ratio or changes to oxygen tension. For example, pulmonary embolism, which is a common complication among patients with cancer, can be provoked by multiple agents (**Table 1**)<sup>18</sup> and is associated with profound exercise intolerance due to V/Q mismatch. There have been a few case reports of interstitial lung disease following treatment with the BCR-ABL TKIs imatinib and nilotinib, which are first-line therapy for chronic myelogenous leukemia, although this is an uncommon complication (estimated at <1%).<sup>19</sup> Interstitial lung diseases are characterized by alveolar and interstitial space damage, pulmonary inflammation, and fibrosis, resulting in decreased pulmonary capacity and impaired gas exchange.<sup>20</sup> Novel hypoxia-inducible transcription factor inhibitors (eg, belzutifan) can cause severe hypoxia for unclear reasons, but it is thought to be related to pulmonary arterial vasoconstriction and V/Q mismatch.<sup>21</sup> Thus, this severe complication of cancer therapy can affect oxygen diffusion capacity within the lungs and likely affects  $V_{O_2}$ peak (**Central Illustration**).

Following the initial convective step of oxygen movement through the lungs to the alveolar capillary

membrane, oxygen is loaded to hemoglobin via diffusion in red blood cells and then is distributed throughout the body via the circulatory system. To facilitate the optimal transfer of oxygen, sufficient hemoglobin must be available. As such, factors that reduce hemoglobin levels, such as defective erythropoiesis or hemolysis, can impair  $V_{O_2}$ peak through a reduction in arterial blood oxygen content and, subsequently, reduced skeletal muscle oxygenation (**Central Illustration**). Several cancer chemotherapies (eg, anthracyclines, platinum-based therapies, antimicrotubule agents) cause anemia by their myelosuppressive effects on erythroid progenitor cells, bone marrow activity, and renal function.<sup>22</sup> The severity of chemotherapy-induced anemia is affected by the type and dose of cancer therapy, and it can affect 20% to 100% of patients with lung, breast, hematological, and colorectal cancer undergoing treatment.<sup>23</sup> Fortunately for most patients, anemia is transient, but even small reductions in hemoglobin concentration (ie, 13%-14%, values commonly seen in patients on cancer therapy) have been associated with 9% to 10% reductions in  $V_{O_2}$ peak in healthy individuals (equivalent to a decade of age-related  $V_{O_2}$ peak decline).<sup>24,25</sup> On the basis of these correlations, treatment-induced reductions in hemoglobin concentration likely contribute to short-term declines in  $V_{O_2}$ peak. The longer-term impacts are less clear, with persistent anemia beyond myelosuppressive treatment rarely reported in the literature. Oxygen loading can also be influenced by shifts in the oxygen-hemoglobin dissociation curve. Under hypoxic settings, there is a leftward shift in the oxygen-hemoglobin dissociation curve, which leads to tighter binding of oxygen to hemoglobin (eg, greater arterial oxygen content for a given  $P_{O_2}$ ). In contrast, acidosis or hyperthermia can cause a rightward shift in the curve, which increases oxygen extraction in the peripheral tissues.

Autoimmune hemolytic anemia occurs because of increased destruction of red blood cells by autoantibodies and complement and other cell types within the immune system. The condition can occur following allogeneic stem cell transplantation<sup>26</sup> and after treatment with ICI therapy in melanomas and lung cancers.<sup>26,27</sup> This severe complication is typically responsive to steroid treatment, with improvement of hemoglobin levels in about 89 days.<sup>27</sup> Although rare (incidence rates are estimated to be <1%), as the use of ICI therapy becomes more widespread, there is the potential that this severe complication might contribute to cardiovascular morbidity and exercise intolerance in patients with cancer.

**TABLE 1 Overview of Cancer Therapies That Affect the Noncardiac Components of the Oxygen Cascade**

Therapy	Cancer Indications (On and Off Label)	Toxicities Affecting the Noncardiac Components of the Oxygen Cascade		
		Diffusive Oxygen Loading	Convective Oxygen Delivery	Diffusive Oxygen Conductance and Metabolism
<b>Antitumor antibiotics</b>				
Anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin)	Breast, Wilms' tumor, neuroblastoma, soft tissue sarcoma, osteosarcoma, ovarian, bladder, thyroid, gastric, bronchogenic, ALL, AML, HL, NHL		Arterial stiffening, <sup>35-47</sup> arterial thrombosis, <sup>88</sup> endothelial dysfunction, systemic HTN <sup>144</sup>	Microvascular rarefaction, <sup>95</sup> capillary leak, <sup>103</sup> decreased muscle oxidative capacity, <sup>95,105,106</sup> reduced mitochondrial biogenesis, number and/or function, <sup>95,106</sup> muscle atrophy, <sup>105,110,112</sup> myosteatosis <sup>110-113</sup>
Bleomycin	Head, HL, neck, testicular	Pulmonary HTN, <sup>145</sup> pulmonary fibrosis <sup>145</sup>		
<b>Alkylating agents</b>				
Platinum-based (carboplatin, cisplatin, oxaliplatin)	Bladder, breast, cervical, endometrial carcinoma, head, neck, HL, pleural mesothelioma, MM, NHL, esophageal, gastric, osteosarcoma, ovarian, penile, SCLC, testicular, CRC, ovarian		Arterial stiffening, <sup>48-50</sup> arterial thrombosis, <sup>146</sup> endothelial dysfunction, systemic HTN, <sup>18,87</sup> arterial vasospasm, <sup>18,30,31</sup> atherosclerotic disease <sup>18,30</sup>	Capillary leak, <sup>103</sup> myosteatosis <sup>112</sup>
Non-platinum-based (busulfan, cyclophosphamide, ifosfamide)	ALL, breast, CLL, Ewing sarcoma, HL, MM, NHL, SCLC, HCT conditions including AML, ALL, CLL, CML, MDS, and MPN	Pulmonary HTN, <sup>18,31</sup> pulmonary fibrosis <sup>144</sup>	Arterial stiffening, <sup>45</sup> systemic HTN <sup>87</sup>	Capillary leak <sup>103</sup>
<b>Antimetabolites</b>				
5-fluorouracil, capecitabine, gemcitabine	Anal carcinoma, bladder, breast, cervical, CRC, gastric, hepatobiliary, esophageal, pancreatic, squamous cell carcinomas, ovarian, peritoneal, adenocarcinoma of unknown primary, head, neck, HL, NHL, malignant pleural mesothelioma, SCLC, NSCLC, testicular, uterine	Pulmonary embolism <sup>30</sup>	Arterial stiffening, <sup>49</sup> arterial thrombosis, <sup>107</sup> endothelial dysfunction, <sup>72</sup> systemic HTN, <sup>30</sup> arterial vasospasm <sup>18,30</sup>	Capillary leak, decreased muscle oxidative capacity <sup>108</sup>
<b>Taxanes</b>				
Paclitaxel, docetaxel, cabazitaxel	Adenocarcinoma of unknown primary, bladder, breast, cervical, head, neck, Kaposi sarcoma, NSCLC, esophageal, gastric, ovarian, penile, SCLC, soft tissue sarcoma, testicular germ cell tumors, thymoma	Pulmonary embolism <sup>18,30</sup>	Arterial stiffening, <sup>38,56</sup> endothelial dysfunction, <sup>73</sup> systemic HTN, <sup>18,30</sup> arterial vasospasm <sup>18,30</sup>	Microvascular rarefaction, <sup>95</sup> capillary leak, <sup>103</sup> decreased muscle oxidative capacity, <sup>95,106</sup> reduced mitochondrial biogenesis, number and/or function, <sup>95,106</sup> muscle atrophy, <sup>147</sup> myosteatosis <sup>110-113,147</sup>
<b>Vinka alkaloids</b>				
Vincristine	ALL, CNS tumors, HL, Ewing sarcoma, gestational trophoblastic tumors, MM, NHL, ovarian, primary CNS lymphoma, SCLC, thymoma		Systemic HTN <sup>18</sup>	Capillary leak <sup>103</sup>
<b>Topoisomerase I inhibitors</b>				
Irinotecan	CRC		Arterial stiffening <sup>52</sup>	
<b>Monoclonal antibodies</b>				
Anti-VEGF (bevacizumab, ramucirumab)	NSCLC, breast, glioblastoma, RCC, ovarian, cervical, CRC, peritoneal, fallopian tube, HCC, gastric, HCC, NSCLC, esophageal	Pulmonary embolism <sup>18,30</sup>	Arterial stiffening, <sup>57</sup> arterial thrombosis, <sup>51,88</sup> endothelial dysfunction, <sup>57,69</sup> systemic HTN, <sup>30</sup> atherosclerotic disease <sup>81</sup>	Microvascular rarefaction, <sup>57,69</sup> capillary leak <sup>103</sup>
Anti-EGFR (trastuzumab, panitumumab)	CRC		Arterial stiffening <sup>38,42,52</sup>	Capillary leak <sup>103</sup>
Anti-CD20 (rituximab)	NHL, CLL		Systemic HTN, <sup>30</sup> arterial vasospasm <sup>18,30</sup>	Capillary leak <sup>101,103</sup>

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## CONVECTIVE OXYGEN DELIVERY

Oxygenated blood is distributed to the various capillary plexi in accordance with the metabolic demand of the organ or tissue they supply. The regulation of blood flow depends on the neural, endocrine, and

local control of vascular tone and perfusion pressure in distal conduit arteries and arterioles. Importantly, limitations in oxygen delivery have been observed in cancer survivors and are associated with exercise intolerance.<sup>28,29</sup> In this setting, impaired oxygen delivery has been associated with cardiac dysfunction,

TABLE 1 Continued				
Therapy	Cancer Indications (On and Off Label)	Toxicities Affecting the Noncardiac Components of the Oxygen Cascade		
		Diffusive Oxygen Loading	Convective Oxygen Delivery	Diffusive Oxygen Conductance and Metabolism
<b>TKIs</b>				
VEGFR TKIs (axitinib, cabozantinib, cediranib, lenvatinib, pazopanib, regorafenib, ruxolitinib, sorafenib, sunitinib, telatinib, vandetanib, vatalanib)	RCC, thyroid, HCC, NSCLC, ovarian, soft tissue carcinoma, GIST, CRC, MDS, Angiosarcoma, pancreatic, neuroendocrine tumors, soft tissue sarcoma	Pulmonary embolism <sup>30</sup>	Arterial stiffening, <sup>38,52-55</sup> arterial thrombosis, <sup>82,146</sup> endothelial dysfunction, <sup>67,97,148,149</sup> systemic HTN, <sup>18,87</sup> arterial vasospasm <sup>18,30</sup>	Microvascular rarefaction <sup>54,97</sup>
BCR-ABL1 TKIs (dasatinib, imatinib, nilotinib, ponatinib)	GIST, ALL, CML, MDS, MPN	Pulmonary HTN, <sup>18</sup> interstitial lung disease, <sup>19</sup> pulmonary embolism <sup>18,30</sup>	Arterial stiffening, <sup>58,59</sup> arterial thrombosis, <sup>88</sup> endothelial dysfunction, <sup>76</sup> systemic HTN, <sup>18,30</sup> arterial vasospasm, <sup>150</sup> atherosclerotic disease <sup>18,30,80</sup> Systemic HTN <sup>18,87</sup>	
BTK inhibitors (ibrutinib, acalabrutinib)	CLL, mantle cell lymphoma, Waldenström macroglobulinemia			
<b>Fusion proteins</b>				
Aflibercept	CRC	Pulmonary embolism <sup>18,30</sup>	Systemic HTN <sup>18,30</sup>	Microvascular rarefaction <sup>67</sup>
<b>Proteasome inhibitors</b>				
Carfilzomib, bortezomib	MM	Pulmonary HTN, <sup>18</sup> pulmonary embolism <sup>18</sup>	Arterial stiffness, <sup>60</sup> arterial thrombosis, <sup>146</sup> endothelial dysfunction, <sup>70,151</sup> systemic HTN, <sup>18,30,87</sup> atherosclerotic disease <sup>30</sup>	Capillary leak <sup>103</sup>
<b>HIF-2<math>\alpha</math> inhibitors</b>				
Belzutifan	RCC, pancreatic neuroendocrine tumors, central nervous system hemangioblastomas	Hypoxia <sup>21</sup>		
<b>Immune checkpoint inhibitors</b>				
Atezolizumab, avelumab, ipilimumab, pembrolizumab, nivolumab, cemiplimab, durvalumab	Melanoma, head, neck, HL, mediastinal large B-cell lymphoma, gastric, cervical, breast, NSCLC, SCLC, urothelial, esophageal, HCC, Merkel cell carcinoma, RCC, endometrial, malignant pleural mesothelioma, cutaneous basal cell carcinoma, cutaneous squamous cell carcinoma	Hemolytic anemia, <sup>27</sup> pulmonary embolism <sup>152</sup>	Arterial thrombosis, <sup>83</sup> atherosclerotic disease <sup>86</sup>	Capillary leak <sup>103</sup>
<b>Immunomodulatory agents</b>				
Cytokines (IL-2, IFN $\alpha$ )	Hairy cell leukemia, Kaposi sarcoma, lymphoma, malignant melanoma	Pulmonary HTN, <sup>18</sup> pulmonary embolism <sup>27,30</sup>	Systemic HTN, <sup>30</sup> atherosclerotic disease <sup>18,30</sup>	Capillary leak <sup>101,103</sup>
Lenalidomide	CLL, diffuse large B-cell lymphoma, mantle cell lymphoma, MM, MDS	Pulmonary embolism <sup>30</sup>	Arterial thrombosis, <sup>153</sup> endothelial dysfunction, <sup>154</sup> systemic HTN <sup>30</sup>	
CAR T-cell therapy	ALL, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, MM			Capillary leak <sup>102,103</sup>
<b>Hematopoietic cell transplantation</b>				
Autologous and allogeneic	Aplastic anemia, AML, ALL, CML, CLL, lymphomas, MM, MDS, MPN	Pulmonary HTN, <sup>155</sup> hemolytic anemia <sup>26</sup>	Arterial stiffening, <sup>66</sup> arterial thrombosis, <sup>156,157</sup> endothelial dysfunction, <sup>71</sup> systemic HTN, <sup>158</sup> atherosclerotic disease <sup>156,157</sup>	Capillary leak, decreased muscle oxidative capacity, <sup>12,109,159</sup> muscle atrophy <sup>12,159</sup>
Radiation therapy	Breast, head, neck, cervical, prostate, thyroid, osteosarcoma, esophageal, CRC, pancreatic, HCC, neuroblastoma, meningioma, soft tissue carcinoma, HL, NHL, MM, AML, ALL, CLL, CML, MDS, and MPN	Pulmonary HTN, <sup>160</sup> pulmonary fibrosis <sup>160</sup>	Arterial stiffening, <sup>51</sup> endothelial dysfunction, <sup>75,161</sup> arterial vasospasm, <sup>18,30</sup> atherosclerotic disease <sup>84</sup>	

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**TABLE 1 Continued**

Therapy	Cancer Indications (On and Off Label)	Toxicities Affecting the Noncardiac Components of the Oxygen Cascade		
		Diffusive Oxygen Loading	Convective Oxygen Delivery	Diffusive Oxygen Conductance and Metabolism
Hormone therapy				
Aromatase inhibitors (anastrozole, exemestane, letrozole)	Breast		Arterial stiffening, <sup>61,62</sup> endothelial dysfunction, <sup>61,74</sup> systemic HTN <sup>87</sup>	
Androgen deprivation therapy	Prostate		Arterial stiffening, <sup>63-65</sup> systemic HTN <sup>87</sup>	Muscle atrophy, <sup>114</sup> myoosteatosis <sup>115,116</sup>

This list is not all encompassing but serves to highlight the strongest clinical evidence linking cancer therapies with impairments in the noncardiac components of the oxygen cascade. Cancer indications are based on reported indications from the U.S. Food and Drug Administration or, where not possible, treatment guidelines.

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; BTK = Bruton tyrosine kinase; CAR = chimeric antigen receptor; CLL = chronic lymphocytic leukemia; CML = chronic myeloid leukemia; CNS = central nervous system; CRC = colorectal cancer; EGFR = epidermal growth factor receptor; GIST = gastrointestinal stromal tumor; HCC = hepatocellular carcinoma; HIF-2α = hypoxia-inducible transcription factor 2α; HL = Hodgkin's lymphoma; HTN = hypertension; IFN = interferon; IL = interleukin; MDS = myelodysplastic syndrome; MM = multiple myeloma; MPN = myeloproliferative neoplasm; NHL = non-Hodgkin's lymphoma; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; SCLC = small cell lung cancer; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor.

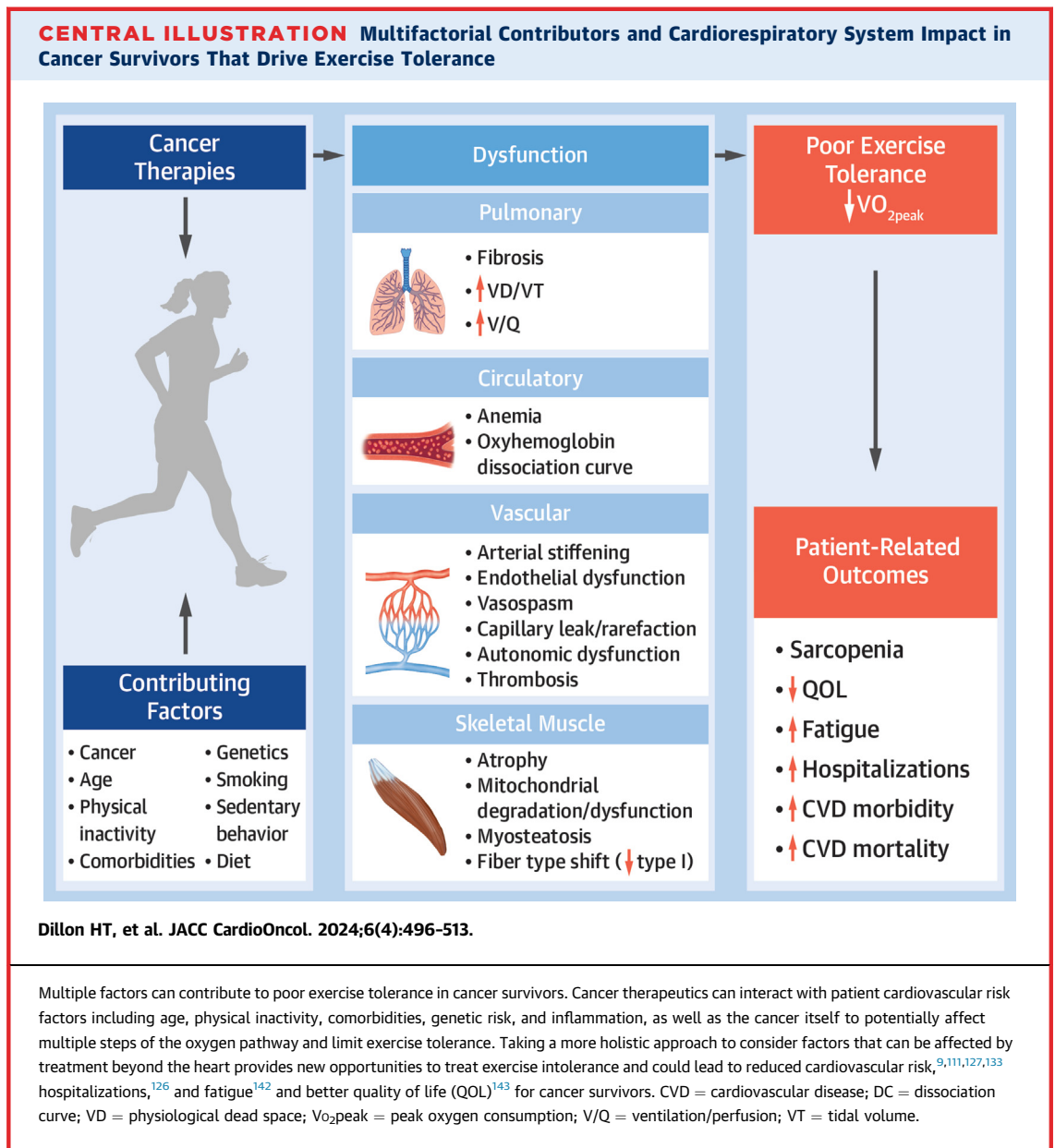
alterations in the structural and mechanical properties of the vasculature, and autonomic dysfunction. The impact of conventional and novel cancer therapies on the noncardiac factors mediating oxygen delivery is highlighted in the **Central Illustration** and **Table 1**.

Vascular toxicities are a frequent complication of a broad range of cancer therapies and contribute to CVD morbidity in cancer survivors.<sup>30,31</sup> Arterial stiffening could theoretically limit oxygen delivery by way of blunting the Windkessel effect (which refers to the elastic reservoir properties of a blood vessel and typically dampens the variations in pulse pressure throughout the cardiac cycle) and increasing systemic vascular resistance, while hypertension could contribute to capillary and tissue malperfusion. Preclinical evidence has shown that chemotherapy (eg, anthracyclines, platinum compounds, 5-Fluorouracil),<sup>32</sup> radiation, proteasome inhibitors, and anti-vascular endothelial growth factor (VEGF) therapies can promote pathologic structural and functional alteration of the vascular wall that prelude or reflect arterial stiffening.<sup>33</sup> The mechanisms underpinning cancer therapy-induced vascular toxicities are emerging, with accumulating evidence implicating oxidative stress and inflammation because of their deleterious impacts on nitric oxide signaling, the elastin/collagen ratio, and smooth muscle cell senescence.<sup>34</sup> A pathophysiologic link between cancer therapy and arterial stiffness has been reported, with a recent meta-analysis demonstrating increased arterial stiffness (aortic distensibility, β-stiffness index, pulse-wave velocity) in patients with cancer following exposure to various cancer therapies (ie, anthracycline-based<sup>35-47</sup> and/or alkylating agent-based<sup>45,48-50</sup> chemotherapy, radiation therapy,<sup>51</sup> and VEGFR TKIs<sup>38,52-55</sup>) compared

with both pretreatment values and noncancer controls (**Table 1**).<sup>40</sup> Subgroup analyses have further demonstrated that anthracycline-based therapies exert a greater vascular toxic effect. Importantly, an inverse relationship between arterial stiffness and Vo<sub>2</sub>peak has been observed in anthracycline-treated breast cancer survivors (R<sup>2</sup> = 0.32-0.38).<sup>41</sup> Arterial stiffening has also been reported in patients with cancer treated with antimetabolite- and taxane-based chemotherapies,<sup>38,49,56</sup> anti-epidermal growth factor receptor and VEGF mAbs,<sup>38,42,52,57</sup> BCR-ABL1 TKIs,<sup>58,59</sup> proteasome inhibitors,<sup>60</sup> aromatase inhibitors,<sup>61,62</sup> androgen deprivation therapy,<sup>63-65</sup> and HCT<sup>66</sup> (**Table 1**). The effects of immunotherapy on arterial stiffness awaits investigation.

Endothelial dysfunction, characterized by reduced vasodilator bioavailability (ie, nitric oxide and prostacyclin) and increased endothelium-derived vasoconstrictor activity (ie, endothelin-1, prostaglandin, and thromboxane), might impair oxygen delivery by increasing peripheral resistance and blunting dilation of arterioles in response to vasoactive stimuli. Preclinical studies have shown that all classes of chemotherapeutic agents,<sup>67</sup> radiation therapy,<sup>68</sup> and select targeted therapy<sup>67</sup> can damage the vascular endothelium and smooth muscle (culminating in impaired vasodilation) via myriad on- and off-target mechanisms. These include DNA damage, down-regulation of critical signaling pathways (eg, VEGF), altered gene expression (eg, redox-regulated transcription factors), as well as oxidative stress, immune system activation, and up-regulation of proinflammatory pathways (all of which are exacerbated in the context of immunotherapy and HCT-mediated cytokine release syndrome).<sup>67,68</sup> Cancer therapy-induced endothelial toxicity has also been documented in the clinical setting (**Table 1**). Longitudinal





studies have demonstrated reductions in endothelium-dependent vasodilation of the brachial artery and microcirculatory vessels in patients with cancer treated with VEGFR TKIs or VEGF mAbs (28%-50% and 39%-49% for macrocirculation and microcirculation, respectively),<sup>67,69</sup> proteasome inhibitors (35% and 24%),<sup>70</sup> HCT (37% for macrocirculation),<sup>71</sup> and various chemotherapeutics (eg, anthracyclines, antimetabolites,<sup>72</sup> taxanes,<sup>73</sup> and platinum-based alkylating agents; 35%-95% and 24%-29%).<sup>67</sup> Evidence of vascular endothelial dysfunction has also been documented in cross-sectional studies in

patients with breast and hematological cancer treated with aromatase inhibitors,<sup>61,74</sup> radiation therapy,<sup>75</sup> and BCR-ABL TKIs.<sup>76</sup> It is important to note that not all findings have been concordant.<sup>67</sup> Jones et al<sup>77,78</sup> reported no appreciable impairment in endothelial function among anthracycline-treated breast cancer survivors despite impairment in VO<sub>2peak</sub>. Similarly, Koelwyn et al<sup>79</sup> observed normal endothelial function and preserved VO<sub>2peak</sub> in anthracycline-treated breast cancer survivors relative to age-matched non-cancer control subjects. Further research is warranted to understand the impact of cancer treatments



(particularly anthracyclines) on endothelial function and exercise tolerance, as these findings may be limited by small sample sizes,<sup>77,78</sup> potential survivor bias in longer-term investigations,<sup>78,79</sup> and selection bias for more physically active patients.<sup>77</sup> In addition, the impact of novel therapeutics such as immunotherapies (eg, ICI, chimeric antigen receptor T-cell therapy, immunomodulatory agents) on endothelial function has yet to be investigated.

The harmful effects of cancer therapy-associated endothelial dysfunction and arterial stiffening on oxygen delivery may be compounded by the coexistence of hypertension, atherosclerosis, thrombosis, or vasospasm. Mechanistically, endothelial dysfunction denotes a state of endothelial activation characterized by vasoconstriction, inflammation, proliferation, coagulation, and thrombosis, while arterial stiffening can evoke similar vascular toxicities through disruptions in laminar blood flow and decreases in wall shear stress. Recent guideline documents, meta-analyses and systemic reviews report increased risks for systemic hypertension, atherosclerotic disease,<sup>80,81</sup> and/or arterial thrombosis<sup>81-83</sup> in cancer survivors treated with radiation therapy,<sup>84,85</sup> chemotherapy, immunotherapy,<sup>83,86</sup> proteasome inhibitors, hormone therapy,<sup>87</sup> and targeted therapies<sup>18,30,81,82,87,88</sup> compared with the general population (**Table 1**). Furthermore, cancer therapy-induced vascular dysfunction may facilitate the development of coronary artery vasospasm.<sup>18,30</sup> Classical examples include 5-fluorouracil and its oral prodrug capecitabine, as well as cisplatin, paclitaxel, gemcitabine, rituximab, sorafenib, nilotinib, and radiation therapy.<sup>18,30</sup> However, whether this phenomenon affects other vascular beds (ie, peripheral arteries) and compromises oxygen delivery and exercise tolerance needs clarification.

Beyond local pathologic vascular alterations, cardiovascular autonomic dysfunction has emerged as a particularly deleterious complication of chemotherapy and radiation.<sup>89</sup> It is not yet known if cancer therapies increase sympathetic outflow, which could compromise oxygen delivery during exercise by counteracting the protective inhibition of sympathetic vasoconstriction in exercising muscle (ie, functional sympatholysis).

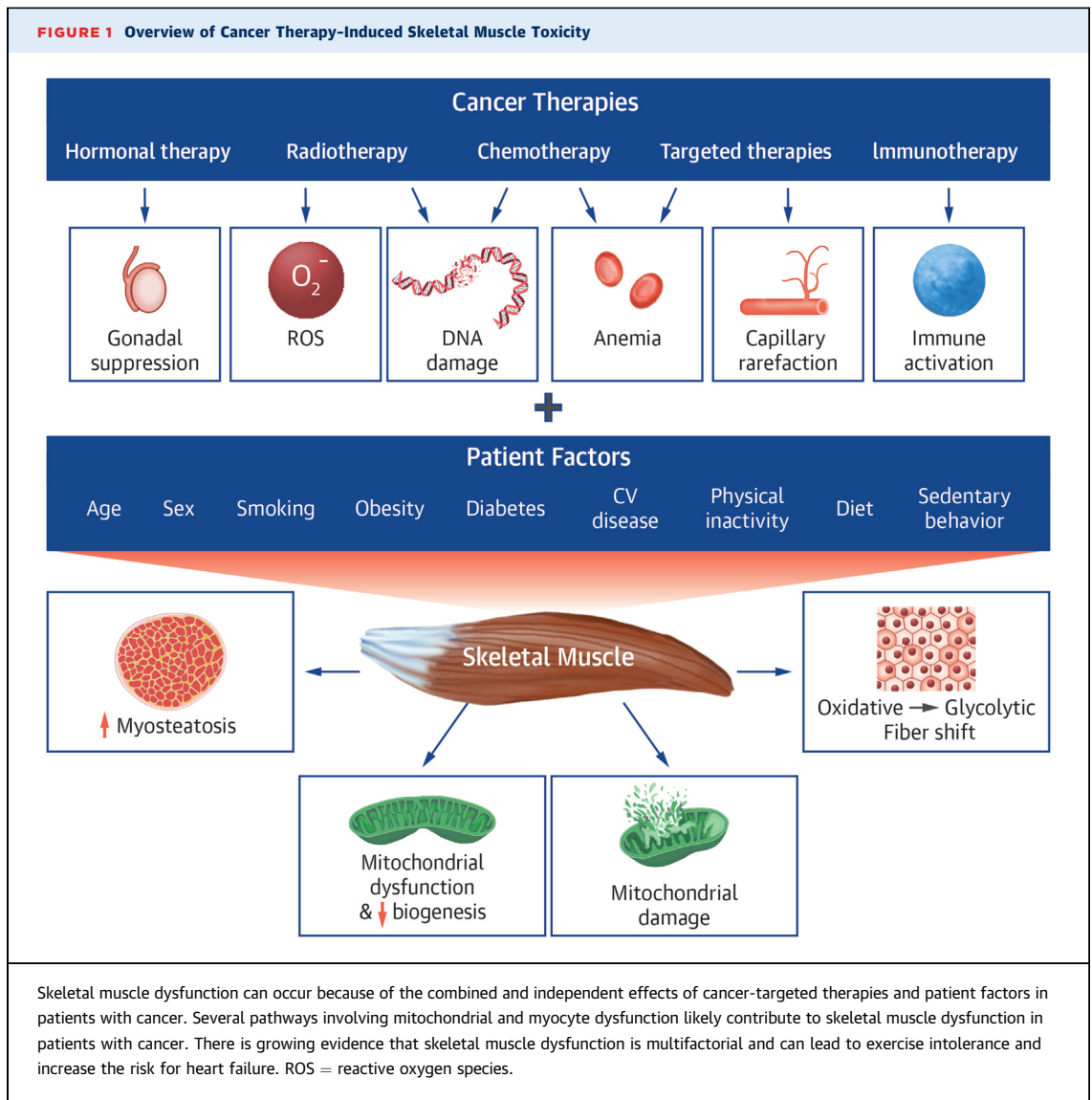
### DIFFUSION OF OXYGEN FROM CAPILLARIES TO MITOCHONDRIA AND CELLS AND METABOLISM

Oxygen diffusion from the microcirculation to the cells and mitochondria (where oxygen is the final electron acceptor in oxidative phosphorylation)

represents the final steps of oxygen use in skeletal muscle and tissues. The pressure gradient for oxygen between the capillary and cells, and the capacity for oxygen diffusion into skeletal muscle (muscle oxygen diffusive conductance [DMO<sub>2</sub>]) governs oxygen diffusion into tissues. Importantly, exercise intolerance in individuals with chronic cardiopulmonary disease is driven not solely by limited oxygen delivery. Exercise intolerance is also caused by impairment in skeletal muscle oxygen diffusion, secondary to pathologic reductions in hemoglobin levels, density of the skeletal muscle capillary network, and the oxidative capacity of skeletal muscle.<sup>17</sup>

A dysfunctional microvascular network resulting from cancer therapy may contribute to impaired DMO<sub>2</sub> by reducing the surface area for the diffusion of oxygen from red blood cells to the myocyte (**Central Illustration, Figure 1**).<sup>90</sup> Preclinical studies have shown that first-line (neo)adjuvant therapies for several tumor streams, including radiotherapy<sup>91</sup> anthracycline chemotherapy (eg, doxorubicin), but also emerging targeted therapies, including VEGFR TKIs and fusion proteins (eg, axitinib, aflibercept), cause microvascular rarefaction (ie, reduced density of the capillary network).<sup>92,93</sup> This reduction in capillarity has the flow-on effect of reducing the surface area for oxygen diffusion into skeletal muscle (and other cells) and contributes to tissue hypoxia. In the context of small molecule TKIs and fusion proteins that directly inhibit VEGFR and platelet-derived growth factor receptor signaling, capillary rarefaction results from accelerated microvascular endothelial cell death and endothelial dysfunction, which precipitates thrombosis and a further decrease in vascular perfusion and consequential microvessel destruction.<sup>93</sup> The mechanisms underlying anthracycline-induced capillary rarefaction are incompletely understood, but reports that VEGF-B gene therapy inhibits doxorubicin-induced capillary rarefaction suggest that similar antiangiogenic mechanisms may also contribute.<sup>94</sup> These findings are confirmed by studies of adult patients with cancer demonstrating that anthracycline-taxane-containing chemotherapy and VEGFR TKIs (eg, pazopanib, sunitinib, telatinib) and mAbs (eg, bevacizumab) provoke capillary rarefaction in the skeletal muscle<sup>95</sup> and skin,<sup>57,69,96,97</sup> respectively (**Table 1**).

Cancer therapies can also impair microvessel permeability and integrity (**Table 1**). Capillary leak syndrome is an example of this process and is characterized by capillary hyperpermeability to protein, resulting in edema, hemoconcentration, and hypoalbuminemia. The resultant reductions in local blood volume and increase in oxygen diffusion distance



may impair skeletal muscle perfusion and  $\text{DMO}_2$ . The pathogenesis of capillary leak syndrome remains unclear, but preclinical and clinical evidence suggests that it may be a consequence of poor endothelial integrity secondary to an increase in cytokines and up-regulation of angiotensin-2 and VEGF,<sup>98,99</sup> but it could also develop from direct toxicity of the anti-cancer agents on the capillary system.<sup>100</sup> Capillary leak syndrome is a common side effect of HCT and various cancer immunotherapies (eg, interleukin-2, interferon- $\alpha$ , chimeric antigen receptor T-cell therapy), with estimated incidences of 6.8% to 52.7%<sup>101</sup> and 11.8% to 85.5%,<sup>101-103</sup> respectively. Capillary leak syndrome has also been reported following exposure to select targeted therapies (eg, axitinib, bevacizumab, bortezomib, imatinib, rituximab,

trastuzumab) and all major classes of chemotherapeutics.<sup>101,103</sup> Currently, there is no targeted treatment for this syndrome, though emerging evidence suggests that tocilizumab, an interleukin-6 inhibitor, and dexamethasone may reduce the risk for cytokine release storm and consequently capillary leak syndrome.<sup>103</sup> Accordingly, deleterious effects of anti-cancer agents on microvascular integrity could persist long after treatment cessation, contributing to abnormal oxygen uptake in skeletal muscles.<sup>98,99</sup>

Despite the critical nature of skeletal muscle oxidative capacity for aerobic energy production, the impact of cancer therapy on skeletal muscle has received relatively scant attention in clinical studies. There is strong preclinical evidence that many common cancer therapies (most chemotherapies,

VEGF-targeted therapies, immunotherapy) can negatively affect skeletal muscle protein synthesis and oxidative capacity via increased reactive oxygen species production, long-term activation of proinflammatory pathways, and direct damage to mitochondria, sarcoplasmic reticulum, and contractile proteins.<sup>104</sup> Clinical studies of patients undergoing anthracycline- and/or taxane-based chemotherapy have shown skeletal muscle degradation,<sup>12,105</sup> reductions in high-energy phosphate metabolism,<sup>105</sup> decreased mitochondrial number and/or enzymes,<sup>95,106</sup> down-regulation in mitochondrial biogenesis and quality control pathways,<sup>82,107</sup> and a reduced proportion of the highly oxidative type I fibers<sup>95,106</sup> (Table 1). These could result in changes in oxygen metabolism in peripheral tissues, which could be compounded by additional toxicities due to anemia and venoarterial thrombosis. Moreover, a small study of colorectal cancer survivors undergoing capecitabine chemotherapy combined with radiation therapy coincided with a 20% reduction in  $\dot{V}_{O_2}$  peak (equivalent to 2 decades of age-related decline) and a 26% reduction in in vivo measures of muscle oxidative capacity (measured using phosphorous spectroscopy).<sup>108</sup> Similarly, a longitudinal study of patients with hematologic cancer undergoing allogeneic HCT reported a 7% reduction in exercise tolerance (measured by the 6-minute walk test) that was significantly correlated with a decline in muscle oxygenation ( $R^2 = 0.42$ ).<sup>109</sup>

Cancer therapy is also associated with increased fat infiltration in muscle between muscle fibers (termed myosteatosis) (Table 1). Myosteatosis may act as a barrier that impedes oxygen diffusion from capillary to muscle mitochondria. Several longitudinal studies have demonstrated that many chemotherapy regimens commonly used for breast and hematologic malignancies (often including an anthracycline, taxane, and/or platinum compound with or without radiotherapy and/or human epidermal growth factor receptor 2) are associated with increases in myosteatosis ranging from 2% to 28%.<sup>110-112</sup> Importantly, myosteatosis in anthracycline-treated cancer survivors was associated with reductions in  $\dot{V}_{O_2}$  peak ( $R^2 = 0.30-0.68$ ) and reduced gastrocnemius oxygen extraction during plantar flexion exercise.<sup>110,113</sup> Given the important regulatory functions of sex hormones on skeletal muscle, gonadal suppression related to chemotherapy, surgical intervention (eg, hysterectomy, oophorectomy) or pharmacologic hormonal therapy may also have an important impact on muscle composition and myosteatosis. Indeed, androgen

deprivation therapy for prostate cancer is associated with muscle atrophy (2%-4% reduction in lean body mass)<sup>114</sup> and increased myosteatosis (8%-19% increase),<sup>115,116</sup> with noticeable changes that can develop within 12 to 15 weeks of therapy. In women, surgically induced menopause from hysterectomy (with or without oophorectomy) is also associated with lower lean body mass (−0.9% to −1.5%),<sup>117</sup> likely due to marked and rapid declines in circulating estrogens and androgens. Although aromatase inhibitors are associated with significant myalgias and muscle weakness, there is no clear evidence that these symptoms are secondary to muscle atrophy or myosteatosis.<sup>118</sup> Similarly, selective estrogen receptor modulators (eg, tamoxifen) do not appear to induce adverse changes in muscle composition, and paradoxically, preclinical models<sup>119</sup> and early clinical studies<sup>120</sup> of Duchenne muscular dystrophy suggest that tamoxifen may have muscle protective effects (possibly due to an agonistic estrogen receptor effect in skeletal muscle).

## INTEGRATION OF THE OXYGEN PATHWAYS IN CARDIO-ONCOLOGY

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Although the field of cardio-oncology has traditionally sought to understand the complications of cancer therapy through a cardiac-centric lens, there is a clear need for a more integrative conceptualization. The oxygen pathway is an “in-series” system, whereby each step interacts with both preceding and subsequent steps. This means that focusing on only one step in isolation can lead to an underappreciation of the pathobiological causes of a patient’s limitations. Applications of this integrative approach<sup>121,122</sup> have provided important insights into the pathobiology of exercise limitations in patients with chronic thromboembolic pulmonary hypertension and heart failure with preserved ejection fraction, respectively. These studies revealed that most patients had defects in multiple steps of the oxygen pathway, and the traditional culprits of reduced oxygen delivery (ie, cardiopulmonary dysfunction) explained a modest degree of impairment in exercise performance. Consequently, a clearer understanding of the multifactorial causes of cardiotoxicity and exercise intolerance in cancer survivors may require a similar integrative approach to patient assessment and therapeutic strategies. For instance, emerging evidence highlights the presence and contribution of altered ventricular-arterial coupling to cardiotoxicity in chemotherapy-treated cancer survivors.<sup>123</sup>

Similarly, there is a growing understanding that coronary microvascular dysfunction and/or rarefaction related to chemotherapy, chest-targeted radiation and VEGF-targeted therapies may contribute to cardiotoxicity and heart failure.<sup>30</sup>

Evidence from heart failure populations suggests that skeletal muscle plays a role in cardiovascular dysfunction, disability, and clinical outcomes. For example, the effects of chronic inflammation and oxidative stress seen among patients with heart failure are thought to up-regulate the skeletal muscle metaboreflex (ergo- and mechanoreflex).<sup>124</sup> The metaboreflex refers to the neural reflex system that senses changes in local mechanical and metabolites to aid in the regulation and matching muscle blood flow to metabolic demands.<sup>124</sup> Excessive activation of this reflex, which has been reported in individuals with heart failure, results in increases in sympathetic nerve activity and increased systemic vascular resistance that contributes to increased symptoms of breathlessness and, chronically, might also drive subsequent cardiovascular dysfunction.<sup>125</sup> Importantly, the evidence highlighted in the preceding sections suggests that these same pathophysiologic processes may also be at play in the cancer setting. Moreover skeletal muscle alterations associated with cancer and cancer therapy, such as reduced muscle mass and/or increased myosteatosis, are emerging as important predictors of frailty, rehospitalization, and mortality in patients with heart failure.<sup>126</sup> A similar association has also been observed in cancer survivors, in whom measures of muscle mass and/or myosteatosis have been predictive of cardiotoxicity<sup>111</sup> and cancer-related and all-cause mortality.<sup>127</sup>

The integrative approach proposed in this review also highlights the need to understand the pathology of cardiotoxicity from a holistic viewpoint. Cardiotoxicity is likely a consequence of multiple hits to the cardiovascular system prior to, during, and following cancer therapy. In addition to the direct insults to the oxygen cascade induced by cancer therapy, there are numerous other processes (beyond the cardiotoxic agents) contributing to dysfunction. Just as in heart failure, this likely reflects the additional direct and indirect insults from cardiovascular risk factors including age, sex, physical inactivity, sedentary behavior, obesity, hypertension, smoking status, and diet, as well as biological processes such as chronic inflammation, oxidative stress, and gonadal/ovarian suppression that could be accelerated by cancer, its treatment (eg, androgen deprivation therapy), and additional risk factors.

## FUTURE DIRECTIONS AND CLINICAL IMPLICATIONS

**IDENTIFICATION OF EXERCISE INTOLERANCE AND ITS PHYSIOLOGICAL UNDERPINNINGS.** An important clinical question is how best to identify those with or at risk for reduced exercise intolerance across the cancer treatment and survivorship continuum (Table 2). The current approach to assess functional capacity from an oncology perspective is to evaluate performance status using the Karnofsky performance status and Eastern Cooperative Oncology Group scales. Although this approach is routinely used in contemporary clinical practice, the utility of these scales is limited to identifying those patients with severe impairment.<sup>128</sup> Thus, given that the impact of functional status is an important predictor of survival in patients with cancer, more accurate quantification of functional status in at-risk populations is warranted. The current gold-standard approach to measure exercise tolerance is cardiopulmonary exercise testing with gas exchange measurement to directly quantify  $\text{V}_{\text{O}_2\text{peak}}$ . If not feasible, alternative assessments such as a graded exercise test (estimating  $\text{V}_{\text{O}_2\text{peak}}$ ) or a 6-minute walk test can provide more accessible but less sensitive measures of exercise capacity. The growing use of wearable smart technology that captures measures of exercise performance (eg, walking speed, physical activity) alongside physiological measures (eg, resting and exercise heart rate) may be an untapped resource to understand temporal changes in exercise capacity, functional performance, and disease risk on a large scale.<sup>129,130</sup> Regardless, these methods may identify the presence of exercise intolerance but alone are unable to provide a clear diagnosis as to the unique defects in the oxygen pathway contributing to this. Given that the symptoms of exercise intolerance occur during exertion, reliance on resting or nonexercise measures of cardiac, vascular, and pulmonary function also may provide limited insight. The combination of cardiopulmonary exercise testing, to quantify  $\text{V}_{\text{O}_2\text{peak}}$  and respiratory limitations with concurrent measurements of hemodynamic and blood gases is a promising approach for the integrative evaluation of individual and combined oxygen pathway defects.<sup>121,122</sup> Combining cardiopulmonary exercise testing with echocardiographic measures of cardiac output allows the assessment of the Fick determinants of oxygen consumption (cardiac output and subsequent back-calculation of arteriovenous oxygen difference), and this may be more scalable approach that has been applied in the assessment of

**TABLE 2 Proposed Therapies to Modify Noncardiac and Peripheral Function and Improve Peak Oxygen Uptake**

Therapy	Potential Mechanisms
Exercise training (aerobic ± resistance training)	Diffusive oxygen loading: improved respiratory muscle strength and increased V/Q matching. <sup>162-165</sup> Convective oxygen delivery: reduced inflammation and oxidative stress, <sup>162</sup> increased nitric oxide availability, <sup>162,163</sup> decreased sympathetic nerve activity contributing to decreased vascular resistance, <sup>163,165</sup> increased arterial compliance, <sup>163</sup> improved peripheral vasodilation. <sup>163</sup> Diffusive oxygen conductance and oxidative metabolism: increased capillarity, <sup>162,163,166</sup> improved microvascular function, <sup>162,163,166</sup> increased proportion of oxidative muscle fibers, <sup>162</sup> decreased myosteatosis, increased mitochondrial number and oxidative enzymes. <sup>162</sup>
Physical activity and sedentary behavior reduction (wearable activity trackers ± behavioral counseling)	Convective oxygen delivery: improved endothelial function, decreased vascular stiffness, improved peripheral vasodilation. <sup>167</sup> Diffusive oxygen conductance and oxidative metabolism: improved microvascular function and oxidative enzymes. <sup>168,169</sup>
Diet (eg, diet quality, consumption of unsaturated fatty acids, supplementation, caloric restriction)	Convective oxygen delivery: decreased inflammation and oxidative stress, and improved nitric oxide bioavailability resulting in decreased vascular resistance, increased arterial compliance, improved peripheral vasodilation. <sup>170</sup> Diffusive oxygen conductance and oxidative metabolism: improved microvascular function, decreased myosteatosis and intramuscular triglyceride content. <sup>171</sup>
Sodium-glucose transport protein 2 inhibitors	Convective oxygen delivery: decreased vascular stiffness, increased arterial compliance, improved peripheral vasodilation. <sup>172,173</sup> Diffusive oxygen conductance and oxidative metabolism: preferential fatty acid oxidation for substrate utilization. <sup>174</sup>
Iron supplementation/blood transfusion	Convective oxygen delivery and diffusive oxygen conductance: increased hemoglobin and affects cellular oxygen storage and metabolism in cardiomyocytes and skeletal muscle. <sup>175,176</sup>
PDE5 inhibitors	Diffusive oxygen loading and convective oxygen delivery: inhibition of PDE3, PDE4, and PDE5 preventing cGMP or cAMP degradation increasing their levels in smooth muscle cells causing vasodilation. <sup>177</sup>
Inorganic nitrates	Convective oxygen delivery and diffusive oxygen conductance: vasodilator, improved mitochondrial energetics, protection against oxidative damage and activation of cyclic guanosine monophosphate. <sup>178</sup>
Elamipretide	Diffusive oxygen conductance and oxidative metabolism: decreased mitochondrial reactive oxygen species generation and improved ATP production. <sup>179</sup>

ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; PDE = phosphodiesterase; V/Q = ventilation/perfusion.

the overarching central and peripheral factors contributing to unexplained dyspnea and heart failure.

A limitation of these approaches is that because of the necessary expertise and equipment, these assessments may not be feasible at all centers. Furthermore, in a setting in which fatigue and shortness of breath are common side effects of treatment, further work is needed to understand which patients may benefit the most from these time- and labor-intensive approaches. Moreover, validated thresholds are needed to better classify the presence of central vs peripheral limitations. Technological advances in bioinformatics, multiomics, and machine learning are making it increasingly possible to characterize the complex molecular changes that underlie the acute and chronic responses to exercise. Indeed, recent findings highlight the potential of this approach to identify particular phenotypes, whereby metabolomic exercise biomarker signatures have been found to be associated with cardiometabolic risk factors<sup>131,132</sup> and independently predict long-term CVD and mortality.<sup>133</sup> Whether these approaches can identify exercise intolerance and provide insight into the physiological underpinnings remains to be determined. Application of these approaches (and

their insights) in the cancer setting may be an additional pathway toward a personalized understanding of exercise limitations across the cancer treatment continuum.

**THERAPEUTIC STRATEGIES.** Therapeutic guidelines for the prevention and management of cancer treatment-induced CVD are focused on the use of standard pharmacotherapies (eg, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-adrenergic blockers, calcium-channel blockers, statins) for cancer treatment-induced CVD.<sup>5,87</sup> Although these approaches could address some steps in the oxygen cascade, such as convective oxygen delivery, the impact of cardiovascular pharmacotherapy on  $\text{V}_{\text{O}_2\text{peak}}$  or the individual components of the oxygen cascade in cancer survivors remains unclear. Modeling of the oxygen cascade in individuals with other forms of cardiovascular pathology has shown that correcting isolated defects in oxygen delivery (such as improving cardiac output and vascular conductance) without addressing other steps (such as impaired  $\text{DMO}_2$ ) limits improvement in exercise intolerance.<sup>121,122</sup> These findings highlight the importance of evaluating alternative therapies (such as sodium-glucose transport protein 2



<b>TABLE 3 Future Directions</b>
<p>Dynamics of and populations at risk for exercise intolerance</p> <ul style="list-style-type: none"> <li>• Broader use of direct measures of exercise tolerance in clinical trials and cohort studies.</li> <li>• Determine accuracy of wearable technology to capture changes in exercise tolerance during and following cancer therapy.</li> </ul>
<p>Physiological mechanisms underlying exercise intolerance</p> <ul style="list-style-type: none"> <li>• Characterizing the impact of cancer therapy on oxygen cascade combining exercise testing with imaging, metabolic gas exchange, or hemodynamic assessment (eg, exercise stress, CPET, right heart catheterization, heart rhythm monitoring).</li> <li>• Comprehensive assessment of exercise tolerance and clinical and physiological measures of pulmonary, cardiac, vascular, hematologic, and skeletal muscle parameters.</li> <li>• Use of bioinformatics and multiomics to determine molecular signature of toxicities and exercise intolerance phenotypes.</li> </ul>
<p>Therapeutic strategies</p> <ul style="list-style-type: none"> <li>• Understand the impact of current cardiovascular pharmacotherapy on noncardiac drivers of exercise intolerance.</li> <li>• Evaluate the effects of periphery-targeted therapeutics on exercise tolerance and the oxygen cascade.</li> <li>• Assess the potential benefits of systemic therapies targeting multiple steps of the oxygen cascade (eg, exercise ± nutrition).</li> </ul>
<p>CPET = cardiopulmonary exercise testing.</p>

inhibitors, phosphodiesterase 5 inhibitors, inorganic nitrates, and elamipretide) that may be able to target these less considered toxicities induced by cancer treatment (Table 2). Indeed, sodium-glucose transport protein 2 inhibitors have shown promising results in terms of improving cardiovascular outcomes in patients with cancer<sup>134</sup> and exercise tolerance in some patients with heart failure,<sup>135,136</sup> though the mechanisms of benefit are unclear, and there is currently limited evidence of therapeutic effectiveness for cancer survivors. The lack of evidence for effective therapies to improve exercise tolerance is an area of research that requires urgent attention. Furthermore, addressing these systemic effects through pharmacotherapy alone introduces challenges from the perspective of polypharmacy and economic burden to the individual and health care system. Consequently, lower cost approaches that have the capacity to address multiple defects such as exercise training, physical activity, and dietary interventions may also be worth investigating. Indeed, structured exercise training is considered a cornerstone for improving  $\text{V}_{\text{O}_2\text{peak}}$  across the continuum of both CVD and cancer,<sup>137</sup> with a meta-analysis of 48 randomized controlled trials (encompassing 3,632 patients with cancer) demonstrating a clinically meaningful improvement in  $\text{V}_{\text{O}_2\text{peak}}$  (2.13 mL/kg/min) with structured aerobic with or without resistance exercise training compared with usual care.<sup>138</sup> A key feature of exercise training (defined as planned, structured, and purposeful movement of moderate intensity or

greater at a sufficient volume or dose to improve physical fitness) is its ability to systemically target multiple steps in the oxygen cascade, including one of the few efficacious strategies for targeting the microvasculature and skeletal muscle (Table 2). For example, Mijwel et al<sup>95</sup> demonstrated that 16 weeks of moderate- to high-intensity aerobic exercise with or without resistance training during anthracycline-paclitaxel chemotherapy prevented reductions in skeletal muscle capillarity, mitochondrial content, muscle fiber area, and the proportion of oxidative muscle fibers. Similarly, 12 months of combined progressive aerobic and resistance training markedly improved  $\text{V}_{\text{O}_2\text{peak}}$  (+3.5 mL/kg/min) and cardiac output (increasing convective oxygen delivery) in women undergoing treatment for breast cancer.<sup>137</sup> The optimal exercise dose and modality to address deficits in the oxygen pathway are unclear, with very few studies directly comparing aerobic exercise with resistance exercise and evaluating relevant outcomes. In studies evaluating resistance training alone during anticancer treatment, it was shown to favorably affect body composition (increasing lean mass and decreasing fat mass) and to improve strength.<sup>139</sup> Whether these benefits translate to improvements in skeletal muscle diffusion capacity and intracellular oxidative function remains to be determined and is an important area for future research (Table 3). Alternatively, physical activity interventions (focused on increasing general daily activity and reducing sedentary time) are another approach to improving cardiometabolic health that may counter the acceleration of peripheral toxicity induced by sedentary behavior during and after cancer therapy. Indeed, a meta-analysis of 35 randomized controlled trials investigating the impact of physical activity interventions using wearable technology (pedometers and/or physical activity monitors such as Fitbits) with or without behavioral counseling in cancer survivors demonstrated moderate to large effects on the weekly volume of total (standardized mean difference [SMD] = 0.62) and moderate to vigorous physical activity (SMD = 0.61) and increases in cardiorespiratory fitness (SMD = 0.51).<sup>140</sup> However, the mechanisms in the oxygen pathway mediating this improvement are yet to be established. Although the direct impact of dietary interventions on  $\text{V}_{\text{O}_2\text{peak}}$  remains unclear, strategies such as caloric restriction, time-restricted feeding, increased diet quality (eg, Mediterranean diet, Dietary Approaches to Stop Hypertension diet) or more targeted supplementation (eg, inorganic nitrates<sup>141</sup>) may help address factors such as ectopic fat accumulation, chronic inflammation, and oxidative

stress that contribute to the underlying peripheral toxicities.

## CONCLUSIONS

Exercise intolerance is an important, but underappreciated marker of the increased cardiovascular risk and functional limitations experienced by cancer survivors. Traditionally, impairments in  $\text{V}_{\text{O}_2\text{peak}}$  are attributed to cardiac limitations, but there is growing evidence that current and emerging cancer therapy induce substantial impairment on the noncardiac components of oxygen uptake, delivery, and use. Improving our understanding of and appreciation for these noncardiac effects may yield critical insights necessary for targeted, multifaceted diagnostic and therapeutic strategies necessary to address functional limitation and adverse cardiovascular outcomes in this complex population.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Cancer therapy related peripheral toxicities in cardio-oncology are routinely considered as contributors to patient CVD risk.

**TRANSLATIONAL OUTLOOK:** Treating the effects of cancer therapy on the periphery could lower the future risk of CVD and improve cancer survivorship.

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