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Determinants of Impaired Peak Oxygen Uptake in Breast Cancer Survivors: *JACC: CardioOncology* Primer

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Although breast cancer (BC) survivors experience excellent cancer-specific survival outcomes, a common feature across the survivorship continuum is reduced exercise tolerance, which can be measured objectively as decreased peak oxygen uptake (VO_2peak) during whole-body exercise, and is linked to functional disability and decreased survival.[1] This primer summarizes current evidence regarding the physiological mechanisms along the O_2 cascade that are responsible for the lower VO_2peak in women with BC (**Figure 1**). In accordance with the Fick equation, VO_2peak is determined by the product of cardiac output (CO) and the arteriovenous O_2 difference (a-vO_2diff). Consequently, VO_2peak limitations can be separated into factors governing O_2 delivery from the lung to skeletal muscle (eg, arterial O_2 saturation, hemoglobin, CO) and factors governing O_2 diffusion and utilization within the skeletal muscle (eg, muscle composition, capillarity, and oxidative capacity). An understanding of which factors influence exercise intolerance in BC survivors is critical to guiding targeted therapies to address this impairment.

VO_2PEAK IN BC SURVIVORS: ROLE OF O_2 DELIVERY

Decreased O_2 delivery is a contributor to decreased VO_2peak in BC survivors.[1] An important step governing O_2 delivery is the transfer of O_2 from the lung to the circulation where it is transported, primarily bound to hemoglobin. Studies assessing hemoglobin and peak exercise arterial O_2 saturation in long-term BC survivors post-adjuvant therapy (n = 16-17; ≥12 months post-chemotherapy) have shown they are both comparable to healthy age-matched non-cancer control subjects or pretreatment values (**Figure 1**) and as such, likely do not explain the persistent impairment in VO_2peak.[2,3] Several studies have assessed the contribution of impaired peak exercise cardiac function to decreased VO_2peak in BC survivors (n = 9-49) vs healthy controls (n = 9-23).[2-7] These studies have utilized several techniques including exercise cardiac magnetic resonance imaging (ExCMR),[2,3,5] exercise echocardiography,[4,6] acetylene rebreathe,[4] and impedance cardiography.[3,7] As shown in **Figure 1**, the decreased VO_2peak reported in these studies (5% to 33% lower than control subjects) is clearly associated with a decreased peak exercise CO (7% to 17% lower).[2-7] Notably, all studies consistently reported that peak exercise heart rate is comparable to control subjects, highlighting that the attenuated peak exercise CO is primarily driven by a smaller stroke volume (SV)—which on average is 11% to 19% lower than the control values.[2-7] This is further supported by the longitudinal study of Foulkes et al[2] (n = 17), which showed a

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ABBREVIATIONS AND ACRONYMS

a-vO_2diff = arteriovenous oxygen difference

BC = breast cancer

CO = cardiac output

ExCMR = exercise cardiac magnetic resonance imaging

GLS = global longitudinal strain

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

SV = stroke volume

VO_2peak = peak oxygen uptake

progressive reduction in peak exercise CO and SV over the 12 months following anthracycline chemotherapy (−13% and −14% lower than baseline values, respectively). These data provide an important link showing persistently decreased VO_2peak in BC survivors is partly driven by decreased peak cardiac function.

The mechanisms underpinning the decreased exercise SV exhibited by BC survivors may be driven by a combination of factors including impairments in myocardial contractility, increased left ventricular and vascular stiffness (afterload), and decreased ventricular size. Augmentation in contractility is 1 key factor for driving an increase in SV during exercise. Comprehensive ExCMR imaging evaluations have shown that BC survivors (n = 16) have decreased peak exercise left ventricular global longitudinal strain (GLS) and/or ejection fraction (LVEF) responses vs matched control subjects.[3,8] Moreover, Kirkham et al[3] showed that peak exercise GLS (R^2 = 0.69) and LVEF (R^2 = 0.30) were significantly correlated with VO_2peak in anthracycline-treated BC survivors (n = 16) >12 months post-therapy. Similarly, the longitudinal study of Foulkes et al[2] reported that the progressive impairment in VO_2peak and peak exercise SV over a 12-month period following anthracycline-based chemotherapy coincided with a progressive reduction in peak LVEF. The impaired GLS and LVEF responses may be indicative of decreased intrinsic contractility, but may also be related to increased afterload. Several cross-sectional studies of BC survivors assessed >12 months post-therapy (n = 9-16)[3,4] have shown systemic vascular resistance is 11% to 25% higher compared with age-matched, non-cancer control subjects (**Figure 1**).

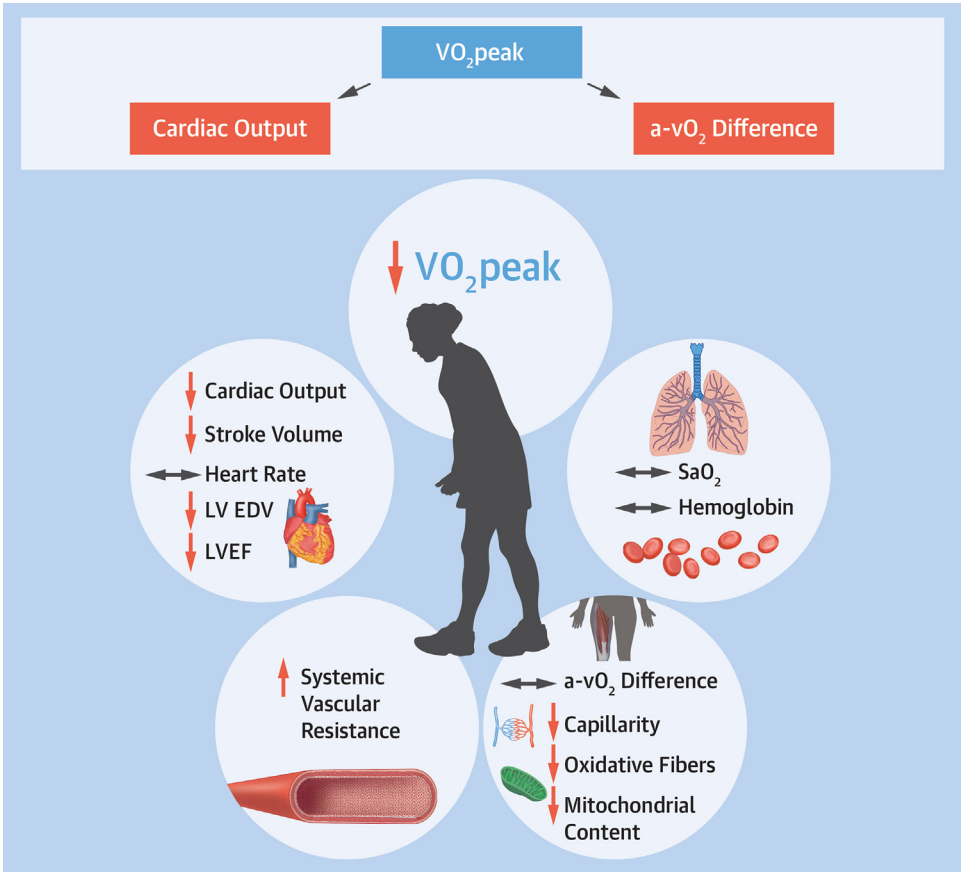
Decreased VO_2peak and CO in BC survivors may also be related to having smaller, stiffer hearts. Indeed, a smaller ventricle has a reduced absolute capacity (at rest or during exercise) and a decreased ability to augment function during exercise. In a cross-sectional study of 185 middle-to-older aged females, Foulkes et al[9] demonstrated that females with the smallest hearts (classified as the lowest quartile for resting left ventricular [LV] end-diastolic volume [LVEDV]) had the lowest VO_2peak and peak CO (measured by ExCMR), which was secondary to a decreased resting and peak exercise SV, as well as a blunted ability to decrease end-systolic volume during exercise. As highlighted in **Figure 1**, the ventricular size for BC survivors (n = 16-29) is significantly smaller than seen in non-cancer control subjects (10% to 15% smaller as determined by resting LVEDV).[2,3,5] Notably, in addition to having smaller LVEDV, Beaudry et al[4] showed that older long-term BC survivors (n = 9; mean age: 67 years, mean time post-anthracycline chemotherapy: 9.8 years) have increased LV stiffness during submaximal exercise (as measured by E/e'-to-LVEDV ratio, an indirect surrogate of LV stiffness), which was 15% higher than age-matched non-cancer control subjects (n = 9). The increased LV stiffness may be partly a consequence of the myocardial injury and fibrosis associated with BC treatments such as anthracycline-based chemotherapy. Indeed, in a series of ExCMR studies, Kirkham et al[3,8] showed that anthracycline-treated BC survivors (n = 16; 12 ± 5 months postchemotherapy) have increased myocardial T_1 times (a measure of myocardial fibrosis) compared with control subjects (n = 16), which was a significant predictor of VO_2peak (R^2 = 0.64). The relationship between myocardial T_1 times and VO_2peak was partly mediated by a blunted ability to decrease end-systolic volume and augment CO during exercise.[3] Taken together, increased vascular stiffness may be an important contributor to the reduced O_2 delivery underlying reduced VO_2peak in BC survivors.

The degree to which the negative cardiac alterations described in the preceding text is a direct effect of BC therapy as opposed to indirect injury caused by sedentary deconditioning remains an important question. Interestingly, Grigoriadis et al[6] reported comparable values for VO_2peak and exercise cardiac function between BC survivors (n = 23) and non-cancer control subjects (n = 23). However, physical activity levels were also comparable between groups (and exceeded the current physical activity guidelines), and VO_2peak levels of the BC group were 7% to 62% higher than other studies.[2-4,7] This suggests that physical activity and/or regular exercise may be an important factor mediating VO_2peak and cardiac function impairment in BC survivors. This is also supported by the findings of Kirkham et al[8] that showed that anthracycline-treated BC survivors (n = 4) with normal

HIGHLIGHTS

- Exercise intolerance is common among breast cancer survivors.
- Exercise intolerance in breast cancer survivors is related to cardiac, vascular, and skeletal muscle impairments.
- Holistic rehabilitation or pharmacological therapies are needed to address these impairments.

FIGURE 1 **Determinants of Reduced VO_2peak in BC Survivors**



↑ indicates significantly increased; ↓ indicates significantly decreased; ↔ indicates no significant difference vs healthy controls or pre-chemotherapy values in studies that assessed VO_2peak determinants in breast cancer (BC) survivors.[2-7,11] a-vO_2 difference = arteriovenous oxygen content difference; LV EDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; SaO_2 = arterial oxygen saturation; VO_2peak = peak oxygen uptake.

VO_2peak (defined as VO_2peak ≥100% of age-predicted values) had comparable myocardial T_1 times, VO_2peak, and peak CO compared with age-matched non-cancer control subjects with normal VO_2peak (n = 10). More conclusive evidence linking exercise to alterations in VO_2peak and cardiac function with BC therapy comes from the BREXIT (BReast cancer Exercise InTervention) trial (N = 104),[10] in which 12 months of exercise training over the course of (neo)adjuvant BC therapy resulted in improvement in VO_2peak and peak exercise CO, SV, and LVEF.

VO_2peak IN BC: ROLE OF O_2 UTILIZATION

No studies have reported a significant reduction in a-vO_2diff in BC survivors vs control subjects (Figure 1). However, it should be noted that the assessment of the a-vO_2diff is technically challenging and was indirectly calculated in all of these studies from CO and VO_2peak measures.[3,4,6,7] As such, these results require confirmation from studies utilizing direct assessment of arterial and venous O_2 content with invasive measures. Regardless, one should not assume that VO_2peak in BC survivors is not limited by peripheral factors as the finding that the peak exercise a-vO_2diff is similar between BC and non-cancer control subjects despite a lower CO (which allows greater time for skeletal muscle O_2 extraction) suggests that skeletal muscle abnormalities may also contribute to the reduced VO_2peak. Indeed, the few studies performed to-date have demonstrated that BC survivors (n = 10-16) have greater myosteatosis (increased thigh intermuscular fat to skeletal muscle ratio),[3] and experience decreases in vastus lateralis type I (oxidative) fibers, capillary rarefaction and reduced mitochondrial content over the course of

chemotherapy (Figure 1).[11] Moreover, increased thigh myosteatosis was associated with decreased VO_2peak ($R^2 = 0.68$).[3] Taken together, this indicates skeletal muscle and its vasculature may also be an important target of therapy to attenuate the decline during BC therapy or to improve VO_2peak after BC therapy.

KNOWLEDGE GAPS AND RECOMMENDATIONS FOR FUTURE RESEARCH

The few studies that have examined the mechanisms of exercise intolerance have primarily focused on middle-aged women with BC during or in the short-term period (<5 years) post-adjuvant therapy. Therefore, future research should focus on: 1) understanding the pathophysiology of exercise intolerance along the BC survivorship continuum (eg, before, during, and after therapy) with special emphasis on older BC survivors who are at the greatest risk of developing and dying from cardiovascular disease—in particular heart failure; 2) identify novel targeted therapies that incorporate transdisciplinary lifestyle interventions (across the spectrum from reducing sedentary behavior, increasing physical activity through to participating in structured multimodal cardio-oncology rehabilitation) to mitigate fatigue, or prevent a decline in VO_2peak, physical function, and quality of life while reducing cardiovascular disease risk; and 3) standardizing an approach to the assessment of the mechanisms underlying reduced VO_2peak in BC survivors. Importantly, there is growing awareness that skeletal muscle structural and mitochondrial defects may be an important therapeutic target—particularly for the long-term, older, and/or frail BC survivor for whom cardiac defects may be harder to address with traditional rehabilitation programs or pharmacotherapy. As such, the efficacy of muscle or mitochondrial targeted therapies such as resistance training or emerging pharmacotherapies (glucagon-like peptide receptor agonists; sodium-glucose cotransporter-2 inhibitors) is an important area for future research. There is also interest in assessment approaches that combine VO_2peak and noninvasive imaging (eg, combining cardiopulmonary exercise testing with stress echocardiography or ExCMR) to provide insights into "cardiac" and "extracardiac" mechanisms underlying reduced VO_2peak. Importantly, ExCMR has the added advantage that it allows for the assessment of several potential mechanisms including structural and functional measures of cardiac, vascular, and skeletal muscle factors underpinning VO_2peak with excellent precision. It should also be noted that the majority of studies have a primary focus on anthracycline-treated BC survivors. As such, there is also a need for studies focused on unravelling the individual and additive impact of other BC therapies (non-anthracycline-based chemotherapies, human epidermal growth factor receptor-2-targeted therapies, and chest-directed radiation) on VO_2peak and the components of the O_2 cascade.

CONCLUSIONS

Exercise intolerance is a primary feature in women with BC across the survivorship continuum. The mechanisms underpinning the reduced VO_2peak are not completely understood; however, both cardiac and noncardiac factors appear to be important contributors. Future studies are required to examine the mechanisms of exercise intolerance before, during, and in the short- to long-term after completing (neo) adjuvant therapy, and the role of lifestyle interventions to mitigate or prevent exercise intolerance and reduce cardiovascular disease (and heart failure) risk with a particular focus on older long-term BC survivors.

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