LITERATURE REVIEW

The mechanisms responsible for exercise intolerance in early-stage breast cancer: What role does chemotherapy play?

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KEYWORDS
breast cancer; cardiomyopathy; cardiotoxicity; chemotherapy; exercise tolerance

Abstract In this narrative review of the literature, we discuss the influence of chemotherapy treatment on peak aerobic power (VO2peak) for women with breast cancer and the mechanisms for exercise intolerance. In specific, we examine the central, peripheral, and oxygen transport mechanisms responsible for exercise intolerance in women living with breast cancer. Our findings indicate that reduced ventricular contractility, reduced left ventricular (LV) compliance, and increased afterload are (in part) responsible for exercise intolerance secondary to chemotherapy treatment. It appears that changes in central haemodynamics and morphology often occur preceding clinical diagnosis of cardiotoxicity (LV ejection fraction <55%), which explain the attenuated exercise tolerance for this population. Patients with breast cancer are unable to make use of the Frank-Starling mechanism to increase stroke volume in response to an increase in end-diastolic volume. They may be able to increase preload during exercise conditions; however, reduced LV filling mechanics (in part due to an increase in pericardial restraint) and decreased contractile reserve may ultimately contribute to a reduced exercise tolerance for women with breast cancer. Recent evidence indicates that peripheral maladaptations and alterations in haemoglobin concentration are additional mechanisms that may limit VO2peak and exercise tolerance in patients with breast cancer.

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Introduction

Breast cancer is the leading cause of death and the most common form of cancer amongst women worldwide. In 2008, the International Agency for Research on Cancer estimated that there were approximately 1.38 million women diagnosed with breast cancer worldwide accounting
for approximately 23% of all diagnoses of cancer [1]. With advancement in treatment methodologies and improvements in early detection, approximately 89% of women survive up to 5 years following treatment cessation [2]. With improvements in survivorship (i.e., the period from diagnosis to the end of life), more individuals are at higher risk of age-related co-morbidities (most survivors are over the age of 65), disease sequelae, and cytotoxic ailments associated with treatment [3].

Treatment for early-stage breast cancer is focused on cure and prevention of relapse of disease and usually consists of chemotherapy, radiation, endocrine, human epidermal growth factor receptor 2 (HER2)-targeted therapies or a combination of these treatments. Emerging evidence suggests that molecular targets of cancer therapies are not tissue specific and may result in significant myocardial tissue and vascular injury. Traditionally, chemotherapy-induced cardiotoxicity is associated with left ventricular (LV) dysfunction leading to progressive heart failure (HF) with changes in diastolic and systolic function. Cardiotoxicity is often defined as a reduction in LV ejection fraction (LVEF) of at least 5% from baseline to less than 55% with signs or symptoms of congestive HF, or an asymptomatic decline in LVEF of at least 10% from baseline to below 55% [4]. Across the cancer trajectory, there is a profound reduction in exercise tolerance (particularly during chemotherapy) [5]. However, resting LVEF and other resting indices of LV function have been shown to correlate poorly with exercise tolerance and not all women present with impaired LVEF during and following treatment [6,7]. It has been argued that the lack of relationship between resting indices of cardiac function and exercise tolerance suggests that other myocardial morphological changes or peripheral factors are major determinants of exercise tolerance in women with breast cancer. However, resting indices of cardiac function are also poor predictors of exercise cardiac function. As such, exercise measures of cardiac function are evaluated to more clearly determine the relationship with exercise intolerance in breast cancer (similar to other chronic conditions) [8].

Peak aerobic power (VO2peak) is the gold standard for assessing cardiovascular fitness and is a significant independent predictor of overall health and survival in individuals with cancer [9,10]. In specific, VO2peak has been shown to predict chemotherapy-induced LV dysfunction and predict cardiovascular disease (CVD) risk factors (e.g., blood pressure, lipid profile, C-reactive protein) for individuals with cancer [11,12]. The VO2peak for individuals with a history of breast cancer is consistently 30% below that of age- and gender-matched inactive individuals without a history of breast cancer [13]. This research is compelling, because VO2peak is an indication of overall well being and a minimal threshold of VO2peak has been established for functional independence (i.e., 15.4 mL/kg/min for women) [9]. Many individuals with breast cancer are at an increased risk of functional dependence and reduced health status. Therefore, it is important to consider those factors that limit VO2peak. In patients with breast cancer in order to gain a complete understanding of the disease and its available treatment options. According to the Fick equation, limitations in VO2peak contribute to a reduction in cardiac output (Q) or arteriovenous oxygen difference and their respective determinants. The arteriovenous oxygen difference is often considered classically as a peripheral determinant of oxygen consumption. However, the central determinants of oxygen consumption are generally related to oxygen transport, which is a product of the oxygen-carrying capacity of blood and Q. More recent studies have also examined the molecular mechanisms by which central oxygen delivery and peripheral oxygen utilization may be affected by chemotherapy. Accordingly, in this current narrative review, we examine the underlying central, peripheral, and molecular mechanisms that contribute to a reduction in VO2peak. Values and exercise intolerance in women with breast cancer.

Cytotoxic treatments

Some of the most active agents used in traditional chemotherapy treatment are anthracyclines, such as doxorubicin and epirubicin [14]. Trastuzumab (Herceptin), a recombinant DNA-derived humanized monoclonal antibody targeting the proto-oncogene in HER2/neu cancer cells, is a newly recognized drug used in the treatment of early-stage breast cancer. Bevacizumab, the newest cytotoxic agent, and other tyrosine kinase inhibitors attenuate tumour growth by inhibiting angiogenesis. Despite their clinical efficiency, these drugs have been associated with cardiac and vascular injury leading to adverse cardiac events [15–19].

Anthracyclines

Anthracyclines are active agents used for the treatment of breast cancer; however, their clinical use is limited due to the toxicity profile of the myocardial tissue. The molecular mechanisms responsible for the antitumour effects of anthracycline treatment are different from those responsible for their cardiotoxic effects. They diffuse across the cellular membrane and are responsible for DNA and RNA interactions, resulting in inhibition of DNA and RNA synthesis, which ultimately induces cell death [20,21]. Anthracycline-mediated cell death of tumour cells is linked to the activation of apoptosis signal-transduction pathways through intrinsic and extrinsic activation of caspases, a common death effector molecule [22]. The tumour necrosis factor-α and CD45 are key signal pathways that are responsible for recruitment of adaptor molecules, such as Fas-associated protein with death domain that is responsible for caspase activation, subsequently inducing cell death. Conventionally, anthracyclines also converge on the mitochondria, thereby increasing permeabilization and induction of intrinsic apoptotic pathways. This leads to a mitochondrial release of cytochrome c, increased activation of tumour suppressor p53, and pro-apoptotic Bcl-2 family of proteins BAD and BAX [23]. Sequentially, there is an influx in cellular reactive oxygen species (ROS) and alcohol metabolites [24], which exacerbates mitochondrial DNA damage, subsequently impairing the function of the electron-transport chain, reducing adenosine triphosphate (ATP) synthesis, and altering calcium and iron homeostasis in myocardial tissues [25]. Specifically, oxidative stress initiates mitochondrial permeability leading to alterations in mitochondrial calcium transport. As a result, tissue injury
and impaired cardiac contraction may occur, which causes an irreversible reduction in mitochondrial calcium-loading capacity [26].

 Anthracycline-induced cardiotoxicity, in part contributed to an increase in ROS production, ultimately altering myocardial function and integrity [27]. Oxidative stress leads to damage of the cardiomyocytes, altering their structure and arrangement in series resulting in myocardial remodelling [28]. This can result in LV eccentric remodelling, decreased LV wall thickness, and impaired LV compliance. Moreover, anthracycline therapy contributes to altered homeostasis of energy reserves of the myocardium including decreased ATP and phosphocreatine levels in mammalian cardiac tissues [29]. In the same way, adenosine monophosphate-activated protein kinase levels are reduced, inhibiting ATP production and decreasing phosphorylation of acetyl-CoA carboxylase, a downstream mediator of oxidative metabolism. As such, systolic and diastolic function may be compromised due to suppressed ATP production, which cannot sustain adequate contraction and relaxation [28].

 Because of these changes in myocardial performance, systolic and diastolic function may be impaired for individuals with breast cancer. Mercuro et al [30] demonstrated that administration of low doses of epirubicin, cumulative dose of 300 mg/m², was associated with a significant impairment in diastolic function despite changes in resting LVEF. These patients present with impaired ventricular filling mediated by a reduction in ventricular compliance and inappropriate relaxation, despite a preserved ejection fraction secondary to chemotherapy treatment. Systolic impairment is also evident in a long-term follow-up of childhood cancer survivors treated with anthracyclines who underwent echocardiographic measures. Results of this investigation demonstrate that latent effects of anthracyclines are associated with HF and systolic dysfunction. Of those treated with anthracyclines, 41% presented with cardiac abnormalities and 31% of the patients had an increase in end-systolic wall stress. Abnormalities in the LV systolic function were also evident using rate-corrected mean velocity of circumferential fibre shortening and fractional shortening measurements with impaired LVEF [31]. Taken together, these results demonstrate that both systolic and diastolic dysfunctions are associated with anthracycline treatment. Although these clinical outcomes are important, even without an evident reduction in LVEF due to breast cancer therapies, these treatments may impose considerable long-term risk of HF following early-stage breast cancer treatment.

**Trastuzumab**

Trastuzumab is a humanized monoclonal antibody directed against the extracellular domain of the tyrosine kinase receptor (HER2) and has been shown to exert a variety of antitumour effects for breast cancer cells with HER2 overexpression. Overexpression of this receptor occurs in 20–30% of women with early breast cancer and is associated with poor prognosis and resistance to chemotherapy [32–34]. Receptor-specific ligand binding of the HER2 receptor induces both cell proliferation and survival through phosphorylation of intracellular tyrosine kinase domains. Phosphorylation of the intracellular kinase domains activates the lipid kinase phosphoinositide 3-kinase (PI3K)/Akt-transforming factor (AKT) pathway driving cell survival, cell growth, and cell cycle entry through phosphorylation of other host proteins [35]. The PI3K/AKT pathway signalling promotes cell survival by inhibiting the activity of pro-apoptotic B-cell lymphoma 2 (Bcl-2) family members (BAD and BAX) [36]. The AKT pathway also hinders negative regulation of the transcription factor nuclear factor-κB and forkhead transcription factors, thereby leading to increased transcription of antiapoptotic and pro-survival genes and a reduction in the production of cell death-promoting proteins, respectively [37]. In parallel, ligand binding of the HER2 receptor phosphorylates the SH2 domain of guanosine triphosphatase-activating protein, which leads to the activation of the mitogen-activated protein kinase/extracellular signal-regulated kinases pathway, thereby driving cell proliferation and survival. Downstream targets of this pathway also support the activation of vascular endothelial growth factor (VEGF) supporting angiogenesis and tumor growth. Mutational activation of the PI3K/AKT pathway including gene amplification and activation of key components of the PI3K/AKT pathway such as PIK3CA and AKT1, or loss of tumour suppressor gene phosphatase and tensin homologue are common in breast malignant tumours [38]. Trastuzumab inhibits these signalling cascades by inhibiting cell growth and proliferation.

Despite the clinical efficacy of trastuzumab for its antitumourigenic effects, clinical studies have proposed that the expression of HER2 and associated ligands is essential for cardiac structure, function, and cardiac response to stress. In specific, cardiac expression of HER2 receptors protect the heart from structural changes, whereas disruption in HER2 expression leads to decreases in LV function and cardiomyopathy [39]. Basic science research demonstrates that conditional mutations of ErBb2/HER2 lead to both LV dilation and hypertrophic changes, and subsequently a marked reduction in LV contractility in adulthood. These changes were accompanied with a decrease in survival when subjected to pressure overload with aortic banding [40]. Interestingly, no changes in the rates of apoptosis or myofibril structure were observed in this investigation. Further, trastuzumab treatment is suggested to impair cardiomyocyte differentiation and reduce ATP synthesis in human cardiac stem cells [41]. Indeed, administration of trastuzumab is associated with functional changes in cardiomyocytes; however, changes in the structural integrity of the cardiomyocytes are not certain. Neuregulin 1 (Nrg1), an agonist for the activation of ErBb2 signalling, and downstream targets ERK and Akt pathways are important for cardiac development [42]. Trastuzumab blocks this activation and leads to alterations in the levels of the Bcl-X family members, mitochondrial dysfunction, energy compromise, and cytochrome c release [43]. Further, a two-hit model of trastuzumab-induced cardiotoxicity has been suggested in which administration of trastuzumab results in a loss of HER2-mediated signalling and interferes with the heart’s ability to respond to stress [44]. When administered with anthracyclines, the increased mitochondrial damage and increased ROS production
imposes a subsequent cardiac stress, and the HER2-deficient hearts are more susceptible to the risk of irreversible cardiotoxicity. However, following treatment cessation, cardiotoxicity in some cases is reversible, whereas for others it may result in long-term irreversible cardiac damage. These clinical consequences increase the patient’s risk of CVD, an outcome that is increasingly recognized as an important co-morbidity associated with HER2-directed therapies.

Significant cardiac safety concerns from anticancer therapy have been described with trastuzumab treatment. The mechanisms underlying the early impairment of diastolic function with respect to systolic function are not well established. An analysis of the data reported by Sawaya et al [45] found that administration of trastuzumab was associated with abnormalities in LV function with an 11% reduction in longitudinal strain rate, a measure of systolic LV function, and an early indicator of cardiac dysfunction of the midwall, anterior, and lateral segments preceding a decrease in LVEF. Chemotherapy-induced cardiac injury may result in microvascular abnormalities through VEGF inhibition and lead to interstitial fibrosis. The LV longitudinal strain depends on the subendocardial layers of the myocardium and influences diastolic function [46], suggesting that diastolic function may be impaired before clinical changes in systolic function, which are indicated by a reduction in strain rate. Echocardiographic measures suggest that trastuzumab treatment may be associated with systolic dysfunction, which may be accompanied by reduced diastolic LV function preceding a decrease in LVEF for women with breast cancer.

**Angiogenesis Inhibition**

Some of the newest agents used in the treatment of breast cancer are receptor tyrosine kinase inhibitors such as bevacizumab designed to target the VEGF family of peptide growth factors and its cognate receptor VEGFR2, which are central regulators of angiogenesis and metastatic propagation [47]. The VEGF expression has been reported in over 60% of breast cancer specimens and correlates with shorter survival time following diagnosis [48], suggesting the effectiveness of anti-VEGF therapy in the oncology setting. Angiogenesis-targeting therapies result in decreased endothelial cell proliferation and an increase in apoptosis with the release of cytochrome c to the cytosol-activating caspase 9, which initiates the mitochondrial apoptotic pathways [49]. The effect of VEGF signalling on cardiovascular function highlights that signalling systems are not tissue specific. Hypertension is often associated with VEGF-target therapies due to its role in regulating the release of potent vasodilators, nitric oxide, and prostaglandins [50]. When the heart is placed under hypertensive stress resulting in hypoxia or ischaemia, VEGF and endothelium-specific mitogens stimulate angiogenesis [18]. The VEGF activation of VEGF receptor on endothelial cells initiates vasodilation and angiogenesis in the heart and allows for compensatory cardiac hypertrophy to occur. Impedance of this cascade of events with chemotherapeutic treatments results in an increase in blood pressure [51] and may hinder the ability of the myocardium to compensate for an increase in afterload on the heart. Hypertension due to VEGF inhibition places an increase in afterload on the heart, and may lead to similar morphological changes of the myocardium as HF associated with diastolic dysfunction. Belcik et al [52] demonstrated that mice treated with VEGF receptor tyrosine kinase inhibitors exhibited concentric LV remodelling and reduced stroke volume (SV) in the absence of impaired LV contractility determined by LV peak change in pressure over time (dp/dt).

**Exercise tolerance in breast cancer**

Peak aerobic capacity is an individual’s capacity to transport oxygen from the atmosphere to the mitochondria of the muscle for ATP resynthesis requiring the integrative capacity of the respiratory, circulatory, and musculoskeletal systems [53]. Impedance along the oxygen cascade as a result of injury, toxicity, or dysfunction of the respiratory, circulatory, musculoskeletal systems will lead to a decrease in VO$_{2\text{peak}}$ and a consequent decrease in exercise tolerance. Conventional breast cancer therapies may impede the function and integrity of the cascade involved in oxygen transport leading to the development of important cardiovascular consequences. The reduced exercise tolerance for patients with breast cancer may also contribute to indirect lifestyle perturbations (e.g., physical inactivity, weight gain) preceding cancer therapy or as a direct consequence of cancer and its treatment.

**Central haemodynamics**

There is substantial evidence related to the relative change in central haemodynamics in women with breast cancer both during and following cytotoxic therapies. Considering this, central haemodynamics may play an important role in governing exercise intolerance in women with breast cancer. Jones et al [54] demonstrated that postmenopausal women with breast cancer during survivorship had a 19% reduction in VO$_{2\text{peak}}$ compared with age-matched healthy controls. A reduction in VO$_{2\text{peak}}$ was associated with a reduction in the SV and Q response with no significant differences in arteriovenous oxygen difference during maximal exercise conditions. Systemic vascular resistance was also significantly increased during exercise conditions for survivors of breast cancer suggesting a limitation to forward flow from the aorta during ejection of the LV. These findings suggest that the SV and Q response to exercise may be reduced in breast cancer patients with reduced ability to increase VO$_{2\text{peak}}$ to the same end as their healthy counterparts and that central haemodynamics may play a very important role in exercise intolerance for women with breast cancer.

Improvements in VO$_{2\text{peak}}$ have been achieved with aerobic exercise training for women with breast cancer without a change in LVEF [55] when adherence predicted a change in VO$_{2\text{peak}}$. This is not surprising, because resting LVEF does not necessarily correlate with improvements in VO$_{2\text{peak}}$, as shown previously in patients with chronic HF [6]. Because of this, other central haemodynamic measures (and peripheral adaptations) are considered to determine their role owing to the change in VO$_{2\text{peak}}$ for this
population. The central haemodynamics governing (Q) reserve is of important interest. The Q response during incremental aerobic exercise is dependent on heart rate and SV. Factors that influence each of these variables will have considerable influence on the Q response to exercise. Previous work from our laboratory has highlighted that the Q response during incremental aerobic exercise is dependent on heart rate, end-diastolic volume (EDV), ejection fraction, and mitral regurgitant fraction and factors influencing these variables will have a considerable influence on VO2peak and exercise tolerance [8]. Given this, herein we highlight the importance of these factors in the reduced exercise tolerance of women with breast cancer.

**Reduced Q reserve with exercise: impaired cardiac function**

Early-stage breast cancer therapies may result in myocardial injury causing functional and structural changes to the myocardium, ultimately limiting the Q and SV response during exercising conditions for women with breast cancer. Many women with breast cancer present with a reduction in LVEF and a significant reduction in strain rate in the longitudinal, radial, and circumferential regions of the myocardium [56] and markers of reduced LV systolic function at rest. Chronic HF patients with LV systolic dysfunction appear to use the Frank–Starling mechanism as a compensatory mechanism to maintain SV with eccentric remodelling. During exercise conditions, patients with a history of breast cancer are able to increase EDV; however, reduced contractile reserve may hinder the SV response to meet the metabolic demands of the peripheral tissue. Haykowsky et al [55] demonstrate that patients with an evidence of LV dilation secondary to trastuzumab treatment are unable to increase VO2peak during chemotherapy treatment when systolic function was compromised. These findings provide evidence that during exercise conditions, patients with breast cancer are able to increase EDV (preload); however, the Q reserve was limited with a marked increase in end-systolic volume (ESV). Although EDV increases during exercise conditions to maintain SV, the Q response to exercise is limited by reduced function and contraction of the LV resulting in an increase in ESV.

In the current oncology setting, an assessment of cardiac function primarily relies on change in resting LVEF using echocardiographic measures. However, resting LVEF may not be a sensitive measure of early myocardial injury and evidence suggests that diastolic cardiac performance may prevent any change in asymptomatic LVEF. Moreover, resting LVEF is a poor measure of exercise cardiac function. Data from the study of Stoodley et al [57] assessed 53 women 1 week before and 1 week after the administration of anthracyclines using tissue Doppler imaging to determine changes in cardiac performance following chemotherapy. These data indicated that anthracyclines impaired diastolic function with reduced LV relaxation mechanics in the entire cohort of women with no change in LVEF. Patients with LV diastolic dysfunction have normal contractile function; however, they are unable to make use of the Frank–Starling mechanism during exercise conditions. Diastolic dysfunction (as demonstrated by an inability to increase EDV during exercise) may be a latent effect of cytotoxic treatment in breast cancer survivors. As a result, end-diastolic pressure increases augmenting early LV filling. Anthracycline-induced cardiotoxicity leads to impaired diastolic filling and increased diastolic pressures at rest [58]. However, it is not known whether exercise intolerance is mediated by reduced diastolic function and ventricular compliance resulting in increased diastolic filling pressures during exercise conditions. Pulmonary capillary wedge pressure and right atrial pressure are direct indicators of diastolic function and clinical measures of inputs to the heart. Right atrial pressure will determine blood flow back to the heart (and therefore, EDV) and it is important to maintain right ventricular filling to sustain global Q during periods of exercise. To our knowledge, no studies to date have used these direct measures of diastolic function during exercise conditions to determine its influence on exercise intolerance for women with breast cancer.

At present, diastolic ventricular function and its role in exercise tolerance during incremental or maximal exercise is not well studied for women with breast cancer. As described previously, EDV may increase during exercise for women with breast cancer. However, an acute increase in intracardiac volume that occurs during moderate to heavy aerobic exercise may result in a concurrent augmentation in pericardial pressure that elevates the external constraint to LV filling [59]. It may be plausible that a rise in EDV during acute incremental exercise may be associated with pericardial restraint leading to modulation of LV compliance and filling for women with breast cancer. An acute increase in intraventricular volume resulting in pericardial restraint may induce changes in compliance that influence both passive and active LV filling [60] during exercise conditions. Further, pathological changes following breast cancer treatment may also lead to an acute myopericarditis and focal endocardial fibrosis with thickened and tense pericardium, limiting ventricular compliance under exercise conditions [61]. Overall, patients with breast cancer may be able to increase preload during exercise conditions; however, reduced LV-filling mechanics (in part, due to an increase in pericardial restraint) and decreased contractile reserve may ultimately lead to changes in central haemodynamics that contribute to a reduced exercise tolerance for women with breast cancer.

**Negative inotropic influence**

Sympathetic innervation of the myocardium is autonomically controlled by the central nervous system and is responsible for heart rate control. A change in ventricular inotropy controlled by sympathetic innervation of the heart may be responsible for changes in EDV and ESV and sequential changes in VO2peak. Chemotherapy treatment is associated with neuropathic injury making it possible that sympathetic innervation of the myocardium may be impaired. Tjeerdasma et al [62] investigated asymptomatic (LVEF >50%) women with metastatic breast cancer for autonomic regulation with a 24-hour Holter monitor using time domain frequencies of the R–R interval following anthracycline treatment. This investigation revealed impaired autonomic control of heart rate in 85% of patients,
particularly time-domain parameters related to lower parasympathetic activity. Further, a reduction in parasympathetic activity may also result in ventricular tachycardia noted in this investigation, leading to adverse cardiovascular events and reduced Q reserve. Autonomic incompetence plays an important role in the increase of Q during exercise, and therefore, has a large influence on VO\textsubscript{2peak}. The findings of this investigation are concurrent with the results of other studies, in which vagal-mediated fluctuations in heart rate variability were reduced, and markers of sympathetic activity were unchanged [63]. Of concern, autonomic control and diastolic function predicted outcomes of dyspnea with exertion, hindering activities of daily living for these individuals. Despite these findings, the function of autonomic impairment following cytotoxic treatment remains controversial. Feola et al [64] found nonsignificant changes in heart rate following anthracyclines treatment in the entire cohort of 53 breast cancer patients with a statistically significant change in LVEF at 1-month follow-up. These data suggest that during resting conditions, sympathetic control of heart rate may be impaired, which may influence heart rate during exercise conditions. As seen in children with multiple malignancies, heart rate was significantly lower during maximal exercise conditions following anthracycline treatment when compared with healthy individuals [65]. The consequence of impaired sympathetic activity on heart rate control during maximal exercise conditions and its influence on Q reserve for women with breast cancer requires further investigation.

**Impaired vascular function**

The effects of breast cancer treatments on vascular function and possible injury are not well studied. However, numerous reports have demonstrated that treatments for breast cancer are associated with an increased risk of hypertension and impaired endothelial function. Anthracycline-induced oxidative stress and impaired VEGF receptor signalling will likely have detrimental effects on the vascular system. This may lead to induction of the atherosclerotic cascade associated with adhesion molecule proliferation, nitric oxide uncoupling, increased pro-inflammatory cytokines, and impaired endothelial vasodilation [66,67]. These detrimental outcomes have been demonstrated in clinical trials. Arterial pressure during systole (and therefore, afterload) is largely dependent on the function and structure of large elastic and muscular arteries, which can be determined by the stiffness of the aortic vessel [68]. Aortic stiffness, which is determined by measuring central pulse wave velocity and aortic distensibility, has been shown to be impaired following cytotoxic treatments [69]. Thus, afterload on the heart, or the aortic pressure the LV must overcome to eject blood into systemic circulation may be increased following cytotoxic treatment resulting in an increase in aortic stiffness. It is plausible that during submaximal exercise conditions aortic stiffness plays a key role in the limitation of LV mechanics, whereas at higher workloads other factors including cardiac reserve or pericardial restraint may be more important.

Clinical studies have shown that rapid depletion of systemic nitrogen oxide bioavailability occurs following a single dose of anthracyclines, resulting in endothelial dysfunction measured noninvasively by flow-mediated dilation [70]. Resultant outcomes of the change in endothelial function may lead to acceleration of atherosclerosis and hypertension following chemotherapy treatment for women with breast cancer. Direct inhibition of VEGF receptors with angiogenesis inhibitors or indirect inhibition with HER2 therapy is also limited in clinical use due to marked increases in hypertension during and following treatment. Mayer et al [71] demonstrated significant changes in haemodynamic profiles for women with breast cancer with an increase in systolic blood pressure, diastolic blood pressure, and mean arterial pressure within 6 weeks of vandetanib and metronomic chemotherapy treatment. These participants were also assessed for nitrogen oxide bioavailability and forearm vascular resistance. Forearm vascular resistance was increased and nitrogen oxide bioavailability was reduced. The ability to increase cardiac output during exercise without an abnormal elevation in left atrial pressure depends on the capacity of the LV to enhance its diastolic filling [72]. However, elevated systolic arterial blood pressure (a surrogate of afterload) impairs diastolic performance. Thus, it is likely that elevated afterload impairs Q reserve during exercise for women with breast cancer.

**Muscle function**

Early-stage breast cancer treatments may lead to overt insult of the peripheral muscle tissue, whereas direct lifestyle perturbations increase the risk for muscle atrophy and impaired metabolic activity. Muscular atrophy is a serious complication of chemotherapy treatment causing extreme fatigue and weakness. Deterioration of skeletal muscle results in symptomatic reduction in exercise tolerance and altered peripheral muscle perfusion [73]. Improvements in VO\textsubscript{2peak} are also associated with increased muscular strength and size [74]. However, a reduction in muscle size cannot fully explain their reduction in exercise tolerance. Maladaptation of skeletal muscle or reduced oxidative metabolism due to mitochondrial DNA damage may exist within the skeletal muscle [75]. The consequence of compromised peripheral blood perfusion, oxidative phosphorylation, and abnormal cellular structure of the skeletal muscle may contribute to a reduced exercise tolerance for women with breast cancer.

Bruera et al [76] examined the muscular function of patients with advanced breast cancer and compared the data with healthy individuals, the results of which suggested that persons with breast cancer have lower maximum strength after supramaximal stimulation, a reduction in relaxation velocity, and a higher loss of contractile strength, after 30 seconds of stimulation. These findings suggest that breast cancer treatment may exert confounding alterations in muscular function. Lifestyle factors including obesity or lack of physical activity in patients with breast cancer may aggregate reduced muscle mass and function that may further impair their work capacity.

Anthracycline-mediated muscular toxicity is associated with increased autophagy gene transcription in peripheral muscle. The influx of super-anion production at complex 1
of the electron transport chain and ROS production cause damage to calcium-handling proteins that are responsible for the activation of the autophagy genes [77]. Nevertheless, anthracycline-induced toxicity is also mediated by accumulation of ROS leading to oxidative damage and activation of pro-apoptotic genes and deregulated calpain and caspase-3 systems within muscle fibres [78]. An investigation by Smuder et al [79] provides some evidence of skeletal muscle apoptosis due to ROS accumulation within the skeletal muscle, which may be mediated by similar mechanisms previously described in the heart. Importantly, endurance exercise before the administration of doxorubicin attenuated autophagy gene amplification and skeletal muscle apoptosis of the soleus muscle, suggesting that endurance exercise is effective for protecting against loss of skeletal muscle mass and function induced by chemotherapy treatment. A series of cellular changes is also evident following chemotherapeutic drug administration for the treatment of breast cancer in peripheral muscle influencing contractile impairment of slow-twitch and fast-twitch muscle fibres [80]. Many authors have shown impaired regulation of intracellular calcium reuptake and production from the sarcoplasmic reticulum of skeletal muscle in animals treated with anthracyclines due to mitochondrial ROS generation [81,82]. Accumulation of intracellular calcium due to an increase in calcium release and depressed reuptake are associated with impaired force frequency, relaxation times, and contractile impairment of fast-twitch and slow-twitch muscle fibres [80]. Despite these findings, individuals with breast cancer experience a loss of function and reduced peripheral muscle mass following chemotherapy treatment, leading to a reduction in oxygen uptake and metabolism. Further investigation is needed to determine peripheral muscle adaptations in human studies and their influence on exercise tolerance for women with breast cancer.

Oxygen transport

Anaemia is a common side effect of breast cancer and its treatments and is also associated with the chemotherapeutic agents administered, their dosing schedule, and duration of cytotoxic exposure [83]. Kirshner et al [84] reported the incidence of moderate to severe anaemia in patients with breast cancer undergoing adjuvant chemotherapy with doxorubicin and cyclophosphamide in up to 40% of patients. Anaemia is associated with a reduction in haemoglobin concentrations leading to fatigue and reduced exercise tolerance [85]. Further, significantly large proportions of women have low haemoglobin concentrations preceding treatment and are associated with poorer disease prognosis [83]. Low haemoglobin concentrations preceding cancer diagnosis may explain a proportion of the attenuated exercise tolerance for these women, which is augmented with the disease and related treatments.

Aerobic training has been shown to improve symptoms of fatigue and increase exercise tolerance in women with breast cancer [86,87]. Haemoglobin is a key determinant of oxygen-carrying capacity, oxygen transport, VO2peak, and exercise capacity [88]. The relative haemoglobin mass in healthy individuals is a significant predictor of exercise tolerance; however, changes in haemoglobin mass do not necessarily correlate with improvements in VO2peak [89]. Dolan et al 2010 [90] suggested that women with breast cancer who receive chemotherapy and undergo an aerobic training or resistance training intervention are able to maintain their VO2peak during chemotherapy despite a significant decline in haemoglobin levels with a moderate relationship between haemoglobin and VO2peak. On average, the participants had normal resting haemoglobin concentration, and were able to maintain these levels following treatment. Therefore, although a reduced haemoglobin concentration clearly can affect oxygen transport and aerobic capacity, it is not clear whether a reduced haemoglobin concentration plays a major role in the reduced exercise capacity often observed during or after chemotherapy.

Courneya et al [91] demonstrated favourable outcomes for VO2peak in cancer patients with anaemia. This research group combined darbepoetin alpha, a common drug used to increase red blood cells in the treatment of anaemia, with aerobic training and compared the outcome with a group that received darbepoetin alpha alone. The darbepoetin alpha plus aerobic training group showed greater improvements in VO2peak and increased haemoglobin concentrations at a lower dose of the drug compared with the darbepoetin alpha alone group. The darbepoetin alpha group alone did not improve their VO2peak following the intervention despite an increase in haemoglobin levels. The potential for a reduction in haemoglobin following cancer treatment is clear; however, more investigation is required to fully elucidate the effects of reduced haemoglobin on exercise intolerance in breast cancer.

Conclusion

Direct myocardial and vascular insults may hinder VO2peak in patients with breast cancer resulting from chemotherapy treatment and the disease. Centrally, the inability to increase SV and Q during exercise is secondary to changes in both systolic and diastolic functions with considerable individual variations. Interventions to enhance LV mechanics/function while increasing SV, Q, and VO2peak during exercise are of importance for this population, and may attenuate a myriad of co-morbid cardiotoxicities associated with treatment. Breast cancer and its treatments may also result in a sequence of peripheral maladaptations that may affect VO2peak. In specific, peripheral muscle maladaptations lead to reduced muscle mass and impaired muscle function as a consequence of breast cancer treatments and/or lifestyle perturbations. Finally, there is evidence to suggest that chemotherapy treatment may reduce resting haemoglobin levels for women with breast cancer, which may further attenuate VO2peak for this patient population. Interventions to improve or maintain VO2peak are needed for individuals with breast cancer to improve the overall quality of life and preserve functional independence during survivorship.

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