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Cancer therapy-induced autonomic dysfunction in early breast cancer: Implications for aerobic exercise training

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Breast cancer is the most common malignancy affecting women and the second leading cause of cancer death in women in the United States [1]. Due to improvements in detection and adjuvant therapy, breast cancer specific mortality has decreased significantly in women with early stage disease, and the five-year relative survival rate for early stage disease has increased from 80% in 1950 to 89% today [1]. Increased breast cancer specific survival, however, is at risk of being offset by the potential late occurring cardiovascular toxic effects of oncologic therapy. Indeed, among women with early breast cancer, particularly those over age 65, cardiovascular disease (CVD) is now the predominant cause of mortality, and these women are also at increased risk of CVD compared with age-matched women without a history of breast cancer [2].

Long-term autonomic imbalance is associated with increased risk of CVD and mortality in non-cancer populations [3]. Importantly, there is evidence of a sustained increase in sympathetic activity and a reduction in parasympathetic input to the sinoatrial node in patients treated for early stage breast cancer. For example, the resting heart rate (RHR) of early stage breast cancer patients following the completion of primary adjuvant therapy is, on average, 9% to 16% [7–16 beats·min^{-1} (bpm)] higher compared to age-matched controls [4]. Several studies have also shown that heart variability (HRV) and baroreflex sensitivity is reduced among women with a history breast cancer [5]. Accordingly, based on a growing

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understanding of bi-directional interactions between the sympathetic and parasympathetic efferent pathways, autonomic imbalance is one potential pathway involved in both the etiology and the clinical course of breast cancer therapy-induced CVD (Fig. 1).

Despite the potential long-term ramifications of autonomic dysfunction in early breast cancer, the development of safe and effective mitigation strategies remains elusive. Aerobic exercise training (AET) is one non-pharmacological therapy that may attenuate cardiovascular abnormalities in the early breast cancer setting; however the mechanisms by which AET mitigates autonomic dysfunction are not fully understood. The current evidence base indicates that the central pathways responsible for decreasing sympathetic outflow and increasing cardiac vagal tone after AET are, in part, dependent on changes in the renin–angiotensin–aldosterone system (RAAS), nitric oxide (NO), and reactive oxygen species (ROS) (Fig. 2). It is well established that the signaling pathway RAAS plays an important role in chemotherapy-induced cardiotoxicity [6]. Given that angiotensin II is known to exert powerful inhibitory effects upon the cardiac vagus nerve, suppression of this hormone or a precursor via AET could ultimately play an important role in the prevention of cardiac dysfunction. Breast cancer therapies also inhibit vascular NO release, consequently promoting vasoconstriction, increased peripheral resistance, and increased blood pressure [7]. Thus the upregulation of NO with AET could improve autonomic function. Interestingly, our group recently found that AET improved peripheral arterial endothelial function (a surrogate measure of NO bioavailability) in women with operable breast cancer receiving neoadjuvant doxorubicin [8]. Finally, chemotherapy-induced generation of reactive oxygen species (ROS) is the central mediator of numerous adverse acute and chronic biological effects in the cardiovascular system, including alterations in autonomic outflow [9]. Accordingly, attenuation of ROS generation and/or activity holds considerable therapeutic promise. Our group recently found that AET during chronic anthracycline exposure in mice lowered serum and cardiac levels of ROS and attenuated LV remodeling [10]. These results indicate that AET may protect cardiac cells against chemotherapy-induced toxicity through ROS inhibition.

In conclusion, CVD is a frequent and devastating adverse complication of breast cancer therapy leading to morbidity, poor quality of life, and premature mortality. As reviewed here, there is emerging evidence indicating that autonomic function is one component involved in the etiology and the clinical course of breast cancer therapy-induced CVD. Immediate work is now required to minimize, or optimally eliminate, breast cancer-associated CVD. As a first step in addressing knowledge gaps, hypothesis driven prospective studies evaluating the time course and clinical importance of RHR, HRV, and baroreflex sensitivity in early breast cancer are now warranted. Furthermore, elucidation of the potential molecular mechanisms by which AET reduces therapy-induced autonomic dysfunction is needed. For instance, the establishment of the existence of a relationship between AET, RAAS, NO and ROS would ascertain if AET can decrease sympathetic outflow and increase cardiac vagal tone in the setting of early breast cancer. Collectively, hypothesis-driven translational studies are required to define the nature and magnitude of autonomic dysfunction in early breast cancer, their relationship to cardiac dysfunction as well as to characterize the underlying mechanisms of AET in preventing and/or treating autonomic dysfunction and CVD. To this end, we propose that in combination with

continual advancements in anticancer therapy, the testing and use of AET as adjuvant therapy may optimize health and longevity in cancer survivors by lowering therapy-associated alterations in autonomic function and CVD.

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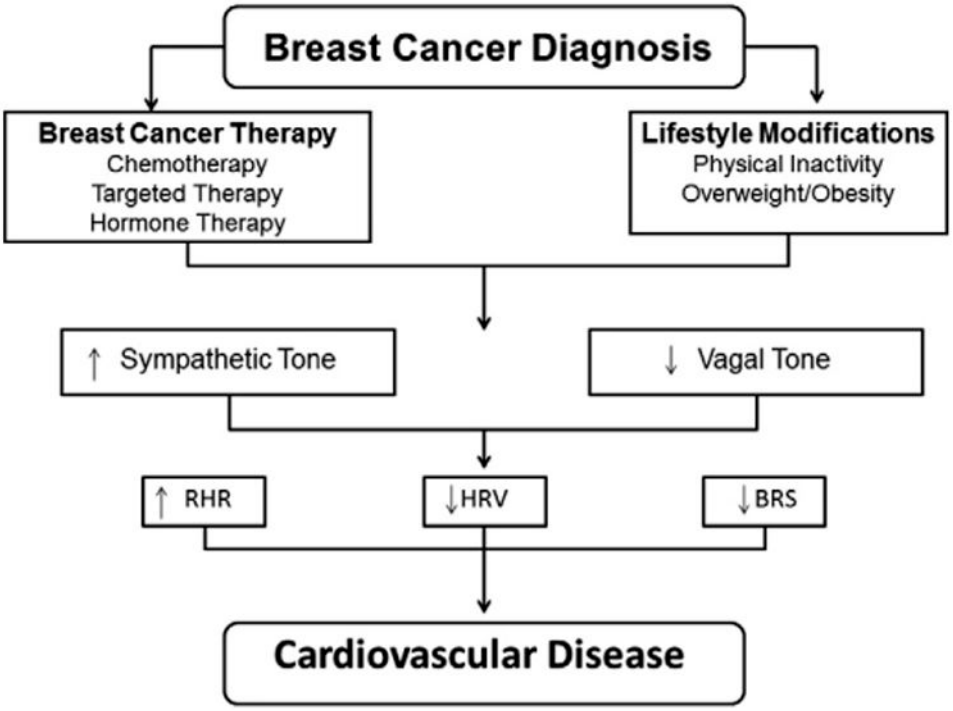

Fig. 1.

Relationship between breast cancer and autonomic dysfunction. Breast cancer diagnosis is associated with therapy-induced cardiovascular injury and lifestyle perturbations leading to increased sympathetic and decreased vagal tone in the heart. In turn, this autonomic imbalance increases RHR and decreases HRV and BRS leading to cardiovascular disease. RHR, resting heart rate; HRV, heart rate variability; BRS, baroreflex sensitivity.

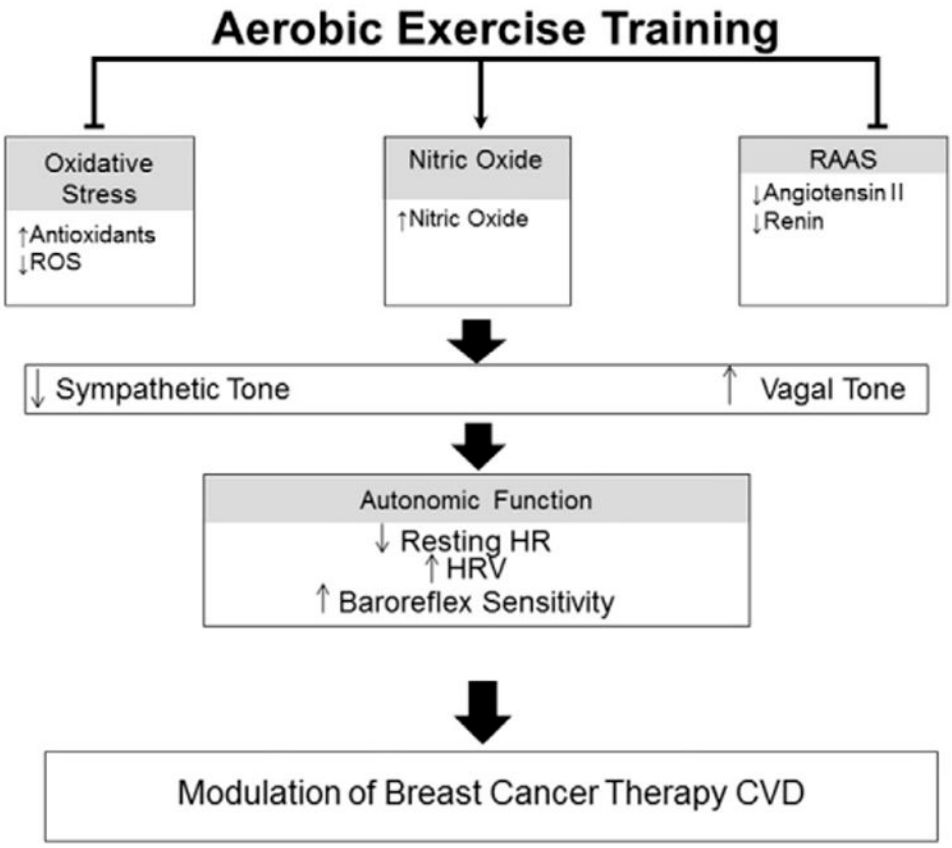

Fig. 2.

Modulation of autonomic dysfunction with aerobic exercise. Aerobic exercise training decreases oxidative stress and the RAAS while upregulating nitric oxide bioavailability. This results in decreased sympathetic tone and increased vagal tone, which in turn, decreases resting HR and increases HRV and baroreflex sensitivity. CVD, cardiovascular disease; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; HR, heart rate; HRV, heart rate variability.