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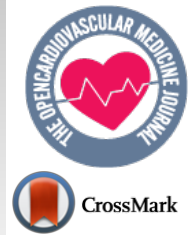
REVIEW ARTICLE

Cardiovascular Dysautonomia in Patients with Breast Cancer

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Abstract:

Breast cancer is the most frequent malignant disease among women, being responsible for a considerable percentage of fatalities and comorbidities every year. Despite advances in early detection and therapy, evidence shows that breast cancer survivors are at increased risk of developing other chronic conditions, such as cardiovascular diseases.

Autonomic dysfunction is an emerging, but poorly understood topic that has been suggested as a risk factor for cardiovascular disease in breast cancer patients. It clinically manifests through persistently elevated heart rates and abnormal heart rate variability, even before any signs of cardiovascular dysfunction appear. Since changes in the left ventricular ejection fraction only manifest when myocardial injury has already occurred, it has been hypothesized that autonomic dysfunction can constitute an early biomarker of cardiovascular impairment in breast cancer patients.

This review focuses on the direct and indirect effects of cancer and its treatment on the autonomic nervous system in breast cancer patients. We highlight the mechanisms potentially involved in cancer and antineoplastic therapy-related autonomic imbalance and review the potential strategies to prevent and/or attenuate autonomic dysfunction.

There are gaps in the current knowledge; more research in this area is needed to identify the relevance of autonomic dysfunction and define beneficial interventions to prevent cardiovascular disease in breast cancer patients.

Keywords: Autonomic dysfunction, Breast cancer, Antineoplastic therapies, Autonomic neuropathy, Cardiotoxicity, Patients.

1. INTRODUCTION

Worldwide, breast cancer is the most frequent malignant disease among women, with 24% of new cases and 15% of cancer fatalities in 2018, and according to the GLOBOCAN Cancer Tomorrow prediction tool, incident cases will increase by >46% by 2040 [1].

Advances in early detection and therapy of breast cancer are responsible for the reduction of mortality in women with breast cancer. However, this process may give rise to other chronic conditions, such as cardiovascular (CV) disease, jeopardizing the well-being of the survivors [2].

In fact, women who have breast cancer are at a great risk of developing CV disease and are more prone to die of it compared to the ones who do not have this disease [3].

Furthermore, factors such as ageing, advances in breast cancer-specific survival, sustained use of cardiotoxic chemotherapy, and other mechanisms related to the presence of cancer, contribute to the growth of this problem [2].

Typical repercussions of antineoplastic treatments in the long term include asymptomatic reduction in left ventricle function and heart failure [4]. Alterations in left ventricle ejection fraction (LVEF) at rest are currently used in oncology practice to evaluate the impact of cytotoxic therapy on the CV system. However, it is important to note that myocardial function decline can be initially compensated through increases in heart rate (HR), contractility, and preload. This results in a normal LVEF in the early stages of dysfunction, manifesting its reduction only when a significant myocardial injury has occurred [2].

Arrhythmias are also an increasingly identified complication. Atrial tachyarrhythmias, mainly atrial fibrillation, are the most common, but ventricular arrhythmias,

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including those related to treatment-induced QT prolongation, and bradyarrhythmias can also occur [5]. Despite increased recognition, prospective studies evaluating incidence are lacking.

Preliminary associations between autonomic impairment-related CV dysfunction and increased risk or severity of CV disease and all-cause mortality have been proposed by some reviews of epidemiological- and clinical trial-based research [6].

In fact, autonomic dysfunction (AD), which occurs during or after chemotherapy, is associated with excessive sympathetic nervous activity and decreased parasympathetic nervous system activity, and is one of the proposed risk factors of CV disease in breast cancer patients [2].

This imbalance promotes activation of the hypothalamic-pituitary-adrenal (HPA) axis, the renin-angiotensin-aldosterone system (RAAS) and the endocannabinoid system, simultaneously increasing HR and left ventricular (LV) contractility. These disturbances further stimulate oxidative stress, inflammation, progression of atherosclerosis, and reduce vasodilation, leading to CV disease. The clinical manifestations of autonomic dysfunction include persistently elevated HR, atrioventricular node conduction and left ventricular contractility, and abnormal heart rate variability (HRV), constituting a potential early biomarker of CV impairment in breast cancer patients subjected to antineoplastic therapies [2].

However, the clinical implications are insufficient. Recent systematic reviews and meta-analyses show only minimal improvements in LVEF by beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin II receptor blockers (ARBs) during chemotherapy [7, 8] with unsettling effect on the incidence of heart failure [8, 9] and without effect on overall survival [10], which raises questions about the causal involvement of autonomic dysfunction in chemotherapy-induced cardiotoxicity (CT).

1.1. Impact of Cancer on Autonomic Function

Currently, a limited number of studies address the effect of cancer and antineoplastic treatments on autonomic function. However, it is recognized that AD is more prevalent in cancer patients and cancer survivors than in healthy controls [11].

ANS, as a functionally important and widely distributed system, can be disturbed by cancer and by the adverse events produced by its treatment [12]. It is postulated that AD commonly affects both the sympathetic and parasympathetic systems, promoting inflammation and endothelial dysfunction, contributing to the development of CV disease in cancer survivors [13 - 15].

Direct complications of cancer in ANS include primary tumours arising in anatomical autonomic structures and the autonomic impairment produced by primary brain tumours or metastases, while indirect complications include those associated with antineoplastic treatment (chemotherapy, radiotherapy and/or surgery) and those related to paraneo-plastic autonomic syndromes [12]. Other aspects of cancer contribute to AD, such as psychological stress, sleep dis-turbances, weight gain, and loss of cardiometabolic fitness [2].

1.2. Direct Action

Peripheral autonomic structures may be directly affected by systemic cancer, either through direct infiltration, intravascular dissemination, as in haematological neoplasms, by compression, or, less frequently, by direct metastasis on nerves [12].

The most common sites to which breast cancer metastasizes are lymph nodes, bone, lung, liver, adrenals and skin [16]. Lesions of postganglionic sympathetic innervation to the lumbosacral plexus or peripheral nerves beneath L3 cord division can appear through the direct extension of breast cancer, but other abdominal and pelvic tumours manifest as unilateral warm and dry feet, hypohidrosis and pain. Additionally, breast cancer metastasis to lateral axillary lymph nodes near the lower brachial plexus may result in warmth and dryness of the upper extremity affecting sympathetic nerves [12].

In advanced cancer, namely in patients with breast cancer metastasis, ANS dysfunction is a common problem with a high prevalence [17]. However, this was based on a small number of studies, and almost half of advanced breast cancer patients were unable to complete Ewing's battery of tests, emphasising the need to explore alternative methods for evaluation of autonomic function in this population [18, 19].

Other primary tumours can also cause Horner syndrome through the same mechanism and by lesions of the sympathetic cervical chain or the carotid sinus. Involvement of the last may also cause syncope and hypotension. Patients with cancer outside the nervous system can, and often do, experience autonomic dysfunction even in the absence of direct involvement of autonomic structures by the tumour [16].

Several studies support the role of the ANS in the aetiology and progression of solid tumours. Recently, McCallum and co-workers, using a triple-negative mammary cancer mouse model, have recorded neural activity directly within the tumour mass, and concluded that there is a strong connection between the ANS and tumour growth and metastasis [20].

A recent review summarized experimental animal studies that have consistently indicated that sympathetic nerves, innervating the tumour microenvironment, increase the progression of any cancer type investigated and are related to stress-induced cancer behaviour [21]. The evidence indicates that sympathetic nerves may suppress adaptive immunity to cancer; sympathetic nerves may induce bone metastasis by modifying the bone marrow microenvironment [22]; or the sympathetic nerves may stimulate tumour-associated macrophages (TAMs), which promote the distant metastasis of implanted breast cancer cells under stress [21, 23].

In contrast, a low parasympathetic nerve fibre density in tumours is associated with poor clinical outcomes, revealing that parasympathetic nerves in tumour tissue might be negative regulators in breast cancer [24].

2. PARANEOPLASTIC ACTION

Paraneoplastic neurological syndromes are remote manifestations of systemic neoplasms caused by immune

system damage to autonomic nerves, and are not recognised as effects of the primary tumour mass, metastasis, or nutritional, metabolic, infectious, or treatment-related abnormalities. Neuronal antigens expressed by the tumour induce an immune response, with a production of onconeural antibodies that inappropriately recognise endogenous nervous system elements as "non-self" [12, 25], although also non-humoral mechanisms have been reported [26].

Beyond breast carcinoma, the tumours most commonly associated with these syndromes are small-cell lung cancer, ovarian carcinoma, lymphoma and thymoma [27]. Neurological symptoms may appear before the diagnosis of malignancy in a significant percentage of patients, determining the importance of early detection of these neurological manifestations, allowing the diagnosis of cancers that, in this phase, tend to be confined and approachable to therapy [12, 27].

However, paraneoplastic neurological syndromes related to breast cancer are rare and include cerebellar degeneration, sensory and motor-type neuropathies, stiff person syndrome, opsoclonus-myoclonus syndrome, encephalomyelitis, and retinopathy. Antibodies in the serum and cerebrospinal fluid are present in 60-70% of breast cancer patients with paraneoplastic neurologic syndrome [26]. The most frequent paraneoplastic syndrome-associated antibody is the anti-Hu antibody. The patients develop an autoimmune response directed to the Hu antigen, an AU-rich 3′-untranslated m-RNA sequence that is expressed by all neurons and by many small-cell lung cancer cells, although it may also be expressed in breast cancer cells [28].

Paraneoplastic neuropathies affecting ANS usually occur in a subacute manner; nevertheless, the time course can vary from an insidious beginning throughout several months to acute autonomic failure [27].

Autonomic features include orthostatic hypotension and sudomotor dysfunction, reflecting sympathetic failure, and pupillomotor anomalies, diminished cardiovagal function with tachycardia and decreased HR response, xeropthalmia, erectile dysfunction, constipation and urinary retention, reflecting parasympathetic failure [27, 28]. Autonomic dysfunction may present as part of a paraneoplastic syndrome or be an isolated paraneoplastic symptom [28].

For example, paraneoplastic enteric neuropathy may also occur without any other autonomic features, and usually antedates the diagnosis of cancer. It can manifest as intestinal pseudo-obstruction, severe gastroparesis, and constipation, with patients presenting early satiety, nausea, bloating, abdominal pain, weight loss, regurgitation and even compromised fluid ingestion contributing to dehydration in serious cases [27, 29].

3. ANTINEOPLASTIC TREATMENT-RELATED ACTION

Chemotherapy agents used in antineoplastic therapy represent a particularly effective measure to restrain cancer evolution, acting through several mechanisms aimed at eradicating the rapidly dividing neoplastic cells. However,

these drugs can also damage healthy cells/structures, leading to the need for dose reduction or even discontinuation of treatment [30].

Antineoplastic agents may induce lesions on nervous system structures and, depending on the different composite, produce a multiplicity of neuropathies: large and small sensory and/or motor, demyelinating and axonal, cranial and autonomic [31]. The consequential effects of antineoplastic therapy on the nervous system diverge among the groups of drugs, influenced by the particular physical and chemical characteristics and single or cumulated dosages [30, 32].

Moreover, small, unmyelinated nervous fibres are usually the ones affected by autonomic neuropathy; thus, antineoplastic agents recognized to impair this type of fibres are the most likely to harm ANS function [6].

Symptoms of chemotherapy-induced polyneuropathy usually develop during the first two months of treatment, frequently stabilizing after its cessation. However, it is crucial to consider the "coasting" phenomenon, where neuropathic symptoms persist and may even worsen, explained by the persistence of drugs in nerve axons after treatment, prolonging toxicity [33].

Consequently, individuals might have cured cancer but may continue to experience incapacitating neuropathy induced by antineoplastic treatment [34].

Pre-existing peripheral nerve injuries related to diabetes mellitus, ethanol consumption, hereditary neuropathies, and others may predispose to the development of CT-induced neurotoxicity [28]. Additional potential risk factors may include genetic factors, single nucleotide polymorphisms, decreased creatinine clearance due to compromised renal function and smoking history [34].

Chemotherapy-induced polyneuropathy manifests predominantly by sensory symptoms, with occasional motor and autonomic involvement. The last may include constipation, abdominal pain, bladder disturbances, delayed gastric emptying, postural hypotension and reduced HRV [33].

Drugs typically used in breast cancer treatment are anthracyclines, taxanes, 5-fluorouacil (5-FU)/capecitabine, cyclophosphamide, platinum agents, gemcitabine, vinorelbine and eribulin for chemotherapy; tamoxifen and aromatase inhibitors for endocrine therapy; pertuzumab and trastuzumab as target-therapy.

Anthracyclines, taxanes, vinca alkaloids, and platinum-based agents have all been associated with AD [35]. Although, for cyclophosphamide, capecitabine, 5-FU, gemcitabine, and tamoxifen, there is still no clinically significant evidence of their adverse effects on the ANS [36, 37].

Lesions caused by platinum compounds, such as carboplatin and cisplatin, selectively affect large sensory neurons, thus rarely affecting autonomic neurons. However, a prospective clinical study in 28 metastatic germ cell cancer patients receiving cisplatin, vincristine, and bleomycin showed, in 10 of them, abnormal HR responses to deep breathing, active standing and/or Valsalva manoeuvre, indicating parasympathetic dysfunction. Postural hypotension and

reduction in the 30/15 ratio were also present in two other small studies using cisplatin-based combination chemotherapy and oxaliplatin-based chemotherapy [35]. Although there are some studies concerning the effect of platinum compounds on ANS, none of them is based on a breast cancer population.

In a study on 31 ovarian cancer patients subjected to treatment with taxane paclitaxel and carboplatin, orthostatic hypotension occurred in 19% of them after 3-4 months, with resolution at 6-8 months. Persistent abnormalities were also demonstrated, with changes in cardiac rhythm in response to standing position, reflecting parasympathetic cardiac innervation [35].

Moreover, changes in HR response to Valsalva and deep breathing manoeuvres and abnormal pressor response to isometric handgrips were reported in women with ovarian or breast cancer treated with paclitaxel, suggesting parasympathetic and sympathetic dysfunction [38].

Anthracyclines, such as doxorubicin and epirubicin, have been the backbone of adjuvant CT for breast cancer in the last years, and they seem to alter autonomic function through direct action on adrenergic nerve tissue [39]. High circulating levels of norepinephrine (NE) were detected in patients exposed to anthracyclines, with decreased cardio-autonomic regulation reflected by abnormal HRV before left ventricular dysfunction [40]. Myocardial NE uptake was also decreased with increasing anthracycline exposure, as demonstrated by studies using radiolabelled metaiodobenzylguanidine (MIBG) scintigraphy [2].

These alterations in cardiac and circulating NE concentrations were dose-dependent, being detected before the occurrence of LV dysfunction, which corroborates the hypothesis that anthracyclines affect autonomic signalling through alterations in plasma NE concentration before clinically evident heart failure occurs [2].

The role of anthracyclines in AD in breast cancer patients has been reported in other small clinical studies. A study [41] involving 47 breast cancer patients subjected to a 3-year follow-up post-chemoendocrine adjuvant therapy revealed significantly elevated resting HR despite normal LVEF, compared to age-matched controls. Sinus tachycardia was present in half of the patients who received treatment, including anthracycline and trastuzumab for HER2-positive breast neoplasm, compared to 0% age-matched controls. Furthermore, it was shown that breast cancer patients had a superior mean resting HR during and after adjuvant therapy associated with metastatic disease, compared to breast cancer patients before adjuvant therapy [42]. The causes of higher mean resting heart rate during and after therapy are poorly understood but may include the effects of treatment-induced CT, anaemia and/or autonomic neuropathy, being a strong independent predictor of CV disease [43].

In a study on 20 breast cancer patients with normal LVEF and with asymptomatic AD, previously treated with high-dose anthracycline-based chemotherapy and radiotherapy (RT), HRV was evaluated for time-and-frequency domain indicators, revealing anomalies in 85% of patients, in particular with parasympathetic indicators [35].

Trastuzumab, used to treat HER2-positive breast cancer that is either early- or advanced-stage or metastatic, can cause sympathoexcitation by raising plasma NE and BP values and decreasing neuregulin [44].

Another study with 20 breast cancer patients treated with the combination of anthracycline and trastuzumab or just anthracycline suggested an association between anthracycline use and elevated cardiac sympathetic activity, while the addition of trastuzumab caused an even higher adrenergic hyperactivity. The cardiac sympathetic activity was evaluated by 123I-MIBG, and its changes seemed to precede reductions in LVEF and clinical signs of heart failure [45].

Feng and co-workers suggested the use of deceleration capacity (DC) of HR, a non-invasive tool for the quantitative evaluation of vagus nerve tension, as a measure to predict trastuzumab-associated CT in a study among 150 breast cancer patients. DC values before trastuzumab treatment were robustly correlated with subsequent CT, with lower DC values predisposing to greater risk and earlier beginning of CT [46].

Eribulin and vinorelbine can also be used as later lines of therapy in triple-negative breast cancer [37]. A study with 110 metastatic breast cancer patients revealed a higher incidence of autonomic neuropathy (constipation, paralytic ileus, impotence, bladder atony, orthostatic hypotension, and cardiac problems, assessed by a 12-question questionnaire) with vinorelbine, compared to eribulin, despite the higher number of treatment cycles in the eribulin group [47].

Aromatase inhibitors and tamoxifen can be used for breast cancer treatment with positive hormone receptors. Gonzaga *et al.* found that postmenopausal women with breast cancer using aromatase inhibitors for its treatment (n=15), compared to postmenopausal women without breast cancer (n=33), presented reductions in HRV [48].

Vincristine can be used in the treatment of breast cancer, although currently, it is a last-line choice, given its adverse effects. Vincristine-induced autonomic neuropathy occurs in up to 30% of subjects [30], and includes constipation, paralytic ileus, urinary retention, and orthostatic hypotension, suggesting both sympathetic and parasympathetic involvement [49]. Vinca alkaloids also provoked anomalous changes in HR and BP reaction to tilt testing, hand grip, standing, and deep breathing, which have beenreported in small studies. The onset of autonomic damage occurs early after the beginning of exposure, with recuperation usually occurring after drug discontinuation [35].

In addition to chemotherapy, radiotherapy (RT) also plays an important role in the treatment of breast cancer, reducing local recurrence rates following conservative surgery.

A large study comparing 448 breast cancer survivors with age-and sex-matched controls reported elevated HR at rest and abnormal HRV, frequently seen in the breast cancer cohort. The majority (2/3) of these breast cancer survivors had been subjected to RT [35].

In an observational study involving 171 women (106 outpatient breast cancer survivors and 65 age-matched controls), 54% of the patients had previously undergone CT,

while 72% had undergone RT, and all 106 women were treated with endocrine therapy and/or HER-2-directed therapy. Breast cancer survivors had higher resting HR, slightly higher diastolic BP, lower total RR variance, and RR interval absolute power (i.e., variance in msec2) of low-and high-frequency components of RR variability compared to controls. Patients also presented a significantly lower spontaneous baroreflex sensitivity and a minimal stand-induced change in the low frequency (LF component of HRV, suggesting an impaired vagal performance) [50]. Besides this evidence, studies are lacking on the question of whether radiation for the treatment of breast cancer or anthracycline and/or other cytotoxic agents alone independently impact autonomic function.

4. ADDITIONAL MECHANISMS LEADING TO AUTONOMIC DYSFUNCTION IN BREAST CANCER

In addition to CT and RT, other mechanisms seen in breast cancer patients have been explored as enhancers of AD and, subsequently, CV risk. These mechanisms can be present at the moment of diagnosis or be a result of diagnosis and treatment, constituting modifiable risk factors for autonomic imbalance [2].

Evidence shows that cancer diagnosis and consequent treatment have a major impact on patients' lives, giving rise to psychological problems, such as anxiety, depression, and fatigue in a considerable percentage of cancer patients [51].

Depression is observed in 25-35% of breast cancer patients, commonly co-occurring with anxiety, which is present in >20% of patients throughout their cancer care [52]. Moreover, depressed patients with breast cancer are more prone to reveal AD compared to their equivalents without depression [2].

Psychological stress can be described as a perception of a chronic threat to which our body responds through the activation of two systems: the sympathetic-adrenal-medullary system (SAM) and the HPA axis. This chronic stimulation leads to upregulation of the SAM axis with the release of catecholamines, inciting chronically increased CV activity [53]. Additionally, repeated activation of the HPA axis results in increased levels of cortisol release from the adrenal cortex [53].

Cancer-related fatigue has been reported by >30% of breast cancer survivors and is associated with higher levels of NE and decreased HRV [2]. Patients who have breast cancer with AD also exhibit a decreased exercise capacity [50].

Therefore, patients with depression, anxiety, and/or fatigue exhibit reduced HRV, being a crucial factor that contributes to CV comorbidity [51].

Up to 80% of breast cancer patients also report sleep disturbances [54], as well as 38% of disease-free survivors of breast cancer 5 years following diagnosis. Specific factors present in breast cancer patients are known to contribute to sleep problems, particularly psychological issues, like depression, anxiety and fatigue [55].

Essential physiological processes are regulated by a biological clock located in the hypothalamic suprachiasmatic nucleus that establishes a rhythm to alternate from activity to repose. This rhythm, called circadian, is strictly connected with the light-dark cycle, with a duration of approximately 24 h [56]. Circadian rhythms are vital for the sleep/wake cycle and CV function, influencing other biological activities in coordination with peripheral structures, such as the cardiomyocyte and hepatic circadian clocks, among others [2].

There is a decrease in heart rate and BP at night, being lowest during deep non-REM (Rapid Eye Movement) sleep, reflecting a physiologic parasympathetic cardiac modulation increase. Sympathetic activity and consequent BP and HR are similar during REM sleep and waking hours, increasing in the early morning. The evidence says that the cardiomyocyte circadian clock "schedules" cardiac recovery and growth processes at the beginning of the rest period when the cardiac workload is expected to be lower. Therefore, night time is considered a period of relative protection from CV events due to increased parasympathetic cardiac modulation [2, 57].

Thus, disturbances in the sleep/wake cycle observed in breast cancer patients disrupt the physiological properties of sleep on CV control, creating a mismatch between the increase in CV activity due to lack of sleep at night, and the decreased CV activity expected by circadian rhythms, increasing atherosclerosis burden and, eventually, the risk of CV events during the day, especially the morning hours [57]. In fact, insomnia symptoms were found to be linked to an increased risk of acute myocardial infarction [2].

Weight changes have also shown a strong correlation with autonomic functioning, with weight gain being linked to sympathetic activation and weight loss related to improvements in parasympathetic activity and heart rate recovery (HRR) [2]. Breast cancer patients tend to gain weight, with increases of 2 to 6 kg common in women undergoing chemotherapy [58]. In fact, it is known that this modest weight gain in non-obese patients can potentiate SNS activation, regardless of whether they become obese [59].

Cardiorespiratory fitness decrease is another factor hypothesized to be related to AD in women with breast cancer, although there are few studies on this topic. Assessed objectively as oxygen uptake during maximal exercise (VO2max), cardiorespiratory fitness refers to the highest rate of transport and consumption of oxygen by the body during maximal exercise [60], making it a robust marker of CV risk.

Breast cancer patients undergoing adjuvant chemotherapy experience significant impairments in cardiorespiratory fitness, with lower fitness sustained several years after treatment, to which lifestyle factors, such as weight gain and physical inactivity, may also contribute [58, 61]. Exercise training has been shown to induce increases in vagal tone, simultaneously decreasing sympathetic activity [62]. Additionally, evidence shows that exercise training increases or at least preserves VO2max and functional capacity in women with breast cancer undergoing chemotherapy [63, 64]. Although the facts described above are suggestive of a link between cardiorespiratory fitness and AD since they both improve with exercise training, no studies report the influence of cardiorespiratory fitness loss on autonomic function.

4.1. Changes in Sympathetic and Parasympathetic Nervous System Activity in Early and Advanced Breast Cancer Patients

As described in the sections above, breast cancer treatments produce a shift toward a sympathetic dominant status, with decreased vagal heart tone. Consequently, this autonomic imbalance stimulates the hypothalamic-pituitary-adrenal axis, the renin-angiotensin-aldosterone system, and the endocannabinoid system, leading to increased oxidative stress, reduced vasodilation, increased inflammation, and atherosclerosis progression, predisposing cancer survivors to chronically higher resting metabolic rates, giving rise to several CV risk factors [2, 6]. Indeed, this sympathetic hyperactivity seems to precede LVEF deterioration and heart failure, acting as a prognostic marker for future CV disease [2, 65].

In recent years, the sympathetic nervous system has also emerged as an important regulator of breast cancer progression and metastasis. In fact, β-adrenergic activation in bone promotes an increase in osteolysis and potentiates the vicious metastatic cycle, although the mechanisms by which it promotes disease progression is still complex and information on the sympathetic interactions between breast cancer and bone cells is still scarce [66].

Interestingly, the relation between the sympathetic nervous system and breast cancer in the bone metastatic niche is bidirectional. Not only is sympathetic activity able to induce breast cancer cell engraftment and proliferation, but in opposition, breast cancer may also be able to regulate adrenergic dynamics in the bone niche [66, 67]. Furthermore, adrenergic signalling has been shown to promote proliferation, angiogenesis, immune system modulation, and extracellular matrix invasion [66].

Chronic sympathetic overdrive interferes with beta-receptor distribution, mainly β1-receptors, which become sparse and less responsive to stimulation (desensitization of the receptors), while β2-receptor abundance remains equal, resulting in a relative increase of the latter. The impact of SNS activity on the heart is achieved mainly through β1-receptor stimulation, resulting in increased heart rate and enhanced myocardial contractility, associated with sodium ion channels and calcium ion influx [68]. Increased heart rate reduces the duration of diastole, which is the moment when coronary arteries are perfused, thereby leading to greater myocardial oxygen consumption and decreased myocardial perfusion. Additionally, downregulation of β1 receptors further contributes to decreased strength and contraction frequency, eventually leading to diminished cardiac output.

Evidence suggests that sympathetic stimulation can lead to hyperglycaemia and insulin resistance, and an association with increased leptin levels is also reported [68], contributing to the development of metabolic syndrome, characterized by central obesity, dyslipidaemia, hypertension and elevation of fasting glucose [69]. In fact, insulin and leptin may also have central sympathoexcitatory effects [70]. Moreover, chronic catecholamine stimulus induces endothelial dysfunction, counteracts the vasodilatory properties of NO, accelerates atherosclerosis development, and promotes additional CV

damage [71].

Activated SNS also stimulates the liberation of renin by the kidney, which in turn increases angiotensin and aldosterone concentrations, which are important for the regulation of BP and electrolyte balance [68]. Angiotensin II exerts its primary effects at the cell surface AT1 receptor, inducing vasoconstriction, cell proliferation, aldosterone and antidiuretic hormone release, oxidative stress, inflammation and immune activation, as well as sympathetic stimulation and baroreflex dysfunction [72]. Consequent to these actions, angiotensin II has also been shown to induce cardiac hypertrophy and fluid retention; however, studies have reported that SNS activation itself also has pro-hypertrophic effects on cardiomyocytes [68, 72]. In the long term, the overdrive of SNS could influence myocardial necrosis and apoptosis through abnormal intracellular calcium handling and calcium overload, inducing remodelling of the left ventricle and ultimately heart failure [68].

Regarding parasympathetic activity, increased vagal nerve activity has an inhibitory effect on sympathetic nervous system overactivity, oxidative stress, DNA cell damage and inflammation, being vital in the prognosis of cancer [73 - 75]. It has been proposed as an important candidate route by which the brain receives information about preclinical visceral tumour signals, modulating partly the tumour development and progression [75].

As shown in Table **1**, several studies have suggested an increase in heart rate and a reduction in parasympathetic activity, assessed as high frequency (HF) in breast cancer patients and survivors when compared to healthy controls. Nevertheless, there is a lack of evidence in the literature concerning the effect of breast cancer *per se* on HRV. In fact, the results are inconsistent because the majority of these studies involved patients who had already completed different oncologic treatments, which can influence HRV parameters in addition to other factors, such as type of surgery, time since surgery, BMI, and psychological factors.

Likewise, the effects of the breast cancer stage on HRV remain uncertain. Bettermann *et al.* compared metastatic patients with non-metastatic patients, and HRV was found to be similar [76]. In contrast, in a recent study, others suggested an association between HRV and breast tumour stage, showing that advanced breast cancer patients had significantly reduced HRV compared to the benign and early-stage patient groups, with no statistically significant difference observed between the benign and early-stage groups [77]. Similarly, in patients before any type of cancer treatment, the advanced-stage breast cancer group had lower vagal modulation than early-stage and benign groups; also, the advance-stage group had lower overall HRV compared to those with benign conditions [78]. Examination of resting heart rate across the breast cancer continuum showed mean resting heart rate as lower in breast cancer patients prior to adjuvant therapy compared to during adjuvant therapy, after adjuvant therapy, or in those with metastatic disease, who presented higher resting heart rate [42]. In patients with metastatic or recurrent breast cancer, Giese-Davis *et al.* found that higher resting HF power, which is highly correlated with the vagal tone, significantly predicted

longer overall survival [79]. These studies suggested vagal nerve tone as a long-term predictor of cancer survival and also indicated that, particularly in advanced-stage cancer patients, HF strongly positively correlates with prognosis.

Table 1. Summary of selected studies investigating the changes in autonomic nervous system activity in breast cancer patients and survivors.

Selected Articles	Population	Methodology	Clinical Findings	Conclusion
Wu S *et al*, 2021 [74]	133 patients with BC or benign breast tumors. 3 groups: benign, early-stage (T1–2, N0–1, and M0, and T3N0M0 cancers), and advanced-stage group (T0–4, any N, and M0–1 cancers)	HRV Analysis (Fast Fourier Transform): linear and nonlinear HRV parameters. Multiple logistic regression models to test the independent contribution of HRV to breast tumor stage	Advanced-stage group: ↓SDNN, ↓RMSSD, ↓VLF, ↓LF, ↓HF, ↓TP, ↓SD1, ↓SD2 and ↓CD vs benign and early-stage groups. Benign and early-stage groups: ↔ HRV parameters	These findings suggest an association between HRV and breast tumor stage, and HRV parameters may help construct an effective early diagnostic and clinical prognostic model
Escutia-Reyes D *et al*, 2021 [77]	27 BC survivors (BCS) and 31 controls without cancer	HRV Analysis: linear and nonlinear parameters and body composition measures	BCS: ↓RR intervals, ↑HR, ↓2UV (parasympathetic cardiac activity) and ↑visceral fat vs control	BCS manifest cardiac autonomic modifications and HRV pattern changes compared controls
Stachowiak P *et al*, 2018 [78]	44 BC patients treated with anthracycline	HRV evaluated before, after the first cycle (24h) and after chemotherapy cessation	↓SDNN, ↓SDNN index, and ↓SDANN; ↔HR, ↔ LF, ↔ HF, ↑NT-proBNP	HRV parameters worse 24 h after drug administration and persisted until the end of chemotherapy. Changes in HRV correlate with an increase in NT-proBNP
Arab C *et al*, 2018 [75]	BC patients: early-stage cancer (n = 42; stage I or II BC: Tis-2, N0-1 and M0), advanced-stage cancer (n = 37; stage III or IV BC: T0-4, any N, M0-1) and women with benign breast tumors to serve as a control (n = 37)	HRV (in time and frequency domains, FFT) and questionnaires (International Physical Activity Questionnaire-short form and the Hospital Anxiety and Depression Scale) before cancer treatment	The advanced-stage cancer group had ↓HF vs early-stage group. ↓HF and ↓overall HRV in the advanced-stage group vs benign group. HRV was influenced by age and menopausal status in early-stage group, and by BMI in advanced group	HRV seems to be a promising non-invasive tool for early diagnosis of ANS dysfunction in BC and detection of cardiovascular impairments at cancer diagnosis. Cardiac autonomic modulation is inversely associated with BC staging
Sun F *et al*, 2016 [79]	110 early-stage BC patients with type 2 diabetes. 2 groups: chemotherapy alone (chemo: epirubicin and cyclophosphamide) and chemo+dexrazoxane (chemo+DRZ)	HRV evaluated before and after 6 cycles of chemotherapy by resting heart rate (RHR) and heart rate variability (HRV), which was evaluated by both time and frequency domains	Before chemotherapy, both patients' groups: ↔ HRV After chemotherapy, chemo BC patients: ↓LF, ↓HF, ↑LF/HF and ↑HR vs Chemo+DRZ group	DRZ protects the cardiac ANS in epirubicin-treated early-stage breast cancer patients with diabetes
Palma MR *et al*, 2016 [83]	45 BC patients. 2 groups: BCG1 (undergone BC surgery within the last 18 months) and BCG2 (those whose postoperative periods were more than 18 months) and a control group	HRV indices in the time and the frequency domain and geometric indexes	BC group: ↓RMSSD, ↓SD1, ↓ SD2, ↓BCG2, ↓SDNN and ↓HF vs control group. BCG2: ↓SD1 vs BCG1	BCS exhibited a decrease in overall variability and both sympathetic and parasympathetic activity when compared to women without the disease. The BCG2 manifested more pronounced ANS changes
Azambuja E *et al*, 2015 [80]	82 BC patients with a median follow-up of 18 years. Compared six cycles of oral cyclophosphamide, methotrexate, fluorouracil (CMF) *Versus* two epirubicin-cyclophosphamide regimens	Echocardiographic evaluation and LVEF assessment by magnetic resonance imaging (MRI) compared to CMF-treated ones.	Epirubicin-treated patients: ↑HR, ↑BNP, more abnormal US and ↓LVEF by MRI. ↔ LVEF assessed by echocardiogram or troponin T levels.	After 18 years, epirubicin-treated patients had a lower LVEF by MRI, more abnormal echocardiograms, higher HR compared to patients treated with CMF. However, no major delayed cardiotoxicity was observed

(Table 1) contd.....

Adams SC *et al*, 2015 [6]	13 patients (mixed diagnoses) were assessed immediately before and after 4 cycles of chemotherapy and compared to 12 sex- and age-matched controls	Tilt-table, respiratory sinus arrhythmia and Valsalva maneuver and quantitative sudomotor axon reflex test. Astrand-Ryhming cycle ergometer protocol for cardiovascular reactivity assessment during exercise	ANS impairment at baseline in 30.8 % of patients, which persisted in 18.2 % of patients at follow-up, compared to 0 % of controls at baseline or follow-up	ANS impairment and sudomotor dysfunction provide evidence of cancer- and chemotherapy-related parasympathetic dysfunction as a possible contributor to the pathogenesis of CV disease in cancer survivors
Giese-Davis *et al*, 2015 [76]	87 BC patients with metastatic or recurrent BC (MRBC). A total of 50 patients died during a median follow-up of 7.99 years	HRV analysis and all-cause mortality and survival data. Cox proportional hazards models: association between resting baseline HF-HRV on survival	Patients with MRBC had ↑HF and predicted longer survival. A combination of HF-HRV and HR improved survival prediction. ↓HR predicted longer survival	Vagal activity of MRBC patients predicted their survival, extending the known predictive window of HF-HRV in cancer beyond palliative care
Vigo C *et al*, 2015 [47]	171 sedentary women. 106 BC survivors and 65 controls	ECG, respiratory activity, blood pressure, RR and arterial pressure variability evaluation. Frequency domain method for assess the spontaneous arterial baroreflex control of RR	BC patients: ↓ total RR variance, ↓ LF and ↑HF of RR interval variability and ↓ spontaneous baroreflex sensitivity vs control group	Breast cancer survivors show autonomic impairments: reduced aerobic fitness, altered metabolic proxies, and feelings of fatigue
Jones LW *et al*, 2012 [39]	248 BC patients. 4 cross-sectional cohorts: (1) before, (2) during, and (3) after adjuvant therapy for nonmetastatic disease (stage I through IIIC), and (4) during therapy in metastatic disease (stage IV)	Cardiopulmonary Function (VO2peak); Clinical Parameters and Performance Status	After adjuvant therapy: ↑HR in all BC patients Metastatic disease patients showed higher HR and lower VO2peak. VO2peak was significantly different across breast cancer cohorts	BC patients have marked HR increase and VO2peak impairment across the entire survivorship continuum. This can be an independent predictor of survival in metastatic disease
Jones LW *et al*, 2007 [81]	47 breast cancer patients (average follow-up of 3 years post-chemoendocrine adjuvant therapy) and 11 age-matched healthy controls	VO2peak and cardiovascular function (stroke volume, cardiac output, cardiac power output, and cardiac reserve). Body mass index, lipid profile, and fasting insulin and glucose; C-reactive protein and BNP	↑HR, ↔ LVEF in patients compared with age-matched controls. BC patients had significantly lower peak exercise stroke volume, cardiac output, cardiac power output, cardiac power output reserve, and VO2peak	BC patients treated with adjuvant CET have a significantly and markedly lower cardiorespiratory fitness and cardiac functional reserve compared with age- and sex-matched controls
Jones LW *et al*, 2007 [82]	26 BC patients with HER2/neu-positive treated with Anthracycline-Taxane–containing adjuvant chemotherapy and/or Trastuzumab (mean, 20 months post-chemotherapy) and 10 healthy controls	14 metabolic and vascular established cardiovascular disease (CVD) risk factors, body mass index, cardiorespiratory fitness, and left ventricular systolic function	↑HR in 50% of BC patients (resting HR >110 bpm) vs 0% controls. LVEF <50% in 8% of patients, LVEF remained >10% below pre-treatment values in 38%. ↑BNP in 40% of BC patients	BC survivors treated with adjuvant chemotherapy are at a higher risk of developing late-occurring CVD than age-matched controls due to direct and indirect treatment-related toxicity
Bettermann H *et al*, 2001 [73]	37 BC patients were compared with 37 age-matched healthy women and 40 age-matched female diabetic patients who serve as pathological controls.	HRV analysis (FFT) during day (5 a.m. to 1 a.m.) and night sleep (1 a.m. to 5 a.m.)	During night sleep, all parameters showed a tendency towards lower variability, complexity, or rhythmicity of HRV in BC patients	Metastatic patients and non-metastatic patients had a similar HRV

Breast cancer (BC), controls (CTL), heart rate (HR), heart rate variability (HRV), standard deviation of normal to normal (SDNN), low frequency band (LF), high frequency band (HF), 2UV index (2UV), a symbolic index characterized by three heart periods with two significant unlike variations to assess parasympathetic modulation, frequency-domain parameter total power (TP), standard deviation of short-term variability (SD1), standard deviation of long term variability (SD2), correlation dimension (CD), breast cancer survivors (BCS), standard deviation of the 5 min average NN intervals (SDANN), fast Fourier transform (FFT), body mass index (BMI), autonomic nervous system (ANS), dexrazoxane (DZR), root mean square of the successive differences (RMSSD), breast cancer group 1 (BCG1) and group 2 (BCG2), ultrasonography (US), brain natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), cyclophosphamide, methotrexate and fluorouracil (CMF), magnetic resonance imaging (MRI), cardiovascular (CV), metastatic or recurrent breast cancer (MRBC), electrocardiography (ECG), peak oxygen uptake (VO2peak), carboplatin, 4-epiadriamycin and teniposide (CET).

Besides the retrospective design, small sample sizes, diverse measures of autonomic function, and lack of evaluation of racial differences, age, BMI and lack of long-term follow-up, these studies support AD as an indicator of CV disease risk and the occurrence of AD in patients with advanced breast cancer. However, future studies are needed for a better understanding of the relationship between breast cancer outcomes and HRV parameters and to extend these findings to earlier-stage breast cancers [80 - 86].

Table **1** Summary of selected studies investigating the

changes in autonomic nervous system activity in breast cancer patients and survivors. Breast cancer (BC), controls (CTL), heart rate (HR), heart rate variability (HRV), standard deviation of normal to normal (SDNN), low frequency band (LF), high frequency band (HF), 2UV index (2UV), a symbolic index characterized by three heart periods with two significant unlike variations to assess parasympathetic modulation, frequency-domain parameter total power (TP), standard deviation of short-term variability (SD1), standard deviation of long term variability (SD2), correlation dimension (CD), breast cancer survivors (BCS), standard deviation of the 5 min average NN intervals (SDANN), fast Fourier transform (FFT), body mass index (BMI), autonomic nervous system (ANS), dexrazoxane (DZR), root mean square of the successive differences (RMSSD), breast cancer group 1 (BCG1) and group 2 (BCG2), ultrasonography (US), brain natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), cyclophosphamide, methotrexate and fluorouracil (CMF), magnetic resonance imaging (MRI), cardiovascular (CV), metastatic or recurrent breast cancer (MRBC), electrocardiography (ECG), peak oxygen uptake (VO2peak), carboplatin, 4-epiadriamycin and teniposide (CET).

4.2. Strategies to Improve Autonomic Function

Breast cancer patients experience autonomic function alterations (sometimes silently) early during the disease, being at increased risk for CV repercussions. Few studies have addressed appropriate prevention and treatment strategies. However, exercise practice, weight loss, music therapy, and pharmacologic methods are some of the strategies proposed to counterbalance the effects of breast cancer on autonomic and, ultimately, on CV function. Additionally, it is important to have a team-based approach to health care, with psychologists and exercise therapists, following the strategies presented in the American Heart Association (AHA) scientific statement on cardio-oncology rehabilitation [86].

4.3. Exercise Practice

There is a considerable amount of literature reporting exercise practice not only as a way of improving ANS function, potentially decreasing the cardiovascular risk of breast cancer survivors, but also improving strength and performance, quality of life, and cancer-related fatigue [87].

Aerobic and resistance training contribute to the maintenance of muscle mass, improvement in oxygen transport to muscle mitochondria, decreased oxidative stress and RAAS activation, and upregulate NO bioavailability, resulting in decreased sympathetic tone and increased vagal tone, ultimately decreasing resting HR and increasing HRV and baroreflex sensitivity [65].

Structured aerobic exercise training, during or after cancer therapy, has been shown to reverse AD in breast cancer patients. Kirkham and co-workers studied the effect of supervised aerobic and resistance exercise during and after breast cancer treatment (CT ± RT) in 73 patients, revealing a 6-beat improvement in HR at rest and heart rate recovery (HRR) during CT ± RT, with at least twice/week supervised exercise attendance [3].

Other studies have already reported the effect of exercise on autonomic function: Niederer and co-workers studied cancer patients during and post-treatment, who participated in a 16-week moderate aerobic exercise intervention, with resulting improvements in cardiac autonomic regulation, mainly in HRV [88]. A recent study on cancer patient survivors (n=76) who participated in a 26-week intervention consisting of combined aerobic and resistance training showed improvements in HR at rest [89]. Exercise training also improved direct (muscle sympathetic nerve activity) and indirect (HRR and HRV) measures of autonomic function in heart failure and post-acute myocardial infarction patients [90].

In breast cancer patients subjected to adjuvant therapy, one month of exercise training increased HF and decreased LF and LF/HF ratio in comparison to baseline and breast cancer patients without exercise [62].

In another study on breast cancer patients subjected to adjuvant therapy, one month of exercise training increased HF and decreased LF and LF/HF ratio compared to baseline and breast cancer patients without exercise [62]. Another small study including 17 breast cancer survivors who underwent supervised exercise, three times/week for 12 weeks, showed improvements in CV fitness (with increased VO2max from pre- to post-intervention) and cardiovagal tone and sympathetic activity in patients with outlying pre-intervention assessments [91].

A recent systematic review and meta-analysis that explored the effects of exercise programs on the autonomic modulation, measured by the HRV of patients with cancer and its survivors, showed that exercise programs may lead to positive effects on the overall autonomic control, with an increase in standard deviation of the normal-to-normal (NN) intervals (SDNN; overall HRV), root mean square of successive RR interval differences (RMSSD), and HF, reflecting the stimulation of parasympathetic activity. Significant changes were also found in the LF and the LF/HF ratio between exercise and control groups. Also, beneficial changes may occur with resistance and endurance workouts [92].

Due to the low number of studies, small sample sizes, diverse measures of autonomic function, and lack of long-term follow-up, no further conclusions can be made. Further research is needed to substantiate the findings from these different studies and to provide additional information about the type and exercise intensity required to improve the overall autonomic control and reduce CT in breast cancer patients.

4.4. Weight Loss

Costa and co-workers reported weight loss to be associated with greater parasympathetic activity, as opposed to the sympathetic predominance occurring with weight gain. Diet and exercise seem to be important players in the weight loss process, as they increase parasympathetic activity and decrease sympathetic activity [93]. Furthermore, breast cancer survivors with a high percentage of body fat have increased serum inflammatory markers (*e.g.*, interleukin 6 and C-reactive protein) and endothelial dysfunction, contributing to the poor vascular condition, which could be attenuated by weight loss [58].

4.5. Music Therapy

Music therapy is another strategy to diminish AD, possibly improving anxiety, depression, pain, and fatigue levels in cancer patients. A randomized controlled study on 84 individuals in a palliative context showed that one session of music therapy could induce considerably superior relaxation and welfare, as well as modifications in the HF component of the HRV [87]. A similar study on 100 women with breast cancer demonstrated that a single 45-min music session intervention after 1 week of CT decreased the symptom cluster (fatigue and depression sleep disturbance) compared to the control group, particularly in women with higher sympathetic tone activity [94]. This might be explained by the fact that prolonged sympathetic overactivity causes inadequate energy demands on the body and parasympathetic activity facilitates energy conservation [95]. Although the detailed mechanism is still inconsistent, sympathetic overactivity and parasympathetic underactivity may be important biomarkers of cancer-related fatigue.

Another study on anthracycline-treated breast cancer patients attending long-term music therapy (8 weekly sessions, each lasting 2 h) demonstrated a significant increase in time and frequency-domain parameters of HRV after 8 weeks, particularly those reflecting parasympathetic activity. It is suggested that music therapy activates the parasympathetic nervous system, possibly protecting against congestive heart failure, by reducing the levels of both epinephrine and NE [96].

4.6. Pharmacologic Strategies

Evidence has shown that beta-blockers decrease the risk of anthracycline-induced cardiomyopathy in breast cancer patients and reduce the occurrence of heart failure. Reasons for this might include β-blockade's protective character in cardiac failure by counteracting chronically enhanced sympathetic activity [97]. However, no direct links concerning beta-blockade and AD have been clarified. More studies are needed to investigate the role of beta-blockers in preventing chemotherapy-induced AD and subsequent CV disease in breast cancer patients.

The RAAS, a key pathway implicated in autonomic function, has a significant role in regulating BP and extracellular volume, contributing as well to CV control of neuroendocrine function [72]. Cardioprotective properties of ACE inhibitors and ARBs in patients undergoing CT have been reported [98, 99], but their role in improving CT-induced dysautonomia is less known. Suppression of angiotensin II and its known inhibitory effects on the cardiac vagus nerve could be an important measure in preventing cardiac dysfunction [65]. In the heart failure context, ACE inhibitors and ARBs have been proved to decrease sympathetic muscle activity and cardiac sympathetic tone, and increase baroreflex sensitivity.

Furthermore, spironolactone, an aldosterone antagonist, has proved to improve HRV, decreasing rises in HR in the first morning hours associated with sympathetic reactivity in heart failure patients [72, 100]. A study of 83 patients with breast cancer taking spironolactone every day during anthracycline treatment alleviated the decrease in LVEF [101].

A randomized prospective double-blind placebo-controlled clinical trial showed that in HER2- positive breast cancer patients subjected to trastuzumab and anthracyclines, both carvedilol (non-selective β-adrenergic receptor blocker and an α-adrenergic receptor blocker) and lisinopril (ACE inhibitor) counteracted cardiotoxic effects [102]. Moreover, compared to placebo, pharmacological prevention generated fewer interruptions in trastuzumab treatment [102]. Nevertheless, in patients treated with anthracyclines and trastuzumab, β-blockers induced more promising results in preventing LVEF decline compared to ACE inhibitors/ARB [103, 104].

Based on the available data, the use of beta-blockers or ACEI/ABRs has the potential to reduce CT in breast cancer chemotherapy. As shown by a meta-analysis that included patients receiving anthracycline chemotherapy and/or trastuzumab, ACEI/ARB use is associated with a moderate benefit in LVEF, mainly when initiated before the beginning of cancer therapy in selected cohorts [105]. However, a previous meta-analysis showed that only the prophylactic beta-blockers use in patients who received anthracycline chemotherapy alone was associated with a lesser reduction in LVEF and new heart failure diagnosis. In this meta-analysis, ACEI did not attenuate the development of LV dysfunction or heart failure [106].

The effect of ACEI/ARB in patients who only received anthracycline was also evaluated in a recent meta-analysis. According to this meta-analysis, ACEI/ARB reduced LVEF by 3.2% compared to the control group (p-value <0.00001), without a significant increase in hypotensive events or significant correlation with follow-up time, tumour type, drug type, or geography of intervention [107].

In breast cancer patients who already were using beta-blockers, ACEI and/or ARBs before the diagnosis of breast cancer, a meta-analysis of RCTs concluded that beta-blockers minimised LVEF decline when administered prior to anthracycline chemotherapy, compared to alternate agents [108]. However, this data may be underpowered to demonstrate the benefit of ACEI and combination beta-blocker/ACEI prescription.

Statins have also shown benefits for CT prevention during chemotherapy with anthracyclines [109]. In fact, uninterrupted statin use in breast cancer patients subjected to anthracyclines promoted a decrease in heart failure hospitalization [110]. Additionally, prevention therapy with statins was shown to mitigate a decline in LVEF in breast cancer patients taking anthracyclines compared to controls [111].

Although data are lacking, the use of ivabradine may be an attractive option to treat symptomatic inappropriate sinus tachycardia and should be evaluated [5]. The role of ivabradine, a hyperpolarization-activated cyclic nucleotide-gated channel blocker, was investigated in a study with doxorubicin-treated rats. Ivabradine improved LV function, HRV, and baroreflex responses as well as decreased the sympathetic overactivation induced by doxorubicin [112].

Among the various strategies to prevent anthracycline-induced CT in breast cancer patients, dexrazoxane is the only Food and Drug Administration (FDA) approved drug that has been shown to attenuate AD, reduce the risk of clinical heart

failure and cardiac events, without significantly impacting cancer outcomes, but it is seldom used in clinical practice [82].

These results indicate that using ACEI/ARB, beta-blockers, statins and dexrazoxane may moderately attenuate breast cancer therapy-related cardiac dysfunction, with an unsettling effect on the incidence of heart failure [8, 9] and without effect on overall survival [10, 113], which raises questions about the causal involvement of AD in chemotherapy-induced CT. However, since this data was obtained generally with a retrospective design, difficulties in the assessment of treatment duration and adherence, small population size, and with inconsistent results, large-scale randomized controlled trials are needed to evaluate whether the benefits of pharmacological therapy are clinically relevant during breast cancer chemotherapy before its systematic implementation in clinical practice.

5. NONPHARMACOLOGICAL AUTONOMIC MODU-LATION THERAPIES

Autonomic modulation therapies, including stimulation of the vagal nerve and carotid baroreceptor, may be considered for selected patients with advanced disease [35].

These treatment options may positively influence HRV, baroreflex sensitivity and plasma NE, reducing the expression of inflammatory cytokines (*e.g.*, tumour necrosis factor (TNF)-alfa, interleukin-1 and interleukin-6), which have been associated with the pathogenesis of heart failure, including abnormal β-adrenergic signalling, augmented myocyte apoptosis and myocardial fibrosis, and ultimately unfavourable LV remodelling [114].

Moreover, several experimental studies have shown that vagal nerve activation improves cancer prognosis while vagotomy accelerates tumour growth [115]. Therefore, since breast cancer patients have a low vagus nerve activity, if this nerve is stimulated in these patients, it may reduce therapy-induced inflammation, leading to symptom cluster reduction and prolonged survival [74, 116].

CONCLUSION

Several factors during breast cancer may impair autonomic function in several ways, making this group of patients vulnerable to CV morbidity/mortality.

Although there are some theories, the association between autonomic dysfunction and CV disease in breast cancer patients is still not fully understood, reflecting the importance of future studies with emphasis on autonomic dysfunction and its influence on short-and long-term CV diseases.

It is equally important to develop more and larger clinical trials confirming the effect of antineoplastic treatments on the autonomic nervous system of breast cancer patients, especially focusing on the timing of the autonomic insult.

In addition, research efforts are needed to support the use of the mentioned pharmacological and non-pharmacological strategies aimed at attenuating AD and potentially reduce long-term CV toxicity in this patient population. Routine autonomic testing could serve as an objective measure to evaluate the

response to these strategies.

The emergence of the CV autonomic dysfunction concept in breast cancer patients should generate greater awareness among clinicians for the development of cardio-oncology protocols with a team-based approach to health care.

It is essential to screen and treat autonomic dysfunction as early as possible, preventing its progression to CV disease and improving the prognosis and quality of life, thereby decreasing the morbidity/mortality of breast cancer survivors.

LIST OF ABBREVIATIONS

LVEF	=	Left Ventricle Ejection Fraction
HR	=	Heart Rate
CT	=	Cardiotoxicity
RT	=	HeaRadiotheraphy

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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