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EDITORIAL COMMENT

Autonomic Dysfunction Among Adult Survivors of Childhood Cancer

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Radiation- and chemotherapy-associated neuropathy, including autonomic dysfunction, has been recognized since the mid-1960s.[1] The cumulative effects of chemotherapy and radiation-induced cardiovascular aging and autonomic dysfunction can be debilitating and are associated with increased all-cause mortality among cancer survivors.[2] Moving beyond the initial diagnosis and traditional therapies for autonomic dysfunction, which have heavily relied on extrapolation from other disease states (diabetes mellitus, multisystem atrophy, and Parkinson's disease), there is a current focus on the development of standardized diagnostic criteria, testing, scoring systems, and treatments individualized to patients with cancer.[3-5]

Autonomic dysfunction in patients with cancer can be the result of multiple etiologies, including the cancer itself (direct invasion of autonomic nerves, paraneoplastic syndromes), cancer therapies (chemotherapy, radiation therapy, surgery), medications (opioids, antihypertensives), chronic pain/stress/insomnia, malnutrition/cachexia, or obesity/inactivity, as well as metabolic, electrolyte, and volume imbalances (**Figure 1**). These etiologies frequently overlap, making autonomic dysfunction a challenging condition to treat. Furthermore, the timing of when autonomic dysfunction manifests in patients with cancer or cancer survivors can vary widely, and present at variable timepoints after cancer diagnosis and treatment.

In this issue of *JACC: CardioOncology*, Groarke et al[6] present a cross-sectional study reporting the burden and functional significance of autonomic dysfunction among adult survivors of childhood cancer from the St. Jude Lifetime Cohort. We commend these efforts to assess the total burden of and risk factors for autonomic dysfunction in a large population of carefully phenotyped adult survivors of childhood cancer previously treated with anthracyclines (low, moderate, or high dose), other chemotherapeutic agents, radiation to the mediastinum or head and neck area, or chemoradiation combinations, using community control subjects for comparison. Measures of autonomic dysfunction included the following: elevated resting heart rate (heart rate >80 beats/min) obtained after 10 minutes of quiet sitting, decreased heart rate reserve ([heart rate at peak exercise − resting heart rate]/[age-predicted maximum heart rate − resting heart rate] <80% or <62% if on beta-blockers), decreased systolic blood pressure response to exercise (exercise-induced decrease in systolic blood pressure or failure to increase ≥20 mm Hg from baseline during exercise), or delayed heart rate recovery (difference between heart rate at peak exercise and heart rate measured 2 minutes into recovery of ≤42 beats/min). Participants were placed into 1 of 4 groups defined by the total number of abnormal autonomic function measures (0, 1, 2, and ≥3). Prevalence of each measure of autonomic dysfunction was more than 2-fold higher among cancer survivors compared with controls. Carboplatin, chest-directed radiation therapy, and cranial radiation were associated with an increased likelihood of having ≥2 measures of autonomic dysfunction. Finally, cancer survivors with ≥2 measures of autonomic dysfunction were at increased risk for impaired cardiorespiratory fitness, defined as peak oxygen consumption (V_{O_2}) <80% predicted, compared with survivors without autonomic dysfunction.

Importantly, this study of a large cohort of patients who have survived cancer for at least a decade, not only informs us of the prevalence of autonomic

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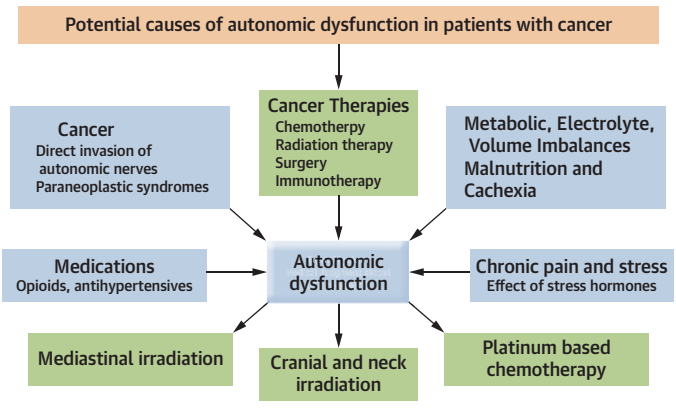
dysfunction, but also describes 3 risk factors of autonomic dysfunction related to exposures: chest radiation, cranial radiation, and platinum-based chemotherapy.

Radiation therapy delivered to the chest is an integral part of the treatment of lung, breast, and esophageal cancers, as well as lymphoma. Although there are clear benefits with cancer control, radiation therapy is also linked to cardiovascular toxicity. Generation of reactive oxygen species, cellular senescence, apoptosis, and subsequent fibrosis are elements of radiation-induced acute and chronic inflammation that can affect, not only the autonomic nervous system, but also the cardiovascular organ system, which can contribute to the development of autonomic dysfunction. Similarly, cranial irradiation can cause acute inflammatory and chronic fibrotic injury to the carotid sinus nerve leading to afferent baroreflex failure and autonomic dysfunction. The third identified risk factor of chronic autonomic dysfunction by the study of Groarke et al[6] was platinum-based chemotherapy. Platinum-based chemotherapy has been used for the treatment of a wide range of both hematologic cancers (leukemias/lymphomas) and solid cancers (head and neck, lung, breast, ovarian, testicular, cervical cancers, and sarcomas). Neurotoxicity is a well-established toxicity associated with platinum-based chemotherapy, and even though the exact mechanism is not fully understood, it has been linked to DNA and mitochondrial damage, oxidative stress, axonal degeneration, and impaired neuronal repair, as well as the inflammatory response it induces. Chemotherapeutic agents that have been associated with autonomic dysfunction in other published studies include taxanes and proteasome inhibitors. With immune and targeted therapies, today's "fourth dimension" of cancer treatment, we only have case reports of autonomic dysfunction available, and an unanswered question remains about the prevalence and mechanism of their short- and long-term adverse effects, including autonomic dysfunction.

Despite our current limitations with understanding and treating autonomic dysfunction in cancer survivors, we believe persistence, resilience, and optimism will lead to meaningful advancements in the care of these patients. Early detection of autonomic dysfunction, when it is still may be reversible, and identification of all possible causes/mechanisms involved, are important steps for the development of successful treatment strategies and guidelines.

FIGURE 1 Possible Causes of Autonomic Dysfunction in Patients With Cancer



Previous literature suggests that the possible causes of autonomic dysfunction in cancer patients include cancer, by direct invasion or paraneoplastic syndromes, cancer therapies (chemotherapy, radiation therapy, immunotherapy, or surgery), medications, chronic pain and stress, malnutrition and cachexia, or metabolic, electrolyte, and volume imbalances.

Furthermore, towards that aim, we propose the use of standardized autonomic dysfunction definitions and testing, such as those recommended by the American Autonomic Society,[7] along with a high suspicion and low threshold of testing among patients with cancer and cancer survivors. Use of standardized definitions and testing can guide future clinical trials that examine the efficacy of treatments aimed at patients with confirmed autonomic dysfunction to discover strategies that can reduce morbidity and mortality, and improve quality-of-life. Although agents such as metoprolol, ivabradine, midodrine, and fludrocortisone have been used empirically in the treatment of cancer patients with autonomic dysfunction, with some documented benefits, they still need to be tested in large prospective trials. We remain hopeful for the continued generation of additional evidence to advance the care of this population.

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