Review Article

Autonomic dysfunction in early breast cancer: Incidence, clinical importance, and underlying mechanisms

Susan G. Lakoski, MD, MS,[a] Lee W. Jones, PhD,[b] Ronald J. Krone, MD,[c] Phyllis K. Stein, PhD,[d] and Jessica M. Scott, PhD[e] *Burlington, VT; New York, NY; St Louis, MO; and Houston, TX*

Autonomic dysfunction represents a loss of normal autonomic control of the cardiovascular system associated with both sympathetic nervous system overdrive and reduced efficacy of the parasympathetic nervous system. Autonomic dysfunction is a strong predictor of future coronary heart disease, vascular disease, and sudden cardiac death. In the current review, we will discuss the clinical importance of autonomic dysfunction as a cardiovascular risk marker among breast cancer patients. We will review the effects of antineoplastic therapy on autonomic function, as well as discuss secondary exposures, such as psychological stress, sleep disturbances, weight gain/metabolic derangements, and loss of cardiorespiratory fitness, which may negatively impact autonomic function in breast cancer patients. Lastly, we review potential strategies to improve autonomic function in this population. The perspective can help guide new therapeutic interventions to promote longevity and cardiovascular health among breast cancer survivors. (Am Heart J 2015;170:231-41.)

Because of significant improvements in early detection and adjuvant therapy, early breast cancer patients are now expected to live long enough to be at risk for competing causes of death.[1] Cardiovascular disease (CVD) is rapidly becoming the predominant cause of mortality in breast cancer survivors older than 60 years.[2] The magnitude of this problem is likely to increase with the aging of the US population, improvements in breast cancer–specific survival, and the continued use of antineoplastic agents with cardiovascular toxicities. Thus, given the nearly 3 million breast cancer survivors in the United States, the number of women at excess risk for CVD is likely to increase dramatically over the next 2 decades, requiring specific strategies to predict and mitigate these risks.

From the [a]Department of Internal Medicine, Vermont Center on Behavior and Health, Vermont Cancer Center, University of Vermont, Burlington, VT, [b]Memorial Sloan Kettering Cancer Center, New York, NY, [c]Washington University School of Medicine, St Louis, MO, [d]Division of Cardiology, Washington University School of Medicine, St Louis, MO, and [e]NASA Johnson Space Center; Universities Space Research Association, Houston, TX.

Conflicts of interest: Dr Lee Jones is a cofounder of a commercial company, Exercise by Science, Inc.

Dr Lakoski is supported in part by the National Institute of General Medical Sciences/ National Institutes of Health (P20GM103644-01A1). Dr Jones is supported in part by grants from the National Cancer Institute.

Submitted March 28, 2015; accepted May 25, 2015.

Reprint requests: Susan G. Lakoski, MD, University of Vermont, Department of Internal Medicine, 208 South Park Dr, Colchester, VT 05446.

E-mail: susan.lakoski@uvm.edu

0002-8703

http://dx.doi.org/10.1016/j.ahj.2015.05.014

Adjuvant therapies used in the current treatment of early breast cancer are associated with unique and varying degrees of direct (eg, cardiac dysfunction) as well as indirect (eg, unfavorable CVD risk factors) sequential and progressive cardiovascular insults.[3] In current oncology practice, the "cardiovascular" impact of cytotoxic therapies is evaluated solely by changes in resting left ventricular ejection fraction (LVEF). However, LVEF is load, rate, and contractility dependent; and acute declines in myocardial function can be initially compensated for to maintain cardiac output.[4] Thus, left ventricular dysfunction is a *late* marker, only becoming evident after significant myocardial damage has already occurred. Therefore, alternative tools are required to identify patients at high risk for adverse cardiovascular impacts before significant damage develops.

The term *autonomic dysfunction* describes a loss of normal autonomic regulation of the cardiovascular system associated with both excessive sympathetic nervous system (SNS) activation and a reduced ability of the parasympatheic nervous system (PNS) to deactivate appropriately. Autonomic dysfunction can result in increased heart rate, atrioventricular node conduction, and left ventricular contractility.[5] The autonomic nervous system also regulates various hormonal systems including the hypothalamic-pituitary-adrenal axis, the renin-angiotensin-aldosterone system (RAAS), and the endocannabinoid system. Thus, autonomic dysfunction may also promote oxidative stress, reduce vasodilation, increase chronic inflammation, and accelerate atherosclerosis progression leading to CVD.[6,7] Clinically, the onset and progression of autonomic

dysfunction can manifest through chronically elevated heart rates and a loss of normal heart rate variability (HRV), which becomes both a marker of increased risk and, through decreased cardiac resilience, a mediator of adverse cardiovascular consequences.[8,9]

The current review will highlight the emerging data on autonomic dysfunction as a cardiovascular risk marker among breast cancer patients. We will review current methods for assessing cardiac autonomic function and the effects of antineoplastic therapy on autonomic function. We will also discuss secondary exposures—such as psychological stress, sleep disturbances, weight gain/metabolic derangements, and loss of cardiorespiratory fitness—that occur in breast cancer patients and may adversely impact autonomic function. Finally, potential strategies to prevent and/or mitigate autonomic dysfunction will be discussed. Ultimately, this review sets the stage for future studies to unravel potential interventions via the autonomic pathway to prevent competing risk of CVD among breast cancer patients.

Measures of cardiac autonomic function

Healthy autonomic function is the capacity of the autonomic nervous system to deliver appropriate stimulatory and inhibitory signals through sympathetic and parasympathetic pathways. The interplay between sympathetic and parasympathetic inputs is vital for the regulation of cardiac output via changes in heart rate, electrical conduction, left ventricular contractility, vascular tone, and blood pressure.[10]

Changes in cardiac autonomic function can be tracked by several techniques (Table I). The simplest measure of cardiac autonomic status is resting heart rate. Greater autonomic dysfunction is associated with increasing resting heart rates over time.[11] A more robust measure of autonomic function is HRV, which is measured using continuous heart rate monitoring. Heart rate variability is a set of parameters that reflects interval fluctuations between sequential beats of the heart.[12] Measures derived from interval differences between *successive* beats reflect parasympathetically modulated changes in heart rate. Other HRV measures reflect the combined signaling of the 2 arms of the autonomic nervous system and reflect both intrinsic (eg, baroreflex, renin-angiotensin, sleep cycles, circadian) and extrinsic (activity, rest) rhythms.[13] In general, decreased or decreasing HRV would be a signal for worse cardiac autonomic dysfunction. However, a higher, but more disorganized, HRV pattern, detectable by certain "nonlinear" HRV measures, also reflects greater cardiac autonomic dysfunction.[14] Ideally, HRV is measured using a 24-hour ambulatory monitoring that can capture both daytime heart rate patterns and heart rate patterns during sleep, providing insights into circadian rhythm, sleep quality, and possible sleep-disordered breathing or periodic limb movements,[15] all of which affect cardiac autonomic functioning. However, significant clinical information can be obtained from shorter recordings performed, perhaps, at the time of clinical visits and in association with standard "bedside autonomic tests."[16]

Heart rate recovery (HRR) and chronotropic competence, assessed after submaximal or maximal exercise stress testing, also reflect the health of cardiac autonomic regulation. Traditionally, HRR is measured as the difference in heart rate assessed at peak exercise and 1-minute postexercise. A reduction of <12 beat/min or the 10th percentile within the first minute reflects inadequate reactivation of the parasympathetic nervous system poststress.[17] Chronotropic competence describes the ability of the heart to adjust its intrinsic rate appropriately for the level of cardiovascular demand during exercise testing. Chronotropic competence is commonly determined from measurement of heart rate reserve (difference between heart rate at peak exercise compared with rest) or achievement of age-predicted maximal heart rate.

Autonomic dysfunction is a prognostic marker of short-term and long-term CVD risk

The importance of autonomic dysfunction as a marker of CVD risk was first demonstrated in a series of studies of canines subjected to transient ischemia in the post–myocardial infarction (MI) setting. In these studies, the presence of parasympathetic activity (or lack of sympathetic activation) was associated with a lower incidence of sudden cardiac death.[18] A subsequent study in humans demonstrated that decreased HRV and an impaired baroreceptor reflex were prognostic of cardiac death independent of baseline LVEF among post-MI patients. After 21 months of follow-up, impaired 24-hour HRV was associated with a 3-fold higher risk of cardiac mortality in men and women (hazard ratio, 2.8; 95% CI, 1.2-6.2) compared with individuals with normal HRV measures.[19] Cole et al[20] extended these findings by showing that HRR after exercise testing was strongly predictive of all-cause mortality after multivariable adjustment (hazard ratio, 2.0; 95% CI, 1.5-2.7) among individuals referred for exercise testing. This has been corroborated by others and found to be independent of angiographic severity and cardiac function.[21] Importantly, more recent studies suggest that resting heart rate, the simplest measure of autonomic functioning, is also a powerful predictor of future CVD events and survival. Cooney et al[22] found that, among 10,519 men and 11,334 women followed in a Finnish population-based study, a 15-beat increase in resting heart rate was associated with a 24% and 32% increase in future cardiovascular death in men and women, respectively. Moreover, in a 2012 study of 112,680 men and women pooled from 12 cohort studies, higher resting heart rate (≥80 beat/min compared with <65 beat/min) was associated with an increased risk of both CVD events