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COMMENTS AND CONTROVERSIES

Running on Empty: Cardiovascular Reserve Capacity and Late Effects of Therapy in Cancer Survivorship

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Seminal investigations by Frank[1] and Starling[2] provided the first evidence that the heart possesses inherent reserve capacity—a key principle that is a pillar of modern cardiology research and practice. After 150 years of research, we now understand that cardiovascular reserve capacity (CVRC) is determined by the integrative ability of cross-system mechanisms (eg, neurohormonal, central, and peripheral oxygen delivery[3]), which collectively possess remarkable adaptive capacity. Sequential as well as concurrent pathologic perturbations to either one or more of these mechanisms are offset by initial compensatory adaptive responses in other component systems to maintain whole-body homeostatic regulation—a process termed coordinated adaptation.[4] Unfortunately, CVRC is finite, and continued insults ultimately lead to overt dysfunction (eg, acute coronary syndromes, left ventricular dysfunction). Pathologic impairments in CVRC are etiologic in many chronic disease conditions and are thus an integral consideration in daily practice. The purpose of this commentary is to provide an overview of the guiding principles and application of CVRC in the oncology setting using early breast cancer as an illustrative model.

Measurement of CVRC

In current oncology practice, evaluation of CVRC is almost exclusively determined via resting assessment of left ventricular ejection fraction (LVEF) via echocardiography or radionuclide angiography, typically before administration of potentially cardiotoxic adjuvant therapy. Using these approaches, the incidence of heart failure with modern anthracycline- and trastuzumab-containing regimens is $< 5\%$, with corresponding rates of asymptomatic LVEF reductions between 10% and 50%.[5-7] Resting LVEF, however, provides a snapshot of cardiac performance under optimal circumstances. Moreover, in addition to being load, rate, and contractility dependent, resting LVEF is not a sensitive measure of early myocyte (subclinical) damage[8] and is not prognostic in patients with preserved LVEF ($> 50\%$).[9] Emerging techniques such as tissue Doppler imaging,[10,11] speckle-tracking strain echocardiography,[12] and magnetic resonance imaging[13] may provide more sensitive detection of cardiac injury, although supporting evidence is currently limited. Impairments in other cardiac parameters such as diastolic relaxation and filling also occur after breast cancer treatment, despite preserved LVEF.[14-16]

The application of system stress is a hallmark method to detect subclinical myocardial impairments and coronary artery disease (CAD).[17] Both nonpharmacologic (exercise) and pharmacologic (eg, dobutamine, dipyridamole) stress are commonly applied in conjunction with conventional imaging approaches to detect obstructive CAD.[17,18] In this setting, exercise testing and determination of inotropic (contractile) reserve are independent predictors of prognosis beyond clinical factors, coronary anatomy, and LVEF.[19,20]

Extending Beyond the Heart

CVRC is determined by the integrative capacity of the cardiopulmonary system; thus it seems plausible that therapy-induced myocardial injury may occur in conjunction with (mal)adaptation in other organ components. Many anticancer therapies cause unique and varying degrees of injury to the cardiovascular system (ie, pulmonary-vascular/blood-skeletal muscle axis). For example, radiation and certain forms of systemic therapy (eg, chemotherapy, molecularly targeted therapies) can cause pulmonary dysfunction, anemia, endothelial dysfunction, and arterial stiffness and likely skeletal muscle dysfunction (eg, reduced oxidative phosphorylation).[21-25] These direct insults occur in conjunction with indirect lifestyle perturbations (eg, physical inactivity) that synergistically cause marked impairments in CVRC. We have termed this phenomenon the multiple-hit hypothesis.[21] Hence, tools with the ability to evaluate integrated cross talk between cardiovascular organ components may arguably provide the most accurate characterization of global (whole-body) CVRC.

To this end, incremental exercise tolerance testing, which evaluates cardiorespiratory fitness (ie, efficiency of the cardiopulmonary system to deliver and use oxygen to resynthesize ATP), is a powerful predictor of cardiovascular and all-cause mortality in a broad range of adult populations.[26,27] Of relevance, we found that despite preserved LVEF $\geq 50\%$, cardiorespiratory fitness was significantly impaired in patients with early breast cancer a mean of 3 years after the completion of adjuvant therapy, compared with women of the same age without a history of breast cancer.[28] Specifically, patients reached a predicted cardiorespiratory fitness for a particular age group (eg, 40 years) approximately 20 to 30 years earlier than age-matched women without a history of cancer. The combination of global CVRC assessment with cardiac biomarkers could also provide a powerful approach. Cardiac troponin T, troponin I, and *N*-terminal pro-brain natriuretic peptide are independent predictors of cardiovascular disease (CVD) mortality

in healthy populations[29,30] and of cardiotoxicity in patients with hematologic and solid malignancies.[31,32]

Clearly, a number of tools are available to oncology professionals to both detect and monitor therapy-induced cardiovascular injury. When used appropriately, such tools should accurately characterize CVRC and provide additional decision-making information beyond that provided by current established techniques, allowing more accurate prognostication and early intervention. Evidence-based recommendations to guide the selection of method(s) are not available in the oncology setting but are well established in cardiovascular medicine.[33] For example, the American College of Cardiology/American Heart Association recommend that CVRC evaluation of patients presenting with heart failure include subjective symptomatic classifications (ie, New York Heart Association functional classification) as well as exercise tolerance testing.[33] Although guidelines are not currently available, we contend that evaluation of CVRC should be initially considered for patients receiving antitumor agents/regimens known to cause cardiac damage or for those presenting with CAD risk factors that increase the risk of cardiotoxicity. However, anticancer agents likely cause unique and varying degrees of injury to all components of the cardiovascular system; thus assessment of CVRC could arguably be considered for all patients initiating adjuvant therapy. Such recommendations are not evidence based at present, and the ideal method(s) for predicting acute and/or late-occurring CVD in the oncology setting has not been established.[34] Additional studies are now required to determine the feasibility, cost, and clinical importance of CVRC testing in breast as well as other cancer populations.

Increasing Importance of Evaluating CVRC in Early Breast Cancer

The Childhood Cancer Survivor Study (CCSS), a prospective cohort of more than 20,000 adult survivors of childhood cancer, has demonstrated that significant improvements in cancer-specific survival come at the expense of considerable increased risk of competing causes of morbidity and mortality.[35] Specifically, in comparison with a sibling comparison group, the relative risk of congestive heart failure, CAD, and cerebrovascular events was 15.1 (95% CI, 4.8 to 47.9), 10.4 (95% CI, 4.1 to 25.9), and 9.3 (95% CI, 4.1 to 21.1), respectively, 25 years after primary diagnosis.[36] The long-term follow-up ($>$ 25 years) results highlight the prolonged latency required from initial exposure to development of major events. Of similar importance, significant improvements in early detection and adjuvant therapy have also resulted in dramatic reductions in the risk of cancer-specific mortality after a diagnosis of early breast cancer.[37] Consequently, younger and middle-age patients with breast cancer now have sufficient survival to be at risk for competing mortality. Thus, is it plausible to ask whether the CCSS experience provides a relevant benchmark to estimate the future extent and magnitude of cardiovascular late effects in the estimated 2.5 million adult breast cancer survivors?

Clearly, the mechanisms of injury are likely unique between children and adults, given that anticancer therapy is administered during cardiac development in the pediatric oncology population. Nevertheless, juvenile hearts possess tremendous reserve capacity, which is in contrast to adult patients with cancer, in whom anticancer therapy is generally initiated when CVRC is already significantly diminished because of aging and comorbid conditions (especially in those age $\geq$ 65 years).[38,39] As such, it could be speculated that therapy initiated in elderly patients could cause equal or possibly accelerated manifestation of CVD. Intriguingly, emerging evidence indicates that CVD is now the predominant cause of mortality in the population of women diagnosed with early-stage breast cancer, especially in those diagnosed at age $>$ 50 years.[40-43] Moreover, it seems that patients with breast cancer may have excess CVD risk compared with age-matched control women without a history of cancer.[44,45] It is important to remember, however, that the burden of CVD in recently published studies reflects the management patterns for early-stage breast cancer 15 to 20 years ago, not those associated with modern therapeutic approaches. On one hand, the risk of late-occurring CVD may be lower because of the introduction of newer radiotherapy techniques and wide recognition of anthracycline-induced cardiotoxicity. On the other hand, these advances could be offset by more aggressive use of anthracyclines (higher doses and shorter intervals between cycles), approval of newer adjuvant cytotoxic agents (taxane-based regimens) and hormonal regimens (aromatase inhibitors), and introduction of molecularly targeted therapies (human epidermal growth factor receptor 2– directed therapies), all of which have different cardiovascular safety profiles than historical regimens. Modern adjuvant therapy is also generally administered for longer durations, with a growing trend toward extended adjuvant therapy, which increases the period of exposure and possibly the extent of cardiovascular injury.

A conceptual model to illustrate the suspected trajectories of therapy-induced declines/recovery in CVRC, based on prior work in early breast cancer,[28,47,48] is presented in Figure 1. As outlined, the trajectory of change in CVRC across the breast cancer treatment continuum is contingent on the interaction between patient CVRC at

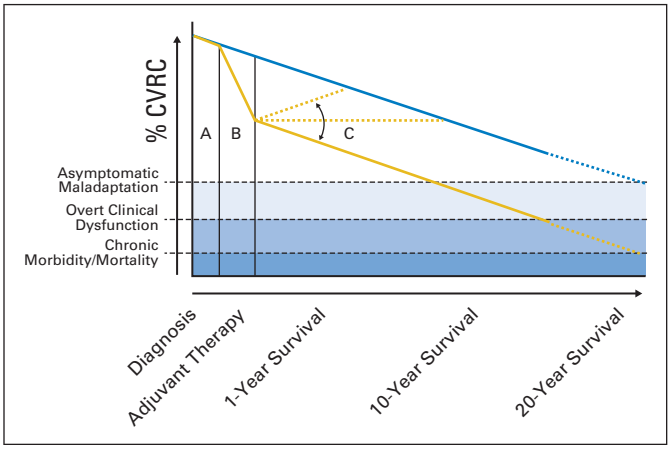

Fig 1. Trajectory decline in cardiovascular reserve capacity (CVRC) across the breast cancer survivorship continuum. The postulated trajectories of decline in CVRC in patients with early-stage breast cancer (gold lines) compared with age-matched decline in women without a history of breast cancer (blue line). Specifically, (A) at diagnosis, baseline CVRC is determined by nonmodifiable (age, genetic predisposition) and modifiable risk factors (eg, hypertension, obesity, physical inactivity). (B) After initiation of adjuvant therapy, the extent and magnitude of decline in CVRC is determined by the direct and indirect effects of the selected treatment management plan and its interaction with modifiable and nonmodifiable risk factors. Several trajectories of change in CVRC, as assessed by left ventricular ejection fraction and cardiorespiratory fitness, have been observed (C) after completion of adjuvant therapy: continued declines in CVRC,[28,49] spontaneous acute recovery,[50] and plateau.[51] Ultimately, however, similar to age-matched women without a history of cancer, patients with breast cancer are subjected to normal age-related and comorbid pathologies. As CVRC depletes below a critical threshold, asymptomatic maladaptation occurs, which, without intervention, leads to overt clinical dysfunction (eg, heart failure, myocardial infarction) and ultimately chronic morbidity and premature mortality.

diagnosis, which is determined by nonmodifiable (eg, age, genetic predisposition) and modifiable (eg, lifestyle, CVD risk factors) determinants, and the direct as well as indirect effects of the selected treatment management plan. After adjuvant therapy, a proportion of patients will experience an acute spontaneous recovery in CVRC[49,50]; a larger proportion, however, will sustain a marked, potentially irreversible,[49] impairment in CVRC. As with healthy women, breast cancer survivors are ultimately subjected to the normal age-related increases in risk factor burden and comorbidities that contribute to the established trajectory declines in CVRC.[46] Unfortunately, those women experiencing irreversible CVRC impairments during adjuvant therapy will lack the required CVRC to withstand normal age-related pathologies. As a result, the incidence of clinical overt dysfunction occurs at a much earlier age (Fig 1) than that observed in age-matched women without a history of breast cancer.

Where to Go Next

If the tenets of the multiple-hit hypothesis are true, why is there not a greater extent of acute and long-term cardiovascular toxicity in recent phase III trials[51-53] and meta-analyses?[54,55] Several potential explanations may explain this incongruence: one, evaluation of subclinical cardiotoxicity or CVRC is seldom studied or reported in the adjuvant setting; two, most trials, with few exceptions, have limited cardiac follow-up and variable cardiac end point reporting; three, adjudication of cause of death can be unreliable; four, few trials report even 10-year outcomes; five, long-term outcomes are not yet available for adjuvant trastuzumab or third-generation aromatase inhibitor trials; and six, data on the real-world incidence of cardiovascular toxicity are limited in a nontrial context and could be expected to be higher given the preponderance to exclude women with more unfavorable cardiovascular risk profiles.[56]

Clearly, many questions remain to be addressed, and the clinical utility of CVRC in the oncology setting is in its infancy. Of relevance, the CCSS investigators recently established the St Jude Lifetime Cohort, which will, among other things, evaluate physiologic mechanisms underlying therapy-induced late effects in adult childhood cancer survivors using a wide battery of quantitative assessments together with collection of patient-reported outcomes and tissue specimens.[57] The establishment of similar cohort studies in adult patients with breast and other cancers that include evaluation of CVRC are urgently required to fully understand the prevalence, magnitude, and pathophysiologic mechanisms of therapy-induced late cardiovascular effects. Such efforts, in conjunction with existing tools used in the oncology setting, should inform treatment stratification, mortality-risk prediction, and surveillance of therapy-induced toxicity/recovery across the cancer survivorship continuum. Furthermore, this information, in turn, can guide the design and implementation of preventive and early-intervention strategies to abrogate or reverse impairments in CVRC.

In conclusion, it is becoming increasingly apparent that surviving early-stage breast cancer comes with the risk of late-occurring CVD. The importance of CVD is likely to further increase with continual improvements in breast cancer–specific outcomes, along with the rapidly aging population. If current trends continue, adjuvant therapy–associated CVD may hinder further improvement in overall survival after a diagnosis of early breast cancer. The landscape of breast cancer prognosis and survivorship has and will continue to change dramatically over the next two decades; with such changes, the central tenets and implications of CVRC are poised to become increasingly important concepts in individualizing the curative-intent management and long-term surveillance of breast cancer and other adult oncology populations.

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