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EDITORIAL COMMENT

Moving the Pendulum for Earlier Detection of Systolic and Diastolic Dysfunction in Cancer Survivors*

Rafael E. Toro-Manotas, MD, Sebastian D. Santos-Patarroyo, MD, Hector R. Villarraga, MD

New advances in cancer treatments, multiple prevention strategies, and screening campaigns have improved the early diagnosis and consequently reduced the death rate for patients with cancer. Survival for these patients has improved in the past 4 decades, and now attention to long-term adverse effects of cancer therapies, such as heart failure (HF), is becoming essential.[1,2] Cardiotoxicity is an important complication of cancer treatment and has been addressed now in the cardio-oncology literature as cancer therapeutics-related cardiac dysfunction (CTRCD). Classically, CTRCD is defined by a reduction in left ventricular ejection fraction (LVEF) of ≥10% to a value <50%; besides LVEF, other methods that can diagnose subclinical cardiac dysfunction, such as global longitudinal strain (GLS), are also available in the toolbox.[3] GLS has emerged as a sensitive and reproducible measurement to be performed in oncology patients and was included in the 2022 cardio-oncology guidelines from the European Society of Cardiology as a surrogate of CTRCD when a relative decline of >15% from baseline GLS occurs.[4] Current recommendations state that echocardiography is the first-line imaging modality to assess cardiac function in patients with cancer before, during, and at follow-up for cardiotoxic treatments.[4,5]

GLS measured by 2-dimensional speckle-tracking echocardiography has gained great momentum as a novel technique for the evaluation and early detection of myocardial systolic dysfunction. Change in GLS occurs before a decline in LVEF, and its clinical usefulness has been demonstrated extensively in cardio-oncology.[3,6,7] Systolic impairment is often accompanied by diastolic abnormalities; for that reason, identification of patients with diastolic dysfunction (DD) before a drop in ejection fraction but with abnormal GLS may play an important role in this patient population.

Although changes in left ventricular (LV) systolic function are considered the cornerstone of CTRCD, assessment of diastolic function is an integral part of the comprehensive evaluation of patients treated for malignancies, but its prognostic value has been modest.[8] Some studies have demonstrated an impact of chemotherapeutic agents on diastolic function,[8,9] but these findings have been inconsistent, and its association with further systolic dysfunction remains controversial.[10] A recent study incorporated the newer classifications of DD grading that divides patients into 3 groups according to a stepwise evaluation of the different diastolic echocardiographic variables.[8] It revealed that baseline DD did not correlate with a decline in systolic function, but new onset or worsening grade of DD was associated with a change in GLS and subsequent LVEF decline with the development of CTRCD.[8]

In this issue of *JACC: CardioOncology*, Palmer et al[11] present the largest cohort of adult survivors of childhood cancer from the SLIFE cohort treated with anthracycline-based chemotherapy, with and without chest radiation. A total of 3,342 patients, with median age at diagnosis of 8.1 years (IQR [Q1-Q3]: 3.6-13.7 years) underwent echocardiography with

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From the Department of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota, USA.

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evaluation and grading of DD at a median age of 30.1 years for baseline echocardiography and 36.6 years for follow-up. Patients were survivors of different childhood malignancies, including hematological, central nervous system, bone, and soft tissue. Diastolic parameters evaluated were E/e′ ratio, septal and lateral e′ velocity, tricuspid regurgitant velocity, and left atrial volume index. DD was graded as per current guidelines.[12] DD was present in 15.2% of patients at baseline echocardiography and in 15.7% at follow-up, with predominant grade I DD at both time points in all comers. The group with normal LVEFs showed an incidence of DD of 2.2% at baseline and 3.7% at the second echocardiographic examination, and the most important contribution from this study is that in patients with normal LVEFs and abnormal GLS (cutoff value −15.9%) as a surrogate of LV systolic dysfunction, DD incidence substantially increased to 9.2% and 9.0% at baseline and follow-up, respectively. In patients with reduced LVEFs, DD was present in 86.3% at baseline echocardiography and in 91.8% at follow-up. These findings show that subclinical identification of LV systolic dysfunction by GLS has a role in the identification of patients with DD after cancer treatment even when LVEF is within normal limits.

Diastolic function assessment plays an important role in the comprehensive evaluation of patients with HF. The latest guidelines recommend evaluation of diastolic parameters in every patient with newly diagnosed HF, independent of baseline LVEF.[13,14] Likewise, different studies have extensively linked DD in patients without HF with subsequent development of this disease.[15,16]

However, the relevance of DD as a prognostic tool in HF with reduced ejection fraction has been overlooked. Recent studies have demonstrated that altered diastolic parameters such as E/e′ ratio are associated with worse HF at diagnosis and increased mortality, showing the important role of DD in risk assessment in these patients.[17]

DD also plays a significant role in the pathophysiology and development of HF with preserved ejection fraction, as well as in its diagnosis.[13,14,18] DD has an impact on clinically relevant adverse outcomes, such as symptoms, HF hospitalization, and mortality. Although DD has a central relevance in HF with preserved ejection fraction, not every patient with DD will develop the disease, and other cardiovascular risk factors, such as obesity, hypertension, old age, and use of cardiotoxic agents, are important in the spectrum of this condition.[18] Given that HF occurs in patients treated for cancer, especially with anthracyclines,[2] diastolic function assessment becomes relevant in the comprehensive follow-up of cancer survivors.

This important study from the SJLIFE cohort contributes significant information to the understanding of long-term cardiovascular impairments related to cancer treatment. It is the first study to evaluate the prevalence and progression of DD in this population, especially in those with subclinical systolic myocardial dysfunction by GLS criteria. Despite the current definitions of CTRCD focusing on systolic function, these results show that the incidence of DD occurs in adult survivors of childhood cancer and provide evidence that supports diastolic assessment as part of the comprehensive evaluation of cancer treatment-related cardiac toxicity. Additionally, these findings suggest that the use of GLS adds an extra layer in the earlier detection of LV systolic dysfunction and may identify cancer survivors at risk for CTRCD before changes in LVEF occur. These changes described in the SLIFE cohort could be explored as predictors of the future development of CTRCD and HF.

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ADDRESS FOR CORRESPONDENCE: Dr Hector R. Villarraga, Mayo Clinic, Department of Cardiovascular Medicine, 200 First Street SW, Rochester, Minnesota 55905, USA. E-mail: villarraga.hector@mayo.edu.

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