JACC: CARDIOONCOLOGY VOL. 5, NO. 4, 2023

EDITORIAL COMMENT

Predicting Left Ventricular Dysfunction in Childhood Cancer Survivors

In Search of the Echocardiography Holy Grail*

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In the United States, an estimated 9,910 children younger than 15 years of age will be diagnosed with cancer in 2023. With contemporary treatment approaches, the 5-year overall survival rate is approximately 85%.[1] However, despite significant therapeutic advances in the field of pediatric oncology, these high survival rates do not come without cost. Long-term cardiovascular toxicity is the leading noncancer cause of late morbidity and mortality in childhood cancer survivors (CCS),[2] with left ventricular (LV) dysfunction and heart failure being among the most significant contributors.[3]

Individualized heart failure risk prediction models informed by treatment exposures, age, gender, and even cardiometabolic risk factors in CCS have been developed using longitudinal cohort data from the Childhood Cancer Survivor Study and validated in other cohorts of CCS.[4,5] However, the quest for a complementary screening predictor, particularly an echocardiographic predictor, to inform risk more precisely for cardiac dysfunction remains elusive. This ideal echocardiographic "holy grail" would consist of a noninvasive imaging modality and/or index that is readily available, affordable, highly reproducible and able to accurately predict risk for future progressive cardiac dysfunction in an individual CCS. Early identification prior to progressive cardiac remodeling and dysfunction may provide a critical window for secondary prevention to ameliorate the disease process. Myocardial deformation indexes such as global longitudinal and circumferential strain have been proposed as early markers of regional cardiac dysfunction predictive of subsequent declines in LV ejection fraction (LVEF).[6] Studies performed in a variety of heart failure populations suggest that global longitudinal strain (GLS) is the first dimension of myocardial deformation to become impaired, potentially reflecting vulnerability of the subendocardium.[7] Cohort studies in adult oncology have reported the association of early declines in GLS with subsequent decrease in LVEF.[8-10] However, its predictive role in CCS is unclear.

In this issue of *JACC: CardioOncology*, Merkx et al[11] present their findings from a cardiac substudy of the nationwide Dutch Childhood Cancer Survivor Study (DCCSS LATER 2 CARD). They performed a nationwide, prospective, cross-sectional outpatient clinic evaluation of ≥5-year CCS treated before the age of 18 years between January 1, 1963, and December 31, 2001. They used contemporary 2-dimensional echocardiographic techniques to evaluate cardiac function (LVEF using Simpson's biplane method and LV GLS) and diastolic function (LV diastolic function grade on tissue and pulsed-wave Doppler).[12] Because of the cross-sectional design of the study, the investigators focused on the prevalence and risk factors of cardiac dysfunction detected by their comprehensive echocardiographic protocol.

They evaluated 1,397 CCS at a median age of 34.5 years and median time from cancer diagnosis of 26.7 years. This is similar to the population evaluated

*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2023.07.003

using echocardiography in the SJLIFE (St. Jude Lifetime) cohort study (1,820 CCS at a median age of 31 years and a median time from cancer diagnosis of 22.6 years).[13] In the Dutch study, Merkx et al[11] found that the prevalence of abnormal LVEF in CCS was 24.2%, which is significantly higher than the 5.8% prevalence reported in the SJLIFE study. However, some of this difference may be explained by the use of 3-dimensional LVEF in the SJLIFE study and their definition of LV dysfunction of LVEF < 50% for both sexes, whereas Merkx et al[11] used LVEF cutpoints of <52% in men and <54% in women. In addition, the Dutch cohort had a higher proportion of patients treated with very high dose anthracycline and mitoxantrone. Interestingly, the prevalence of abnormal GLS was similar in both studies, at 29.8% in the DCCSS LATER 2 CARD study compared with 31.8% in the SJLIFE study. Even more intriguing, the study by Merkx et al[11] revealed that 20.2% of CCS with normal LVEFs had abnormal GLS, but also, 39.1% of CCS with abnormal LVEFs had normal GLS. This finding of an abnormal LVEF with normal GLS directly contradicts the current perception that abnormal GLS precedes abnormal LVEF and can be used as an early indicator of impending LV dysfunction. Merkx et al[11] found that the distributions of abnormal GLS and abnormal LVEF were not equal and that risk factors differed, indicating potentially different types of cardiac injury. For example, although the combination of abnormal LVEF and GLS was associated with all cardiotoxic exposures, LVEF abnormalities were associated primarily with anthracycline dose. Conversely, GLS showed a strong association with radiation dose. This may indicate that isolated abnormalities in LVEF or GLS may in fact be reflective of different pathophysiological mechanisms. The investigators suggest that these 2 measures of LV systolic function may not be interchangeable but rather complementary and emphasize the importance of further work to elucidate this complex relationship in CCS.

Merkx et al[11] should be commended for their extremely detailed and meticulous assessment of cardiac function in their cohort of CCS. They have shed light on the impact of childhood cancer therapy on various measures of cardiac function and the influence of risk factors on each. Their findings add depth to our current understanding of cardiotoxicity in CCS treated with older treatment modalities. However, if we zoom out to the 10,000-foot view, how close are we to truly reaching the "holy grail" of finding that predictive echocardiographic marker of future cardiac dysfunction? A systematic review and meta-analysis of the assessment of prognostic value of LV GLS for the early prediction of chemotherapy-induced cardiotoxicity showed a high risk for bias in the published studies and limited data on the incremental value of GLS or its optimal cutoff values.[6] New echocardiographic technologies are prone to early adoption and enthusiasm, especially in the realm of novel functional measures. However, if indeed our true aim is to find early signals of impending cardiac dysfunction, we must be wary of placing undue emphasis on the "newest and shiniest" measure of LV function. By remaining relatively agnostic in our selection of echocardiographic indexes, we may avoid "new technology bias" and perhaps find more helpful echocardiographic signals hiding in plain sight. This requires large cohort studies of CCS treated with more contemporary therapies that include detailed echocardiographic follow-up and the creation of robust echocardiographic biorepositories. In fact, in a study of younger CCS, longitudinal decline in many standard echocardiographic parameters of cardiac function were found years prior to crossing the traditionally defined threshold of LV dysfunction.[14] Perhaps if we can detect a slope of progression in a given echocardiographic index or set of indexes highly predictive of subsequent cardiac dysfunction, we may have the ability to change the trajectory of cardiotoxicity in CCS and prevent progression toward clinically relevant cardiac morbidity and mortality. Then, existing CCS cardiovascular risk calculators could be enhanced with early echocardiographic indexes to estimate cardiovascular risk, allowing more accurate individualized surveillance and together with the incorporation of longitudinal echocardiographic data improve early detection and positively influence outcomes. If we can get to that point, then perhaps we have truly attained the echocardiographic "holy grail" for survivors of childhood cancer.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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JACC: CARDIOONCOLOGY, VOL. 5, NO. 4, 2023
AUGUST 2023:486–488

REFERENCES

1. American Cancer Society. Cancer facts and figures 2023. Accessed June 30, 2023. https://www.cancer.org/cancer/types/cancer-in-children/key-statistics.html

2. Lipshultz SE, Adams MJ, Colan SD, et al. Long-term cardiovascular toxicity in children, adolescents, and young adults who receive cancer therapy: pathophysiology, course, monitoring, management, prevention, and research directions: a scientific statement from the American Heart Association. *Circulation*. 2013;128:1927–1995.

3. Brouwer CA, Postma A, Vonk JM, et al. Systolic and diastolic dysfunction in long-term adult survivors of childhood cancer. *Eur J Cancer*. 2011;47:2453–2462.

4. Chow EJ, Chen Y, Kremer LC, et al. Individual prediction of heart failure among childhood cancer survivors. *J Clin Oncol*. 2015;33(5):394–402.

5. Chen Y, Chow EJ, Oeffinger KC, et al. Traditional cardiovascular risk factors and individual prediction of cardiovascular events in childhood cancer survivors. *J Natl Cancer Inst*. 2020;112(3):256–265.

6. Oikonomou EK, Kokkinidis DG, Kampaktsis PN, et al. Assessment of prognostic value of left ventricular global longitudinal strain for early prediction of chemotherapy-induced cardiotoxicity. *JAMA Cardiol*. 2019;4(10):1007–1018.

7. Kalam K, Otahal P, Marwick TH, et al. Prognostic implications of global LV dysfunction: a systematic review and meta-analysis of global longitudinal strain and ejection fraction. *Heart*. 2014;100(21):1673–1680.

8. Narayan HK, Finkelman B, French B, et al. Detailed echocardiographic phenotyping in breast cancer patients: associations with ejection fraction decline, recovery, and heart failure symptoms over 3 years of follow-up. *Circulation*. 2017;135(15):1397–1412.

9. Negishi K, Negishi T, Hare JL, et al. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. *J Am Soc Echocardiogr*. 2013;26(5):493–498.

10. Thavendiranathan P, Poulin F, Lim K, et al. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol*. 2014;63(25 Pt A):2751–2768.

11. Merkx R, Leerink JM, Feijen EAM, et al. Extensive cardiac function analyses using contemporary echocardiography in childhood cancer survivors: a DCCSS LATER study. *J Am Coll Cardiol CardioOnc*. 2023;5:472–485.

12. Merkx R, Leerink JM, Feijen E, et al. Echocardiography protocol for early detection of cardiac dysfunction in childhood cancer survivors in the multicenter DCCSS LATER 2 CARD study: design, feasibility, and reproducibility. *Echocardiography*. 2021;38:951–963.

13. Armstrong GT, Joshi VM, Ness KK, et al. Comprehensive echocardiographic detection of treatment-related cardiac dysfunction in adult survivors of childhood cancer: results from the St Jude Lifetime Cohort Study. *J Am Coll Cardiol*. 2015;65:2511–2522.

14. Border WL, Sachdeva R, Stratton KL, et al. Longitudinal changes in echocardiographic parameters of cardiac function in pediatric cancer survivors. *J Am Coll Cardiol CardioOnc*. 2020;2:26–37.

KEY WORDS alkylating therapy, anthracycline, cancer survivorship, cardiomyopathy, echocardiography, epidemiology, imaging, risk factor, screening