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VIEWPOINT

Optimal Detection of Cardiac Sequelae

The Need for Rigorous, Harmonized Magnetic Resonance Studies in Pediatric Survivors

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Advances in pediatric oncology have seen overall survival rates increase to 85% for patients across the developed world. These improvements have led to a growing number of long-term survivors for whom the most significant cause of morbidity and mortality, aside from disease recurrence, is cardiovascular disease. As published in large cohorts, cardiac sequelae include myocardial infarction, coronary disease, heart failure, and hypertension. Childhood cancer survivors have demonstrated an increased risk of developing long-term sequelae compared to their siblings, with a 10- and 15-fold increased risk of coronary artery disease and heart failure, respectively. Newer targeted therapies are also associated with cardiac side effects across multiple drug classes (i.e., tyrosine kinase inhibitors, immunotherapy, proteasome inhibitors, and vascular endothelial growth factors). Although anthracycline cumulative dose is associated with increased cardiotoxicity risk, it is also established that there is no "safe dose" of anthracycline. Understanding the increased risk of developing cardiac dysfunction in childhood cancer survivors has led to a focus on screening. Although an important initiative to harmonize international guidelines was made by the International Late Effects of Childhood Cancer Guideline Harmonization Group in 2015 (1), this effort focuses on the use of screening 2-dimensional (2D) echocardiogram. However, we believe, and as we express in this viewpoint, that there is an important need to prioritize rigorously executed and harmonized multicenter studies by using cardiac magnetic resonance imaging (CMRI) in patients with pediatric cancer.

Although it is accepted that diminished left ventricular ejection fraction (LVEF) can predict cardiac outcomes in the general population, LVEF has low sensitivity when evaluating small changes in left ventricular function. In adult patients, detailed characterization of cardiac abnormalities in the assessment of cancer therapy-related cardiac dysfunction (CTRCD) using CMRI is becoming increasingly popular. CMRI is favored over echocardiogram because of its robust, highly accurate, and reproducible assessment of cardiac function and myocardial damage within the same study. To this end, current adult cardio-oncology guidelines incorporate the use of CMRI for comprehensive phenotyping of cardiac dysfunction. CMRI has the advantages of being noninvasive as well as exquisitely sensitive. Admittedly, the general anesthesia requirement in some pediatric patients has limited its use despite its excellent tissue characterization and potential for early detection of CTRCD.

We comprehensively evaluated published reports to understand the effect size of potentially cardiotoxic therapies on CTRCD in pediatric, adolescent, and young adult oncology patients using CMRI. Only 9 papers fit these criteria (**Figure 1**) (2–10). LVEF was

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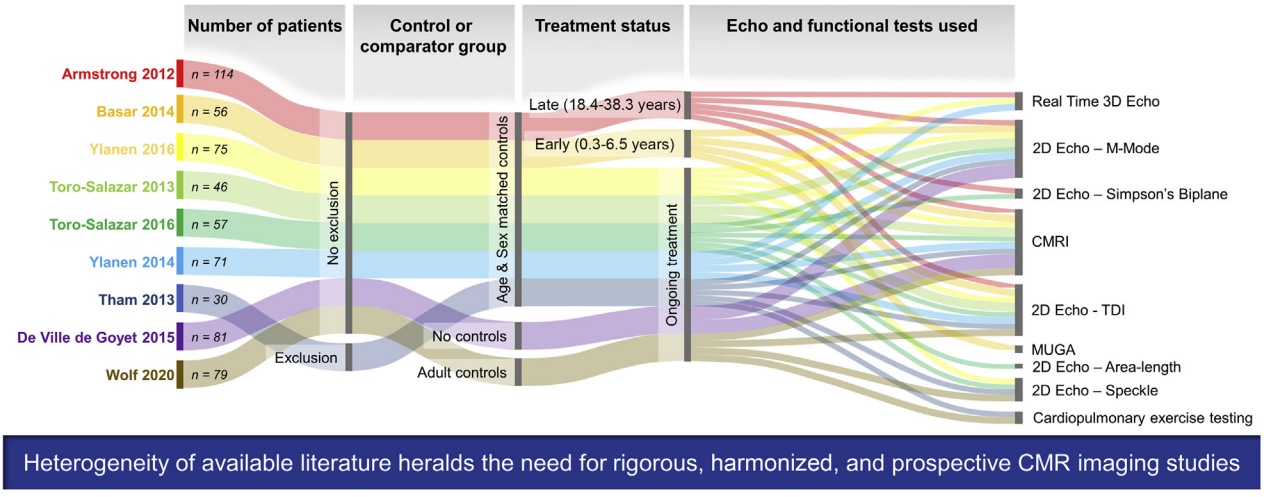
FIGURE 1 Publications Using CMRI in Pediatric and Young Adult Patients With Cancer



We analyzed the effect size of cardiac toxic medications on cancer therapeutic-related cardiac dysfunction measured by CMRI in comparison to echocardiogram and identified 9 papers that fit our inclusion criteria using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) screening criteria. Extensive heterogeneity among the studied cohorts was demonstrated with respect to: 1) exclusion or lack of exclusion of patients with previous anthracycline cardiotoxicity; 2) use of a control/comparator group; 3) timing of study enrollment related to treatment status; and 4) echocardiogram and functional measurement endpoints collected in addition to CMRI. The heterogeneity of the studies resulted in an inability to perform a meta-analysis to determine the effect size. Further prospective studies are required to determine the role of CMRI in pediatric and young adult patients and the effect size of cancer therapeutics on cancer therapy-related cardiac dysfunction. CMRI = cardiac magnetic resonance imaging; Echo, echocardiography; MUGA = multigated acquisition; TDI = tissue Doppler imaging.

the primary endpoint evaluated in all studies; all studies evaluated the use of echocardiography as well as CMRI. However, there was marked variation in how LVEF was derived and in the assessment of additional measures of cardiac function, including 3 studies that used real-time 3-dimensional (3D) echocardiography, 7 that used M-mode echocardiography, 2 that used 2D Simpson's biplane echocardiography, 9 that also used tissue Doppler imaging echocardiography, and 2 that also used speckle tracking. Furthermore, 1 study included the use of multigated acquisition, and 2 used cardiopulmonary exercise testing together with serum biomarkers. The 9 studies differed in a number of additional aspects: 1) the timing of patient enrollment (i.e., on treatment in 7 studies, early off treatment in 1 study, and late in 1 study); 2) inclusion in 8 studies or exclusion in 1 study of patients with previously determined cardiac dysfunction; 3) prospective or retrospective analysis of imaging modalities; 4) the definition of cardiac toxicity; and 5) use of age- and sex-matched control individuals in 7 studies. There were only 2 studies that directly compared LVEF by 2D or 3D echocardiography to CMRI. These studies found that many of the endpoints measured via echocardiography or CMRI were poorly comparable. Nevertheless, CMRI was found to be more reproducible for measurement of LVEF. The most compelling study, by Armstrong et al. (2), showed that echocardiography methods correlated poorly with CMRI with wide ranges of agreement using Bland-Altman analysis. Compared with a CMRI-determined threshold of an LVEF of <50% to categorize patients with CTRCD, echocardiography methods demonstrated reduced sensitivity (2D biplane, 25%; 2D apical 4-chamber, 25%; Teichholz, 29%), and 3D echocardiography demonstrated the strongest sensitivity of 53%. Interestingly, a small group of participants with an LVEF of <50% by CMRI were identified as having an LVEF of >50% by echocardiography. Only 2 studies screened patients for subclinical dysfunction, and they concluded that echocardiographic measurements of systolic function have a low sensitivity to detect small changes in LVEF. Furthermore, although reduced LVEF is a late indicator of cardiac dysfunction, Toro-Salazar et al. (5) concluded that 3D LVEF of <55%, a speckle tracking-derived global longitudinal strain magnitude cutoff of -17.5%, and a decrease in early atrial myocardial velocity at the intraventricular septum of <10 cm/s were the most sensitive transthoracic echocardiography parameters to detect subclinical cardiotoxicity.

Our review of the published reports demonstrates that although both echocardiography and CMRI are common imaging modalities, there is a sparsity of data in published pediatric cancer reports comparing these approaches. As a result, there is not enough evidence to assess whether CMRI should be the gold standard in the pediatric population nor to answer additional research questions, like the effect sizes of cancer therapies on CTRCD or the value of CMRI in detecting subclinical cardiac dysfunction. To overcome these gaps in knowledge, we suggest that prospective international trials assessing CMRI as a screening tool, alongside the current standard of care (2D echocardiogram), are necessary. Although feasibility and the requirement for general anesthesia may still be an obstacle in young patients, many patients older than 7 years should be able to undergo a CMRI while awake, particularly with the increasing use of distraction technology (virtual reality, movies in the machine, and so forth). A concerted approach by large trial groups could facilitate such studies and ensure adequate patient numbers (in those >7 years of age) to determine if there is a benefit of CMRI over the current standard of 2D echocardiogram. We propose that integrated multicenter trials with standardized protocols performed prospectively will address the best standard of care for surveillance and define the effect sizes of cancer therapeutics on CTRCD in pediatric and young adult patients. This approach is an exciting opportunity and challenge for the pediatric cardio-oncology field.

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