Feasibility of Echocardiographic Techniques to Detect Subclinical Cancer Therapeutics–Related Cardiac Dysfunction among High-Dose Patients When Compared with Cardiac Magnetic Resonance Imaging

Olga H. Toro-Salazar, MD, Joanna Ferranti, MPH, Raymond Lorenzoni, MD, Steven Walling, RDCS, Wojciech Mazur, MD, Subha V. Raman, MD, MSEE, Brooke T. Davey, MD, Eileen Gillan, MD, Michael O'Loughlin, MD, Berthold Klas, BS, and Kan N. Hor, MD, *Hartford, Connecticut; Bronx, New York; Cincinnati and Columbus, Ohio; and Chicago, Illinois*

Background: Cardiac magnetic resonance imaging (CMR) is the gold standard for the quantification of global and regional myocardial function and can detect subclinical myocardial dysfunction in anthracycline-induced cardiomyopathy. The aim of this study was to ascertain reliable echocardiographic parameters that can be used for the early identification of cancer therapeutics–related cardiac dysfunction, compared with CMR.

Methods: Fifty-seven pediatric cancer survivors, 10 to 42 years of age, with cumulative anthracycline doses $\geq$ 200 mg/m^2, were studied with transthoracic echocardiography and CMR 2.4 to 26.9 years after chemotherapy.

Results: Three-dimensional echocardiography had the highest sensitivity in identifying subjects with CMR-derived ejection fractions < 55%. Subjects with end-systolic volume index values > 29 mL/m^2 were more likely to have CMR-derived ejection fractions < 55%. Three-dimensional speckle-tracking echocardiographic peak global longitudinal strain magnitude < −17.5% best identified subjects with abnormal peak midwall longitudinal strain magnitude by CMR. A decrease in early atrial myocardial velocity of <10 cm/sec at the interventricular septum also identified subjects with lower average peak midwall longitudinal strain and peak midwall circumferential strain magnitudes by CMR.

Conclusions: Three-dimensional echocardiographic ejection fraction < 55%, end-systolic volume index > 29 mL/m^2, three-dimensional speckle-tracking echocardiographic peak global longitudinal strain magnitude < −17.5%, and a decrease in early atrial myocardial velocity at the interventricular septum of <10 cm/sec by Doppler tissue imaging are the most sensitive transthoracic echocardiographic parameters to identify subjects with subclinical myocardial dysfunction by CMR. (J Am Soc Echocardiogr 2015;■:■-■.)

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Potentially cardiotoxic cancer therapy, including the use of anthracyclines, continues to be a cornerstone in the treatment of a variety of childhood cancers. Echocardiography is the most widely used imaging modality for the serial evaluation of left ventricular (LV) structure and function in patients exposed to anthracycline therapy. Unfortunately, traditional echocardiographic measures of global systolic function, including M-mode-derived shortening fraction and two-dimensional (2D) echocardiographic assessment of ejection fraction (EF) using the biplane method of disks (modified Simpson's rule), typically remain within the normal range until late in the course of the disease. Furthermore, compared with CMR, they do not achieve the desired levels of sensitivity and specificity in individual patients.[1,2]

Modern echocardiographic techniques, including three-dimensional (3D) echocardiography (3DE), Doppler tissue imaging, and speckle-tracking echocardiography (STE), have not been routinely incorporated in the early identification of anthracycline-induced cardiotoxicity in survivors of childhood cancer. Recent consensus guidelines

From the Connecticut Children's Medical Center, Hartford, Connecticut (O.H.T.-S., J.F., R.L., S.W., B.T.D., E.G.); Hartford Hospital, Hartford, Connecticut (O.H.T.-S., M.O.); Montefiore Medical Center, Bronx, New York (R.L.); The Heart and Vascular Center, The Christ Hospital, Cincinnati, Ohio (W.M.); The Ohio State University Medical Center, Columbus, Ohio (S.V.R.); TomTec Corporation, Chicago, Illinois (B.K.); and Nationwide Children's Hospital, Columbus, Ohio (K.N.H.).

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Reprint requests: Olga H. Toro-Salazar, MD, Connecticut Children's Medical Center, 282 Washington Street, Hartford, CT 06106 (E-mail: *otoro@connecticutchildrens.org*).

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Abbreviations

AUC = Area under the curve

CMR = Cardiac magnetic resonance imaging

CTRCD = Cancer therapeutics–related cardiac dysfunction

EF = Ejection fraction

εcc = Midwall peak circumferential strain

εll = Midwall peak longitudinal strain

ESFS = End-systolic fiber stress

ESVI = End-systolic volume index

GCS = Global circumferential strain

GLS = Global longitudinal strain

ICC = Intraclass correlation coefficient

IVS = Interventricular septum

LV = Left ventricular

MV = Mitral valve

ROC = Receiver operating characteristic

STE = Speckle-tracking echocardiography

3D = Three-dimensional

3DE = Three-dimensional echocardiography

TTE = Transthoracic echocardiography

2D = Two-dimensional

by the American Society of Echocardiography and the European Association of Cardiovascular Imaging advocate the use of standard transthoracic echocardiographic techniques in addition to 2D strain and 3D imaging acquisition for the diagnosis of cancer therapeutics–related cardiac dysfunction (CTRCD) in adult patients during and after cancer therapy.[3]

Cardiac magnetic resonance imaging (CMR) is the gold standard for the quantification of global and regional myocardial function and can detect subclinical myocardial dysfunction in the setting of a wide variety of myocardial disease processes, including anthracycline-induced cardiomyopathy.[4-6] Early CMR features of CTRCD include low normal global LV systolic function with an increase in end-systolic volume and reductions in myocardial deformation parameters, including low midwall peak circumferential strain (ε_{cc}) and midwall peak longitudinal strain (ε_{ll}) magnitudes.[2,7,8] The use of CMR is constrained by its availability and cost compared with transthoracic echocardiography (TTE), which limits its utility as a first-line technique for routine clinical surveillance of ventricular dysfunction. Limited data are available to formulate evidence-based recommendations for early echocardiographic diagnosis of CTRCD in pediatric patients with cancer exposed to anthracyclines. Accordingly, the objective of this study was to establish the best transthoracic echocardiographic indicators of early CTRCD and to ascertain the diagnostic performance of TTE-derived systolic, diastolic, and myocardial deformation parameters compared with CMR.

METHODS

Study Population

For this single-center study, 57 eligible subjects were identified and prospectively enrolled through a registry of pediatric cancer survivors treated with anthracyclines between 1985 and January 2011. All subjects in the registry are followed at Connecticut Children's Medical Center with yearly physical examinations and periodic echocardiography on the basis of age at treatment, radiation dose, and cumulative anthracycline dose. Inclusion criteria for this study are shown in Figure 1. Age > 9 years was selected to avoid need for general anesthesia or sedation. Informed consent was obtained at the time of enrollment. The medical records of all enrolled subjects were reviewed to identify known risk factors associated with cardiotoxicity. Conversions to isotoxic equivalents of anthracycline antibiotics were performed to calculate total cumulative dose. This study was approved by the institutional review board at Connecticut Children's Medical Center.

Echocardiography

Echocardiographic assessments were performed using a Philips iE33 echocardiographic system. TTE was performed for the evaluation of systolic and diastolic function, including 2D and 3D imaging, M-mode, spectral and tissue Doppler parameters of diastolic function, and measurements of ventricular afterload (end-systolic wall stress) and contractility (stress/velocity index), using American Society of Echocardiography guidelines.[9]

Echocardiographic Image Analysis. Advanced postprocessing of echocardiographic images was performed on Xcelera version 3.11 (Philips Medical Systems, Best, The Netherlands) and QLAB version 9.0 (Philips Medical Systems). Systolic parameters were entered in the Boston Children's Hospital database for calculation of *Z* scores. By entering height and weight, pediatric *Z* scores are automatically calculated. This database uses normative data obtained from 305 normal subjects.[10] Data derived from these normal subjects are used to determine the normal range for each of the echocardiographic parameters on the basis of age, sex, and body surface area. Diastolic parameters and tissue Doppler indices were compared with published normative data in children.[11,12] Two-dimensional myocardial strain analysis was performed on standard short-axis transthoracic echocardiographic images of the midventricle (at the level of the papillary muscles) and two- and four-chamber apical views. Sector size and depth were adjusted to achieve optimal visualization of the entire LV myocardium at the highest possible frame rate. Two-dimensional peak global circumferential strain (GCS) and global longitudinal strain (GLS) magnitudes were analyzed offline using vendor-independent clinical speckle-tracking echocardiographic software (2D Cardiac Performance Analysis version 1.2; TomTec Imaging Systems, Munich, Germany). Three-dimensional GCS and GLS were analyzed using 4D LV-Analysis version 3.1 (TomTec Imaging Systems) according to the American Society of Echocardiography's 16-segment model for chamber quantification.[13] To assess interobserver variability of strain analyses, a second expert reader performed the same analysis in a subset of eight randomly selected subjects in a blinded fashion (O.H.T.-S., S.W.). Similar to other investigators, we found radial strain (as measured by speckle-tracking in the short-axis parasternal view) to be unreliable, and therefore it was not included in the analysis.[14,15] Normative 2D and 3D STE-derived GCS and GLS values were obtained in 12 age- and gender-matched control subjects (mean age, 22 ± 3 years). Three separate measurements of all systolic, diastolic, and myocardial deformation parameters were obtained and averaged for analysis.

CMR Techniques

Subjects were imaged on a 1.5-T (GE CV software version 16.0/M4; GE Medical Systems, Milwaukee, WI) using the following protocol: (1) standard multislice, multiphase cine imaging was performed using a steady-state free precession acquisition technique (fast imaging employing steady-state acquisition) in the two-chamber,