Echocardiography Core Laboratory Reproducibility of Cardiac Safety Assessments in Cardio-Oncology

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Background: As the potential for cancer therapy–related cardiac dysfunction is increasingly recognized, there is a need for the standardization of echocardiographic measurements and cut points to guide treatment. The aim of this study was to determine the reproducibility of cardiac safety assessments across two academic echocardiography core laboratories (ECLs) at the University of Pennsylvania and the Duke Clinical Research Institute.

Methods: To harmonize the application of guideline-recommended measurement conventions, the ECLs conducted multiple training sessions to align measurement practices for traditional and emerging assessments of left ventricular (LV) function. Subsequently, 25 echocardiograms taken from patients with breast cancer treated with doxorubicin with or without trastuzumab were independently analyzed by each laboratory. Agreement was determined by the proportion (coverage probability [CP]) of all pairwise comparisons between readers that were within a prespecified minimum acceptable difference. Persistent differences in measurement techniques between laboratories triggered retraining and reassessment of reproducibility.

Results: There was robust reproducibility within each ECL but differences between ECLs on calculated LV ejection fraction and mitral inflow velocities (all CPs < 0.80); four-chamber global longitudinal strain bordered acceptable reproducibility (CP = 0.805). Calculated LV ejection fraction and four-chamber global longitudinal strain were sensitive to small but systematic interlaboratory differences in endocardial border definition that influenced measured LV volumes and the speckle-tracking region of interest, respectively. On repeat analyses, reproducibility for mitral velocities (CP = 0.940–0.990) was improved after incorporating multiple-beat measurements and homogeneous image selection. Reproducibility for four-chamber global longitudinal strain was unchanged after efforts to develop consensus between ECLs on endocardial border determinations were limited primarily by a lack of established reference standards.

Conclusions: High-quality quantitative echocardiographic research is feasible but requires a commitment to reproducibility, adherence to guideline recommendations, and the time, care, and attention to detail to establish agreement on measurement conventions. These findings have important implications for research design and clinical care. (J Am Soc Echocardiogr 2018;31:361-71.)

Keywords: Cancer, Cardiotoxicity, Echocardiography, Reliability, Reproducibility

As cardiac morbidity in patients with cancer is increasingly recognized, accurate diagnostic tools are critical to identify patients at risk for cancer therapy–related cardiac dysfunction (CTRCD).[1] Echocardiography provides essential structural, functional, and hemodynamic insights into cardiac pathophysiology and, as a low-cost, widely available, and safe test is frequently used to assess the cardiac consequences of cancer and cancer therapy.[2] However, variability related to imaging quality, biologic variation, and interpretive differences can limit the reliability of

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Conflicts of Interest: None.

The Penn and Duke Clinical Research Institute echocardiography core laboratories received funding from the National Cancer Institute, Division of Cancer Prevention, for work related to this study (grants U10CA45809 and U10CA81920).

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0894-7317/$36.00

https://doi.org/10.1016/j.echo.2017.11.018

Abbreviations

2D = Two-dimensional

CP = Coverage probability

CTRCD = Cancer therapy–related cardiac dysfunction

DCRI = Duke Clinical Research Institute

ECL = Echocardiography core laboratory

GLS = Global longitudinal strain

GLS_{4CH} = Apical four-chamber global longitudinal strain

LV = Left ventricular

LVEF = Left ventricular ejection fraction

ROI = Region of interest

echocardiographic results.[3] In clinical practice, variability of conventional echocardiographic parameters of left ventricular (LV) function (i.e., LV ejection fraction [LVEF]) can extend across treatment eligibility thresholds and affect critical decisions regarding cancer therapy.[4] In cancer trials, clinical LVEF data from site echocardiography laboratories are often used to determine study eligibility and evaluate the cardiac consequences of novel cancer therapies,[5,6] although reproducibility of results across clinical sites is rarely reported. Echocardiographic parameters that assess cardiac mechanics, including myocardial deformation and ventricular-arterial coupling, may improve sensitivity for early CTRCD beyond LVEF.[2] However, data in patients with cancer are predominantly derived from single-center studies[7] that may not account for factors recognized to potentially diminish measurement reproducibility.[8]

As cardio-oncology progresses toward larger clinical trials, standard echocardiographic measurements and thresholds for treatment, with validated reproducibility of such measures, are vital. Multicenter cardiovascular clinical trials generally use echocardiography core laboratories (ECLs) to provide expertise and consistency for image acquisition and measurements as well as for assessments of imaging eligibility criteria and safety end points. In this regard, ECLs can reduce variability of imaging data and ensure the validity of study results.[9-12] Cardio-oncology studies have used ECLs,[13] but the practice is not widespread.

Against this background, the National Cancer Institute Division of Cancer Prevention awarded substudies of the PREDICT MDA 2007 0914 (ClinicalTrials.gov identifier NCT01032278) and SCUSF 0806 (ClinicalTrials.gov identifier NCT01009918) trials for the central review of echocardiograms to ECLs at the University of Pennsylvania (Penn) and the Duke Clinical Research Institute (DCRI), respectively. As a condition of the awards, the ECLs were instructed to collaborate with the potential goal of pooling echocardiographic data from the trials. To determine the feasibility of pooling the data, as well as the impact of central echocardiography review in cardio-oncology clinical trials, the ECLs at Penn and DCRI aimed to (1) determine the reproducibility of echocardiographic assessments in cardio-oncology within and across two academic ECLs, (2) identify sources of variability and corrective solutions, and (3) propose recommendations for echocardiographic research in the detection and monitoring of CTRCD, with potential implications for clinical care.

METHODS

Penn and DCRI ECL Group Reads

To align data collection elements, the Penn and DCRI ECLs reviewed two-dimensional (2D) and Doppler echocardiographic parameters of cardiac size and systolic and diastolic function relevant to clinical cardiovascular outcomes in patients with cancer.[13,14] A harmonization process between ECLs ensued. Sonographers and principal investigators at both ECLs conducted serial calls and multiple Web-conference group reads from October 2013 to March 2014 to share standard operating procedures, review sample echocardiograms, and align ECL perspectives on image quality, border selection, and tracing conventions. Group readings illustrated differences between ECLs on tracing conventions for certain parameters. These included nonconsensus on the angle of the minor axis for LV internal dimensions (e.g., parallel to mitral valve plane vs perpendicular to the LV long axis) and LV endocardial border definitions (e.g., depth of exclusion of trabeculae) during measurements of LV internal dimensions (Figure 1) and volumes (Figure 2), respectively. Harmonization efforts were aimed at achieving consensus on the application of measurement conventions outlined in national guidelines recommendations[2,15,16] and culminated in the development of consensus reading instructions (please see the Online Appendix, available at www.onlinejase.com) as well as a common comprehensive case report form across ECLs.[17-20]

Echocardiographic Acquisition and Creation of Analysis Repository

After developing consensus reading instructions, each ECL contributed echocardiograms for reproducibility analyses. A total of 25 patient echocardiograms were selected from transthoracic echocardiograms previously acquired at both institutions from patients who had completed treatment with potentially cardiotoxic anticancer agents (i.e., doxorubicin with or without trastuzumab) for breast cancer. More detailed clinical data were not made available, as each ECL was blinded to patient characteristics. Selected echocardiograms were required to have visible LV endocardium unobscured by undergaining or artifact and no significant apical foreshortening in 2D acquisitions. Echocardiograms were obtained by dedicated sonographer teams in the Intersocietal Accreditation Commission clinical laboratories at both institutions. All images were acquired using Vivid 7 or E9 machines (GE Healthcare, Milwaukee, WI) at 60 to 90 frames/sec and digitally archived at the acquisition frame rate. Digital echocardiographic images were deidentified and transferred in standard Digital Imaging and Communications in Medicine format to TomTec (TomTec Imaging Systems, Unterschleissheim, Germany) and DigiView (Digisonics, Houston, TX) analysis workstations at the Penn and DCRI ECLs, respectively. Both ECLs used TomTec 2D Cardiac Performance Analysis version 1.1 for strain analysis.

Measurement of Echocardiography Parameters

After image transfer, measurements of echocardiography parameters were assigned to two readers at each ECL ($n = 4$ total readers). Readers included three highly experienced research sonographers and a cardiologist with level III certification in echocardiography. Each reader independently analyzed two uniquely identified copies of the 25 patient echocardiograms and recorded 50 measurement results per analyzed parameter. Each result was treated independently (i.e., no averaging within or between readers).

At laboratory A, LV volumes and strain were measured by a single reader; Doppler parameters (i.e., velocities and timing intervals) were measured by a separate reader, according to reader expertise and existent laboratory practices. At laboratory B, each reader measured every parameter. The measurement results generated per echocardiogram by the readers in each ECL are depicted in more detail in Figure 3A.