**Supplementary Methods**

Echocardiograms were obtained using Philips IE33 ultrasound machines and standard imaging protocols, and were archived at 30 frames per second; this frame rate has been adequate for analysis in prior studies.1, 2 Quantitation of echocardiographic measurements was performed at the University of Pennsylvania Center for Quantitative Echocardiography of the Hospital of the University of Pennsylvania (Philadelphia, PA). A single observer, blinded to participant characteristics, performed 2-dimensional (2D), M-mode, and strain measurements using TomTec Imaging Systems software (Unterschleissheim, Germany).

Cardiac structural assessments, including cavity diameter, wall thickness, and mass were quantitated in order to characterize structural remodeling with anthracycline therapy.3 The interventricular septal thickness at end-diastole (IVSTD), left ventricular inner dimension at end-diastole (LVIDD) and end-systole (LVIDS), and posterior wall thickness at end-diastole (PWTD; referred to as “posterior wall thickness” within the analyses) were measured from M-Mode images of the left ventricle in the parasternal short axis view at the mid-papillary level. If M-Mode images were not available or analyzable, these measurements were performed utilizing 2D images in the same plane (6% of analyzed studies). Left ventricular mass was calculated to be 0.8 \* (1.04 \* [LVIDD + PWTD + IVSTD]3 - LVIDD3) + 0.6.4, 5 Relative wall thickness was calculated to be twice the PWTD divided by the LVIDD.

In order to provide insight into contractility, peak systolic strain, the percent change in myocardial fiber length, was determined in the circumferential and radial dimensions from the LV short axis views. The endocardial border was manually traced at the end-systolic frame in the parasternal short axis view at the mid-papillary level, with care taken to exclude papillary and trabecular structures. Automatic tracking was assessed across the cardiac cycle and borders were adjusted in segments with poor tracking. Peak systolic strain values were automatically generated via speckle tracking, and averaged across segments. Images were excluded from strain analysis if there was poor visualization of the endocardium due to undergaining or artifact or if short axis images were oblique rather than circular. Utilizing these criteria, strain was not analyzable in 14% of studies.

Wall stress, an index of afterload, was assessed via measures of meridional and circumferential end-systolic stress (ESS). These parameters were derived from the same linear structural measurements described above in addition to blood pressure cuff measurements, as has previously been described.6, 7 Finally, SF, an assessment of global systolic function, was determined to be (LVIDD-LVIDS)/LVIDD. Longitudinal strain and ejection fraction were not analyzed for the purpose of this study due to limitations of image quality in the apical views.

The average intraobserver coefficients of variation (CVs) for M-mode derivation of SF, LVIDD, LVIDS, wall thickness, LV mass, and relative wall thickness ranged from 0.7% - 4.3%. The intraobserver CVs for M-mode derivation of meridional and circumferential ESS in this subsample were 5.2% and 3.1% respectively. Intraobserver CVs for circumferential and radial strain were 9.4%, and 26.2% respectively.

**Supplementary Table 1. Characteristics of Subjects With and Without an Analyzable Third Echocardiogram**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic** | **Complete Data\* (n=57)** | | **Echo Data Not Available at T2\* (n=28)** | ***P*†** |
| Age, years | 13.19 (4.9) | | 12.52 (5.3) | 0.57 |
| Sex |  | |  |  |
| Male | 29 (51) | | 19 (68) | 0.14 |
| Female | 28 (49) | | 9 (32) |
| Race |  | |  |  |
| White | 43 (75) | | 21 (75) | 0.28 |
| Black | 7 (12) | | 6 (21) |
| Other | 7 (12) | | 1 (4) |
| Prior Anthracycline Exposure |  | |  |  |
| No | 56 (98) | | 28 (100) | 0.48 |
| Yes | 1 (2) | | 0 (0) |
| Cancer Diagnosis |  |  |
| Ewing sarcoma | 22 (39) | | 12 (43) | 0.21 |
| Osteosarcoma | 24 (42) | | 6 (21) |
| Rhabdomyosarcoma | 4 (7) | | 3 (11) |
| Other Soft Tissue Sarcoma | 7 (12) | | 7 (25) |
| Cancer Stage |  | |  |  |
| Localized | 45 (79) | | 18 (64) | 0.067 |
| Metastatic to Lungs | 8 (14) | | 3 (11) |
| Widely Metastatic | 4 (7) | | 7 (25) |
| Cumulative Doxorubicin Dose,  mg/m2 [median (IQR)] | 375 (375, 450) | | 375 (225, 375) | 0.003‡ |
| Dexrazoxane |  |  |
| Unexposed | 19 (33) | | 4 (14) | 0.063 |
| Exposed | 38 (67) | | 24 (86) |
| Chest Radiation |  |  |
| No | 55 (97) | | 23 (82) | 0.024 |
| Yes | 2 (4) | | 5 (18) |
| Body Surface Area, m2 | 1.49 (0.47) | | 1.48 (0.55) | 0.98 |
| Body Mass Index, mg/m2 | 20.7 (5.3) | | 22.0 (6.2) | 0.33 |
| Systolic Blood Pressure, mmHg | 115 (14) | | 114 (15) | 0.77 |
| Diastolic Blood Pressure, mmHg | 64 (10) | | 63 (10) | 0.69 |

\*Except where specified, values shown are mean (standard deviation) or number of subjects (% of total)

† Except where specified, *P*-values are derived from a two-sided t-test for continuous variables or two-sided Pearson’s chi square test for categorical variables

‡ *P*-value derived from a Wilcoxon rank sum test

IQR: interquartile range

**Supplementary Table 2**. **Comparison of Changes from Baseline in Measures Early after (T1) and 1-2 years Post Anthracycline Therapy (T2)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Echocardiography Measure** | **Change Early After Therapy (T1)\***  **(n = 57)**† | **Change 1-2 Years After Therapy (T2)\***  **(n = 57)**† | ***P***‡ |
| SF, % | -2.7 (6.6) | -2.5 (6.3) | 0.84 |
| LVIDD, cm/BSA0.45 | 0.1 (0.4) | 0.1 (0.4) | 0.27 |
| LVIDS, cm/BSA0.45 | 0.2 (0.4) | 0.2 (0.3) | 0.26 |
| Posterior Wall Thickness, cm/BSA0.4 | 0.0 (0.1) | 0.0 (0.1) | 0.060 |
| LV Mass, gr/BSA1.25 | 3.9 (16.8) | -1.2 (13.6) | 0.014 |
| Relative Wall Thickness | -0.01 (0.08) | -0.02 (0.08) | 0.28 |
| Circumferential Strain, %‡ | 2.6 (5.4) | 2.9 (4.4) | 0.62 |
| Radial Strain, % | -4.6 (25.7) | -7.4 (23.6) | 0.40 |
| Meridional ESS, 103 dynes/cm2 | 1.0 (31.1) | 7.2 (36.0) | 0.20 |
| Circumferential ESS, 103 dynes/cm2 | -3.9 (31.5) | 3.2 (37.0) | 0.18 |

\* Mean (standard deviation) changes are depicted for subjects with data at all 3 time points

†Analyses were restricted to those subjects with available data at T2 to allow comparison

‡ P-values are from two-sided paired t-tests comparing mean values at T1 and T2

BSA=body surface area; ESS=end-systolic stress; LV=left ventricular; LVIDD=LV inner dimension in diastole; LVIDS=LV inner dimension in systole; SF=shortening fraction

**Supplement References:**

1. Zhang KW,French B,Khan AM,et al.Strain improves risk prediction beyond ejection fraction in chronic systolic heart failure.J Am Heart Assoc.2014;3:e000550.

2. Hung C-L,Verma A,Uno H,et al.Longitudinal and Circumferential Strain Rate, Left Ventricular Remodeling, and Prognosis After Myocardial Infarction.J Am Coll Cardiol.2010;56:1812–1822.

3. Lopez L,Colan SD,Frommelt PC,et al.Recommendations for Quantification Methods During the Performance of a Pediatric Echocardiogram: A Report From the Pediatric Measurements Writing Group of the American Society of Echocardiography Pediatric and Congenital Heart Disease Council.J Am Soc Echocardiogr.2010;23:465–495.

4. Devereux RB,Reichek N.Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method.Circulation.1977;55:613–618.

5. Vogel M,Staller W,Bühlmeyer K.Left ventricular myocardial mass determined by cross-sectional echocardiography in normal newborns, infants, and children.Pediatr Cardiol.1991;12:143–149.

6. Reichek N,Wilson J,St John Sutton M,Plappert TA,Goldberg S,Hirshfeld JW.Noninvasive determination of left ventricular end-systolic stress: validation of the method and initial application.Circulation.1982;65:99–108.

7. De Simone G,Devereux RB,Roman MJ,et al.Assessment of left ventricular function by the midwall fractional shortening/end-systolic stress relation in human hypertension.J Am Coll Cardiol.1994;23:1444–1451.