VOL. 11, NO. 8, 2018
ISSN 1936-878X/$36.00

iMAIL

LETTERS TO THE EDITOR

Effect of Traditional Heart Failure Risk Factors on Myocardial Dysfunction in Adult Survivors of Childhood Cancer

Childhood cancer treatments are associated with increased risk of heart failure (HF), which represents end-stage disease with limited potential to change trajectory. Our objective was to quantify the relative impact of conventional heart failure risk factors (HFRFs) on cardiac dysfunction in childhood cancer survivors.

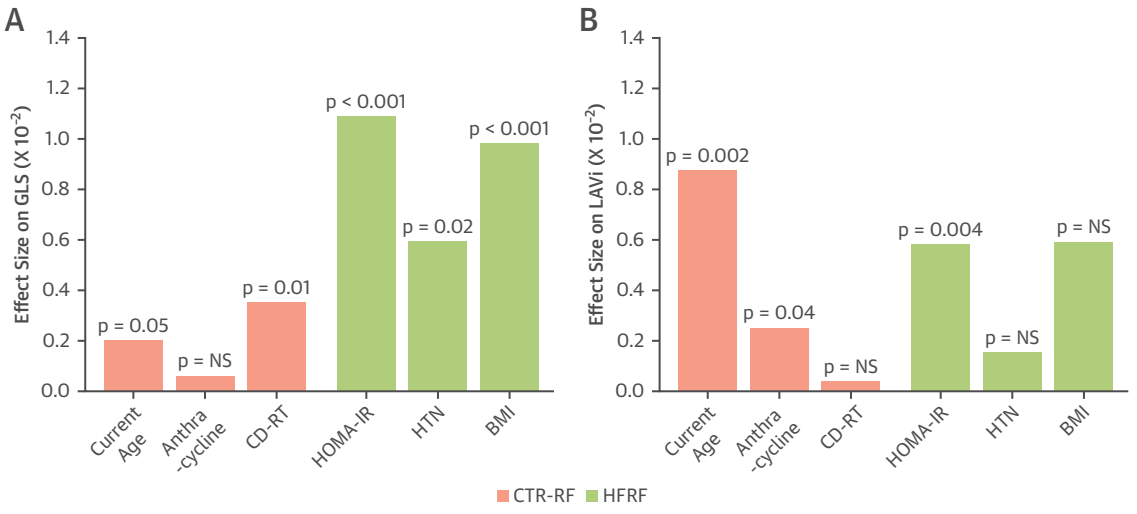
Participants were recruited from the SJLIFE (St. Jude Lifetime cohort study) (1); they were ≥18 years of age and ≥10 years from diagnosis and received anthracycline and/or chest-directed radiotherapy. Based on established associations in the general population with incident HF (2), hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg), insulin resistance (homoeostatic model assessment for insulin resistance >2.86), obesity (body mass index ≥30 kg/m^2), and smoking status (self-reported current, former, or never) were assessed. Abnormal echocardiography included 3-dimensional (3D) left ventricular ejection fraction (LVEF) <53%, global longitudinal strain (GLS) >2 SDs from age/sex-based population norms (3), and diastolic dysfunction determined using American Society of Echocardiography 2016 criteria (4). HFRFs were evaluated using Bayesian model averaging to automatically select final logistic regression model for testing. Variables with $p < 0.10$ on univariable analysis were included in multivariable analysis; variables known to be associated with abnormal cardiac function (sex, anthracycline cumulative dose, chest radiotherapy, age at diagnosis, current age) were included in separate models for each echocardiography outcome. Effect sizes (ES) were estimated using semi-partial omega-square method, an estimate of how much of the variance in outcome measure is explained by covariates in the population (small: 0.01; medium: 0.06; large: 0.14) and considered the least biased ES when there is ≥1 outcome measures and ≥2 explanatory variables. For ES calculations, indexed left atrial volume was used as a surrogate marker for diastolic dysfunction.

There were 1,807 participants (48% female; median age 32 years, range 18 to 66 years; median interval from diagnosis 23 years, range 10 to 48 years; 58% treated with anthracyclines, 17% treated with chest radiotherapy, and 25% treated with both). On echocardiographic assessment, 14% had 3D-LVEF <53%, 32% had abnormal GLS values, and 32% had diastolic dysfunction. Hypertension was associated with abnormal 3D-LVEF (odds ratio [OR]: 1.82; 95% confidence interval [CI]: 1.25 to 2.63; $p = 0.002$) and diastolic dysfunction (OR: 1.40; 95% CI: 1.0.2 to 1.93; $p = 0.04$). Insulin resistance was associated with abnormal GLS (OR: 1.72; 95% CI: 1.30 to 2.27; $p < 0.001$), and diastolic dysfunction (OR: 1.43; 95% CI: 1.07 to 1.91; $p = 0.01$). Obesity was associated with abnormal GLS (OR: 1.59; 95% CI: 1.19 to 2.13; $p = 0.002$) and diastolic dysfunction (OR: 1.92; 95% CI: 1.43 to 2.59; $p < 0.001$). Smoking was not significantly associated with any echocardiographic abnormality.

Standardized coefficients were estimated to compare the ES of the impact of HFRFs with traditional factors (**Figure 1**). In this relatively young population, treatment-related risk factors had significant impact on myocardial dysfunction; for example, cumulative anthracycline dose significantly affected 3D-LVEF (1.51×10^{-2}; $p < 0.001$) and current age significantly affected GLS (ES: 0.20×10^{-2}; $p = 0.05$). In comparison, ES of selected HFRFs were of the same order of magnitude or higher. Hypertension significantly affected 3D-LVEF (ES: 0.55×10^{-2}; $p = 0.01$). Insulin resistance (ES: 1.09×10^{-2}; $p < 0.001$) and obesity (ES: 0.98×10^{-2}; $p < 0.001$) were significantly associated with abnormal GLS. Insulin resistance was associated with abnormal indexed left atrial volume (ES: 0.58×10^{-2}; $p = 0.04$).

These results extend prior findings of our group (5) and add new information about the relative impact of traditional HFRFs on subclinical echocardiographic markers of myocardial dysfunction. Limitations of our study included cross-sectional design and that only 57% of eligible subjects underwent echocardiography. Effect sizes of several HFRFs were equal to or higher than for traditional factors, including cumulative anthracycline dose. Given the younger age of this population, applying conventional HFRF screening and treatment guidelines would likely lead to under-treatment and adverse outcomes. A more aggressive approach by cardiologists to treating HFRFs in this population is warranted.

FIGURE 1 Effect Sizes of Impact of Treatment-Related Risk Factors and Conventional HFRFs



(A) Systolic function (GLS) and **(B)** diastolic function (LAVi). Anthracycline refers to cumulative anthracycline dose. BMI = body mass index; CD-RT = chest-directed radiotherapy; CTR-RF = cancer diagnosis and treatment-related risk factors; GLS = global longitudinal strain; HFRF = heart failure risk factor; HOMA-IR = Homeostatic Model Assessment Insulin Resistance; HTN = hypertension; LAVi = indexed left atrial volume; NS = not significant.

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https://doi.org/10.1016/j.jcmg.2017.12.011

Please note: Support to St. Jude Children's Research Hospital by the National Cancer Institute (U01 CA-195547, Drs. Hudson and Robison, principal investigators), the Cancer Center Support grant (CA21765, Dr. Roberts, principal investigator), and the American Lebanese-Syrian Associated Charities. Dr. Marwick has received research grants from General Electric (>$50,000); and equipment support from Siemens and Philips. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Richard Steingart, MD, served as the Guest Editor for this paper.

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Molecular Imaging of Apoptosis in Cancer Therapy-Related Cardiac Dysfunction Before LVEF Reduction

Detecting chemotherapy-related cardiac dysfunction (CRCD) before a decrease in left ventricular ejection fraction (LVEF) or an enzyme leak may help employ strategies to preserve ventricular function. Although the mechanisms of CRCD are not fully elucidated, myocyte apoptosis has been proposed to play an important role (1). Previous studies suggest that apoptotic cardiomyocyte injury is associated with asymmetric expression of phosphatidylserine and phosphatidylethanolamine on the outer leaflet of the cell membrane (2). Radiolabeled duramycin binds specifically to phosphatidylethanolamine (3,4) and might permit early detection of CRCD.

Male Sprague-Dawley rats (n = 54) were divided into 9 groups. We tested 7 dosing regimens to