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RESEARCH LETTER

Deep Inspiration Breath Hold and Global Longitudinal Strain in Women Undergoing Left-Sided Breast Irradiation

Adjuvant radiotherapy (RT) reduces breast cancer recurrence and improves survival. However, studies showed patients undergoing RT for left-sided breast cancer can develop subclinical myocardial dysfunction.[1] Deep inspiration breath hold (DIBH) during breast RT lowers radiation doses to the heart.[2] This pilot study compared 2-dimensional left ventricular (LV) global longitudinal strain (GLS) in patients undergoing RT for left breast cancer who were treated with either DIBH or free breathing (FB) at baseline and at 6 months post-treatment. We hypothesized that radiation induced LV dysfunction is less significant in patients treated with DIBH.

Forty consecutive patients (30 DIBH, 10 FB controls) were recruited. Exclusion criteria were age <18 years, pregnancy, patients who were to receive volumetric modulated arc therapy techniques or regional nodal irradiation, LV ejection fraction (LVEF) <50% or previous myocardial infarction, and moderate or severe valvular stenosis or regurgitation. The study was approved by the local research ethics committee. All patients provided written informed consent.

Transthoracic echocardiography was performed and analyzed using Vivid E95 and EchoPAC v203 (GE-Vingmed), respectively. LV GLS was calculated using 2-dimensional speckle tracking analyses performed on standard grey scale images in the apical 2-, 3-, and 4-chamber views.

All patients were planned and treated supine. The breast, chest wall, and relevant organs at risk were contoured in accordance with guidelines. The dose/fractionation regimen was either conventional (50 Grays [Gy]/25 fractions) or hypofractionated (42.5 Gy/16 fractions). The contribution of any photon boost (10 Gy/5 fractions or 8 Gy/4 fractions) to the total dose was included for the analysis. Analyzed parameters included the mean heart dose in Grays, and the volume of heart (in cubic centimeters) receiving 5 Gy (V5), 20 Gy (V20), and 40 Gy (V40). All radiation doses were converted to the equivalent dose in 2 Gy.

Continuous variables and residuals were tested for Gaussian distribution. Continuous variables were presented as mean ± 1 SD. Linear mixed model for repeated measures was used to identify determinants of GLS over time, with time, patient group, and time × patient group interaction entered as fixed effects, radiation dosage parameters entered as covariates, and residual errors considered correlated with unstructured covariance structure. The Bonferroni post hoc method was used for multiple pairwise comparisons. A 2-tailed P value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows software version 25 (IBM).

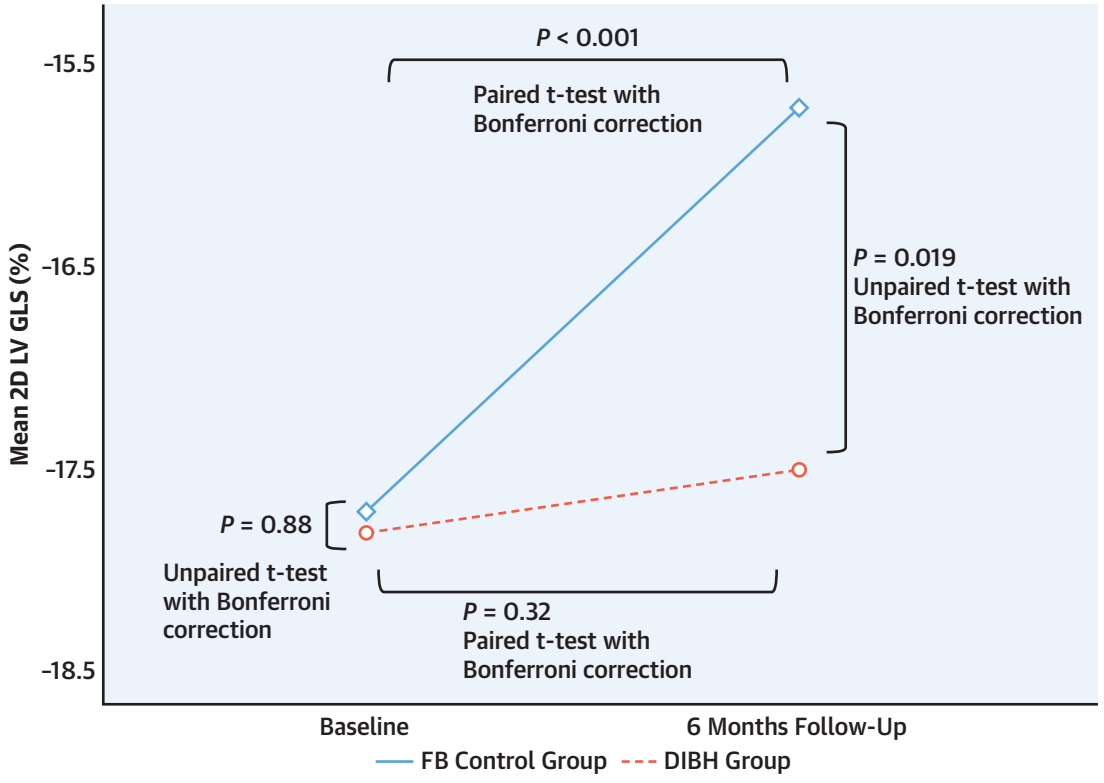
There were no significant differences in the baseline clinical and echocardiographic parameters (including GLS; $P = 0.84$) between the 2 groups. Anthracycline-based adjuvant chemotherapy was administered to 5 patients in DIBH and 3 patients in FB groups. Trastuzumab was administered to 2 patients in DIBH and 2 patients in FB groups.

Mean cumulative dose delivered to the tumor bed was 52.5 ± 5.5 Gy in the FB cohort and 50.9 ± 4.6 Gy in the DIBH cohort ($P = 0.37$). There was no difference in mean heart dose (1.72 ± 0.91 Gy vs 2.17 ± 0.98 Gy; $P = 0.19$) and V5 ($P = 0.21$) between the DIBH and FB groups, but V20 (3.00 ± 6.13 Gy vs 14.3 ± 15.6 Gy; $P = 0.009$) and V40 (0.57 ± 2.02 Gy vs 6.07 ± 8.63 Gy; $P = 0.002$) were significantly different.

GLS in the FB group worsened from −17.7% ± 2.6% to −15.7% ± 2.2% ($P < 0.001$), whereas GLS in the DIBH group did not significantly change (−17.8% ± 1.7% vs −17.5% ± 1.9%; $P = 0.32$). The FB group experienced a greater worsening in GLS compared with the DIBH group (−2.0% ± 1.8% vs −0.3% ± 1.6%; $P < 0.001$) (**Figure 1**). There was a significant correlation between V5 and the change in GLS ($r = -0.34$; $P = 0.038$).

A linear mixed model for repeated measures showed that DIBH had significantly less decline in GLS compared with FB. The time × patient group interaction term was a significant determinant of GLS ($P = 0.012$). The time × patient group interaction term

FIGURE 1 Mean LV GLS at Baseline and at 6 Months Follow-Up



Patients in the free breathing control group had significantly greater decline in GLS compared with the patients in the DIBH group.
2D = 2-dimensional; DIBH = deep inspiration breath hold; FB = free breathing; GLS = global longitudinal strain; LV = left ventricular.

remained a significant determinant of GLS when V5 was replaced with either V20 or V40. The study results did not change when the use of adjuvant chemotherapy was forced into the model.

This pilot study showed that DIBH during RT for left-sided breast cancer was associated with less worsening in GLS compared with FB, and the degree of GLS worsening at 6 months was correlated with radiation dose. The biological mechanism of cardiac radiation injury is likely multifactorial including myocyte ischemia/injury, inflammation, fibrosis, oxidative stress, cytokine activation, and micro- and macrovascular dysfunction. However, in addition to radiation dose, the extent of cardiac toxicity is potentially influenced by other factors such as baseline cardiac risk, degree of diaphragm flattening/lung expansion, chest/cardiac anatomy, and variability in organ position when performing DIBH both within and between treatments.

It is well-accepted that GLS is superior to LVEF in detecting subtle contractile dysfunction, and impaired GLS is independently associated with long-term adverse cardiovascular outcomes despite normal LVEF.[3] Our study demonstrated impaired GLS in patients at 6 months post-RT, and cardiac radiation dose was independently associated with the change in GLS. Similar to a previous study, our results showed that DIBH had significantly lower V20 and V40 compared with FB.[2] However, our study is novel in demonstrating that a lower cardiac irradiation dose from DIBH translated to less impaired GLS compared with FB.

This study has several limitations. First, we did not evaluate regional differences in longitudinal strain because present guidelines do not recommend segmental strain analysis. Second, this was a small study, and the results need to be corroborated by larger studies with longer follow-up.

In conclusion, this pilot study showed that DIBH during RT for left-sided breast cancer was associated with less worsening in GLS compared with FB, likely due to lower cardiac radiation dose. The degree of decline in GLS was correlated with radiation dose delivered to the heart. This has important implications for women who are surviving or living with breast cancer.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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