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Article

# Myocardial Function in Premenopausal Women Treated With Ovarian Function Suppression and an Aromatase Inhibitor

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## Abstract

**Background:** Premenopausal women with high-risk hormone receptor (HR)-positive breast cancer often receive ovarian function suppression (OFS) with aromatase inhibitor therapy; however, abrupt menopause induction, together with further decrements in estrogen exposure through aromatase inhibition, may affect cardiovascular microcirculatory function. We examined adenosine-induced changes in left ventricular (LV) myocardial T1, a potential subclinical marker of LV microcirculatory function in premenopausal women undergoing treatment for breast cancer. **Methods:** Twenty-one premenopausal women (14 with HR-positive breast cancer receiving OFS with an aromatase inhibitor and 7 comparator women with triple-negative breast cancer [TNBC] who had completed primary systemic therapy) underwent serial resting and adenosine cardiovascular magnetic resonance imaging measurements of LV myocardial T1 and LV volumes, mass, and ejection fraction. All statistical tests were 2-sided. **Results:** After a median of 4.0 months (range = 3.1-5.7 months), the stress to resting ratio of LV myocardial T1 declined in women with HR-positive breast cancer (−1.3%, 95% confidence interval [CI] = −3.4% to 0.7%) relative to those with TNBC (3.2%, 95% CI = −1.2% to 7.6%, $P = .02$). After accounting for age, LV stroke volume, LV ejection fraction, diastolic blood pressure, and breast cancer subtype women with HR-positive breast cancer experienced a blunted T1 response after adenosine relative to women with TNBC (difference = −4.7%, 95% CI = −7.3% to −2.1%, $P_{difference} = .002$). **Conclusions:** Over the brief interval examined, women with HR-positive breast cancer receiving OFS with an aromatase inhibitor experienced reductions in adenosine-associated changes in LV myocardial T1 relative to women who received nonhormonal therapy for TNBC. These findings suggest a possible adverse impact on LV myocardial microcirculatory function in premenopausal women with breast cancer receiving hormone deprivation therapy.

Breast cancer recurrence and survival outcomes for premenopausal women are inferior to those of menopausal women (1-5). In the United States, approximately 20% of all diagnoses occur in women younger than 50 years and 4% in women younger than 40 years (6). For women younger than 50 years, the incidence of hormone receptor (HR)-positive breast cancer increased during 2000-2016 in contrast to HR-negative breast cancer, for which incidence decreased over this time period (7). Premenopausal women diagnosed with HR-positive breast cancer remain at risk for recurrence many years, even decades, after diagnosis, with 10-year survival for those with high-grade HR-positive disease similar or inferior to those with HR-negative breast cancer (7,8). Recent reports from large clinical trials have demonstrated that concurrent treatment with ovarian function suppression (OFS) and an aromatase inhibitor (AI) (OFS+AI) in premenopausal women at high risk for recurrence improves the rate of freedom from breast cancer (9-11). Care guidelines now recommend this therapeutic modality for premenopausal women with high-risk HR-positive breast cancer (12,13).

The long-term health sequela from treatment with OFS+AI remains unknown and is a concern for premenopausal women who are at risk for both breast cancer recurrence and

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treatment-related toxicity (14,15). Among the most concerning potential adverse sequela is cardiotoxicity, specifically long-term events, such as need for coronary revascularization, myocardial infarction, or cardiac death. These events may not become clinically apparent for years, at which point irreversible injury may have occurred (16). Notably, the abrupt hypoestrogenemia of oophorectomy was strongly associated with coronary artery disease in the Women's Ischemia Syndrome Evaluation study (17) and other registry and cohort studies evaluating the impact of oophorectomy for noncancer indications in premenopausal women (18–20). In addition to loss of ovarian estrogen production, women treated with OFS+AI therapy experience further estrogen decline, with aromatase inhibition blocking estrogen synthesis in adipose, muscle, adrenal, and other extragonadal tissue (21,22). Prior studies comparing tamoxifen with aromatase inhibitors have suggested limited increased cardiovascular risk from aromatase inhibition though a trend toward more frequent myocardial infarctions, and angina with aromatase inhibition is reported (10,23-27). Until recently, aromatase inhibitors were generally prescribed for women who experienced natural menopause. The cardiovascular impact of abrupt dual-hit hypoestrogenemia from OFS+AI in premenopausal women is largely unstudied.

Accordingly, in premenopausal women receiving OFS+AI therapy, we assessed the impact of OFS+AI on left ventricular (LV) myocardial T1 measures (a potentially indirect assessment of LV microcirculatory function) using before and after intravenous infusion of an endothelial independent vasodilator (adenosine) during cardiovascular magnetic resonance (CMR) imaging exam. Additionally, we determined these measures in women with triple-negative breast cancer (TNBC) who were at a similar juncture in breast cancer care but had not received OFS+AI therapy.

## Methods

### Study Design

Premenopausal women, as defined by the National Comprehensive Cancer Network guidelines (12), aged 55 years and younger and within 3 years of diagnosis of either stage I-III HR-positive breast cancer or TNBC were enrolled in this study (Figure 1). Women with HR-positive breast cancer were eligible if they were receiving OFS+AI therapy and were within 3 years of initiating antiestrogen therapy. Women with TNBC were eligible if they were within 3 years of completing chemotherapy. Target accrual was 21 women with a 2:1 enrollment of those with HR-positive breast cancer to those with TNBC. Noncontrast adenosine stress CMR imaging examinations were performed at enrollment and at a 3- to 6-month interval following enrollment in each group, with the primary endpoint of describing differences in LV myocardial T1 reactivity to adenosine (ΔT1%) between the groups. Secondary endpoints included describing changes in other measures of cardiovascular function between the groups including myocardial rest T1 (myocardial fibrosis burden) and LV ejection fraction (LVEF); describing the relationship of clinical and demographic variables in relation changes in ΔT1%; and evaluating study feasibility. This study was approved by the Wake Forest University School of Medicine institutional review board and registered with the US National Institutes of Health [NCT03505736 (28)]. All participants provided witnessed, signed informed consent.

Participants self-reported demographic information, including race or ethnicity , at the time of enrollment. Other

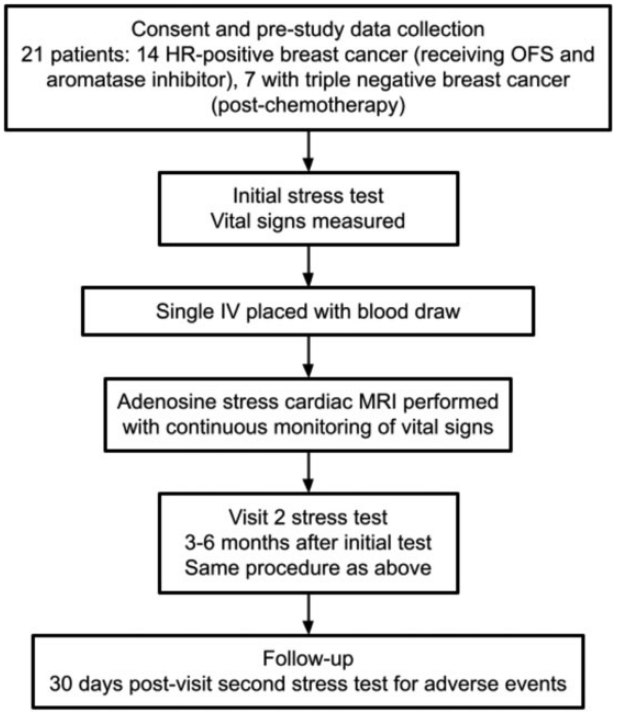


**Figure 1.** Study schema. HR = hormone receptor; IV = intravenous catheter; MRI = magnetic resonance imaging; OFS = ovarian function suppression.

demographic and clinical variables collected included age, weight, height, diagnosis of anemia, hypertension at breast cancer diagnosis, current tobacco use, treatment with anthracycline, treatment with radiation therapy, and current use of cardiovascular medications, including an angiotensin-converting enzyme (ACE) inhibitor, beta-blocker, or calcium channel blocker. Additional cardiovascular tests and addition of cardiovascular medications during the study period were also recorded.

### CMR Technique and Measurements

All CMR examinations were performed on a 1.5 T Siemens Avanto magnetic resonance imaging scanner (Siemens Medical Solutions, Malvern, PA) at Wake Forest Baptist Health. Standard steady-state free-precession (SSFP) cine images were acquired of the LV at rest in short-axis and long-axis views according to standardized protocols (29). Next, native (noncontrast) quantitative T1 maps were performed in 3 LV short-axis planes. Noncontrasted, stress T1 maps were then acquired (with identical imaging prescriptions as native T1 maps) during infusion of 0.14 mg/kg/min of adenosine for 1-5 minutes. After the collection of stress T1 maps, the adenosine infusion was stopped, and SSFP cine images were repeated after heart rate recovery to ensure no wall motion abnormalities were induced. All images were transferred offline for postprocessing in CircleCVI42 software version 5.10 (Circle Cardiovascular Imaging, Inc; Calgary, Alberta, Canada). Imaging analyses were conducted by investigators (J.J., S.P., A.K.) blinded to all study participant identifiers and visit type (baseline vs follow-up).

*Primary Endpoint: ΔT1% Analysis.* Each T1 map (native and stress) was contoured to identify the volume of tissue between the endocardial and epicardial borders of the LV with a 10% erosion factor to ensure exclusion of cavitary blood or epicardial fat. A global

myocardial value for native and stress T1 was taken as the average of basal, mid-cavity, and apical short axis slices. During normal responses to adenosine-induced vasodilation, the measured myocardial T1 is increased due to the higher contribution of blood, which has a higher T1, in the myocardial voxels. This increase in blood flow during vasodilator adenosine stress infusion, or T1 reactivity (ΔT1%), was calculated per slice and globally according to the following formula (30):

$$\Delta T1\% = 100\% \times \frac{(Stress\ T1 - Native\ T1)}{Native\ T1}$$

#### *Secondary Cardiovascular Measurement Endpoints: LV Volumes, Mass, and Ejection Fraction*

The LV volumes were contoured from the endocardial boundary of the LV blood pool at end-diastole and end-systole on each slice of the SSFP LV short-axis cine stack of images and summed by Simpson's rule to determine the LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV). The LV stroke volume (SV) was calculated as the difference between LVEDV and LVESV. The LV mass was determined from the volume of tissue between the endocardial and epicardial boundaries of the LV in the same SSFP LV short-axis cine stack of images and summed to determine total myocardial volume and converted to LV mass using the constant for healthy myocardial specific density. The LV volumes and mass were indexed to the body surface area, and the LVEF was calculated as LVSV/LVEDV.

### Statistical Analysis

This pilot study was designed to accrue 21 total women, 14 with HR-positive breast cancer and 7 with TNBC, to allow for several goals to be achieved. First, the total sample size in each group was chosen to allow for a 3.8% percentage point difference in ΔT1% to be detected between groups (assuming a SD for ΔT1% of 3.4%) when adjusting for baseline ΔT1% levels (31). Second, the 2:1 ratio was chosen to allow for more precision in estimating the possible cardiotoxicity of OFS+AI.

Descriptive statistics, including mean ± SD for continuous measures and frequencies and percentages for categorical measures, were calculated for all study participants. Within-group differences were assessed using paired *t* tests examining the baseline to follow-up changes in key outcomes. Between-group comparisons were made using 2-sample *t* tests or ANOVA (for radiation effect only) comparing the baseline to follow-up changes in key outcomes. Further, an exploratory predictive model was developed to examine whether any baseline characteristics might be predictive of a change in global T1 reactivity. Accordingly, we fit a simple regression model with follow-up ΔT1% as the outcome and baseline ΔT1% as a predictor to account for differing initial ΔT1%. We then used a stepwise regression model to determine whether any additional baseline variables (including breast cancer subtype) were predictive of follow-up ΔT1% using a *P* value of .1 to allow potential variables to enter (or be removed) from the model. The variables considered in this model were determined based on clinically meaningful measures that were gathered at baseline. These included breast cancer subtype, age, blood pressure, and a series of magnetic resonance imaging–based assessments (ie, LVEF, SV, etc). Feasibility metrics were defined as accrual rates (time to full accrual and proportion of women approached) and retention rate (proportion of women completing baseline study who completed the follow-up study). All analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC) with *P* values less than .05 considered statistically significant (2-sided).

## Results

### Accrual and Feasibility

Our target enrollment was 21 premenopausal women who were receiving care for either HR-positive breast cancer (n = 14) or TNBC (n = 7). A total of 41 women were approached to consider the study; 14 declined to participate. Twenty-seven women completed consent; however, 2 were screen failures and 3 either declined or could not complete the initial study. One woman with TNBC declined to return for a second visit. Because participants were neither randomly assigned nor treated in this pilot study and the sample size for TNBC was modest (n = 7), we replaced this woman to attain the total desired sample size. The women were consecutively recruited during a 16-month period from the breast cancer clinics at Wake Forest Baptist Comprehensive Cancer Center.

### Patient Characteristics

The mean age of the women enrolled was 44.8 years (HR-positive) and 43.0 years (TNBC) (Table 1). For the full cohort, age ranged from 30 years to 53 years. Body mass index was elevated and comparable between the cohorts. Five women identified as Black or African American (hereafter, Black), 2 as Hispanic, and 2 reported partial American Indian descent. Hypertension was the most common cardiovascular risk factor for both groups (21.4% HR-positive breast cancer, 42.9% TNBC). Most women with HR-positive breast cancer (n = 9, 64.3%) and all (n = 7, 100%) with TNBC received anthracycline-based therapy. Women with HR-positive breast cancer tended to be early in OFS+AI therapy. Women with TNBC tended to be near completion of chemotherapy. Median time between CMR studies was similar between the groups (overall median = 4.0 months; overall range = 3.1-5.7 months). During the study period, 3 women with HR-positive breast cancer underwent further cardiac testing, and 2 of these referrals were prompted by the study CMR. Of the 3 women referred for further cardiovascular evaluation, 2 had new cardiovascular medications prescribed. No additional cardiovascular tests or medications were recommended for women with TNBC during the study period.

### Cardiovascular Measures

Resting cardiovascular functional measures (LVEDV, LVESV, LV SV, LVEF, and myocardial mass) remained unchanged within each group during the study period (Table 2; P > .06 for all), and no statistical differences were noted for these variables when comparing the group changes over time (*P* > .12 for all). Of note, myocardial mass tended to decline from 48.1 g/m$^2$ to 44.6 g/m$^2$ in the HR-positive group (*P* = .08), and LVEF increased slightly in the TNBC group (55.2% to 59.9%, *P* = .06). The 3- to 6-month change in global ΔT1% was statistically significantly different between treatment groups, notably driven by a decrease in ΔT1% among HR-positive women compared with an increase in ΔT1% among women with TNBC (HR-positive: −1.3%, 95% confidence interval [CI] −3.4% to 0.7%; TNBC: 3.2%, 95% CI = −1.2% to 7.6%, *P* = .02) (Figure 2). A strong increase in ΔT1% in the TNBC group in the apical region was also observed (*P* = .009) and differed from that in the HR-positive group (*P* = .005). In the HR-positive group, there was no

**Table 1.** Patient characteristics

| BC subtype | HR-positive BC (n = 14) | TNBC (n = 7) |
|---|---|---|
| Mean age (SD), y | 44.8 (6.0) | 43.0 (7.6) |
| Mean body mass index (SD), kg/m$^2$ | 31.4 (6.3) | 31.1 (5.2) |
| Race or ethnicity, No. | | |
| Caucasian | 10 | 5 |
| Hispanic | 0 | 2 |
| Caucasian or AIAN, non-Hispanic | 0 | 1 |
| Black | 4 | 1[a] |
| Hispanic | 0 | 0 |
| Comorbidities, No. (%) | | |
| Hypertension | 3 (21.4) | 3 (42.9) |
| Diabetes | 0 | 0 |
| Hyperlipidemia | 1 (7.1) | 1 (14.3) |
| Current tobacco use | 1 (7.1) | 1 (14.3) |
| Breast cancer treatment, No. (%) | | |
| Anthracycline | 9 (64.3) | 7 (100) |
| Radiation (laterality) | 9 (64.3) | 4 (57.1) |
| Left-sided | 7 | 2 |
| Right-sided | 2 | 2 |
| Median time on OFS and aromatase inhibitor (HR-positive) or time since chemotherapy (TNBC), mo | 9.1 | 7.6 |
| Median time between paired CMR exams, mo | 4.0 | 4.1 |

[a]AIAN = American Indian or Alaska Native; BC = breast cancer; CMR = cardiac magnetic resonance imaging; HR = hormone receptor; OFS = ovarian function suppression; TNBC = triple-negative breast cancer.

**Table 2.** CMR study measures[a]

| CMR measure | HR-positive BC (OFS+AI) (n = 14) | | | TNBC (n = 7) | | | |
|---|---|---|---|---|---|---|---|
| | Study 1 Mean (95% CI) | Study 2 Mean (95% CI) | P[b] | Study 1 Mean (95% CI) | Study 2 Mean (95% CI) | P[b] | $P_{difference}$[c] |
| LVEF, % | 55.9 (50.7 to 61.1) | 56.2 (50.9 to 61.6) | .82 | 55.2 (50.4 to 60.1) | 59.9 (54.9 to 64.9) | .06 | .12 |
| $EDV_{index}$, mL/m$^2$ | 70.6 (63.7 to 77.5) | 69.9 (63.5 to 76.3) | .73 | 65.2 (58.0 to 72.3) | 66.8 (51.4 to 82.1) | .74 | .60 |
| $ESV_{index}$, mL/m$^2$ | 31.3 (26.2 to 36.5) | 30.4 (26.2 to 34.5) | .37 | 29.4 (23.8 to 35.0) | 27.1 (19.4 to 34.8) | .36 | .55 |
| $SV_{index}$, mL/m$^2$ | 39.3 (34.3 to 44.2) | 39.5 (33.9 to 45.1) | .90 | 35.8 (32.3 to 39.3) | 39.7 (31.2 to 48.2) | .23 | .29 |
| Myocardial mass index, g/m$^2$ | 48.1 (42.7 to 53.6) | 44.6 (40.0 to 49.3) | .08 | 43.5 (40.2 to 46.8) | 41.0 (33.3 to 48.7) | .42 | .77 |
| Global T1 reactivity, % | 2.8 (1.1 to 4.4) | 1.4 (−0.4 to 3.3) | .19 | 1.4 (−0.9 to 3.7) | 4.6 (0.9 to 8.4) | .13 | .02 |
| Basal SAX T1 reactivity, % | 2.2 (0.7 to 3.7) | 1.4 (0.3 to 2.5) | .26 | 1.8 (0.2 to 3.4) | 2.1 (−1.7 to 5.9) | .85 | .46 |
| Mid SAX T1 reactivity, % | 2.4 (−.3 to 5.2) | 0.5 (−1.5 to 2.7) | .22 | 1.2 (−1.9 to 4.2) | 3.3 (−0.9 to 7.6) | .36 | .12 |
| Apical SAX T1 reactivity, % | 3.4 (1.2 to 5.7) | 2.1 (−1.4 to 5.7) | .49 | 0.8 (−2.6 to 4.1) | 8.8 (3.7 to 13.9) | .009 | .005 |

[a]All volumetric and mass measures are indexed to body surface area. AI = aromatase inhibitor; BC = breast cancer; CI = confidence interval; CMR = cardiovascular magnetic resonance; EDV = end diastolic volume; ESV = end systolic volume; HR = hormone receptor; LV = left ventricular; LVEF = left ventricular ejection fraction; OFS = ovarian function suppression; SAX = short-axis slice; SV = stroke volume; TNBC = triple-negative breast cancer.
[b]Two-sided paired *t* test.
[c]P value for difference in change by group, 2-sided 2 sample *t* test.

difference across radiotherapy laterality (left, right, or none), or comparing left vs right-sided ($P = .40$ for both).

### Predictive Model of Change in Global Myocardial Perfusion Reactivity

The stepwise linear regression model demonstrated several statistically significant and clinically meaningful predictor variables. This model included baseline ΔT1% (forced into the model to control for different possible starting ΔT1% values), age, LVEF, breast cancer subtype group (HR-positive/TNBC), end-diastolic volume (EDV), and diastolic blood pressure (DBP) and had an adjusted $R^2$ value of 68%. Of note, the difference between the breast cancer subtype groups was −4.7% (95% CI −7.3% to −2.1%), suggesting that the women with TNBC had higher ΔT1% at follow-up than those with HR-positive breast cancer ($P_{difference} = .002$) (Table 3). Alternatively stated, adjusting for these factors, the OFS+AI group had a statistically significantly blunted response to adenosine stress at follow-up compared with the TNBC group (4.7% difference; $P = .002$). This model further suggested that increasing age and DBP predicted lower ΔT1%, whereas increased LVEF and EDV predicted higher ΔT1%.

## Discussion

This pilot study had several findings that may affect a large group of women with breast cancer, although our results need to be interpreted with caution due both to the small sample size

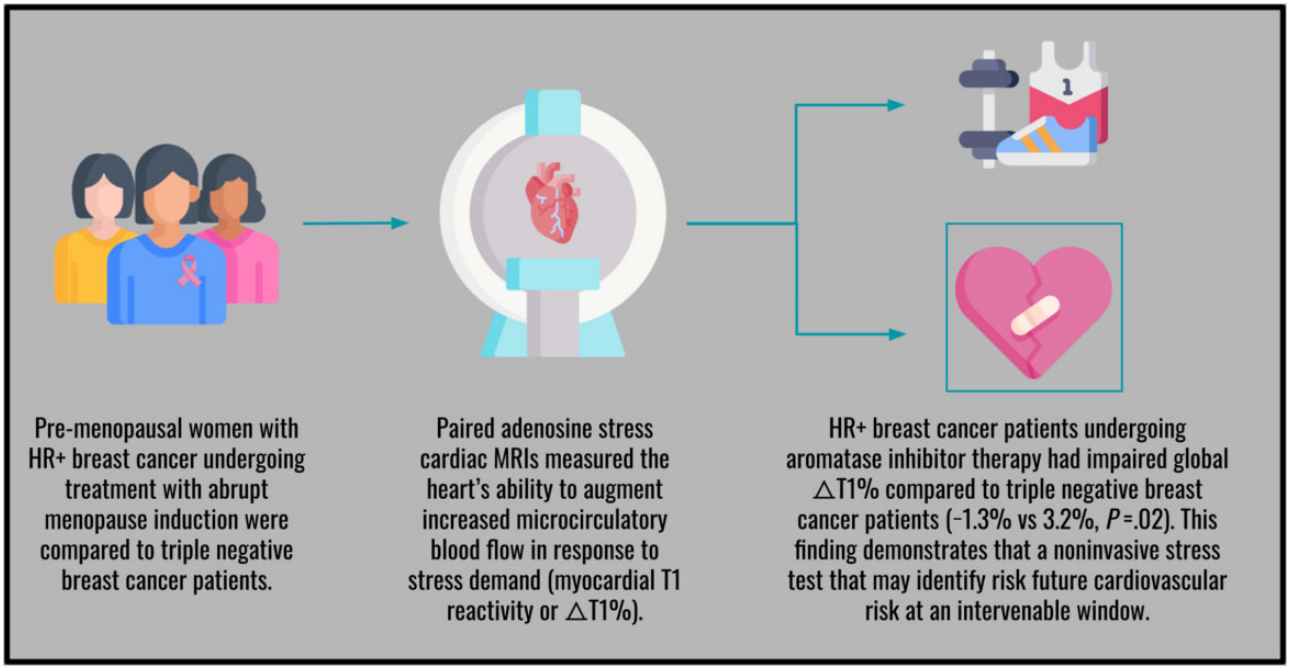


**Figure 2.** Central illustration. *P* value for difference in change by group, 2-sided 2 sample *t* test. HR = hormone receptor; MRI = magnetic resonance imaging.

and the noncontrasted CMR technique. The study suggests early preclinical cardiovascular decline for women receiving OFS+AI therapy and suggests that a model using imaging and clinical variables may inform a tool to predict risk. In this pilot work, conducting a study with paired adenosine stress CMR imaging with relatively rapid accrual, a high retention rate, and a sizeable proportion of women from minority populations was highly feasible. Collectively, if validated in a larger study with newer CMR techniques, these findings could offer tools to identify women at risk of cardiovascular compromise from OFS+AI.

The question of cardiotoxicity from OFS+AI or other antiestrogen therapy is likely to be relevant for an ever-growing number of premenopausal women with HR-positive breast cancer. This subtype of breast cancer, already a highly prevalent malignancy, is increasing in incidence among premenopausal women (7). Initial data on OFS+AI treatment supported this for premenopausal women with higher-risk breast cancer (9-11). More recent literature has demonstrated that premenopausal women with intermediate-risk HR-positive breast cancer who appear to have some, albeit limited, improvement in outcomes with chemotherapy experience this benefit in part due to chemotherapy-induced menopause (32), thereby further expanding the group of women likely to receive OFS+AI (13) .

Compared with typical contrasted adenosine stress testing in which one either visually or quantitatively appreciates a lack of contrast flow into a region of the myocardial tissue (29,33), our study used noncontrasted stress T1-mapping based methods to further minimize contrast-associated risks (31,34). Stress T1 mapping assesses the change in T1 relaxation of the tissue before and after adenosine infusion. Because the T1 relaxation time constant is higher in blood than myocardial tissue, the adenosine-induced vasodilation causes an increase in the measured T1, whereas a smaller change indicates a poor vasodilation response.

This study suggests that it is feasible to enroll women with breast cancer into a trial that requires serial stress CMR imaging. Adenosine causes transient symptoms, and CMR studies, although of minimal risk, do have some risk, which was reviewed with eligible women . Further, these women had to make time for study visits that lasted several hours. In this pilot work, we found women highly motivated to address these questions for themselves as well as for the breast cancer community. The accrual of women from minority populations is important because recent biomarker studies from the Carolina Breast Cancer Study demonstrated that Black women in our region have higher-risk, harder-to-treat HR-positive breast cancer than women of other groups (35). Understanding important sequela of treatment for these tumors could ultimately improve treatment delivery and minimize treatment-related toxicities with the goal of overcoming cancer-related health disparities.

Despite the relatively modest sample size (n = 21), analyses of these data showed a statistically significant and clinically meaningful model for risk prediction. Importantly, the factors in this model—age, LVEF, EDV, and DBP—can be readily obtained without adenosine stress testing. This effect was larger than the prespecified 3.8% effect that the trial was designed to detect, thus confirming that there appears to be a clinically meaningful and statistically significant difference in ΔT1% between women on OFS+AI and women treated for TNBC. This suggests that if validated in larger cohorts, a facile predictive model could identify women on OFS+AI who are at risk for cardiovascular injury. Though radiotherapy may also lead to changes in myocardial microvasculature (36,37), our small sample did not show a relationship between stress perfusion reactivity and radiotherapy. Future studies should consider cardiac dosimetry as a factor in this population.

Future work should seek to replicate these findings, and then, if needed, elucidate the mechanisms underlying these changes. In this study, women with TNBC had improvement in ΔT1% as well as LVEF. This could be incidental due to the small cohort. Other explanations include that these women experienced resumption of ovarian function after chemotherapy-induced amenorrhea and could have had short-term improvement on this basis. In future work, with a larger cohort, the role

**Table 3.** Linear model with stepwise regression approach to determine statistically significant contributors to global myocardial T1 reactivity (ΔT1%) at 3-6 months

| Variable | Parameter estimate (95% CI) % | P[a] |
|---|---|---|
| Baseline ΔT1% | 1.1 (−40.7 to −42.8) | .96 |
| Age (for 5-y increase) | −1.3 (−2.4 to −0.2) | .03 |
| LVEF (for 5% decrease) | −0.8 (−1.6 to 0.0) | .05 |
| Breast cancer subtype (HR-positive or TNBC) | −4.7 (−7.3 to −2.1) | .002 |
| EDV (for 5-mL decrease) | −1.1 (−1.8 to −0.4) | .005 |
| DBP (for 5-mm Hg increase) | −0.7 (−1.4 to −0.8) | .03 |

[a]Estimates derived from multiple linear regression model, 2-sided. CI = confidence interval; DBP = diastolic blood pressure; EDV = end diastolic volume; HR = hormone receptor; LVEF = ejection fraction; TNBC = triple-negative breast cancer.

of cardiovascular medications and biomarkers such as troponin and B-type natriuretic peptide, as well as the relative contributions of end diastolic and end systolic volumes in LVEF changes, could be elucidated. At the time of this study, we implemented a noncontrast CMR technique (adenosine stress T1 mapping) to reduce risk when evaluating myocardial perfusion. Newer contrasted CMR techniques are now able to create quantitative perfusion maps directly measuring blood flow in each pixel and could be explored in future studies of this population (34,38).

In summary, if validated in a larger study with newer CMR techniques, these findings suggest that a preclinical decrement in cardiovascular function can be identified in women receiving OFS+AI therapy. There is also a promising suggestion of tools that could be used to develop predictive risk models for this population. Given the growing prevalence of this subtype of breast cancer in premenopausal women and the decades of risk for treatment-related toxicities experienced by these younger women, future studies examining the cardiotoxicity of these therapies as well as the opportunity to intervene before the cardiovascular events occur will be critical. Such investigations hold the promise of offering these women many healthy years that balance both the risks of cancer and treatment-related cardiotoxicity.

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**Author contributions:** Conceptualization: JHJ, RBD, PR, WGH, AT. Resources: JHJ, KA, ED, SM, SS, SV, WGH, AT. Data curation: JHJ, ED, SP, AK, AT. Formal analysis: RBD, NSO. Supervision: JHJ, WGH, AT. Funding acquisition: JHJ, RBD, WGH, AT. Writing—initial draft: JHJ, AT. Writing—review and editing- all authors.

**Prior presentations:** This work has previously been presented, in part at the 2020 San Antonio Breast Cancer Symposium and the 2021 Society for Cardiovascular Magnetic Resonance Scientific Sessions.

## Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

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