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Respiratory Maneuvers Decrease Irradiated Cardiac Volume in Patients with Left-Sided Breast Cancer

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ABSTRACT

Late cardiac morbidity and mortality among left breast cancer survivors treated with radiation therapy is related to cardiac volume included in the radiation portals. To determine if respiratory maneuvers can help decrease cardiac volume included in the radiation portals for left-sided breast cancer, 17 women with breast cancer, who had undergone left breast radiation therapy, underwent cardiac magnetic resonance imaging (MRI). Cardiac volume within the radiation portals was assessed from a transverse stack of eight, 10-mm thick, contiguous slices, covering the entire heart and obtained during breathholding at (1) endtidal volume (ETid) and (2) deep inspiration. Fourteen subjects (93% of those who completed the study) had inclusion of at least a portion of their heart within the radiation portals at ETid (median: 25.9 cm^3, range 4.2–119.1 cm^3). In all subjects, inspiratory breathholding decreased irradiated cardiac volume [median change: $-18.1\,cm^3$ (-49%), $p \leq 0.001$ vs. ETid]. In 21% of patients, the entire heart could be displaced outside the

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radiation field with deep inspiration. Age was not correlated with change or percentage change in cardiac volume with respiratory maneuvers. We conclude that in breast cancer patients, deep inspiratory maneuvers significantly decrease irradiated cardiac volume included in the left breast radiation field. Such an approach during delivery of radiation therapy allows preservation of radiation dosage to the breast, while reducing cardiac involvement and possible associated cardiovascular toxicity.

Key Words: *Cardiac magnetic resonance imaging; Cardiotoxicity; Breast cancer; Radiation therapy; Respiratory maneuvers; Women*

INTRODUCTION

Late cardiac morbidity and mortality have been reported among left breast cancer survivors treated with radiation therapy (1–8). In contrast, radiation to the right breast is not associated with late cardiotoxicity (1–8). Cardiotoxicity appears to reflect direct radiation of the coronary arteries and/or myocardium, which are commonly included in the left breast radiation field (8–10). At therapeutic levels of irradiation, the likelihood of cardiotoxicity is directly correlated with the volume of heart included in the high-dose region (4).

Use of combination radiation therapy with chemotherapy has resulted in substantial improvement in quality of life and possibly survival in patients with breast cancer (11). Although, newer methods of breast irradiation have attempted to decrease cardiac involvement, there remains concern that radiation therapy is cardiotoxic, especially when used in conjunction with chemotherapy. These considerations have led to significant interest in improved radiotherapy techniques, which minimize the cardiac volume irradiated.

The position of the heart within the chest cavity is determined by chest size, cardiac size, and the phase of the respiratory and cardiac cycles. Respiratory maneuvers, such as deep inspiration, pull the diaphragm and heart inferiorly while expanding the anterior chest wall, thereby increasing the distance between breast tissue and the heart. Therefore, simple respiratory maneuvers that alter the position of the heart relative to the breast may reduce radiation to the heart, without altering dosage delivered to the breast. Preliminary MRI studies in healthy female volunteers demonstrated that deep inspiration decreased the volume of heart included in the left breast radiation field by 40% (12). However, patients and healthy volunteers differ significantly in their ability to perform respiratory maneuvers (13). In particular, breast cancer patients are often older and may have different anterior chest or cardiac anatomy. Here we report on the first use of MRI to demonstrate that respiratory maneuvers in patients with breast cancer decrease the heart volume in the left breast radiation field.

METHODS

Patient Selection

Seventeen women (mean age, 53.5 years, range 40–76 year; weight, 112–185 lb) who had not undergone mastectomies were studied. They had each undergone radiation therapy for left-sided breast cancer 4–68 months previously at the Joint Center of Radiation Therapy, Boston, MA, and were in sinus rhythm and had no contraindication to MRI. All subjects had necessary radiation portal data available to replicate the radiation therapy treatment position. Patients with a history of cardiac disease prior to diagnosis of breast cancer were excluded. Informed consent was obtained from all participants. The study was approved by the institutional review boards of the Dana Farber Cancer Center and the Beth Israel Deaconess Medical Center and in accordance with the Declaration of Helsinki.

All the patients were imaged in the identical position as when they received radiation therapy. Each patient was setup by an experienced radiation therapy technologist (LMR), using port films and standard techniques. The patient was positioned supine with arms positioned above the head. Electrocardiographic (ECG) leads were placed on the anterior thorax.

Magnetic-resonance-imaging-visible tubing (filled with 0.2% copper sulfate solution) was positioned on the patient's anterior chest to replicate exactly the radiation portals for left breast radiation therapy. The medial entrance of the radiation portals was at the midline. The MRI scanning table was modified with a “flat-table” top to reproduce identically the treatment setup position. The respiratory maneuvers were explained to the subjects, who practiced the maneuvers before entering the magnet. Patients were trained to sustain breathholding at (1) endtidal volume and (2) deep inspiration. Total breathhold duration for each maneuver was approximately 17 sec.

With the patients lying supine, cardiac MRI was performed using a 1.5-T Gyroscan NT (Philips Medical Systems, Best, the Netherlands) with a 20-cm circular surface coil (C1) as a radiofrequency (RF) receiver. The MR images were acquired using an ECG-gated turbo-field echo/echo-planar imaging (TFE/EPI) sequence [field-of-view = 360 mm, 125×256 matrix, repetition time (TR) = 2.2 msec, echo time (TE) = 6.0 msec, flip angle = 30°, EPI factor = 11]. Thoracic scout images in the coronal, transverse, and sagittal planes were obtained to confirm visualization of the markers and location of the heart with respect to other thoracic structures. A transverse (axial) stack of eight, 10-mm thick contiguous slices, covering the entire heart, was obtained during each of the two respiratory maneuvers. Position of the radiation portals with respect to their projection on the transverse stack was delineated by the MRI markers.

True long-axis and short-axis views of the left ventricle, and four-chamber view of the heart were obtained. Imaging parameters included TR of 750 msec, TE of 9.2 msec, 30° flip angle, EPI factor = 7123×256 image matrix with a field of view of $256 \times 320\ mm^2$ and 10-mm thick, contiguous slices. The entire setup and imaging portion of the protocol was < 1 hr.

Data Analysis

Cardiac volume included within the radiation field for each of the respiratory maneuvers was determined by using a multislice summation technique (modified Simpson’s rule). Area of the heart (consisting primarily of the apical LV wall and adjacent LV cavity) within the radiation portals was manually traced in each transverse image by an observer blinded to respiratory state, with use of standard system software. Cardiac volume within the radiation field (50% isodose line) was calculated for the respiratory positions: endtidal cardiac volume (ETid), and deep inspiratory cardiac volume (Insp).

Inspiratory changes (Insp Δ) in cardiac volume from baseline ETid and percentage inspiratory change were calculated (Eqs. (1) and (2)):

$$\text{Insp}\,\Delta\,(\text{cm}^3) = \text{Insp} - \text{ETid} \quad (1)$$

$$\%\text{Insp}\,\Delta = (\text{Insp}\,\Delta) \times 100/\text{ETid} \quad (2)$$

If no cardiac involvement was found in a patient at ETid (baseline), then inspiratory maneuvers data were not included in the above analysis.

Anteroposterior (AP) diameter from the posterior sternum to the anterior spine was measured in all patients at the transverse level corresponding to the four-chamber view of the heart. Patient compliance with inspiratory breathholding was assessed, by confirming an *increase* in AP chest diameter.

Statistical Analysis

All data are presented as both medians (range) and means (standard deviations). Comparison among respiratory maneuvers was performed with the use of the Wilcoxon paired test. All tests were two-tailed with a p value of ≤ 0.05 considered significant. The 95% confidence interval (CI) used the exact binomial calculation. Relationship of age to change in cardiac volume and to percentage change in volume used the Kendall’s test of correlation.

RESULTS

A total of 17 patients were imaged with cardiac MRI. Two patients were excluded, one because of inability to comply with breathholding instructions and another one because of equipment malfunction. The data from the remaining 15 patients were analyzed. All patients had normal resting global and regional left and right ventricular global systolic function. No regional wall motion abnormalities were noted within the radiation plane.

At baseline (ETid), one patient out of fifteen had no cardiac involvement in the XRT fields; this patient was not included in the subsequent analysis of change with inspiratory maneuvers. Fourteen patients (93%, 95% CI 66–100%) had inclusion of, at least, a portion of the heart within the left breast radiation portals at ETid. The median cardiac volume in the radiation field at baseline was $25.9\ cm^3$, and the range was $4.2–119.1\ cm^3$. The mean volume was 39.1 (standard deviation = 33.0) cm^3 (Table 1). Figures 1 and 2 show representative coronal and transverse images from a representative subject at endtidal volume and at deep inspiration.

Table 1

Decrease in Cardiac Volume with Inspiration

Subject No.	Age, years	Etid Vol. (cm^3)	Insp Vol. (cm^3)	Absolute Change (cm^3)	% Change
1	76	4.2	4.0	− 0.2	− 5%
2	56	33.7	12.9	− 20.9	− 62%
3	62	48.6	20.6	− 28.1	− 58%
4	41	76.4	40.3	− 36.1	− 47%
5	49	14.0	2.2	− 11.8	− 84%
6	62	15.9	0.0	− 15.9	− 100%
7	60	119.1	86.4	− 32.7	− 27%
8	60	22.8	17.8	− 5.0	− 22%
9	45	80.8	45.3	− 35.5	− 44%
10	64	20.2	0.0	− 20.2	− 100%
11	44	23.0	18.1	− 4.9	− 21%
12	42	12.5	0.0	− 12.5	− 100%
13	47	47.6	23.1	− 24.4	− 51%
14	40	28.7	23.1	− 5.6	− 19%
15	55	0.0	0.0	0.0	0%

Typical images at endtidal volume show the left ventricular apex (arrow) in close relationship to the left breast (Fig. 1A). However, on deep inspiration (Fig. 1B) the diaphragm is displaced downward, the lung volume increases, and the mediastinum is pulled caudally. The left ventricular apex has been moved medially and is further away from the chest wall and left breast.

Transverse images (Fig. 2) during respiratory maneuvers show that the heart becomes displaced posteriorly, as well as medially, upon deep inspiration. In the study shown in Fig. 2, the LV lies directly between the fiduciary marks at endtidal volume (A). However, deep inspiration (B) causes a medial and posterior movement of the LV, displacing it almost completely from the radiation portals.

In all patients with cardiac involvement in the XRT field at endtidal volume, inspiratory breathholding

Figure 1. Effect of inspiratory breathholding on position of the heart relative to the left breast. These are coronal MR images of the thoracic cavity in a representative patient. (A) Image obtained at endtidal breathholding. Note that the apex of the left ventricle (arrow) lies in close proximity to the left breast. (B) Image taken at deep inspiratory breathholding. The diaphragm is pulled inferiorly, the lungs are expanded and the apex of the heart (arrow) moves away from the chest wall and left breast, as compared with the endtidal image.

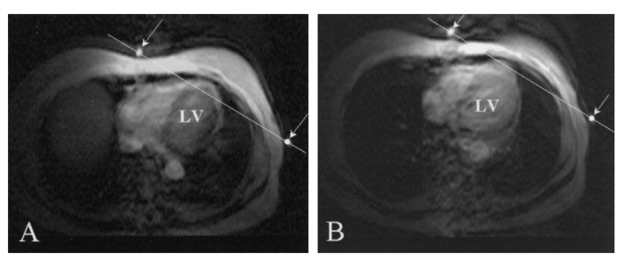

Figure 2. Area of the heart included within the radiation field (50% isodose line). Transverse images through the chest at the level of the midventricle. The circular white markers (white arrows) correspond to the radiation field tatoos, whereas the solid white line corresponds to the radiation therapy posterior field edge. Radiation portals for the left breast lie anterior to this line. This example shows the decrease in cardiac involvement with breathholding at deep inspiration (B) relative to endtidal volume (A) at the same anatomic level.

decreased cardiac volume within the radiation portals. The median decrease in cardiac volume in the XRT field (Table 1) was $-18.1\,cm^3$ ($p \leq 0.001$ vs. ETid) and the range was -0.2– $-36.1\,cm^3$. The mean decrease in cardiac volume in the XRT field was $-19.6\,cm^3$ (s.d. $= 23.5\,cm^3$). Inspiratory breathholding eliminated all cardiac involvement in the XRT field in three patients (21.3%) (Fig. 3). The median percentage decrease in cardiac volume within the radiation portals was 49% (range 5–100%; $p \leq 0.001$ vs. Etid) and the mean percentage decrease was 53% (s.d. = 32%). There was no correlation between age and either the change in cardiac volume or percentage change in cardiac volume with respiratory maneuvers.

DISCUSSION

In this study of women with breast cancer who had received left breast radiation, we found that at least a portion of the heart is included in the radiation portals in the vast majority of patients. In all patients with cardiac inclusion, deep inspiratory breathholding decreased the volume of myocardium included in the left breast radiation portals. We found that compliance with inspiratory breathholding was good, suggesting that application of deep breathholding will be easy to implement in a clinical setting.

All attempts to minimize cardiotoxicity, by decreasing cardiac involvement in breast radiation portals, are especially relevant for long-term breast cancer survivors since cardiovascular disease remains the leading cause of mortality in women after menopause (14). Three large studies demonstrated the increase in cardiovascular mortality associated with radiation therapy with large left breast radiation portals. Rutqvist reported that patients treated with left-sided tangent fields received the highest dose of radiation to the myocardium and had a three-fold greater relative risk of death from heart disease as compared with patients who received no radiation or right-sided tangent fields (4). Data from the Early Breast Cancer Trialist's Collaborative Group data showed an increased risk for death from heart disease in patients who have received left-sided adjuvant XRT (15). Recently, Paszat found a greater likelihood of fatal myocardial infarction among patients who had received XRT before the age of 60, for left-sided breast cancer (16). The observed 10–15 year latency of fatal cardiac deaths in these long-term survivors is compounded by the increased risk of women for age-related atherosclerotic coronary artery disease after menopause (14,17). While

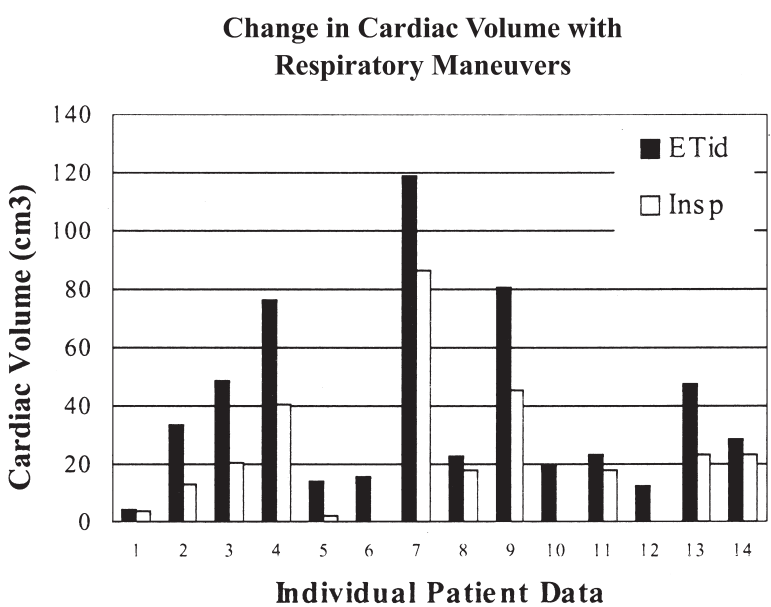

Figure 3. Cardiac volume with respiratory maneuvers. Individual data for each of the 14 patients with cardiac involvement is displayed. Inspiration completely removes the heart from the radiation field in three patients (patients 6, 10, and 12). The figure shows that inspiratory breathholding (Insp) substantially and consistently decreases cardiac volume included in the radiation portals.

there is some evidence that newer methods of XRT may not be associated with the same cardiac morbidity and mortality, it is prudent to minimize all cardiac involvement, especially given the increasing usage and cumulative effects of radiation therapy with chemotherapy (18,19).

Radiation therapy is currently delivered by a continuous administration during an approximately 45-sec period, while the patient breathes quietly. Endtidal volume was chosen as the baseline for all our analyses since it most closely approximates a patient's quiet breathing during continuous delivery of radiation therapy. In almost one-quarter of our subjects, inspiratory breathholding displaced the entire heart out of the left breast radiation field.

There is a theoretical possibility that inspiratory breathholding could expose greater amounts of lung parenchyma to radiation. However, there is evidence that this is not the case. Studies in lung cancer patients have demonstrated that inspiratory breathholding increases the lung volume irradiated but does not increase the actual amount of lung parenchyma irradiated, since air displaces lung parenchyma out of the radiation portals, and, thus, decreases actual lung density radiated (21,22). These data suggest that treating patients at the breathholding configuration should not increase the risk of pulmonary complications.

While the results of our study confirm studies using MRI in normal volunteers (12), and using CT in breast cancer patients (20), there are some notable differences. First, in the current study, breast cancer patients were imaged in the same anatomic position as when they received radiation therapy, rather than being studied relative to hypothetical radiation portals in healthy subjects. Second, patients in the present study were older and are more likely to be representative of other patients with breast cancer. A previous study performed at a different institution with a different patient population used CT and found beneficial effects of breathholding (20). However, our analysis of breast cancer patients with MRI allows higher resolution, multiplanar imaging, and better differentiation of cardiac tissue from pericardial fat, and, thus, may provide more accurate quantitative data. In the long run, MRI's ability to provide clear delineation of both cardiac anatomy and other structures in the chest without need for intravenous contrast, and without ionizing radiation, may make the use of MRI advantageous during simulation for radiation therapy.

Another implication of this study is that delivery of multiple short radiation bursts coupled with inspiratory breathholding would be preferable to the current practice of continuous delivery of radiation during quiet breathing. Current technology already allows for delivery of minifractions of radiation i.e., three sets of fifteen-second exposures. However, some additional modifications are required to automatically confirm constant breath-hold position before delivery of short radiation bursts. Though such technology is not yet commercially available, active investigation by several institutions may soon allow practical implementation of this technique (23).

CONCLUSIONS

Simple inspiratory maneuvers significantly decreased cardiac volume included within the radiation portals in breast cancer patients. Utilization of this approach during delivery of radiation allows for preservation of radiation dosage to the breast, while reducing cardiac involvement and decreasing risk of associated late cardiovascular morbidity and mortality.

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