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Research Article

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MRI-based analysis of organ at risk stability during prolonged voluntary deep inspiration breath-hold in prone and supine breast cancer radiotherapy

Vincent Huybrechts, MD*,[1,2], Vincent Vakaet, MD, PhD[1], Renée De Noyette, MSc[1], Bruno Speleers, MSc[1,2], Michael Stouthandel, PhD[1], Hans Van Hulle, PhD[1], Sophie Pommé, MD[1], Frederik Vanhoutte, PhD[1,2], Wilfried De Neve, MD, PhD[1], Françoise Kayser, MD, PhD[3], Pascal Pellegrin, Ir[3], Marc Coppens, MD, PhD[4,5], Werner De Gersem, PhD[1,2], Liv Veldeman, MD, PhD[1,2]

[1]Department of Human Structure and Repair, Ghent University, Gent 9000, Belgium
[2]Department of Radiation Oncology, Ghent University Hospital, Gent 9000, Belgium
[3]Departement of Radiology, CHU UCL Namur, Namur 5000, Belgium
[4]Department of Anesthesia, Ghent University Hospital, Gent 9000, Belgium
[5]Department of Basic and Applied Medical Sciences, Ghent University, Gent 9000, Belgium

*Corresponding author: Vincent Huybrechts, MD, Department of Radiation-Oncology, University Hospital Ghent, Corneel Heymanslaan 10, Gent 9000, Belgium (vincent.huybrechts@ugent.be)

Abstract

Objectives: Deep inspiration breath-hold (DIBH) is commonly used in breast cancer radiotherapy to reduce radiation exposure to the heart and lungs. Recent techniques incorporating oxygen supplementation and hyperventilation have enabled DIBHs exceeding 2.5 minutes. However, data on internal organ stability during prolonged breath-holds (L-DIBH) remain limited.

Methods: In this prospective observational physiological study, 10 healthy female volunteers performed 2 L-DIBHs (2 minutes 8 seconds each) in both prone and supine positions, following a validated hyperventilation and oxygenation protocol. Serial 3D MRI scans were acquired every 16 seconds during each L-DIBH to assess positional stability of the heart, lungs, and left-sided breast. Cumulative distance-volume histograms (cDiVHs) were used to evaluate spatial relationships between organs and quantify internal displacement over time.

Results: A total of 319 high-quality 3D MRI series were analysed. cDiVHs demonstrated consistent organ positions across timepoints and sessions. While left breast position remained stable throughout all L-DIBHs, minor but statistically significant heart displacement was observed during each L-DIBH increasing over time, more pronounced in the prone position than supine.

Conclusions: L-DIBHs of 2 minutes and 8 seconds are achievable and demonstrate stability in left breast positioning, with minimal movement of adjacent internal organs. Small but progressive shifts of the portion of the heart nearest the breast were detected, particularly in prone positioning.

Advances in knowledge: To account for these minimal displacements during L-DIBH, asymmetrical safety margins around the heart of 3 mm in prone and 2 mm in supine positions may be appropriate.

Keywords: breath-hold; MRI; radiotherapy; female; breast neoplasm; oxygen; hyperventilation; stability; prone; distance-volume histogram.

Introduction

Adjuvant radiation therapy has a well-established role in the treatment of breast cancer complementing surgery and systemic treatment in improving survival and local control in both local and regional disease.[1,2] However, the long-term follow-up shows increased cardiac morbidity and mortality as well as secondary lung cancers following breast irradiation. The risk of heart disease is greatest in patients receiving a higher dose to the heart, that is, left-sided breast cancer and irradiation of the internal mammary lymph nodes.[3] There does not appear to be a safe threshold for mean heart dose.[4,5] Reducing the heart dose can be achieved by improved planning techniques, treatment in prone position, and the use of a deep-inspiration breath-hold (DIBH).[6-10]

During a DIBH the patient takes a deep breath, causing the lungs to expand and shifting the heart away from the breast and nodal areas.[8] Guidelines regarding the implementation of DIBH in clinical practice were recently published by ESTRO.[11] A learning curve is present with an increase in DIBH times and depth over a treatment period.[12,13]

Simple breast-only treatments require a limited amount of DIBHs and intra-fraction motion is limited.[14,15] More advanced radiation techniques for complex treatments including the internal mammary nodes require more beam-on time and require a greater amount of DIBHs to complete.[16] A greater number of DIBHs can increase the risk of inter- and intrafraction movement.[12,15,17,18] Multiple consecutive DIBHs could also be stressful and unachievable for certain patients.[19]

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An alternative to multiple short DIBHs is the use of few prolonged DIBHs (L-DIBHs). Multiple groups have experimented with the use of hyperventilation and oxygenation to achieve L-DIBH times of 3 or more minutes.[20-24] Both mechanically assisted and voluntarily L-DIBHs have been used. Assistance of a mechanical ventilator offers a better control over the hyperventilation frequency and the depth of the L-DIBH, at the cost of a more complex setup.[21,23] Voluntary L-DIBH is easier to perform and implement but may lead to reduced stability.[18]

Interfraction differences of the internal organs are easily assessed using CBCT.[12] The intrafraction stability of the breast or thoracic wall can be evaluated with guidance systems (eg, surface guided radiation therapy [SGRT]).[23] A diaphragmatic drift has been described during a mechanically assisted L-DIBH, but little data exist regarding the intra-DIBH movement and stability of the heart and lungs.[25] Our goal was to analyse the stability of the internal organs and the whole breast target volume during a voluntary L-DIBH in prone and in supine position.

Methods

Volunteers

The prospective observational physiological study was performed on 10 healthy female volunteers. All volunteers gave written informed consent prior to inclusion. The study was approved by the Ethics Board of the Ghent University Hospital (EC/2019/BC-06347), the Ethical board of CHU UCL NAMUR: 182/2020 and registered on ClinicalTrials.gov, number NCT04091542.

Eligibility criteria included women above the age of 18 who were non-smokers and without major pulmonary or cardiac morbidity. Exclusion criteria were pregnancy, WHO Obesity ≥class II or treatment with antihypertensive medication.

Protocol

The preparatory hyperventilation and oxygenation was based on the protocol developed and validated in previous trials at our centre.[22,24] Using an Optiflow Thrive system, the volunteers received 40 L of humidified and heated oxygen per minute at a concentration of 60%. They were asked to hyperventilate at a rate of 16 breaths per minute for 2 minutes after which they started the L-DIBH.

All volunteers participated in an individualized 45 minute training session where they practiced the L-DIBH using the described preparatory protocol. When the volunteers were capable of reaching a 2 minutes and 30 seconds L-DIBH time, they were allowed to proceed to the MRI.

MRI data acquisition

Volunteers were scanned on a 3T Verio MRI scanner (Siemens, Erlangen, Germany), using a T1-weighted sequence with fat saturation (T1 VIBE FS) in a transverse plane, with a slice thickness of 3 mm without spacing. No contrast media injection was performed.

Every subject performed 2 L-DIBHs in both the prone and supine position. The order in which they performed the prone or supine L-DIBH was randomized between subjects. During each L-DIBH an MRI-scan was performed every 16 seconds for a total of 8 scans over a total duration of 128 seconds. The volunteers were instructed to breath out after the final MRI series was taken. No visual feedback system was used during the L-DIBH. These 4 series were performed in a single session the same day.

Organ delineation and data analysis

Using Raystation 12th edition, the following regions of interest (ROIs) were delineated by a single trained resident who was a trial investigator: heart, left and right lung, sternum, and anatomical left-sided breast. Jaccard-Indexes of volume of the heart and the left-sided breast were calculated by dividing the intersect of the delineations of the first and last MRI series by their union: $J(A, B) = |A \cap B|/|A \cup B|$. The first MRI series were used as the reference images. The delineated ROIs of the last series were copied to the reference series for the calculation of the Jaccard-Indexes.

Cumulative distance-volume histograms (cDiVHs) of the heart to the left breast and the left lung to the left breast were created. These cDiVHs display the volume of the organ of interest in function of the distance to the left-sided breast. For every point in an organ of interest the minimal distance to the outer surface of the second structure (the breast) is computed. The summation of these points at every distance results in a distance-volume histogram. These cDiVHs show the volume (y-axis) of the ROI that is at least a certain distance (x-axis) removed from the left breast: starting at a 100 percent at baseline (0 cm) and decreasing in function of the distance. The concept is illustrated in Figure 1.

Statistical analysis

All analyses and data visualisations were performed with R-studio (version 4.4.2). Using the cDiVHs, Di5 and Di50 values were calculated. These are the first distances within which 5% and 50%, respectively, of the volume of the organ are located. These values are used to easier evaluate the shift in distance between the breast and certain volumes of the ROI (5% and 50%) over the course of the L-DIBH. The Di values are named with the relevant ROI (to the left-sided breast) in subscript: eg, $Di50_{heart}$ and $Di50_{left\_lung}$.The $Di5_{heart}$ value is used in the Heart to Breast cDiVH as the closest 5% of the heart is most likely to receive significant dose in breast irradiation. Linear Mixed Models (using the "Restricted Maximum Likelihood" estimation method) were used to analyse the calculated Di5 and Di50 values; "Time," "Position," and "DIBH cycle" were used as parameters in these Mixed

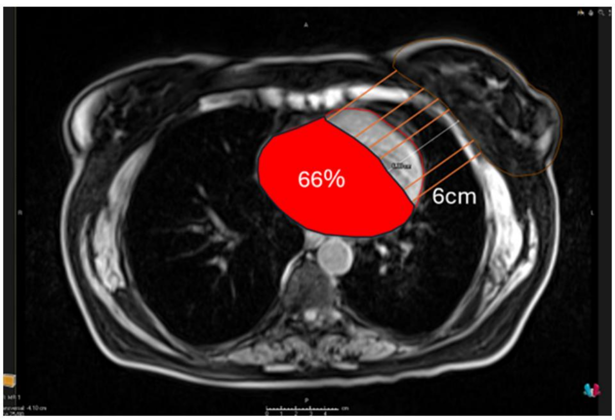

Figure 1. Example of a cumulative distance-volume histogram (DiVH) for the heart relative to the left breast. In this example, the DiVH shows that 66% of the heart volume lies at a distance of 6 cm or more from the left breast.

Models. The intercept value that is reported in the Mixed Model is the estimated value when all predictor variables are set to 0 (for numeric variables) or their reference category (for categorical variables). Wilcoxon signed rank tests were used to analyse the Jaccard-Indices distributions.

Results

Volunteers and ROI delineation

A total of 10 volunteers were included in the trial and a total of 320 3D series were recorded. The median age was 45 years (IQR, 29-54) and all were of normal body habitus. After the training session, all were capable of a 2 minutes and 30 seconds DIBH time. All volunteers completed the MRI protocol without interruptions or adverse events.

After delineation of the relevant ROIs, only a single MRI series was deemed of insufficient quality to include in the analysis due to subject movement, which precluded accurate delineation. That series and its counterpart in the second DIBH were excluded in paired analyses. A total of 319 image series were analysed, 159 in prone position and 160 in supine position.

Distance-Volume histograms

Figures 2 and 3 show the cDiVHs of every subject in both prone and supine positions for the heart and left lung respectively. The average values of the 2 DIBH that the subjects performed are used for every series.

These DiVHs are generally stable over the different MRI series and timepoints. In the majority of the subjects, the distance between heart and breast is larger in supine position and the distance between left lung and breast is larger in prone position.

$Di50_{heart}$, $Di50_{left\_lung}$, and $Di5_{heart}$ values were summarised in both prone and supine position and are visually represented in Figure 4.

Linear mixed model

Using a linear mixed model we calculated the estimated $Di5_{heart}$ and $Di50_{heart}$ values from the Heart to Breast cDiVHs and the fixed and random effects. Table 1 shows the baseline/intercept value and the impact of the fixed and random effects on that intercept value. The fixed effects are time (DiBH duration), position (supine vs. prone) and the DIBH cycle (first or second). The random effects includes the variance between subjects and the random variance within a subject.

The estimated baseline $Di50_{heart}$ value (intercept) is 5.841 cm. For every additional time point (each representing 16 seconds—the duration of a single MRI acquisition), the $Di50_{heart}$ value decreases by 0.018 cm. In supine position, the $Di50_{heart}$ value is estimated to be 1.028 cm higher than in the prone position. The second DIBH performed by subjects was, on average, 0.098 cm worse than the first. All these fixed effects are statistically significant. The estimated between-subject variance is 0.22 cm^2, meaning subject-specific baseline values for $Di50_{heart}$ are normally distributed around the overall intercept of 5.841 cm, with a standard deviation of 0.47 cm. Therefore, we expect that 95% of subjects will have baseline $Di50_{heart}$ values within approximately ±0.92 cm of the group-level intercept.

The results of the linear mixed-effects models for the $Di50_{heart}$ and $Di5_{heart}$ values, as well as the $Di50_{left\_lung}$ values, are presented in Table 1. A subgroup analysis of $Di50_{heart}$ and $Di5_{heart}$ values by patient position (prone vs. sup toine) is provided in Table 2. Time had a statistically significant negative effect on both $Di5_{heart}$ and $Di50_{heart}$ values,

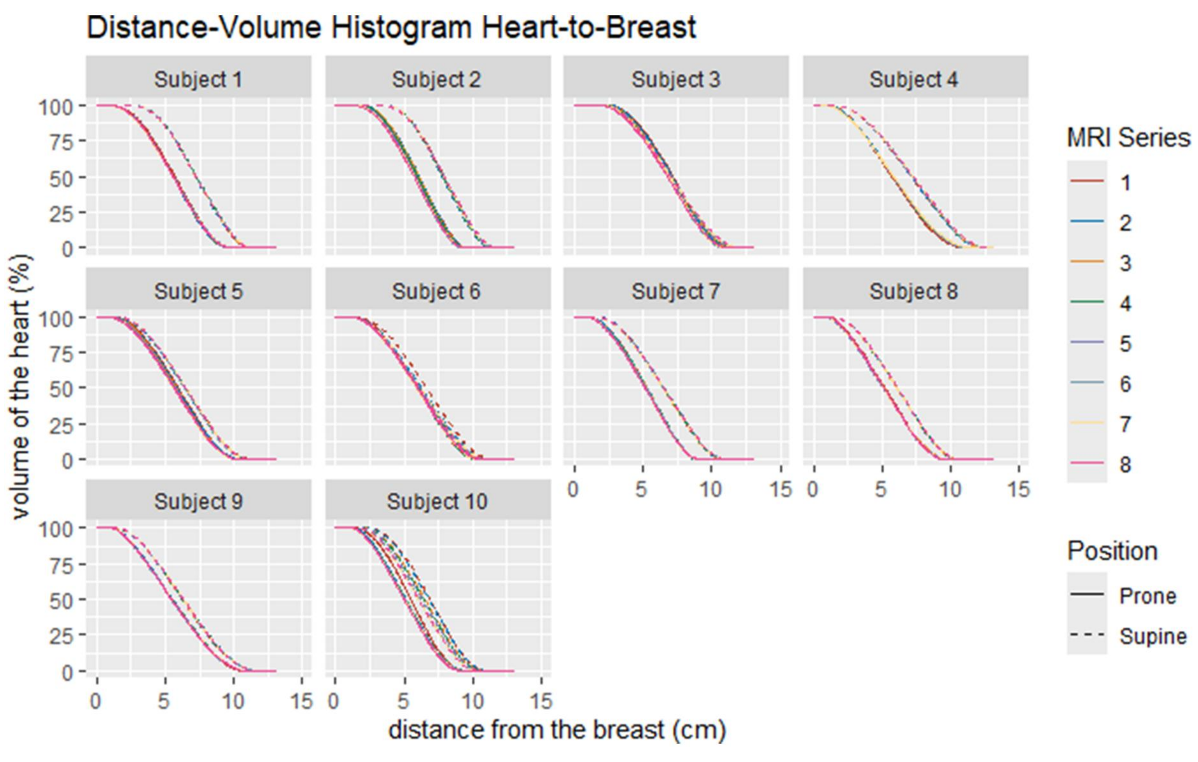

Figure 2. Distance volume histograms of "the Heart to the Breast." The average values of the 2 deep inspiration breath holds (DiBH) are taken for every subject per position. The *y*-axis show the total volume of the heart, the *x*-axis is the distance removed from the (left sided) breast. Every coloured line represents a MRI Series (timepoint).

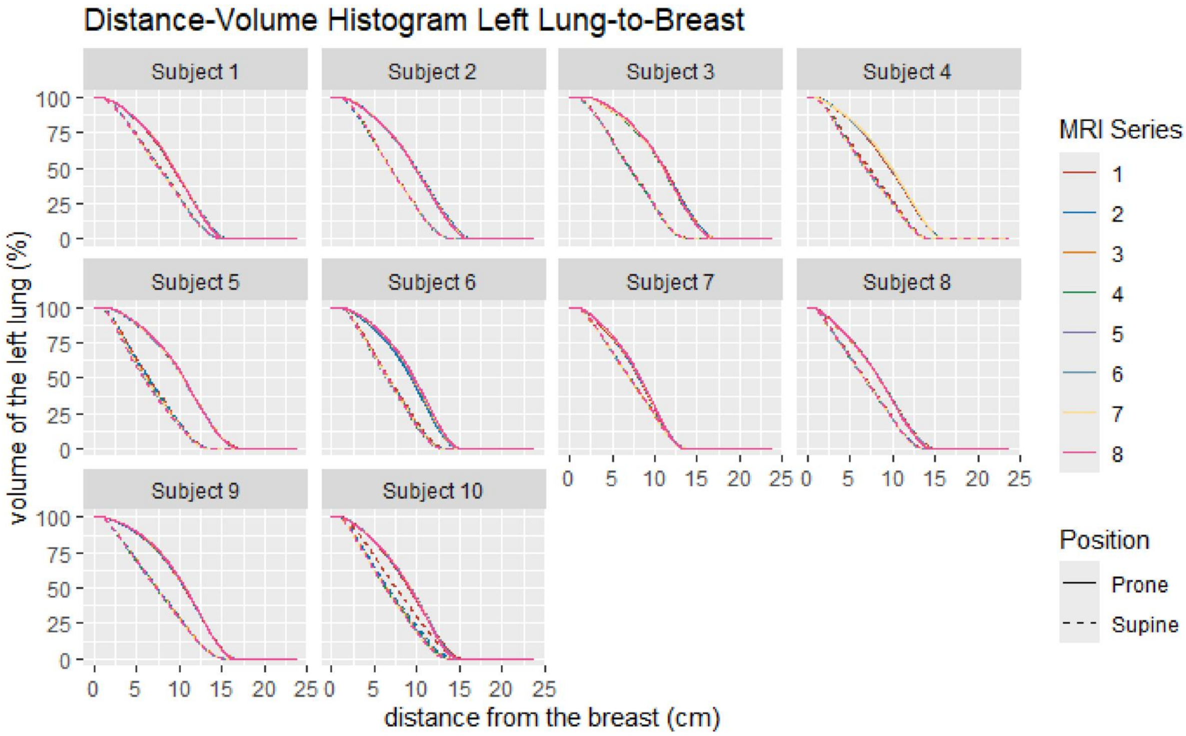

Figure 3. Distance Volume Histograms of "the left lung to the Breast." The average values of the 2 deep inspiration breath holds (DiBH) are taken for every subject per position. The *y*-axis show the total volume of the left lung, the *x*-axis is the distance removed from the (left sided) breast. Every coloured line represents a MRI Series (timepoint).

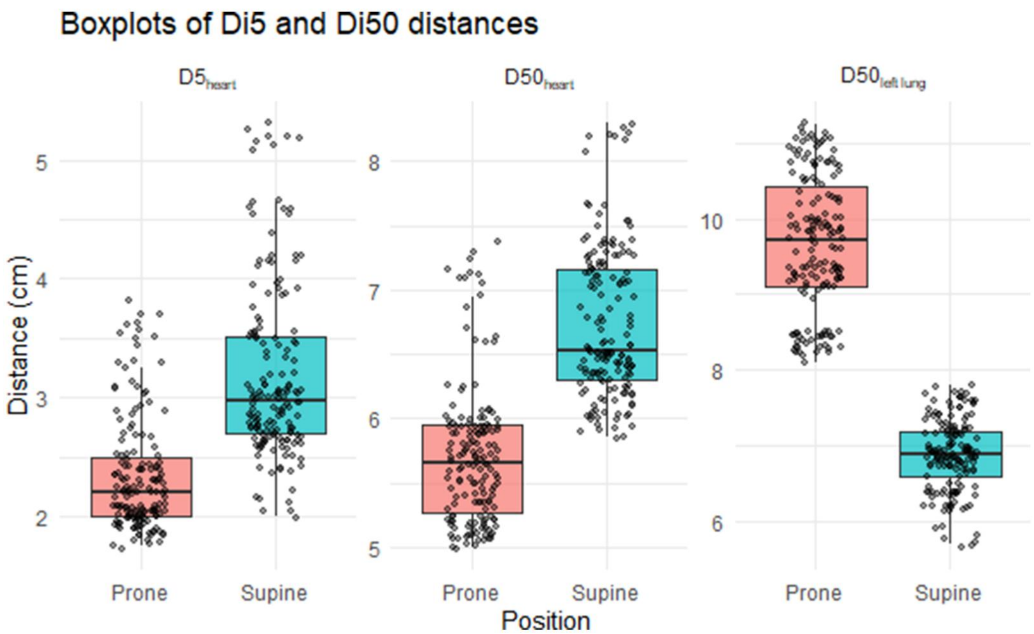

Figure 4. Boxplots of the $Di5_{heart}$ and $Di50_{heart}$ values of the "Heart to Left Breast" cumulative Distance-volume Histogram (cDiVHs) and $Di50_{left\_lung}$ values of the "Left Lung to Left Breast" cDiVH of all participants in both prone and supine positions.

with a more pronounced effect observed for $Di5_{heart}$. Similarly, the time-dependent decrease in distance was more marked in the prone position compared to the supine position for both $Di5_{heart}$ and $Di50_{heart}$ metrics. At 2 minutes and 8 seconds the decrease in $Di5_{heart}$ values are −0.270 cm in prone position and −0.142 cm in supine position.

Jaccard-Index

In 39 of the 40 L-DIBHs the delineations of the first and last MRI series were of sufficient quality to utilise for the calculation of Jaccard-Indices (J-I). Table 3 shows a summary of the Jaccard-Indices of the heart and the left breast. Figure 5 shows an example of the difference between the first and last MRI series.

Table 1. Results of the linear mixed-effects model analysing predictors of heart-to-breast distance-volume histogram at the 50th percentile ($Di50_{heart}$) and 5th percentile ($Di5_{heart}$) and left lung-to-breast distance-volume histogram at the 50th percentile ($Di50_{left\_lung}$).

	$Di50_{heart}$			$Di5_{heart}$		
Predictors	**Estimates (cm)**	**CI (cm)**	***P***	**Estimates (cm)**	**CI (cm)**	***P***
Intercept	5.841	5.533 to 6.148	**<.001**	2.539	2.185 to 2.893	**<.001**
Time	−0.018	−0.034 to −0.002	**.027**	−0.029	−0.046 to −0.012	**.001**
Position [S]	1.028	0.954 to 1.102	**<.001**	0.854	0.777 to 0.931	**<.001**
Cycle [2]	−0.098	−0.172 to −0.024	**.010**	−0.137	−0.214 to −0.061	**<.001**
Random effects						
Residual variance σ^2	0.11			0.12		
Subject-level variance $\tau_{00\ subject}$	0.22			0.30		
ICC	0.66			0.71		
$N_{subject}$	10			10		
Observations	319			319		
Marginal R^2/conditional R^2	0.447/0.813			0.314/0.801		

	$Di50_{left\_lung}$		
Predictors	**Estimates (cm)**	**CI (cm)**	***P***
Intercept	9.717	9.373 to 10.061	**<.001**
Time	−0.012	−0.037 to 0.014	.368
Position [S]	−2.787	−2.904 to −2.670	**<.001**
Cycle [2]	0.010	−0.107 to 0.127	.862
Random effects			
σ^2	0.28		
$\tau_{00\ subject}$	0.25		
ICC	0.47		
$N_{subject}$	10		
Observations	319		
Marginal R^2/conditional R^2	0.787/0.886		

Fixed effects include *time* (per 16-second increment), *position* (supine [S] vs. prone [reference]), and *DIBH cycle* (cycle 2 vs. cycle 1 [reference]). The model includes a random intercept for subject ID. All *P* values are unadjusted for multiple comparisons due to the exploratory nature of the analysis, significant values are in bold.

When comparing prone and supine position using a Wilcoxon signed rank exact test, there is a statistically significant difference (*P* value = .001) in the heart J-I with a median difference of −0.0676 (95% CI, −0.1020 to −0.0388) in favour of supine position. A Wilcoxon signed rank exact test shows a statistically significant difference (*P* value = .036) in breast J-I with a median difference of 0.0305 (95% CI, 0.0046 to 0.1353) in favour of prone position.

Discussion

After our group developed a feasible protocol for the use of a voluntarily L-DIBH[22,24] concerns regarding the stability remained. One of the disadvantages of a voluntary DIBH in comparison to the mechanical ventilator assisted technique is less control over the breathing depth and reproducibility.[23] These subject-related stability concerns could result in more uncertainty when planning and calculating the cardiac dose.[12,14]

In this trial, we confirmed that after training and a short preparatory protocol the subjects could perform multiple voluntarily L-DIBHs of at least 2 minutes and 30 seconds. Analysis of these data focussed on the distance between the left breast and the heart and left lung as these organs are most at risk for radiation induced morbidity and mortality following breast irradiation.[3,4]

We do notice that the estimated decrease in $Di50_{heart}$ value from baseline steadily grows over the course of the L-DiBH. An estimated −0.018 cm shift from baseline is observed every 16 seconds resulting in a −0.126 cm shift at the end of the 2 minute L-DIBH. This increasing difference is also seen in the $Di5_{heart}$ values and is more pronounced in the prone position. The largest decrease is observed in the $Di5_{heart}$ value in prone position where an estimated −0.039 cm change per timepoint would result in a −0.273 cm shift at the end of the 2 minute L-DIBH.

van Kesteren et al[25] noted a diaphragmatic drift of 3.0 mm/minute when analysing MRI images attained during ventilation assisted L-DIBHs. Parkes et al[26] also noted a thoracic deflation in their mechanically L-DIBH. Vander Veken et al[23] used a 4-mm margin for heart reproducibility when using a mechanically L-DIBH. Further increasing the length of the L-DIBH could thus also reduce the stability. Small shifts in cardiac position have also been noted in short DiBHs.[14,18]

In our trial, the second L-DIBH the subjects performed resulted in statistically worse $Di50_{heart}$ and $Di5_{heart}$ values in both prone and supine position. An intra-fraction difference when using this technique is to be expected, but the dosimetric impact might be limited. In the trial by Deseyne et al[17] small differences in heart volumes were observed between repeated DIBHs with no significant difference in cardiac dose when irradiating the breast and regional lymph nodes in prone position.

In nearly all subjects the heart is closer to the breast in prone position than in supine position, but other anatomical and planning related factors result in a lower heart dose in prone position.[6,10]

The dosimetric impact of this −0.126 cm shift of the centre of the heart on the cardiac dose might be limited. Nevertheless, a shift of the lateral edge of the heart of

Table 2. Results of the linear mixed-effects model analysing predictors of heart-to-breast Distance-volume histogram at the 50th percentile ($Di50_{heart}$) and 5th percentile ($Di5_{heart}$) in prone and supine position subgroups.

$Di50_{heart}$ prone				**$Di50_{heart}$ supine**		
Predictors	**Estimates (cm)**	**CI (cm)**	***P***	**Estimates (cm)**	**CI (cm)**	***P***
Intercept	5.879	5.536 to 6.222	**<.001**	6.831	6.465 to 7.198	**<.001**
Time	−0.025	−0.034 to −0.016	**<.001**	−0.013	−0.026 to 0.001	.064
Cycle [2]	−0.120	−0.161 to −0.079	**<.001**	−0.074	−0.135 to −0.012	**.019**
Random effects						
Residual variance σ^2	0.02			0.04		
Subject-level variance $\tau_{00\ subject}$	0.29			0.33		
ICC	0.95			0.89		
$N_{subject}$	10			10		
Observations	159			160		
Marginal R^2/conditional R^2	0.021/0.946			0.006/0.895		
$Di5_{heart}$ prone				**$Di5_{heart}$ supine**		
Predictors	**Estimates (cm)**	**CI (cm)**	***P***	**Estimates (cm)**	**CI (cm)**	***P***
Intercept	2.578	2.274 to 2.882	**<.001**	3.354	2.877 to 3.830	**<.001**
Time	−0.039	−0.047 to −0.030	**<.001**	−0.020	−0.034 to −0.006	**.005**
Cycle [2]	−0.134	−0.170 to −0.097	**<.001**	−0.140	−0.205 to −0.075	**<.001**
Random effects						
Residual variance σ^2	0.01			0.04		
Subject-level variance $\tau_{00\ subject}$	0.23			0.57		
ICC	0.94			0.93		
$N_{subject}$	10			10		
Observations	159			160		
Marginal R^2/conditional R^2	0.048/0.947			0.012/0.930		

Fixed effects include *time* (per 16-second increment) and *DIBH cycle* (cycle 2 vs. cycle 1 [reference]). The model includes a random intercept for subject ID. All P values are unadjusted for multiple comparisons due to the exploratory nature of the analysis, significant values are in bold.

Table 3. Summary statistics of the Jaccard Index (JI) values for heart and left-sided breast volumes during prolonged Deep Inspiration Breath-Hold (L-DIBH), between the first and last timepoint ($n = 39$).

***n* = 39**	**JI heart**	**JI heart prone**	**JI heart supine**	**JI breast**	**JI breast prone**	**JI breast supine**
Min	0.4871	0.4871	0.5173	0.1958	0.8084	0.1958
Max	0.9193	0.8367	0.9193	0.9936	0.9936	0.9776
Mean	0.7547	0.7200	0.7876	0.8949	0.9433	0.8489
SD	0.1160	0.0979	0.1245	0.1574	0.0480	0.2069
Median	0.7828	0.7652	0.8223	0.9397	0.9557	0.9268
q25	0.6935	0.6885	0.7558	0.9107	0.9192	0.8748
q75	0.8268	0.7847	0.8874	0.9636	0.9762	0.9530

JI values were calculated to assess spatial stability. Data are presented for all positions combined, as well as separately for prone and supine positions.

−0.270 cm in prone position or −0.142 cm in supine position might result in unwanted high dose on the left ventricle.[3] The accuracy of the planned heart position—and therefore the dose at the lateral heart edge—decreases with longer L-DIBH durations. To improve planning robustness, an asymmetric margin of 3 mm in the prone position and 2 mm in the supine position, directed from the heart towards the left breast, may be considered to account for the intra-L-DIBH instability.

No statistically significant decrease in $Di50_{left\_lung}$ value was observed over the course of the L-DIBH. A steady reduction in lung volume as well as a diaphragmatic drift have been reported during L-DIBHs.[25] The prone position is known to decrease the average and maximum lung dose compared to supine position, an increased irradiated lung volume has also been noted.[6,27] This difference in lung volume and the different anatomy of the breast in prone position compared to supine position likely explain the difference in estimated $Di50_{left\_lung}$ value calculated using DiVHs between the 2 positions: −2.787 cm.

The left breast itself remained reasonably stable over the course of the L-DIBH. The Jaccard-Indices show excellent similarity of the position of the breast at the start and the end of the L-DIBH with a median overlap of 0.9433 (IQR, 0.9192-09762) in prone position and 0.9268 (IQR 0.8748-0.9530) in supine position. This small thoracic drift could be explained by lung deflation as was observed in other L-DIBH investigations.[25,26]

Limitations of our study are the younger age and general fitness of our subjects that may result in better L-DIBH quality, however, this technique was validated on breast cancer patients with excellent results.[22] The maximum duration of L-DIBH captured on MRI was 2 minutes and 8 seconds leaving uncertainty regarding the stability in longer voluntary DIBHs. As this trial focussed on intra-DIBH stability, we cannot report on inter- and intra-fraction variability when using

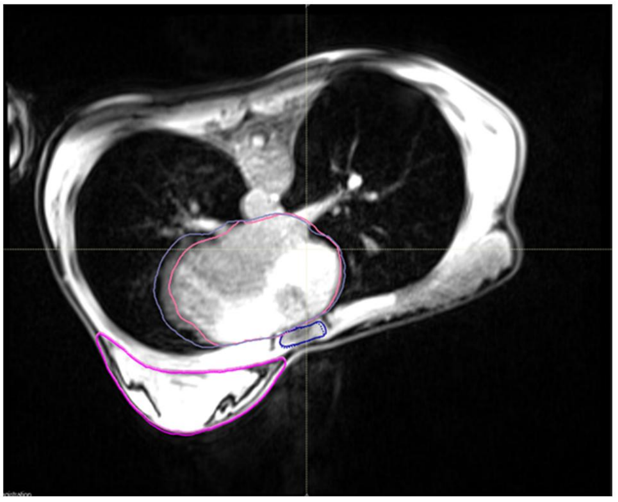

Figure 5. Image of the fusion between the first MRI (heart in pink) of the DIBH and the eighth/last MRI (heart in light blue) of the 2 deep inspiration breath holds (DiBH). A stable breast can be seen, though with a lateral shift of the heart.

L-DIBH. The top and base of the lungs were not captured within the MRI field of view. While this is not expected to significantly affect the $Di50_{left\_lung}$ value, it does limit the ability to assess potential changes in lung volume throughout the L-DIBH.

Conclusion

In this research, we analysed the Intra-DIBH stability of the internal organs during a voluntary L-DIBH. A voluntarily L-DIBH of 2 minutes and 8 seconds is feasible with relatively stable measurements of the heart and lung volume in relation to the left breast. Small instabilities are seen between the breast and the volumetric centre of the heart in prone position (−0.175 cm) and between the breast and the ipsilateral lung in supine position (−0.325 cm). Similar changes are seen in the closest 5% of the heart with a shift of −0.270 cm in prone position and −0.142 cm in supine position. Further increasing the L-DIBH time could magnify these instabilities. Whether these differences have a dosimetric or clinical relevant impact is uncertain. To improve planning robustness, an asymmetric margin of 3 mm in the prone position and 2 mm in the supine position, directed from the heart towards the left breast, may be considered.

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Conflicts of interest

None declared.

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