Assessment of deep inspiration breath hold (DIBH) amplitude and reduction in cardiac dose in left breast cancer patients

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Introduction

Due to the anatomical position of the heart, patients treated with radiotherapy for left sided breast cancer are at a greater risk of cardiac morbidity due to radiation exposure of cardiac tissues[1]. It is widley accepted that any achievable reduction in cardiac irradiation will aid the reduction of long-term side effects[2]. However it is often unavoidable to exclude all cardiac tissues and structures when treating left sided breast cancer[3]. Radiotherapy delivery using deep inspiration breath hold (DIBH) is one recognised method of achieving this[4-8].

Many studies have indicated a significant reduction in cardiac irradiation using DIBH compared to standard radiotherapy techniques for left-sided breast cancer patients[4-8]. A large, single centre study (n=319) found a 70% (p>0.0001) reduction in V20Gy (volume of cardiac tissue receiving over 20Gy) when free breathing (FB) was compared with DIBH (7.8% to 2.3% respectively)[9] . V40Gy (volume of cardiac tissue receiving over 40Gy) and mean heart dose were also statistically significantly (p>0.0001) reduced by 91% and 48% respectively when the DIBH technique was used. These results were consistent with a study by Hayden, Raines and Tiver[7] who identified a cardiac V30Gy (volume of cardiac tissue receiving over 30Gy) reduction from 7.1% to 2.4% when DIBH was compared to FB (n= 30). Both studies did state that there appeared to be no predicting factors to indicate whether an individual patient will benefit from DIBH[7,9].

While the benefits of DIBH are well acknowledged[4-7], problems such as breath hold level reproducibility, verification and patient co-operation are limiting factors[5]. Audio and visual coaching has been found to be effective in standardising patients' amplitude between fractions[5,10]. However, this has expensive resource and training implications and can increase scanning, treatment and set-up time due to the addition of a training session prior to scanning or multiple breath holds to deliver treatment[5]. Due to additional time and resource implications it may be necessary to identify cases where maximum benefit from DIBH techniques can be achieved. It has been shown that DIBH can be successfully delivered without the use of additional resources and patient monitoring systems [4], however there are currently no studies that investigate amplitude levels associated with DIBH, and any resulting correlations in DIBH benefit.

The primary aim of the study was to investigate the impact of breath hold amplitude on subsequent cardiac V30 and mean heart dose in women treated for a left sided breast cancer in relation to the use of DIBH technique during radiotherapy. The V30 and mean heart dose were chosen as these represent standard dose constraint measures used in clinical practice. The secondary aim investigated if patient age influenced DIBH amplitude; there was concern that older patients may not be able to achieve the same amplitude of breath hold as younger patients.

Method

A retrospective study including patients treated in the previous two years was completed . All patients included in the study underwent two planning scans (one free breathing FB scan and one Deep Inspiration Breath hold DIBH scan).

Ethical considerations and data protection:

As the study was retrospective, there were no ethical risks to the patient as the study could not influence or impact the patient's treatment. Patient confidentiality and privacy were maintained throughout with Computerised Tomography (CT) scans and breathing traces given an anonymous identifier. The study was approved and supported by the hospital trust and Sheffield Hallam University.

Patient cohort

The sample size was calculated using correlation co-efficient linear regression which indicated the sample size required a total of 30 patients to identify statistical significance. Patients were randomly selected from the total number of patients scanned in both FB and DIBH using a random number generator. A total of 62 eligible patients were assigned ascending consecutive numbers; 30 numbers were then identified from the random number generator, the patients with the matching number were included in the study.

Radiotherapy procedure

Patients were scanned on an inclined breast board, using 3mm slices on a 16-slice Philips Big Bore CT scanner (Philips Healthcare, Andover, MA). Due to capacity and resource implications, DIBH scans were usually acquired during a separate appointment from the FB scan. It is acknowledged this may be a limitation of the study, however this was performed due to logistics and resource limitations. Patient position for DIBH scan was reproduced to match that of the FB scan. A minimum of three practice breath holds were performed to ensure patients understood the instructions, could maintain breath hold for the required time and that breath hold level was consistent. Varian Real-time Position Management (RPM) (Varian Medical Systems, Inc, Palo Alto, CA) was used to record and monitor breathing.

Treatment planning

A single experienced planning radiographer retrospectively virtually simulated plans on Prosoma planning software (MedCom, Darmstadt, Germany). Plans were produced on the FB and DIBH CT scans using standard field borders to cover the breast tissue. For patients requiring supraclavicular fossa (SCF) irradiation, field borders described by Wheatley et al [11] were used, as followed by the IMPORT high protocol [12]. Pinnacle version 9.8 (Philips Medical Systems, Fitchbourg, WI) was used for heart contouring, planning and dosimetric comparison. The heart was contoured following the guidelines from the FAST Forward protocol [13].

A dose of 40Gy in 15 fractions over 3 weeks using 6MV or 10MV photons was prescribed, corrections were applied for tissue heterogeneity and treatment plans were optimised with 3D dose compensation with wedges or segments for dose homogeneity. Planning was comparable with other studies [13,14] such that all plans produced were within the guidance of ICRU 62[15]:

The RPM trace from the planning scan was used to determine the amplitude of normal breathing and that of DIBH. It is acknowledged that the true amplitude of breath is not known for the FB scan as RPM was not used during the FB scan. However, before the DIBH scan, the patient was asked to breathe normally which was recorded on the RPM trace.

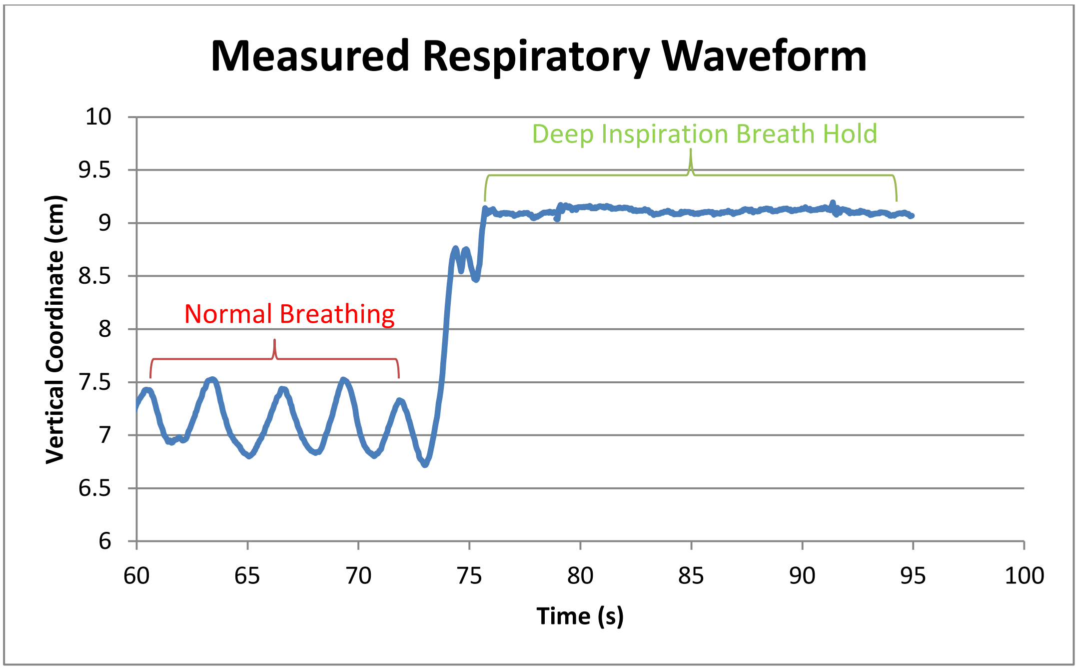

Figure 1: Example RPM trace showing normal breathing and deep inspiration breath hold.

Data Analysis

Amplitude data was taken from the RPM trace exported into Microsoft Excel 2010 with statistical analysis performed using SPSS v22. Cardiac V30 and cardiac mean doses were calculated using Pinnacle (Philips Medical Systems, Fitchbourg, WI). For each patient, data was collected from FB and DIBH datasets. Descriptive data analysis was performed followed by Spearman's rank correlation.

Minimising bias

In order to improve the reliability and assess the validity of the researchers planning, 10 of the 30 patients were randomly selected, re-outlined and re-planned by the experienced planning radiographer to confirm consistency and intra-rater reliability. The heart was also re-contoured for one patient 5 times to calculate the error in heart contouring. The intra class correlation co-efficient was 1.0 (95% CI 0.99 – 1.00) and 1.0 (95% CI 1.00 – 1.00) respectively, indicating excellent consistency between the contours.

Results

All 30 female left sided breast cancer patients were aged between 35 and 63, mean age 48.4 years.

Overview: FB and DIBH amplitudes

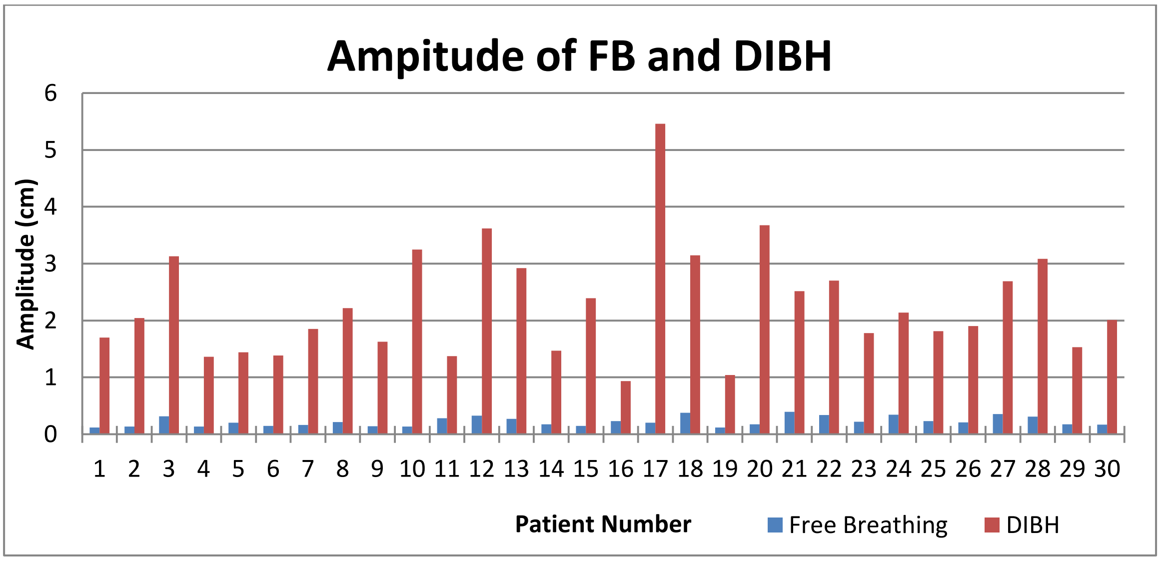

Figure 2: Amplitude of FB and DIBH.

Amplitude of breath for FB and DIBH for each patient is shown in figure 2. FB amplitude ranged from 0.12cm to 0.39cm (range 0.27cm), average 0.22cm (95% CI 0.19cm-0.26cm) and median 0.20cm. DIBH amplitude ranged from 0.93cm to 5.46cm (range 4.52cm), mean 2.27cm (95% CI 1.91cm–2.64cm) and median 2.02cm.

The ratio of amplitude increase [$Ratio\ increase\ in\ amplitude = \frac{DIBH\ amplitude}{FB\ amplitude}$] ranged from 4.0 times to 27 times FB to DIBH (range 23 times) the mean was 10.96 times (95% CI 8.98-12.94).

Ninety three percent (n=28) of patients achieved a ratio of amplitude increase of over 5 times from FB to DIBH, 43% (n=13) over 10 times and 17% (n=5) over 15 times increase from FB to DIBH.

Overview: FB and DIBH impact on cardiac V30

FB cardiac V30 ranged from 1.1% to 7.3%, mean 3.76% (95% CI 3.0%–4.52%) and median 3.1%. DIBH cardiac V30 ranged from 0% to 1.6%, mean 0.31% (95% CI 0.14%–0.47%) and median 0.08%.

A 90% relative dose reduction of cardiac V30 was achieved by 73% of patients (n=22); n=8 of these patients achieved a full 100% reduction. The 27% (n=8) that achieved less than 90% V30 dose reduction ranged between 38-89% reduction. The average relative cardiac V30 dose reduction was 90% (95% CI 83.1%–96.0%) and median 97% with range of 62%.

Cardiac V30 dose reduction and ratio of amplitude increase

The ratio of amplitude increase required to achieve a 100% cardiac V30 reduction ranged from 6.3 times to 27.2 times that of FB. Of the 5 patients achieving an amplitude increase of at least 15 times FB, cardiac V30 reduction of 99-100% was achieved.

Analysis indicated that a weak positive correlation exists between the ratio of amplitude increase from FB to DIBH and relative cardiac V30 dose reduction (R=0.38) which is statistically significant (p=0.04).

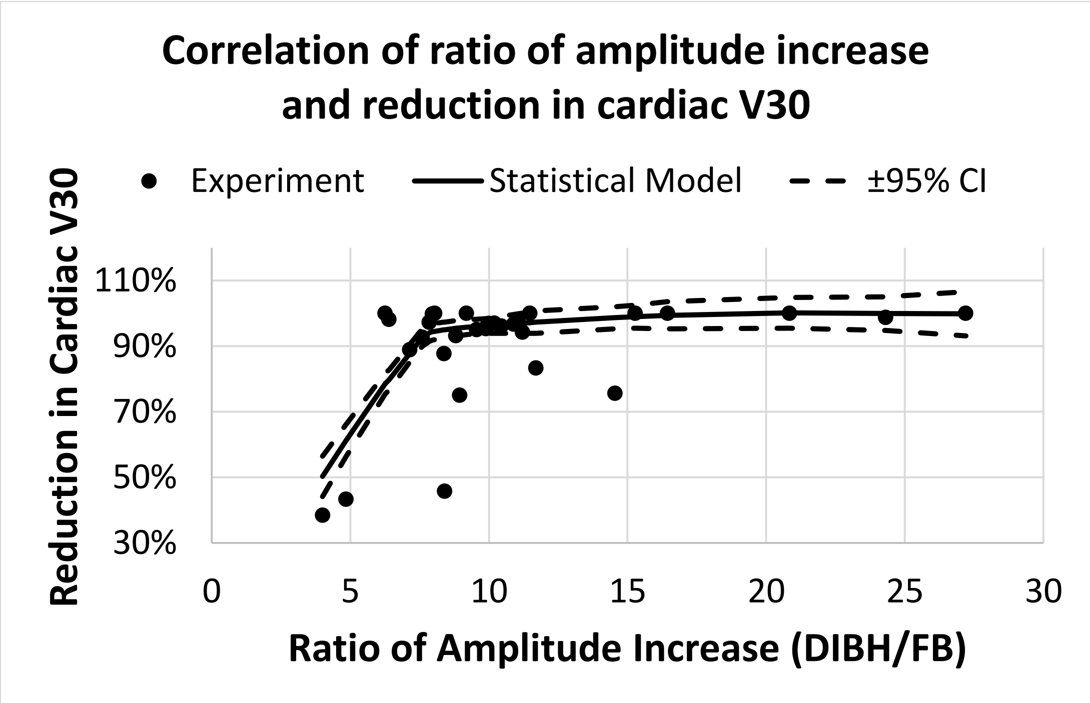

Figure 3: Correlation of ratio of amplitude increase from FB to DIBH with cardiac V30 dose reduction using locally weighted polynomial regression.

The correlation of ratio of amplitude increase from FB to DIBH with reduction in cardiac V30 using Loess best fit line is shown in figure 3. This indicates the following cardiac V30 reductions with DIBH amplitudes of:

- 5 times FB, V30 reduction is 60%
- 7 times FB, V30 reduction is 80%
- 10 times FB, V30 reduction is 95%
- 15 times FB, V30 reduction is 100%

Thirteen outliers (determined as those outside the 95% CI) were also observed; no obvious cause was identified for these.

Cardiac V30 dose reduction and DIBH amplitude

The patient with the smallest DIBH amplitude (0.93cm) achieved the smallest V30 dose reduction (38%). The patients with the second and third lowest cardiac V30 dose reductions (43% and 46%) had DIBH amplitudes of 1.38cm and 1.46cm respectively. However, there were four patients with lower DIBH amplitudes achieving over 75% V30 dose reduction. All patients with DIBH amplitudes over 2cm achieved over 80% V30 dose reduction. A positive correlation between DIBH amplitude and cardiac V30 dose reduction (R=0.48) was identified, although only a moderate correlation this is statistically significant (p=0.007).

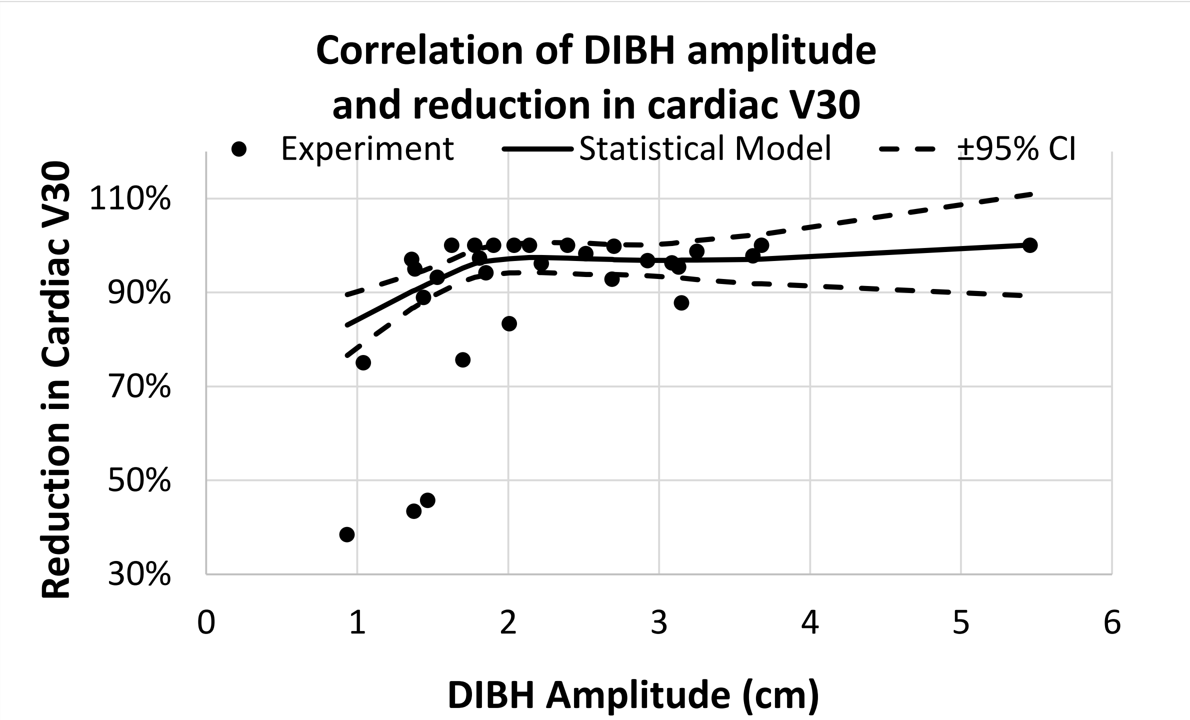

Figure 4: Correlation of DIBH amplitude with cardiac V30 dose reduction using locally weighted polynomial regression.

The correlation of DIBH amplitude with cardiac V30 dose reduction with Loess best fit line is shown in Figure 4. This indicates with a DIBH amplitude of over 1.4cm there will be a 90% reduction in V30 dose and with DIBH amplitudes over 2cm there will be a 97% reduction in V30 cardiac dose.

Overview: cardiac mean dose

Cardiac mean dose ranged from 1.8Gy-5.6Gy with FB, mean 3.4Gy and median 3.2Gy whilst for DIBH cardiac mean dose ranged from 0.6Gy-2.2Gy, mean 1.3Gy and median 1.2Gy. Cardiac mean dose reduction ranged from 15.1%-81.1%, average 59% (95% CI 52.4%–65.0%) and median 62%.

Cardiac mean dose reduction and ratio of amplitude increase

Seventy seven percent of patients (n=23) achieved a relative cardiac mean dose reduction greater than 50%; with 27% (n=8) patients obtaining more than 70% reduction in cardiac mean dose. Of the 8 patients who received over 70% reduction in cardiac mean dose, 5 of these patients also had full V30 dose reduction.

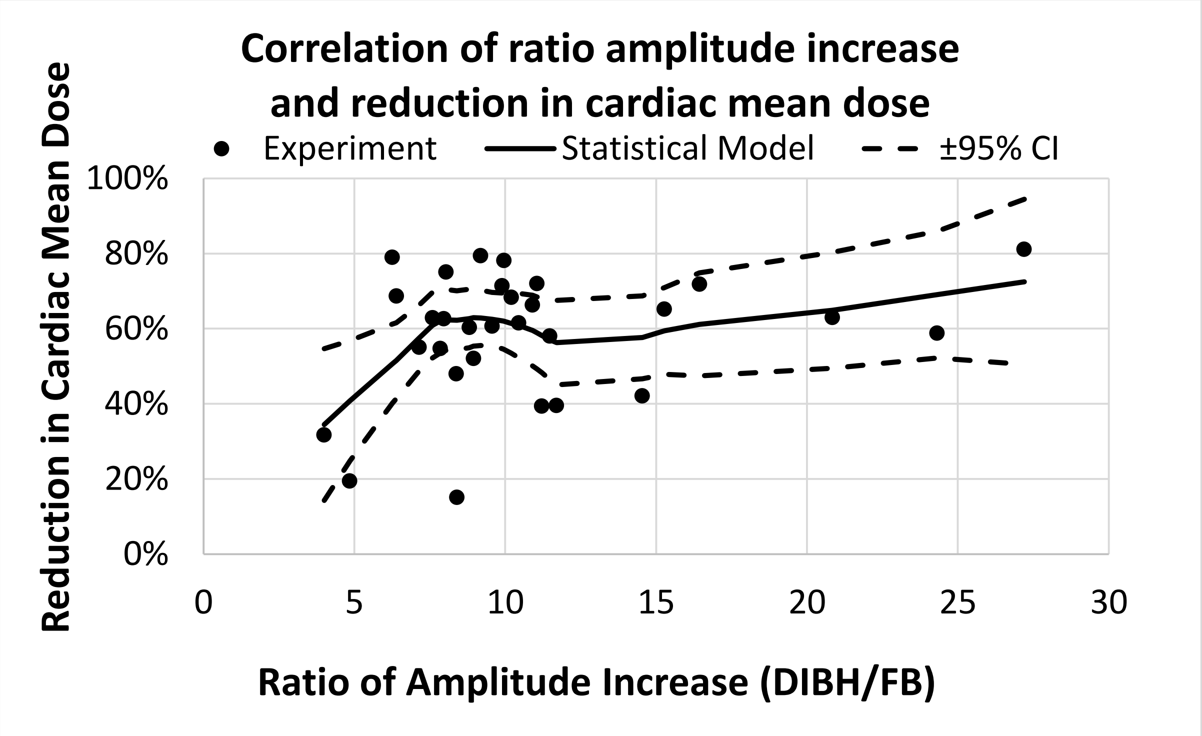

Figure 5: Correlation of ratio of amplitude increase from FB to DIBH with cardiac mean dose reduction using locally weighted polynomial regression.

Loess best fit line (Figure 5) indicates cardiac mean dose can be reduced by over 40% for amplitude increase 5 times greater for DIBH compared to FB. For those patients where amplitude increase is 10 times greater with DIBH cardiac mean dose is reduced by 60%. No obvious cause was found for the 14 outliers (identified as those outside of the 95% CI). The spread of the confidence intervals suggest no significant association between the two variables exists in this sample.

Cardiac mean dose reduction and DIBH amplitude

The patient with the smallest DIBH amplitude (0.93cm) had the third lowest mean cardiac dose reduction (31.7%). The patient with the lowest mean cardiac dose reduction (15%) had DIBH amplitude of 1.47cm however there were six patients with smaller DIBH amplitudes but greater cardiac mean dose reductions.

The patient with the largest DIBH amplitude (5.46cm) did achieve the greatest reduction in cardiac mean dose (81.1%). Seventy seven percent (n=23) achieved a cardiac mean dose reduction over 50% (DIBH amplitude range 1.04cm-5.46cm).

The results indicate generally smaller DIBH amplitude achieves lower mean cardiac dose reduction. The correlation was tested with Spearman's rank and indicated a moderate positive correlation between DIBH amplitude and cardiac mean dose reduction (R=0.523) which is statistically significant (p=0.003).

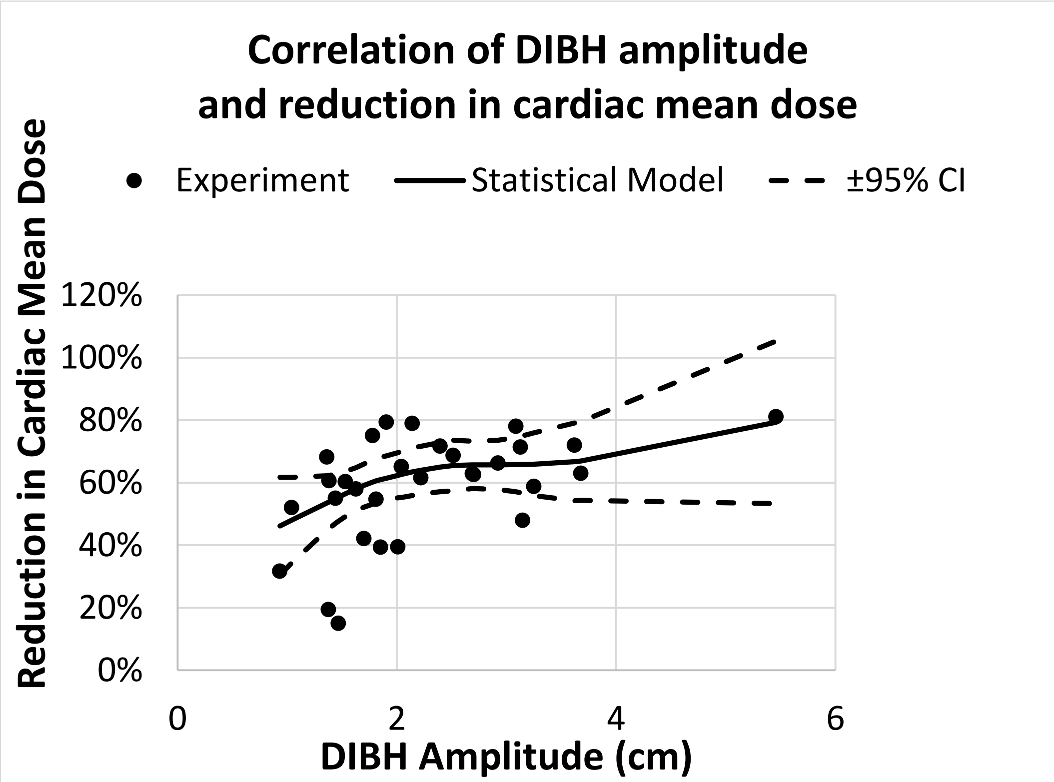

Figure 6: Correlation of DIBH amplitude with cardiac mean dose reduction using locally weighted polynomial regression.

Correlation of DIBH amplitude and reduction in cardiac mean dose is shown in Figure 6. With DIBH amplitudes of 1cm there is a 48% cardiac mean dose reduction achieved, with over 50% at DIBH amplitudes of 1.4cm or greater. Sixty percent mean cardiac dose reduction is seen at 2cm DIBH amplitude, 66% reduction at 3cm DIBH amplitude and 70% at 4cm DIBH amplitude.

Age and ratio of amplitude increase from FB to DIBH

No correlation was identified between patient age and amplitude of DIBH (R=0.099, p=0.602).

Discussion

Breath hold level and cardiac V30?

A V30 reduction of at least 90% was achieved by 73% (n=22) of patients with ratio increase ranging from 6.25 - 27.2 times that of normal breathing. However a 99-100% reduction in cardiac V30 was obtained for all patients when ratio increased at least 15 times normal breathing for DIBH, this was achieved by 17% (n=5) of patients. This therefore indicates some patients may not need to take as deeper breath to still achieve a 100% decrease in cardiac V30 dose. Conversely it also indicates where patients may need to take a deeper breath in order to fully remove heart from the field. These results are comparable with the existing literature from Nissen and Appelt [9] who identified a 91% reduction in 319 patients aged under 60 years old using DIBH, in the present study only two patients were aged over 60 (oldest patient 63 years). A comparable mean cardiac V30 reduction of 90% was achieved by the majority of patients (73%). Conversely Hayden, Raines and Tiver [7] identified a mean V30 reduction of 66.8% when using DIBH in 30 patients. However, despite using RPM to monitor patients breathing no assessment of amplitude was conducted, making comparison of the results difficult. Results from the present study indicate there is a weak positive correlation between ratio of amplitude increase and V30 reduction, which is statistically significant (R=0.38,p=0.04).

In the present study, only three patients achieved less than 70% V30 reduction, two of these patients also achieved the lowest increase in amplitude ratio from FB to DIBH, further indicating a link between amplitude and V30 reduction. However 8 patients achieved lower amplitude ratio increase (6.25 to 8.38) but received a greater relative cardiac V30 dose reduction (ranging 89%-100%), which demonstrates there is a component associated with individual anatomy where large increases in amplitude ratio still do not result in large V30 reduction. There are many factors which would need thorough investigation to identify potential causes for this such as lung capacity, patient anatomy and pre-existing medical conditions; investigation of these factors was beyond the limits of the current study.

Is there a correlation between breath hold level and cardiac mean dose reduction?

Cardiac mean dose reduction from FB to DIBH ranged from 15.1%-81.1%, average 59% (95% CI 52.4%–65.0%), median 62% and range 66%. These results were slightly increased from a study by Nissen and Appelt[9] who identified mean heart dose reduction of 48% compared to FB. While benefit of mean heart dose reduction appears decreased in comparison to V30 reduction this is to be expected as inevitably some portion of heart tissue will remain in the field despite using a DIBH technique. In the current study ratio of amplitude increase and mean cardiac dose reduction were not correlated, this could be as a result of the sample size used, it is possible with a much larger sample the data may show a stronger relationship but based on this sample no conclusions can be drawn. Conversely DIBH amplitude and mean cardiac dose reduction were moderately correlated (p=0.003,R=0.523), with 77% of patients achieving a mean cardiac dose reduction greater than 50% with amplitudes ranging from 1.04cm-5.46cm. Eight patients achieved over 70% mean cardiac dose reduction with amplitudes ranging from 1.78cm to 5.46cm. No patient achieved full mean cardiac dose reduction despite patients achieving up to a maximum ratio increase of amplitude of 27.2 times that of normal breathing (5.46cm amplitude). However, it is important to state that plans were not optimised, instead for consistency, set field borders were adhered to; in practice it may be possible to achieve full mean cardiac dose reduction as plans can be compromised on an individual basis dependent on histology and tumour bed location.

When assessing DIBH amplitude alone, patients with smaller DIBH amplitudes had smaller cardiac dose reduction compared to those with larger DIBH amplitudes. Of all the factors tested, DIBH amplitude and cardiac mean dose reduction had the greatest correlation with mean heart dose, however this was still only a moderate positive correlation (R=0.523,p=0.003).

Is there a minimum ratio increase in amplitude of breath hold below which no benefit in minimising cardiac dose is achieved?

All patients achieved mean cardiac dose reduction and V30 dose reduction when using DIBH, despite the amplitude increase achieved, with only 10% (n=3) patients achieving less than 70% reduction in V30, and 23% (n=7) patients less than 50% reduction in cardiac mean dose.

It has been identified from the current study that an amplitude increase of at least 15 times that of FB will result in 100% V30 dose reduction and for DIBH amplitudes greater than 2cm there will be at least 60% reduction in mean cardiac dose and 97% reduction in cardiac V30. This potentially allows those patients who will achieve the greatest benefit of DIBH to be identified. For those patients unable to achieve such a large increase of breath the study has shown, DIBH amplitude increases of 5 times that of FB will reduce V30 dose by 60% and increases of 10 times that of FB will reduce V30 dose by 95%. In relation to DIBH amplitude, amplitudes of 1.4cm will reduce V30 by 90% and mean cardiac dose by 50%. For 3cm DIBH amplitude there is a 66% reduction in cardiac mean dose and a 70% reduction with DIBH amplitudes of 4cm. It is important to note there is no available pre-existing literature specifically investigating DIBH in relation to amplitude, therefore comparison of results is not possible and further research in a larger study is recommended.

Is there a correlation between patient age and level of breath hold achieved?

There are no pre-existing studies investigating benefit of DIBH in relation with patient factors. The present study found no correlation between age in relation to increase in amplitude (R=-0.099).

While it is clear from the results that DIBH techniques can reduce cardiac dose, much of this evidence is from small single centre studies and the optimal practice for its use has not yet been clarified. The literature may be lacking in a number of areas and still requires evidence to identify which specific patient characteristics might be predictive of indicating patients that may benefit most from DIBH.

Conclusion

Results indicated statistical significance in relation to the correlation of DIBH amplitude and mean cardiac dose reduction (R=0.523, p=0.003), DIBH amplitude and V30 dose reduction

(R=0.48,p=0.007) and ratio of amplitude increase from FB to DIBH and V30 dose reduction (R=0.38,p=0.04). A threshold of 15 times normal breathing has been shown to achieve 100% dose reduction in V30. However, there are some cases where much lower ratio increase (as low as 6.25 times FB) can also result in 100% V30 reduction. There currently appears to be no obvious link to identify the cause for this. Cardiac mean dose reductions of over 50% were achieved with DIBH amplitudes of 1.4cm or greater however was also observed in patients with DIBH amplitudes as little as 1.04cm. This study provided some insight into what levels of dose reduction can be achieved for a range of breath hold amplitudes allowing prior assessment of potential patients where individual coaching may be employed to enhance the impact of breath hold on cardiac dose reduction. The study identified that even patients with small amplitude increases achieved significant cardiac dose reduction. This has important implications for practice, particularly if arbitrary thresholds are used to determine suitability for adaptive breathing.

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