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Prolonging deep inspiration breath-hold time to 3 min during radiotherapy, a simple solution

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ABSTRACT

Background and purpose: Deep inspiration breath-hold is an established technique to reduce heart dose during breast cancer radiotherapy. However, modern breast cancer radiotherapy techniques with lymph node irradiation often require long beam-on times of up to 5 min. Therefore, the combination with deep inspiration breath-hold (DIBH) becomes challenging. A simple support technique for longer duration deep inspiration breath-hold (L-DIBH), feasible for daily use at the radiotherapy department, is required to maximize heart sparing.

Materials and methods: At our department, a new protocol for multiple L-DIBH of at least 2 min and 30 s was developed on 32 healthy volunteers and validated on 8 breast cancer patients during radiotherapy treatment, using a pragmatic process of iterative development, including all major stakeholders. Each participant performed 12 L-DIBHs, on 4 different days. Different methods of pre-oxygenation and voluntary hyperventilation were tested, and scored on L-DIBH duration, ease of use, and comfort.

Results: Based on 384 L-DIBHs from 32 healthy volunteers, voluntary hyperventilation for 3 min whilst receiving high-flow nasal oxygen at 40 L/min was the most promising technique. During validation, the median L-DIBH duration in prone position of 8 breast cancer patients improved from 59 s without support to 3 min and 9 s using the technique ($p < 0.001$).

Conclusion: A new and simple L-DIBH protocol was developed feasible for daily use at the radiotherapy center.

1. Introduction

Radiation treatment has an established role in breast cancer, complementing surgery and systemic therapies to prevent recurrences and improve survival, both in women with node negative and node positive disease [1]. Long term follow-up, however, shows that the beneficial effect on survival is weakened by radiation-induced cardiac and lung cancer mortality [2,3]. The risk is highest for left-sided breast radiation therapy and irradiation of the internal mammary nodes, due to the proximity of the heart and subsequent higher heart doses [4]. Deep inspiration breath-hold (DIBH) is an established technique to reduce cardiopulmonary doses in breast cancer irradiation treatment [5–8]. Since a deep breath increases the distance between the target volume and the heart [9]. Besides DIBH and heart blocks, ASTRO guidelines recommend prone positioning as one of the options to reduce heart dose [10]. Furthermore, prone position results in reduced acute and late toxicity and lower ipsilateral lung dose [11–14]. For most radiation treatments of the breast, the duration of beam-on time is around 1

Abbreviations: DIBH, deep inspiration breath-hold; L-DIBH, prolonged deep inspiration breath-hold; BMI, body mass index; FiO2, fraction of inspired oxygen; HFNO, high flow nasal oxygen; HFPV, high Frequency Percussive Ventilation; IMRT, intensity modulated radiotherapy; RR, respiratory rate.

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to 2 min [15]. However, when more complex techniques are used, e.g. multi-beam intensity modulated radiotherapy (IMRT) for whole breast with lymph node irradiation, beam-on time can be extended to up to 5 min, especially in combination with hypofractionated schedules [15,16]. Therefore, a high number of consecutive short DIBHs are required, leading to stress for the patient, position changes and the inability of treatment in DIBH due to exhaustion for many patients [17,18]. Also, previous research has shown a moderate correlation between positional errors, mostly in the superior-inferior direction, and the number of DIBHs required, especially when treating the lymph node regions.

Three mechanisms to prolong breath-holding are well established. Firstly, hyperventilation as a method to prolong DIBH times is extensively used by breath-hold divers, due to inducing hypocapnia and decreasing the CO_2-drive to breath [19,20]. Secondly, pre-oxygenation increases oxygen reserve and delays the onset of hypoxia up to 8 min [21]. Thirdly, an increase in lung inflation increases breath-hold duration [22]. A combination of these three methods has already been tested in breast cancer patients as a technique to prolong breath-holding during radiotherapy [23,24].

The protocol from Parkes et al. uses a mechanical ventilator for 15 min of forced hyperventilation which can increase DIBH duration to 5 min, whereas Roth et al. uses the mechanical ventilator for 4-minutes of oxygenation followed by a one-minute period of voluntary hyperventilation, increasing DIHB duration to 2 min and 45 s in patients [23,24]. To our knowledge, these protocols have not been implemented at radiotherapy departments, possibly due to the complexity of the mechanical ventilator, the required capital expenditure, and the high set-up time. Simpler methods of oxygenation like high-flow nasal oxygen or an oxygen mask have not been investigated in this context. Our goal was to develop a simpler protocol to deliver the treatment in multiple consecutive longer DIBHs (L-DIBHs) of at least 2 min and 30 s. We developed the protocol on healthy volunteers; followed by a validation on breast cancer patients after a radiotherapy session.

2. Materials and methods

2.1. Volunteers and patients

The protocol was developed on 32 healthy female volunteers and validated on 8 patients receiving curative radiotherapy for breast cancer. All volunteers and patients gave a written informed consent, and the study was approved by the ethics committee of Ghent University Hospital and registered on ClinicalTrials.gov, number NCT04091542. Eligibility criteria included women above the age of 18 without any history of cardiac or pulmonary disease. Exclusion criteria were currently smoking, not able to perform a single unassisted DIBH of over 20 s, previous breath-holding experience, and WHO obesity class II (BMI > 35 kg/m^2).

2.2. Protocol development and validation phase

In 4 successive development cycles of 8 volunteers, the protocol was optimized to achieve our L-DIBH target of reaching at least 2 min and 30 s based on 3 additional goals: comfort for the patient, ease of use and the time required for set-up and patient preparation. For these criteria, no strict cut-off values were chosen but each criterion was evaluated in a joint meeting by a group of stakeholders including radiation oncologists, anesthesiologists, and radiotherapy technologists. The number of cycles was not predefined.

The 8 volunteers in each cycle were randomized to different nests of volunteers and they performed 3 unassisted baseline DIHBs. Each nest performed the baseline protocol as well as a specific range of predefined variations. The first baseline protocol was an adaptation of Roth et al. using a mechanical ventilator for oxygenation [24]. The volunteers performed 4 different examinations on 4 separate days during a working week, each time performing 3 consecutive L-DIBHs and ending when they chose to breath-out (e.g. due to discomfort). Each L-DIBH was preceded by a preparatory phase of voluntary hyperventilation, using audio-assistance, and oxygenation. The hyperventilation frequency was predefined, and the volunteers were asked to breathe deeply, following the tempo. Prior to the first examination the volunteers did not receive any preparatory instructions, except for information on the types of oxygenation devices used during their examinations. During each examination, the vital parameters of the volunteer were monitored using a Carescape B650 anesthesia monitor (GE Healthcare, Finland). Unfortunately, high flow nasal oxygen does not allow for EtCO2 measurements within clinically acceptable levels of accuracy [25]. When the level of hypocapnia cannot monitored by an accurate measurement of EtCO2 during hyperventilation, the examiner looked for signs of hypocapnic tetany. The hyperventilation phase was stopped by the examiner if any of those signs were noted. The full details of an examination and the safety criteria can be found in Appendix A. After each examination of 3 consecutive L-DIBHs the side effects and comfort of the technique were evaluated using patient questionnaires (Appendix B).

Throughout the cycles, the following parameters were optimized: oxygenation device, duration of hyperventilation, hyperventilation frequency (RR), fraction of inspired oxygen (FiO2); L-DIBH position and flow rate (L/min) both during hyperventilation and breath-holding. The following three oxygenation devices, ordered by higher ease of use and lower set-up time, were investigated (Fig. 1): 1) mechanical ventilator (Leon Plus, Löwenstein, Germany) and a face mask (Series 6700, Hans Rudolph, USA) in pressure support ventilation at 25 mbar peak pressure, 2) High-flow nasal oxygen or HFNO (Optiflow Thrive, Fisher & Paykel, New Zealand), 3) non-rebreathing mask with oxygen reservoir (Ecolite, Intersurgical, UK), also called a Hudson mask. The following hyperventilation frequencies were examined (in breaths/minute): 12, 16, 20 and volunteer choice. For the mechanical ventilator or HFNO, a maximum FiO2 of 80% was allowed to reduce the risk of absorption atelectasis [26].

After 4 development cycles, the stakeholders decided that the protocol met all preset requirements and was ready to be validated on a group of 8 patients. They were examined on 4 days after a radiotherapy session for breast cancer, and they performed 3 consecutive L-DIBHs on each day. These examinations were not part of their curative radiotherapy treatment.

2.3. Statistical analysis

Study data were collected and managed using REDCap electronic data capture tools hosted at Ghent University Hospital. All analyses and data visualizations were done with R-studio (version 3.6.2). During protocol development median and corresponding interquartile range (IQR) for L-DIBH durations, and, the comfort and pain assessments were compared pairwise using the Wilcoxon rank sum test within the same subject. The non-parametric Friedman test was used to compare median breath-hold durations, during the validation phase. A two-sided significance level of 0.05 was chosen.

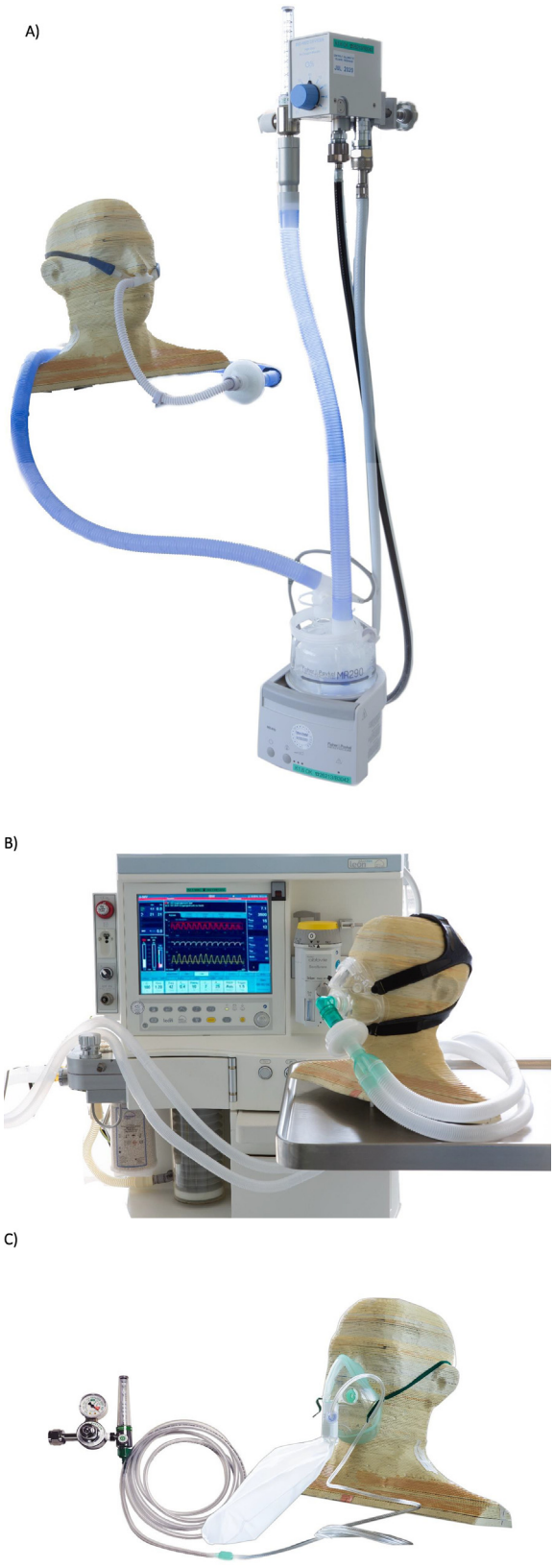

Fig. 1. Oxygenation methods tested during protocol development. A. High-flow nasal oxygen (Optiflow Thrive device), delivery of a heated and humidified oxygen mixture through a nasal cannula. B. Mechanical ventilator with facemask. C. Non-rebreather mask with oxygen reservoir or Hudson mask.

Table 1
Baseline characteristics and results of baseline examination for healthy volunteers and patients.

	Healthy volunteer	Patient during RT	Total
n=	32	8	40
Baseline characteristics			
Age, years	43 (34–51)	56 (41–60)	44 (36–54)
Length, cm	168 (163–172)	162 (158–171)	167 (162–172)
Weight, kg	63 (57–63)	62 (59–69)	62 (58–70)
BMI	22 (21–24)	24 (22–27)	23 (21–25)
Current alcohol use	23 (72%)	7 (88%)	30 (75%)
Former smoker	8 (25%)	3 (38%)	11 (28%)
Medication use	19 (59%)	7 (88%)	26 (65%)
Comorbidities			
Thyroid disease	0 (0%)	3 (38%)	3 (8%)
Diabetes	0 (0%)	0 (0%)	0 (0%)
Back pain	12 (38%)	5 (63%)	17 (43%)
Shoulder pain	4 (13%)	3 (38%)	7 (18%)
Cancer treatment			
Previous chemotherapy		6 (75%)	
Hormonal therapy		3 (38%)	
Baseline examination			
Unassisted DIBH time – m:ss	1:02 (0:52 – 1:17)	0:59 (0:40 – 1:08)	1:02 (0:46 – 1:15)
Systolic blood pressure – mmHg	125 (109–134)	136 (115–140)	126 (112–136)
Diastolic blood pressure – mmHg	68 (61–78)	72 (63–89)	68 (62–78)
Heart rate - BPM	67 (60–77)	68 (62–74)	67 (61–77)
Respiratory rate - /min	12 (10–16)	17 (12–25)	12 (10–16)

Data are median (IQR) or number (%). Some percentages do not total 100 because of rounding.
BMI body mass index, BPM beats per minute, RT: radiotherapy

3. Results

From March 2019 until December 2019 a total of 32 healthy volunteers were included in the development phase, and 8 patients in the validation phase. Baseline characteristics of the volunteers and patients can be found in Table 1. Unassisted DIBH times were 1 min and 2 s for the volunteers and 59 s for the patients. Table 2 contains a summary of the most common volunteer and patient reported side effects during and after the examinations.

3.1. Protocol development

A summary of median L-DIBH durations can be found in Table 3. In total 390 L-DIBHs were performed and 21 L-DIBHs were missing: 12 L-DIBHs due to involuntary breathing of a single volunteer, 3 due to claustrophobia when putting on the ventilator mask, 2 because of mask leakage, 2 due to incorrectly following the instructions on the first try, and 2 because of a technical issue. A total of 369 L-DIBHs were used for the optimization of the protocol.

3.1.1. First cycle

The first cycle focused on the difference between a mechanical ventilator and HFNO (Fig. 1A & B). No significant difference was found in median L-DIBH duration ($p = 0.2$) between both oxygenation devices. Since there were no differences in median L-DIBH duration or comfort, but HFNO has a shorter set-up time and is easier in use, the stakeholders decided to continue using HFNO. Other parameters were investigated in smaller nests of 2 volunteers. Increasing the duration of hyperventilation from 2 min to 6 min resulted in a 1 min and 40 s longer median L-DIBH duration. Based on these results, the stakeholders decided to investigate 3

Table 2
Overview of side effects both during the examination and after ending the examination.

Side effects during examination		Side effects after examination	
Number of examinations	n = 160	Number of examinations	n = 160
Did you feel any?		*Do you now feel any?*	
Tingling feeling in fingers/feet or limbs	40 (25%)	Dizziness	20 (13%)
Pain	25 (16%)	Fatigue	16 (10%)
Need to cough	21 (13%)	*Do you now have?*	
Dizziness	16 (10%)	Dry mouth	41 (26%)

Table 3
Median L-DIBH durations of the volunteers in m:ss (Interquartile range m:ss – m:ss) in all the comparisons made during the iterative development.

N*	Standard protocol	mm:ss (IQR)	P-value†	mm:ss (IQR)	Alternative protocol
	Cycle 1				
8	Mechanical ventilator	3:25 (2:47 – 3:53)	0.2	3:39 (2:39 – 4:10)	High Flow Nasal Oxygen
2	2 min of hyperventilation	3:12 (2:36 – 4:31)	N/A‡	4:52 (4:10 – 5:44)	6 min of hyperventilation
2	Supine position	3:40 (2:51 – 4:09)	N/A‡	3:08 (2:32 – 3:38)	Prone position
2	16 breaths/minute during hyperventilation	3:36 (3:11 – 3:55)	N/A‡	3:13 (2:44 – 4:00)	20 breaths/minute during hyperventilation
2	60% fraction of inspired oxygen	2:55 (2:26 – 3:43)	N/A‡	2:48 (1:54 – 3:07)	80% fraction of inspired oxygen
	Cycle 2				
8	High Flow Nasal Oxygen	2:58 (2:00 – 3:40)	0.001	2:37 (1:44 – 3:13)	Hudson mask
4	3 min of hyperventilation	2:52 (2:14 – 3:28)	0.2	3:02 (2:23 – 3:47)	5 min of hyperventilation
4	Supine position	2:57 (1:31 – 3:46)	0.3	2:36 (1:37 – 3:21)	Prone position
	Cycle 3				
8	3 min of hyperventilation	3:28 (2:40 – 4:28)	0.002	3:09 (2:34 – 3:51)	2 min of hyperventilation
8	16 breaths/minute during hyperventilation	3:28 (2:40 – 4:28)	0.2	3:24 (2:40 – 4:20)	12 breaths/minute during hyperventilation
8	40L/minute flow during hyperventilation	3:28 (2:40 – 4:28)	0.001	2:59 (2:19 – 4:03)	20L/minute flow during hyperventilation
	Cycle 4				
8	16 breaths/minute during hyperventilation	2:53 (2:00 – 4:00)	0.2	3:42 (1:49 – 4:18)	Volunteer choice during hyperventilation
8	60% fraction of inspired oxygen	2:53 (2:00 – 4:00)	<0.001	2:13 (1:23 – 2:43)	21% fraction of inspired oxygen
8	20L/minute flow during L-DIBH	2:53 (2:00 – 4:00)	0.3	3:36 (2:30 – 4:04)	0L/minute flow during L-DIBH

* Number of volunteers in the comparison † Wilcoxon signed rank test within a volunteer performing the baseline and alternative protocol ‡ P-values not shown due to the small number of subjects investigated (N = 2)

and 5 min of hyperventilation and prone and supine positioning in the second cycle.

3.1.2. Second cycle

The second research cycle investigated whether oxygenation using a simple Hudson mask (Ecolite, Intersurgical, UK) is equal to HFNO (Fig. 1A & C). Median L-DIBH duration was 22 s longer using HFNO (p = 0.002), and both methods scored similarly on comfort. Since set-up time is not shorter with a Hudson mask, the stakeholders decided on further using HFNO. Longer hyperventilation, above 3-minutes, did not result in longer L-DIBH duration.

3.1.3. Third and fourth cycle

Decreasing hyperventilation time from 3 min back to 2 min, significantly decreased median L-DIBH duration by 19 s (p = 0.002). Normal air decreased the L-DIBH duration by 40 s (p < 0.001). Reducing the flow rate to 20 L/min. during hyperventilation, significantly decreased L-DIBH durations with 29 s (p = 0.001). After the third and fourth cycle no major changes to the protocol were made compared with the second cycle and the protocol was accepted by the stakeholders for validation in breast cancer patients.

3.2. Validation phase

The final protocol that was validated on 8 breast cancer patients after a radiotherapy session uses 3 min of hyperventilation at 16 breaths/min with pre-oxygenation using HFNO (FiO2 of 60%; 40 L/min. during hyperventilation and 20 L/min. during breath-hold), in prone position. Median L-DIBH duration improved from 59 s (IQR 41 s: 1 min 8 s) without support to 3 min and 9 s (interquartile range (IQR) 2 min 6 s: 3 min 45 s) using the protocol (p < 0.001). As seen in Fig. 2, median L-DIBH times were significantly better for each consecutive L-DIBH attempt during a single examination (Friedman test, p < 0,001) at 2:25 (IQR 1:49 – 3:03), 3:18 (IQR 2:04 – 3:55) and 3:35 (IQR 2:44 – 4:30), for the first, second and third attempt respectively. On each consecutive day, the median total L-DIBH duration of the three attempts increased significantly (Friedman test, p = 0,001) at 7:43 (IQR 4:24 – 9:19) on the first day, 8:16 (IQR 6:52 – 9:03) on the second day, 10:09 (IQR 9:19 – 11:18) on the third day, and 11:50 (IQR 9:16 – 12:09) on the final day.

4. Discussion

We developed a protocol, feasible to use at a radiotherapy department, using the combination of voluntary hyperventilation and oxygenation. Validation on 8 breast cancer patients showed that this technique can prolong the DIBH duration of at least 2 min and 30 s (Fig. 2), both in prone and supine position. This should permit most treatment plans to be delivered in a single L-DIBH, unlike the current delivery using multiple short DIBHs [15,27]. Furthermore, up to 3 consecutive L-DIBHs are achievable, thus permitting more extensive treatments or cone-beam CT (CBCT) using L-DIBH. Also, fewer DIBHs should minimize intrafraction motion [17]. Our protocol could be especially important for plans that include the internal mammary nodes, which have average delivery times of 7 min and 30 s with IMRT requiring a very high number of 30 s DIBHs [16].

Prolonging breath-hold using a combination of deep inspiration, hyperventilation and pre-oxygenation has previously been investigated in breast cancer patients using a mechanical ventilator (Fig. 1B) [23,24]. We compared pressure support mechanical ven-

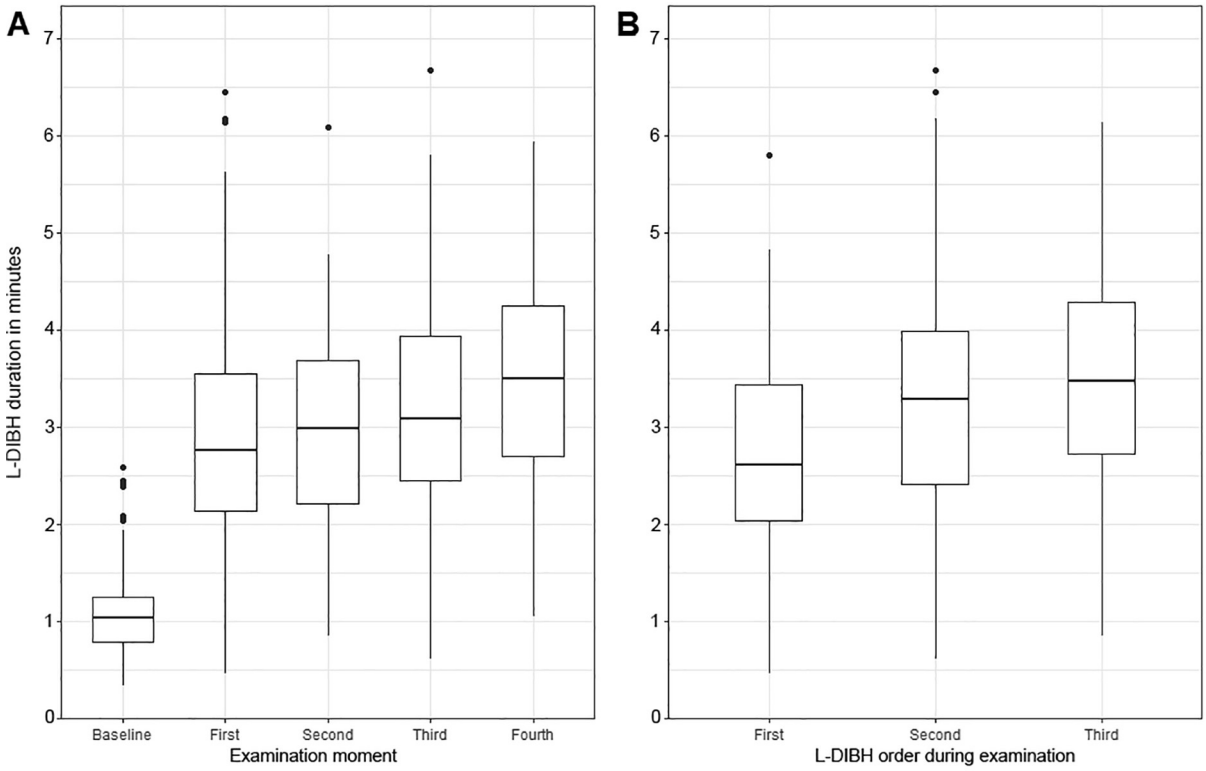

Fig. 2. Boxplots of the L-DIBH durations during validation with 8 breast cancer patients a) according to the day of the examination or b) according to the order of L-DIBHs during each examination day. *The box shows the upper and lower quartile, showing the interquartile range (IQR). The line dividing the box represents the median. The upper- and lower whiskers represent the upper and lower values within 1.5 times the IQR. The dots represent the outliers outside 1.5 times the IQR above the upper quartile and bellow the lower quartile.*

tilation with HFNO using an Optiflow Thrive device (Fig. 1A & B). No differences in L-DIBH durations were observed, but HFNO has several advantages. Firstly, ease of use is higher compared to the mechanical ventilator. As described by Parkes et al., the ventilator parameters need to be adapted to the volunteer [28], and this requires training for appropriate operation. Secondly, set-up of the mechanical ventilator takes significantly longer and is prone to failure since an air-tight fit of the face mask is essential [29]. Thirdly, the HFNO system with nasal cannula is perceived as less claustrophobic and preferred by most of the volunteers. Schwabbauer et al. also showed HFNO is more comfortable and preferred by patients with acute hypoxic respiratory failure [30]. We also compared HFNO to a Hudson mask (Fig. 1A & C) for preoxygenation. HFNO enables around 20 s longer median L-DIBH durations.

We propose a 3-minute period of voluntary hyperventilation before L-DIBH. This is similar to the preoxygenated hyperventilated hypocapnic apnea-induced radiation (PHAIR) protocol [24], but considerably shorter than the protocol of Parkes et al. [23] In the PHAIR protocol, volunteers were asked to perform 1 min of hyperventilation after 4 min of oxygenation, resulting in slightly shorter L-DIBH duration compared with our protocol. However, our protocol has a shorter preparation time, allows consecutive L-DIBHs and does not require a mechanical ventilator. It seems that most of the effect of hyperventilation is reached after 3 min. Besides the large individual differences, we found that the duration of the preparation phase had the most impact on L-DIBH duration. Further prolonging hyperventilation probably leads to longer L-DIBH duration due to more profound hypocapnia, as also shown by Parkes et al. reaching durations over 5 min with 15 min of preparation. But longer preparation is time-consuming and therefore difficult to implement in the daily routine of a radiotherapy department. Even with our technique, the setup and on-couch time will probably still be longer than with repeated short breath holds. The technique is unnecessary for most breast radiotherapy treatments, which have a beam-on time of around 1 to 2 min, but the aim of this research is to find a solution for complex treatments [15]. Future research on individual adaptation of the hyperventilation duration, based on patient training results and treatment characteristics, could minimize overall treatment time and success rate in daily practice. Another solution to further decrease time slots, would involve shortening of the preparation time following the first L-DIBH. Parkes et al. found that after thorough preparation, a short 1-minute break can allow an equally long second L-DIBH, compared to the first L-DIBH [31]. Further research is necessary to confirm these finding using our technique.

Other techniques have been developed to prolong DIBH duration in breast cancer, not using hyperventilation and oxygen. High Frequency Percussive Ventilation (HFPV) was developed for unanesthetized patients with lung or breast cancer. Very long apnea is achievable using HFPV, with 3 patients reaching single apnea durations of over 7 min [32,33]. However, adaptation to the individual patient is necessary and a leak-free seal, crucial to prevent motion drift due to air leakage. Finally, a mechanical ventilator can be used to change breathing patterns and reduce motion variability of the tumor [28,34,35]. This approach requires both an airtight face mask and expertise in mechanical ventilation at the radiotherapy department. In contrast to all previous techniques, our protocol is simple, requires minimal set-up time and equipment and limited training.

The volunteers and patients could easily perform 3 consecutive L-DIBHs with only a minimal resting-time in-between 2 L-DIBHs and this during 4 successive sessions. Important to note, is the ability for patients to perform this technique in prone, since the com-

bination of prone and DIBH leads to minimal heart and lung doses [9,36]. Hyperventilation has been known to cause symptoms of dizziness, tingling and lightheadedness [37,38]. No serious adverse events were observed, besides a grade 2 laryngitis in an immunocompromised patient. L-DIBH duration increases with each successive breath-hold during a single examination session, and progressively throughout the 4 sessions, which highlights the possible benefit of a training phase before using the technique during radiotherapy treatment [39]. Our L-DIBH durations could potentially be further increased by using visual feedback in addition to audio guidance [40,41] and by instructing patients to perform home practice [42,43]. The proposed protocol was developed and validated in 32 volunteers and 8 patients, who were all highly motivated and presenting with low comorbidity.

The actual adoption of our protocol in daily practice still requires additional research, including imaging studies to determine the L-DIBH reproducibility, intra- and interfraction motion and planning margins, and the development for a training program for patients. In general, patients are highly motivated to perform a DIBH during breast cancer radiotherapy, resulting in a high rate of compliance, and we found the same to be true of the volunteers and patients during our L-DIBH examinations [6,7,39]. Especially in patients which can only hold their breath for a short duration, support by our technique could result in better confidence. All participants understood the technique, they could execute it well and felt satisfied afterwards. During the examinations we focused on creating a safe and repeatable environment with clear and simple instructions, since previous research has shown this improves the patient experience [18,39]. To create this environment, appropriate monitoring of the patients is required. Our research utilized anesthesia grade equipment, but since no severe adverse events were captured, further reduction in monitoring equipment to pulse oximetry is probably safe, lowering the capital costs to implement the technique [23].

In conclusion, HFNO combined with a short period of voluntary hyperventilation significantly prolongs DIBH durations, allowing for treatments with multiple consecutive L-DIBHs of at least 2 min and 30 s.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2021.02.007.

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