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FULL PAPER

Safely achieving single prolonged breath-holds of > 5 minutes for radiotherapy in the prone, front crawl position

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Objective: Breast cancer radiotherapy is increasingly delivered supine with multiple, short breath-holds. There may be heart and lung sparing advantages for locoregional breast cancer of both prone treatment and in a single breath-hold. We test here whether single prolonged breath-holds are possible in the prone, front crawl position.
Methods: 19 healthy volunteers were trained to deliver supine, single prolonged breath-holds with pre-oxygenation and hypocapnia. We tested whether all could achieve the same durations in the prone, front crawl position.
Results: 19 healthy volunteers achieved supine, single prolonged breath-holds for mean of 6.2 ± 0.3 min. All were able to hold safely for the same duration while prone (6.1 ± 0.2 min *ns*. by paired ANOVA). With prone, the increased weight on the chest did not impede chest inflation, nor the ability to hold air in the chest. Thus, the rate of chest deflation (mean anteroposterior deflation movement of three craniocaudally arranged surface markers on the spinal cord) was the same (1.2 ± 0.2, 2.0 ± 0.4 and 1.2 ± 0.4 mm/min) as found previously during supine prolonged breath-holds. No leakage of carbon dioxide or air was detectable into the facemask.
Conclusion: Single prolonged (>5 min) breath-holds are equally possible in the prone, front crawl position.
Advances in knowledge: Prolonged breath-holds in the front crawl position are possible and have the same durations as in the supine position. Such training would therefore be feasible for some patients with breast cancer requiring loco-regional irradiation. It would have obvious advantages for hypofractionation.

INTRODUCTION

Radiotherapy has an established role in management of patients with breast cancer, complementing surgery and systemic therapies to prevent recurrences and improve survival. But movement of the chest and internal organs with breathing presents a major problem for radiotherapy. Reducing the movement of the breast, and increasing the distance between the breast and the heart, has been achieved by introduction of deep inspiratory breath-holds (DIBHs) for breast radiotherapy.[1–10] Here, the dose delivered in each treatment session is divided over multiple (~10) and short (~20 s) breath-holds, each after inhaling room air.[11] This increases accuracy and decreases radiation-induced cardiac morbidity and mortality, proportional to the reduction in radiation dose.[12–17]

One possibility to reduce the patient burden and simultaneously, the length of the radiotherapy fraction is to prolong the breath-hold. We have developed the "single prolonged breath-hold" technique in the supine position, using pre-oxygenation and asymptomatic hypocapnia induced by mechanical hyperventilation.[18–22] Healthy volunteers and patients with breast cancer are equally able to maintain safely and comfortably single prolonged breath-holds of

>5 min. Even multiple prolonged breath-holds in a single session are feasible and safe.[23]

Our prolonged breath-holding technique could be especially useful for patients requiring breast/thoracic wall and regional lymph node (locoregional) irradiation, since the inclusion of the lymph nodes, especially the intramammary nodes (IMNs), leads to higher mean heart dose.[24] Additionally, locoregional irradiation including the IMN can lead to delivery times above 7 min.[25] Using our technique, an entire locoregional radiotherapy treatment could be delivered in one or two prolonged (>5 min) breath-holds.

Prone positioning is another technique to reduce heart and especially the lung dose of local or locoregional irradiation.[26–28] Reducing lung dose is important, since it can lead to secondary lung tumours..[14,15] In a direct comparison of four techniques (prone or supine and shallow breathing or multiple short breath-holds) prone multiple short breath-holds achieved the lowest cardiac and lung doses for left-sided whole breast treatments, showing both techniques can work in tandem.[29] However, inclusion of the locoregional lymph nodes in prone position is difficult due to blocking of the beam by either the arms of the patient or the positioning device.

The "prone, front crawl" position, with one arm next to the body and one above the head, and our support device, address these problems. Direct access to axillar, periclavicular and internal mammary lymph nodes using ventral and craniolateral beam directions is illustrated in figure of Deseyne et al[30]. Speleers et al[31] studied the prone front crawl position in breast and regional lymph node irradiation including the internal mammary chain for photon- and proton therapy. In this clinical setting, lung and heart doses could be lowered to levels not previously attained with any other technique. In our clinical experience, we find that a locoregional radiotherapy session in our prone, front crawl position requires more ($\geq$14) and slightly longer (~30 sec) short breath-holds with air. This in turn represents a greater physical and mental effort for all but the most able patients.

No previous study, however, has attempted single prolonged breath-holds with pre-oxygenation and hypocapnia in the prone position. There are a number of reasons why this might be more even more difficult.

First, in the prone position, there is a greater compression by body weight on the chest, so patients might find it harder to inhale maximally or to hold air in. Escape of air through the mouth and nose might be unnoticeable, yet also cause the chest to deflate (the spine to move in the anterior direction) faster and hence shorten the breath-hold.

Secondly, the greater compression weight and reduced accessibility of the facemask (now underneath the patient) means it is even more important, yet also perhaps more difficult, to adjust and ensure the correct seal between the facemask and patient. Failure to do so prevents induction of sufficient hypocapnia to prolong the breath-hold equally to that achieved in the supine position.

Thirdly, prone breath-holding on a board is less comfortable (because there are more pressure points directly onto bony surfaces), which may hasten the urge to break.

Before starting to train patients to attempt single prolonged breath-holds in the prone position, we therefore addressed the practical issues of undertaking prolonged breath-holds in the prone position by testing whether healthy volunteers could hold single prolonged breath-holds for as long as in supine position.

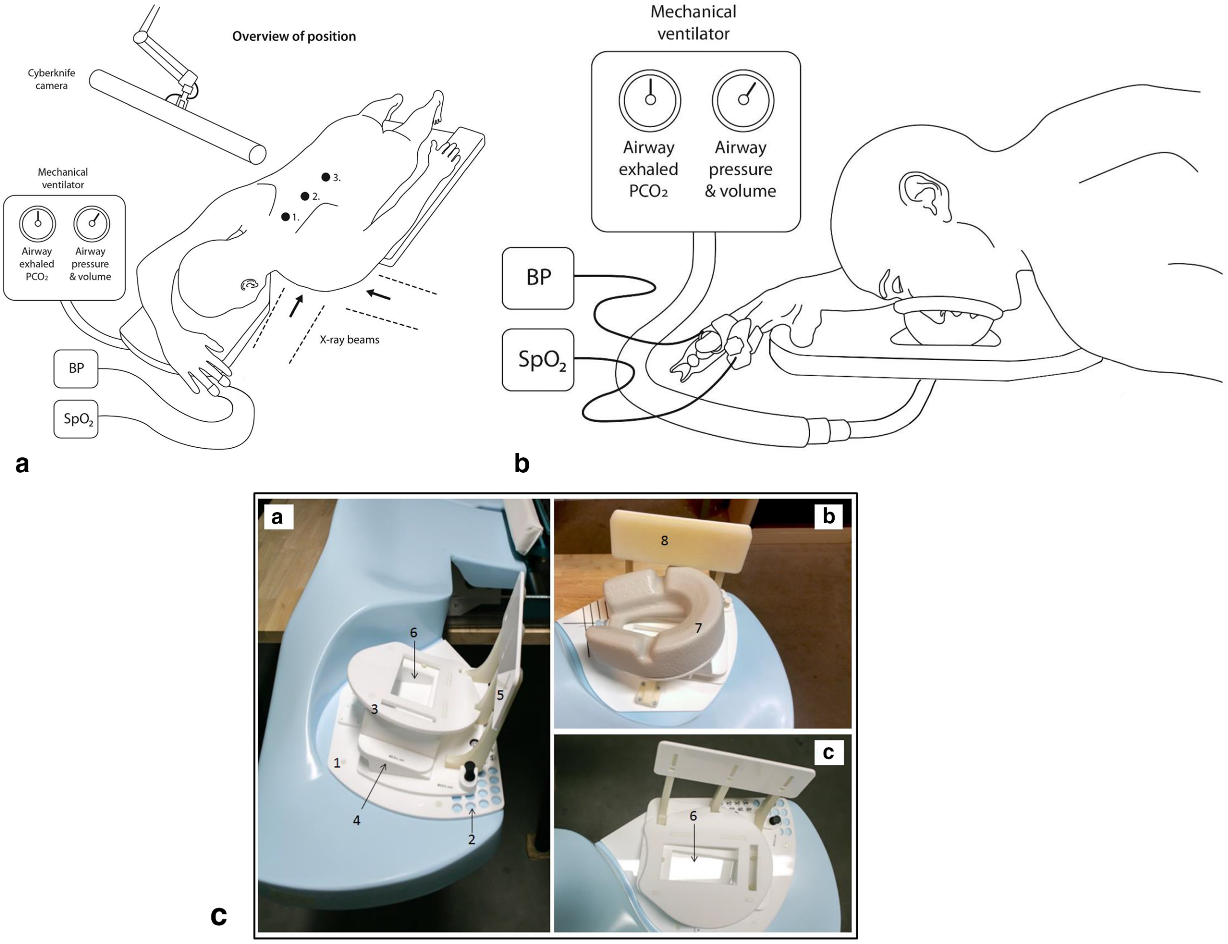
METHODS AND MATERIALS

Experiments were conducted in the NIHR/Wellcome Trust Clinical Research Facility following the Declaration of Helsinki[32] and with approval of University Hospitals Birmingham research ethics committee, as described previously.[18,21–23] 19 healthy subjects agreed to take part (9 were female), the age-range was 20–25 years oldand volunteers had no previous experience of breath-holding. They listened to music through headphones throughout and were not allowed to watch a clock. Subjects lay at rest on a bed in a supine or semi-recumbent position (depending on their comfort) and were instrumented to measure systolic blood pressure (sBP) non-invasively (and normalised to the level of the heart) using an Finometer (Finapres Medical Systems, Enschede, The Netherlands), oxygen saturation (SpO_2, Datex Ohmeda 3800 Pulse oximeter, GE Healthcare systems, Buckinghamshire, UK), the partial pressure of carbon dioxide in their expired gas at end expiration ($PetCO_2$, Hewlett-Packard 78536A or Hamilton CO_2 sensor) and airway pressure (Neurolog pressure transducer and amplifier, Digitimer Ltd, Welwyn Garden City, Herts, UK). All devices were connected to a programmable CED1401 (Cambridge Electronic Design, Cambridge, England) for data collection and analysis. If any breath-holds reached our pre-determined safety limits of sBP consistently above 180 mmHg and or SpO_2 levels consistently <94%,[22] the breath-hold was terminated by instructing subjects to break (*i.e.* to breathe again).

Training for single prolonged breath-holds in the supine position

We allowed 2 h for the following training on Day 1. First, they breath-held from air *ad-lib*. They were trained to relax, how best to inflate and deflate the chest and breath-hold and to breathe through a facemask and be mechanical ventilated in the supine (semi-recumbent) position. We used a Drager Evita 2 (Drager Medical GMBH, Lubeck, Germany) or Hamilton TI (Hamilton Medical, Zurich) mechanical ventilator. They then held from 60% O_2. Next, they were mechanically hyperventilated with 60% O_2 (~16 breaths.min^{-1} and ~1–2 litres tidal volume) with the supporting strap ensuring the seal between mask and face adjusted until there was no audible leak. Hyperventilation was to a $PetCO_2$ of 20 mmHg and was maintained for 5 min. Subjects then performed the single prolonged breath-hold. We allowed 45 min for subsequent practice of the single prolonged breath-hold on different days until they could deliver it consistently on demand, usually by the fourth attempt. Data from their final

Figure 1. (a) Overview of the prone body position for treatment of the left breast. (b) Overview of the facemask in the prone position. (c) Overview of the Crawl Breastcouch. Head positioning components;- (a): base plate (1) with indexed holes (2). Head support platform (3) with wedge (4) and lateral support of the head (5). Aperture (6) for ventilator tubing - not shown (with head support platform removed). (b) full assembly with Q-fix Prone HeadrestTM (7) mounted on the head support platform and soft foam pad (8) mounted on the lateral support of the head. (c): View from above showing the location of the aperture (6) for ventilator tubing- not shown, with head support platform removed).



training day provided the numbers used for their single prolonged breath-holds. Training to achieve single prolonged breath-holds in the supine position was completed before attempting breath-holds in the prone position.

Single prolonged breath-holds in the prone position

Figure 1 show subjects lying on the prone Crawl Breastcouch designed and built in the Department of Radiotherapy and Experimental Cancer Research, University of Gent.[30,33] They were connected to the ventilator as for supine ventilation. The camera system from a Cyberknife (Accuray Inc. California) recorded the movement and position of three light emitting diode (LED) markers placed on the skin on the midline, dorsal to the spinous processes of the upper, middle and lower thoracic vertebrae (Figure 1a). Figure 1b shows the location of the face mask and its connection to the ventilator in the prone position. Subjects held on the prone board on only two occasions and the results represent the mean of both. Figure 1c shows the prone, front crawl breastboard.

Physiological data analysis

We always measure breath-hold duration from the start of the last inhalation until the start of the next inhalation. Heart rate and blood pressure were averaged over 2 min periods of eupnea, over 5 beats at 15 sec before, *i.e.* "pre-"the start of the breath-hold, the five beats leading up to, *i.e.* "at breakpoint" and we also measured $PetCO_2$ and SpO_2 levels during eupnea and at breakpoint. Breath-hold duration is not different between males and females,[34,35] so all data were combined.

Data analysis from the Cyberknife Camera for prone breath-holds

To measure chest deflation rate during prone breath-holds, the position of the LED markers was tracked in three dimensions using the optical camera system from a Cyberknife tracking system (Figure 1a). This camera system is designed to record the relative motion of the surface of a patient. The camera was positioned at a constant distance and orientation to the bed using a room laser system. Once the volunteer was positioned on the bed and the markers fitted, the bed height was re-adjusted such that the height of the camera *vs* marker 1 was constant for all volunteers.

The Cyberknife tracking system was only acquired late in this study, so was available only for five subjects (of whom two were female).

Calibration of the tracking system in the patient's frame of reference was performed in the patient laboratory using a CIRS dynamic thorax phantom {Product 008A CIRSinc.com) located where the patient's middle would be on the bed. Sinusoidal (Cos4) waveforms of 5 amplitudes from 5 to 25 mm in 5 mm increments were applied and measured three times. Variability in amplitude was quantified as the standard deviation of the three means normalised as a percentage of their mean.

Changing the angle of the camera to the optical marker position will introduce a parallax error from the true vertical motion to that observed. To quantify this, we measured the error in sine wave amplitude by changing the camera angle to focus on the two potential extremes of optical marker positions on the bed. Error in amplitude was measured as the difference in mean amplitude at extreme positions 1 & 2 *vs* the middle position and normalised as a percentage of the middle position.

Position data during prone breath-holding were analysed using Spyder (Python 3) software. Here, deflation rate was measured from a least squares linear regression line fitted to the movement from the time after initial settlement until the breakpoint.

Statistical analysis for multiple comparisons was by repeated measures ANOVA with one within subject factor followed by pairwise contrasts. Student's *t* test was used for single comparisons. Significance was taken at $p < 0.05$ with two-sided tests. Data are expressed as mean ± standard error (se).

RESULTS

Statistical analysis and phantom calibration

ANOVA indicated significant F values for all variables except heart rate (where F (2, 40)=1.083, $p = 0.354$). Thus, F values for breath-hold durations were F(3,49)=228 ($p < 0.001$), for $PetCO_2$ F(3,46)=25 ($p < 0.001$), for SpO_2 were F(4,61)=17 ($p < 0.001$), for blood pressure were F(2,37)=46 ($p < 0.001$). These justified the paired comparisons cited in subsequent text and figures.

Tracking system calibration was excellent as evidenced by variability in sine wave amplitude being not more than 1% and its error at the two extreme positions being only 1 and −3%. It is therefore reasonable to accept millimetres from the Cyberknife system measurements as millimetres in the patient co-ordinate system.

Normal breath-hold durations in the supine position

All 19 subjects had normal resting (eupneic) physiological variables (heart rate was 72 ± 3 b.p.m., systolic blood pressure was 101 ± 5 mmHg, $PetCO_2$ was 35 ± 1 mmHg and SpO_2 (97±0 %) levels). All subjects had normal first ever breath-hold durations. These improved as we previously found[18,19,22,23] with training and pre-oxygenation and all measurements at breakpoint were normal.

Thus on Day 1, their first ever mean breath-hold duration with air was 0.9 ± 0.1 min. After training, breath-hold duration with air increased significantly to 1.6 ± 0.1 min ($p < 0.001$), with a breakpoint $PetCO_2$ level of 45 ± 1 mmHg ($p < 0.001$ *vs* their mean eupneic $PetCO_2$ level) and breakpoint SpO_2 level of 95±1% ($p < 0.001$ *vs* their mean eupneic SpO_2 level). Only two subjects had their breath-holds terminated because the safely levels were exceeded. SpO_2 fell below 94% in both, but returned to normal within 20 sec of restarting breathing.

Inhaling 60% oxygen significantly raised their eupneic SpO_2 to 99±0% ($p < 0.001$). Inhaling 60% O_2 significantly increased their mean breath-hold duration to 2.5 ± 0.2 min ($p < 0.001$) and significantly raised their breakpoint $PetCO_2$ level to 49 ± 1 mmHg ($p < 0.001$), whereas SpO_2 now did not fall at breakpoint (remaining at 99±0%, *n.s. vs* the eupneic SpO_2 level with 60% O_2).

After training all could, as expected,[18,22,23] safely achieve a mean single prolonged breath-hold duration in the supine position of 6.2 ± 0.3 min ($p < 0.001$ *vs* that with 60% O_2) with preoxygenation and hypocapnia. At breakpoint, there were the usual[18,22,23] significant rises in mean systolic blood pressure (to 140 ± 5 mmHg, $p < 0.001$) and in $PetCO_2$ (45 ± 2 mmHg, $p < 0.001$), but no significant change in mean SpO_2 (98±0%) nor in heart rate (77 ± 4 b.p.m.). None could reach the safety limits when breath-holding with 60% O_2 nor with 60% O_2 and hypocapnia.

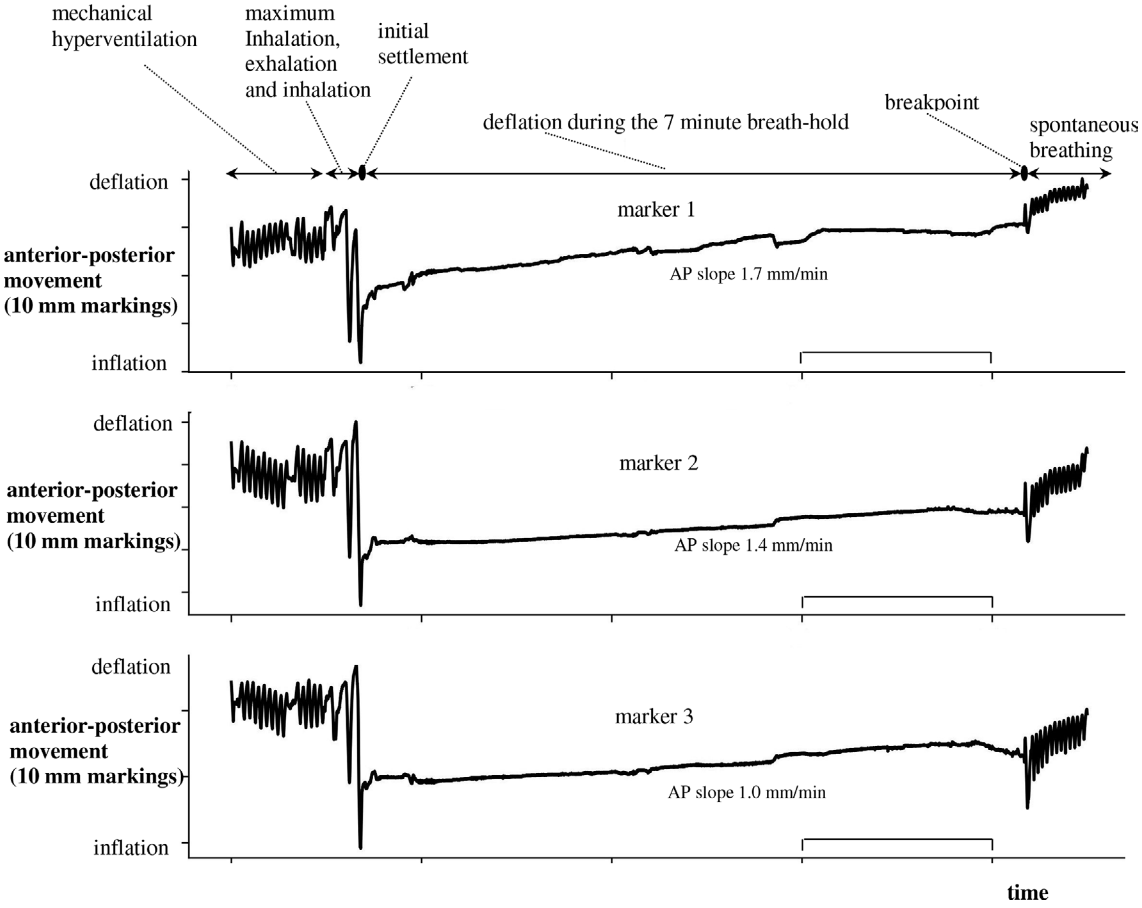
Equally normal breath-hold durations in the prone position

Subjects appeared as comfortable in the prone as supine position. Thus, adopting the prone position had no significant effect during mechanical ventilation on resting heart rate (72 ± 3 b.p.m, *n.s. vs* that in the supine position), SpO_2 (99±0%, *n.s*) or $PetCO_2$ (38 ± 1, *n.s*), but systolic blood pressure was 14 mmHg higher (at 115 ± 3 mmHg, $p < 0.005$). On analysing the data separately for males and females, again only systolic pressure rose significantly (by 15 mmHg in females).

In prone, the weight of the head ensured a good seal between mask and face. It became so easy for the subject to remove any audible leak with simple head movements that the supporting strap was unnecessary and subjects proposed that it was removed.

Subjects found no greater difficulty in achieving prolonged breath-holds in the prone position. Mean breath-hold duration in the prone position (6.1 ± 0.2 min) was not significantly different from that in the supine position. At breakpoint, neither were any other physiological measurements significantly different (mean $PetCO_2$ was 46 ± 2 mmHg, heart rate was 76 ± 3 b.p.m., systolic blood pressure was 148 ± 4 mmHg and SpO_2 was 98±0 %), even if data were analysed separately for males and females.

Figure 2. Movement of the spinal markers during mechanical hyperventilation, breath-holding and spontaneous breathingin the prone position. Polygraph record using the Cyberknife tracking system shows the movement (and slopes) of the three markers during mechanical hyperventilation, maximum inhalation, exhalation and inhalation, the initial settlement and the deflation throughout the 7 minute breath-hold, at the breakpoint and during spontaneous breath-holding in the subject with the longest breath-hold in the prone position. AP, anteroposterior.



Only one subject had one breath-hold terminated (because it reached the SpO_2 safety limit at 4.9 min). This effect however was not consistent, because this subject held for longer (5.5 min) in the other prone breath-hold without reaching this limit.

Three subjects said they preferred the supine position (one was female, their heights ranged from 170 to 180 cm, weights from 65 to 95 kg, BMI from 23 to 29), but the remainder found the comfort levels similar in both.

We found no greater rate of chest deflation during the prone position. Figure 2 shows the anteroposterior movement of the spinal markers during mechanical hyperventilation, breath-holding and spontaneous breathing in the subject with the longest breath-hold in the markers experiments. In five subjects, the mean deflation movement of the spinal markers 1–3 during breath-holding (1.2 ± 0.2, 2.0 ± 0.4 and 1.2 ± 0.4 mm/min.) was almost the same as we found previously[21] for the deflation movement of breast surface markers in the supine position (1.9 ± 0.3 mm/min).

Furthermore, we confirmed that none surreptitiously exhaled during the prolonged breath-hold, as evidenced by no detectable exhaled CO_2 nor pressure rises in the facemask during the breath-hold.

DISCUSSION

We demonstrate for the first time that single prolonged breath-holds are as safe and easy in the prone as in the supine position. The 6 min breath-holds in the supine position achieved with training, pre-oxygenation and hypocapnia are consistent with our previous studies.[18,23] For hypofractionation, it is also important to note that even just by training and spontaneously breathing 60% O_2, we attained here a mean breath-hold duration of 2.5 min while supine and 3 min has been attained in the prone position.[36]

Breath-holding in the prone position

We deliberately gave no prior prone training to subjects to reveal any greater difficulties with the prone position. Whereas all were highly experienced at prolonged breath-holding in the supine position (having typically done this on more than 20 previous occasions), they had never lain on a prone board before, had had no prior practice and were expected to perform as well as they could with only two prone breath-holds.

In the prone position, there were no measurable differences in mean breath-hold duration nor in resting nor breakpoint heart rate, SpO_2 nor PCO_2 compared with supine breath-holding. The only measurable difference was that mean systolic blood pressure at rest was 14 mmHg higher. This small rise may be due to the novelty of adopting the prone position. It had no effect on the systolic pressure rise at breakpoint (therefore, the absolute pressure rise during prone breath-holding was less than in supine breath-holding).

The greater compression of the chest by body weight in the prone position did not impede subjects' ability to inflate their chests maximally as evidenced by the fact that mean breath-hold duration was the same as in the supine position.

Furthermore, the greater compression did not impede the ability to hold air within the chest, as indicated by their being no greater measured rate of chest deflation during prone breath-holding, nor any detectable escape of CO_2 nor rise in air pressure in the facemask.

No breast movement would be expected during prolonged breath-holds in the prone position. But, there will be a small linear movement of the dorsal part of the thorax in the posterior to anterior direction because the chest deflates by ~300 ml/min as O_2 is absorbed from alveolar air, but is not replaced by an equal volume of gaseous carbon dioxide.[19] We have previously measured this deflation to cause a surface marker on the left breast to move in the anteroposterior direction at <2 mm/min during single prolonged breath-holds.[21] Here, we measure for the first time the movement of the dorsal thoracic midline during prone breath-holding. As expected, the dorsal thoracic midline moves by a similar amount (at 1–2 mm/min) in the posteroanterior direction during prone breath-holding as the breast moves in the anteroposterior direction during supine breath-holding.

There was no greater difficulty connecting the prone patient to the ventilator, indeed it was so much easier to ensure a perfect seal between the face and facemask that the facemask strap (used for supine breath-holding) was found to be unnecessary.

Subjects were questioned after each prone breath-hold. They did not consistently report any difficulties in achieving single prolonged breath-holds in the prone position and only 3/19 commented that it was less easy than when supine. The facts that all willingly returned, had the same breath-hold duration as supine, had normal blood pressure and blood gases and made no consistent comments when questioned, satisfied us that it was comfortable. If they had not liked it, they would have delivered short breath-holds and/or refused to return a second time and would have informed us in no uncertain terms.

Any greater discomfort was related mainly to the hardness of the prone breast board at particular pressure points and to the fact that the board was designed for only one body size. But our healthy subjects have never previously experienced lying on a breast board (whereas breast cancer patients will have) and our board was not specifically designed for this range of body sizes (heights 147–191 cm weights 57–103 kg (BMI 20–29).

Current status of prone breath-holding

Currently, prone breath-holding may be less favoured following the conclusions of the UK HeartSpare study that in larger-breasted females, supine voluntary breath-holds (multiple short breath-holds) provided superior cardiac sparing and reproducibility than in prone free-breathing.[6] Yet strictly, this study did not compare like with like, *i.e.* breath-holding in the supine *vs* prone position. More recently a direct comparison of four techniques[29] (prone or supine and shallow breathing or multiple short breath-holds) found prone with multiple short breath-holds achieved the lowest cardiac and lung doses for left-sided whole breast treatments. Furthermore, a recent meta-analysis found mean ipsilateral lung dose, without breathing adaption, for whole breast or chest wall radiotherapy was the lowest for tangents in prone (1.2 Gy) or lateral decubitus (0.8 Gy) positions, compared to supine position (8.4 Gy).[37] There may therefore be increasing interest in considering the prone position.

The particular benefits of the front crawl position for locoregional treatment also indicate that this might benefit such treatment on the right side, if a mirror-imaged right board is available.

Benefits of the prolonged breath-hold for prone patients

It would now be feasible to train patients requiring locoregional irradiation of the breast to undertake single prolonged breath-holds in the prone, front crawl position, since we show here that healthy volunteers can achieve equally long prolonged breath-holds in the prone as the supine position. We found previously that patients with breast cancer have no difficulty in performing single prolonged breath-holds in the supine position under simulated treatment conditions. Thus, female patients with breast cancer, (mean age 54, range 37–74) can perform single prolonged breath-holds equally long (>5 min)[21] as young healthy volunteers (aged 20–22)[22] of whom only 25% were female. Our male subjects represent a fair measure of the practical difficulties of set up in the front crawl position, but will not have experienced any additional discomfort associated with compression of the right breast by the board. Such discomfort could be abolished by adding a corresponding hole to the right side of the board. Neither was the statistical significance of any data different if females were analysed separately from males.

Having resolved all the practical issues of prolonged breath-holds in the prone position, we anticipate no particular difficulties in training patients with breast cancer to perform them. Our training times are deliberately generous (since healthy volunteers have less motivation for mechanical ventilation and prone, front crawl) but can easily accelerated. Offering radiographers the opportunity to breath-hold for >5 min in the front crawl position (and the competition between radiographers for who can hold longest) is enormously helpful in their motivating patients and accelerating patients through the training.

Radiotherapy is moving towards five fraction regimes. The substantial advantage for this here is that the breasts will not move during prolonged breath-holds of >5 min in the prone position. The further advantage over multiple short prone breath-holds each of ca. 30 sec will be the ability to deliver the entire radiation dose in one or two prolonged breath-holds and therefore reduce the risk of intrafraction motion. These long breath-holds could allow for position verification using cone-beam CT and subsequent irradiation within the breath-hold. Another possible advantage is an improvement in the duty cycle of the treatment machine, by reducing the number of breath-holds.

Such advantages should be offset against any increase in patient training and delivery times. But our patient training can be conducted outside the radiotherapy clinic and we have now measured by how much we can reduce the delivery time of the >5 min breath-hold in each session (Parkes *et al.,* manuscript in submission).

In conclusion, we have established that prolonged breath-holds of >5 min in the prone, front crawl position are feasible in healthy subjects. It would now be appropriate to undertake a treatment planning study of this on patients. Here, we could quantify the dose sparing effects to the heart and lungs, position reproducibility, the obvious potential for increased dose delivery with hypofractionation in five fractions together with a study of the logistical issues of delivering each session on patients and analysis of the overall cost–benefit ratio.

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