Technical Innovations & Patient Support in Radiation Oncology 26 (2023) 100208

Contents lists available at ScienceDirect

Technical Innovations & Patient Support in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/technical-innovations-and-patient-support-in-radiation-oncology

Efficacy of preoxygenation administration in volunteers, in extending the end-expiration breath-hold duration for application to abdominal radiotherapy

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ARTICLE INFO

Keywords:
Preoxygenation
End-expiration Breath Hold
Radiotherapy
Abdomen
Hyperventilation

ABSTRACT

Background and purpose: End expiration breath hold (EEBH) is the preferred motion management method for abdominal Stereotactic Ablative Body Radiotherapy (SABR) treatments. However, multiple short EEBHs are required to complete a single treatment session. The study aimed to determine the efficacy of preoxygenation with hyperventilation in extending an EEBH duration.

Materials and methods: We randomised 10 healthy participants into two arms, each included breathing room air and oxygen at a rate of 10 L per minute (l/min) without hyperventilation for four minutes, and normally for four minutes and with hyperventilation for one minute at a rate of 20 breaths/minute for hyperventilation. The type of gas was blinded from the participants for each test. EEBH durations were then recorded, as well as systolic blood pressure, SpO_2 and heart rate. A discomfort rating was also recorded after each breath hold.

Results: A significant increase in duration of almost 50% was observed between normal breathing of room air and breathing oxygen normally followed by hyperventilation. Vital signs remained consistent between the 4 tests. The tests were well tolerated with 75% of participants recording none or minimal discomfort.

Conclusion: Preoxygenation with hyperventilation could be used to increase the EEBH duration for abdominal SABR patients which would assist in the accuracy of these treatments and possibly resulting in a reduction of overall treatment times.

Introduction

End-expiration breath-hold (EEBH) is currently the preferred method of respiratory management when treating some patients who are receiving radiotherapy to the abdomen. EEBH enables greater stability of organs within the abdomen when compared to Deep Inspiration Breath-Hold (DIBH) and free breathing, which improves reproducibility [1 –5].

Treatment times for Volumetric Modulated Arc Therapy (VMAT) abdominal SABR treatments can last as long as 30 min [3,4,6], in which time the patient is required to remain perfectly still. Each breath-hold (BH) can lead to possible changes in organ and target positions, reducing the accuracy of treatment delivery. It can take up to 13 BHs to complete an EEBH abdominal SABR treatment [7].

It has been demonstrated that by administering oxygen at a rate of 10 l/min as well as hyperventilating with oxygen prior to an inspired BH, an increase in BH duration of up to 700% can be achieved [8]. There are several other studies demonstrating that the administration of oxygen prior to treatment using DIBH, can at least double the BH duration [8 –15]. In contrast, there are very few studies showing similar results for EEBH [16].

The issue with EEBH is that most patients are unable to hold an expired BH for more than 20 s [2 –4,17 –18]. As a result, many BH cycles are required for each treatment, as well as recovery time between BHs. An increased number of treatment BHs combined with BHs for verification image acquisition and positional adjustments, result in extended overall treatment sessions. Hence, this study aimed to evaluate the efficacy of preoxygenation administration in extending the EEBH duration

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https://doi.org/10.1016/j.tipsro.2023.100208
Received 24 January 2023; Received in revised form 2 April 2023; Accepted 18 April 2023
Available online 4 May 2023

during simulated abdominal radiotherapy. The protocol by Roth *et al.* [8] was adapted to provide gas flow rate, hyperventilation rate and length of ventilation durations.

Materials and methods

Study design

This study was a crossover, randomised study to investigate the effect of preoxygenation and hyperventilation on EEBH durations for future potential application on abdominal SABR patients. All participants were provided with a detailed information sheet of the study and gave written informed consent. Ethical approval was obtained from the Nepean Blue Mountains Local Health District Human Research Ethics Committee (2022/ETH00298).

Selection criteria

Staff over the age of 18 years at the Nepean Cancer Care Centre who volunteered were included.

Randomisation

Participants were randomised into one of the two methods: breathing air as Method A and with oxygen supplement as Method B; The participants were then crossed over to the other method after 5 min of wash out period. The allocation of the randomisation was concealed from the participants. The gases were administered via an adult nasal cannula and the participants were blinded to which method was used first.

Intervention procedure

Each method consisted of two tests which were performed when breathing both air and oxygen: 1) normal breathing rate for 4 min, and 2) normal breathing for 4 min and immediately hyperventilating for 1 min at a maximum rate of 20 breaths per minute. Four tests were completed by all participants with a 5-minute wash out period between the tests. The tests measured duration of EEBH in 4 situations: after

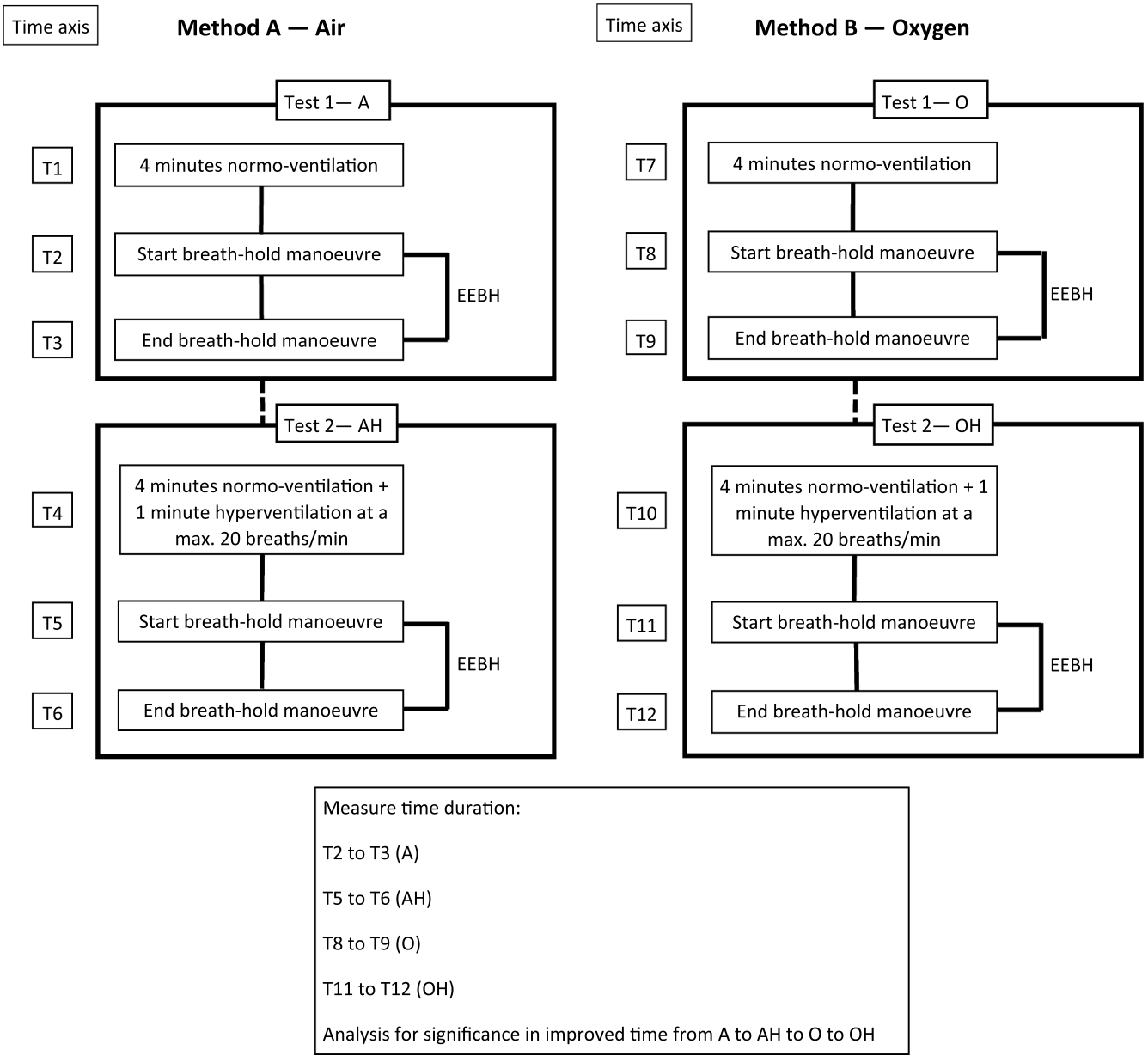

Fig. 1. Study schema outlining testing timeline with air (A), air and hyperventilation (AH), oxygen (O) and oxygen and hyperventilation (OH).

normal breathing with air (A), after normal breathing and then hyperventilation with air (AH), after normal breathing with oxygen (O), and after normal breathing and then hyperventilation with oxygen (OH). An audible metronome was used to guide participants with the breathing rate for hyperventilation. Gas flow rates for both air and oxygen were set to 10 l/min. Fig. 1 shows the schema used to collect four test measurements for each participant.

Outcome measures

The primary end point of the study was to determine if the administration of oxygen and hyperventilation resulted in an increased duration of EEBH.

A stopwatch was used to time the duration in seconds (s) of EEBH. At the end of the allocated timing of breathing, participants indicated by nodding that they had started the EEBH, another nod would indicate that a breath was taken, and the stopwatch was stopped. Participants were instructed to take one last fully inspired breath at the end of the ventilation cycles (Fig. 1 Time axis T1, T4, T7 and T10), and then fully expire and hold the expired breath for as long as comfortably possible, which is consistent with departmental guidelines.

Participants were positioned supine with arms above their heads to replicate the position an abdominal patient would be in for treatment. Systolic blood pressure (BP), heart rate beats per minute (bpm) and oxygen saturation (SpO_2 %) were monitored throughout the procedure, starting when ventilation commenced, and data for each recorded before and after each EEBH using a GE Dash 4000 monitor. After each BH, participants were asked to score their discomfort level on a 10-point scale, where 1 was no discomfort and 10 was severe discomfort.

Statistical analysis

Friedman Test was used to analyse the paired comparisons of all groups followed by a pair-wise analysis performed using Wilcoxon signed-rank test with Bonferroni correction for multiple testing. A p-value of less than 0.05 was considered as statistically significant.

Results

Between June 2022 and August 2022, 11 participants were recruited, with one excluded due to non-compliance. The remaining 10 participants consisted of eight women and two men. Other participant baseline characteristics can be found in Table 1. The participant that was non-compliant failed to consistently breathe via the nasal cannula and engaged in verbal communication throughout the procedure.

The median (IQR) baseline BH duration (A) was 24 (21.75–29.25) s. When hyperventilation was added (AH) the BH duration increased to 34 (28.25–41.75) s. With the inclusion of oxygen (O) the median BH duration increased to 38 (31.0–41.5) s. BH duration that included oxygen and hyperventilation (OH) had a median time of 49 (40.75–58.0) s. (Fig. 2).

Table 1
Participant and environmental characteristics.

	Median	IQR
Biometrics		
Age (years)	38.5	35.5 – 40.75
Weight (kg)	68.5	58.6 – 70.9
Body Mass Index (BMI)	24.3	21.4 – 26.2
Waist to hip ratio	0.82	0.79 – 0.87
Baseline systolic BP	109	103.25 – 115.8
Baseline heart rate (bpm)	67.5	66–79
Baseline SpO_2 (%)	100	98–100
Environment		
Air temperature (°C)	20	19.5–21
Barometric pressure (hPa)	1012	1012–1014

Table 2 shows a pairwise comparison of A, AH, O and OH with Bonferroni correction. The only significant improvement in EEBH duration was between A and OH.

There were no significant differences in SpO_2, systolic blood pressure or heart rate among the four intervention groups (Table 3).

A total of 40 discomfort ratings were recorded across the 4 test scenarios, with 75% being scored at either none (1) or minimal (2). 17.5% of participants scored a rating of mild (3) and 7.5% scored uncomfortable (4) (Fig. 3). There were a small number of comments that the gas flow rate felt quite high and uncomfortable.

Discussion

This study was designed to determine if preoxygenation with hyperventilation is feasible to increase the EEBH duration to minimise the number of BH cycles required for an abdominal SABR treatment. It has been well established that inspiration BH durations can be significantly increased with the use of preoxygenation [8,10 –13,15,19]. We demonstrated that there was a substantial increase in duration in EEBH time between breathing oxygen and hyperventilating compared with breathing room air which is consistent with Roth *et al.* [8]. While our results demonstrated that breathing room air with hyperventilation and breathing oxygen without hyperventilation did not significantly improve EEBH times, these methods may still provide limited gains in reducing overall treatment times for patients treated with SABR to the abdomen, and therefore should not be discounted. If equipment is not available to administer oxygen, training the patient to hyperventilate room air prior to treatment may still be somewhat effective.

We did not see any significant changes in heart rate or SpO_2 which agrees with previous studies [10,11,14,15]. We also found no significant change in blood pressure for each of the tests which is different to the findings of other authors [10,11,14,15]. This difference is likely due to the relatively shorter duration of BHs when compared to the BH durations as high as 5 min [11,15]. It should be noted that each test on their own may not have affected these vital signs, though in a treatment context where multiple BHs are required in relatively short succession may influence these vital signs but may not be of any clinical concern.

This study demonstrated that when an EEBH is initiated immediately after breathing oxygen and hyperventilating that we can extend the duration of a single BH. We would need to investigate if this would have a sustained effect for a patient undergoing an extended length of treatment which would require as many as 13 BHs [7], or if the oxygen would need to be available throughout the treatment session and during the recovery breaths between BHs. Parkes *et al.* has shown that after preoxygenation successful repeated inspired breath holds can be given up to at least 9 times.

A 10-point discomfort rating was utilised to provide more variance in the levels of discomfort and provide a higher degree of precision than a commonly used Wong Baker FACES Pain Rating Scale, which consists of 6 points. At the immediate conclusion of each BH, the participants were asked to rate their discomfort, rather than obtaining these later via paper or electronic means. This was to ensure that there was minimal memory distortion. The rating scale range consisted of numbers corresponding to descriptor: 1 – none, 2 – minimal, 3 – mild, 4 – uncomfortable, 5 – moderate, 6 – distracting, 7 – distressing, 8 – unmanageable, 9 – intense, 10 – severe. This scale is a modified Numerical Pain scale which commonly consists of 11 points. The last point was removed as this is usually described as Immobilizing Pain. This was not applicable in the current study.

Anecdotally there were some participants who commented that the gas flow rate felt quite high and uncomfortable. Further investigation should be done to find a gas flow rate which provides both patient comfort and ongoing effectiveness of administered oxygen.

A limitation of this study was that it did not include the use of coaching or training for participants in the method of breath holding or in the equipment that was used prior to the procedure. The only

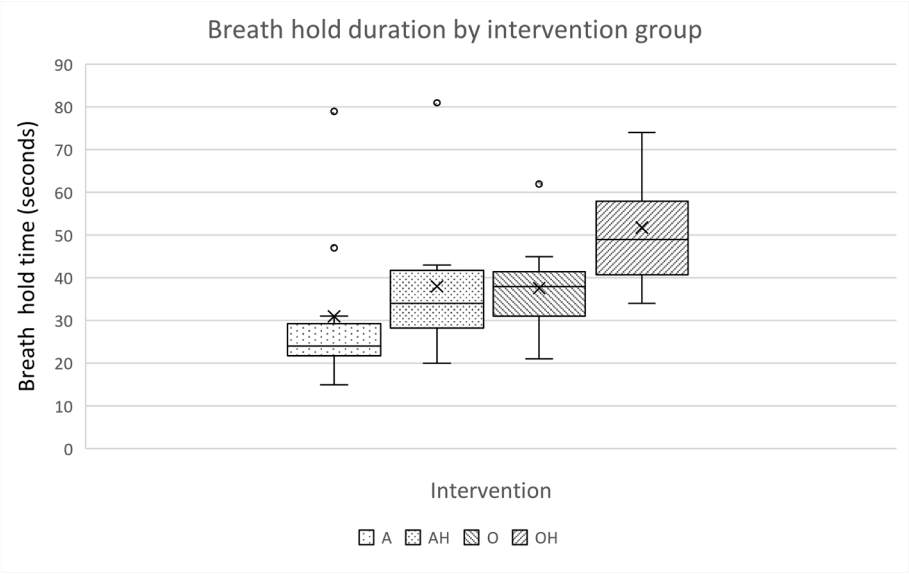

Fig. 2. Box and whisker plot demonstrating the duration of breath hold with each intervention. Mean, median, minimum, maximum, 1st and 3rd quartile durations of tests A, AH, O, OH. The diagram demonstrates an increase in duration in breath hold as each intervention is introduced, with the most significant increase seen at OH. Abbreviations: A: Air, AH: Air-hyperventilation, O: Oxygen, OH: oxygen - hyperventilation.

Table 2
A: BH after normal breathing air only (baseline), AH: BH after normal breathing air and hyperventilating air, O: BH after normal breathing oxygen only, OH: BH after normal breathing oxygen and hyperventilating oxygen. Abbreviations: A: Air, AH: Air-hyperventilation, O: Oxygen, OH: oxygen - hyperventilation.

Comparison groups		p-value	p-value adjusted
A	AH	0.041	0.248
A	O	0.185	1.000
A	OH	0.004	0.023
AH	O	0.609	1.000
AH	OH	0.011	0.065
O	OH	0.009	0.055

instruction provided was for the participants to take a last full breath in and then fully expire at the conclusion of each ventilation period and to hold the breath for as long as comfortably possible. This was mainly due to time constraints. All participants were staff of the Nepean Cancer Care Centre, and the procedure was undertaken during operational hours. It has been well established by other investigators that coaching, and training of participants would provide consistent BH manoeuvre and familiarity of the equipment [3,8,10,12,17,20]. A consistent level of a fully expired BH could not be measured for each test, therefore it may be possible that some BH durations may have slight over or under timing depending on the level of expiration compared to the baseline expiration with breathing air alone. If this study was to be repeated, participant preparation would be incorporated into the protocol which may improve outcomes further than what has been noted with this current study. Another limitation was the small number of participants enrolled, however as this was a feasibility study, this number was thought to be sufficient.

A further limitation of this study is the method of starting and ending the timing of the BHs with the use of a nod from the participant. There may have been some latency of the participant nodding to indicate that they had commenced or ended a BH to when the observer began and ended the timer. The latency would be minor, therefore overall results would not be affected.

A consideration for future studies would be to assess the normal respiratory rate of each participant to determine the appropriate rate of hyperventilation. This study adopted the respiration rate for hyperventilation by Roth *et al.* of 20 breaths per minute. This is at the upper range of normal respiration [21,22]. There are some conditions that affect a person's respiration rate; therefore 20 breaths per minute for some patients may be too rapid which may result in the side effects of hyperventilation, or too slow that the inspiration of oxygen may not have a significant effect on BH duration as seen in the oxygen only test.

Future studies are needed to determine if the same breathing protocol can be used to reduce the inter BH recovery durations. Combining this with the current study would demonstrate if there were any overall benefit to preoxygenation for reducing treatment durations and EEBH abdominal SABR treatments. Additionally, as the BH stability was not assessed in this study, further investigation and protocol development would be required to determine if BH levels and internal stability could be maintained over multiple BH cycles. Furthermore, as this was a feasibility study performed on volunteers, results from a patient population may differ, therefore a study with a patient cohort would also be required.

Table 3
Table demonstrating vital signs measured at baseline and after each intervention BH. There was no change in vital signs from baseline measurements. Abbreviations: A: Air, AH: Air-hyperventilation, O: Oxygen, OH: oxygen - hyperventilation.

	Baseline Median (range)	After A Median (range)	After AH Median (range)	After O Median (range)	After OH Median (range)	Friedman chi squared	p-value
HR (bpm)	67.5 (64–84)	70.5 (67–93)	70.5 (60–89)	71 (62–85)	72.5 (64–98)	4.10	0.25
sBP (mmHg)	109 (93–121)	105.5 (85–124)	108.5 (93–121)	97 (95–134)	103.5 (91–140)	3.36	0.34
SpO_2 (%)	99 (96–100)	99.5 (98–100)	99.5 (95–100)	100 (99 – 100)	100 (98–100)	1.85	0.60

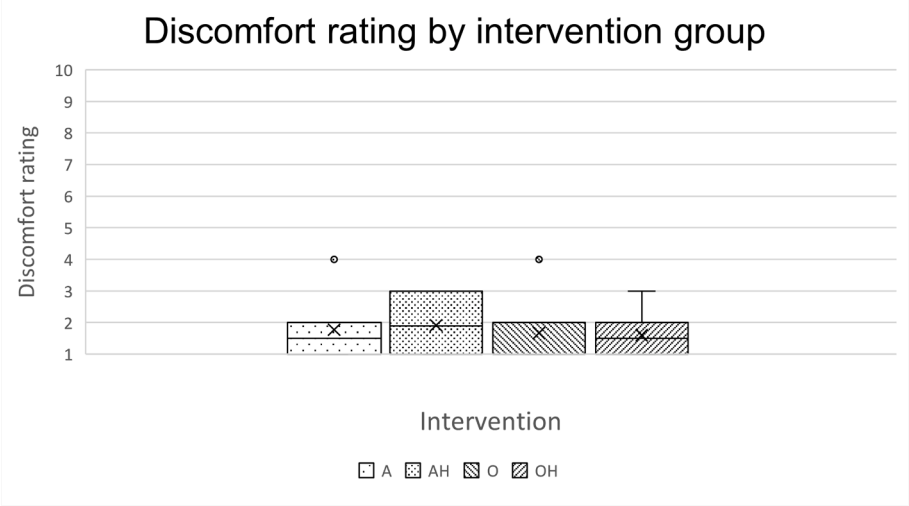

Fig. 3. Box and whisker plot demonstrating discomfort rating to the interventions. Mean, median, minimum, maximum, 1st and 3rd quartile discomfort rating of tests A, AH, O, OH. The diagram shows that most participants either had no discomfort (rating 1) or minimal discomfort (rating 2). Abbreviations: A: Air, AH: Air-hyperventilation, O: Oxygen, OH: oxygen - hyperventilation.

Conclusion

This feasibility study demonstrated that preoxygenation and hyperventilation resulted in a significant improvement in duration of EEBH. Further studies would be required to determine the impact of this on overall duration of abdominal SABR with multiple BHs and recovery breaths.

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.

Acknowledgements

This study was supported by the Department of Radiation Oncology Cancer Care Centre, Nepean Hospital, NSW, Australia.

Informed Participant Consent.

The authors confirm that written informed consent has been obtained from the involved participants; and, they have given approval for this information to be published in this manuscript.

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