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DOI:
10.1016/j.radonc.2019.06.014

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Parkes, MJ, Green, S, Kilby, W, Cashmore, J, Ghafoor, Q & Clutton-Brock, TH 2019, 'The feasibility, safety and optimization of multiple prolonged breath-holds for radiotherapy', *Radiotherapy & Oncology*, vol. 141, pp. 296-303. https://doi.org/10.1016/j.radonc.2019.06.014

Radiotherapy and Oncology 141 (2019) 296–303

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

The feasibility, safety and optimization of multiple prolonged breath-holds for radiotherapy

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ARTICLE INFO

Article history:
Received 19 January 2019
Received in revised form 15 May 2019
Accepted 11 June 2019
Available online 18 September 2019

Keywords:
Breath-hold
Radiotherapy
Mechanical ventilation
Hypocapnia
Oxygen

ABSTRACT

Background & purpose: Multiple, short breath-holds are now used in single radiotherapy treatment sessions. Here we investigated the feasibility and safety of multiple prolonged breath-holds in a single session. We measured how long is a second breath-hold if we prematurely terminate a single, prolonged breath-hold of >5 min either by using a single breath of oxygen (O_2), or by reintroducing preoxygenation and hypocapnia. We also investigated the feasibility and safety of undertaking 9 prolonged breath-holds in a row.

Materials & methods: 30 healthy volunteers with no previous breath-holding experience were trained to perform single prolonged breath-holds safely.

Results: Their mean single, prolonged breath-hold duration was 6.1 ± 0.3 se minutes (n = 30). In 18/18 subjects, premature termination (at 5.1 ± 0.2 min) with a single breath of 60% O_2, enabled a 2nd safe breath-hold lasting 3.3 ± 0.2 min. In 18/18 subjects, premature termination at 5.3 ± 0.2 min) by reintroducing preoxygenation and hypocapnia, enabled a 2nd safe breath-hold lasting 5.8 ± 0.3 min. 17/17 subjects could safely perform 9 successive prolonged breath-holds, each terminated (at 4.3 ± 0.2 min) by reintroducing preoxygenation and hypocapnia for 3.1 ± 0.2 min. The 9th unconstrained breath-hold (mean of 6.0 ± 0.3 min) lasted as long as their single breath-hold.

Conclusions: Multiple prolonged breath-holds are possible and safe. In a ~19 min treatment session, it would therefore be possible to have ~13 min for radiotherapy treatment (3 breath-holds) and ~6 min for setup and recovery. In a 65 min session, it would be possible to have 41 min for radiotherapy and 25 min for setup and recovery.

Movement with breathing of all structures in the thorax and abdomen presents a major problem for thoracic MRI, PET-imaging and radiotherapy. One means of reducing this movement is for patients to hold their breath and such techniques [1–9] offer clear advantages [10].

For the currently used breath-holding technique (“Deep Inspiration Breath-Hold” (DIBH)), suitable treatment times are built up by performing multiple, short [1,4] breath-holds with room air. The precise number of breath-holds and their precise durations however are not usually specified. We have previously developed a technique adding preoxygenation (60% oxygen (O_2)) and hypocapnia and again using a deep inspiration breath-hold. This enables healthy volunteers and patients with breast cancer to achieve safely and consistently a single, prolonged breath-hold of over 5 min under simulated radiotherapy treatment conditions [11–15].

For radiotherapy, it would be useful to know if performing more than one prolonged breath-hold is possible in a single session. We are unaware of any previous proposal for, or investigation of this possibility with prolonged breath-holds. This should be possible because

1) it is the act of releasing the breath-holding muscles [12,16,17] – rather than refreshing arterial blood gas levels [16,17] – that enables the next breath-hold
2) multiple prolonged breath-holds from preoxygenation and hypocapnia should be easier and safer than those from air, because the first breakpoint starts from remarkably benign arterial blood gas levels [11,14,15] and therefore the necessary re-ventilation period may be quite short.

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https://doi.org/10.1016/j.radonc.2019.06.014
0167-8140/

There are however obvious concerns;

a) in the last 25% of the duration of a single prolonged breath-hold [14], blood pressure rises by ~20 mmHg per minute and afterwards takes ~20 s to recover [14,15]. So a progressive blood pressure rise might accumulate and require progressively longer recovery times
b) subjects may just find it too difficult.

We have therefore measured the preparation time, duration, safety and feasibility of

- a second prolonged breath-hold after relieving the first with one maximum inhalation of 60% oxygen
- a second after relieving the first with re-introduction of preoxygenation and hypocapnia
- an arbitrary number of 9 successive and prolonged breath-holds, each relieved with preoxygenation and hypocapnia

Methods

Experiments were conducted in the NIHR/Wellcome Trust Clinical Research Facility following the Declaration of Helsinki [18] and with approval of the University Hospitals Birmingham research ethics committee, as described previously [11,14,15]. We used a total of 30 healthy subjects (20 were male) aged 20–25 years old, with no previous experience of breath holding. Not all were available for all experiments, with 18 used for the premature terminations with oxygen, 18 for those with preoxygenation and hypocapnia and 17 for the multiple prolonged breath-holds. They listened to music through headphones throughout and were not allowed to watch a clock. Subjects lay at rest in a semi-recumbent position and were instrumented to measure systolic blood pressure (sBP) non-invasively, oxygen saturation (SpO_2), a 3 lead electrocardiogram (ECG), the partial pressure of carbon dioxide in their expired gas at end expiration ($P_{et}CO_2$) and airway pressure. All were connected to a programmable CED1401 (Cambridge Electronic Design, Cambridge, England) and subjects breathed through a facemask connected to a mechanical ventilator, with equipment as described previously [11,14,15]. If any breath-holds reached our pre-determined safety limits (sBP consistently above 180 mmHg and or SpO_2 levels <94% [14]), the breath-hold was terminated by instructing subjects to break (*i.e.,* breathe again).

Training for single prolonged breath-holds

On day 1 subjects first breath-held from air *ad-lib.* They were trained, as previously described [15] to relax, how best to inflate and deflate the chest and breath-hold and to breathe through a facemask and be mechanically ventilated. 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) to a $P_{et}CO_2$ of 20 mmHg for 15 min, and performed the single prolonged breath-hold. We allow 2 hours for this training on day 1. On different days they practiced the single prolonged breath-hold until they could deliver it consistently on demand. Each session took ~40 min and they were usually consistent after the 4th single prolonged breath-hold. Data from their final training day provided the numbers used for their single prolonged breath-holds.

Two breath-holds in one session

First, at an arbitrary ~80% of their single, prolonged breath-hold duration, subjects were told to break. They then exhaled maximally, inhale 60% O_2 maximally and held again.

Secondly at the same arbitrary 80% of their single, prolonged breath-hold duration, subjects were told to take ~3 spontaneous breaths of 60% O_2. Then they were mechanically re-ventilated with 60% O_2 to 20 mmHg $P_{et}CO_2$ for ~1.5 min and stabilized for ~1.5 min. They then held their breath again.

Multiple prolonged breath-holds in one session

At an arbitrary ~70% of their single prolonged breath-hold duration, they were told to break and were re-ventilated as above, with each attempting an arbitrary number of 8 such prolonged holds. For their 9th they were unconstrained and just instructed to hold for as long as possible.

Data analysis

Data were analysed as described previously [14,15]. At breakpoint some first inhale whereas others first exhale. To make our data analysis more consistent therefore we always measured breath-hold duration from the start of the last inhalation until the start of the next inhalation. To quantify how long it took to lower and to maintain hypocapnia, we measured the time it took for re-ventilation to first reach 21 mmHg $P_{et}CO_2$ and then exactly how long hypocapnia was maintained at 20 mmHg. Heart rate and blood pressure were averaged over 2 min periods of eupnea, over 5 beats at 15 s before *i.e.,* "pre-" the start of the breath-hold, the 5 beats leading up to *i.e.,* "at breakpoint" and $P_{et}CO_2$ and SpO_2 at breakpoint. Breath-hold duration is not different between males and females [19,20] so all data were combined.

Statistical analysis for multiple comparisons was by repeated measures ANOVA with one within subject factor followed by pair-wise contrasts. For single comparisons, analysis was by two tailed paired or unpaired t tests as appropriate. Significance was taken at $p < 0.05$. Data are expressed as mean ± standard error (se).

Results

Statistical analysis

Significant *F* values for single relieving breaths for sBP (Fig. 1a) were 50 ($p < 0.000$), for $P_{et}CO_2$ (Table 1) 46 ($p < 0.000$) and for

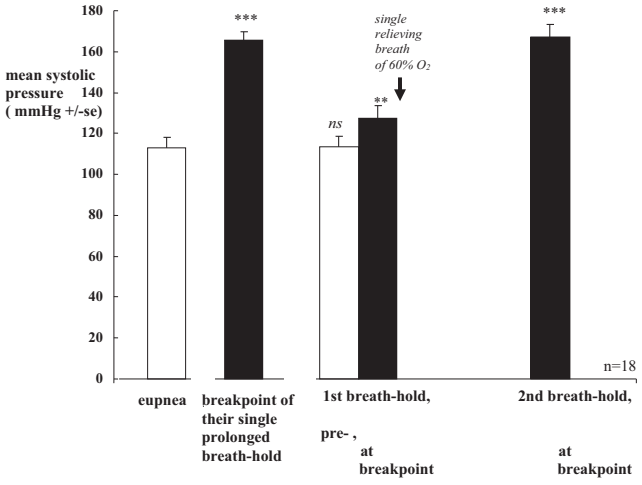

Fig. 1a. After relieving with a single breath of 60% O_2, systolic pressure rises further at the second breakpoint in 18 subjects. Open columns indicate the eupnea and pre-breath-hold values and filled columns indicate the breakpoint values. *N.B.* because the relieving breath takes only ~2 s, the systolic pressure just before the start of breath-hold 2 is almost indistinguishable from that at breakpoint 1. So these 2 values are not statistically comparable and a pre- value for the second breath-hold is not drawn. *ns* $p > 0.05$ *vs.* eupnea $^{*}p < 0.05$ *vs.* eupnea $^{**}p < 0.01$ *vs.* eupnea $^{***}p < 0.001$ vs. eupnea.

Table 1
For all breath-holds, mean $P_{et}CO_2$ rises at breakpoint but SpO_2 and heart rate remain unchanged.

means +/-se	their single prolonged breath-hold		1st breath-hold (at ~80% of the single prolonged breath-hold)	2nd breath-hold (relieved by a single breath)	their single prolonged breath-hold		1st breath-hold (at ~80% of the single prolonged breath-hold)	2nd breath-hold (relieved with re-ventilation and ~1 min of hypocapnia)	their single prolonged breath-hold		mean for the 8 successive ~70% breath-holds	Mean for the 9th unlimited breath-hold
	eupnea	at breakpoint	at breakpoint	at breakpoint	eupnea	at breakpoint	at breakpoint	at breakpoint	eupnea	at breakpoint	at breakpoint	at breakpoint
$P_{et}CO_2$	34 ± 1	42 ± 2††	45 ± 1^{ns}	51 ± 1^{***,xxx}	35 ± 1	41 ± 1†	44 ± 1†††	46 ± 1$^{***,x,\bullet\bullet\bullet}$	36 ± 1	40 ± 1††	44 ± 1*	46 ± 2***
Heart rate	70 ± 3	74 ± 3^{ns}	77 ± 3^{ns}	72 ± 3^{ns}	72 ± 3	79 ± 4^{ns}	74 ± 3^{ns}	77 ± 4^{ns}	72 ± 2	74 ± 3^{ns}	75 ± 2*	80 ± 4^{ns}
SpO_2	99 ± 0	98 ± 0^{ns}	99 ± 0^{ns}	99 ± 0^{ns}	98 ± 0	98 ± 0^{ns}	99 ± 0^{ns}	99 ± 0^{ns}	97 ± 0	98 ± 0^{ns}	99 ± 0^{ns}	99 ± 0^{ns}

Table 1 shows the mean values for the numbers of subjects in each of the 3 experimental conditions (as used for the paired statistical comparisons).
N.B. The means for all 30 subjects together are from data taken on a different day and are cited separately in the text of the results section.
^{ns} $p > 0.05$ *vs.* single prolonged breath-hold or eupnea.
* $p < 0.05$ *vs.* single prolonged breath-hold.
** $p < 0.01$ *vs.* single prolonged breath-hold.
*** $p < 0.001$ *vs.* single prolonged breath-hold.
^{x} $p < 0.05$ *vs.* the 1st breath-hold.
^{xxx} $p < 0.001$ *vs.* the 1st breath-hold.
† $p < 0.05$ *vs.* eupnea.
†† $p < 0.01$ *vs.* eupnea.
††† $p < 0.001$ *vs.* eupnea.
$^{\bullet\bullet\bullet}$ $p < 0.001$ *vs.* at breakpoint relieved by a single breath.

reventilation for sBP (Fig. 1b) were 40 ($p < 0.000$) and for $P_{et}CO_2$ (Table 1) 36. *F* values for heart rate were not significant. For multiple breath-holds we used repeated measures ANOVA with polynomial contrasts. There was a significant linear rise for each pre-breath-hold sBP level ($F = 12$, $p = 0.003$) so we calculated the slope for each subject and hence a mean slope and maximum rise for all. There was a significant quadratic rise for each breakpoint pressure level ($F = 9$, $p < 0.01$) so we calculated the peak and final rise for all subjects. There was no significant change of heart rate between pre- and breakpoint ($F = 0.01$, *ns*), nor a linear change in pre- heart rate levels ($F = 2$, $p = 0.1$) but there was a linear rise in heart rate over the 8 breath-holds of 6 beats per minute ($F = 2.9$, $p = 0.025$). There was no significant change in time taken to reach 21 mmHg ($F = 1.6$, $p = 0.16$) nor in duration of the hypocapnia ($F = 1.0$, $p = 0.41$). *F* was 40 ($p = 0.000$) for the $P_{et}CO_2$ levels in eupnea *vs.* means at breakpoint.

Reaching our safety limits for breath-holding

For all breath-holds, 20/30 subjects (67%) never reached our safety limits [14]. 4 reached them once (13%) and were asked to break, 3 twice (10%), 1 three (3%) and 2 four times (7%). This includes the multiple prolonged breath-holds, where no subject reached the limits in the first 8 breath-holds, but 3 reached the limit on the 9th.

When asked to break, 15 had reached the sBP limit (71%), 6 the SpO_2 limit (28%) and one once reached both simultaneously. The durations achieved indicate that all subjects were highly motivated to breath-hold as long as possible, but even then only one subject ever managed eventually to breath-hold consistently to reach our safety limits.

Single prolonged breath-holds

Table 1 and Fig. 1a show that during eupnea our 30 healthy subjects had normal mean resting levels of heart rate (74 ± 2 b. p.m.), SpO_2 (98 ± 0%), $P_{et}CO_2$ (35 ± 1 mmHg) and sBP (114 ± 3 mmHg). On day 1 their first ever mean breath-hold duration with air was 1.1 ± 0.1 min (and 2 breath-holds were

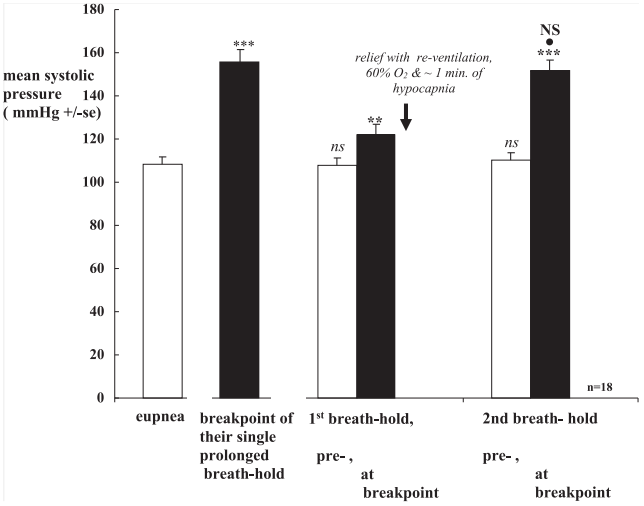

Fig. 1b. After relieving with re-ventilation and ~1 min of hypocapnia, systolic pressure has recovered by the start of the second breath-hold and rises less at the second breakpoint in 18 subjects. Open columns indicate the eupnea and pre-breath-hold values and filled columns indicate the breakpoint values. *ns* $p > 0.05$ *vs.* eupnea $^{**}p < 0.01$ *vs.* eupnea $^{***}p < 0.001$ *vs.* pre-breath-hold $^{\bullet}p < 0.05$ *vs.* breakpoint of 2nd breath-hold in Fig. 1a NS $p > 0.05$ *vs.* breakpoint of their single prolonged breath-hold.

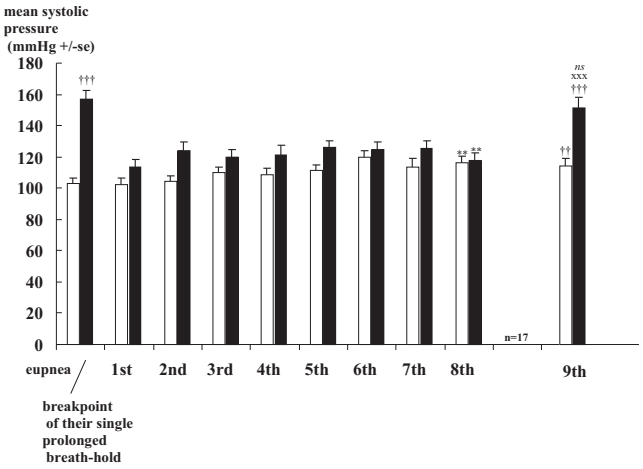

Fig. 1c. Over the 8–70% breath-holds, pre- breath-hold systolic pressure rises significantly by 13 mmHg and breakpoint systolic pressure by 5 mmHg in 17 subjects. Open columns indicate eupnea and pre- breath-hold conditions and filled columns indicate the breakpoint values. $^{**}p < 0.01$ for polynomial (linear or quadratic) contrasts. $^{\dagger\dagger}p < 0.01$ *vs.* eupnea $^{\dagger\dagger\dagger}p < 0.001$ *vs.* eupnea $^{xxx}p < 0.001$ *vs.* pre-*ns* $p > 0.05$ *vs.* breakpoint of their single prolonged breath-hold.

terminated when the SpO_2 limit was reached). On day 1 after training their mean breath-hold duration for maximum lung inflation with air was significantly longer at 1.6 ± 0.1 min ($p < 0.001$), with a mean $P_{et}CO_2$ at breakpoint of 43 ± 1 mmHg.

After training, they could safely achieve a mean single prolonged breath hold duration of 6.1 ± 0.3 min ($n = 30$) with preoxygenation and hypocapnia, with a mean breakpoint $P_{et}CO_2$ level of 41 ± 1 mmHg ($p < 0.001$), an sBP rise at breakpoint to 161 ± 4 mmHg ($p < 0.001$), but with no rise in mean heart rate (74 ± 2b.p.m., *ns*) and no fall in mean SpO_2 (98 ± 0%, *ns*).

3 min 2nd breath-hold after relieving with one breath of 60% oxygen in 18/18 subjects

Fig. 2a shows that terminating the first breath-hold at ~80% duration (at 5.1 ± 0.2 min) with a single breath of 60% oxygen, enabled another safe breath-hold, for a mean of 3.3 ± 0.2 min ($p < 0.00001$ *vs.* their mean of 6.1 ± 0.4 min). Table 1 shows that at breakpoint there was no significant change in either mean heart rate or SpO_2 for either breath-hold. Table 1 shows that mean $P_{et}CO_2$ (45 ± 1 mmHg) at breakpoint of the ~80% breath-hold had not risen significantly above their mean single prolonged breakpoint level (42 ± 2 mmHg). But at the second breakpoint it had risen significantly, to 51 ± 1 mmHg ($p < 0.001$), indicating some gradual accumulation of carbon dioxide.

Fig. 1a shows that sBP had risen significantly by 14 mmHg at breakpoint of the ~80% breath-hold (to 127 ± 6 mmHg, $p < 0.05$). It took a mean of only 2 ± 1 s between stopping the first and restarting the second breath-hold. This is too short for sBP to return to normal [14]. Moreover, since the large inhalation of the second breath-hold itself causes swings in sBP, there was insufficient time to make a valid pressure measurement to distinguish the pressure at the first breakpoint from the pre-period of the second breath-hold. Nevertheless, starting the second breath-hold from the slightly higher pressure had no cumulative effect of raising pressure at the second breakpoint, where sBP had risen only to 167 ± 6 mmHg ($p < 0.01$). This level is not significantly higher than that at the breakpoint they normally achieved for their single prolonged breath-hold (166 ± 4 mmHg, *ns*) nor than that at breakpoint we found previously in healthy subjects during such prolonged breath-holds (at 165 ± 6 mmHg, *ns* [14]), nor than that in our previous breast cancer patients (at 168 ± 4 mmHg, *ns* [15]).

6 min 2nd breath-hold by re-introducing 60% O_2 and hypocapnia in 18/18 subjects

Fig. 2b shows that relieving an ~80% breath-hold (a mean of 5.3 ± 0.2 min) with re-ventilation, preoxygenation and ~1 min of hypocapnia, enabled a second breath-hold. Its mean duration (5.8 ± 0.3 min) was not significantly different from their normal single prolonged breath-hold (*ns vs.* 6.2 ± 0.4 min, $n = 18$). Table 1 shows there was no significant change in mean heart rate nor SpO_2 for either breath-hold at breakpoint. Mean $P_{et}CO_2$ level at the 80% breakpoint (44 ± 1 mmHg) was slightly higher than their level obtained on a different day for their single prolonged breath-hold (41 ± 2 mmHg, $p < 0.05$). It took a mean of 1.7 ± 0.1 min to lower $P_{et}CO_2$ back to 21 mmHg and hypocapnia was maintained at 20 mmHg for 0.9 ± 0.1 min. So the total time between breath-holds, *i.e.,* to restart a second breath-hold, was 2.5 ± 0.2 min. Because hypocapnia had been renewed, the $P_{et}CO_2$ level at the second breakpoint was significantly lower (at 46 ± 1 mmHg) than that at the second breakpoint relieved by a single breath (51 ± 1 mmHg).

Fig. 1b shows that mean sBP had risen significantly by 14 mmHg at breakpoint of the 80% breath-hold (to

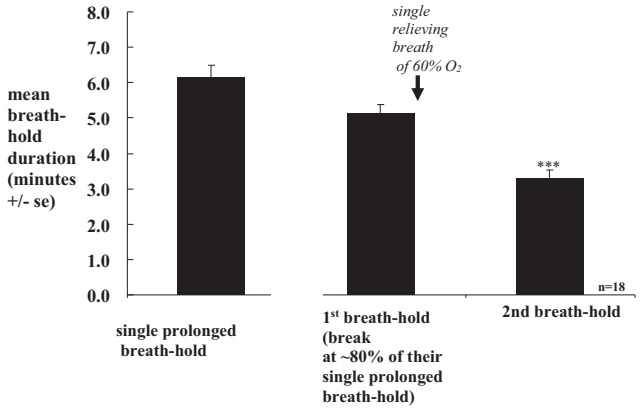

Fig. 2a. 3 min. 2nd breath-hold after relieving at a mean of 82 ± 4% of their single prolonged breath-hold duration with a single breath (exhaling then inhaling 60% oxygen) in 18 subjects $^{***}p < 0.001$ *vs.* single prolonged breath-hold.

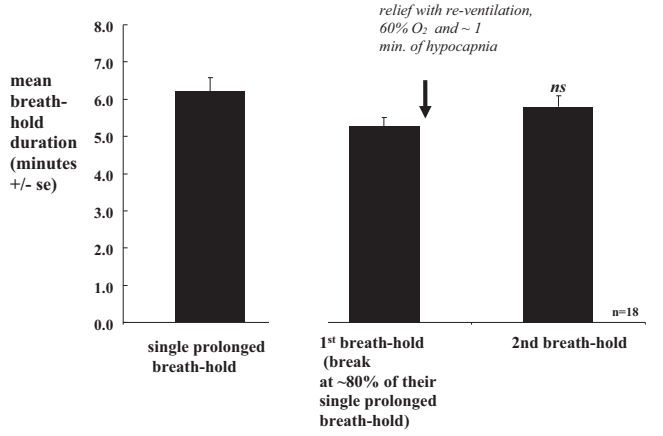

Fig. 2b. 6 min. 2nd breath-hold after relieving at a mean of 82 ± 4% of their single prolonged breath-hold duration with re-ventilation and ~1 min of hypocapnia in 18 subjects. 7 subjects from Fig. 1a appear in Fig. 1b. *ns* $p > 0.05$ *vs.* single prolonged breath-hold.

122 ± 4 mmHg, $p < 0.01$). The 2.5 min relieving period here was sufficient for mean sBP to recover to normal levels (110 ± 4 mmHg, *ns vs.* resting levels) before the second breath-hold. Indeed, it was sufficient to have no further effect on the sBP at the second breakpoint. Thus at the second breakpoint (mean duration 5.8 ± 0.3 min), mean sBP had risen to only 152 ± 5 mmHg, which was not significantly different from the mean at breakpoint of their single prolonged breath-hold (156 ± 6 mmHg). It was actually significantly lower ($p < 0.05$) than that at their second breakpoint with the single relieving breath (167 ± 6 mmHg), despite the second breath-hold here being almost twice as long. Moreover, this 152 ± 5 mmHg level was also significantly lower than that we found previously at breakpoint of single prolonged breath-holds in our 15 breast cancer patients (168 ± 4 mmHg, $p < 0.01$, mean duration 5.3 ± 0.2 min [15]), but was not significantly different from that at breakpoint in our in previous 12 healthy subjects (165 ± 6 mmHg, *ns* mean duration 5.5 ± 0.5 min [14]).

Nine multiple prolonged breath-holds in 17/17 subjects

Fig. 2c shows that all 17 subjects were able successfully and safely to complete 8 successive 70% prolonged breath-holds (each with a duration of 4.3 ± 0.2 min). All 17 stated that they could have performed more. Table 1 shows over the 8 breath-holds that there were no significant changes in SpO_2, but mean heart rate had risen significantly from 72 to 75 beats per minute ($p < 0.05$) and mean $P_{et}CO_2$ at breakpoint (44 ± 1 mmHg) remained consistent.

Fig. 1c shows that pre breath-hold sBP rose by 13 mmHg between the 1st and 8th breath-hold, indicating a detectable but small cumulative rise. Its effect on the breakpoint pressure level was negligible however as, by the eighth, pre- sBP (116 ± 4 mmHg) was only 3 mmHg higher ($p < 0.01$) than that at the 1st breakpoint (at 113 ± 5 mmHg).

Fig. 3 shows that it was as easy (took no longer) for reventilating to induce hypocapnia and sustain it by the eighth breath-hold. The mean recovery and preparation period between each successive breath-hold was 3.1 ± 0.2 min.

Fig. 2c shows that subjects had no difficulty in continuing to breath-hold by the 9th (unconstrained) breath-hold (6.0 ± 0.3 min, $n = 17$). Remarkably, the duration of their 9th unconstrained breath-hold (6.0 ± 0.3 min) was not significantly different from their normal single prolonged breath hold, indicating no obvious fatigue or dissatisfaction. This was significantly longer than all 70% breath-holds ($p < 0.001$).

The 9th breath hold was equally safe. Thus despite its duration being nearly 40% longer than the other 8, table 1 shows no change in mean breakpoint heart rate (80 ± 4 b.p.m.) nor SpO_2 (99 ± 0%). Mean sBP level at the end of the ninth (151 ± 6 mmHg) was not significantly different from their mean pressure at breakpoint for their normal single prolonged breath-hold (157 ± 6 mmHg, $n = 17$), nor that at breakpoint of single prolonged breath-holds we found previously in previous healthy subjects (165 ± 6 mmHg, [14]) and was significantly lower than that we found previously in patients (168 ± 4 mmHg, $p < 0.05$, [15]). The breakpoint $P_{et}CO_2$ level for the ninth breath-hold (46 ± 1 mmHg) was only 2 mmHg higher than the mean of the other eight.

Using just 3 of these multiple breath-holds, in a session of ~19 min it would be possible to have ~ 13 min of potential radiotherapy treatment time (3 breath-holds) and ~ 6 min for setup and recovery. Using all 9 breath-holds, this could be extended to a 65 ± 2 min session with 41 ± 1 min for radiotherapy (breath-holding) and 25 ± 2 min for setup and recovery.

Discussion

The possibility of using multiple prolonged breath-holds for radiotherapy treatment has not previously been considered. Here we demonstrate that healthy subjects can deliver safely 9 multiple prolonged breath-holds, potentially offering delivery of 41 min of reproducible breath-hold durations for radiotherapy treatment in a single session of 65 min.

Despite our safety limits being very cautious, most subjects (20/30 = 67%) never reached them. If reached, then they usually reached the sBP limit (71%) and only one was eventually able to reach them consistently. Previously we found similar incidences of reaching these safety limits with single prolonged breath-holds in breast cancer patients (53% never reaching them and, if reached, then mostly reaching the pressure limit (63%). None could reach them consistently [15]).

Training to perform prolonged breath-holds

The entire training can be completed outside a radiotherapy department. For administrative convenience we spread this over

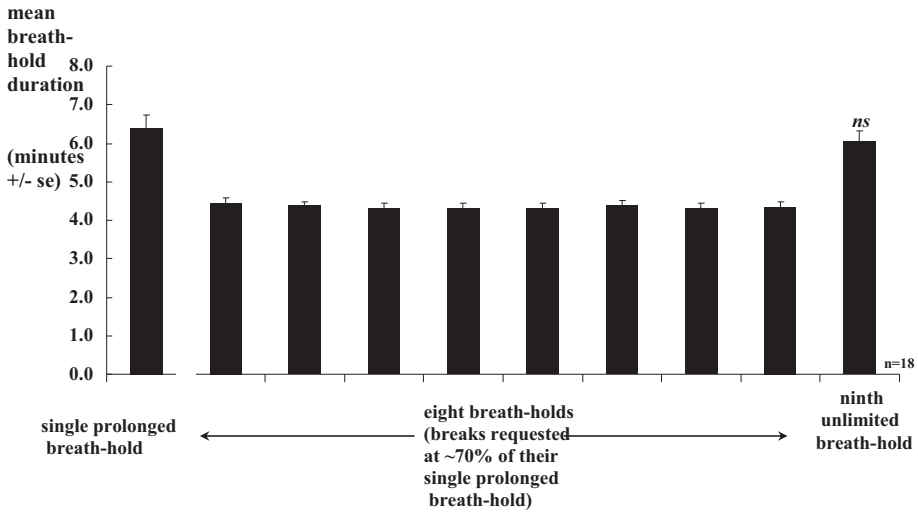

Fig. 2c. Ability to perform 9 successive breath-holds after relieving each at a mean of 68 ± 4% of their single prolonged breath-hold duration with re-ventilation and ~1 min of hypocapnia in all 17 subjects. 6 subjects from Fig. 1a and 11 from Fig. 1b appear in Fig. 1c. *ns* $p > 0.05$ *vs.* single prolonged breath-hold.

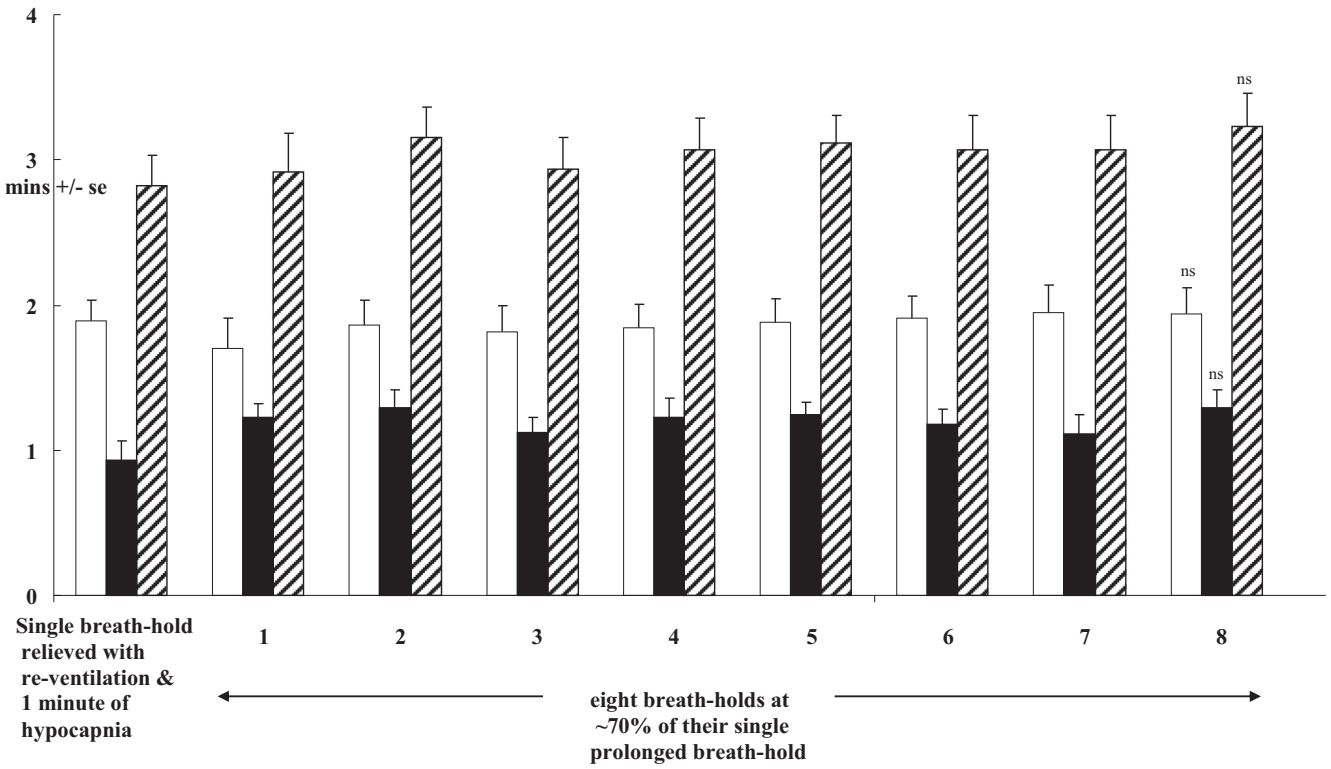

Fig. 3. Mean reset times for the next breath-hold do not change over the 8–70% breath-holds. Figure shows the time to lower $P_{et}CO_2$ from the breakpoint level to 21 mmHg (open bars), the duration of the hypocapnia (black bars) and the total time between each breath-hold (the sum of the time to 21 mmHg and the duration of the hypocapnia) for the single breath-hold relieved with re-ventilation & 1 min of hypocapnia and the 8 breath-holds relieved with re-ventilation & 1 min of hypocapnia. *ns* $p > 0.05$ *vs.* the 1st breath-hold.

4 days, but it could be completed in 2. It takes about 1 min for healthy volunteers to accept being mechanically ventilated.

3 min 2nd breath-hold with a single breath of oxygen

While we (above) and others report that normal healthy subjects breath-hold in air for only <1 min [12], we show that they can easily and safely extend hold their breath-hold duration with preoxygenation and hypocapnia to >5 min (6.1 ± 0.3 min.). We show here that, by taking a single breath of 60% oxygen (which does not restore their $P_{et}CO_2$ nor sBP to normal levels), they can hold for a further 3.3 ± 0.2 min. So if either patient or radiographer had for some reason to terminate even just that last ~1 min of the breath-hold (*i.e.,* at ~80%), a single breath of 60% oxygen recovers and extends the total breath-hold duration (*i.e.,* treatment time) to 8.4 min (5.1 + 3.3 = 8.4 min). Our choice of relieving at ~80% of their single prolonged breath-hold duration was entirely arbitrary. Presumably the shorter the first breath-hold, the easier it is to take (the longer will be) a second prolonged breath-hold. So we deliberately made this more challenging by lengthening the first breath-hold. By waiting until ~80% of their mean single prolonged breath-hold duration (a mean of 5.1 ± 0.2 min), we believe success with this challenge reveals how useful and straightforward is the ability to take a second breath-hold.

We confirm that it cannot be asphyxia that terminates our prolonged breath-holds, because our blood gases at breakpoint are so normal. The breakpoint mechanism is believed to originate from contraction of the breath-holding musculature (mainly the diaphragm) causing the accumulation of metabolites that stimulates muscle metabolo-receptors [12]) that in turn stimulate the brain [12].

As well as causing the breakpoint, a muscle metaboloreflex is also believed to cause sBP to rise [14]. sBP does not recover completely on relieving with a single breath, but this can be ignored since at the second breakpoint its level was no greater than found in their single prolonged breath-holds.

This 2nd 3 min breath-hold is possible because SpO_2 is still 99%, the diaphragm has been partially reperfused and normocapnia exists.

This ability also demonstrates the importance of preceding the first breath-hold with a long enough period (15 min) of stable hypocapnia to equilibrate fully the $P_{et}CO_2$ level between blood and all other the extra- and intracellular CO_2 stores [21]. Thus while mean $P_{et}CO_2$ had risen to 44 mmHg at the first breakpoint (normocapnia), some useful hypocapnia must persist at a cellular level.

6 min 2nd breath-hold with reventilation and hypocapnia

After terminating a prolonged breath-hold at 80% of its normal duration, we can completely recover the single prolonged breath-hold by re-ventilation (taking ~3 min). This 2nd 6 min breath-hold is possible because SpO_2 is 100%, the diaphragm has been completely reperfused and hypocapnia has been re-established. So by terminating in the last ~1 min, reventilation extends the total treatment (breath-holding) time to a mean of 11.1 min (5.3 + 5.8 = 11.1 min and sBP now recovers).

Limitations of multiple short breath-holds with air

The technique of using multiple, short, and deep inspiratory breath-holds, and only using air [1–10] has recently been developed in radiotherapy practice to build up a total treatment time that is greater than what is perceived to be a realistic single

breath-hold duration for patients with cancer. While now widely and successfully used clinically [1–10], this still merits improvement.

First, the diaphragm continues to move by up to 1.5 cm during the first ~15 s of a short breath-hold [22], due to diaphragm settlement while patients initially relax into their breath-hold. There is an urgent need for MRI quantification of the residual motion of all relevant internal organs in the thorax and abdomen during breath-holding, the relevant inter- and intra- fraction baseline drifts and their relationships to the corresponding movement of surface markers.

Secondly, why in 2019 are we still using only room air (21% O_2) for breath-holding? Historically there was concern over the proximity of high oxygen levels and high voltage radiotherapy equipment, but this can now be revisited. There may be advantages in replacing the inhaled gas from room air to 60% O_2. It has been known since at least 1946 that preoxygenation doubles breath-hold duration [12,23]. Furthermore we have previously demonstrated that preoxygenation (60% O_2) alone is simple, safe and effective at doubling breath-hold duration in both healthy volunteers (to 3 min) and in patients with breast cancer (to 2 min on their first attempt) [11,12,14,15].

9 multiple prolonged breath-holds

We demonstrate for the first time that multiple prolonged breath-holds are possible. The duration of the 9th breath-hold was not significantly shorter than their single prolonged breath-hold, indicating that subjects could have performed even more. The fact that nine are possible further re-enforces the latest explanation of the breakpoint mechanism [12,16,17] as being caused not by arterial asphyxia, but by the act of breath-holding (some contraction of the diaphragm muscle) causing the accumulation of metabolites in the diaphragm that then stimulate metabolo receptors in the diaphragm. This accumulation can be easily (and repeatedly) cancelled by the act of releasing the diaphragm, which is then reperfused and the accumulated metabolites are flushed out.

Since no-one has thought of attempting multiple prolonged breath-holds before, we wanted the challenge of terminating as late as possible. But we felt that it might be too difficult to perform multiple breath-holds if terminating as late as 80%, so we reduced this slightly, to 70%. Once we found, to our surprise, that this was so successful, we pursued this as quickly as possible, rather than undertaking further pilot experiments to see if it still works above 70% and at what percentage it breaks down.

This technique will have particular application for tumours subject to breathing movement that require longer treatment times. It may also be compared with other strategies to prolong the absence of breath-holding movements *e.g.,* [24]. An example application might be a typical treatment session for a patient with a small lung or liver tumour, who might undergo treatment with stereotactic ablative radiotherapy using VMAT at University Hospitals Birmingham: this would include a cone-beam CT scan, a first arc of a VMAT delivery, potentially a second cone beam CT and a second arc of VMAT, each taking 1–2 min plus time for adjustment and re-positioning. Here is a clear application for multiple prolonged breath-holds.

Strictly, here we have only used healthy volunteers aged 20–25. So far, 37–74 years old patients with breast cancer are the only other group of cancer patients in which the single prolonged breath-hold has been attempted. Since they too can achieve single prolonged breath-holds of >5 min while supine and on a breastboard [15], we anticipate no difficulty in principle in achieving multiple prolonged breath-holds for at least some other patients with cancer. But until this is tested on other patient groups (*e.g.,* lung or liver) with severe co-morbidities that can have huge impacts on breathing (*e.g.,* COPD, cirrhosis, altered performance status, emphysema, cardio-vascular disease), we cannot be certain that this will be possible for all cancer patients.

Over the 8 breath-holds, the sBP rise of only 13 mmHg (to 116 ± 5 mmHg) is inconsequential and had no influence on the sBP of the 9th (151 ± 6 mmHg). We cannot be certain how patients with hypertension will respond, but if their pressure is under control, only careful monitoring should be necessary.

As with previous breath-holding studies, it will also be important to determine the internal and external motion during multiple prolonged breath-holds, and both inter and intra fraction variations in tumour position.

Furthermore, we are not aware of any clinical studies on the effects of our preoxygenation and hypocapnia on tumour oxygenation and its responsiveness to radiotherapy. Nevertheless the expectation would be that our preoxygenation and hypocapnia would certainly not worsen tumour responsiveness.

Future clinical developments

Possibly the breath-hold durations we demonstrate here are too long and therefore unnecessary for radiotherapy. Nevertheless, by demonstrating how easily and safely these are achieved, more imaginative radiotherapy treatment strategies to compensate for breathing motion can now be considered. The average duration of breath holds in the range of 5 min may also be useful for PET imaging and thoracic MRI.

Finally, although introduction of proton therapy into the National Health Service in the UK is imminent, this will only be for tumours that do not move with breathing, whereas outside the UK, proton therapy is applied to tumours that do move. The introduction of proton therapy could be facilitated by the ability to undertake multiple prolonged breath-holds, combined with detailed knowledge of the internal movement during prolonged breath-holds of all relevant organs in the thorax and abdomen.

In conclusion, we show for the first time that multiple prolonged breath-holds are feasible and safe in healthy subjects. We look forward to applying these to patients with a variety of thoracic and abdominal cancers.

Declaration of Competing Interest

The authors declare they have no financial and personal relationships with other people or organizations or conflictions of interest that could inappropriately influence (bias) this work.

Acknowledgements

We are grateful for support from Accuray Inc., Cambridge Electronic Design Ltd, Dr David McIntyre (programming), Dr Peter Nightingale (statistical analysis), Dr Elizabeth Sapey and the National Institute for Health Research (NIHR)/Wellcome Trust Birmingham Clinical Research Facility. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR/Wellcome Trust or the Department of Health.

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