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Original Article

Mechanically-assisted and non-invasive ventilation for radiation therapy: A safe technique to regularize and modulate internal tumour motion

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ABSTRACT

Background and purpose: Current motion mitigation strategies, like margins, gating, and tracking, deal with geometrical uncertainties in the tumour position, induced by breathing during radiotherapy (RT). However, they often overlook motion variability in amplitude, respiratory rate, or baseline position, when breathing spontaneously. Consequently, this may negatively affect the delivered dose conformality in comparison to the plan. We previously demonstrated on volunteers that 3 different modes of mechanically-assisted and non-invasive ventilation (MANIV) may reduce variability in breathing motion. The volume-controlled mode (VC) constraints the amplitude and respiratory rate (RR) in physiologic condition. The shallow-controlled mode (SH), derived from VC, increases the RR and decreases amplitude. The slow-controlled mode (SL) induces repeated breath holds with constrained ventilation pressure. In this study, we compared these mechanical ventilation modes to spontaneous breathing or breath hold and assessed their tolerance and effects on internal tumour motion in patients receiving RT.

Material and methods: The VC and SH modes were evaluated in ten patients with lung or liver cancers (cohort A). The SL mode was evaluated in 12 left breast cancer patients (cohort B). After a training and simulation session, the patients underwent 2 MRI sessions to analyze the internal motion of breast and tumour.

Results: MANIV was well tolerated, without any adverse events or oxymetric changes, even in patients with respiratory comorbidities. In cohort A, when compared to spontaneous breathing (SP), VC reduced significantly inter-session variations of the tumour motion amplitude ($p = 0.01$), as well as intra- and inter-session variations of the RR ($p < 0.05$). As to SH, the RR increased, while its variations within and across sessions decreased when compared to SP ($p < 0.001$). SH reduced the median amplitude of the tumour motion by 6.1 mm or 38.2% ($p \leq 0.01$) compared to VC. In cohort B, breast position stability over the end-inspiratory plateaus obtained spontaneously or with SL remained similar. Median duration of the plateaus in SL was 16.6 s.

Conclusion: MANIV is a safe and well tolerated ventilation technique for patients receiving radiotherapy. MANIV could thus make current motion mitigation strategies less critical and more robust. Clinical implementation might be considered, provided the ventilation mode is carefully selected with respect to the treatment indication and patient individualities.

Radiation Therapy (RT) for patients with thoracic or upper abdominal tumours involves complex motion mitigation strategies to ensure accurate irradiation of the target [1]. These strategies, however, have shortcomings. For instance, patient-specific margin strategies like Internal Target Volume (ITV) or MidPosition, which encompass the tumour trajectory, inevitably, either completely or probabilistically, lead to futile irradiation of healthy tissues, while breathing-synchronized strategies like gating and tracking are more complex and require dedicated equipment and software [2–5]. Behind these shortcomings hides yet another issue, namely, unpredictable irregularities of tumour motion while breathing spontaneously, which are not well accounted for in these strategies. They may degrade the accuracy of the delivered dose.

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Patient-specific margins rely on a planning 4D CT scan, acquired while breathing spontaneously, over just a few seconds or minutes. This short sample of the breathing signal might not be representative enough when considering longer observation times, like the whole duration of a treatment fraction, typically about 10 min. A high variance might then be associated with the estimation of the margin, making it hardly robust when unseen variations in tumour motion occur within a treatment fraction or across fractions [6,7]. Gating and tracking can also be pushed to their limits by irregular breathing, likely to desynchronize treatment delivery and tumour motion. This may alter the treatment delivery and prolong treatment duration, potentially leading also to patients' discomfort. In proton therapy, the dose distribution can be distorted even more severely, due to complex interplay effects between pencil beam scanning and respiratory motion, and density changes in the moving anatomy [8,9]. In order to improve the reliability of the above strategies, several guidance techniques have been investigated to regularize breathing, like video and audio coaching [10]. Similarly, gated RT with breath hold (BH) or active breathing control showed encouraging results and good reproducibility [11–13]. However, these techniques require some training and understanding from the patient; stressed-out or medically unfit patients might not tolerate them [11]. New non-invasive ventilation techniques have also been developed to prolong BHs up to several minutes (>5 min) with or without additional percussive ventilation [14–16]. Stability of the internal tumour position over a single prolonged BH or repeated ones remains under investigation.

Along the same line, mechanically-assisted and non-invasive ventilation (MANIV) has been proposed to regularize breathing, but also to modulate it with minimal patients' involvement [17,18]. As demonstrated with healthy volunteers in our previous study, MANIV can be used to overtake spontaneous breathing with a simple face mask, without general anaesthesia. MANIV allowed us to constrain safely both the respiratory rate (RR) and the tidal volume to regularize breathing. Furthermore, the breathing amplitude and its variations were reduced by simultaneously increasing the RR and decreasing the tidal volume. Finally, by constraining ventilation pressures, MANIV could also induce repeated end-inspiratory breath holds lasting for more than 10 s [19]. In this trial, we evaluated tolerance to MANIV in patients receiving radiotherapy for lung, liver, or left breast cancers. We quantified with MRI the impact of the different ventilation modes on the internal motion of the tumour or breast, and compared it to the motion observed with spontaneous breathing or voluntary breath hold.

Material and methods

Ethics

This trial followed the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, was approved by our local ethics committee (B403201732715), and was registered in ClinicalTrials.gov (NCT03226925). Informed consent was obtained from all patients before their inclusion.

Objectives

Two key potential applications of MANIV emerged from our clinical practice and lead to the following explorations:

- SABR treatments for lung and liver tumours are planned following the mid-position strategy, that is based on patient-specific margins drawn on the 4D CT and spontaneous breathing during delivery [20,21]. In this trial, we wanted to assess if MANIV could regularize the tumour motion and reduce its amplitude safely.
- Patients with left breast cancer are treated under deep inspiration breath holds (DIBHs), which last for 20 s and must be repeated to complete the fraction delivery. We wanted to assess here if MANIV could safely produce continuously repeated end-inspiratory plateaus, with a stable position over the whole fraction time, in order to facilitate gated delivery.

Patient tolerance to MANIV was also assessed during this trial.

Patients and MANIV modes (Fig. 1)

All patients were connected to the mechanical ventilator (imtmedical AG, Bellavista 1000) with a silicone face mask without any sedation.

Cohort A included patients treated with SABR for lung or liver tumours. The volume-controlled mode (VC) and the shallow-controlled mode (SH) were assessed following our previous methodology [19]. Briefly, in the VC mode, the RR and tidal volume were determined for each patient in physiologic conditions. In the SH mode, these ventilation parameters were adapted with a tidal volume reduction proportional to the RR increase. This mode aims to reduce the tumour motion amplitude as much as possible. However, we had to find the best compromise between the RR increase and patients' comfort.

Cohort B included patients receiving left breast irradiation. The slow-controlled mode (SL) was specifically assessed in this cohort, since it could induce continuously repeated end-inspiratory plateaus based on high and low levels of individually adapted pressures, depending on patients' tolerance [19]. In contrast with our preliminary trial, breath hold duration with MANIV was empirically prolonged to 20 s in this trial.

Trial design (Fig. 1)

The patients who were enrolled in this trial underwent 4 sessions that were scheduled over a maximum of 10 days before the start of their treatment:

(1) the training session took place in a consultation room and lasted for 30–40 min. It allowed patients to get acquainted with the different ventilation modes, while their ventilation parameters were also adjusted.
(2) the simulation session was planned a few days later to test MANIV in treatment position in the simulation room. It lasted 20–30 min. Ventilation parameters could be further tuned, depending on the patient's need and comfort.
(3) the first MRI session and
(4) the second MRI session were scheduled on different days with no more than two days in between. Their purpose was to quantify the tumour or breast internal motion while breathing spontaneously (SP) or holding breath (DIBH), and undergoing the ventilation modes. The parameters of MANIV remained unchanged in the MRI sessions.

The radiotherapy treatments were delivered without MANIV.

One radiation oncologist, trained specifically to use the ventilator and manage its modes, was assigned to this trial. No other medical staff has been required.

MRI

The MR images were acquired in order to quantify, in real time, the motion of the lung or liver tumour (cohort A) or the breast (cohort B). The patients were scanned with dynamic MRI (3T, Ingenia, Philips Healthcare, Best, the Netherlands) using the same acquisition protocol as in [19]. In short, two planes were set

manually, crossing each other at the tumour or the nipple (coronal and oblique plane in cohort A, transversal and oblique plane in cohort B – Fig. 1). Dynamic MR images were acquired using a single-slice Balanced Turbo Field Echo (bTFE) sequence with a pixel size of 0.89 × 0.89 mm and a slice thickness of 10 mm. Three images per second were acquired during 6 min, with alternating planes every minute, resulting in 1080 images per sequence of 6 min (Fig. 1). In cohort A, dynamic MRI sequences were acquired with the VC and SH modes. An additional MRI sequence was performed under SP for comparison purposes. Similarly, in cohort B, dynamic MR sequences were acquired in SL mode, and compared to spontaneous DIBH. In SL, the repeated plateaus were continuously recorded whereas with DIBH only one plateau per minute was acquired, accounting for free breathing intervals (Fig. 1). All MRI sequences were repeated during the second MRI session to assess inter-session reproducibility. Afterwards, these dynamic images were collected and played back to quantify the breathing-related internal motion of the tumour or nipple on each plane using the same methodology as described in [19].

Motion assessment

On each MRI sequence, the minimal and maximal peak positions of the tumour or the nipple were reported for all the breathing cycles observed during the 6 min of acquisition.

In cohort A, tumour motion was characterized by its amplitude (peak-to-peak distance between end-exhalation and end-inhalation positions in each breathing cycle), respiratory rate (in breaths per minute, bpm), and mean position (average of the end-inhalation and end-exhalation positions for each breathing cycle). The median position of the tumour over one whole sequence was then calculated (median value of all the mean position values – Fig. 1). All measurements were finally summarized by giving their median and interquartile range (IQR) [P25–P75]. Variation in amplitude and RR were analysed with respect to the latter. The maximal difference between all the tumour mean positions over one sequence was calculated for intra-session baseline shift purposes. Differences between the median position in MRI 1 and 2 corresponded to the inter-session baseline shift.

In cohort B, each end-inspiratory plateau was characterized by its mean position (average of the positions within one plateau), its duration, and its range (distance between the maximal and minimal positions within one plateau). All plateau parameters were then calculated within each MRI and summarized by their median and IQR [P25–P75]. The maximal distance between plateaus within one sequence was calculated for the intra-session baseline shift. Differences between the median position in MRI 1 and 2 corresponded to the inter-session baseline shift.

Tolerance assessment

Pulsed oxygen saturation (SpO2), end-tidal carbon dioxide (etCO2), and heart rate (HR) were monitored with a pulsed oximeter and etCO2 detector (Bellavista 1000®) during the training and simulation sessions. Global comfort was assessed after each session using multiple-choice questionnaires that rated the comfort

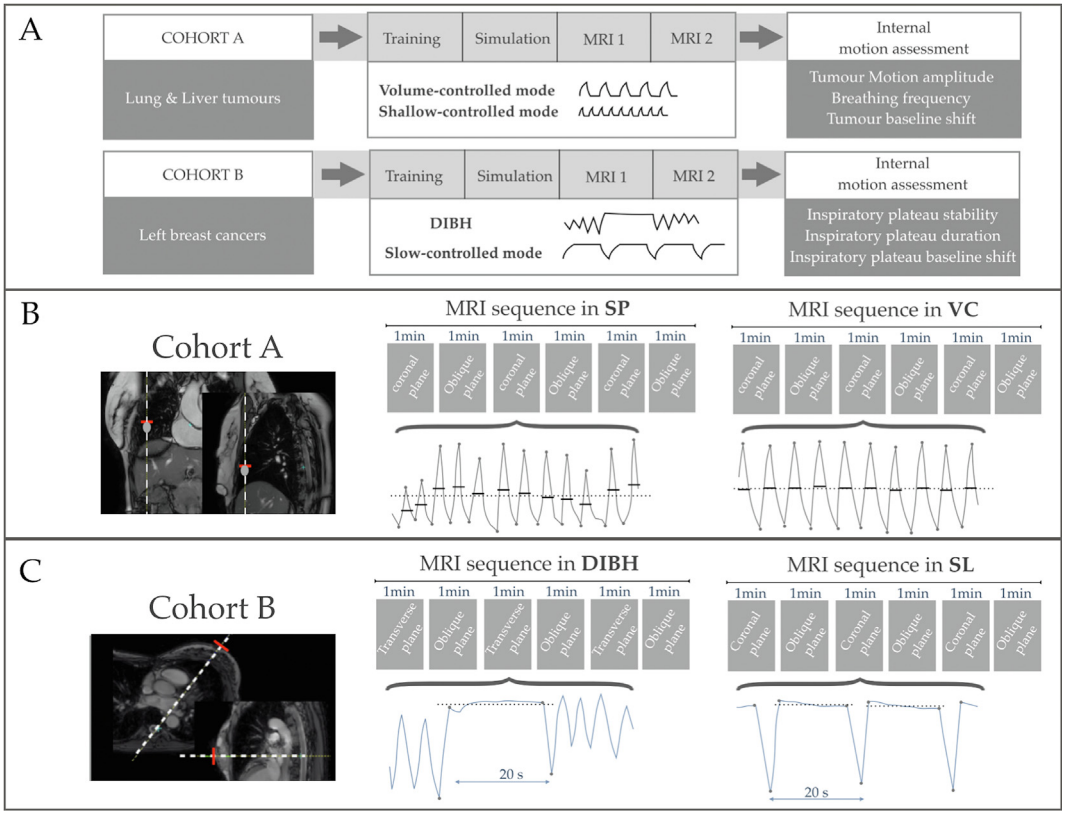

Fig. 1. Trial design and methodology. (A) Patients underwent 4 sessions with mechanically-assisted ventilation: training, simulation, MRI 1 and MRI 2. Internal motion analyses were performed afterwards by tracking the tumour or the nipple on MR images. (B) In cohort A, dynamic MRI sequences were acquired with the volume-controlled mode (VC) and shallow controlled mode (SH) and compared to spontaneous breathing (SP). MRI sequences lasted for 6 min, alternating planes (coronal and oblique planes) every minute. The small dots on the breathing curves represent the end-exhalation and end-inhalation peak positions of the tracked tumour. The dashes represent the mean position of the tumour for each breathing cycle. The dotted line represents the median position of the tumour over a whole sequence. (C) In cohort B, dynamic MRI sequences were acquired in slow-controlled mode (SL) and compared to spontaneous breath hold (BH). MRI sequences lasted for 6 min, alternating planes (transverse and oblique planes) every minute. End-inspiratory plateau lasted for 20 s with DIBH whereas they were shorter with SL since the 20 s duration set on the ventilator included the inhalation time. The dotted line represents the median position of the nipple over one BH.

level with a Likert scoring scale (Excellent = 5; Good = 4; Neutral = 3; Bad = 2; very bad = 1). Patients were asked to point out the reason(s) of their discomfort (unknown situation, stress, environment, position, facial mask, MRI environment, ventilation, other). The level of ventilation comfort was assessed with a Visual Analogic Scale (VAS) on 100 mm, ranging from 0 (very bad) to 100 (perfect).

Statistical analyses

Motion characteristics were analysed in the MRI acquisitions for each ventilation mode. In cohort A, comparisons were carried out between SP and VC, SP and SH, VC and SH, as well as MRI 1 and 2. In cohort B, SL and DIBH were compared, as well as MRI 1 and 2. Intra-session results were assessed using non-parametric tests for independent samples and univariate ANOVA (ANalyses Of VAriance) analyses. The Tamhane's T2 correction factor was used to counteract for the multiple comparisons made for the individual analyses. Inter-session analyses were assessed using non-parametric tests for related samples. Group effect analyses were also performed using mixed model analyses since multiple measurements were done on the same subject (with patients as a second level grouping factor and the ventilation mode set as a fixed effect).

In cohort A, aberrant data corresponding to swallowing or inaccurate tracking (due to tumour misdetection) were excluded from our analyses. This amounts to a median data exclusion of 2.3% [0–3.80%] of the whole time for SP, 1.95% [0–5.67%] for VC, and 5.97% [3.84–11.08%] for SH. Finally, 18,273 images were analysed in SP, 17,787 in VC and 16,750 in SH.

Results

Between March and October 2018, 31 patients were enrolled in this trial, and 22 remained for analyses. One patient was excluded since the radiation treatment was cancelled, 3 patients interrupted the trial for convenience purposes, 4 patients interrupted the trial due to MRI-phobia, and one had a tumour that could not be tracked at MRI.

Patients characteristics (Table 1)

In cohort A, ten patients, from 61 to 83 years old, were included: 5 with lung tumours and 5 with liver tumours. Notably, one suffered from chronic obstructive pulmonary disease (COPD) stage GOLD II, and one patient presented a Cheyne-Stokes breathing disorder (breathing characterized by periods of apnea alternating with hyperpnoea and tachypnoea) combined with an Obstructive Sleep Apnea-Hypopnea Syndrome (OSAHS), treated with a continuous positive airway pressure device at night (cPAP). In cohort B, twelve women treated for left breast cancer were included, from 49 to 77 years old. Four were former smokers, with one still smoking at the inclusion time, and 2 presenting an OSAHS treated with cPAP.

Table 1
Demographics data of the patients included in the 2 cohorts: Cohort A included patients with a lung or liver tumour; Cohort B included left breast cancer patients.

	Cohort A	Cohort B
Total	10	12
Location	5 liver tumours 5 lung tumours	12 left breast cancers
Tumour		
Primary tumour	4	12
Metastasis	6	0
Age (years)	61–83	49–77
Sex ratio (M/F)	8/2	0/12
ECOG/WHO PS		
0	5	11
1	4	1
2	1	0
≥3	0	0
BMI (kg/m^2)		
<18.5	0	1
18.5–24.9	3	7
≥25	4	3
≥30	3	0
≥35	0	1
Smoking status		
Non-smoker	5	9
Former	4	3
Active	1	0
COPD		
GOLD I	0	0
GOLD II	1	1
≥GOLD III	0	0
Previous chemotherapy		
Yes	4	3
No	6	9
OSAHS	1	2
cPAP	1	2
Breathing trouble		
	1 (Cheyne-stokes disorder)	0
Cirrhosis if liver tumour		
No	2	/
Child-Pugh A	1	
Child-Pugh B	2	

M: male; F: female; ECOG PS: Eastern Cooperative Group of Oncology performance status; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; OSAHS: Obstructive Sleep Apnea-Hypopnea Syndrome; cPAP: continuous positive airway pressure device.

Internal tumour motion analyses in cohort A (Table 2)

The median amplitudes were 6.8 mm [5.9–9.1 mm] in SP, 13.8 mm [10.5–17.9 mm] in VC, and 8.2 mm [5.2–10.9 mm] in SH. The smallest median tumour motion amplitude was observed in SP rather than in SH for the whole cohort. When considering individual results for SH and SP, 4/10 patients had a significantly smaller median tumour motion amplitude in SP (patients 2-4-6-9, Fig. 2, Table 2), whereas 4/10 patients had significantly smaller ones with SH (patients 3-7-8-10) and 2/10 patients had non-significant differences (patients 1–5). Amplitude variations over time reduced in both VC and SH (median values of 2.6 mm and 2.4 mm, respectively, compared to 3.4 mm in SP), although non-significantly ($p = 0.15$). Switching from VC to SH led to a significant reduction in amplitude with a median reduction of 6.1 mm [2.7–7.6 mm] or 38.2% [25.9–41.6] ($p \leq 0.001$) (Fig. 2).

Inter-session differences in amplitude were significantly reduced in VC when compared to SP (0.4 mm [0.2–2.0 mm] in VC versus 3.5 mm [2.0–4.9 mm] in SP, $p = 0.01$). VC was thus the most stable ventilation mode. In SH, these inter-session differences in amplitude were also reduced compared to SP, although not significantly (1.8 mm [1.0–2.5 mm] in SH, $p = 0.5$).

The median RR in SP was 15 bpm [12–16 bpm], whereas it was 11 bpm [9–14 bpm] in VC and 22 bpm [20–24 bpm] in SH. A median 2-fold increase [1.8–2.6-fold increase] was observed with SH compared to VC. The RR variations over time were significantly reduced when using MANIV, with a 35% reduction with VC when compared to SP ($p < 0.05$) and a 45% reduction with SH ($p < 0.001$).

As to inter-session analyses, the VC and SH modes significantly reduced the RR variations compared to SP with a 95% RR variation reduction in VC ($p < 0.001$) and a 63% RR variation reduction in SH ($p < 0.001$). In SP, these variations ranged indeed from 0 to 11 bpm, whereas no variation occurred whatsoever in VC and a maximum difference of 1 bpm was observed in SH for all patients but one. Only the patient with the Cheyne-Stokes breathing disorder (Table 2, patient 3) had a RR difference in VC (4 bpm) or SH (2 bpm).

Table 2
Detailed results for cohort A: Median internal tumour motion amplitude (in mm) and breathing cycles duration (in ms) by ventilation mode. The 5 first patients were addressed for liver tumours whereas the 5 latter for lung tumours.

AMPLITUDE (mm)	Spontaneous breathing				Volume-controlled mode				Shallow-controlled mode			
Patient	Median	P25	P75	IQR	Median	P25	P75	IQR	Median	P25	P75	IQR
1	9,12	8,40	9,98	1,58	15,26	14,28	16,56	2,28	8,27	7,40	9,40	2,01
2	5,86	5,10	8,56	3,46	10,36	8,45	11,82	3,37	8,11	6,24	9,11	2,88
3	26,34	18,36	33,77	15,42	22,71	18,31	26,02	7,71	13,40	11,20	15,52	4,32
4	8,91	6,94	10,25	3,31	18,59	17,41	19,81	2,40	11,41	9,28	15,19	5,90
5	6,84	3,84	9,37	5,54	10,94	10,09	12,10	2,01	6,80	5,60	8,17	2,57
6	2,38	1,92	5,23	3,31	3,61	3,37	3,92	0,55	2,75	2,43	3,02	0,59
7	11,92	10,43	14,18	3,75	18,45	16,68	20,26	3,59	10,73	9,82	11,78	1,96
8	6,72	3,82	7,79	3,97	4,81	3,47	6,39	2,92	4,36	3,24	5,42	2,18
9	5,96	4,69	7,52	2,83	16,07	14,69	17,46	2,77	10,90	9,37	13,20	3,83
10	5,75	4,88	6,28	1,40	12,40	11,05	13,46	2,41	3,00	2,51	3,53	1,02

PERIOD (ms)	Spontaneous breathing					Volume-controlled mode					Shallow-controlled mode				
Patient	Median	P25	P75	IQR	BR (bpm)	Median	P25	P75	IQR	BR	Median	P25	P75	IQR	BR (bpm)
1	3570	3387	3757	370	17	3939	3770	4245	475	15	2495	2200	2500	300	24
2	5685	5221	6088	795	11	5350	5340	5758	413	11	2985	2820	3210	405	20
3	3985	3351	4530	1255	15	3928	3300	6057	983	15	2500	2161	2659	423	24
4	3755	3416	4130	730	16	5398	5340	5700	350	11	2990	2850	3140	320	20
5	7140	6598	7800	838	8	10,073	9586	10,296	799	6	3298	3210	3570	360	18
6	3920	3570	4050	460	15	5870	5520	6240	739	10	2560	2195	2570	370	23
7	4283	3624	4685	841	14	6600	6384	6911	523	9	2923	2710	3340	555	21
8	3795	3637	4090	630	16	3770	3570	3920	350	16	2495	2170	2520	360	24
9	3515	3214	3889	630	17	6015	5684	6281	425	10	2860	2823	3210	360	21
10	5460	5140	5770	640	11	8525	8380	8740	295	7	2510	2200	2531	328	24

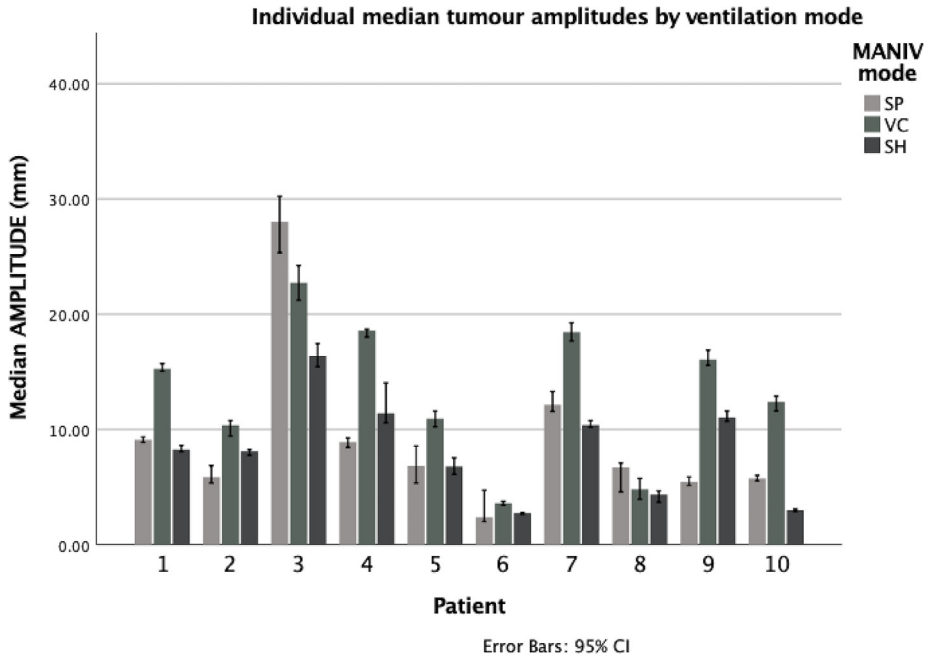

Fig. 2. Individual internal median tumour amplitudes by ventilation mode in cohort A. Switching from VC to SH (by increasing with a median 2-fold the respiratory rate) lead to a systematic median amplitude reduction. The median reduction was 6.1 mm [2.7–7.6 mm], or 38,2% [25.9–41.6] ($p \leq 0{,}001$). SP: spontaneous breathing; VC: volume-controlled mode; SH: shallow-controlled mode. Error bars corresponds to 95% confidence interval.

The median intra-session baseline shift was 4.2 mm [2.5–5.0 mm] in SP, 5.2 mm [4.0–7.3 mm] in VC and 4.9 mm [3.3–6.5 mm] in SH on coronal slices. On oblique slices, it was 4.3 mm [2.6–6.1 mm] in SP, 4.1 mm [3.1–7.4 mm] in VC and 5.1 mm [2.6–8.5 mm] in SH. None differed significantly ($p \geq 0.13$).

Inter-session baseline shift tended to reduce with VC and SH ($p \geq 0.41$). On coronal slices, the median baseline shift in SP was 10.6 mm [3.4–15.2 mm] whereas it decreased to 5.8 mm [2.9–9.5 mm] in VC and 7.0 mm [2.7–13.9 mm] in SH. On oblique slices, it was 6.4 mm [1.9–10.1 mm] in SP, whereas it reduced to 4.9 mm [1.1–11.5 mm] in VC and 5.3 mm [3.4–13.0 mm] in SH.

Breast motion analyses in cohort B

The median duration of the SL end-inspiratory plateaus was 16.6 s [16.4–17.2 s], whereas it was 20.8 s [19.8–21.4 s] in DIBH.

The shorter BH plateau duration with SL was expected since the 20 s duration set on the ventilator also included the inhalation time before reaching the end-inhale plateau (Fig. 1). As to plateau range variations, SL showed similar variation values than DIBH (0.8 mm [0.5–1.2 mm] and 0.7 mm [0.5–1.2 mm] respectively) ($p = 0.98$). Plateau baseline shift tended to decrease in SL (5.7 mm [4.1–8.2 mm]), compared to DIBH (6.3 mm [3.4–11.6 mm]) ($p = 0.43$).

In inter-session analyses, plateau durations and ranges in DIBH or in SL did not differ significantly ($p \geq 0.11$ and $p \geq 0.46$, respectively) (Fig. 3). Regarding baseline shift, significant differences were observed for both DIBH (3.67 mm [1.46–8.51 mm]) and SL (5.04 mm [3.37–8.49 mm]).

Tolerance

All 22 patients went through the 4 sessions without any adverse event. During the training and simulation sessions, all oxymetric values remained within normal ranges (SpO2 values ≥95%, maximal difference in etCO2 of 8.6 mmHg, and maximal change in HRB of 13/min).

Looking at the Likert scales (rating from 0 = very bad, to 5 = excellent), the global comfort level in cohort A was excellent for 15/40 sessions (37.5%), good for 24/40 sessions (60%), neutral for 1/40 sessions (2.5%), with no bad or very bad experience being reported. In cohort B, the global comfort level was excellent for 7/48 sessions (14.6%), good for 31/48 sessions (64.6%),

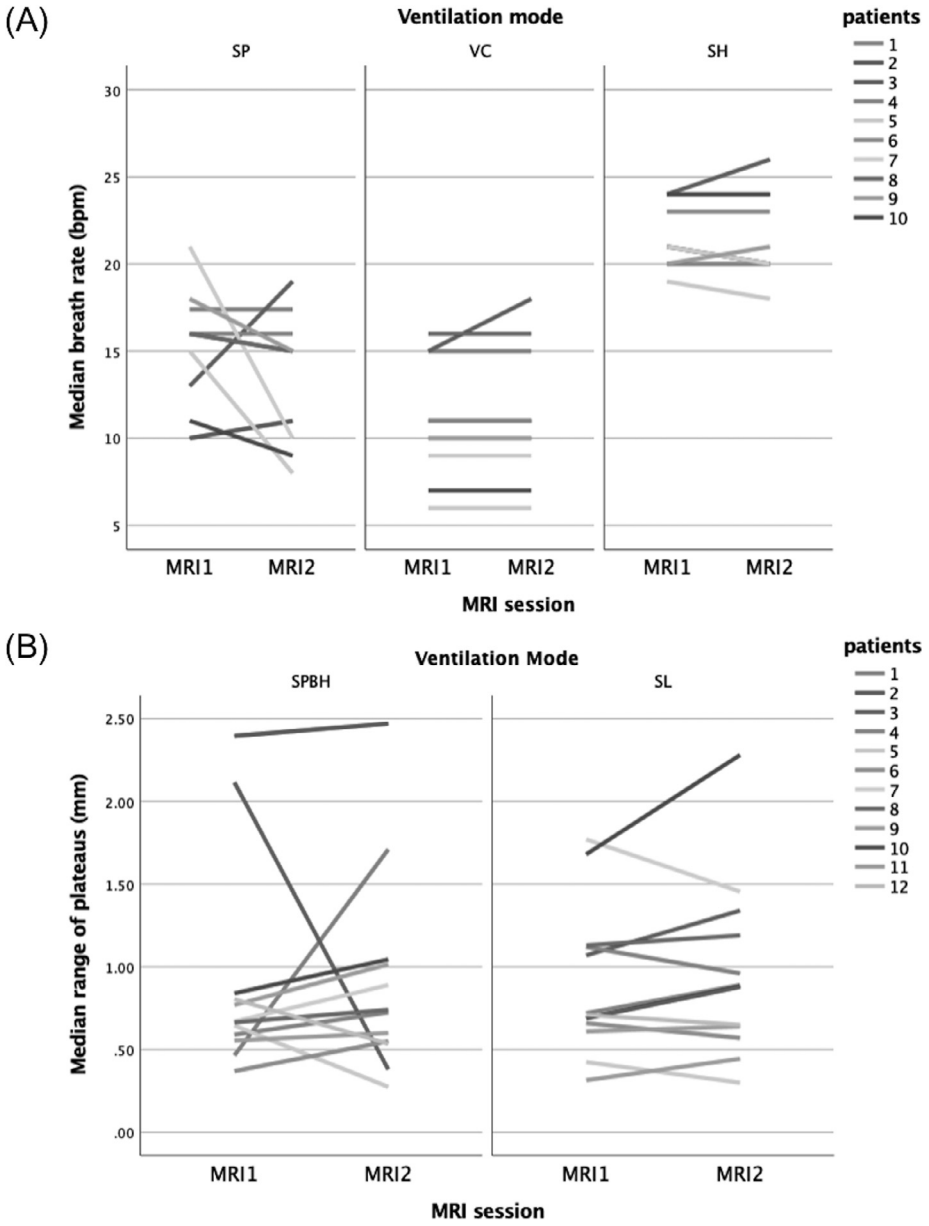

Fig. 3. Inter-session analyses in cohort A and B: (A) Individual median respiratory rates (in bpm) by MRI and by ventilation mode in cohort A. During spontaneous breathing, we observed large inter-session variations in respiratory rates while on volume controlled (VC) or Shallow-controlled (SH) modes, there were nearly no inter-session variation ($p < 0.001$). The SH mode was obtained after increasing the respiratory rate by a median 2-fold [1.8–2.6-fold]. (B) Individual median ranges (in mm) by MRI and by ventilation mode in cohort B. Inter-session variations varied both in spontaneous breath-holding (SPBH) and Slow-controlled mode (SL), but some patients showed higher variation rates in SPBH than with SL. However, on global analyses, these results were not significant ($p \geq 0.46$).

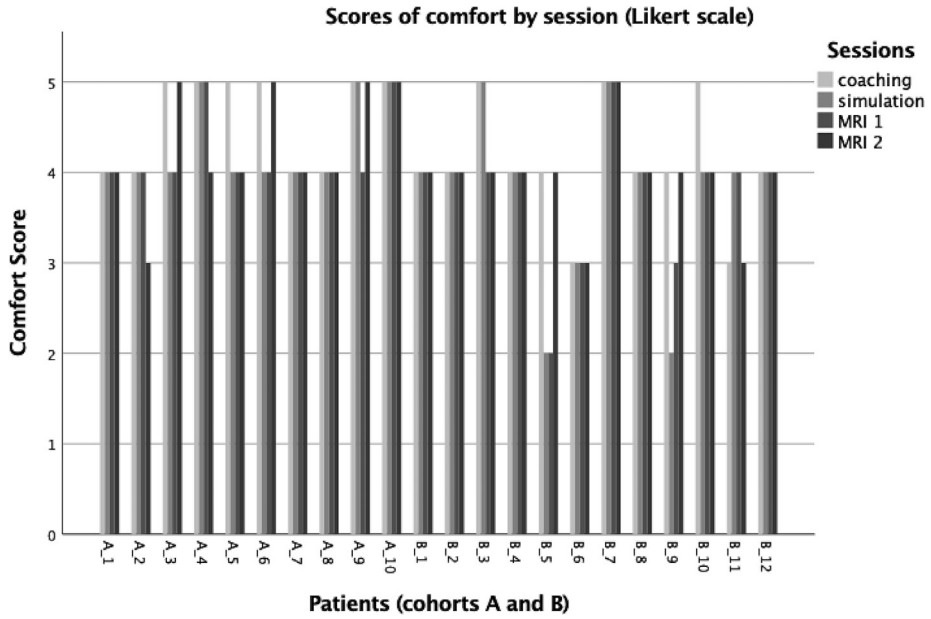

Fig. 4. Comfort evaluation by patient (cohort A and B) and by session. The comfort was rated on a 5-Points-Likert scale (Excellent = 5, Good = 4, neutral = 3, bad = 2, very bad = 1). Results showed a good level of comfort during the trial with 17/22 patients giving scores always ≥4. Over the 88 sessions, 22 (25%) were perceived as excellent, 55 (62.5%) were good, 8 (9%) were neutral, and only 3 (3%) were bad and none were very bad.

neutral for 7/48 sessions (14.6%), bad for 3/48 sessions (6.2%), with no very bad experience (Fig. 4). The cause of discomfort that was pointed out most often in cohort A was the arm position (35%), followed by the face mask (27.5%), and then the ventilation itself (7.5%). But in 40%, no discomfort was reported at all. In cohort B, the face masks were most frequently pointed out (37.5%), followed by the ventilation (28.8%), and then the arm position (4.2%). In 29.2% of all the sessions, no discomfort was reported at all.

Using the VAS assessment, the 2 MANIV modes analysed in cohort A did not significantly degrade the comfort level compared to SP, with median VAS scores of 66 [49–71] for VC and 63.5 [49–69] for SH, versus 68.5 [49.75–79.25] for SP ($p = 0.93$). In cohort B, no significant differences were observed between DIBH and SL, with median VAS scores of 65 [50–67] and 59 [50–68] respectively ($p = 0.69$).

Discussion

This trial aimed to investigate whether MANIV could improve motion management in our department for breast and thoracic or upper-abdominal tumours. In comparison with our clinical routine, one training session was added prior to the simulation, but this did not delay the start of treatment. Patients could thereby get acquainted with MANIV in a quiet and dedicated session, keeping in mind that simulation and CT scanning can be major sources of anxiety [22]. Patients with different tumour sites (liver, lung, left breast), tumour stages (primary tumour versus metastasis), previous history of treatment (chemotherapy, surgery), or comorbidities (OSAHS, COPD, Cheyne-stokes disorder) were included in this trial. This allowed us to validate the feasibility of MANIV on a wide range of patients in real life conditions [23]. Since our trial design added 3 sessions to the usual treatment preparation (1 training session and 2 MRI sessions), only patients with sufficient performance status were included. Nevertheless, our results about tolerance and motion management supported the feasibility of a clinical implementation MANIV.

Our tolerance results agree with those observed with volunteers in our previous trial and those reported by West et al. [18,19], who assessed 2 shallow-controlled modes (20 and 25 bpm) with 10 healthy volunteers, although using higher FiO2 levels. All their subjects tolerated the procedure well with a low level of anxiety and normal oxymetric parameters. Parkes et al. also reported good tolerance results in a trial of mechanical ventilation to prolong breath holds in cancer patients [15]. We observed similar results. Our quantitative tolerance indicators measured normal SpO2, etCO2, and HR values, reflecting the absence of physiological stress. The qualitative tolerance indicator, based on a Likert scale, reached highly satisfactory values, without any trial interruption directly related to MANIV. The four interruptions that occurred at the first MRI session were indeed due to anxiety about MRI.

A main source of discomfort with MANIV was the face mask. This motivates its adaptation in future trials or practice. Another major source of discomfort was the treatment position, and more specifically the arm position. This should draw our attention to optimising patient positioning in all routine treatments requiring the elevation of the patients' arms. Ventilation discomfort was pointed out second in cohort B and third in cohort A. However, the VAS scales did not report any significant differences between the comfort of ventilation with spontaneous breathing or breath holding and the MANIV modes, suggesting that MANIV hardly affects comfort.

Tumour or breast motion results also agree with those of our previous trial or other investigators' trials on mechanical ventilation [18,19]. Unlike those, we directly assessed internal tumour or breast motion, not diaphragm motion.

In cohort A, VC significantly reduced the inter-session amplitude variations compared to SP (0.4 mm in VC versus 3.5 mm in SP, $p = 0.01$) and both the intra- and inter-session variations of RR by 35% ($p < 0.05$) and 95% ($p < 0.001$), respectively. With SH, a 2-fold increase in RR allowed for significant reductions of the median amplitude by 38.2%/6.1 mm ($p \leq 0.001$), compared to VC, and the BR variations by 45% ($p < 0.001$), compared to SP, both without any degradation of comfort. Even the patient with the Cheyne–Stokes disorder, for whom constraining breathing was more challenging, benefitted evidently from breathing regularization (Table 2, patient 3).

In cohort B, the repeated end-inspiratory plateaus achieved with the SL mode did not significantly differ from those obtained spontaneously in terms of intra- or inter-fraction range variation or baseline shift. The plateau duration obtained in this trial suffices already to allow for gating in some indications, such as breast radiotherapy. In comparison with our previous trial in which the plateau lasted for 11.1 s on average, median plateau duration was prolonged to 16.6 s without loss of comfort. Longer durations may be achievable, even more if we consider increasing FiO2 levels such as proposed by Parkes et al. [15], although this requires further investigation.

This trial demonstrates once again that the current use of motion mitigation strategies (margins, gating, tracking) with spontaneous breathing cannot be completely reliable. Analyses in SP showed large variations in breathing frequency and tumour amplitude within or between sessions. These changes may compromise treatment quality or efficiency [6]. The motion mitigation strategies may thus be made less critical in different ways when applied on top of MANIV.

Considering safety margin strategies first, they are used either to encompass in an ITV the different tumours positions over the breathing cycle or to integrate probabilistically these geometrical uncertainties directly into the computation of the PTV margin, around a mean time-weighted tumour position based on a midposition-CT [2,21]. However, both approaches necessarily result in large margins with futile irradiation to healthy tissues and are not robust against unexpected changes in the breathing/tumour motion patterns, if they are not observed during the short acquisition time of the 4D planning CT. Reducing both the motion amplitude and variability in time would translate into smaller and yet reliable margins. This provides the SH mode with an obvious application. This ventilation mode significantly reduced motion amplitude, compared to VC, as well as the intra- and inter-session variations of tumour amplitude, compared to SP. Even if 40% of the patients in our cohort had a slightly less ample tumour motion with SP, another 40% of the patients had significant tumour motion reduction with SH, while all patients benefited from the breathing regularization of the mechanical ventilation. This may also diminish occurrences of sighs or breathing pauses that cause significant tumours shifts. This is more often observed in pulmonary frail patients, such as observed in patient 3, who had a Cheynes–Stokes breathing disorder. Last, the SH mode failed to reduce the tumour baseline shift in this trial, although this was observed in our previous cohort of volunteers. This difference should be further investigated.

Deep-inspiratory breath hold is a gating technique used widely in left breast cancer treatment. Patients are taught to hold their breath to irradiate a nearly immobilized breast and also to reduce the dose exposure to an inflated lung and to the heart moved away from the breast. This technique is also increasingly considered for thoracic or upper abdominal tumours. However, spontaneous breath hold duration can hardly exceed 30 seconds. A treatment fraction delivery requires thus several BHs, ideally with the same breast or tumour position across BHs, in order to ensure accurate treatment delivery. Complementary techniques have been developed to address this issue, like verbal coaching of patients or the ABC technique (Active Breath hold Coordinator), connected to a spirometer guiding the patient towards reproducible BHs [12,24]. These techniques, however, require a good level of understanding from the patient, as well as their active involvement. Other techniques are also explored to prolong the BH duration beyond the treatment delivery time, to avoid reproducibility issue. Parkes et al. developed a technique prolonging BH for more than 5 min with mechanical ventilation [15]. Other approaches prolong apnea-like BHs up to 20 min with high-frequency or jet ventilation [14,16,25–27]. Although promising, the available studies mainly reported results about external motion surrogates, rather than internal or tumour motion, and involved mostly healthy volunteers. In this trial, we addressed tumour position reproducibility differently. Ensuring mechanically a reproducible position of the breast or the tumour across BHs could also facilitate gating. Our results showed that SL induced repeated plateaus with similar reproducibility (in range and intra-session baseline shift) as several DIBH performed with verbal coaching and free breathing breaks. Moreover, as these BHs are induced mechanically with end-inspiratory plateaus supported by the high pressure level, this technique requires little patient involvement. Neither early breaks in breath holding nor early drifts were observed in our cohort. This may also improve treatment efficiency as these events, when occurring during treatment, usually trigger early beam interruptions. This may be of particular interest for old or highly stressed out patients. However, future trials should aim to improve the end-inspiratory plateau stability across the repeated BHs, and especially to reduce their inter-session baseline shift variations.

Real-time tumour tracking can deliver accurate stereotactic treatments, regardless of motion amplitude. However, delivery can last longer than planned due to erratic and irregular breathing patterns, which reinitialise the internal-external correlation model [28]. The VC mode could address this issue by providing the most regular breathing pattern, particularly in comparison with SP. Thereby, it could improve treatment duration by reducing the frequency of correlation model updates, thereby also improving patient comfort. This should be investigated in future clinical trials.

Finally, other perspectives also appear for particle therapy. Dose deposition in these treatments may be affected dramatically by density changes along the beam path, and thus by unexpected changes in tumour position due to irregular breathing. Motion mitigation strategies are therefore even more crucial to ensure accurate treatment delivery. Strategies that allow for tumour position immobilization and gated treatment delivery are thus here highly interesting. SL may be considered.

Limitations of our trial are its current small population, and 2D nature of dynamic MRI.

First, even if this trial focused on several types of patients requiring a radiotherapy, our results may not be extrapolated to all patients. However, the breathing parameters in VC and SH modes were all individually adjusted according to physiological breathing parameters and individual comfort. This allows thus for flexibility and wider application. Regarding the SL mode, the high pressure level was progressively settled, allowing also for adjustments that ensure safety and individual comfort. Therefore, we believe that MANIV could be proposed to patients with more severe comorbidities, or with severe respiratory impairment, provided the ventilation parameters are carefully adjusted.

Second, our results are based on small cohorts of patients. For example, the baseline shift results tended to improve with MANIV, but not significantly. This may result from the lack of power of the statistical analyses. Larger cohorts would validate more firmly the potential of the abovementioned approaches, for different indications, in different centres. The ventilation protocol was therefore designed to be simple. MANIV was always performed using room-air (FiO2 21%) with a user-friendly ventilator (Bellavista 1000®), readily available on the market. The use of ventilators in radiotherapy departments does not require expensive additional material and should not prevent further and larger investigations.

Third, our results are conditioned by the 2D nature of dynamic MRI and the manual selection of the planes in which the tumour or the nipple was tracked. This manual operation limits the accuracy of the target tracking and the inter-session analyses.

In conclusion, this trial further validates the use of MANIV in a wide range of patients without loss of comfort. It also confirms that MANIV may safely complement motion mitigation strategies like

margins, gating, and tracking, by regularizing breathing in the first place. Each ventilation mode showed specific advantages in terms of breathing pattern regularization (volume-controlled) or modulation (shallow-controlled and slow-controlled modes), which could find dedicated applications in RT. Moreover, MANIV can be used in a large number of departments without increasing significantly the costs of equipment, software, or medical skills. MANIV may thus contribute to more accurate and personalised radiation treatments.

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.

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