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Orignal Article

Mechanically-assisted non-invasive ventilation: A step forward to modulate and to improve the reproducibility of breathing-related motion in radiation therapy

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ABSTRACT

Background and purpose: When using highly conformal radiotherapy techniques, a stabilized breathing pattern could greatly benefit the treatment of mobile tumours. Therefore, we assessed the feasibility of Mechanically-assisted non-invasive ventilation (MANIV) on unsedated volunteers, and its ability to stabilize and modulate the breathing pattern over time.

Materials and methods: Twelve healthy volunteers underwent 2 sessions of dynamic MRI under 4 ventilation modes: spontaneous breathing (SP), volume-controlled mode (VC) that imposes regular breathing in physiologic conditions, shallow-controlled mode (SH) that intends to lower amplitudes while increasing the breathing rate, and slow-controlled mode (SL) that mimics end-inspiratory breath-holds. The last 3 modes were achieved under respirator without sedation. The motion of the diaphragm was tracked along the breathing cycles on MRI images and expressed in position, breathing amplitude, and breathing period for intra- and inter-session analyses. In addition, end-inspiratory breath-hold duration and position stability were analysed during the SL mode.

Results: MANIV was well-tolerated by all volunteers, without adverse event. The MRI environment led to more discomfort than MANIV itself. Compared to SP, VC and SH modes improved the inter-session reproducibility of the amplitude (by 43% and 47% respectively) and significantly stabilized the intra- and inter-session breathing rate ($p < 0.001$). Compared to VC, SH mode significantly reduced the intra-session mean amplitude (36%) ($p < 0.002$), its variability (42%) ($p < 0.001$), and the intra-session baseline shift (26%) ($p < 0.001$). The SL mode achieved end-inspiratory plateaus lasting more than 10 s.

Conclusion: MANIV offers exciting perspectives for motion management. It improves its intra- and inter-session reproducibility and should facilitate respiratory tracking, gating or margin techniques for both photon and proton treatments.

Radiotherapy of mobile tumours entails many challenges due to the uncertainties of the target position caused by breathing. Indeed, the breathing amplitude and frequency may deeply and unexpectedly vary from cycle to cycle, as they are subject to deep conscious and unconscious variations. These changes can occur either within a same treatment fraction (intra-fraction variation), or from one day to another (inter-fraction variation). In proton-therapy, the uncertainties in target position are even worsened by the proton range variations within the crossed tissues and the interplay effect (the interferences between the target motion and the spot scanning beam) that can unpredictively distort the dose distribution. This may jeopardize the radiation therapy (RT) accuracy, with potential detrimental effect on the treatment outcomes [1,2].

Therefore, many motion mitigation strategies have been established. Some are simple to implement (safety margins), whereas others require advanced technological skills (real-time tracking, respiratory gating) [3,4]. But they still can be impaired to varying

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degrees. For example, large variations in breathing pattern or baseline shifts (changes in average position over time) can make the planning 4D-CT unreliable [5–7]. Regarding tracking and gating strategies with coupled internal and motion surrogates, an erratic breathing movement results in longer treatment times and discomfort for the patient. This problem is also a strong limiting factor for tracking in proton-therapy because of the system's response delay while changing the energy of the beams. Even audio/visual coaching that attempts to regularize the breathing pattern still leaves some variations of the breathing pattern, and critically depends on patient's compliance [8].

In order to address this complex issue, mechanically-assisted ventilation can be applied to take complete control of the breathing. However, conventional ventilation or even specific ventilation techniques such as High Frequency Ventilation (HFV) performed under anaesthesia are demanding and invasive approaches [9,10]. As an alternative, non-invasive ventilation techniques have been investigated. Peguret et al. proposed radiation treatments under High Frequency Percussive Ventilation that allowed prolonged apnoea-like breath-holds without sedation. Parkes et al. demonstrated that mechanically-assisted non-invasive ventilation (MANIV) using conventional ventilators was feasible, allowed to prolong breath-holds over 5 min after a preparatory mechanically-assisted hyperventilation, and doing so, regularized the breathing pattern [11–14].

The purpose of our study was to further explore MANIV aiming to broaden the scope of its use beyond the breath-hold application. MANIV may offer a good compromise between spontaneous breathing and general anaesthesia as it requires no sedation and relies on the ventilator ability to completely constrain the tidal volume and the breathing frequency. This concept might thus considerably simplify all motion management strategies in both photon- and proton-therapy.

Different ventilation modes were investigated on volunteers, aiming to stabilize and also modulate the breathing pattern for the needs of specific and personalized respiratory-synchronized techniques.

Materials and methods

Ethics

This trial has been carried out on healthy volunteers in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, approved by our local ethics committee (B403201732715) and registered in ClinicalTrials.gov (NCT03226925) [15]. Informed consent was obtained from all participants before to start the trial.

Design

This was a 3-step-trial: (1) coaching session, (2) MRI session 1 and (3) MRI session 2 (Fig. 1). During the coaching session, the volunteers were positioned in the simulation room with the arms above the head, a customized head holder and triangle-shaped pillow under the knees. They were connected to the mechanical ventilator (imtmedical AG, Bellavista 1000®) through a facial mask covering the mouth and nose (Fig. 1). The MRI were acquired with

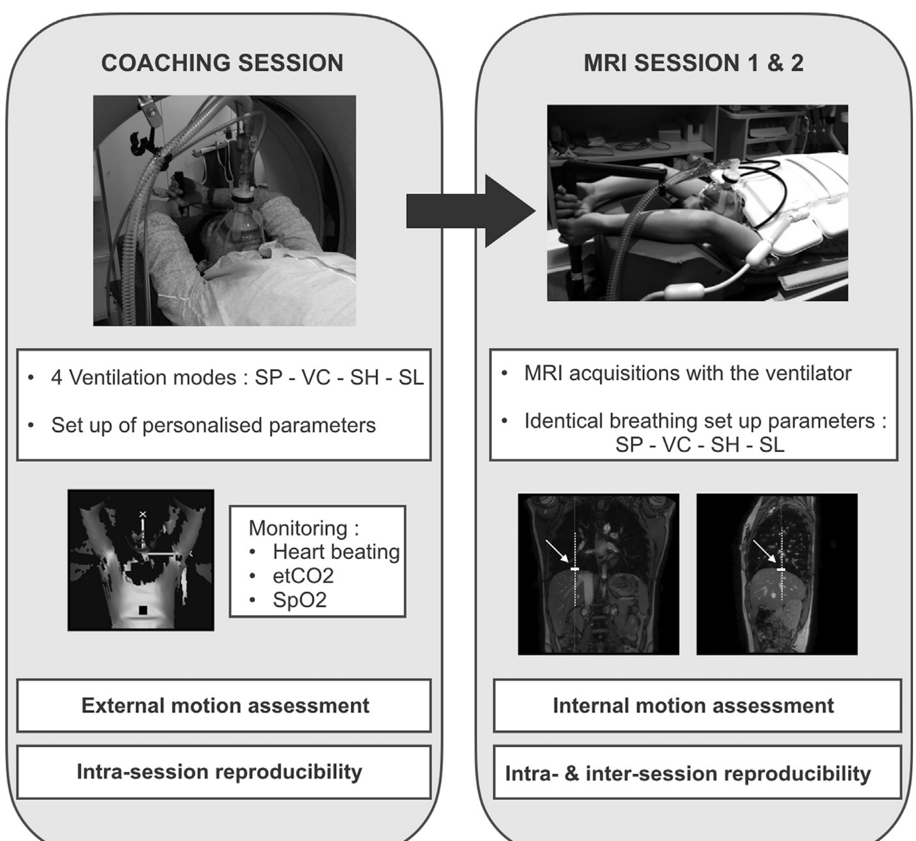

Fig. 1. Trial design. During the coaching session in the simulation room, all the volunteers were familiarized with the ventilator and the different ventilation modes (SP: Spontaneous breathing – VC: Volume-controlled ventilation mode – SH: Shallow-controlled ventilation mode – SL: Slow-controlled ventilation mode). The external motion was measured with an infra-red surface camera (GateRT®, VisionRT®). Personalized breathing parameters on the ventilator were defined during the coaching session then applied identically during the 2 MRI sessions to assess the intra- and inter-session reproducibility of the motion under ventilation. Coronal and sagittal images were alternated every minute for 16 min during each MRI in order to track the diaphragm (arrow on MRI images) in 3 directions.

the ventilator in order to observe the internal motion that was subsequently quantified and analysed.

Mechanically-assisted non-invasive ventilation

The following ventilation modes were successively assessed (Fig. 2):

Volume-controlled mode (VC): this mode is generally used to constrain the tidal volume and the breathing rate. In this trial, it attempted to impose a regular breathing pattern in physiologic conditions. Tidal volume and breathing rate parameters were first determined from individual spontaneous breathing observation, reported on the ventilator and fine-tuned to improve the volunteer's tolerance.

Shallow-controlled mode (SH): this mode is a variation of the previous one. Keeping the minute ventilation (the volume of gas exchanged per minute) constant to respect individual metabolic needs, the breathing rate (BR) was accelerated up to 30 breaths per minute (bpm) while the tidal volume was reduced proportionally. As a result, this mode would allow to reduce the internal motion amplitude.

Slow-controlled mode (SL): This mode is an adaptation of the bi-level positive pressure ventilation mode of the ventilator. It intended to mimic constrained and repeated short breath-holds (<15 s). The breath rate was set at 3 breath-holds per minute, with 3 end-inspiratory plateaus per minute. The high pressure level (18 mbar) imposed the end-inspiratory breath-hold, while the low level of pressure (0–2 mbar) allowed the exhalation.

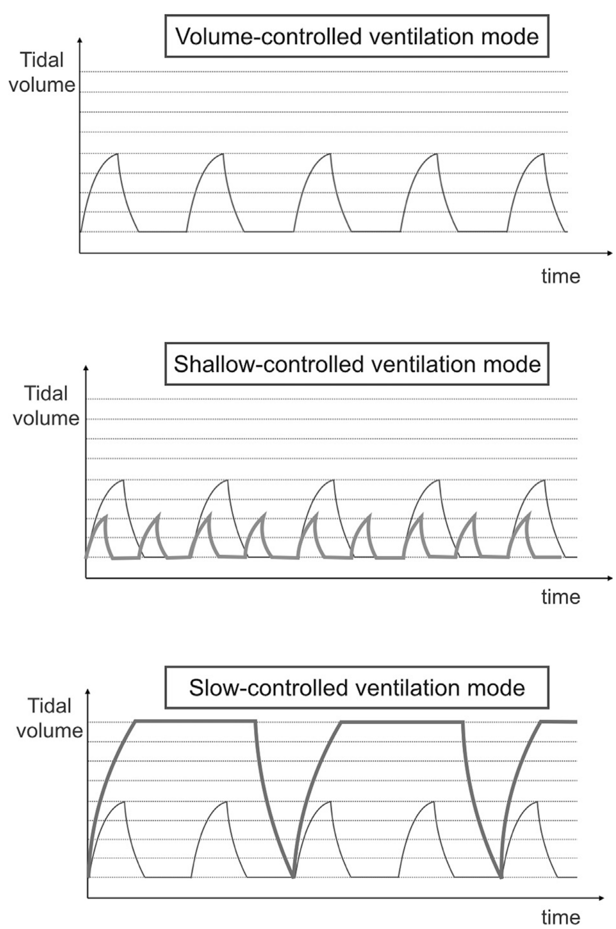

Fig. 2. Mechanically-assisted non-invasive ventilation modes. Three different ventilation modes were evaluated during this trial: (A) The Volume-controlled ventilation mode stabilized the breathing pattern with constrained but individualized tidal volume and breathing rate, (B) The Shallow-controlled ventilation mode accelerated the breathing rate and reduced the motion amplitude. (C) The Slow-controlled ventilation mode created repeated and long-lasting end-inspiratory plateaus.

The spontaneous breathing (SP) of each volunteer was recorded prior to the mechanically-assisted ventilation modes to serve as reference for comparison purposes. Volunteers were asked to breathe normally, without connection to the ventilator or any coaching.

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 coaching session (objective tolerance assessment). Subjective assessment was based on a five-point scoring scale (5 = excellent; 4 = very good; 3 = good; 2 = bad; 1 = very bad) rated after each ventilation mode on MRI. The volunteers scored both their general comfort (MRI environment, noise, mask, position) and their specific ventilation-related comfort.

External motion quantification

During the coaching session (Fig. 1), the external motion was measured with an infra-red surface camera (GateRT®, VisionRT®) from a tracked point positioned close to the xiphoid process at the base of the thoracic surface. The position variations of the tracked point were registered by the camera as a function of time. The detection of consecutive minima and maxima determined the peak-to-peak motion amplitude. Only intra-session variations of the motion were assessed as external measures were only performed once (VisionRT® not available on MRI device).

Internal motion quantification

The volunteers were scanned with dynamic MRI (3T, Ingenia, Philips Healthcare, Best, the Netherlands) using a single-slice Balanced Turbo Field Echo (bTFE) sequence with a slice thickness of 7 mm. To allow 3D motion assessment, images were acquired on 2 perpendicular slices (coronal and sagittal) that were manually selected based on well-identified anatomical structures (vascular cross points). Dynamic MRI images were then acquired alternatively on coronal and sagittal slices every minute, for a total of 16 min. This acquisition time was set to be representative of a usual radiotherapy treatment slot duration (including IGRT and treatment time delivery).

Three sagittal and four coronal images per second were acquired, corresponding to 3360 images by 16-min-MRI. A dynamic MRI was acquired for each ventilation mode (SP – VC – SH – SL). Images were then played in a cinema-mode to quantify the breathing-related internal motion. After the first session (MRI 1), the acquisitions were all repeated over a few days (MRI 2) to assess the inter-session reproducibility of the internal motion.

The motion analyses were performed afterwards on the MRI images with an in-house tool allowing to track the motion of a single-point selected along a 1D-navigator manually placed on the images across the diaphragm. This point was first placed on the coronal slices and then automatically reported by the in-house tool on the corresponding sagittal slices (Fig. 1).

Motion parameters of the diaphragm were measured, including breathing amplitude (peak-to-peak distance between end-exhalation and end-inhalation position of each breathing cycle) and breathing period. The results were expressed by mean ± 1 SD (standard deviation). Their spread (minimal and maximal values) within a given mode is reported in Table 1. Their reproducibility during each MRI session (intra-session reproducibility) and between MRI sessions (inter-session reproducibility) was also analysed. For the SL mode, the duration and the range (difference

Table 1
Intra- and inter-session motion and baseline shift analyses for Spontaneous breathing (SP), Volume-controlled (VC) and Shallow-controlled (SH) ventilation modes.

A. INTRA-SESSION motion analyses								
Amplitude (mm)	External				Internal			
	Mean	SD	Min	Max	Mean	SD	Min	Max
SP	/	/	/	/	20.2	7.4	9.1	58.5
VC	3.5	0.4	1.7	6.1	30.5	8.1	16.5	56.4
SH	1.8	0.2	1.0	2.8	19.4	4.7	8.0	39.9
Period (sec)	External				Internal			
	Mean	SD	Min	Max	Mean	SD	Min	Max
SP	/	/	/	/	4.1	0.5	2.6	11.6
VC	5.6	0.2	3.5	7.5	5.5	0.2	3.5	7.5
SH	2.0	0.1	2.0	2.0	2.0	0.2	2.0	3.7
Baseline shift (mm)	External				Internal			
	Mean	SD	Min	Max	Mean	SD	Min	Max
SP	/	/	/	/	4.6	2.2	1.6	11.1
VC	2.3	1.3	0.4	4.7	5.0	2.9	1.1	16.2
SH	1.8	1.2	0.4	3.4	3.7	2.0	0.5	10.4

B. INTER-SESSION motion analyses (MRI 1 – MRI 2)						
Amplitude (mm)	Mean	Min	max	SD	Min	Max
SP	5.3	0.5	13.2	1.7	0.1	8.9
VC	3.0	0.1	6.3	1.0	0.2	3.3
SH	2.8	0.5	8.6	0.8	0.2	2.8
Period (sec)	Mean	Min	max	SD	Min	Max
SP	0.8	0	2.3	0.2	0	0.8
VC	0	0	0.1	0	0	0.1
SH	0	0	0.2	0	0	0.1
Baseline shift (mm)	Cranio-caudal direction			Left-right direction		
	Median	P25	P75	Median	P25	P75
SP	9.1	4.0	14.0	4.7	1.5	7.1
VC	5.2	2.6	10.0	3.4	0.8	7.1
SH	3.5	1.8	8.5	4.4	1.4	10.7

SD: standard deviation; Min: minimum; Max: maximum

between the maximal and minimal positions) of each end-inspiratory plateau were recorded and expressed by mean ± 1SD [min – max]. Finally, baseline shifts were measured. Within each MRI, the position of the tracked point was averaged every minute (16 mean positions). The distance between the maximal and minimal mean positions corresponded to the intra-session baseline shift. Inter-session baseline shifts analyses were addressed differently. For each MRI, the position of the tracked point was averaged over the 16 min (1 mean position per MRI) and compared to the average position of the second MRI-session. In order to compare these average positions properly (as the frame settings differed from one to another MRI session), the distance between a same fixed vertebral body and the tracked point were recorded, and decomposed into left–right (LR) and cranio-caudal (CC) components. Shifts were expressed in millimetres.

Statistical analysis

Motion parameters were compared between the different ventilation modes for global and individual results using a mixed model (with the mode as fixed effect and the patient as random effect) since several measurements were performed on the same subject. The global effect of the mode was assessed using a Type III test, while the effect of each mode (compared to a reference mode) was assessed using *t*-test on the corresponding coefficient. Bonferroni correction was used to counteract the multiple comparisons for individual analyses.

Some data were excluded from our analyses. First, aberrant data corresponding to swallowing (3.6% of the whole time during SP, 1.7% during VC, 4.5% during SH) were excluded. Second, some banding artefacts were observed on MRI images within the tracked area. These artefacts are typically induced by the use of rapid dynamic MRI sequences (bTFE) [16]. They hindered the inter-session baseline shift analysis from sagittal slices in SP, VC, SH modes and from coronal slices in SL mode for 151680 out of 322560 images (47% of the whole images). The results from the inter-session baseline shift analyses were therefore expressed in median and quartiles (Median [P25–P75]).

Results

Volunteers

Between June and August 2017, twelve volunteers were enrolled in this trial, 5 women and 7 men, aged from 26 to 60 years old. One was a former smoker, and another an active smoker. None of them presented any active comorbidity and all had a very good performance status (ECOG 0).

Tolerance

MANIV was well-tolerated by all the volunteers. The whole cohort went through the different ventilation sessions without any interruption or adverse event. During the coaching session, none of the volunteers experienced neither hypoxaemia nor hypo- or hyper-capnoea. SL induced the greatest variations, although mean deviations remained below 1% of SpO2, 2% of etCO2, and 8 beats per minute for HR. On average, general and

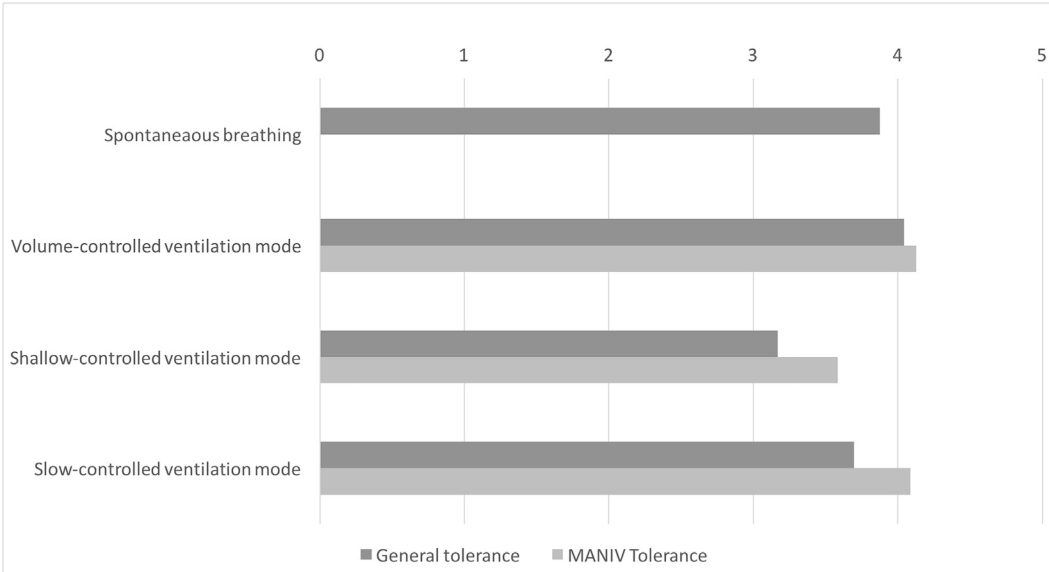

Fig. 3. Mean general and ventilation-specific tolerance scores. After each step of the trial, the volunteers rated their general and ventilation comfort on this 5-items scoring scale (1 = very bad; 2 = bad; 3 = good; 4 = very good; 5 = excellent). On average, all the ventilation modes were scored by the volunteers with at least a "good" level of tolerance.

ventilation-specific comfort were both scored as "good" (mean scores >3/5) (Fig. 3). VC obtained the best scores (general tolerance: 4.0/5 – ventilation-specific tolerance: 4.1/5), followed by SL (general tolerance: 3.7/5 – ventilation-specific tolerance: 4.1/5) then SH (general tolerance: 3.2/5 – ventilation-specific tolerance: 3.6/5). SP got a score of 3.9/5 for general tolerance. The MRI environment (noise, vibes, tight space) was the main reason of discomfort (incriminated in 29% of cases), followed by the facial mask (25%) and the position (21%), far ahead the ventilation itself (8%).

Motion analyses for SP, VC and SH modes

Amplitude (Table 1, Fig. 4)

Intra-session: Regarding internal motion, the average amplitude was 20.2 ± 7.4 mm in SP, 30.5 ± 8.1 mm in VC and 19.4 ± 4.7 mm in SH. The amplitudes in SP were smaller than in VC although we expected comparable motion ($p = 0.04$) but SP was consistently associated with higher BR. Switching from VC to SH led to a mean amplitude reduction of 36% (11.1 mm) ($p \leq 0.002$) and an absolute reduction of its variability of 42% (3.4 mm) ($p < 0.001$). As shown in Table 1, external motion analyses showed comparable results.

Inter-session: The mean inter-session variations in amplitude were 5.3 ± 1.7 mm in SP, 3.0 ± 1.0 mm in VC and 2.8 ± 0.8 mm in SH. Therefore, MANIV reduced inter-session variations compared to SP, although non-significantly. Five volunteers had an inter-session variation greater than 5 mm in SP, with three of them exceeding 10 mm. By comparison, only three had variations higher than 5 mm in VC and two in SH, but none of them exceeded 10 mm.

Period (Table 1)

Intra-session: The mean intra-session breathing period was 4.1 ± 0.5 s in SP, 5.5 ± 0.2 s in VC and 2.0 ± 0.2 s in SH. MANIV imposed a very regular breathing period with only 5% difference between the observed and expected periods in VC, and 1% in SH. It also reduced the individual variability by 67% compared to SP ($p < 0.001$).

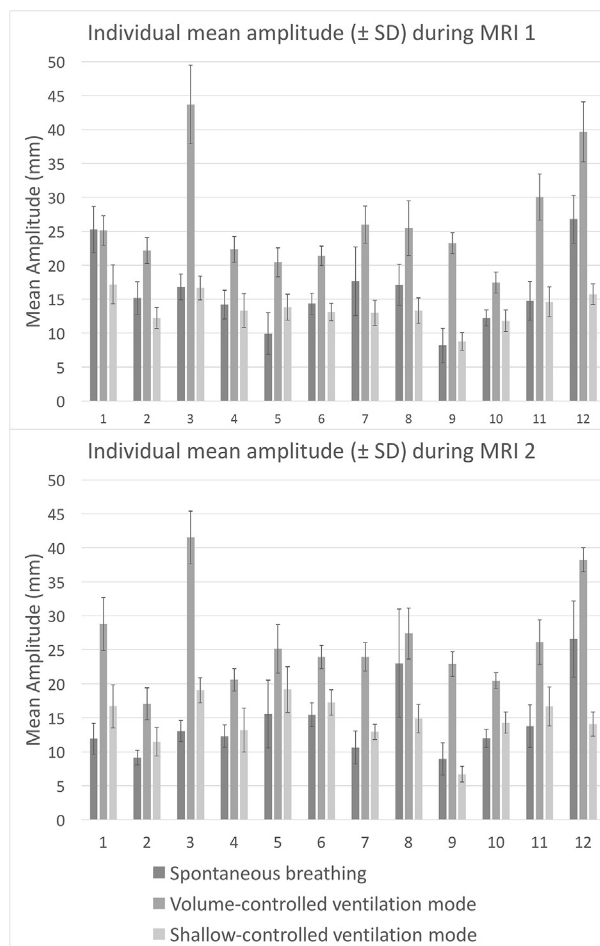

Fig. 4. Mean amplitudes of the internal motion by ventilation mode for the twelve volunteers during the 2 MRI sessions. Motion amplitudes and intra-/inter-session variabilities were significantly reduced when switching from the VC to the SH mode.

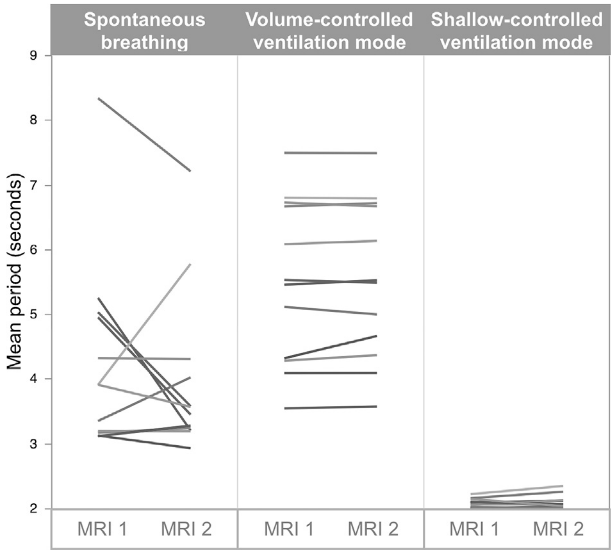

Fig. 5. Mean breathing period by ventilation mode for the twelve volunteers during the 2 MRI sessions. MANIV modes dramatically improved the period reproducibility from MRI 1 to MRI 2 ($p < 0.001$). No significant period difference was observed with the Volume-controlled or the Shallow-controlled ventilation modes.

Inter-session: The mean inter-session differences in breathing periods were 0.8 ± 0.2 s in SP, whereas there was no significant difference for VC or SH. MANIV with VC and SH dramatically reduced the inter-session period variations compared to SP ($p < 0.001$) (Fig. 5).

Baseline shift (Table 1)

Intra-session: Compared to the mean baseline shift in SP (4.6 ± 2.2 mm) and in VC (5.0 ± 2.9 mm), the mean baseline shift in SH was significantly reduced (3.7 ± 2.0 mm) ($p < 0.001$). Interestingly, 81% of the baseline shifts were smaller than 5 mm in SH, while only 58% in VC and 69% in SP.

Inter-session: Although non-significant, a trend towards better reproducibility was observed with MANIV in the CC direction, since the smallest variations were observed in SH followed by VC and then SP ($p = 0.69$). The CC median baseline shifts were 9.1 mm [4.0–14.0] in SP, 5.2 mm [2.6–10.0] in VC and 3.5 mm [1.8–8.5] in the SH mode. The LR median baseline shifts were 4.7 mm [1.5–7.1 mm] in SP, 3.4 mm [0.8–7.1] in VC, and 4.4 mm [1.4–10.7] in SH.

Motion analyses for SL mode

Intra-session

The mean duration of the end-inspiratory plateaus was 11.1 ± 0.8 s [9.0–13.2]. The mean range of the plateaus was 4.9 ± 3.8 mm [0.7–23.9] with 90% having a range below 10 mm. The mean baseline shift was 10.7 ± 5.6 mm [3.6–25.7].

Inter-session

The median inter-session baseline shift was 0.6 mm [0.1–2.5] in the LR direction and 8.2 mm [2.2–11.8] in the CC direction.

Discussion

In this trial, we confirmed that MANIV could safely be applied in a non-invasive way on unsedated subjects, but we also demonstrated that MANIV applications can be extended beyond the previous experiments done with mechanical ventilators.

Regarding the safety, we never had to interrupt the ventilation for hypoxaemia or hypo/hypercapnia. Our good safety results echo with those previously reported by Parkes when using mechanically-assisted ventilation to induce hyperventilation in order to prolong apnoea [12–14]. In contrast to our approach, Parkes wanted to induce hypocapnoea and defined the setup parameters in order to exceed the metabolic rate. Since our parameters were rather set to respect the metabolic needs of each subject, no significant fluctuation in oximetry were observed whatever the ventilation mode.

In addition, the three ventilation modes assessed in our study had a favourable impact on motion characteristics.

The VC mode, which was designed to stabilize the breathing-related motion in comfortable and physiologic conditions, achieved very stable breathing periods compared to SP within a same session (mean intra-session SD of ±0.2 s vs ±0.5 s) and between sessions (mean inter-session period and SD of 0 ± 0 s vs 0.8 ± 0.2 s). It also tended to reduce inter-session motion amplitude variability (mean inter-session variation of 3.0 ± 1.0 mm vs 5.3 ± 1.7 mm) and baseline shifts (5.2 mm vs 9.1 mm in CC and 3.4 mm vs 4.7 mm in LR), although those results were not statistically significant.

The SH mode had the same stabilizing effect on the breathing period than VC, but further lowered the inter-session variability of the motion amplitude compared to SP (2.8 mm ± 0.8 mm vs 5.3 ± 1.7 mm) and the inter-session baseline shift (3.5 mm vs 9.1 mm in CC and 4.4 mm vs 4.7 mm in LR). Furthermore, the modulation of the breathing pattern with accelerated BR significantly reduced the intra-session motion amplitude compared to VC (19.4 ± 4.7 mm vs 30.5 ± 8.1), and the intra-session baseline shift (3.7 ± 2.0 mm vs 5.0 ± 2.9 mm) without significant loss of comfort.

Last, the SL mode achieved repeated end-inspiratory breath-holds lasting for more than 10 seconds (11.1 ± 0.8 s [9.0–13.2]) and was also well tolerated. In contrast to voluntary breath-hold, which relies on audio-visual instructions, the bi-level positive pressure ventilation mode mechanically constrains the high and low levels of pressure and subsequently the inflation volume throughout these plateaus.

Depending on their specific characteristics, these ventilation modes can have dedicated applications for the motion management strategies in radiotherapy.

Firstly, since the ventilator imposes a more reproducible and more predictable breathing pattern between sessions, and thus potentially also between the simulation and the treatment, VC and SH would considerably enhance the reliability of the planning 4D-CT, from which most of motion management techniques are derived.

Secondly, the stabilized breathing pattern achieved with VC and SH may also facilitate the implementation of respiratory-synchronized techniques such as real-time tracking or respiratory gating, for which the efficiency critically depends on the motion reproducibility and tumour position predictability. The breathing curves from the ventilator could also provide a more reliable input to trigger these respiratory-synchronized techniques.

Thirdly, SH may also benefit to strategies that rely on safety margins, such as the ITV, the mid-position and mid-ventilation [3]. The reduced motion amplitude and baseline shift achieved under SH ventilation will translate into smaller safety margins, and thus better preservation of the surrounding healthy tissues [7]. This will mostly benefit to stereotactic RT of lung or liver tumour, that requires a high level of accuracy in anatomical regions subject to large motion. Knowing that most RT centres are using margins to account for tumour motion, as it does not require any dedicated and expensive equipment or advanced skills, this could have a large clinical impact. Furthermore, smaller motion amplitudes are even more critical for PT, to limit its impact on range uncertainties and the interplay effects when Pencil Beam Scanning is considered [17–19].

Lastly, respiratory gating would also directly benefit from reproducible and long-lasting plateaus obtained with SL that would facilitate the delivery of photons or protons within prolonged gating windows, with less patient involvement and increased reproducibility. Furthermore, SL could be implemented easily as it does not require training or any prior conditioning. However, further investigations to increase the plateaus duration up to 20 s would be interesting.

One may argue that the largest motion amplitude observed with VC compared to spontaneous breathing might be detrimental. However, this observation should be interpreted with caution. The environmental stress, and more specifically the MRI-driven anxiety, might have affected the non-constrained spontaneous breathing. This could explain the higher spontaneous BR observed during the MRI acquisitions (mean BR = 16 bpm) compared to the coaching session (mean BR = 12 bpm), and subsequently the reduced motion amplitudes in SP during the MRI acquisitions.

MANIV achieved thus interesting results to stabilize but also modulate the breathing. So far, other techniques already tried to stabilize the breathing pattern but yielded contradictory results. Goldstein et al. have demonstrated that Continuous Positive Airway Pressure (CPAP) devices could significantly reduce motion amplitude by providing a constant stream of pressurized air with the objective to hyper-inflate the lungs, and thereby flatten and stabilize the diaphragm. But Di Perri et al. failed to confirm any impact of it on tumour motion and baseline shift [20,21]. Considering the breath-hold approach, current techniques (voluntary breath-hold, audio and/or visual coaching for breath-hold, or breathing-volume based method with the use of a spirometer) are mostly used to allow better heart sparing during breast irradiation. But these techniques may lack of reproducibility and often request a high level of compliance or understanding from the patients [22–24].

Other perspectives are also under investigation regarding motion management in radiotherapy. High Frequency Ventilation (HFV) or Jet ventilation consists in administrating very small volumes of air at a higher level of pressure and frequency in an attempt to freeze tumour motion and get rid of most motion uncertainties during "Apnoea-like breath-hold" [9–11]. Mechanically-assisted hyperventilation followed by prolonged apnoea is another technique that is also currently developed [12–14]. The ultimate goal of these approaches is to completely get rid of the breathing motion, making the current motion management strategies useless. But so far, these techniques seem more demanding with multiple training sessions, and pre-ventilation conditions (hyperventilation inducing hypocapnoea and/or hyper-oxygenation) [11,12].

This trial however had some cohort-driven, methodological and technical limitations. Regarding our cohort, only healthy volunteers were included for safety reasons. Our results cannot simply be extrapolated to real patients for many reasons. First the motion was quantified from the diaphragm, which is not directly comparable to tumours and has a greater motion. However, it is the main driver of the breathing and is often considered as a good surrogate for motion tracking. Second, patients treated for thoracic or upper abdominal tumours usually have a higher level of stress and (severe) comorbidities, particularly when the indication of radiotherapy relies on surgical contra-indications [25]. They frequently present with impaired respiratory function that can be associated with lung hyperinflation due to air trapping and chronic impairment in respiratory mechanics impacting the diaphragm, the chest wall and the respiratory muscles [26]. Therefore, their breathing pattern could be less stable. However, the use of MANIV might allow to adjust the ventilation parameters according to individual patient's tolerance level, with an optimal setting tailored to each patient's needs.

From a methodological point of view, we willingly excluded swallowing from our data, to focus our analysis on how MANIV interfered with the breathing pattern. Actually, swallowing only occurred during a small proportion of time, varying from 1.7% during VC to 4.5% during SH. These values are similar to those observed during spontaneous breathing (3,6%) or reported in the literature for head and neck patients [27–29]. For example, Bahig et al reported that swallowing occurred during 2.3% of the treatment time (range 0.0–10%) [27].

Stress and anxiety are other factors that may influence the respiratory pattern [30–33]. Dedicated anti-stress techniques might further improve the stability and reproducibility of all mechanically-assisted ventilation modes.

Another methodological limit is the high level of pressure used for the SL mode. It was empirically set to 18–20 mbar. At this level, intra- and inter-session variations of the plateaus were probably linked to the imbalance between the inflating forces and the chest wall resistance. Stepping this high level of pressure down and tailoring it individually during the coaching session would potentially enhance the reproducibility of breath-holds.

Finally, our results were technically limited by the 2D nature of dynamic MRI acquisition, where 3D analyses would have been more accurate, but were not yet available. These images included also some degree of inaccuracy. The initial selection of the 2 orthogonal slices on MRI was manually determined based on well-recognizable anatomical structures (vessel embranchments). This manual procedure may introduce uncertainties in the reselection of the tracked slices during the second MRI acquisition.

In conclusion, mechanically-assisted non-invasive ventilation is a safe and promising technique to improve our current respiratory-related motion management strategies. It does not only improve the stability of the breathing pattern, but also allows its modulation for the needs of specific and personalized radiation treatment in photon- and in proton-therapy. Further investigations on patients are still needed to confirm these results for moving tumours of the breast, lung and upper abdomen and to properly select the indications.

Conflicts of interest statement

All the authors declare they have no conflict of interest.

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