Mechanically-assisted non-invasive ventilation: an innovative step forward for radiation therapy of moving tumours

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Abstract
Background and purpose: Radiotherapy of mobile tumors could greatly benefit from a stabilized breathing for a wide range of motion management techniques (margins, gating, tracking). 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 and expressed in position, amplitude, period and plateaus for intra- and inter-session analysis.
Results: Compared to SP, VC and SH modes increased 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%), and the intra-session baseline shift (26%) ($p<0.001$). The SL mode achieved end-inspiratory plateaus lasting more than 10 seconds. MANIV was well-tolerated by all volunteers, without adverse event. The MRI environment led to more discomfort than MANIV itself.
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.

Highlights
- Mechanically-assisted non-invasive ventilation can safely stabilize and modulate the breathing pattern
- Volume-Controlled mode stabilizes the breathing pattern under physiological conditions
- Shallow-controlled mode lowers the motion amplitude by increasing the breathing rate
- Slow-controlled mode creates end-inspiratory plateaus and mimics breath-hold
- Photon- and proton-therapy could both benefit of this active breathing management technique to improve intra and inter-session reproducibility and to facilitate the current motion mitigation techniques.

Keywords: motion mitigation, ventilation, intra-fraction, inter-fraction

Conflicts of interest: all the authors declare they have no conflicts of interests.

Introduction

Radiotherapy of mobile tumours entails many challenges due to the uncertainties of the target's position caused by breathing. In proton-therapy, these uncertainties are even worsened by the proton range variations within the crossed tissues. This may jeopardize the radiation therapy (RT) accuracy, with potential detrimental effect on the treatment outcomes [1, 2].

Many motion mitigation strategies have been established, from simple to implement (safety margins), to technologically advanced (tracking with correlation between internal and external markers) [3, 4]. But they still can be impaired to varying 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.

So far, the breathing changes in amplitude and rate may deeply and unexpectedly vary from cycle to cycle, either within a same treatment fraction (intra-fraction variation), but also from one day to another (inter-fraction variation). The respiratory-related motion of thoracic or upper abdominal tumours is indeed a complex phenomenon subject to deep conscious and unconscious variations. Even audio/visual coaching that attempts to regularize the breathing pattern still faces some variations of the breathing pattern, and critically depends on patient's compliance [8].

Mechanically-assisted non-invasive ventilation (MANIV) is an innovative promising concept that could considerably simplify all motion management strategies in both photon- and proton-therapy. This approach was first proposed by Michael J Parkes et al who have demonstrated its feasibility in non-sedated patients with striking results in breathing pattern stabilization and tolerance [9, 10]. The purpose of this study was to further explore the impact of MANIV on both internal and external motions in non-sedated volunteers, meanwhile assessing its tolerance. Different ventilation modes were investigated, aiming to stabilize and also modulate the breathing patterns 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 ethical committee (B403201732715) and registered in ClinicalTrials.gov (NCT03226925) [11]. Informed consent was obtained from all participants before to start the trial.

Design

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

Mechanically-assisted non-invasive ventilation

The following ventilation modes were successively assessed (Figure 2):
Spontaneous breathing (SP): in this mode, the volunteers breathed spontaneously without any connexion to the ventilator nor any coaching. This mode was considered as the reference ventilation mode to which the mechanically-constrained ventilation modes were compared.
Volume-controlled mode (VC): it attempted to impose a completely regular breathing pattern in physiologic conditions by constraining the tidal volume and the breathing rate with the ventilator. Individual spontaneous breathing parameters were first recorded, then reported and fine-tuned in the volume-controlled mode on the ventilator to improve the volunteer's tolerance.

Shallow-controlled mode (SH): it intended to reduce the internal motion amplitudes by accelerating the breathing rate (BR) up to 30 breaths per minute (bpm). The metabolic needs and thus the minute ventilation (the volume of gas exchanged per minute) of each volunteer were respected, while taking into account the death space.
Slow-Controlled mode (SL): it intended to mimic constrained breath-holds, using a bi-level positive pressure ventilation mode. Prolonged end-inspiratory plateaus were imposed through the high pressure level with 3 plateaus per minute.

External motion quantification

During the coaching session (Figure 1), the external motion was measured with an infra-red surface camera (GateRT, VisionRT) from a reproducible region of the base of the thoracic surface. The position variations were registered in 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 during the coaching session.

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. Coronal and sagittal slices were manually selected based on well-identified anatomical structures (vascular cross-points) and alternated every minute. MRI acquisitions lasted for 16 minutes for each ventilation mode (SP – VC – SH – SL). This acquisition time was set to be representative of a usual radiotherapy treatment slot duration (including IGRT and treatment time delivery). After a first session (MRI 1), the acquisitions were repeated over a few days (MRI 2) (Figure 1).
We used an in-house tool to track the motion of a single-point selected along a 1D-navigator manually placed across the diaphragm. This point was first placed on the coronal slices and then automatically reported on the corresponding sagittal slices.
Motion parameters including amplitude and period were measured. Their mean (± standard deviation SD), minimal and maximal values were reported. Their reproducibility during each MRI session (intra-session reproducibility) and between MRI (inter-session reproducibility) were then analysed. For the SL mode, the duration and the range (difference between the maximal and minimal positions) of each end-inspiratory plateau were recorded.
Finally, intra- and inter-sessions baseline shifts (changes in average position over time or between the 2 MRI) were also quantified. The latter was based on difference in mean distances between the tracking point and a fixed vertebral body, and was decomposed into left-right (LR) and cranio-caudal (CC) components.

Tolerance assessment

Pulsed Oxygen Saturation (SpO_2), end-tidal Carbon Dioxide ($etCO_2$) and heart rate (HR) were monitored with a pulsed oximeter and $etCO_2$ detector (Bellavista 1000®) during the coaching session (objective tolerance assessment). Subjective assessment was based on a five-points scoring scale (5 = excellent; 4 = very good; 3 = good; 2 = bad; 1 = very bad) completed after each ventilation mode on MRI. The volunteers could score their general comfort (MRI environment, noise, mask, position) and their specific ventilation-related comfort.

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. In addition, the spread of the data within a given mode were also reported. These results were expressed by mean ± 1SD [min-max].

Some data were excluded from our analyses, either for MRI artefacts within the tracked area (sagittal slices in SP, VC, SH modes and coronal slices in SL mode for the inter-session baseline shift analysis), or aberrant data corresponding to swallowing (3.6% of the whole time during SP, 1.7% during VC, 4.5% during SH). Due to the paucity of data for the inter-session baseline shift analysis, these results were expressed in median and quartiles (Median [P25 – P75]).

Results

1. 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).

2. Motion analyses for SP, VC and SH modes

2.1. Amplitude analysis (Table 1, Figure 3)

Intra-session: Considering all the results together, for external motion first, switching from VC to SH led to a mean amplitude reduction of 48% (1.7 mm) and an absolute reduction of the variability of 46% (0.2 mm). Similar results were observed for the internal motion, with 36% (11.1 mm) and 42% (3.4 mm) reduction, respectively ($p \leq 0.002$). The average motion amplitude in SP mode was surprisingly smaller than in VC mode ($p=0.04$), although we expected comparable ranges, but was also associated to a higher BR (see discussion).

Inter-session: The smallest mean inter-session variation was observed with the SH mode (2.8 mm) followed by the VC mode (3.0 mm) and the SP mode (5.3 mm). Compared to SP, VC and SH modes decreased by 43% and 47% the amplitude variation between the 2 MRI sessions, although not significantly ($p>0.07$). Five volunteers had inter-session variation greater than 5mm in SP, with 3 of them exceeding 10 mm. Three volunteers had a variation greater than 5mm in VC, and two in SH, but none of them exceeded 10 mm.

2.2. Period analysis (Table 1)

Intra-session: the ventilator imposed a very regular breathing period, with only a 5% difference between the mean observed and expected periods in VC, and 1% in SH. It also reduced the individual variability by 67% compared to the SP ($p<0.001$).
Inter-session: As illustrated in Figure 4, the inter-session variations were dramatically reduced with the mechanically-constrained modes (Volume-controlled and Shallow-controlled ventilation modes) compared to the spontaneous breathing ($p<0.001$). The mean inter-session differences in period lengths were 0,8 ± 0,8 sec [0 – 2,3] in spontaneous breathing, whereas there were no significant differences in the Volume-controlled or the Shallow-controlled ventilation modes.

2.3. Baseline shift (Table1)

Intra-session: SH significantly reduced the baseline shift (3.7 ± 2.0 mm, range 0.5 – 10.4) compared to VC (5.0 ± 2.9 mm, range 1.1 – 16.2) and SP (4.6 ± 2.2 mm, range 1.6 – 11.1) ($p<0.001$). Interestingly, 81% of the baseline shifts were <5mm in SH, while only 58% in VC and 69% in SP.
Inter-session: Although not significant ($p=0.69$), a trend towards a better reproducibility was observed with MANIV in the CC direction as the smallest variations were observed with SH, followed by VC then SP. The CC median baseline shifts were 3.5 mm [1.9 – 8.5] in SH, 5.2mm [2.6 – 10.0] in VC and 9.1 mm [4.0 – 14.0] in the SP mode. The LR median baseline shifts were 4.4 mm [1.4 – 10.7] in SH, 3.4 mm [0.9 – 7.1] in VC and 4.7 mm [1.5 – 7.1mm] in the SP mode.

3. Motion analyses in Slow-controlled ventilation mode

3.1. Intra-session:

The mean duration of the end-inspiratory plateau was 11.1 ± 0.8 sec [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 10mm. The mean baseline shift was 10.7 ± 5.6 mm [3.6 – 25.7] with 13% of the results below 5 mm.

3.2. 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.

4. Tolerance

During the coaching session, none of the volunteers experienced neither hypoxemia, nor hypo- or hyper-capnea. SL ventilation mode induced the greatest variations, although mean deviations remained below 1% of SpO2, 2% of etCO2, and 8 beats per minute for HR. As observed in Figure 5, all the volunteers scored “good” general and ventilation-specific comfort (mean scores > 3). 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%).

Discussion

In this trial, we confirm that mechanical ventilation can be safely applied in a non-invasive way on unsedated subjects with different ventilation modes. Our good safety results echo with those previously reported by MJ Parkes when prolonging apnoea by means of mechanically-assisted hyperventilation. As Parkes wanted to induce hypocapnea, the setup parameters were defined to exceed the metabolic rate [9, 10, 12]. On the contrary, in this trial, the ventilator parameters were set to respect the metabolic needs of each subject. Therefore, no significant fluctuation in oximetry was expected nor observed, whatever the ventilation mode.

Beyond these safety results, we demonstrated the stabilizing effect of MANIV on the breathing-related motion. Indeed, the breathing pattern was more reproducible with the VC and SH modes, compared to SP. Both external and internal motion amplitude variabilities were significantly reduced during and between sessions, while the breathing rate was remarkably stable over time. On the contrary, the spontaneous breathing pattern was clearly affected by environmental or psychological conditions, which impacted on the breathing rate and subsequently the amplitude. Indeed, the higher spontaneous BR observed during the MRI acquisitions (mean BR=16bpm) compared to the coaching session (mean BR=12bpm), were probably related to MRI-driven anxiety, and led to the reduced motion amplitude.

We moreover demonstrated that MANIV could also advantageously modulate the breathing period and amplitude. On one hand, the breathing rate could be accelerated. Consequently, when compared to VC, this Shallow-controlled mode could reduce significantly the internal motion amplitude (mean reduction of 36%), but also the intra-session amplitude variability and the intra-session baseline-shift (42% and 26% respectively), without important loss of comfort. On the other hand, the Slow-controlled mode achieved repeated end-inspiratory breath-holds lasting for more than 10 seconds. These striking results point out the great potential that MANIV can offer to the current motion mitigation techniques. Giving the more reproducible and predictable pattern of breathing, the reliability of the planning 4D-CT will be enhanced, and the gating and tracking strategies facilitated. Gating technique would also directly benefit of reproducible and long-lasting plateaus that would facilitate the delivery of photons or protons within prolonged gating windows. Safety margin encompassing motion uncertainties would also be more reliable thanks to the regular pattern of VC and also significantly reduced with the smaller motion with SH, resulting in a better preservation of the healthy tissues. 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. This could have a large clinical impact knowing that most RT centres are using margins, which do not require any dedicated or expensive equipment, nor advanced skills. Moreover, since the ventilator keeps the same set up over the treatment and displays continuously the breathing curves, these curves could actually provide a more reliable input to trigger respiratory-synchronized procedures. Finally, smaller motion amplitudes are even more critical for PT, to limit its impact on range uncertainties and interplay effects when Pencil Beam Scanning is considered [13-15].

MANIV achieved thus unprecedented results to stabilize and modulate breathing, where other strategies yielded inconclusive results. In addition, our results are particularly representative of a real treatment time (including IGRT and treatment delivery) since the motion was assessed over a 16-minutes period. Goldstein et al have demonstrated that Continuous Positive Airway Pressure (CPAP) devices could significantly reduce motion amplitude, but Di Perri et al failed to confirm any impact of it on tumour motion and baseline shift[16, 17]. Other devices such as High Frequency Ventilation (HFV) or Jet ventilation are currently under investigation to attempt to freeze tumour motion, and get rid of most motion uncertainties. Even if encouraging results have been reported by Peguret et al in their pilot study, further investigations are still required to improve the intra- and inter-fraction baseline shifts and the duration of these apnoea-like breath-holds before considering their clinical implementation [18].

This trial had also cohort-driven, methodological or technical limitations. Regarding our cohort, only healthy volunteers were included for safety reasons. Therefore, our results cannot be representative of real patients. Indeed, 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. In addition, 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 [19]. 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 chestwall and the respiratory muscles [20]. Therefore, their breathing pattern could be less stable, and the ventilation parameters may require a specific attention to avoid impaired ventilation and adverse events.

From a methodological point of view, we willingly excluded swallowing from our data, to focus more 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 [21-23]. For example, Bahig et al reported that swallowing occurred during 2.3% of the treatment time (range 0.0 – 10%) [21].
Stress and anxiety are other factors that may influence the respiratory pattern [24-27]. Additional training sessions and dedicated anti stress techniques might further improve the stability and reproducibility of all mechanically-assisted ventilation modes.
Last, the high level of pressure used for the SL mode 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 chestwall resistance. Stepping this high level of pressure down and tailoring it individually during the coaching session would probably 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 are 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 (e.g. vessel embranchments). This manual procedure created inevitable uncertainties in the re-selection of the tracked slices during the second MRI acquisitions.

We are currently investigating MANIV on patients with lung and liver tumours (VC – SH) and breast cancers (SL). This will allow to track well-defined tumours or anatomical structures (breast nipple), and to get rid of most of these limitations, while addressing specific clinical issues.

Conclusion

Mechanically-assisted non-invasive ventilation is a safe and innovating 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 analyses on patients are going on in order to confirm these results on moving tumours, and to properly select the indications.

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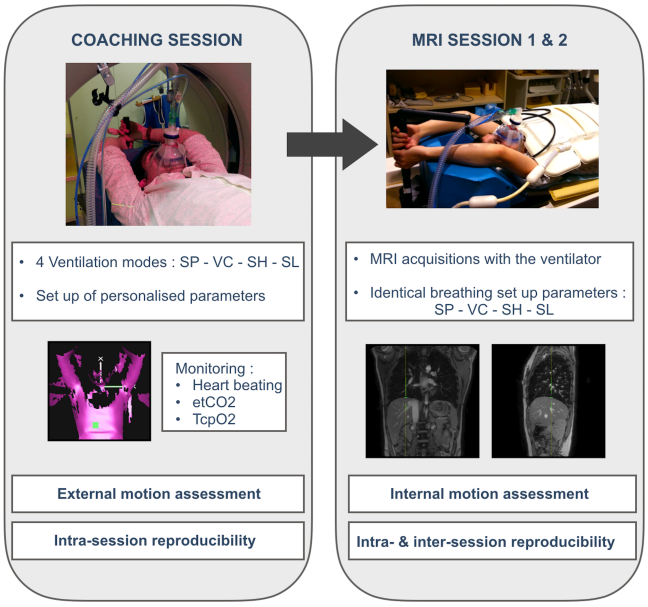

Figure 1. Trial design
During the coaching session in the simulation room, all the volunteers were familiarized with the ventilator and the different ventilation modes (SP: Spontaneous breathing – VC: Volume-controlled ventilation mode – SH: Shallow-controlled ventilation mode – SL: Slow-controlled ventilation mode). Personalized breathing parameters were defined on the ventilator, then applied identically during the 2 MRI sessions to assess the intra- and inter-session reproducibility of the motion under ventilation.

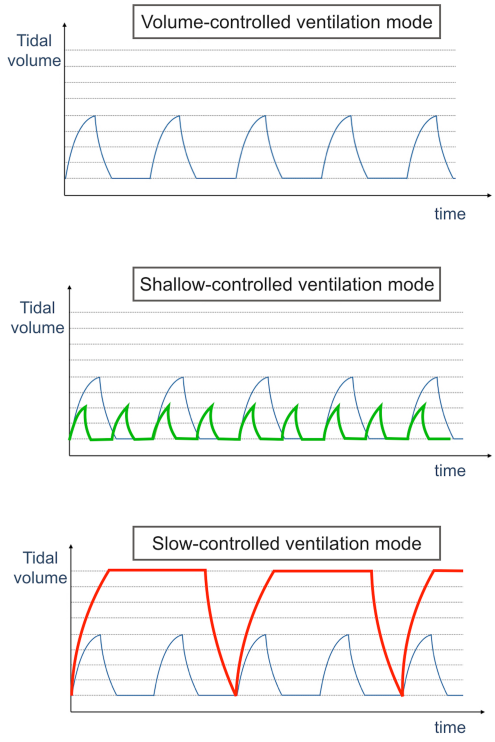

Figure 2. Mechanically-assisted non-invasive ventilation modes.
Three different ventilation modes were evaluated during this trial: (A) The Volume-controlled ventilation mode stabilized the breathing pattern with constrained but individualized tidal volume and breathing rate, (B) The Shallow-controlled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

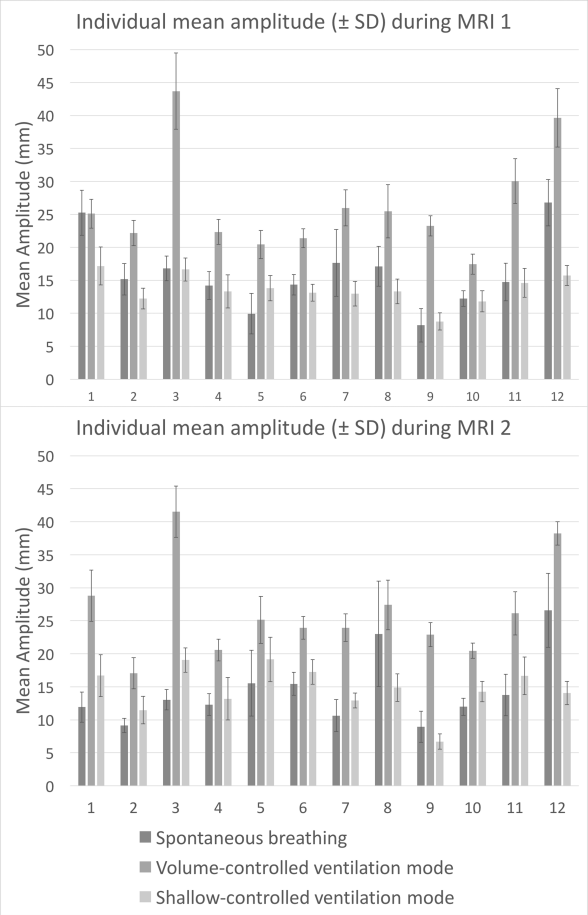

Figure 3. Mean amplitudes of the internal motion by ventilation mode for the twelve volunteers during the 2 MRI sessions.
Motion amplitudes and intra-/inter-session variability were significantly reduced when switching from the VC to the SH mode.

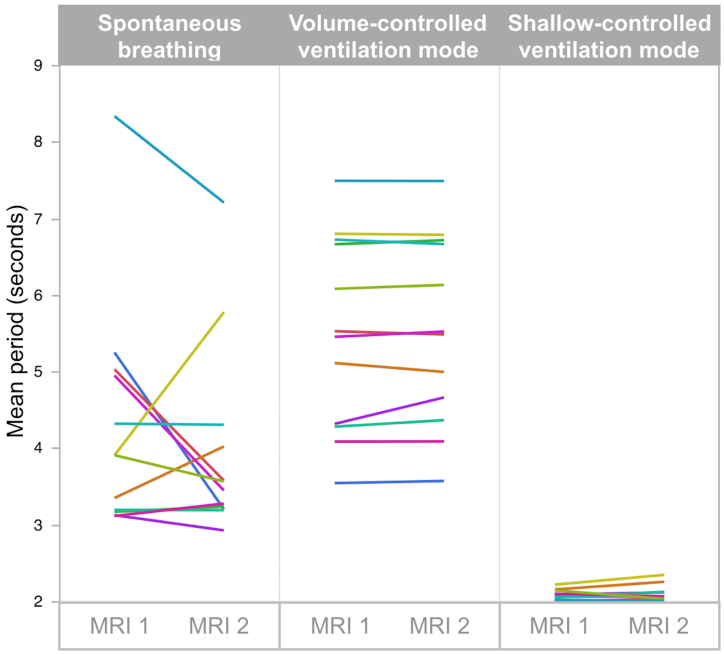

Figure 4. Mean breathing period (± SD) by ventilation mode for the twelve volunteers during the 2 MRI sessions.
MANIV modes dramatically improved the period reproducibility from MRI 1 to MRI 2 ($p<0.001$). No significant differences in periods were observed with the Volume-controlled or the Shallow-controlled ventilation modes.

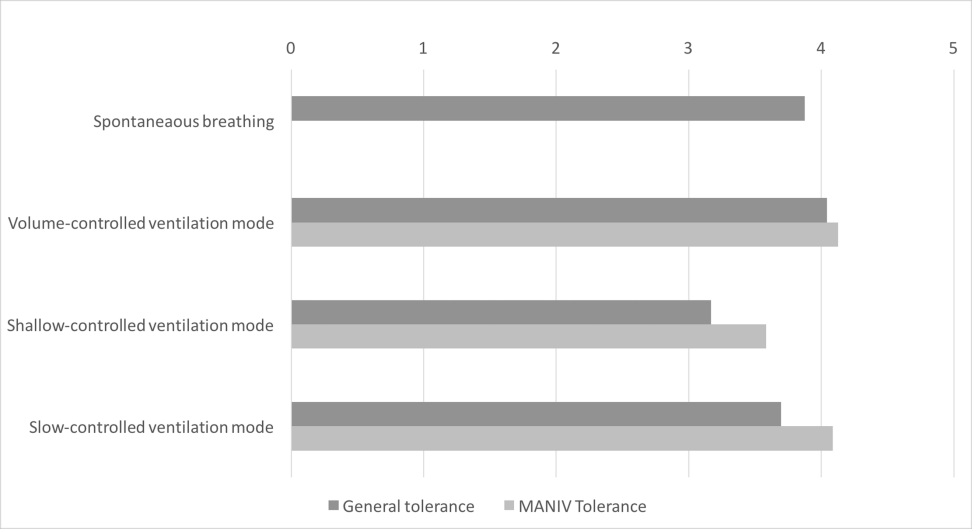

Figure 5. Mean general and ventilation-specific tolerance scores.
After each step of the trial, the volunteers scored their general and ventilation comfort on this 5-items scoring scale (1 = very bad; 2 = bad; 3 = good; 4 = very good; 5 = excellent). All the ventilation modes were scored by the volunteers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

Table 1 : Intra- and inter-session motion for Spontaneous breathing (SP), Volume-controlled (VC) and Shallow-controlled (SH) ventilation modes.
SD: standard deviation; min: minimum; max: maximum

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						
Amplitude (mm)	MRI 1 – MRI 2					
	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)	MRI 1 – MRI 2					
	Mean	Min	max	SD	Min	Max
SP	0.8	0.0	2.3	0.2	0.0	0.8
VC	0.0	0.0	0.1	0.0	0.0	0.1
SH	0.0	0.0	0.2	0.0	0.0	0.1