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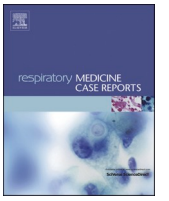

Case report

From bedside to bench - In vivo and in vitro evaluation of mechanically assisted cough treatment in a patient with bulbar Amyotrophic Lateral Sclerosis

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ABSTRACT

When the ability to cough is impaired, secretion clearance may be assisted and augmented by Mechanical Insufflation-Exsufflation (MI-E) treatment. In patients with Amyotrophic Lateral Sclerosis, the efficacy of MI-E may be hampered by counterproductive upper airway responses. Careful adjustment of MI-E settings can be beneficial. During the disease progression, a 41-year-old woman with bulbar Amyotrophic Lateral Sclerosis experienced that treatment with MI-E was exhausting and inefficient. Despite adjustments of settings, all treatment led to retching. A change of MI-E device led to more effective treatment. A bench test revealed variations in flow and pressure waveforms in the two devices. When MI-E treatment fails, differences in equipment delivery need to be considered in addition to the adjustment of MI-E settings.

1. Introduction

Mechanical insufflation-exsufflation (MI-E) is a safe and effective technique to augment cough in persons with neuromuscular disease [1,2]. The effect links to the ability to increase Peak Cough Flow (PCF) and flow bias to the level required to clear airway secretions [1,3]. Use of MI-E in conjunction with non-invasive ventilation (NIV) may delay or prevent intubation or tracheostomy [4].

MI-E therapy applied non-invasively does not always succeed; challenging patients often display disturbed laryngeal function [5,6]. Studies of the upper airways with dynamic transnasal fiberoptic laryngoscopy (TFL) during MI-E indicate that laryngeal structures may adduct and obstruct the airflow in response to positive pressures, both in patients with Amyotrophic Lateral Sclerosis (ALS) [5,6] and in healthy subjects [5,7]. Air filling of the lungs is compromised and the expiratory cough phase is inefficient. Individually adjusted flow and pressure settings, preferably titrated with ongoing upper airway visualization, may prevent laryngeal adduction and prolong successful use of MI-E [5,6].

Abbreviations: MI-E, Mechanical Insufflation-Exsufflation; ALS, Amyotrophic Lateral Sclerosis; PCF, Peak Cough Flow; TFL, Transnasal fiberoptic laryngoscopy; PIP, *Peak Insufflation pressure*; PEP, *Peak Exsufflation pressure*; $Flow_E$: $Flow_I$, *Flow bias ratio*; $Flow_E$-$Flow_I$, *Flow bias difference*; NT, not tested.

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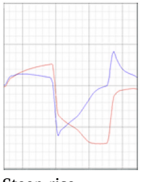
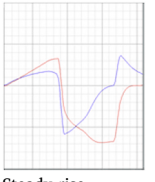
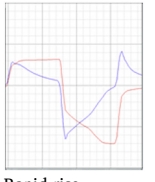
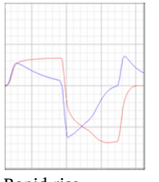
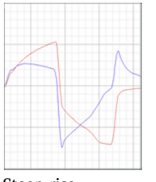
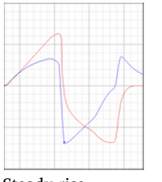
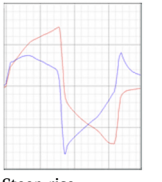
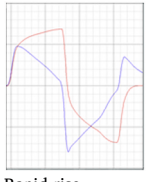
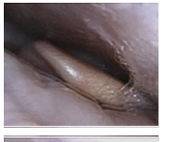
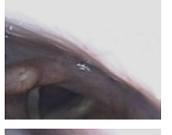
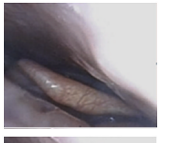
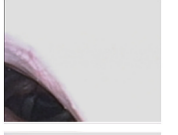
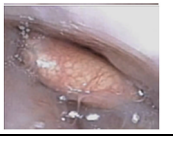
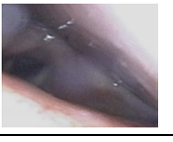
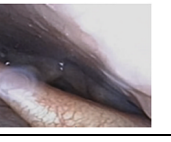
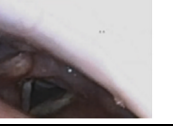
Table 1
Flow and pressure measurements and curves during used MI-E settings in the bench test. The results are mean (SD) values of five MI-E cycles. Snapshots are from the laryngeal visualization with transnasal fiberoptic laryngoscopy during ongoing clinical trial with MI-E.

Pressure		+20/-40 cmH_2O				+40/-40 cmH_2O			
Rise time		Long		Rapid		Long		Rapid	
Device		Cough Assist E70	Clearway 2	Cough Assist E70	Clearway 2	Cough Assist E70	Clearway 2	Cough Assist E70	Clearway 2
PIP cmH_2O)		15.38 (0.18)	19.43 (0.07)	20.88 (5.22)	20.01 (0.03)	31.60 (0.2)	37.73 (0.26)	41.96 (0.48)	41.03 (0.08)
PEP cmH_2O)		42.15 (0.005)	41.22 (0.03)	42.21 (0.09)	41.26 (0.06)	42.27 (0.05)	41.18 (0.06)	41.93 (0.12)	41.16 (0.02)
PIF (l/min)		54.56 (5.72)	56.95 (2.84)	100.25 (9.52)	96.4 (8.00)	89.74 (4.31)	103.35 (2.68)	149.11 (21.58)	155.09 (6.27)
PCF (l/min)		177.92 (1.69)	173.19 (1.46)	195.76 (11.10)	185.62 (1.44)	218.91 (2.09)	209.22 (1.32)	246.17 (1.13)	237.82 (1.14)
$Flow_E$: $Flow_I$		3.30 (0.45)	3.05 (0.19)	1.97 (0.29)	1.94 (0.20)	2.45 (0.15)	2.03 (0.07)	1.69 (0.31)	1.54 (0.07)
$Flow_E$ –$Flow_I$		123.36 (7.37)	116.24 (4.30)	95.50 (18.11)	89.20 (9.43)	129.17 (6.37)	105.87 (3.80)	97.07 (22.68)	82.74 (7.41)
Pressure (red) and Flow (blue) Curves									
Evaluation of curves:									
Insufflation		Steep rise. Convex curve.	Steady rise. Steady rise.	Rapid rise. Peak in the start.	Rapid rise. Peak in the start.	Steep rise. Convex curve.	Steady rise. Steady rise.	Steep rise. Convex curve.	Rapid rise Peak in the start.
Exsufflation		Steep fall to 11–13 cmH_2O, then steady achieving and keeping the set pressures. Immediately peak, then steady declining.							
Laryngeal visualization	Insufflation			NT	NT			NT	NT
	Exsufflation			NT	NT			NT	NT

PIP = Peak Insufflation pressure; PEP = Peak Exsufflation pressure; PIF = Peak Insufflation flow; PCF = Peak Cough flow; $Flow_E$: $Flow_I$ = Flow bias ratio; Flow bias difference = $Flow_E$-$Flow_I$; NT = not tested.

Bench studies indicate variation in performance with different MI-E devices [8,9]. This study describes a patient with ALS with varying treatment effect with two MI-E devices, where subsequent bench testing revealed variations in pressure- and flow waveforms.

2. Case report

A 41-year-old woman was diagnosed with ALS five years earlier. The onset of symptoms was acute spastic paresis in the lower limbs; with rapid progress to spastic tetra paresis during the first year, and subsequent bulbar symptoms with dysarthria. MI-E treatment was initiated with Cough assist E70 (Philips Respironics, Pennsylvania, USA) with asymmetric pressure settings (+20 cmH_2O/-35 cmH_2O, low insufflation flow), this provided effective management of airway secretions. Insufflation volumes varied from 1300 to 1900 ml and PCF was 250 l/min (monitored at the MI-E device). Three years later, she was hospitalized with pneumonia and respiratory failure, and NIV was initiated. To achieve treatment compliance and to avoid invasive treatment, daily adjustments for MI-E and NIV during the stay were required [5,6]. The range of MI-E pressure settings varied from +15 to +35/-20 to −45 cmH_2O, low insufflation flow was used, time settings were shortened when pressures were increased and vice versa. Home treatment was continued with pressure settings +20 cmH_2O/-40 cmH_2O, low insufflation flow, 2.6 sec of insufflation and 1.5 sec of exsufflation.

A year later, the patient experienced that her MI-E treatment was exhausting and led to retching. Insufflation volumes varied from 40 to 1000 ml and PCF from 60 to 160 l/min (monitored at the MI-E device). A home visit was performed to adjust her MI-E treatment and improve adherence. By now, a new MI-E device (Nippy Clearway2, Breas Medical Ltd, Warwickshire, England) was available within the Norwegian national tender, and this device was introduced with settings familiar to her. The patient reported an immediate difference with "*more and different air entry of her lungs",* and she rated it *"much more comfortable"* with no retching. Further, by keeping the longest insufflation rise time (setting 10), she tolerated pressure settings +40 cmH_2O/-45 cmH_2O with 2 s of insufflation and brief (1 s) exsufflation. She was unable to trigger insufflations. Insufflation volumes varied between 1100 and 2300 ml and PCF from 180 to 290 l/min (monitored at the MI-E device). At the following outpatient consultation, we visualized her larynx with TFL during MI-E treatment with both devices with two different pressure settings and the longest insufflation rise time. Laryngeal responses were difficult to compare on all cycles as excessive airway secretions or retching led to poor-quality video recordings. However, the larynx seemed more open during Clearway 2 MI-E treatment (Table 1).

3. Bench test

Due to the self-reported and observed differences in effect, the technical characteristics of the two MI-E devices were compared. We applied varying MI-E pressures and -rise times using a high-fidelity breathing simulator (ASL 5000; IngMar Medical, Pittsburgh, USA) with a two-compartment passive lung model with linear resistance (Rtot 10,0 cmH_2O/L/s) and a non-linear, restrictive sigmoid compliance curve (nominal compliance 50 ml/cmH_2O at FRC, vital capacity 2.2 L), simulating an adult patient with neuromuscular disease. The chest wall mechanics were set to passive, and there was no air leak in the system. The data were sampled at 64 Hz at five MI-E cycles for each setting, collected from the ASL 5000 software and exported to AcqKnowledge 5.0 software (Biopac systems Inc, Goleta, USA) for analysis. See Table 1. When applying the longest insufflation rise time, we found important differences. With Clearway 2, the insufflation pressures and flow waveforms increased steadily throughout the insufflation, and set pressures and peak insufflation flows were achieved by the end of the insufflation. With Cough Assist E70, the pressure slopes were steeper, with peak insufflation flow achieved rapidly after the onset or in the first half of the insufflation before slowly declining, and the set pressures were not achieved. The exsufflation flow curves acted similarly with both devices; creating and immediate PCF before a steady decline. The exsufflation pressures fell steeply to 11–13 cmH_2O before achieving and keeping the set pressures.

4. Discussion

Our patient presented with ineffective MI-E treatment despite repeated settings adjustments, but treatment succeeded with a change of device. Visualization of the upper airways indicated less laryngeal constriction with the new device, and a bench test indicated different patterns of flow and pressure slopes. A steady rise of insufflation flows and -pressures connected to this bulbar patient rating the treatment more comfortable and efficient. Tailoring MI-E treatment should focus on flow and pressure adjustments, and in different cases, perhaps also at studying device flow- and pressure patterns. As this is a "one patient's experience", the findings cannot be generalized.

Clearing the airways for secretions is vital to sustain a healthy respiratory system [10]. Positive pressure from the MI-E device leads to lung insufflation, a subsequent rapid switch to negative pressure leads to lung exsufflation, moving airway secretions proximally. However, MI-E therapy applied non-invasively does not succeed in all patients, as positive airway pressures may cause inappropriate laryngeal responses [11]. Application of more gentle pressures have been advocated [5]. Afferent activation (i.e. pressure and flow receptors) in the larynx plays an important role in modulating upper airway muscle activity, and stimulation of extremely sensitive supraglottic receptors by rapid insufflation may induce laryngeal adduction [5]. Considering the heterogeneous nature of ALS, one may speculate that such responses differ between patients.

Our bench test indicated satisfactory outcomes in terms of PCFs and flow bias with both devices, but variation in flow and pressure waveforms. Careful adjustment of the insufflation rise time was important in our patient, and led to higher treatment volumes and higher PCF. However, it is not given that the same modification of treatment would gain the same effect and in the same direction in other patients.

Bench studies have explored ventilator waveforms [12], but this has not been done to the same extent for MI-E devices. Such evaluations may provide clinically relevant information.

5. Conclusion

Effective airway clearance and subjective tolerance must be targeted to maintain compliance with MI-E therapy in patients with ALS. This may depend not only on skillful adjustment of equipment, but differences in performance between devices. The clinician should be aware of these pitfalls in patients that respond poorly to standard practice.

Declarations of interest and funding

There are no competing interests. This case report did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics and consent to participate

The authors have no ethical conflicts to disclose. This case report is derived from clinical practice *conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.* Patients' name, initials, social security numbers, dates of birth or other personal or identifying information are not used. The individual cannot be identified from the laryngoscopic images. The dynamic functional laryngoscopic visualization of the upper airways during therapeutic interventions is frequently used in our clinical practice when we have challenging individuals with NIV or mechanical insufflation-exsufflation (MI-E). The examination with transnasal fiberoptic laryngoscopy during MI-E was not new for this particular individual; she had performed this examination earlier two times in a clinical context. She consented to perform it during MI-E with both devices and settings, and did not reported discomfort.

Consent to publication

Written informed consent has been obtained from the participant, who is approved the publication of the manuscript:

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