



External heated humidification during non-invasive ventilation set up: results from a pilot cross-over clinical trial

To the Editor:

Patient comfort is important in ensuring adherence to domiciliary non-invasive ventilation (NIV). Oronasal dryness is often reported with NIV use [1], but the use of heated humidification in clinical practice is not uniform [2]. As there are limited data to currently guide clinical practice, we investigated the effect of external heated humidification on neural respiratory drive (NRD), patient-ventilator asynchrony (PVA), patient-reported outcomes, ventilator performance and adherence in a pilot randomised crossover trial in patients with chronic respiratory failure during NIV set up.

The study was approved by the local research ethics committee (11/H0802/10) and registered on clinicaltrials.gov (NCT01372072). Patients with a new diagnosis of chronic respiratory failure and sleep disordered breathing were screened for inclusion into the trial. Following the obtaining of written informed consent, subjects were randomised (sealed envelope method). Patients were allocated to receive NIV with heated humidification (HH+) or without (HH-) heated humidification with an RT040 face mask (Fisher & Paykel, New Zealand). Ventilator settings were set as per local protocol [3]. Patients received HH+ NIV or HH- NIV for 3 weeks, followed by a 2-week wash-out period and then crossed over to the opposite arm of the trial for a further 3 weeks. Temperature setting was adjusted according to patient comfort with no changes in settings during the study nights. NIV adherence was the principal outcome.

NRD was measured using second intercostal space parasternal electromyography (EMG_{para} , $EMG_{para\%max}$) as previously described [4] and PVA was measured as previously reported [5]. Transcutaneous carbon dioxide (P_{tcCO_2}) and oxygen saturations (S_{pO_2}) were measured (Radiometer Medical, Copenhagen, Denmark). Health related quality of life and daytime somnolence were assessed using severe respiratory insufficiency (SRI) questionnaire and Epworth sleepiness score (ESS), respectively.

A Wilcoxon signed-rank test was used to compare differences between groups and Friedman analysis with Dunn's *post hoc* analysis for comparisons from baseline (*i.e.* pre-NIV). Estimates were reported using medians and interquartile range. An intention to treat analysis was performed for NIV adherence. All statistical analyses were performed using Graphpad version 5.0 (Graphpad Software Inc., USA).

15 patients were recruited, aged 59 (50–66) years, body mass index 41.2 (28.5–47.1) $kg\cdot m^{-2}$, six male patients, (five COPD, eight obesity hypoventilation syndrome and two chest wall disease). Two subjects were unable to tolerate HH+. Inspiratory positive airway pressure (IPAP) was 24 ± 5 cmH_2O with expiratory positive airway pressure (EPAP) of 8 ± 4 cmH_2O and inspiratory time (t_i) of 1.2 ± 0.1 s and a back-up rate of 13 ± 3 bpm (93% patients pressure support (PS) mode, 7% patients pressure-controlled (PC) mode).

There was no between-group difference in 3-week NIV adherence (HH+ 283 (156–403) min per night *versus* HH- 307 (69–335) min per night; $p=0.74$). ESS improved in both HH- and HH+ but there was no between group difference ($\Delta HH-$ 4.9 ± 4.8 *versus* $\Delta HH+$ 4.5 ± 4.6 ; $p=0.41$). There was a small increase in SRI at 3 weeks in HH+ group, but these differences were not observed in the HH- group (table 1).



@ERSpublications

Short-term heated humidification has limited effect on physiological and clinical outcomes during non-invasive ventilation set up <http://bit.ly/31cFfGt>

Cite this article as: Mandal S, Ramsay M, Suh E-S, *et al.* External heated humidification during non-invasive ventilation set up: results from a pilot cross-over clinical trial. *Eur Respir J* 2020; 55: 1901126 [<https://doi.org/10.1183/13993003.01126-2019>].

TABLE 1 Patient reported outcome scores and patient-ventilator asynchrony (PVA)

	Baseline	Heated humidification	No humidification
Subjects n	12	12	12
ESS[#]	12 [9–17]	6 [5–11]*	7 [4–12]*
NIV side-effect score[¶]	NA	6 [5–9]	6 [5–9]
SRI-RC	59 [33–77]	72 [63–89]	71 [42–85]
SRI-PF	50 [44–79]	58 [40–83]	58 [42–79]
SRI-AS	50 [23–57]	61 [39–70]*	54 [45–66]
SRI-SR	75 [52–85]	71 [52–88]	67 [54–88]
SRI-AX	45 [23–68]	60 [48–90]*	60 [43–70]
SRI-PWB	58 [47–64]	61 [47–71]	61 [42–79]
SRI-SF	69 [45–80]	69 [50–81]	63 [55–86]
SRI-SS	61 [40–68]	64 [50–76]*	60 [50–80]
PVA			
Subjects n		12	14
Ineffective efforts %		18.2 [1.1–23.8]	3.2 [0–22.5]
Auto-triggering %		37.0 [6.7–54.2]	21.7 [6.2–37.0]
Double triggering %		0 [0–0.3]	0.1 [0–0.2]
Total triggering PVA %		39.3 [6.7–55.0]	21.7 [6.2–37.5]
Premature cycling %		1.0 [0.4–1.8]	0.5 [0.1–2.5]
Delayed cycling %		0.9 [0–2.7]	0.3 [0–3.6]
Total cycling PVA %		3.8 [2.2–8.2]	2.0 [0.9–7.1]
Total PVA %		57.1 [32.3–73.7]	34.3 [11.6–74.6]*

Data are presented as median (interquartile range), unless otherwise stated. ESS: Epworth sleepiness score; NIV: noninvasive ventilation; SRI: severe respiratory insufficiency; RC: respiratory components; PF: physical functioning; AS: attendant symptoms and sleep; SR: social relationships; AX: anxiety; PWB: psychological well-being; SF: social functioning; SS: sum score; NA: not applicable. [#]: score out of 24; [¶]: score out of 44; *: p<0.05 from baseline.

There was a reduction in nocturnal P_{tCO_2} from baseline in both HH+ and HH– groups (P_{tCO_2} Δ HH+ -1.7 (-2.5 to -1.0) kPa; $p=0.0005$; Δ HH– -1.5 (-2.5 to -0.6) kPa; $p=0.0034$), but there was no between group difference observed ($p=0.39$).

There was a reduction in mean nocturnal $\text{EMG}_{\text{para}\% \text{max}}$ observed in both groups compared to the baseline self-ventilation night (baseline 16% (12–26%) *versus* HH+ 6% (5–8%); $p=0.002$; baseline 13% (11–20%) *versus* HH– 6% (4–9%); $p=0.0005$). Importantly, there was a difference observed in $\Delta \text{EMG}_{\text{para}\% \text{max}}$ between the HH+ and HH–, with a greater reduction in the HH+ group (Δ HH+ -10.7% (-17.7 to -5.4%) *versus* Δ HH– -2.2% (-3.8 to 0.2%); $p=0.001$).

Comparison of the set IPAP (24 ± 5 cmH₂O) and mask pressure showed delivered IPAP showed much lower IPAP in the HH+ group (Δ HH+ -8.4 (-10.3 to -2.9) cmH₂O; $p=\text{NS}$; Δ HH– -4.4 (-8.2 to -1.0) cmH₂O; $p=\text{NS}$) with significant difference between Δ HH+ and Δ HH–; $p=0.03$). 22831 breaths were analysed for PVA (table 1) with 100% of patients observed to have an asynchrony index >10 events per h in the HH+ group compared to 79% in the HH– group, although this was not significantly different ($p=0.4$). There was no between-group difference in type or proportion of PVA, although total PVA was greatest in the HH+ group ($p=0.009$) (table 1).

These data have demonstrated short-term NIV adherence of patients with chronic respiratory failure is not enhanced by heated humidification during NIV set-up. Furthermore, NIV with and without heated humidification, showed similar improvements in NRD and overnight gas exchange, health-related quality of life and daytime somnolence. Of clinical relevance, 13% of patients were unable to tolerate heated humidification, with a reduction in ventilator driving pressure observed, compared to the set pressure, with heated humidification (mean reduction of 4 cmH₂O). This is a consequence of the addition of a heated humidification chamber, increasing the ventilator circuit volume and dead space. The effect of an integrated humidifier in the newer devices is unknown. The authors acknowledge that the pressure drop may have been, in part, as a result of mask leak, but that the leak would be expected with and without heated humidification.

It was interesting to observe that despite a higher frequency of PVA in the heated humidification group, there was a reduction in NRD overnight compared to the group without humidification. Although there was a statistical difference with and without humidification at 3 weeks (8.5% mean nocturnal $\text{EMG}_{\text{para}\% \text{max}}$ difference) this was only a small absolute difference between the groups (Δ HH+ -5.3 *versus* HH– Δ -4.6 μV).

Furthermore, the reduction in NRD from baseline in the heated humidification group was greater compared to the group without humidification (10% *versus* 7%) and, importantly, the reduction from baseline was not sustained in the group without humidification despite the less frequent asynchrony events, which suggests that the heated humidification effect on NRD is both immediate and sustained, at least, in the short-term. Although not objectively measured in this study, patient comfort measures should be measured in future. Based on these current data, future trial design for assessment of the effect of heated humidification would be to focus on those patients with chronic respiratory failure that have low short-term NIV adherence as a consequence of oronasal dryness despite tolerating in-hospital NIV set-up. This provides a more clinically relevant target population for the use of heated humidification.

The authors acknowledge that these pilot data report a limited number of patients with a mixture of causes of chronic respiratory failure. However, there is a paucity of data detailing the short-term physiological effect of heated humidification on NRD, ventilator performance and patient-ventilator interaction as well as the clinical effect on overnight gas exchange and ventilator adherence. The current data provides the platform to design a randomised controlled trial to investigate the clinical and cost effectiveness of heated humidification during NIV set-up, similar to the design of previous trials [6].

These clinical data, from a pilot randomised crossover trial, have shown that external heated humidification during NIV set up has limited effect on short-term clinical outcomes, such as overnight gas exchange, health-related quality of life and NIV adherence. In addition, the clinician needs to acknowledge that external humidification negatively impacts ventilator pressure delivery. Future long-term trials of heated humidification should target those patients reporting low short-term NIV adherence as a consequence of oronasal dryness.

Swapna Mandal^{1,2,3}, Michelle Ramsay^{1,2,3}, Eui-Sik Suh^{1,2,3}, Rachel Harding^{1,2,3}, April Thompson^{1,2,3}, Abdel Douiri⁴, John Moxham², Patrick Brian Murphy^{1,2,3} and Nicholas Hart^{1,2,3}

¹Lane Fox Clinical Respiratory Physiology Research Centre, St Thomas' Hospital, King's Health Partners, London, UK.

²King's College London, School of Life Sciences, Centre for Human and Applied Physiological, London, UK. ³Lane Fox Respiratory Service, Guy's and St Thomas' NHS Foundation Trust, London, UK. ⁴School of Population Health and Environmental Sciences, King's College London, London, UK.

Correspondence: Nicholas Hart, Lane Fox Respiratory Service, Guy's and St Thomas' NHS Trust, Westminster Bridge Road, London, SE1 7EH, UK. E-mail: nicholas.hart@gstt.nhs.uk

Received: 16 June 2019 | Accepted after revision: 25 Jan 2020

This study was registered at www.ClinicalTrials.gov with identifier number NCT01372072.

Acknowledgements: A. Douiri and N. Hart acknowledge the support of the National Institute for Health Research (NIHR) Clinical Research Facility at Guy's and St Thomas' NHS Foundation Trust and NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of interest: S. Mandal reports grants from Fisher and Paykel, during the conduct of the study. M. Ramsay has nothing to disclose. E-S. Suh has nothing to disclose. R. Harding has nothing to disclose. A. Thompson has nothing to disclose. A. Douiri reports grants from Philips-Respironics, outside the submitted work. J. Moxham has nothing to disclose. P.B. Murphy reports grants and non-financial support (equipment) from Fischer and Paykel, during the conduct of the study; grants and personal fees for lectures from Philips, Breas, ResMed, and Fischer and Paykel, outside the submitted work. N. Hart reports unrestricted grants from Fisher Paykel within the direct area of work commented on here with the funds held and managed by Guy's and St Thomas' NHS Foundation Trust; N. Hart reports unrestricted grants from Philips and Resmed outside the direct area of work commented on here with the funds held and managed by Guy's and St Thomas' NHS Foundation Trust; financial support from Philips for development of the MYOTRACE technology that has patent filed in Europe (US pending) outside the area of work commented on here; personal fees for lecturing from Philips-Respironics, Philips, Resmed, Fisher-Paykel both within and outside the area of work commented on here; and N. Hart is on the Pulmonary Research Advisory Board for Philips outside the area of work commented on here, with the funds for this role held by Guy's and St Thomas' NHS Foundation Trust.

Support statement: This study was funded by an unrestricted grant from Fisher and Paykel. Funding information for this article has been deposited with the Crossref Funder Registry.

References

- 1 Mehta S, Hill NS. Noninvasive ventilation. *Am J Respir Crit Care Med* 2001; 163: 540–577.
- 2 Crimi C, Noto A, Princi P, *et al.* A European survey of noninvasive ventilation practices. *Eur Respir J* 2010; 36: 362–369.
- 3 Murphy PB, Arbane G, Ramsay M, *et al.* Safety and efficacy of auto-titrating noninvasive ventilation in COPD and obstructive sleep apnoea overlap syndrome. *Eur Respir J* 2015; 46: 548–551.
- 4 Murphy PB, Kumar A, Reilly C, *et al.* Neural respiratory drive as a physiological biomarker to monitor change during acute exacerbations of COPD. *Thorax* 2011; 66: 602–608.

- 5 Ramsay M, Mandal S, Suh ES, *et al.* Parasternal electromyography to determine the relationship between patient-ventilator asynchrony and nocturnal gas exchange during home mechanical ventilation set-up. *Thorax* 2015; 70: 946–952.
- 6 Mandal S, Arbane G, Murphy P, *et al.* Medium-term cost-effectiveness of an automated non-invasive ventilation outpatient set-up *versus* a standard fixed level non-invasive ventilation inpatient set-up in obese patients with chronic respiratory failure: a protocol description. *BMJ Open* 2015; 5: e007082.

Copyright ©ERS 2020