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SCIENTIFIC LETTER

Digital twins of acute hypoxemic respiratory failure and sepsis patients suggest potential benefits of bi-level high flow nasal cannula therapy

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Dear Editor,

High-flow nasal cannula (HFNC) therapy is a form of non-invasive respiratory support that delivers heated, humidified gas at flow rates exceeding 20 L/min [1]. The technical feasibility of delivering different HFNC flow rates during inspiration and expiration (bi-flow HFNC) was recently demonstrated in a proof-of-concept study in healthy volunteers [2]. Here, we aimed to investigate whether the use of bi-flow HFNC could potentially produce clinically relevant benefits in patients suffering from acute hypoxemic respiratory failure (AHRF) or sepsis. To do this, we used detailed physiological data from three previous studies that administered HFNC to patients at multiple flow rates [3–5]. Based on these data, we used a high-fidelity computational simulator of the cardiopulmonary system to create digital twins of 13 AHRF patients and 17 sepsis patients. Global optimisation algorithms were used to match the outputs of each digital twin to arterial blood gases (PaO_2 and $PaCO_2$), esophageal pressure swing (ΔP_{es}), and tidal volume (VT) measured in each patient at two different flow rates (see SM for full details). Comparisons of digital twin outputs with patient measurements are shown in Figs. S4 and S5 and Table S6 in the SM. The mean absolute percentage error/bias between the outputs of the digital twins and the patient data were 2.33%/1.96 mmHg for PaO_2, 1.68%/0.59 mmHg for $PaCO_2$, 6.62%/0.4 cmH_2O for pleural pressure swing (ΔP_{pl} in digital twins, estimated as ΔP_{es} in data), and 10.2%/47.69 ml for tidal volume VT.

After matching to the patient data, all digital twins were simulated at the same high and low flow rates (50 and 30 L/min) to be consistent and facilitate quantitative comparisons. Application of bi-flow HFNC was simulated in the digital twins by applying flow rates of 30 L/min during expiration and 50 L/min during inspiration. Transitions between high and low flow rates were simulated to take 0.4 s after a change between inspiration and expiration. Uni-flow HFNC at 30 and 50 L/min was also simulated in each digital twin. To incorporate the effects of neural feedback, the respiratory muscles' pressure (P_{mus}) in each digital twin was adjusted to preserve an approximately constant $PaCO_2$ across the different simulations, while respiratory rate remained constant (as observed in the original studies). A comparison of the effects of the uni-flow and bi-flow strategies on respiratory effort, gas exchange, lung mechanics, and indices associated with patient self-inflicted lung injury (P-SILI) across the cohort of digital twins is shown in Fig. 1, and in Table S7 of the SM.

In the digital twins, the mean pleural pressure swing ΔP_{pl} reduced from 8.68 cmH_2O at 30 L/min uni-flow and 8.14 cmH_2O at 50 L/min uni-flow to 6.11 during bi-flow HFNC. Our results suggest that a bi-flow HFNC strategy may require less spontaneous respiratory effort

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The members of the HFNC-BiFlow study group are listed in Acknowledgements.

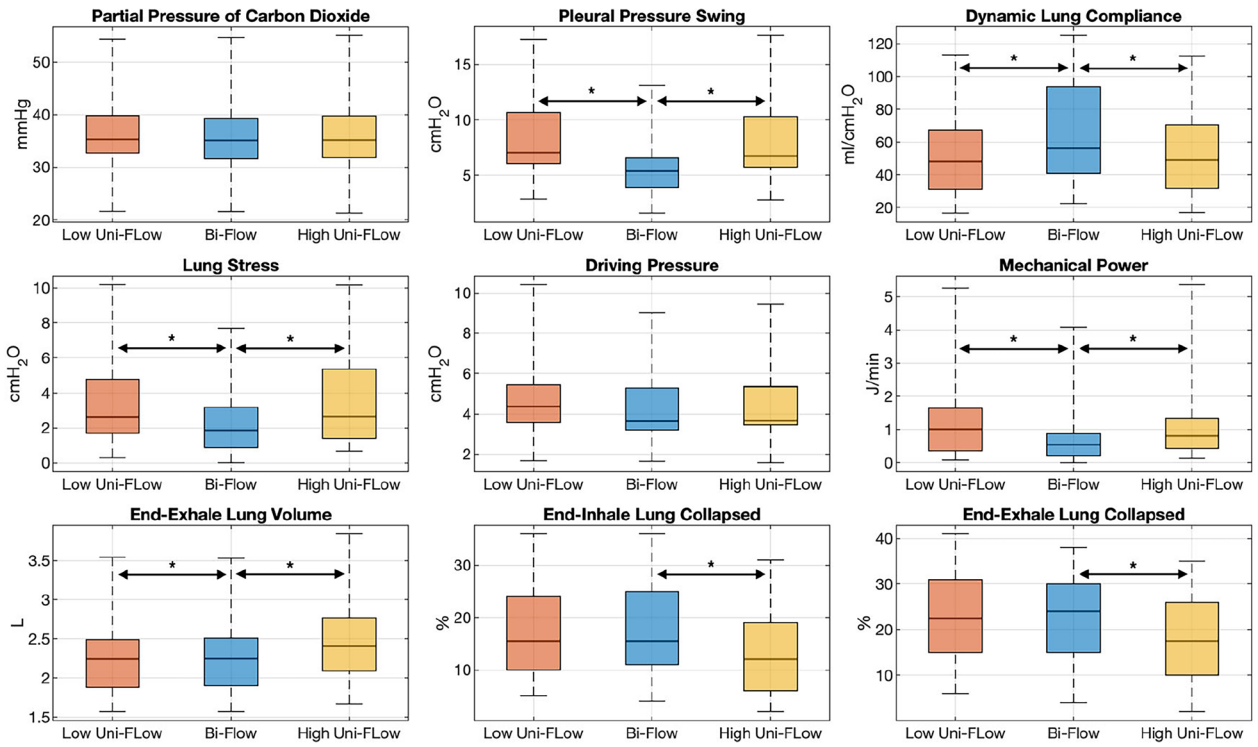

Fig. 1 Box–whisker plots (median, interquartile range, and range) of the effects of the uni-flow and bi-flow strategies on respiratory effort, gas exchange, lung mechanics, and indices associated with P-SILI across the cohort of digital twins. The statistical significance of the change between bi-flow and uni-flow was tested using the Wilcoxon signed-rank test, with * indicating $p < 0.01$

on the part of patients than either the low or high uni-flow strategies. This may be explained by the fact that during uni-flow HFNC, all of the driving pressure (DP: the pressure gradient driving airflow into and out of the lungs) must be provided by the patient, since the flow-dependent pressure at the inlet of the airways provided by HFNC is the same during inspiration and exhalation. In contrast, during bi-flow HFNC, there is a non-zero contribution to the DP by the HFNC, due to the higher pressure at the inlet airways during inhalation and the lower pressure during exhalation. As a result, the ΔP_{pl} generated in the digital twins is lower during bi-flow, improving dynamic compliance (mean VT/ΔP_{pl} increases from 51.17/52.33 ml/cmH_2O during uni-flow to 73.91 ml/cmH_2O during bi-flow) and lowering P-SILI indicators (mean lung stress reduced by > 27%, mean mechanical power by > 59%). In these digital twins, this beneficial effect outweighs the lower recruitment due to the lower PEEP produced by the bi-flow compared to the high uni-flow strategy. The potential advantages of bi-flow HFNC described above are preserved in separate sub-group analyses of the AHRF and sepsis digital twins (see SM, Tables S8 and S9).

Reliable triggering of different flow rates during transitions between inspiration and expiration was demonstrated in the HFNC system implemented in [2], and some standard HFNC delivery systems (e.g., Fisher and Paykel's Airvo 3) already allow the flow rate to be reduced by up to 20% during exhalation. The actual clinical benefits of the approach simulated here remain to be confirmed. However, the practical feasibility of bi-flow HFNC, together with the possible beneficial effects identified in a diverse cohort of digital patients, suggests that this novel mode of non-invasive respiratory support might warrant further investigation in larger clinical studies.

Supplementary Information
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Declarations

Conflicts of interest
All authors declare that they have no competing interests. TM received personal fees from Fisher and Paykel, Drager, Aerogen, outside of the present work.

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