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Experimental assessment of CO2 rebreathing in closed-circuit CPAP therapy with different non-invasive interfaces / De Luca, M., Formaggio, A., Terzini, M., Putame, G., Olivieri, C., Borrelli, S., Audenino, A.L.. - In: JOURNAL OF BIOMECHANICS. - ISSN 1873-2380. - ELETTRONICO. - 189:(2025), pp. 1-7. [10.1016/j.jbiomech.2025.112826]

*Availability:*

This version is available at: 11583/3001627 since: 2025-07-07T14:45:20Z

*Publisher:*

Elsevier

*Published*

DOI:10.1016/j.jbiomech.2025.112826

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## Experimental assessment of CO<sub>2</sub> rebreathing in closed-circuit CPAP therapy with different non-invasive interfaces

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### ARTICLE INFO

#### Keywords:

NIV  
CO<sub>2</sub> rebreathing  
CPAP  
Closed ventilation circuit  
Interface design  
Helmet  
Full-face mask  
Interface volume

### ABSTRACT

Continuous Positive Airway Pressure (CPAP) is a non-invasive ventilation therapy that supports respiratory function by improving functional residual capacity and maintaining open airways through positive pressure. Closed-circuit CPAP configurations are emerging as a promising alternative to conventional open circuits, offering several advantages. However, their effectiveness can be compromised by CO<sub>2</sub> rebreathing. This study aimed to quantify inhaled CO<sub>2</sub> levels during closed-circuit CPAP therapy with different interfaces and explore the effects of interface volume, inlet and outlet port position and airflow rates on CO<sub>2</sub> accumulation.

Four helmets, differing in port positioning, and One-port and Two-ports total-face Masks were tested under three flow conditions (0, 60, and 80 l/min) using an ad hoc test bench to measure CO<sub>2</sub> accumulation inside the interface.

Results demonstrated that interface design strongly influenced CO<sub>2</sub> retention. Lateral Inlet/Lateral Outlet Helmet (current commercial helmet) showed the highest inhaled CO<sub>2</sub> levels (about 2 %), while the Up Inlet/Front Outlet Helmet achieved lower inhaled CO<sub>2</sub> (0.6 % at 80 l/min). Masks, characterized by smaller volumes, consistently exhibited lower CO<sub>2</sub> retention. Notably, the Two-ports Mask maintained inhaled CO<sub>2</sub> levels below 1 % (patient safety threshold) even without additional recirculation airflow. Increasing flow rates effectively reduced CO<sub>2</sub> rebreathing, with the most pronounced reduction occurring between 0 and 60 l/min.

These findings highlight the critical role of interface design, particularly port positioning, in minimizing CO<sub>2</sub> rebreathing. The results enabled selection of safe interfaces for closed-circuit CPAP. Furthermore, these findings can be extended to conventional open-circuit CPAP therapy, enhancing patient safety in non-invasive ventilation.

### 1. Introduction

Continuous positive airway pressure (CPAP) is a non-invasive ventilation (NIV) therapy that supports respiratory function by improving functional residual capacity and maintaining upper airways open through the application of positive pressure (Bello et al., 2018; David-João et al., 2019; Rochweg et al., 2017; Thille et al., 2013). NIV has proven effective in treating conditions such as acute pulmonary oedema, acute hypoxemic respiratory failure, postoperative respiratory failure, and mild to moderate acute respiratory distress syndrome (ARDS) (David-João et al., 2019; Esquinas Rodriguez et al., 2013; Grieco

et al., 2021).

As with all NIV therapies, CPAP can be delivered through interfaces differing in shape, size and volume. Total-face masks, are widely used and generate minimal air leaks but are often less tolerable for extended periods due to sensations of claustrophobia. Helmets offer greater comfort, but pose a higher risk of exhaled carbon dioxide (CO<sub>2</sub>) rebreathing due to retention within the interface, undermining the effectiveness of therapy (Bachour et al., 2019; Cammarota et al., 2022; Pisani et al., 2012). Other types of interfaces are commonly used, such as nasal pillows and oronasal masks, which are less prone to CO<sub>2</sub> accumulation due to their smaller volumes (Esquinas Rodriguez et al., 2013;

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Schettino et al., 2003).

Recently, a closed ventilation circuit for CPAP therapy was proposed (Cavaglià et al., 2021), offering several advantages over conventional open circuits, including reduced daily oxygen consumption, lower risk of viral contamination in the environment, decreased noise levels, and less airway dryness. More recently, this closed circuit was tested to assess its performance (De Luca et al., 2025), demonstrating that it can maintain comparable performance to conventional open circuits. Unlike the latter, where positive pressure is achieved through high flow rates, the closed circuit can maintain positive pressure with minimal flows within the circuit, generated by the patient minute ventilation. During operation, to compensate for pressure fluctuations caused by breathing, a flow of gas enters (fresh gas) and exits (expired gas) the circuit through a turbine, whose location permits a net zero contribution to the flow within the circuit. However, the resulting low flows in the circuit could reduce CO<sub>2</sub> clearance at the interface compared to that achieved with conventional open circuits with high fresh gas flows, highlighting the need to further investigate this aspect (Hui et al., 2006; Popowicz and Leonard, 2022).

Numerous studies show that CO<sub>2</sub> rebreathing during NIV is a multifactorial phenomenon, influenced by both technical and patient-related factors.

A key determinant is the fresh gas flow rate: higher flows enhance CO<sub>2</sub> washout, thereby reducing the risk of rebreathing. The efficiency of CO<sub>2</sub> clearance primarily relies on the balance between the patient specific metabolic CO<sub>2</sub> production and the fresh gas supply (Gil et al., 2021; Mojoli et al., 2008). This balance becomes particularly critical with high-volume interfaces like helmets, where increasing the flow rate significantly reduces inspired CO<sub>2</sub> levels, emphasizing the need for consistent and sufficient fresh gas delivery (Patroniti et al., 2003; Santos Tomaz et al., 2022; Taccone et al., 2004). Interface characteristics also matters: larger volumes increases rebreathing risk (Esquinas Rodriguez et al., 2013; Santos Tomaz et al., 2022; Schettino et al., 2003) as well as the placement of the exhalation ports: Schettino et al. (2003) showed that positioning the exhalation port within the circuit, rather than inside the mask, significantly reduce inspired CO<sub>2</sub> levels. Intentional leak systems and the separation of fresh gas inlet and the exhaled gas outlet are also important (Luján et al., 2023; Signori et al., 2019). Dual-limb circuits, which have separate conduits for inspiratory and expiratory flows, minimize rebreathing compared to single-limb circuits, where adequate fresh gas flow becomes paramount (Luján et al., 2023; Samolski et al., 2016).

These extensive findings underscore that fresh gas flow rate, interface characteristics, and ventilatory settings must be carefully considered to effectively study and prevent CO<sub>2</sub> rebreathing during NIV.

While these studies have quantitatively assessed this phenomenon, none refer to a specific threshold value beyond which the inhaled CO<sub>2</sub> becomes harmful to patients. The ISO 17510-2015 provides guidelines for testing CO<sub>2</sub> rebreathing in mask interfaces, but it is primarily focused on devices for Obstructive Sleep Apnea (OSA) treatment, and it does not define a safety threshold for rebreathing. The clinical significance of CO<sub>2</sub> rebreathing is heavily dependent on the specific clinical scenario and the indication for which NIV is being used, which makes it challenging to select a universally applicable threshold. However, the National Institute for Occupational Safety and Health (NIOSH, 1976) recommends a Time Weighted Average concentration of CO<sub>2</sub> equal to 1 % (10,000 ppm) during a work shift to prevent adverse effects of prolonged exposure to CO<sub>2</sub>-rich environments. This threshold could also be applied to NIV therapies, given their potential for prolonged administration.

As part of a broader effort to further characterize the use of a closed circuit in CPAP therapy, this study aims to experimentally investigate, for the first time, the phenomenon of CO<sub>2</sub> rebreathing within this novel circuit. The investigation includes a comparison of various airflow rates and different interfaces, including total-face masks and helmets with modified port positions.

## 2. Methods

### 2.1. Experimental setup

A schematic representation of the experimental test bench is shown in Fig. 1. The closed circuit was realised with existing commercial components.

A primary turbine (maximum static pressure of 4500 Pa and airflow rate of 0.496 m<sup>3</sup>/min  $\approx$  460 l/min (ebmpapst, RVE45\_3/54/2P, St. Georgen GmbH & Co. KG.) (1), was employed to pressurise the air within the closed circuit. A constant CPAP level was maintained through a feedback control system implemented via a PID controller, using pressure measurements from a sensor (AMS 6915, Analog Microelectronics GmbH, Germany) directly connected to the patient's interface. The closed circuit enabled pressurization with minimal flow—ideally no flow if there are no unintentional leaks—from the primary turbine to the external environment. However, a flow is always present within the closed circuit due to the simulated minute ventilation. Then, to prevent viral contamination inside the breathing circuit, two antiviral filters (Flo-Guard, Intersurgical SpA, Italy) (2) were incorporated. The inclusion of one-way valves (1921000, Intersurgical Ltd) (3) guaranteed unidirectional airflow, preventing backflow. The patient interface (4) was securely attached to a head phantom to minimise leaks and this latter was directly connected to a lung simulator (5) (TestChest® V3, Switzerland). CO<sub>2</sub> was injected into the circuit (6) at the connection between the lung simulator and the head phantom, with its concentration monitored by a downstream sensor (7) (MultiGasAnalyser OR-703, MultiGasAnalyser). A CO<sub>2</sub> absorber (SmartCan™, Intersurgical SpA, Italy) (8) was placed after the patient interface to eliminate CO<sub>2</sub> from the

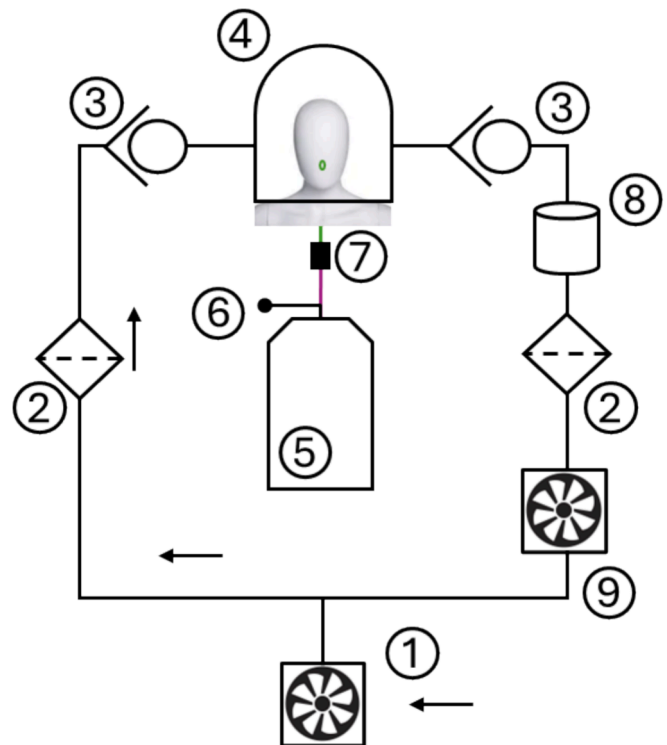


Fig. 1. Block diagram of the experimental test bench. 1) Primary turbine, 2) antiviral filter, 3) unidirectional valve, 4) patient interface, 5) lung simulator, 6) CO<sub>2</sub> source, 7) CO<sub>2</sub> sensor, 8) CO<sub>2</sub> adsorber, 9) secondary turbine. The arrows represent the direction of the airflow. The violet line represents the connection between the CO<sub>2</sub> injection point and the CO<sub>2</sub> sensor; the tubing has an approximate volume of 50 ml. The green line, extending from the CO<sub>2</sub> sensor to the phantom's mouth, has a volume of approximately 27 ml. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

expiratory limb. Preliminary downstream measurements were performed to verify complete CO<sub>2</sub> elimination in the expiratory limb, ensuring that only CO<sub>2</sub>-free air entered the inspiratory limb. A secondary turbine (9) (ebmpapst, RVE45.3/54/2P, St. Georgen GmbH & Co. KG.) was then integrated into the circuit to generate additional recirculation airflow.

## 2.2. Interfaces and recirculation airflow

The investigation of CO<sub>2</sub> accumulation was conducted on four helmet (free volume when mounted on the phantom head: about 20 l) and two mask (about 0.5 l) designs, each distinguished by specific inlet and outlet ports positions (Fig. 2). The standard *Lateral Input/Lateral Output Helmet* (StarMed CaStar R, Intersurgical SpA), commonly used in clinical practice, was tested first. Subsequently, three custom helmets were evaluated: (i) the *Lateral Inlet/Front Outlet Helmet*, modified by sealing the lateral outlet and using a front-facing port typically designated for drug administration, (ii) the *Up Inlet/Up Outlet Helmet*, with both ports positioned overhead; and the (iii) *Up Inlet/Front Outlet Helmet* with the inlet overhead and the outlet in front of the patient's mouth. Additionally, two commercial total-face masks were tested: (i) *One-port Mask* (FitMax™, Intersurgical std), with a single port near the patient's mouth and (ii) *Two-ports Mask* (DiMax ZERO, Dimar), with separate inlet and outlet ports.

CO<sub>2</sub> accumulation in all the interfaces was measured under three recirculation airflow conditions, where *recirculation airflow* refers only to the flow generated by the secondary turbine, and not to the airflow resulting from the patient's spontaneous breathing (patient minute ventilation of approximately 15 l/min, see paragraph 2.3): (i) without recirculation airflow (0 l/min) and (ii) with recirculation airflow rates of

60 l/min and (iii) 80 l/min. These high airflow values are commonly imposed by high-flow CPAP systems (the only ones using helmets as patient interfaces), as they are considered the minimum required to ensure (i) pressure stability in the presence of a PEEP valve, and (ii) adequate CO<sub>2</sub> washout from the interface. The most commonly used flow rates start from 60 l/min (Grieco et al., 2021) and can even exceed 100 l/min, as supported by the capabilities of standard flowmeters (HAROL, FLOW GENERATOR FOR CPAP THERAPY). However, in a closed circuit, it is not possible to exceed 80 l/min, which was therefore set as the upper limit in this study, due to the resulting increase in flow resistance that limits the range of CPAP levels achievable by the primary turbine.

## 2.3. Testing procedure

Before measurements, the CO<sub>2</sub> sensor was calibrated with ambient air following the manufacturer instructions. The testing procedure involved these steps:

- With the lung simulator set to an apnoea condition, the secondary turbine was activated, and its velocity increased until reaching the target flow rate (60 or 80 l/min). This step was omitted in the 0 l/min case.
- The lung simulator was activated to simulate ARDS patient's ventilation with specific parameters: total respiratory compliance (40 ml/mbar), functional residual capacity (880 ml), respiratory rate (36 bpm), minute ventilation (15 l/min), and maximum respiratory effort (17 mbar/100 ms) (Cammarota et al., 2021; Chiumello et al., 2008; Kondili et al., 2002).
- The CPAP therapy level was set at 5 cmH<sub>2</sub>O.

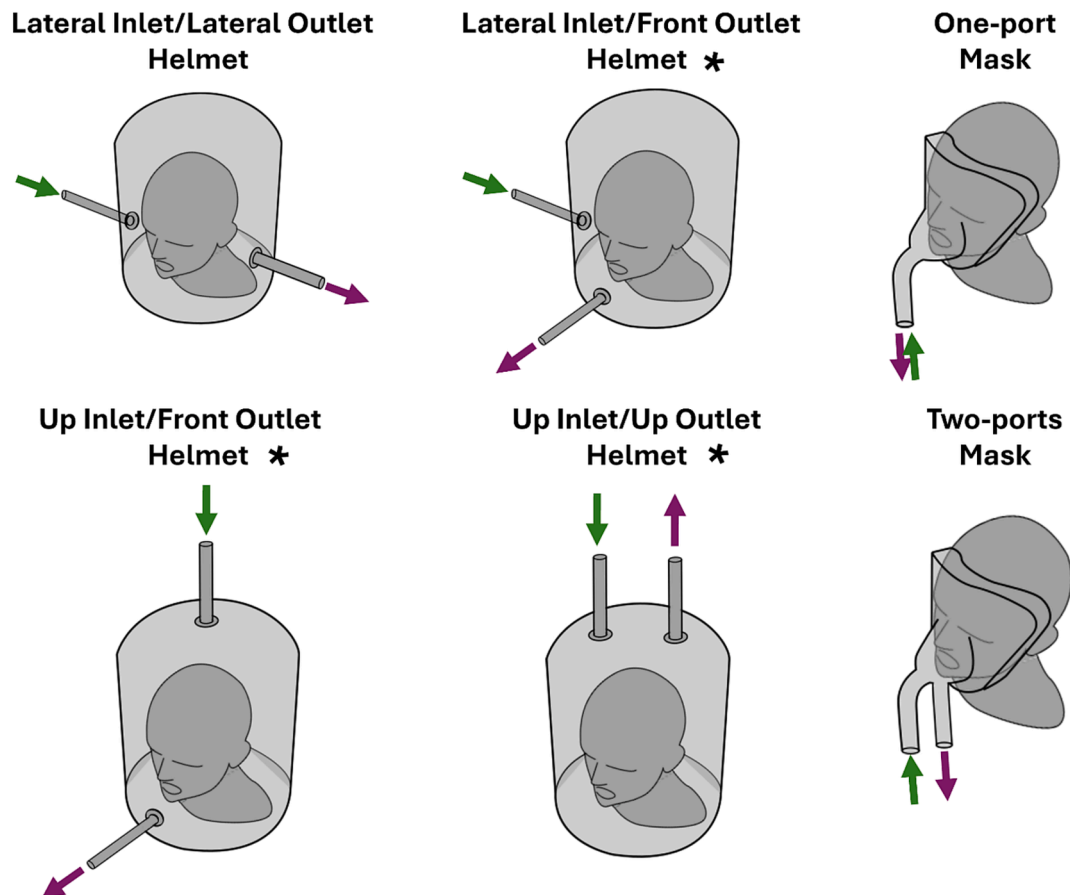


Fig. 2. Tested interfaces. The green and violet arrows represent the flow in the inlet and outlet ports, respectively. \*Indicates custom made interfaces. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

- The exhaled air mixture of a patient with pulmonary fatigue was simulated with a CO<sub>2</sub> concentration of 4–5 % (Al Hussain and Vines, 2022; Messineo et al., 2024). In detail, using the lung simulator as a mixing chamber, a uniform concentration was reached by gradually increasing the CO<sub>2</sub> flow from its source, and by waiting a sufficient amount of time for CO<sub>2</sub> level stabilization.
- The simulated respiratory flow (Fig. 3a) and the CO<sub>2</sub> concentration (Fig. 3b) were measured over 36 breathing cycles at 200 Hz.

From the measured data, inspiratory and expiratory phases were determined by detecting the zero-crossings of the flow curve. In addition, the inhaled CO<sub>2</sub> percentage (Eq. (1)) was calculated by integrating the measured CO<sub>2</sub> concentration over the inspiratory phase (from t<sub>1</sub> to t<sub>2</sub>, Fig. 3c) and normalizing it to the tidal volume (V<sub>t</sub>), which was directly obtained from the lung simulator by integrating the flow curve.

$$\text{Inspired CO}_2 \% = \frac{1}{V_t} \int_{t_1}^{t_2} \text{CO}_2(t) \bullet \text{Flow}(t) dt \bullet 100 \quad (1)$$

The tidal volume measured for each interface is reported in the [Supplementary Materials \(Table S1\)](#) as mean ± standard deviation.

#### 2.4. Statistical analysis

The inhaled CO<sub>2</sub> percentage for each interface and flow rate, was reported as mean and standard deviation over the 36 respiratory cycles. Normality was assessed with the Kolmogorov-Smirnov test.

The effects of interface volume, inlet and outlet positions, and the flow rates on the inhaled CO<sub>2</sub> percentage were analysed across all the 18 different combinations.

A nested ANOVA was performed with inhaled CO<sub>2</sub> percentage as the dependent variable, and interface volume (helmet vs mask), flow rate (0, 60, 80 l/min), and inlet/outlet position (nested within interface volume) as independent variables, to assess both individual and interaction effects on inhaled CO<sub>2</sub>.

Separately, two-way ANOVAs were also conducted for helmets and total-face masks to assess the impact of inlet/outlet positions and the flow rates, followed by Tukey-Kramer post-hoc tests ( $\alpha = 0.05$ ). Analyses were conducted in MATLAB (R2023b, MathWorks, Natick, MA, USA).

### 3. Results

Inhaled CO<sub>2</sub> percentages were calculated for all 18 tested configurations (Fig. 4A), along with the ratio between inhaled and exhaled CO<sub>2</sub> to provide a normalized comparison across variations in exhalation (Fig. 4B).

The results showed high repeatability, with standard deviations ranging from 0.01 to 0.09, contributing to the statistical significance observed in most ANOVA tests.

The nested ANOVA confirmed that both interface volume ( $p < 0.001$ ) and the recirculation airflows ( $p < 0.001$ ) significantly affect inhaled CO<sub>2</sub> levels. The analysis also revealed that, within each interface type (helmet or mask), the position of inlet and outlet ports also had a strong impact ( $p < 0.001$ ).

The two-way ANOVAs run separately for helmets and masks suggested that inlet and outlet positions have a significant combined effect with the recirculation airflow rates ( $p < 0.001$ ).

Among helmets, the *Lateral inlet/Lateral outlet* configuration (the standard in clinical practice) always showed the highest inhaled CO<sub>2</sub> levels (2 % at 0 l/min, 1.3 % at 80 l/min). In contrast, modifying the inlet and outlet positions, significantly reduced rebreathing. The most effective configuration was the *Up Inlet/Front Outlet Helmet*, where inhaled CO<sub>2</sub> levels dropped to 0.6 % at 80 l/min. Across all configurations, increased flow rates led to lower inhaled CO<sub>2</sub> percentage, especially between 0 and 60 l/min (average drop: 0.6 %), with a smaller reduction from 60 to 80 l/min (0.3 %). An exception was the *Up Inlet/Up Outlet Helmet*, which showed a drop of 0.8 % between 0 and 60 l/min, but no further decrease at 80 l/min. For masks, the Tukey-Kramer post-hoc test revealed significant differences between configurations. The *Two-ports Mask* always outperformed the *One-port Mask*, halving CO<sub>2</sub> levels (from 0.4 % at 0 l/min to 0.1 % at 80 l/min). Increasing flow had little effect on mask performance overall. Uniquely the *One-port Mask* exhibited no clear trend: inhaled CO<sub>2</sub> slightly increased from 1.26 % at 0 l/min to 1.43 % at 60 l/min, then dropped slightly to 1.37 % at 80 l/min.

Fig. 4B interestingly mirrored the trend observed in Fig. 4A, confirming the consistency of the results when inhaled CO<sub>2</sub> was normalized to the amount of exhaled CO<sub>2</sub> levels.

Applying a 1 % safety threshold for inhaled CO<sub>2</sub> for patient safety,

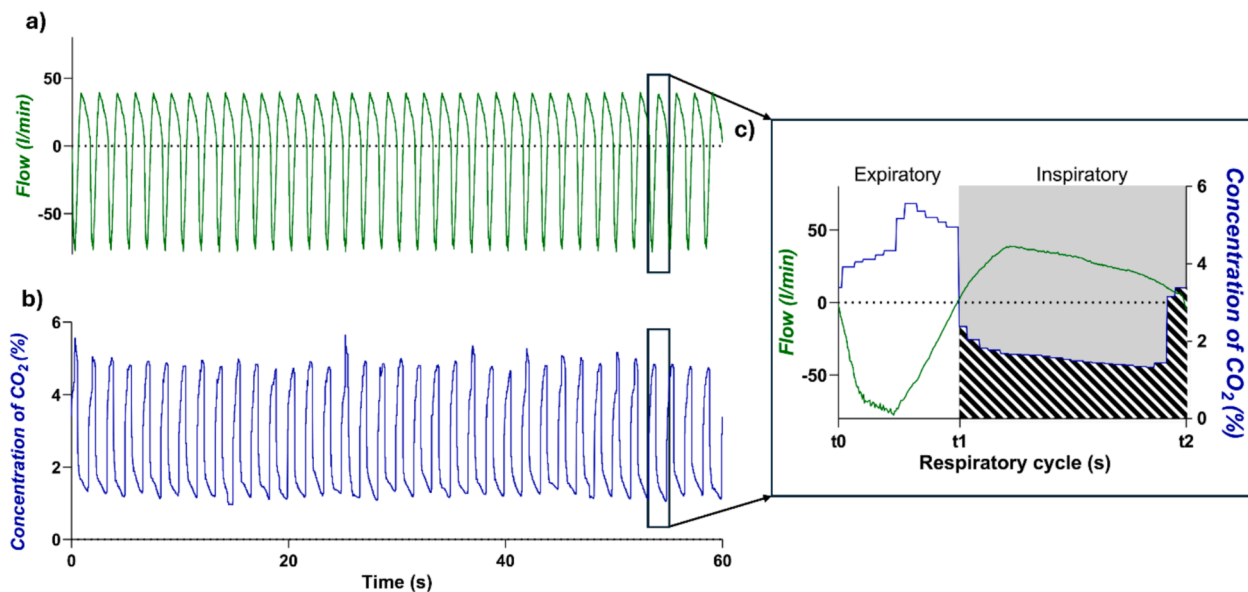
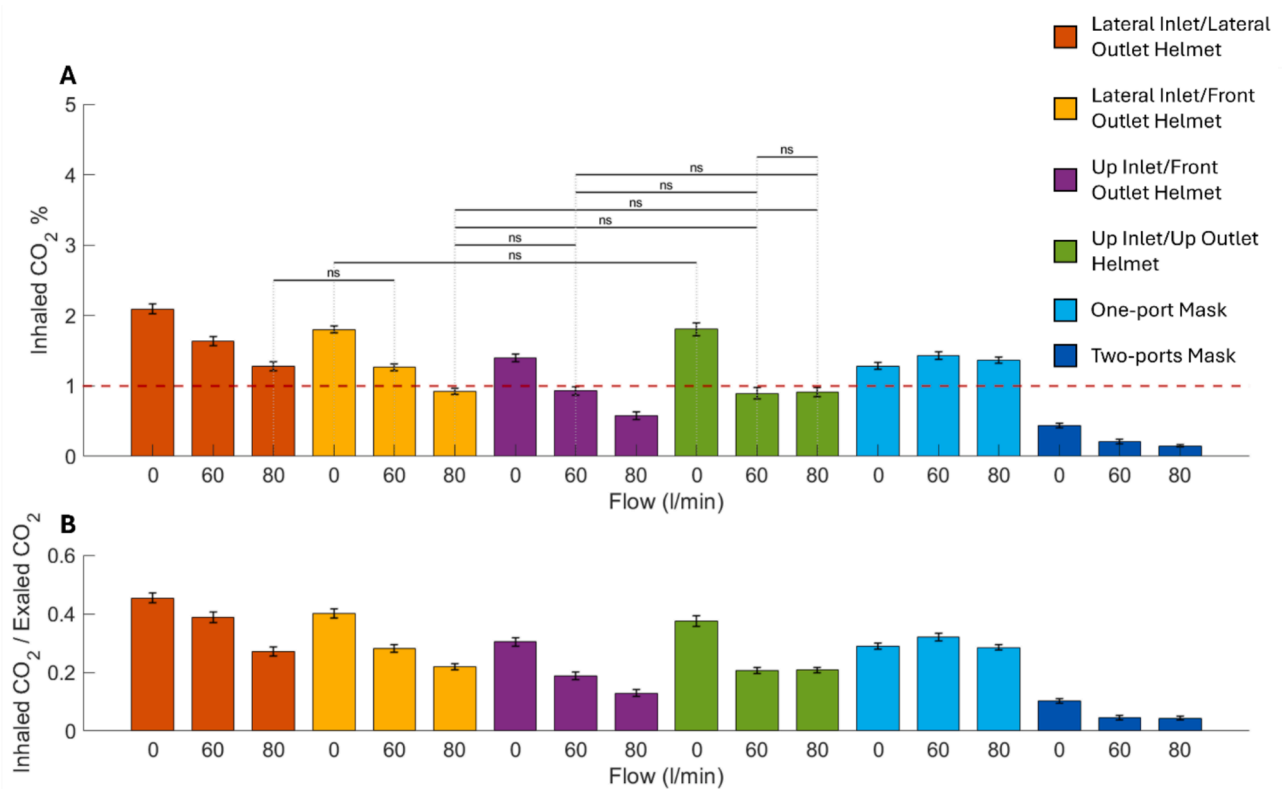


Fig. 3. Example of the curves recorded at patient interface during the experimental tests. a) Flow-time curve. b) Concentration of CO<sub>2</sub>-time curve, measured simultaneously with the flow. c) Detailed view of a single respiratory cycle, showing both the flow and CO<sub>2</sub> concentration curves. The inspiratory phase is highlighted in grey compared to the expiratory phase, with the shaded area indicating the percentage of CO<sub>2</sub> inhaled.



**Fig. 4.** A) Mean inhaled CO<sub>2</sub> percentages ( $\pm$  standard deviation) across the 18 tested configurations at different flow rates (x-axis). The red dashed line at 1 % marks the safety threshold for inhaled CO<sub>2</sub>. Black horizontal bars indicate statistically non-significant (ns) differences between configurations according to the Tukey-Kramer post-hoc test. B) Mean inhaled CO<sub>2</sub>/Exhaled CO<sub>2</sub> ( $\pm$  standard deviation) across the 18 tested configurations at different flow rates (x-axis). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

several configurations met this target. Helmets with optimized port positioning, such as *Up Inlet/Up Outlet Helmet* (at 60 l/min) and *Lateral Inlet/Front Outlet* (at 80 l/min), successfully flushed exhaled CO<sub>2</sub>. Notably, the *Up Inlet/Front Outlet Helmet* maintained CO<sub>2</sub> levels at just 0.5 % at 80 l/min. The *Two-ports Mask* always kept inhaled CO<sub>2</sub> below 1 % in all airflow rates, even without the additional recirculation airflow.

#### 4. Discussion

CO<sub>2</sub> rebreathing remains a significant concern in NIV therapies, including CPAP. While CPAP is typically administered through open circuits, a closed circuit has recently been proposed (Cavaglià et al., 2021), to reduce oxygen consumption and environmental contamination. However, this design may increase CO<sub>2</sub> rebreathing, necessitating a thorough investigation to ensure patient safety. This study aimed to quantify the inhaled CO<sub>2</sub> during closed-circuit CPAP and evaluate how the interface volume, inlet/outlet port positions, and airflow rates influence CO<sub>2</sub> accumulation within patients' interface.

For the study, a custom testbench was developed to measure CO<sub>2</sub> concentration at the interface, integrating a CO<sub>2</sub> absorber in the expiratory limb to eliminate recirculated CO<sub>2</sub>. This setup ensures that all measured CO<sub>2</sub> originates from patient's exhalation and accumulation within the interface, as in conventional or ventilator-delivered CPAP. Therefore, the findings can be generalized across CPAP systems, enhancing the understanding of how interface design and flow rates impact inhaled CO<sub>2</sub>.

In this regard, the choice of proposing a 1 % safety threshold for the inhaled CO<sub>2</sub>, should be considered as a comparative benchmark, aimed at providing a reference for the results obtained across different configurations and potentially serving as a starting point for defining a widely accepted limit for inhaled CO<sub>2</sub> during CPAP therapy.

Consistently, Al Hussain and Vines (2022) reported that inspired CO<sub>2</sub> levels between 1 % and 4 % can significantly increase PaCO<sub>2</sub>.

The experimental results show that CO<sub>2</sub> can be kept below 1 % when using either the *Up Inlet/Front Outlet Helmet* with additional recirculation airflow or the *Two-ports Mask*, even without recirculation airflow. These findings support the potential clinical use of closed-circuit CPAP, as the new configurations already showed comparable pressure dynamics to conventional CPAP configurations, especially with the helmet interfaces (De Luca et al., 2025).

Consistent with previous studies, the results confirm that the volume of the interface is a key factor in CO<sub>2</sub> accumulation, with helmets being more prone due to their larger volume (Esquinas Rodriguez et al., 2013; Messineo et al., 2024). Interestingly, among the tested helmets, the commercial standard *Lateral Inlet/Lateral Outlet Helmet* exhibited the highest CO<sub>2</sub> levels (>1% even at 80 l/min, a flow rate commonly used in open CPAP configuration). In contrast, modifying the position of inlet and outlet ports proved highly effective in mitigating CO<sub>2</sub> retention. The *Up Inlet/Front Outlet Helmet* recorded the lowest CO<sub>2</sub> levels among helmets (0.6 % at 80 l/min), thanks to its optimized directional airflow. This design channels exhaled air more efficiently out of the helmet by placing the outlet directly in front of the patient's mouth, thereby shortening the path of the exhausted air toward the outlet and minimizing its mixing with fresh air.

Although, total-face masks have smaller volumes, their safety concerning CO<sub>2</sub> rebreathing cannot be assumed, as stated by Gil et al. (2021) who noted that their design can cause exhaled gases to accumulate close to the patient's face. Consistently, the *One-port Mask* exceed the safety threshold, regardless of the airflow rate, likely due the shared inlet and outlet port, which determines an additional dead space. This configuration, in our experimental setting, also displayed an unusual behaviour, with the highest inhaled CO<sub>2</sub> percentage observed at 60 l/

min. The One-port mask has indeed a single entry for both inspired and expired air, where a Y-split is connected to separate the two flows. Expired air tends to accumulate between the interface and the split, creating a *dead space* bypassed by the recirculation flow, and contributing to CO<sub>2</sub> buildup in the circuit. In contrast, the *Two-ports Mask* exhibited the lowest inhaled CO<sub>2</sub> levels, remaining below the 1 % even without recirculation flow, and confirming previous findings (Rezoagli et al., 2022) that selective ports for inhaled and exhaled gases in mask improve CO<sub>2</sub> clearance.

Overall, this study corroborates that increasing airflow significantly reduces CO<sub>2</sub> rebreathing across most interface configurations, supporting previous findings by Racca et al. (2008) and Taccone et al. (2004). However, the effectiveness of increased flow varies depending on the interface type. Helmets, in particular, show the greatest improvement between 0 and 60 l/min, aligning with results from Santos Tomaz et al., 2022, who reported that flow adjustments have an optimal range for reducing rebreathing. For instance, in the *Up Inlet/Up Outlet Helmet*, no further CO<sub>2</sub> reduction was observed when flow increased from 60 to 80 l/min. In this configuration, air enters and exits from the top of the helmet, causing the flow to recirculate above the patient's head before reaching the outlet. This flow pattern allows some exhaled air to remain trapped in the helmet's volume, increasing CO<sub>2</sub> accumulation near the patient's mouth. These findings suggest that the most effective interfaces are not only those with separate inlet and outlet ports, but also those designed to guide airflow from the inlet to the outlet, avoiding obstructions or direct flow impingement on the patient's face. For example, the *Up Inlet/Front Outlet Helmet* showed lower inhaled CO<sub>2</sub> levels than the *Lateral Inlet/Front Outlet Helmet*, likely due to the more direct and efficient flow path created by the top inlet. In contrast, total-face masks, due to their smaller volume, showed minimal changes in inhaled CO<sub>2</sub> levels with increasing flow.

While this study offers valuable insights into the onset of CO<sub>2</sub> rebreathing during NIV, certain limitations must be acknowledged. Indeed, the experimental setup, though designed to simulate ARDS patients, may not fully capture the variability of clinical scenarios. Specifically, (i) the continuous and controlled CO<sub>2</sub> delivery in our model does not reflect the dynamic nature of CO<sub>2</sub> production in real patients, which varies with metabolic rate, physical activity, and pathological conditions; (ii) the standardized tidal volumes and breathing patterns do not replicate the variability seen in clinical practice, where respiratory mechanics and patient's effort differ significantly; (iii) our short-term measurements may not account for changes over prolonged therapy durations, such as secretion buildup or alterations in lung mechanics; (iv) system leaks were not quantified during the tests, as minimizing resistance to exhalation is crucial in a closed circuit. The use of flow sensors would have introduced significant resistance, potentially affecting patient effort and test accuracy. Nevertheless, the developed setup enabled the *in vitro* comparison of different configurations of a novel ventilation system under identical simulated respiratory conditions, leading to findings that would otherwise be difficult to obtain due to inter-subject variability of real patients.

## 5. Conclusion

This study demonstrates that, under specific conditions, CPAP closed circuit can maintain inhaled CO<sub>2</sub> levels below the 1 %. The findings on CO<sub>2</sub> rebreathing across different interfaces remain valid also for conventional CPAP configurations and ventilators. Regarding helmets, repositioning the inlet and/or outlet ports, combined with a recirculation airflow of 60 or 80 l/min, significantly reduced rebreathing reducing. In particular, the *Lateral Inlet/Front Outlet Helmet* (at 80 l/min of recirculation airflow) and *Up Inlet/Up Outlet Helmet* and *Up Inlet/Front Outlet Helmet* (at 60 and 80 l/min of recirculation airflow) maintained inhaled CO<sub>2</sub> levels below 1 %. Regarding total-face masks, the *One-port Mask* CO<sub>2</sub> levels between 1 % and 1.5 % even with additional flow rate, whereas the *Two-ports Mask* effectively prevented rebreathing at all

tested flow rates.

These findings highlight the importance of interface design optimization to improve patient safety and therapeutic outcomes during NIV therapy.

## CRedit authorship contribution statement

**Margherita De Luca:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Andrea Formaggio:** Writing – review & editing, Data curation, Conceptualization. **Mara Terzini:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Giovanni Putame:** Writing – review & editing, Data curation, Conceptualization. **Carlo Olivieri:** Writing – review & editing, Supervision, Conceptualization. **Simone Borrelli:** Writing – review & editing, Writing – original draft, Supervision, Data curation. **Alberto L. Audenino:** Writing – review & editing, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

This publication is part of the project NODES which has received funding from the MUR – M4C2 1.5 of PNRR funded by the European Union – NextGenerationEU (Grant agreement no. ECS00000036). The author MDL is supported under Ministerial Decree No. 1061/2021 within the framework of the FSE REACT-EU program – PON Research and Innovation 2014-2020. The author GP is supported under Ministerial Decree No. 1062/2021 within the framework of the FSE REACT-EU program – PON Research and Innovation 2014-2020.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jbiomech.2025.112826>.

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