while the remaining consolidation showed early homogeneous enhancement (<6 s) and delayed washout (>1 min) (Fig. 1B–F). In view of these findings, we decided to biopsy the first of these areas with a 22 G fine needle; it was reported as alveolar metastasis of pancreatic adenocarcinoma (Fig. 1G). Because the rest of the consolidation showed suggestive characteristics of a pneumonia process, we decided to perform fiberoptic bronchoscopy; samples obtained showed a fungal infection (Fig. 1H).

In our patient we were able to differentiate between pneumonia and metastasis, as she presented pre-existing pulmonary consolidation containing a hypoechoic area. On contrast-enhanced ultrasound, the consolidation showed late homogeneous uptake with delayed washout, with the exception of the central and peripheral areas that showed late enhancement but early washout, suggestive of malignancy. This enhancement pattern also helped guide the percutaneous biopsy to the most suspicious target area to improve the diagnostic yield of the samples collected.

Ultrasound-guided biopsy is an alternative to CT-guided biopsy for peripheral or pleural lung lesions[1,3] and achieves a similar diagnostic effectiveness and yield as CT[5]. Additionally, ultrasound-guided percutaneous procedures offer certain advantages, such as real-time monitoring of the procedure, absence of radiation, lower costs and duration of the procedure, and the complication rates are similar to or lower than with CT-guided biopsy[1,2]. In many cases, contrast-enhanced chest ultrasound helps clarify the nature of the lesion under study and, if necessary, guides the biopsy needle towards areas of interest, avoiding necrotic foci[1,2,6] and targeting areas with a greater suspicion of malignancy, as in the case presented.

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High O₂ Flow Rates Required to Achieve Acceptable FiO₂ in CPAP-Treated Patients With Severe Covid-19: A Clinically Based Bench Study

Se requieren altos índices de flujo de O2 para alcanzar una FiO2 aceptable en los pacientes con covid-19 tratados con CPAP: un estudio experimental basado en la clínica

Dear Editor,

During the Covid-19 pandemic, a lack of ventilatory equipment in intensive care units (ICU), or patient comorbidities meant that some patients received non invasive, continuous positive airway pressure (CPAP), with the highest fraction of inspired oxygen (FiO2) as a ceiling treatment.[1–3] In Le Havre hospital (France), between September and December 2020, around 30 patients were treated with bilevel home devices in CPAP mode using vented oronasal masks. In contrast with bench studies that reported high FiO₂ with oxygen flow rates < 30 L/min in optimal experimental conditions (i.e., low minute ventilation, good pulmonary compliance and no leakage),[4,5] many patients required O₂ flow rates > 70 L/min to maintain oxygen saturation (SpO₂) ≥ 90%. We hypothesised that due to the high respiratory demand of patients with severe Covid-19, a high O₂ flow rate would be required to reach adequate pressure levels with CPAP, thereby substantially increasing the oxygen flow rate needed to achieve a high FiO₂. We carried out a bench study to measure the oxygen flow rates needed to reach high FiO₂ levels, using a pulmonary model that reproduced the characteristics of patients with severe Covid-19.

First, we extracted clinical data from 10 consecutive patients who were included in an ongoing clinical trial (EURO-CPAP CT2220141 approved by our institutional review board) from the CPAP built-in software. This case series is presented for descriptive purposes to illustrate our hypothesis. Then, we performed several bench experiments. We used a CPAP device (AirSense 10 AutoSet, ResMed, San Diego, CA, USA) set at 10 cmH₂O, connected to an artificial lung (ASL 5000, Ingmar Medical, Pittsburgh, PA, USA). A low-resistance antibacterial filter (Clear-Guard, Intersurgical, Wokingham, UK), an oxygen inlet connector, a 15 mm single limb circuit, a Whisper Swivel II Exhalation port (Philips Respironics, Murrysville, PA, USA) that simulated intentional leaks, and the artificial lung were placed in series and connected to the CPAP device. A standard 4-mm diameter leak port was placed between the exhalation port and the artificial lung to mimic unintentional leakage. Oxygen was delivered into the system using two O₂ flow meters (EASY MED-O₂, Air Liquide Healthcare, Paris, France) that could both deliver up to 50 L/min. Three different mechanical lung conditions were simulated by modulating the resistance (R) and the compliance (C) of the artificial lung, corresponding to the following experimental models:

A. Normal: $R = 5$ cmH₂O/l s and $C = 60$ ml/cmH₂O.
B. Restrictive: $R = 5$ cmH₂O/l s and $C = 30$ ml/cmH₂O.
C. Normal with by-pass leak using a T-connector as recommended to reduce the risk of droplet aerosolization.[6]

Each model was run at breathing frequencies of 22, 30 and 35 cycles per minute (cpm), associated with inspiratory airway pressure drops of 2.5–6 cmH₂O at 100 ms (P0.1) to reach tidal volumes of around 600 ml. The values of the inspiratory effort settings chosen for the simulation in the ASL5000 were based on pub-
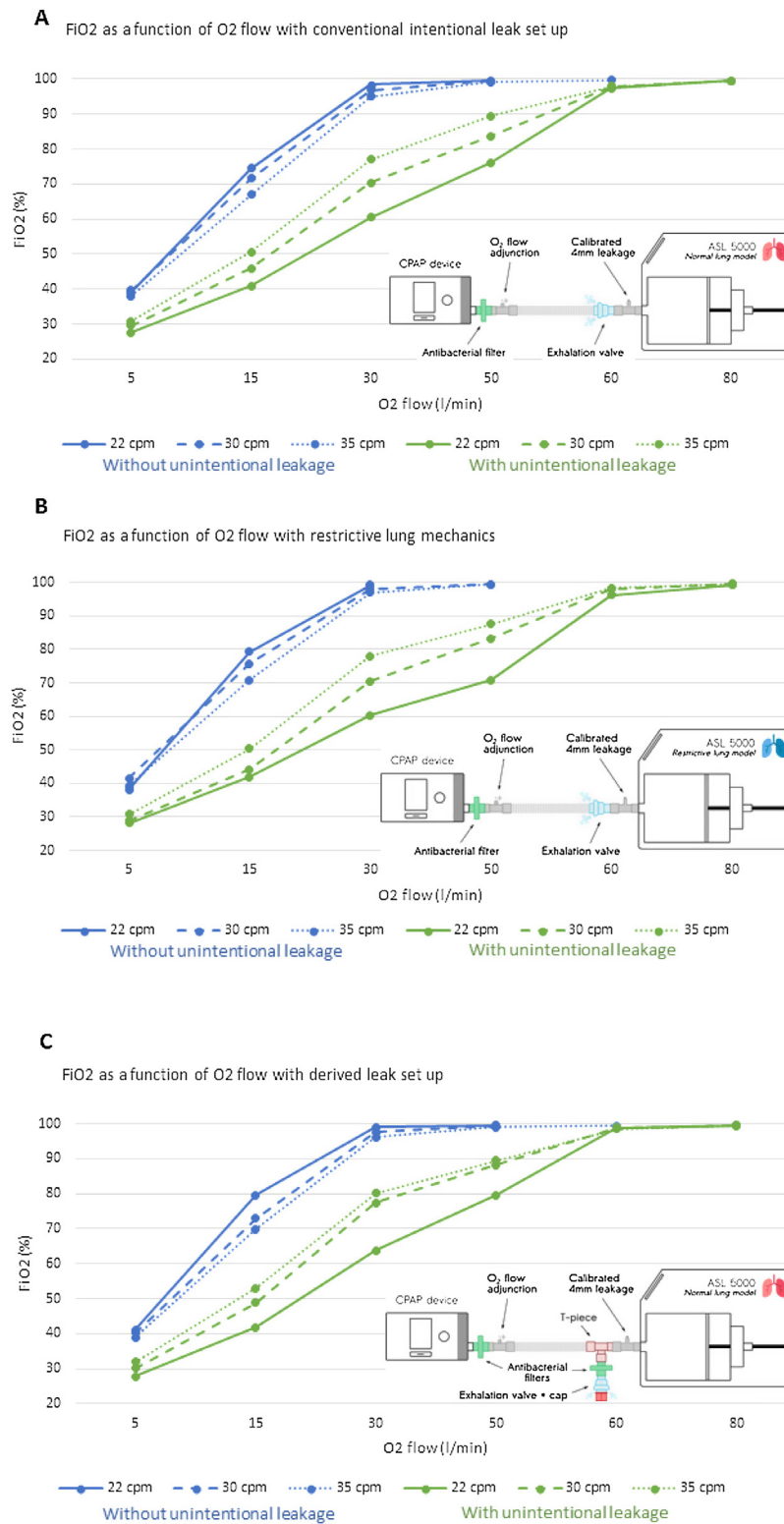
Fig. 1. Dose–response relationship between oxygen (O_2) flow rates delivered into the circuit, and fraction of inspired oxygen (FiO_2) as a function of respiratory rate, presence/absence of non-intentional leakage, lung mechanics and leak port locations. Each Plot represents the mean FiO_2 of the 10 cycles analysed. For each FiO_2, the standard deviation was systematically below 0.3 and is therefore not represented on the graph. Panel A displays the results for the conventional intentional leak model, in which the unintentional leakage port was placed in series between the exhalation valve (intentional leak port) and the ASL 5000. Panel B displays the results for the same model as in panel A, but with restrictive lung mechanics. Panel C displays the results for by-pass leakage ports using an antibacterial filter between the ASL 5000 and both intentional and non-intentional leak ports. The blue lines represent the relationship between O_2 flow and FiO_2 without unintentional leaks, and the green lines represent the relationship between O_2 flow and Fi_2O with unintentional leaks.

Table 1

Descriptive data from 10 consecutive patients treated with CPAP and O_2. Leakage, Tidal Volume (Vt) and Respiratory Rate (RR) were collected from built-in CPAP software during the first 48 h of CPAP treatment.

Patient	Age (years)	Sex	BMI (kg/m^2)	CRF	CF	AH	DT2	PAO$_2$/FiO$_2$ at CPAP initiation	CPAP level (cm H$_2$O)	Median leakage (l/min)	Mean Vt (ml)	Mean RR (cycle per minute)	O$_2$ flow[a] (l/min)	SpO$_2$ (%)
1	87	M	20.8	–	–	–	–	122	10	43.5[a]	490	29	70	96
2	72	M	33.7	–	–	–	Yes	120	7	0[b]	374.5	34.5	15	93
3	61	M	41.3	–	–	Yes	Yes	151	10	5[b]	409.5	23	15	92
4	83	M	29.6	–	Yes	Yes	-	82	8	6[b]	490	38.5	50	95
5	85	M	27.3	–	Yes	Yes	-	143	10	35[a]	927	30.5	30	94
6	70	M	31.9	–	Yes	Yes	Yes	101	10	35[a]	1108	38	100	92
7	80	M	33.3	Yes	-	Yes	Yes	58	7	0[b]	938	34	100	89
8	77	M	23.6	Yes	Yes	Yes	Yes	67	12	7[b]	972.5	38.5	50	93
9	55	M	21	–	Yes	–	–	134	8	43.5[a]	473	24	30	98
10	84	M	26.1	–	Yes	Yes	–	90	10	MD	625	39.5	100	90

Body mass index: BMI; chronic respiratory failure: CRF; cardiac failure: CF; arterial hypertension: AH; type 2 diabetes: DT2; continuous positive airway pressure: CPAP; partial O_2 pressure in arterial blood: PaO_2; fraction of inspired oxygen: FiO_2.

[a] Total leakage.

[b] Unintentional leakage.

lished clinical values.[7–11] Each condition was run with and without unintentional leakage. FiO_2 was measured with 5, 15, 30, 50, 60 and 80 L/min of O_2, and the experiment was stopped when 100% FiO_2 was reached. The sensor used was a paramagnetic oxygen transducer located in the ASL 5000 piston chamber which allowed a fast measurement with a response time below 350 ms. Ten respiratory cycles were analysed after the FiO_2 had reached an asymptote for each model at each O_2 flow rate. Normality and homogeneity were assessed using Shapiro-Wilk and Levene tests, respectively. Welch's ANOVA was used to compare respiratory rates at each O_2 flow rate. A Games-Howell post-hoc procedure was applied for multiple comparisons, with 22 cpm as the reference condition. Significance was set at 0.05. Statistical analysis was performed using IBM SPSS Statistics V25.

Data from 10 consecutive patients with Covid-19 treated with CPAP and O_2 are presented in Table 1. Six patients needed O_2 flow rates ≥ 50 L/min to maintain $SpO_2 > 90\%$. Minimum O_2 flow rate was 15 L/min. All patients had severe infection (i.e., PaO_2/FiO_2 ratio ≤ 150 at CPAP initiation).

Fig. 1 shows the relationship between the O_2 flow rate delivered and the resulting FiO_2 in the simulation. Without unintentional leaks, a flow rate of at least 30 L/min was necessary to reach $FiO_2 > 95\%$. FiO_2 differed significantly for each respiratory rate at each O_2 flow rate with and without unintentional leaks ($p < 0.001$). With unintentional leaks, O_2 flow rates of up to 80 l/min were required to reach 100% FiO_2 (Fig. 1A–C).

The results of this experimental bench study confirmed our clinical observation that high O_2 flow rates are required to achieve a high FiO_2 in patients with severe Covid-19 using CPAP and vented masks. An O2 flow rate of at least 30 L/min, and up to 80 L/min, was required to achieve 100% FiO2 for all three experimental models. Reduced compliance and unintentional leakage dramatically reduced FiO_2. The arbitrary compliance of 30 ml/cmH$_2$O used in model B is similar to that of patients with severe COVID-19.[12] Such a low level of compliance would reduce the FiO_2 with home CPAP and a vented mask, further confirming the need for high O_2 flow rates. In our clinical cohort, three patients required an O_2 flow rate above 80 L/min: this very high rate causes two concerns. Firstly, we did not know the lung compliance of these patients. Secondly, the O_2 flow rate required to achieve a given FiO_2 is likely to be underestimated with the experimental model compared to the clinical situation, since no gas exchange occurs with an artificial lung. For instance, in a patient, with a 21% FiO_2, the partial pressure of O_2 in the inspired air will be 160 mm Hg, while in the expired air (at sea level) it will be 120 mm Hg due to oxygen absorption. Thus, in vivo conditions even higher O_2 flows than those reported in this study may be required.[13]

Another important point is that many teams use helmets to ventilate patients with Covid-19.[2,14] Helmets could be more advantageous than oronasal masks because of the lower rate of unintentional leakage; this would allow lower oxygen flow rates to be used to achieve sufficient FiO_2 levels for patients with severe hypoxemia.

Studies have shown that patients who cannot be intubated require a high FiO_2 to maintain their SpO_2 above 92%,[3,15] and that poor oxygenation is strongly associated with mortality.[3,16] Our study provides valuable data to guide clinicians in the use of O_2 when using home CPAP in patients with severe Covid-19 who cannot be intubated. The results showed that these patients can be successfully treated with home CPAP devices, or NIV devices in CPAP mode, with vented masks, if a high O_2 flow rate is provided. However, close monitoring of unintentional leaks is crucial to ensure a sufficient FiO_2 for the treatment of severe hypoxemia in these patients.

Authors' contribution

All authors participated in the study design, research, and manuscript preparation. Dr. Marius Lebret is the guarantor of the content of the manuscript, including the data and analysis.

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Conflict of interest

ML reports receiving personal fees from Air Liquid Medical Systems and non-financial support from NOMICS over the past 3 years, for work unrelated to the work presented here. ML is a part-time employee of Air Liquide Medical System (Med2lab).

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