Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

sis pulmonares consolidativas. Dado que la consolidación de mayor tamaño, localizada en el lóbulo inferior derecho, presentaba amplio contacto con la pleura periférica, se optó por realizar una biopsia con guía ecográfica. Se administraron 2,4 ml de contraste ecográfico (SonoVue, Rovi, Pozuelo de Alarcón, Madrid, España) y se objetivaron dos zonas diferenciadas según el patrón de captación: un área periférica con captación tardía (más allá de los 6 segundos postinyección) y lavado precoz (desaparición de la captación de contraste a los pocos segundos de iniciarse la captación) y el resto de la consolidación con captación precoz (antes de 6 segundos) y homogénea y lavado tardío (más allá de un minuto) (fig. 1B-F). Ante estos hallazgos se decidió biopsiar la primera de las zonas descritas con aguja fina de 22G con el resultado de metástasis alveolar de adenocarcinoma pancreático (fig. 1G). Debido a que el resto de la consolidación mostró características sugestivas de proceso neumónico se decidió realizar fibrobroncoscopia y toma de muestras que demostraron una infección fúngica (fig. 1H).

El caso expuesto se incluye dentro de este grupo, pues existía una consolidación neumónica preexistente con un área hipoecoica en su interior. Tras el estudio con contraste ecográfico la consolidación presentó una captación tardía y homogénea con lavado tardío a excepción del área central y periférica cuyo comportamiento mostró una captación tardía pero lavado precoz, sugestivo de malignidad. El patrón de captación objetivado permitió además guiar la biopsia percutánea hacia la zona deseada más sospechosa para mejorar la rentabilidad diagnóstica en la obtención de muestras.

La biopsia con guía ecográfica es una alternativa a la realizada mediante TC para las lesiones pulmonares periféricas o pleurales[1,3] y alcanza una efectividad y rentabilidad diagnóstica similar a la obtenida con TC[5]. Adicionalmente, los procedimientos percutáneos guiados por ecografía ofrecen ciertas ventajas tales como la monitorización del procedimiento en tiempo real, la ausencia de radiación, menores costes y duración del procedimiento, con ratios de complicaciones similares o menores a los de la biopsia guiada por TC[1,2]. En muchos casos el estudio con ecografía torácica con contraste ayuda a comprender la naturaleza de la lesión a estudio y guiar, en caso que fuere necesario, la toma de muestras hacia áreas de interés evitando focos necróticos[1,2,6] o hacia las zonas de mayor sospecha de malignidad como en el caso presentado.

Bibliografía

1. Caremani M, Benci A, Lapini L, Tacconi D, Caremani A, Ciccotosto C, et al. Contrast enhanced ultrasonography (CEUS) in peripheral lung lesions: A study of 60 cases. J Ultrasound. 2008;11:89–96.
2. Dong Y, Mao F, Wang WP, Ji ZB, Fan PL. Value of contrast-enhanced ultrasound in guidance of percutaneous biopsy in peripheral pulmonary lesions. Biomed Res Int. 2015;2015:531507.
3. Sartori S, Postorivo S, di Vece F, Ermili F, Tassinari D, Tombesi P. Contrast-enhanced ultrasonography in peripheral lung consolidations: What's its actual role? World J Radiol. 2013;28:372–80.
4. García-Ortega A, Briones-Gómez A, Fabregat S, Martínez-Tomás R, Martínez-García MÁ, Cases E. Benefit of chest ultrasonography in the diagnosis of peripheral thoracic lesions in an Interventional Pulmonology Unit. Arch Bronconeumol. 2016;52:244–9.
5. Lee MH, Lubner MG, Hinshaw JL, Pickhardt PJ. Ultrasound guidance versus CT guidance for peripheral lung biopsy: Performance according to lesions size and pleural contact. AJR Am J Roentgenol. 2018;210:W110–7.
6. Wang S, Yang W, Zhang H, Xu Q, Yan K. The role of contrast-enhanced ultrasound in selection indication and improveing diagnosis for transthoracic biopsy in peripheral pulmonary and mediastinal lesions. Biomed Res Int. 2015;2015:231782.

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High O_2 Flow Rates Required to Achieve Acceptable FiO_2 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 FiO_2 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 O_2 flow rates > 70 L/min to maintain oxygen saturation (SpO_2) ≥ 90%. We hypothesised that due to the high respiratory demand of patients with severe Covid-19, a high O_2 flow rate would be required to reach adequate pressure levels with CPAP, thereby substantially increasing the oxygen flow rate needed to achieve a high FiO_2. We carried out a bench study to measure the oxygen flow rates needed to reach high FiO_2 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 cmH_2O, 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 O_2 flow meters (EASY MED-O_2, 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: $R = 5\ cmH_2O/l\ s$ and $C = 60\ ml/cmH_2O$.

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 ($cm\,H_2O$)	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.

B. Restrictive: $R = 5\ cmH_2O/l\ s$ and $C = 30\ ml/cmH_2O$.
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 cmH_2O 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 published 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 $\geq$ 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 $\leq$ 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_2O 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 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).

YC, CM and GP work as consultants for Air Liquid Medical System.

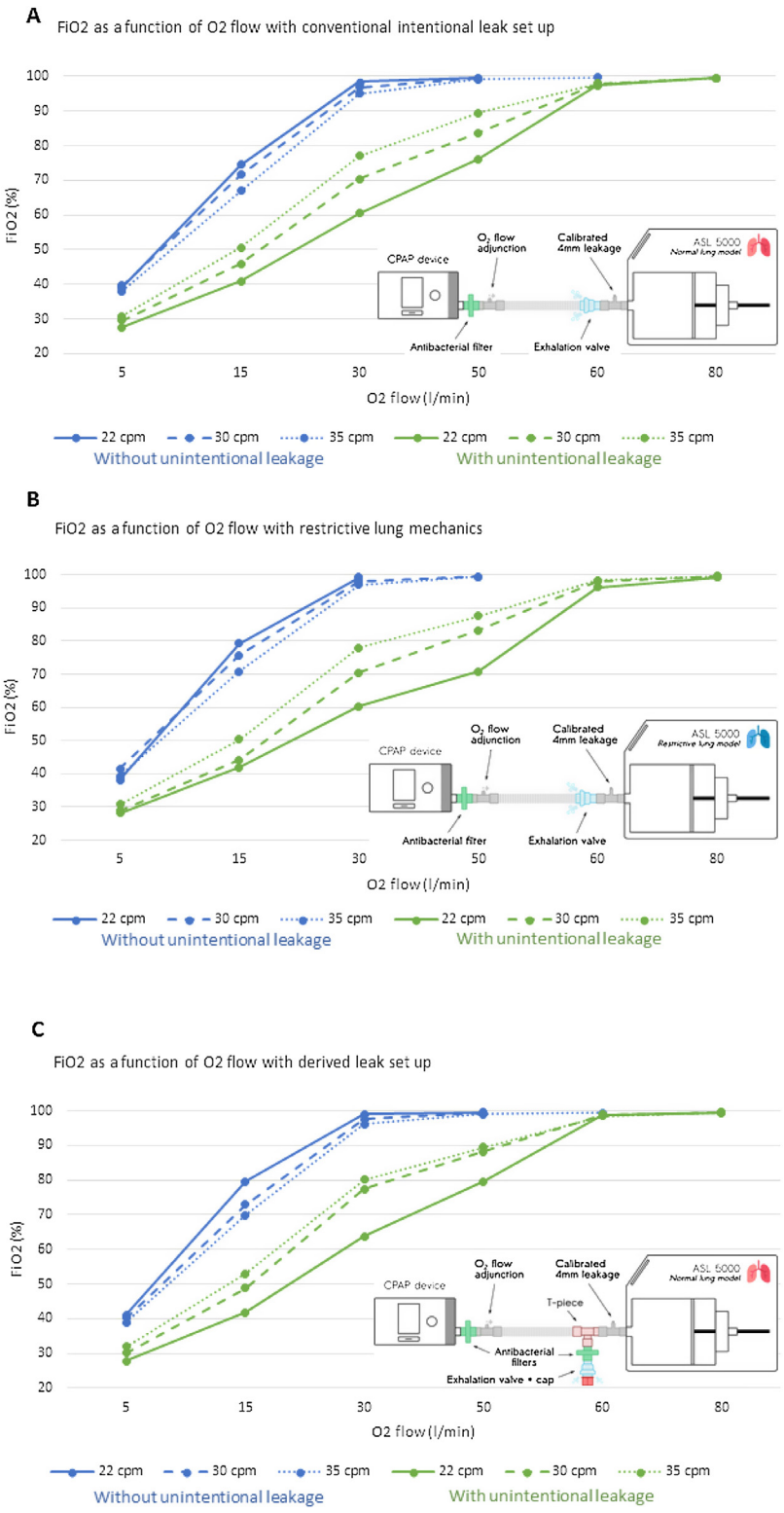

Fig. 1. Dose–response relationship between oxygen (O_2) flow rates delivered into the circuit, and fraction of inspired oxygen (FiO_2) as a function of respiratory rate, presence/absence of non-intentional leakage, lung mechanics and leak port locations. Each Plot represents the mean FiO_2 of the 10 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.

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Bibliografía

1. Alviset S, Riller Q, Aboab J, Dilworth K, Billy P-A, Lombardi Y, et al. Continuous Positive Airway Pressure (CPAP) face-mask ventilation is an easy and cheap option to manage a massive influx of patients presenting acute respiratory failure during the SARS-CoV-2 outbreak: a retrospective cohort study. PLOS ONE. 2020;15:e0240645, http://dx.doi.org/10.1371/journal.pone.0240645.
2. Aliberti S, Radovanovic D, Billi F, Sotgiu G, Costanzo M, Pilocane T, et al. Helmet CPAP treatment in patients with COVID-19 pneumonia: a multicentre cohort study. Eur Respir J. 2020:56, http://dx.doi.org/10.1183/13993003.01935-2020.
3. Bellani G, Grasselli G, Cecconi M, Antolini L, Borelli M, Giacomi F, et al. Noninvasive ventilatory support of covid-19 patients outside the intensive care units (WARd-COVID). Ann Am Thorac Soc. 2021, http://dx.doi.org/10.1513/AnnalsATS.202008-1080OC. Published Online First: 4 January 2021.
4. Landry SA, Mann DL, Djumas L, Messineo L, Terrill PI, Thomson LDJ, et al. Laboratory performance of oronasal CPAP and adapted snorkel masks to entrain oxygen and CPAP. Respirology. 2020;25:1309–12, http://dx.doi.org/10.1111/resp.13922.
5. Mechanical Ventilators for Non-Invasive Ventilation: Principles of Technology and Science – Nova Science Publishers [Internet]. [acceso 10 Feb 2021]. Disponible sur: https://nam03.safelinks.protection.outlook.com/?url=https%3A%2F%2Fnovapublishers.com%2Fshop%2Fmechanical-ventilators-for-non-invasive-ventilation-principles-of-technology-and-science%2F&data=04%7C01%7CM.Valero%40elsevier.com%7C830dea6bd8124dd4e81908d915246021%7C9274ee3f94254109a27f9fb15c10675d%7C0%7C0%7C637564068248117156%7CUnknown%7CTWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D%7C1000&sdata=L9OHd%2FCMQBXK0MQuOrPb1HBy8m5UdqwNbWRxbOap2go%3D&reserved=0
6. Rabec C, Gonzalez-Bermejo J, Mercy M, Grassion L, Pontier S, Patout M, et al. Respiratory support in patients with COVID-19 (outside intensive care unit). A position paper of the Respiratory Support and Chronic Care Group of the French Society of Respiratory Diseases. Respir Med Res. 2020;78:100768, http://dx.doi.org/10.1016/j.resmer.2020.100768.
7. ATS/ERS Statement on Respiratory Muscle Testing. Am J Respir Crit Care Med. 2002;166:518624.
8. Fresnel E, Muir J-F, Letellier C. Realistic human muscle pressure for driving a mechanical lung. EPJ Nonlinear Biomed Phys. 2014;2:7, http://dx.doi.org/10.1140/epjnbp/s40366-014-0007-8.
9. Murciano D, Aubier M, Bussi S, Derenne JP, Pariente R, Milic-Emili JAT Comparison of esophageal, tracheal, and mouth occlusion pressure in patients with chronic obstructive pulmonary disease during acute respiratory failure. Am Rev Respir Dis. 1982;126:837–41, http://dx.doi.org/10.1164/arrd.1982.126.5.837.
10. de Oca MM, Celli BR. Mouth occlusion pressure, CO_2 response and hypercapnia in severe chronic obstructive pulmonary disease. Eur Respir J. 1998;12:666–71, http://dx.doi.org/10.1183/09031936.98.12030666.
11. Baydur A. Respiratory muscle strength and control of ventilation in patients with neuromuscular disease. Chest. 1991;99:330–8, http://dx.doi.org/10.1378/chest.99.2.330.
12. Pandya A, Kaur NA, Sacher D, O'Corragain O, Salerno D, Desai P, et al. Ventilatory mechanics in early vs late intubation in a cohort of coronavirus disease 2019 patients with ARDS: a single center's experience. CHEST. 2021;159:653–6, http://dx.doi.org/10.1016/j.chest.2020.08.2084.
13. Hughes JMB. Review series: lung function made easy: assessing gas exchange. Chron Respir Dis. 2007;4:205–14, http://dx.doi.org/10.1177/1479972307084446.
14. Radovanovic D, Rizzi M, Pini S, Saad M, Chiumello DA, Santus PAT Helmet CPAP to treat acute hypoxemic respiratory failure in patients with COVID-19: a management strategy proposal. J Clin Med. 2020;9:1191, http://dx.doi.org/10.3390/jcm9041191.
15. Vaschetto R, Barone-Adesi F, Racca F, Pissaia C, Maestrone C, Colombo D, et al. Outcomes of COVID-19 patients treated with continuous positive airway pressure outside the intensive care unit. ERJ Open Res. 2021:7, http://dx.doi.org/10.1183/23120541.00541-2020.
16. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021;47:60–73, http://dx.doi.org/10.1007/s00134-020-06294-x.

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