deliver them. According to the consensus document on inhaled therapy prepared by the European Respiratory Society and the International Society for Aerosols in Medicine, when a patient is familiar with a device and is performing the inhalation technique correctly, that device should not be changed, unless the patient agrees and is taught how to use the new system[5]. This recommendation is based on the fact that changing inhalation systems may lead to errors in use, especially if different inhalation techniques are required, resulting in a lack of therapeutic compliance[6–8].

In recent years, remarkable advances in drug development have led to the emergence of new molecules and inhalation devices for the treatment of COPD. However, if we look at the main inhalation systems on the market, we can see that no single device can yet be used with all the drug groups needed for the treatment of this disease (long-acting bronchodilators and inhaled corticosteroids in monotherapy and in double and triple combinations) (Fig. 1). This means that in order to apply escalation and de-escalation strategies during follow-up, it is sometimes impossible to avoid switching inhalation devices or using different combinations.

When selecting an inhalation device in this scenario, it would be logical to bear in mind not only the current treatment, but also possible changes in the future. To this end, choosing inhalation devices that have a similar mechanism of action should be considered as yet another variable in the selection of pharmacological treatment. When selecting inhalers for solutions, the combination of pressurized cartridges with Respimat® covers all possible combinations. Among the multi-dose dry powder devices, the Accuhaler® and Ellipta® combination would also cover all therapeutic options using devices that have similar mechanisms of action. For single-dose dry powder devices, no combination that covers all options will be available until the development of the Breezhaler® with the LABA/ICS combination is completed[9] or triple therapy becomes available.

Each inhalation device has its advantages and disadvantages, so the choice of one or the other should be individualized and determined primarily by the patient's characteristics, the medication they require, the ease with which they use the device, and their own preferences[10,11]. Moreover, based on the above, we believe that escalating or de-escalating pharmacological treatment in COPD should be a further factor to consider when choosing an inhalation device. In the future, we must prioritize therapeutic options that allow us to switch medications during follow-up, while changing the device as seldom as possible. This will help achieve greater clinical effectiveness over the course of the disease.

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Role of contrast-enhanced ultrasound in the differentiation between pneumonia and neoplasia within a lung consolidation☆

Papel de la ecografía con contraste en la diferenciación entre una neumonía y una neoplasia en el seno de una consolidación pulmonar

To the Editor:

Contrast-enhanced ultrasound is of great utility in evaluating lung lesions that are in peripheral locations or contained within a consolidation[1], since it helps identify areas of necrosis and thus improves diagnostic accuracy when obtaining samples[2]. Similarly, contrast-enhanced studies help reach a differential diagnosis, as they highlight specific characteristics of certain diseases, such as pulmonary infarction, atelectasis, aggressive cancers, and obstructive atelectasis due to central lesions[2].

The time to enhancement of the parenchyma or lung lesion varies, depending on whether the vascular component is supplied from the pulmonary arteries (<6 s) or from the bronchial arteries (>6 s). Similarly, the pattern and extent of enhancement as well as the washout time (greater than 60 s) in a consolidated focus or lung lesion helps differentiate between lung collapse, infectious process/abscess, infarction, and tumor. In general, tumors receive arterial vascular supply from the bronchial arteries, as the pulmonary arteries are incapable of neoangiogenesis. The

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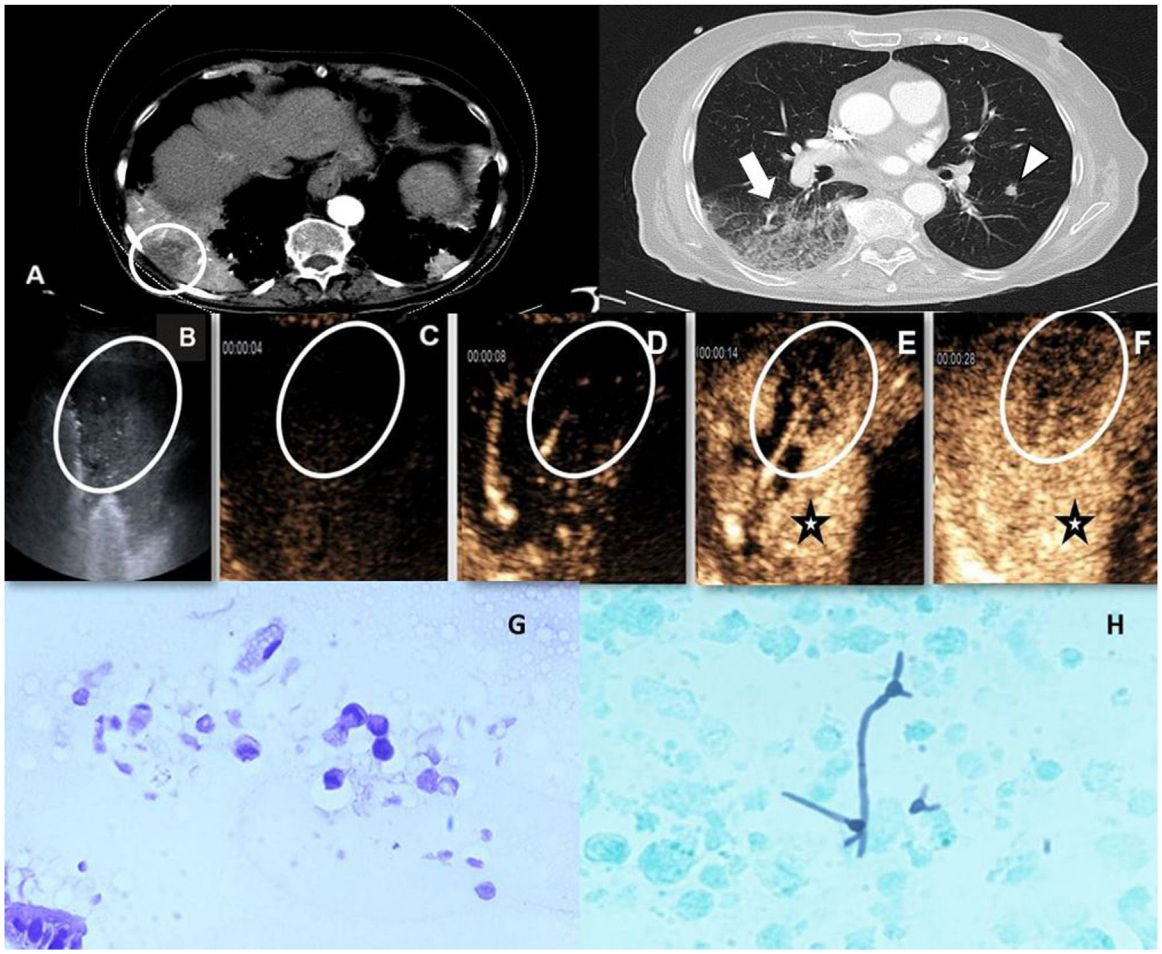

Fig. 1. (A) CT after intravenous iodinated contrast agent. Axial slices are shown in the mediastinum window (left) and pulmonary parenchyma window (right) where heterogeneous consolidation is observed in the right lower lobe with hypodense areas (circle) and areas of ground glass and tree-in-bud pattern (arrow). Some bilateral solid pulmonary nodules (arrowhead) probably associated with metastases are also observed. (B) B-mode ultrasound performed in the same patient showing heterogeneous consolidation without air bronchogram and anechoic subpleural area (oval). (C–F) Ultrasound image after injection of contrast agent showing homogeneous but delayed enhancement (star) of the consolidated pulmonary parenchyma (pneumonia pattern). A subpleural triangular area is observed that shows more delayed enhancement than the surrounding consolidated parenchyma (oval). Moreover, washout of this area is rapid, suggesting malignancy. An ultrasound-guided biopsy of the suspicious area was subsequently performed with histological results confirming pancreatic adenocarcinoma metastases. Later, a fiberoptic bronchoscopy confirmed fungal superinfection in the surrounding parenchyma. (G) Large atypical and vacuolated epithelial cell groups associated with metastatic pancreatic adenocarcinoma. (H) Microbiological analysis of the bronchoalveolar lavage sample from the consolidation area showing branched structures corresponding to hyphae.

delay in uptake by malignant lesions is explained by intrinsic vasoconstrictions, given the intrinsic hypoxic status of the neoproliferative lesion. Benign lesions, in contrast, receive blood from both the pulmonary and bronchial arteries, and therefore show early enhancement[3].

Thus, in the case of passive atelectasis, B-mode shows a homogeneous consolidation containing hyperechoic air bronchogram and early arterial enhancement that persists throughout the examination and may remain for longer than 5 min[4]. The findings for areas of pulmonary infarction will be similar to those of atelectasis in B-mode and we can identify hypoechoic nodules within the area of collapse. After the administration of contrast agent, we will see an absence of enhancement in the infarcted areas[4]. Pulmonary abscesses show delayed enhancement (>6 s) with hypoechoic and hypodense central areas corresponding to necrosis, which may appear in preexisting tumors[4].

Pneumonia and metastatic lesions and malignant lesions are a diagnostic challenge, especially in cases where both entities coexist. Pneumonias in general show early (<6 s) homogeneous arterial enhancement. However, in some cases both pathologies show delayed enhancement (>6 s). They differ in that in pneumonia, homogeneous enhancement is maintained in late phases with late washout (>60 s), while metastatic lesions will show faster washout (<60 s) of the lesion than the surrounding parenchyma[4].

We report the case of a 79-year-old woman with a history of papillary thyroid carcinoma who attended the emergency room for dyspnea that had worsened progressively until it appeared with minimal exertion. Chest X-ray revealed multiple foci of consolidation. A computed tomography (CT) scan was performed that ruled out pulmonary thromboembolism but revealed heterogeneous consolidations in both lower lobes along with areas suggestive of infectious bronchiolitis and some solid nodules (Fig. 1A). A positive test was obtained for tumor markers (CA 19-9 and CYFRA 21-1) and, in view of a suspected malignant origin, a positron emission tomography (PET/CT) with fluorodeoxyglucose was performed, which showed probable pancreatic cancer and possible metastatic consolidations in the lungs. Since the largest consolidation, located in the lower right lobe, was in extensive contact with the peripheral pleura, we decided to perform ultrasound-guided biopsy. We administered 2.4 mL of ultrasound contrast agent (SonoVue, Rovi, Pozuelo de Alarcón, Madrid, Spain) and two distinct areas were observed, differentiated by their uptake pattern: a peripheral area with delayed enhancement (>6 s post-injection) and early washout (disappearance of contrast uptake within a few seconds of uptake),

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 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.
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 pub-