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Original Article

Increased Inspiratory Oxygen Fractions (FIO_2) Using a Conventional Drug Delivery Nebuliser

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ABSTRACT

Nebulised drugs are very useful in COPD exacerbations. The most frequently used propellant is compressed air, which is commonly administered together with nasal oxygen in those patients with respiratory failure. The purpose of this approach is to avoid the risks inherent in breathing high inspiratory oxygen fractions (FIO_2).

Aim: To analyze the actual FIO_2 obtained with such a common method under experimental conditions.

Methods: Volunteers breathed using different patterns (quiet breathing, panting and deep breathing), through either the nose or the mouth, with oxygen flows of 0 vs. 4l/min. Then, they repeated quiet breathing and panting patterns, with nebulisation of saline propelled by compressed air (8l/min) and oxygen flows of 0, 2, 4, 6 and 8l/min. The F_IO_2 was simultaneously determined both in retronasal (RN) and retropharyngeal (RF) areas.

Results: During breathing without simultaneous nebulisation and oxygen flow of 4l/min, FIO_2 reached mean values of 0.42–0.71 (RN) and 0.29–0.38 (RF) for the three ventilatory patterns analyzed. With nebulisations during quiet breathing, mean FIO_2 values were 0.39 (RN) and 0.27 (RF) for 2l/min O_2 flow, 0.47 (RN), 0.34 (RF) for 4l/min, 0.58 (RN), 0.38 (RF) for 6l/min, and 0.68 (RN) and 0.50 (RF) for 8l/min. Similar results were obtained with the panting pattern.

Conclusion: The FIO_2 obtained using the conventional nebulisation system (propulsion with compressed air and simultaneous nasal oxygen therapy) are relatively high, and therefore, might involve risks for COPD patients during exacerbations.

Fracciones inspiratorias elevadas de O_2 con el uso del dispositivo convencional de nebulización de fármacos

Palabras clave:
Nebulizaciones
Hipoventilación
Oxigenoterapia

RESUMEN

Los fármacos nebulizados son de gran utilidad en el tratamiento de las agudizaciones de la EPOC. El gas propulsor más utilizado es aire comprimido, que suele combinarse con oxigenoterapia por vía nasal en pacientes con insuficiencia respiratoria. Este método pretende evitar los riesgos inherentes a la inhalación de fracciones inspiratorias de oxígeno (FIO_2) elevadas.

Objetivo: Analizar experimentalmente las FIO_2 reales obtenidas mediante el dispositivo mencionado.

Método: Los voluntarios respiraron con diversos patrones (basal, jadeo y respiración profunda) por vías nasal u oral y a flujos de oxígeno de 0–4 l/min. Seguidamente, repitieron los patrones basal y de jadeo con nebulización de suero salino impulsada por aire comprimido (8 l/min) y flujos de oxígeno nasales de 0, 2, 4, 6 y 8 l/min. La FIO_2 se determinó en regiones retronasal (RN) y retrofaríngea (RF).

Resultados: Durante la respiración sin nebulización simultánea y O_2 a 4 l/min, la FIO_2 alcanzó valores medios de 0,42–0,71 (RN) y 0,29–0,38 (RF) para los 3 patrones analizados. Durante la nebulización con salino y

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en respiración tranquila, los valores medios de FIO_2 fueron de 0,39 (RN) y 0,27 (RF) para O_2 a 2 l/min, 0,47 (RN) y 0,34 (RF) para 4 l/min, 0,58 (RN) y 0,38 (RF) para 6 l/min y 0,68 (RN) y 0,50 (RF) para 8 l/min. Cifras similares se alcanzaron con patrón de jadeo.

Conclusión: Las FIO_2 obtenidas mediante el sistema estándar de nebulización con aire comprimido y oxigenoterapia simultánea son relativamente elevadas y pudieran suponer un riesgo para los pacientes con EPOC exacerbada.

Introduction

Bronchodilator drugs are the basis for pharmacological treatment of several obstructive respiratory diseases, such as asthma and COPD.[1,2] They are usually administered using different inhalation devices. However, and particularly in COPD exacerbations, nebulisations are frequently used.[1,3,4-8] These are often delivered by means of compressed air propulsion through closed deposits and a diffuser where the bronchodilator drug is placed. The resulting mix reaches the patient through a conventional nasobucal mask or a mouthpiece. Since most acutely ill patients require an oxygen supplement during the procedure, this is supplied through a nasal cannula or a nasal oxygen prong and the oxygen flow must be regulated based on the blood saturation of said gas (oxymetry). The use of oxygen as a nebuliser propulsion gas is not advisable due to the fact that it would imply high oxygen inspiratory fractions (FIO_2) that could be dangerous for the patient.[6,9] On the other hand, the alternative of placing a Venturi system following the deposit or cup of the nebuliser does no ensure appropriate drug propulsion. Finally, the availability of different gas mixes to deliver individual treatment is not efficient, especially in current hospital settings, where gas comes from central reservoirs equipped with distribution systems to treatment points.

However, repeated clinical monitoring of the patients that arrive at the emergency service with an acute exacerbation of their COPD, but preserved ventilation status, has shown that they deteriorate dramatically after nebulisation (appearance or increase of hypercapnia and respiratory acidosis) (unpublished observations), which suggests that hypoventilation could be induced by a relatively high FIO_2 inhalation. It has been known for decades that there is a variable subgroup of patients that hypoventilate and retain CO_2 when inhaling relatively high concentrations of oxygen. The main cause of said hypoventilation seems to be depression of the central response, although there are also negative changes to alveolar dead space that have been attributed to eventual bronchodilatation due to the hypercapnia itself.[10] However, there are few studies that have assessed the incidence of respiratory depression induced by a combination of pharmacologic nebulisation and oxygen therapy.[11-15] Similarly, we have not found any studies that experimentally analyse the oxygen concentration achieved with this standard device used to deliver said combination. As a result, this study was designed to assess the values of actual FIO_2 supplied to subjects during standard nebulisation procedures combined with oxygen therapy. Since there is a not negligible risk for patients, this study has been carried out with healthy volunteers.

Methods

The volunteers were males, from 45-55 years of age, non-smokers and with no history of respiratory or cardiovascular conditions. The study was approved by the Ethics Committee of our institution and the volunteers signed the corresponding informed consent.

Procedure

After placins 2 tubes, a retronasal one and a retropharyngeal one, to sample inspired air, the FIO_2 of different air-flows and ventilation patterns was analysed (Table 1). Specifically, we carried out manoeuvres with 3 different patterns (quiet respiration, panting or high frequency with low tidal volume and low frequency with high tidal volume), with nasal respiration and oral respiration, and both breathing ambient air and with a nasal flow of supplementary oxygen of 4l/min. Subsequently we proceeded to add a continuous air flow through the nebuliser deposit or cup (8l/min) filled with isotonic saline. In this case, the volunteers always breathed through the mouth, both during quiet respiration and during panting and we supplemented with progressive flows of oxygen by the nasal route (0, 2, 4, 6 and 8l/min). We analysed a total of 22 different ventilation situations and collected a total of 7 valid registers in each situation.

Techniques

Figure 1 shows the diagram of the device used to duplicate nebulisation with compressed air and oxygen therapy with a nasal canulla as also the location of the tubes for taking samples and analysing FIO_2. The device had a facial mask (nose and mouth) with a padded fit so as to prevent leakages and two holes for the entry of oxygen therapy and the outlet of physiological signals. These holes were sealed with silicone. The mask was connected to the nebulisation deposit or cup, which, in turn, was connected to the tubes through which the air flowed.

Table 1
Ventilation situations analysed in this study

1. Quiet nasal respiration, ambient air. Without nebulisation
2. Quiet oral respiration, ambient air. Without nebulisation
3. Quiet nasal respiration, O_2 nasal prongs 4 L/min. Without nebulisation
4. Quiet oral respiration, O_2 nasal prongs 4 L/min. Without nebulisation
5. Rapid superficial nasal respiration, ambient air. Without nebulisation
6. Rapid superficial oral respiration, ambient air. Without nebulisation
7. Rapid superficial nasal respiration, O_2 nasal prongs 4 L/min. Without nebulisation
8. Rapid superficial oral respiration, O_2 nasal prongs 4 L/min. Without nebulisation
9. Slow deep nasal respiration, ambient air. Without nebulisation
10. Slow deep oral respiration, ambient air. Without nebulisation
11. Slow deep nasal respiration, O_2 nasal prongs 4 L/min. Without nebulisation
12. Slow deep oral respiration, O_2 nasal prongs 4 L/min. Without nebulisation
13. Quiet nasobucal free respiration, with nebulisation of salin (8 L/min), ambient air.
14. Quiet nasobucal free respiration, with nebulisation of saline (8 L/min), O_2 nasal prongs 2 L/min.
15. Quiet nasobucal free respiration, with nebulisation of saline (8 L/min), O_2 nasal prongs 4 L/min.
16. Quiet nasobucal free respiration, with nebulisation of saline (8 L/min), O_2 nasal prongs 6 L/min.
17. Quiet nasobucal free respiration, with nebulisation of saline (8 L/min), O_2 nasal prongs 8 L/min.
18. Rapid superficial nasobucal free respiration, with nebulisation of saline (8 L/min), ambient air.
19. Rapid superficial nasobucal free respiration, with nebulisation of saline (8 L/min), O_2 nasal prongs 2 L/min.
20. Rapid superficial nasobucal free respiration, with nebulisation of saline (8 L/min), O_2 nasal prongs 4 L/min.
21. Rapid superficial nasobucal free respiration, with nebulisation of saline (8 L/min), O_2 nasal prongs 6 L/min.
22. Rapid superficial nasobucal free respiration, with nebulisation of saline (8l/min), O_2 nasal prongs 8 L/min.

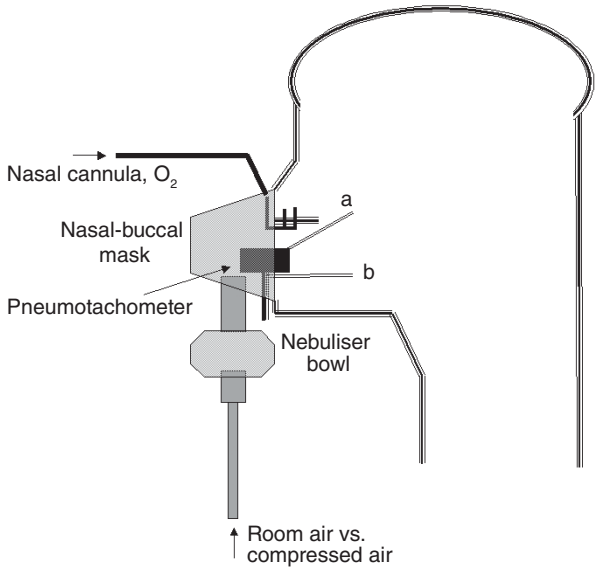

Figure 1. Diagrammatic representation of the device used for the joint administration of drug nebulisations with compressed air and oxygen supplementation. The location of the 2 tubes for registration of oxygen concentration is also indicated, a) Retronasal, b) Retropharyngeal.

In those situations where respiration was through the mouth, the subjects breathed through a mouthpiece connected to a previously calibrated flow transducer (TSD117/SS11LA Biopac Systems, Goleta, CA, USA). After the conversion to volume, this procedure made it possible to analyse the ventilation pattern in different forms of oral respiration. For the different variables of the pattern (RF; respiratory frequency; TV, tidal volume; MV, respiratory minute volume (inspiratory); T_I, time of inspiration ; T_{TOT}, total time of the respiratory cycle] the mean values of at least 15 respirations in each situation were used, discarding stabilization time until a steady state was achieved. The compound variables TV/T_I and T_I/T_{TOT} have been calculated from those obtained directly from the register. The flow signal was not collected during nasal respiration tests. Furthermore, FIO_2 was determined using a parametric analyser (AFT20 gas sampling interface kit and O2100C module, both from Biopac) connected to the sampling tubes. In each case the value of FIO_2 was the mean value during that phase of ventilation, once more in at least 15 respirations. Finally, oxygen saturation was monitored with an oxymeter (TSD123 transducer-catheter and OXY100C amplifier, Biopac). All signals were collected using a digital poligraph (MP100 Data Acquisition System, Biopac) for subsequent analysis (AcqKnowledge ACK100W program, Biopac).

Whenever possible said FIO_2 was calculated as a result of the mixture between volume of inspired air and oxygen supplement administered through the nasal prong. In the case of free breathing, the calculation has taken into account actual inspired air, derived from the ventilation pattern. In the case of nebulisation of 8 L/min, this has been the air-flow considered for calculations.

Statistical Analysis

Descriptive statistics expresses values as mean ± SD. The comparisons between the different situations have been made using a variance analysis for repeated measurements. A value of $p < 0.05$ was considered statistically significant.

Results

Free Intake of Inspired Air (Nebulisation inactive)

The values corresponding to the registers carried out with the nebulisation device but without an additional air-flow (alternatively nasal or oral route) for different ventilations patterns, with and without an oxygen supplement, are shown in Table 2. Said supplement was 4 L/min in all cases always administered by conventional nasal prongs. As expected, and breathing ambient air, the retronasal and retropharyngeal tubes always showed inspiratory concentrations of oxygen of 0.21 with a slight expiratory descent due to the mix with inspired air (Fig. 2). With supplemental oxygen, the retronasal tube showed values higher than the retropharyngeal tube, both for nasal and oral respiration and both for quiet (basal) respiration and for both modes of hyperventilation (panting and deep). These values achieved, both with basal and deep respiration, oxygen levels near to 70% (Fig. 2), which were slightly lower in the panting pattern (Fig. 3). On the other hand, values of measured FIO_2, were, in general, slightly higher than those calculated theoretically, especially in the retronasal compartment.

The basal respiratory pattern obtained with oral respiration was within normal limits and similar to that obtained with respiration of ambient air alone or with the mix formed by the oxygen supplement in the three ventilation situations studied.

Nebulisations with Compressed Air

In the register compiled during compressed air nebulisations, the tubes registered progressive concentrations of oxygen as the flow of oxygen through the prongs increased (Table 3 and Figure 4). Also, the values registered were higher than those registered with the retronasal tube on this occasion. The hyperventilation panting pattern did not substantially modify measured FIO_2 values, in comparison with quiet basal respiration. On the other hand, mouth ventilation patterns were similar to those obtained during ambient air inhalation.

Discussion

The most outstanding finding in this study was that the technique most frequently used to administer drug nebulisations to respiratory patients who furthermore require supplementary oxygen does not insure controlled inspiratory fractions of oxygen. Furthermore, said oxygen concentrations may reach levels that could have significant clinical consequences if they were applied to patients with chronic obstructive disease. Surprisingly, we have not found any previous study where actual oxygen concentrations received by subjects undergoing nebulisations using standard techniques are experimentally analysed.

The treatment of respiratory patients with obstructive conditions implies several elements, among which the most outstanding are bronchodilators and oxygen therapy. The use of bronchodilators makes it possible to improve air-flow by increasing the calibre of the respiratory airways by diverse mechanisms. Their most frequent route of administration is by inhalation, but results can be improved if the drug is nebulised.[7,8] Furthermore, a supply of supplementary oxygen makes it possible to correct some of the consequences of hypoxemia both at tissue level and cardiovascular level. In certain situations such as severe COPD exacerbation, frequently both treatments are used simultaneously (nebulisation with bronchodilators and oxygen).[6,11-17]

On the other hand, traditionally the use of controlled oxygen respiratory fractions is recommended and not too high to prevent potential hypoventilation.[1,7] This condition has been attributed especially to depression of the neurons that control respiration that would no longer perceive the hypoxic stimuli that reinforce respiration. This would be relevant in hypercapnic patients whose receptors are already accustomed to relatively high concentrations of $PaCO_2$, and who therefore respond poorly to subsequent changes in the concentration of this gas.[18] In these patients only the presence of hypoxia will maintain an appropriate stimulation of ventilation.[18,19] Therefore, the importance of not completely eliminating it by the use of excessive oxygen therapy is apparent.

Table 2
FIO_2 obtained with the nebulisation device, free intake of inspired air and supplement of nasal oxygen of 4l/min with different patterns of voluntary respiration

	Basal respiration				Panting				Deep respiration			
	Nasal		Oral		Nasal		Oral		Nasal		Oral	
	Air	Oxygen	Air	Oxygen	Air	Oxygen	Air	Oxygen	Air	Oxygen	Air	Oxygen
		4 L/min		4 L/min		4 L/min		4 L/min		4 L/min		4 L/min
Retronasal tube												
FIO_2	0.21 ± 0.02	0.53 ± 0.08*	0.21 ± 0.01	0,70 ± 0,03*	0.21 ± 0.01	0,42 ± 0,03*	0.21 ± 0.02	0,49 ± 0,06*	0.21 ± 0.01	0,71 ± 0,05*	0.21 ± 0.01	0.21 ± 0.02
FIO_2(min)	0.19	0.41	0.20	0.68	0.20	0.36	0.19	0.42	0.20	0.67	0.20	0.48
FIO_2(max)	0.21	0.55	0.21	0.74	0.21	0.42	0.21	0.56	0.21	0.77	0.21	0.54
Retropharyngeal tube												
FIO_2	0.21 ± 0.01	0,32 ± 0,02*	0.21 ± 0.01	0,37 ± 0,04*	0.21 ± 0.01	0,28 ± 0,03*	0.21 ± 0.02	0,33 ± 0,02*	0.21 ± 0.01	0,29 ± 0,02*	0.21 ± 0.01	0,37 ± 0,04*
FIO_2(min)	0.20	0.30	0.20	0.30	0.19	0.24	0.18	0.30	0.20	0.27	0.19	0.32
FIO_2(max)	0.21	0.35	0.21	0.38	0.21	0.28	0.21	0.34	0.21	0.30	0.21	0.37
FIO_2(theoretical)	0.21	–	0.21	<0,48	0.21	–	0.21	< 0,29	0.21	–	0.21	< 0,34
Inspiratory pattern by mouth												
FR(min^{-1})	NA	NA	17.2 ± 1.3	16.6 ± 1.2	NA	NA	160 ± 21	166 ± 24	NA	NA	17,3 ± 1,5	17.5 ± 1.9
TV(cc)	NA	NA	451 ± 30	458 ± 37	NA	NA	225 ± 17	229 ± 21	NA	NA	1210 ± 187	1152 ± 172
EV(l/min)	NA	NA	7.8 ± 0.8	7.6 ± 1.1	NA	NA	36.0 ± 4.6	38.1 ± 6.8	NA	NA	20.9 ± 4.6	20.2 ± 3.2
TV/T_I(l/s)	NA	NA	0.232 ± 0.040	0.247 ± 0.082	NA	NA	1.642 ± 0.432	1.636 ± 0.623	NA	NA	0.740 ± 0.109	0.691 ± 0.095
T_I(s)	NA	NA	1.939 ± 0.234	1.851 ± 0.185	NA	NA	0.137 ± 0.083	0.140 ± 0.075	NA	NA	1.635 ± 0.332	1.667 ± 0.289
T_{TOT}(s)	NA	NA	3.485 ± 0.532	3.606 ± 0.426	NA	NA	0.375 ± 0.061	0.361 ± 0.083	NA	NA	3.462 ± 0.367	3.426 ± 0.437
T_I/T_{TOT}	NA	NA	0.556 ± 0.098	0.513 ± 0.062	NA	NA	0.365 ± 0.045	0.388 ± 0.053	NA	NA	0.472 ± 0.081	0.487 ± 0.064

NA: Not available; MV: Respiratory minute volume (inspiration); TV: Tidal volume; T_I: Time of inspiration; TI: Total time of the respiratory cycle.
FIO_2 (theoretical): FIO_2 resulting from the mix of the volume of air inspired spontaneously (by mouth) + total flow of oxygen from nasal prong. The use of the expression «< FIO_2» refers to the potential existence of leaks of the second component in the real inspired volume.
*$p < 0.001$ with reference to ambient air.

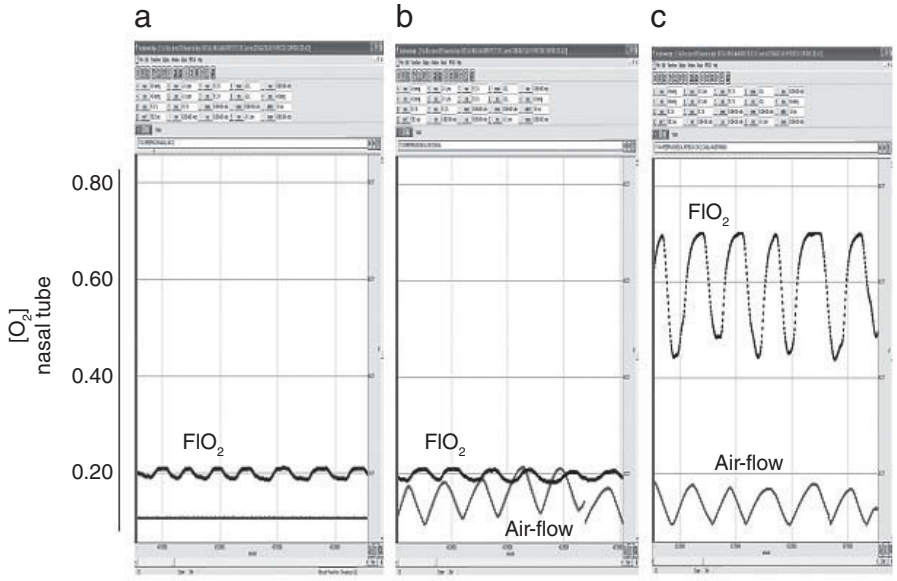

Figure 2. Registers of the oral air-flow and oxygen concentration (O_2) (retronasal tube) during quiet respiration. a) Nasal respiration (there is no register of the flow signal), ambient air. b) Oral respiration, ambient air. c) Oral respiration, oxygen 4 L/min. Oscillations of values of oxygen concentration are related to the respiratory cycle, FIO_2 corresponds to the peaks of the curve.

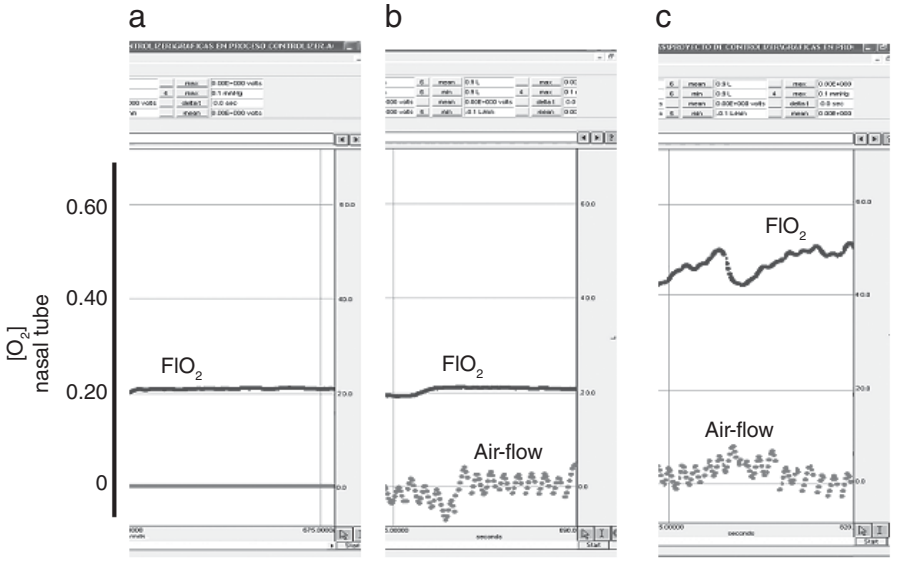

Figure 3. Registers of oral air-flow and oxygen concentration (O_2) (retronasal tube) in panting type respiration. a) Nasal respiration (no register of flow signal), ambient air. b) Oral respiration, ambient air. c) Oral respiration, oxygen 4 L/min. The registers have been enlarged for the measurement of time to better observe flow at high ventilation frequencies.

However, the observation that a certain percentage of patients with chronic obstructive diseases tolerate the administration of relatively high concentrations of oxygen relatively well has led to a certain tolerance in the use of this gas. Indeed, responses only according to hypoxia and hypercapnia vary not only between individuals, but also in the same individual, in different situations of stability and exacerbation.[20-27] However, different reviews have confirmed the danger of an excessive correction of hypoxia in many patients with chronic respiratory disease.[28-30]

On the other hand, and due to the variability of results, an in-depth study has been made to analyse mechanisms due to which high FIO_2 induces hypercapnia and respiratory acidosis in some patients. Therefore, it has been confirmed that patients suffer a reduction of their ventilation due to loss of the hypoxic stimulus.[10] This reduction may reach 20% of basal ventilation. Furthermore, an increase in dead space[31] has been observed, particularly in its alveolar fraction,[10,32] probably as a consequence of the hypercapnia itself and its eventual effect on bronchial caliber.[10] A point to be highlighted is that hypoxia induced reductions in ventilation are observed especially in patients with exacerbation[10], who are precisely those that are most likely to be treated with drug nebulisations and that these reductions are less or absent in patients with stable disease.[21,26] It is interesting to point out that modifications in the ventilation response, although of little degree and slight clinical relevance, would be

Table 3
FIO_2 obtained during nebulisation of 8l/min of compressed air at different flows of supplemental oxygen.

	Basal respiration					Panting				
	Air	2l/m	4l/m	6l/m	8l/m	Air	2l/m	4l/m	6l/m	8l/m
Retronasal tube										
FIO_2	0.21 ± 0.01	0,39 ± 0,04*	0,47 ± 0,03*	0,58 ± 0,03*	0,68 ± 0,03*	0.21 ± 0.01	0,44 ± 0,03*	0,49 ± 0,03*	0,53 ± 0,04*	0,60 ± 0,04*
FIO_2 (min)	0.19	0.33	0.43	0.56	0.65	0.20	0.42	0.46	0.50	0.56
FIO_2 (max)	0.21	0.40	0.48	0.59	0.70	0.21	0.47	0.51	0.54	0.62
Retropharyngeal tube										
FIO_2	0.21 ± 0.01	0,27 ± 0,03*	0,34 ± 0,04*	0,38 ± 0,05*	0,50 ± 0,04*	0.21 ± 0.02	0,38 ± 0,03*	0,44 ± 0,03*	0,46 ± 0,04*	0,51 ± 0,04*
FIO_2 (min)	0.20	0.25	0.32	0.37	0.48	0.19	0.37	0.41	0.42	0.47
FIO_2 (max)	0.21	0.29	0.38	0.44	0.54	0.22	0.41	0.46	0.49	0.54
FIO_2 (theoretical)	0.21	<0,37	<0,47	<0,54	<0,61	0.21	–	–	–	–
FR (min^{-1})	17.1 ± 1.4	7.3 ± 1.2	17.1 ± 1.6	17.2 ± 1.2	16.7 ± 1.8	165 ± 27	170 ± 25	168 ± 27	175 ± 29	169 ± 25
TV (cc)	455 ± 28	449 ± 26	448 ± 32	459 ± 30	453 ± 33	240 ± 20	229 ± 18	236 ± 19	230 ± 20	243 ± 19
EV (l/min)	7.8 ± 0.7	7.8 ± 0.6	7.7 ± 0.6	7.9 ± 0.7	7.6 ± 0.7	39.6 ± 5.2	38.9 ± 4.8	39.6 ± 4.8	40.2 ± 5.0	41.1 ± 5.1
TV/T_I(l/s)	0.236 ± 0.038	0.238 ± 0.036	0.234 ± 0.033	0.242 ± 0.040	0.234 ± 0.038	1.690 ± 0.538	1.647 ± 0.479	1.595 ± 0.506	1.565 ± 0.684	1.800 ± 0.729
T_I (s)	1.927 ± 0.259	1.889 ± 0.279	1.915 ± 0.197	1.895 ± 0.249	1.932 ± 0.195	0.142 ± 0.084	0.139 ± 0.073	0.148 ± 0.083	0.147 ± 0.068	0.135 ± 0.055
T_{TOT} (s)	3.509 ± 0.483	3.468 ± 0.372	3.509 ± 0.425	3.488 ± 0.392	3.593 ± 0.362	0.364 ± 0.072	0.353 ± 0.066	0.357 ± 0.074	0.343 ± 0.071	0.355 ± 0.069
T_I/T_{TOT}	0.549 ± 0.079	0.545 ± 0.068	0.546 ± 0.081	0.543 ± 0.074	0.538 ± 0.063	0.390 ± 0.052	0.394 ± 0.046	0.415 ± 0.059	0.429 ± 0.047	0.380 ± 0.052

NA: Not available; T_I: Time of inspiration; T_{TOT}: Total time of the respiratory cycle, MV: Respiratory minute volume (inspiration); TV: Tidal volume.
FIO_2 (theoretical): FIO_2 resulting from the mix of the flow of nebulised air + total flow of oxygen from the nasal prongs. The use of the expression «< FIO_2» supposes the probable existence of leaks of the second component in the real inspired volume.
*$p < 0.001$ with reference to ambient air.

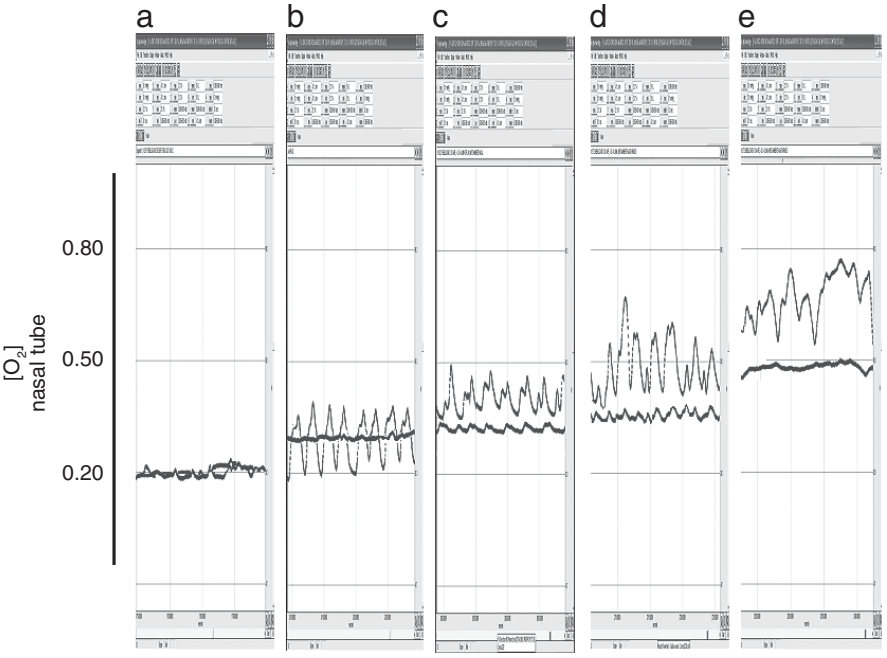

Figure 4. Registers during nebulisation with compressed air (8 L/min), during quiet respiration at different nasal oxygen flows. a) Without oxygen. b) With 2 L/min. c) With 4 L/min. d) With 6 L/min. e) With 8 L/min. With the exception of a), in which both registers overlap, the upper tracing corresponds to the retronasal tube and the lower tracing to the retropharyngeal tube.

present in half the patients that receive home conventional oxygen therapy with a relatively low FIO_2.[33]

On the other hand, it is possible to frequently observe the deterioration suffered during the first hours of admittance to the emergency service of a not negligible number of respiratory patients. Some of these patients have a relatively preserved clinical and gas initial status, but undergo subsequent deterioration with progressive hypercapnia and respiratory acidosis. One possibility is that these patients are receiving a higher concentration of oxygen than is advisable, as seems to happen frequently in our countries,[29] in spite of recommendations not to use a FIO_2 greater than 0.24–0.28. This is especially obvious in the emergency service and it has been shown to have a direct impact on the subsequent patient deterioration.[29,30]

Another possibility that could explain the deterioration in patients with exacerbation is the frequent use of simultaneous treatment with oxygen and bronchodilator drugs in nebulisations. As is known, this last treatment is done with a mask, propelling the diluted drug with a medicinal gas or with air. Knowing the risks of using oxygen for this, usually compressed air is used. The problem arises when the patient additionally requires oxygen because they are in respiratory failure. In general, the most extended solution is the application of a continuous flow of oxygen, using nasal cannula or prongs that are placed inside the mask that receives the air nebulisation. The flow

through the prongs must be kept at levels that ensure acceptable but not excessive oxygen saturation. In general, it is advisable that any therapy that includes oxygen in patients with COPD should maintain saturation levels of 85-92% to prevent the respective risks of hypoxemia and hypercapnia/acidosis.[34,35] However, as has already been mentioned, said saturation levels are frequently exceeded, especially in emergency services.[29,30,35,36] Also too frequently, double therapy (nebulisation with air plus oxygen supplementation) is carried out without monitoring oxymetry. Finally, it must be remembered that SEPAR recommends an oxygen nasal flow of only 2 L/min during nebulisations.[16]

Finally, there is another possibility that could explain the gasometric deterioration (mainly hypoxemia) in patients that are receiving initial treatment for their exacerbation. These are the well-known effects of beta-agonists on cardiac output, which if it increases may cause an increase in perfusion of alveolar units reducing the ventilation/perfusion ratio (V_A/Q).[37] However, this damaging effect has mainly been described after the administration of drugs by the intravenous route in bronchial asthma, and seems to be less when the route of administration is by inhalation.[37] In the concrete case of nebulisations in patients with exacerbated COPD, the beta-agonist effect on the V_A/Q ratio would be very limited.[38] Furthermore, in all cases and due to other factors that have a positive influence on PaO_2, the final impact of arterial gasses seems reduced[37,38]; although, of course, not negligible.

Clinical observation of gasometric deterioration seen in a significant percentage of patients made us suspect that the level of FIO_2 often used during nebulisations was greater than supposed and gave rise to the design of this study. In this study, and under controlled conditions, we analysed the actual level of oxygen supply with the nebulisation device and with different flows (both of air and of oxygen). In the first phase of the study, the subjects were allowed to use different ventilation patterns and free intake of inspired air. Under these conditions, the FIO_2 levels measured were relatively high, and occasionally reached values near 0.70. Said values, however, require a series of comments. In general, inspiratory oscillations were discrete and higher in the retronasal tube in comparison with the retropharyngeal tube. This seems logical since the first location was very close to the permanent source of oxygen and it is possible that there had not yet been an appropriate mix of this gas with the remaining inspired air. The same reason seems to explain the greater difference between both tubes seen with oral respiration in comparison with nasal respiration, especially in the cases of quiet and deep respiration. Finally, the differences between calculated theoretical values of FIO_2 and those actually measured were less in all cases. In summary, real FIO2 values with free respiration are elevated although they would not be alarming if it is supposed that they are only truly registered by the retropharyngeal tube.

Unfortunately, this situation worsens substantially under conditions similar to those of patients who receive nebulisations in whom air and oxygen flows can be much greater. When the study volunteers were submitted to these conditions, both tubes registered high FIO_2. And which is more important, the retropharyngeal tube measured values of up to 40-50% oxygen with flows of this gas that were of common use in patients during nebulisations in a clinical setting.

Having confirmed relatively high FIO_2 administration using traditional nebulisation systems combined with oxygen therapy, it became necessary to carry out a clinical study, randomised and controlled, on the real situation of patients with exacerbation of their COPD. Although to date some studies have been published,[11,12,13,14,15] they all have significant methodological problems.[17]

Limitations of the Study

One of the potential limitations of the study is the possibility that, under certain circumstances (such as hyperventilation with simultaneous nebulisation), there would have been a certain amount of rebreathing, since the high minute ventilation (MV) necessary in this circumstance could not be adequately maintained by the combined oxygen and air flow. In any case, this would have resulted in an underestimation of the FIO_2, that even in spite of this, was elevated. It is also possible that, as in all studies of ventilation patterns, this could have been an artefact of the measurement system. However, in this study we chose to use measurements made using a pneumotachometer since this was more exact than indirect estimations and we ensured that the mask was reasonably well adjusted at all times.

Another possible study limitation is that it was performed with healthy volunteers and not in patients, therefore it is not possible extrapolate it directly to real clinical situations. However, we thought that the first approximation to the problem of oxygen therapy during nebulisations implied verification of the FIO_2 received by the individual. The study of the consequences of an excessively elevated oxygen fraction on patients has already been sufficiently analysed in the literature and we did not consider it ethical or necessary to expose our patients once more to experimental conditions.

Finally, we must understand that it is possible that the results are not appropriate for extrapolation to similar devices. However, although said devices are morphologically different in some details, there are essential elements: oxygen flow as a propellant and the deposit of cup with the drug are common elements in most of them. In other words, our results are not directly quantitatively extrapolable, but the qualitative consequences and potential risks are probably very similar.

In summary, this study is a call for attention from physiology to the daily clinic on the subject of the use of supplementary oxygen during nebulisations. Said use can be dangerous for the patient, especially if FIO_2 and the resulting level of oxygenation are not taken into account, as also the ventilation and/or blood responses that these may induce. In consequence, we believe that safe devices must be investigated that make it possible to control FIO2 during treatments with drugs administered by nebulisation.

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