

Oxygen therapy during exacerbations of chronic obstructive pulmonary disease

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ABSTRACT: Venturi masks (VMs) and nasal prongs (NPs) are widely used to treat acute respiratory failure (ARF) in chronic obstructive pulmonary disease (COPD). In this study, these devices were compared in terms of their potentiality to worsen respiratory acidosis and their capacity to maintain adequate (>90%) arterial oxygenation (S_{a,O_2}) through time (~24 h).

In a randomized cross-over study, 18 consecutive COPD patients who required hospitalization because of ARF were studied. After determining baseline arterial blood gas levels (on room air), patients were randomized to receive oxygen therapy through a VM or NPs at the lowest possible inspiratory oxygen fraction that resulted in an initial S_{a,O_2} of $\geq 90\%$. Arterial blood gas levels were measured again 30 min later (on O_2), and S_{a,O_2} recorded using a computer during the subsequent ~24 h. Patients were then crossed-over to receive O_2 therapy by means of the alternative device (NPs or VM), and the same measurements obtained again in the same order.

It was observed that both the VM and NPs improved arterial oxygen tension ($p < 0.0001$) to the same extent ($p = \text{NS}$), without any significant effect upon arterial carbon dioxide tension or pH. However, despite this adequate initial oxygenation, S_{a,O_2} was $< 90\%$ for 3.7 ± 3.8 h using the VM and for 5.4 ± 5.9 h using NPs ($p < 0.05$). Regression analysis showed that the degree of arterial hypoxaemia ($p < 0.05$) and arterial hypercapnia ($p < 0.05$) present before starting O_2 therapy and, particularly, the initial S_{a,O_2} achieved after initiation of O_2 therapy ($p < 0.0001$) enabled the time (in h) that patients would be poorly oxygenated ($S_{a,O_2} < 90\%$) on follow-up to be predicted.

These findings suggest that, in order to maintain an adequate (>90%) level of arterial oxygenation in patients with chronic obstructive pulmonary disease and moderate acute respiratory failure: 1) the initial arterial oxygen saturation on oxygen should be maximized whenever possible by increasing the inspiratory oxygen fraction; 2) this strategy seems feasible because neither the VM nor NPs worsen respiratory acidosis significantly; and 3) the Venturi mask (better than nasal prongs) should be recommended.

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Patients with chronic obstructive pulmonary disease (COPD) often require hospitalization due to acute respiratory failure (ARF) [1, 2]. The administration of oxygen is a key component of the therapeutic strategy in these circumstances [3, 4]. The aim of O_2 therapy in these patients is to provide adequate arterial (and, presumably, tissue) oxygen saturation (S_{a,O_2}), while other therapeutic measures (bronchodilators, steroids, antibiotics) treat the cause(s) of the exacerbation [3, 4].

The most common O_2 delivery method in COPD patients hospitalized because of ARF is the standard dual-prong nasal cannula (NPs) [3]. Alternatively, Venturi masks (VMs) can also be used [3]. NPs are less bulky and there is less chance of their becoming dislodged during sleep than VMs [5–7]. Therefore, it is conceivable that NPs can provide a more continuous (*i.e.* better) S_{a,O_2} than the VM. However, because they do not maintain a constant inspired concentration of O_2 [5, 6], NPs have the potential to depress ventilatory drive and worsen respiratory acidosis [1, 8–10]. In order to reach a compromise between these two opposite effects, an S_{a,O_2} of ~90% is

generally recommended in clinical practice [3, 4]. To date, however, no studies have assessed the efficacy of NPs or the VM in maintaining adequate S_{a,O_2} through time in patients with COPD and ARF. Further, previous statements regarding the potential ventilatory depressant effects of high inspired concentrations of O_2 are derived from studies in which subjects breathed pure O_2 [1, 8–10], a situation that is highly unusual in clinical practice. To the authors' knowledge, no previous study has investigated the potential worsening of respiratory acidosis associated with the use of NPs used under conditions of standard clinical management of such patients (*i.e.* S_{a,O_2} ~90%).

This study sought to investigate the optimal mode of O_2 administration (NPs *versus* VM) in COPD patients hospitalized because of ARF by: 1) comparing their acute effects upon respiratory acidosis; and 2) assessing their capacity to maintain an S_{a,O_2} of >90% over a ~24-h period. The former may provide information on the safety of use of these devices in this particular clinical setting; the latter may be informative regarding their efficacy in facilitating an

adequate and continuous delivery of O₂ to peripheral tissues. Because ARF in COPD is a frequent and potentially lethal situation, this information is of clinical relevance.

Material and methods

Study subjects

Patients with exacerbated COPD who required hospitalization in our institution were studied. In order to calculate sample size, some *a priori* assumptions were made. Firstly, based upon clinical experience, it was estimated that when using the VM patients would not be adequately oxygenated ($Sa_{O_2} > 90\%$) for 3 ± 1 h·day⁻¹ (dislodgment of the mask, visitors, use of bathroom, etc.). Secondly, it was hypothesized that, when using NPs, this period of time would be reduced to 1 ± 1 h·day⁻¹. Based upon these assumptions, and accepting an α error of 0.05, a β error of 0.1 and a potential 10% of missing values, it was estimated that a sample size of 18 patients would be required.

Accordingly, 18 male COPD patients attending the emergency room of the authors' hospital because of ARF (table 1) were included in the study consecutively. None of them showed clinical or radiological evidence of bacterial pneumonia, pneumothorax, pulmonary embolism, pleural effusion or left ventricular failure. Throughout the study (48 h), medical treatment was standardized in all patients and included aerosolized salbutamol (5 mg every 6 h) and *i.v.* prednisolone (40 mg every 8 h) [11]. No patient received antibiotics or respiratory stimulants. All patients gave their informed consent after being informed of the purpose, characteristics and nature of the study, which had been approved by the Ethics Committee of the institution.

Study design

This was a prospective randomized cross-over study. All patients were studied in the general ward, within 48 h of hospital admission.

Table 1. — Clinical and functional characteristics of the subjects studied

General data	
Age yrs	69.1±10.5
BMI kg·m ⁻²	25.6±3.7
Smoking pack-yrs	71.4±23.0
Parameters recorded on admission	
Cardiac frequency beats·min ⁻¹	98.1±16.4
Respiratory frequency breaths·min ⁻¹	31.4±8.8
P_{a,O_2} mmHg	47.7±8.7
P_{a,CO_2} mmHg	50.4±10.1
Arterial pH	7.38±0.04
Parameters recorded at discharge	
P_{a,O_2} mmHg	61.5±9.1
P_{a,CO_2} mmHg	48.3±7.0
Arterial pH	7.42±0.03
FEV ₁ L % pred	0.9±0.3 (33)
FVC L % pred	1.9±0.5 (54)
FEV ₁ /FVC %	48±9

Data are presented as mean±SD. Spirometric reference values were from a mediterranean population [11]. BMI: body mass index; P_{a,O_2} : arterial oxygen tension; P_{a,CO_2} : arterial carbon dioxide tension; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity.

At 09:00 h, after breathing room air for 30 min, a blood sample from the nondominant radial artery was obtained under local anaesthesia. Arterial oxygen tension (P_{a,O_2}), carbon dioxide tension (P_{a,CO_2}) and pH (baseline values) immediately measured (IL-BG3; Izasa, Barcelona, Spain). Then, patients were randomly allocated to receive O₂ therapy *via* either a VM (n=8) or NP (n=10) (Proclinics, Barcelona, Spain). According to international guidelines [3, 4], all of them received the minimum inspiratory oxygen fraction (F_{I,O_2}) required to increase the transcutaneous Sa_{O_2} (504-US pulseoxymeter; Criticare Systems, Inc., Waukesha, WI, USA) to $\geq 90\%$ (initial Sa_{O_2} on O₂). F_{I,O_2} ranged 0.24–0.28 for the VM, and gas flow 2–4 L·min⁻¹ for NPs. In order to assess the acute effects of the selected mode of O₂ therapy (VM or NPs) on arterial blood gas levels, 30 min later a second arterial blood sample was obtained and analysed as above, and compared to the baseline values obtained before starting O₂ therapy. To investigate the adequacy of arterial oxygenation through time, Sa_{O_2} was monitored continuously during the following ~24 h. The analogue output of the oximeter was digitized on-line and stored using a computer (Atlantis, Lakeshore Technologies, Inc., Chicago, IL, USA) for later off-line analysis. During this study period, the initial F_{I,O_2} was not modified. After ~24 h, patients were switched to the alternative mode of O₂ therapy (VM or NPs) and the same study protocol was repeated. In brief, the minimum F_{I,O_2} required to produce an Sa_{O_2} of $\geq 90\%$ was again used, a third arterial blood sample obtained 30 min later and Sa_{O_2} recorded continuously for a further ~24 h. Because one of the main objectives of the study was to determine the efficiency of O₂ therapy in a real clinical setting, the nursing personnel were not instructed to provide supplemental care, other than that regularly given in these clinical circumstances.

At discharge, forced spirometry (GS plus, Collins, Braintree, MA, USA) was performed [13] and arterial blood gas levels (breathing room air) measured in all patients.

Analysis

To eliminate obvious technical errors, such as cable disconnection, the recorded Sa_{O_2} traces were processed manually (off-line) for each individual and for each Sa_{O_2} recording (using the VM or NPs). From this filtered Sa_{O_2} trace (~21 h of adequate data for each group, $p=NS$), the time spent at an Sa_{O_2} of $< 90\%$, as an index of inadequate oxygenation, was calculated using Pegasus (Lakeshore Technologies, Chicago, IL, USA). Also, to get some insight into the severity of any abnormal oxygenation period, the time spent within Sa_{O_2} intervals of 80–70%, 70–60% and 60–50% was calculated. These calculations were performed separately for the whole filtered recording time (~21 h) and for its daytime (09:00–21:00 h) and night-time (21:00–09:00 h) components.

Results are presented as mean±SD. One-way analysis of variance (followed by *post hoc* contrasts (Scheffe)) or a two-tailed paired t-test were used, as appropriate, to explore the statistical significance of the differences observed. Correlations between variables were explored using Pearson's linear regression analysis. A p -value < 0.05 was considered significant.

Results

Clinical data

In the emergency room, all subjects had ARF as defined by the presence of severe hypoxaemia while breathing room air (P_{a,O_2} 6.34 ± 1.16 kPa (47.7 ± 8.7 mmHg)). Most but not all patients had hypercapnia (P_{a,CO_2} 6.70 ± 1.34 kPa (50.4 ± 10.1 mmHg)) (table 1). None of the variables shown in table 1 were significantly different between those patients who used the VM or those who used NPs first. At discharge, all patients had severe airflow obstruction (forced expiratory volume in one second $33.4 \pm 10.3\%$ of the predicted value).

Acute effects of the Venturi mask and nasal prongs upon arterial blood gas levels

Figure 1 shows the P_{a,O_2} , P_{a,CO_2} and pH values determined in each individual once admitted to the authors' ward while breathing room air (baseline values), and when receiving O_2 therapy via the VM or NPs. At baseline, most patients had moderate respiratory failure (P_{a,O_2} 6.89 ± 1.13 kPa (51.8 ± 8.5 mmHg)) with mild hypercapnia (P_{a,CO_2} 6.85 ± 1.34 kPa (51.5 ± 10.1 mmHg)) and normal arterial pH (7.42 ± 0.03). P_{a,O_2} increased to the same extent ($p=NS$) using the VM (9.56 ± 1.02 kPa (71.9 ± 7.7 mmHg), $p<0.0001$) and NPs (9.08 ± 1.85 kPa (68.3 ± 13.9 mmHg), $p<0.0001$) (fig. 1). Neither P_{a,CO_2} (VM, 6.90 ± 1.45 kPa (51.9 ± 10.9 mmHg), $p=NS$; NPs, 7.04 ± 1.41 kPa (52.9 ± 10.6 mmHg), $p=NS$) nor arterial pH (VM, 7.39 ± 0.05 , $p=NS$; NPs, 7.40 ± 0.04 , $p=NS$) were significantly modified by either mode of O_2 therapy; this was true even in the subgroup of patients with higher P_{a,CO_2} while breathing room air.

Efficiency of the Venturi mask and nasal prongs in adequately providing continuous arterial oxygenation

By design, the initial S_{a,O_2} achieved on O_2 was $\geq 90\%$ in all subjects, both using the VM ($92.9 \pm 2.6\%$) and NPs ($94.3 \pm 2.9\%$, $p=NS$). However, despite this adequate level of initial oxygenation, it was observed that patients subse-

quently had an S_{a,O_2} value $<90\%$ for 3.7 ± 3.8 h using the VM, and 5.4 ± 5.9 h using NPs ($p<0.05$). On average, this corresponded to $\sim 20\%$ of the (filtered) recording time. In extreme cases, however, patients could be poorly oxygenated for as long as 15 h ($\sim 75\%$ of (filtered) recording time) (fig. 2). Differences between daytime and night-time intervals were not statistically significant (fig. 2).

To analyse the severity (rather than the duration) of this poor oxygenation pattern, the times spent below other threshold S_{a,O_2} were determined. It was found that S_{a,O_2} was within the 80–70% interval for 80 ± 109 min, within the 70–60% interval for 38 ± 61 min and within the 60–50% interval for 4 ± 9 min. As shown by the SDS, however, intersubject variability was considerable. Within each of these S_{a,O_2} intervals, differences between devices (VM versus NPs) were not statistically significant.

Factors influencing the adequacy of arterial oxygenation during acute respiratory failure in chronic obstructive pulmonary disease

Figure 3 shows that the amount of time that any given patient spent at $<90\%$ S_{a,O_2} when using the VM was highly related to that spent by the same patient at $<90\%$ S_{a,O_2} when using NPs ($r=0.91$, $p<0.0001$). This suggests that some factor (by and large independent of the type of device but dependent on the patient) strongly influenced the time that each individual was poorly oxygenated; nonetheless, figure 3 also shows that most points lie above the line of identity, suggesting that, for a given individual, NPs tend to provide poorer control of S_{a,O_2} over time than the VM. To explore what patient characteristic might influence the adequacy of arterial oxygenation during ARF, the relationship between the time spent at $<90\%$ S_{a,O_2} and several variables of potential clinical interest (age, body mass index, degree of airflow obstruction, initial S_{a,O_2} on O_2 and arterial blood gas levels at baseline and during O_2 therapy) were analysed. As shown in figure 4, it was found that the degree of arterial hypoxaemia (fig. 4a) and arterial hypercapnia (fig. 4b) present at baseline (*i.e.* before O_2 therapy had been started) and, particularly, the initial S_{a,O_2} achieved at the beginning of O_2 therapy (fig. 4c) were highly predictive of the duration of poor oxygenation.

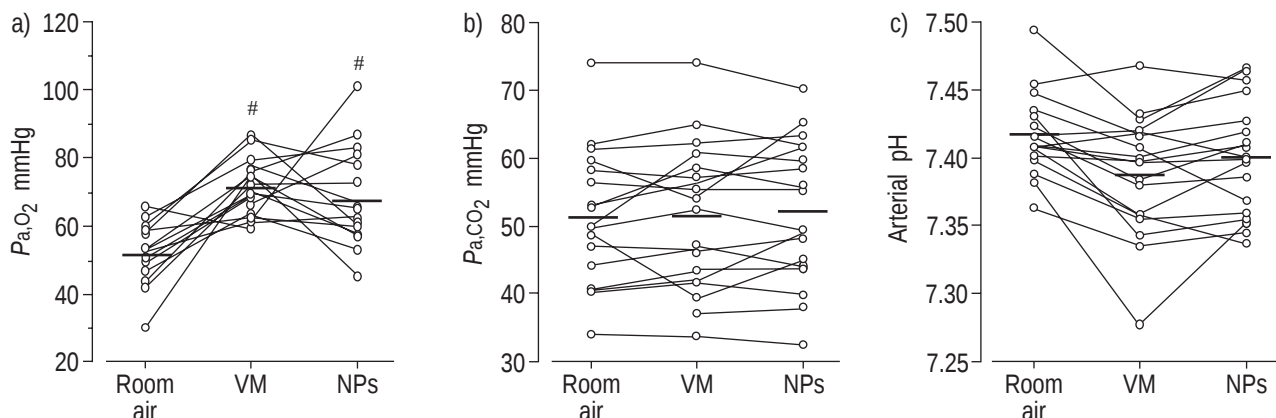


Fig. 1. – Individual and mean (horizontal bars): a) arterial oxygen tension (P_{a,O_2}); b) arterial carbon dioxide tension (P_{a,CO_2}); and c) arterial pH in all patients studied while breathing room air and while receiving oxygen through a Venturi mask (VM) and nasal prongs (NPs). Both the VM and NPs produced similar increments in P_{a,O_2} , but neither modified P_{a,CO_2} or arterial pH significantly. #: $p<0.0001$ versus room air.

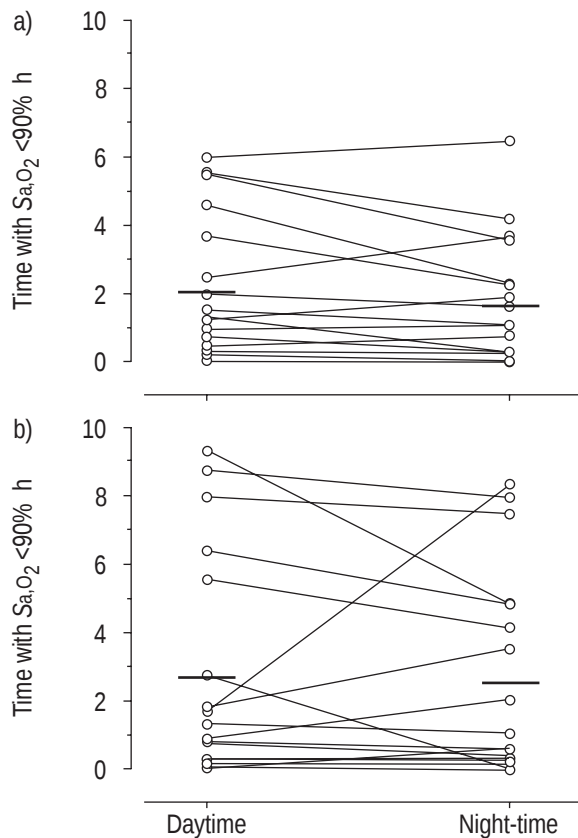


Fig. 2. – Time that each patient spent with an arterial oxygen saturation (S_{a,O_2}) of <90%, during the daytime and night-time periods, while using a) the Venturi mask; and b) nasal prongs. Horizontal bars represent mean values. For further explanation, see text.

Discussion

The most relevant findings of the present study were that, in COPD patients hospitalized because of ARF: 1) the administration of O_2 therapy *via* a VM or NPs did not worsen respiratory acidosis (fig. 1); 2) most patients were

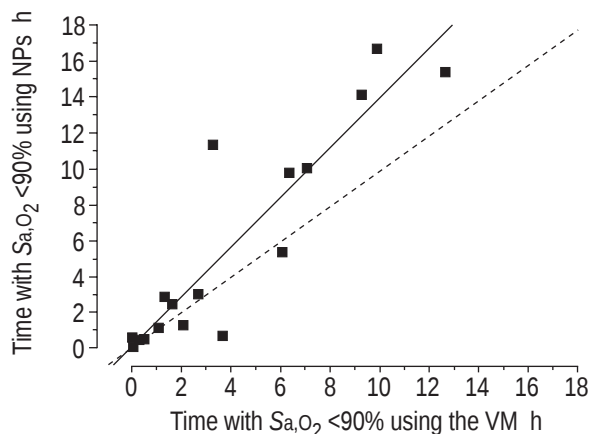


Fig. 3. – Relationship between the time spent with an arterial oxygen saturation (S_{a,O_2}) of <90% in each patient while using the Venturi mask (VM) and nasal prongs (NPs). - - - : line of identity. There is a very significant linear relationship ($r=0.91$, $p<0.0001$), and most patients lie above the line of identity, indicating that, for each individual, NPs provide poorer control of S_{a,O_2} with time than does the VM.

inadequately oxygenated (S_{a,O_2} <90%) for a significant proportion of the day (~20% of the time analysed), although in extreme cases this period of time may be much higher (~75%) (fig. 2); 3) although these observations appear to be more prominent when NPs are used (fig. 2), by and large they are independent of the type of device used (fig. 3); and 4) the severity of arterial hypoxaemia and hypercapnia present before starting O_2 therapy and, especially, the Initial S_{a,O_2} on O_2 can predict the duration of inadequate arterial oxygenation (fig. 4).

Previous studies

The main goal of O_2 therapy in patients with COPD and ARF is to facilitate adequate and continuous arterial oxygenation, whereas other measures treat the cause of the exacerbation [1, 2]. However, when high F_{I,O_2} are used, ventilatory drive can be blunted and respiratory acidosis worsened [8–10, 14]. In order to reach a compromise between these two opposite phenomena, current guidelines recommend the use of the minimum inspired F_{I,O_2} necessary to obtain an initial S_{a,O_2} on O_2 of ~90% [3, 4]. However, no previous study has assessed the adequacy of such initial S_{a,O_2} in maintaining an appropriate (>90%) level of arterial oxygenation through time, or whether the two most common devices used in the clinical setting (VM and NPs) can achieve comparable results. Further, previous investigations assessing the effects of a high F_{I,O_2} investigated patients with stable COPD [5, 14] or undergoing mechanical ventilation [8] or have given pure O_2 to breathe to the participant subjects [9, 10], but none has studied COPD patients with ARF.

Interpretation of results

The present results show that, under the conditions of regular clinical use in patients with COPD hospitalized because of ARF, both the VM and NPs are able to initially oxygenate arterial blood adequately without significantly worsening the pre-existing degree of respiratory acidosis (fig. 1). However, neither of them is able to guarantee an S_{a,O_2} of >90% through time in the majority of patients (fig. 2). Several potential explanations should be considered for this latter observation. Technical recording artefacts can be ruled out because the S_{a,O_2} trace was manually filtered in order to eliminate them. Dislodgement of the device was unlikely because the tight correlation observed between the time with an S_{a,O_2} <90% using the VM and NP (fig. 3) suggests that the mechanism(s) underlying this observation is, by and large, independent of the device and probably dependent on the patients themselves. As shown in figure 4, the degree of abnormal gas exchange before starting O_2 therapy and, more importantly, the initial S_{a,O_2} on O_2 were able to predict the amount of time that the patient would be poorly oxygenated. From this latter observation, the authors would suggest that, in clinical practice and in order to minimize the duration of poor oxygenation, the initial S_{a,O_2} should be maximized by increasing the F_{I,O_2} (particularly in patients with marked gas exchange abnormalities). The authors consider this strategy feasible since O_2 therapy does not appear to significantly worsen respiratory acidosis, even in patients with marked arterial hypercapnia (fig. 1).

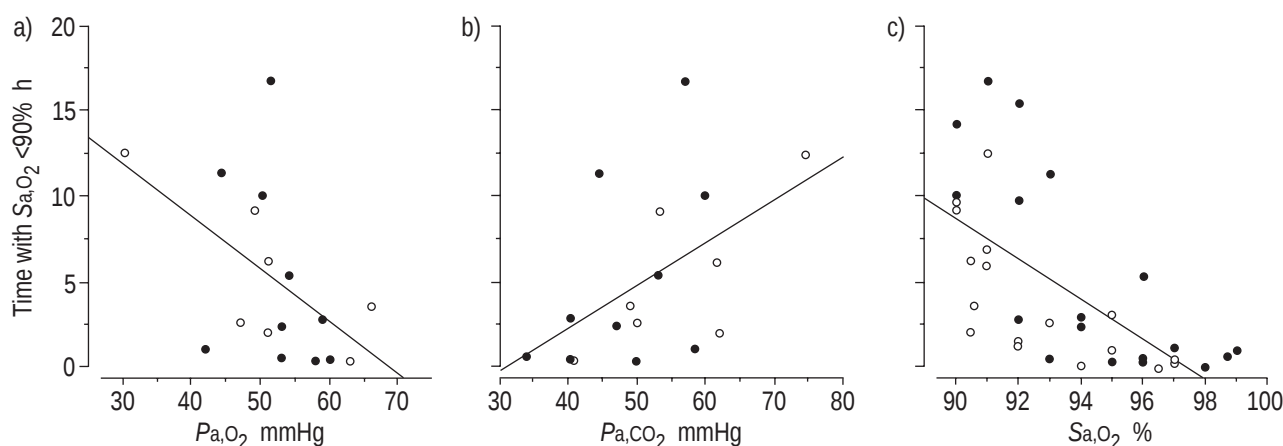


Fig. 4. – Relationship between the duration of poor oxygenation (arterial oxygen saturation (Sa,O_2) <90%) and: a) oxygen tension (P_{a,O_2}) ($r=-0.51$, $p<0.05$); and b) carbon dioxide tension (P_{a,CO_2}) ($r=0.51$, $p<0.05$) measured at baseline while breathing room air (before beginning the study); and c) the initial Sa,O_2 on O_2 ($r=0.66$, $p<0.0001$) using the Venturi mask (○) and nasal prongs (●). For further explanations, see text.

The Venturi mask versus nasal prongs

Despite the frequent occurrence of ARF in patients with COPD, and the relevance of O_2 therapy in these circumstances [1, 2, 15, 16], there have been no detailed studies comparing the potential benefits and risks of the two most common methods of O_2 administration (the VM and NPs) in these patients. In the present study, two observations suggest that NPs provide worse control of arterial oxygenation through time than the VM. Firstly, the time spent with an Sa,O_2 <90% was longer using NPs (5.4 ± 5.9 h) than using the VM (3.7 ± 3.8 h, $p<0.05$). Secondly, when this variable was directly compared in each patient using both devices (fig. 3), most points lay above the identity line. These results, therefore, support the use of the VM rather than of NPs, in patients with COPD hospitalized because of ARF. This observation is interpreted as reflecting, on the one hand, the variation in F_{I,O_2} that occurs when NPs are used [17] and, on the other, the capacity of the VM to provide adequate O_2 therapy even in patients who are mouth breathers.

Potential limitations

Several potential limitations of the present study deserve comment. Firstly, at baseline (fig. 1), the patients were not acidotic and the degree of hypercarbia was modest in approximately half of them. Therefore, the observations should not be directly extrapolated to patients with more severe degrees of respiratory acidosis. However, it is interesting to note that, even in those patients with very high P_{a,CO_2} (fig. 1), no obvious deleterious effects of NPs or the VM could be detected. Secondly, the study was not designed to assess the potential clinical consequences of the inadequate arterial oxygenation seen in most of the patients. Therefore, further studies are needed to investigate whether or not the maintenance of a higher Sa,O_2 during hospitalization would result in a better clinical outcome by enhancing recovery (improved oxygenation of respiratory muscles and other tissues?) and/or minimizing potential complications (less cardiac arrhythmias?). Thirdly, in clinical practice, F_{I,O_2} is normally varied according to Sa,O_2 changes. It is well known that the latter

can change for a wide variety of reasons (use of bronchodilators, altered cardiac output, disease state, etc.). However, it is important to realize that, for the purposes of this study, the F_{I,O_2} was set at the start of the study and left unchanged throughout, and that both groups received the same standardized medical therapy. Finally, it was deliberately decided not to provide extra nursing attention to the patients during the course of the study in order to avoid any interference with their spontaneous use of the VM or NPs in a real clinical setting. Of course, the results may have been altered had the study been carried out differently.

Conclusions

The present study shows that many patients with chronic obstructive pulmonary disease hospitalized because of moderate acute respiratory failure are poorly oxygenated for significant periods of time. In order to avoid this, it was suggested that: 1) arterial oxygen saturation is maximized at the beginning of treatment by increasing the inspiratory oxygen fraction; this appears to be feasible since neither the VM nor NPs worsen respiratory acidosis in these patients; and 2) the Venturi mask is used whenever possible. Overall, these results provide evidence on the basis of which oxygen therapy can be prescribed in patients with chronic obstructive pulmonary disease hospitalized because of acute respiratory failure.

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