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### ► To cite this version:

Julien Nael, Mathilde Ruggiu, Clotilde Bailleul, Sofia Ortuno, Jean-Luc Diehl, et al.. Impact of hyperoxia on patients hospitalized in an intensive care unit for acute heart failure. Archives of cardiovascular diseases, 2019, 112, pp.748 - 753. 10.1016/j.acvd.2019.09.003 . hal-03489148

**HAL Id: hal-03489148**

**<https://hal.science/hal-03489148>**

Submitted on 21 Jul 2022

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## **Impact of hyperoxia on patients hospitalized in an intensive care unit for acute heart failure**

**Abbreviated title:** Hyperoxia in acute pulmonary oedema

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## **Summary**

*Background.* – Oxygen therapy remains a cornerstone of treatment for acute heart failure in patients with pulmonary congestion. While avoiding hypoxaemia has long been a goal of critical care practitioners, less attention has been paid to the potential hazard related to excessive hyperoxia.

*Aim.* – To evaluate the impact of early hyperoxia exposure among critically ill patients hospitalized in an intensive care unit for acute heart failure.

*Methods.* – In this preliminary study conducted in a Parisian intensive care unit, we assessed patients with acute heart failure admitted with pulmonary congestion and treated with oxygen therapy from 1 January 2015 to 31 December 2016. The hyperoxia group was defined by having at least one partial pressure of oxygen measurement > 100 mmHg on the first day following admission to the intensive care unit. The primary endpoint was 30-day all-cause mortality. Secondary endpoints were 30-day unplanned hospital admissions, occurrence of infections and intensive care unit and hospital lengths of stay.

*Results.* – Seventy-five patients were included. Forty-three patients (57.3%) presented hyperoxia, whereas 32 patients (42.7%) did not (control group). The baseline clinical characteristics did not differ between the two groups. The primary endpoint was not statistically different between the two groups (14.0% in the hyperoxia group vs 18.8% in the control group;  $P = 0.85$ ). The secondary endpoints were also not significantly different between the two groups. In the multivariable analysis, hyperoxia was not associated with increased 30-day mortality (odds ratio 0.77, 95% confidence interval 0.24–2.41).

*Conclusion.* – In patients referred to an intensive care unit for acute heart failure, we did not find any difference in outcomes according to the presence of hyperoxia.

## **Résumé**

*Contexte.* – L'oxygénothérapie fait partie des traitements utilisés lors de la prise en charge des patients présentant un œdème aigu du poumon cardiogénique (OAP). Pourtant, des études ont souligné les effets délétères de l'hyperoxie chez les patients hospitalisés en réanimation.

*Objectif.* – L'objectif de notre étude était d'étudier l'impact de l'exposition précoce à une hyperoxie chez les patients hospitalisés pour un OAP grave.

*Méthodes.* – Il s’agissait d’une étude observationnelle, rétrospective et monocentrique conduite entre janvier 2015 et décembre 2016. Les patients présentant un OAP grave étaient inclus. Le groupe hyperoxie (H) était défini par une PaO<sub>2</sub> strictement supérieure à 100 mmHg au gaz du sang artériel au cours des premières 24 heures d’hospitalisation alors que le groupe contrôle (C) définissait les autres patients. Le critère de jugement principal était la mortalité à 30 jours. Les critères de jugement secondaire étaient la réadmission hospitalière à 30 jours, la survenue d’infections en cours d’hospitalisation et les durées de séjours en réanimation et hospitalières.

*Résultats.* – 75 patients avec un âge médian de 76 ans (68–83) ont été inclus. Quarante-trois (57,3 %) patients ont présenté une hyperoxie (H) alors que C comprenait 32 patients (4,7 %). Le critère de jugement principal composite n’était pas significativement différent entre les deux groupes (14,0 % vs 18,8 % ;  $P = 0,85$ ). Les critères de jugement secondaires ne différaient également pas entre les deux groupes. En analyse multivariable, l’hyperoxie n’était ni délétère ni protectrice à 30 jours (OR 0,77, IC95 % 0,24–2,41).

*Conclusion.* – Chez les patients hospitalisés pour OAP graves, il n’existait pas de différence de morbi-mortalité en fonction de la présence de phases d’hyperoxie.

## **KEYWORDS**

Hyperoxia;  
Pulmonary congestion;  
Heart failure;  
Mortality;  
Readmission

## **MOTS CLÉS**

Hyperoxie ;  
USIC ;  
OAP ;  
Mortalité ;  
Réhospitalisation

*Abbreviations:* AHF, acute heart failure; BNP, B-type natriuretic peptide; CI, confidence interval; ICU, intensive care unit; PaO<sub>2</sub>, partial pressure of oxygen; SOFA, sequential organ failure assessment; SpO<sub>2</sub>, saturation of peripheral oxygen.

## Introduction

Acute heart failure (AHF) is the most frequent cause of unscheduled hospital admissions, with over 150,000 hospitalizations in France each year [1, 2]. Among the various clinical phenotypes of AHF, acute pulmonary oedema represents between 16% and 38% of cases [1, 3-5].

Acute pulmonary oedema is the most important indication for oxygen therapy and mechanical ventilation in patients with AHF. Expert guidelines recommend that supplemental oxygen therapy should be considered for patients with saturation of peripheral oxygen ( $SpO_2$ ) < 90% or partial pressure of oxygen ( $PaO_2$ ) < 60 mmHg, to correct hypoxaemia and/or to relieve symptoms related to hypoxaemia [2].

Standard clinician behaviour promotes prompt uncontrolled administration of high-flow high-concentration oxygen therapy to critically ill patients with AHF with acute respiratory distress, with supranormal values of  $PaO_2$  frequently being achieved [1]. Hyperoxia occurs when the partial pressure of intra-alveolar oxygen exceeds normal breathing conditions, thus leading to hyperoxaemia [3].

Although oxygen is essential for cell metabolism and organ function, it can trigger free radical formation and cause potential iatrogenic harm to innate immunity and the functioning of the heart and lungs [3]. Noxious effects of hyperoxia have been reported in critically ill patients with septic shock, cardiac arrest and acute myocardial infarction [3, 4, 6-8]. In a single-centre, open-label, randomized trial, the authors aimed to assess whether a conservative protocol for oxygen supplementation could improve outcomes in 434 critically ill patients. Compared with standard management ( $SpO_2$  values between 97% and 100%), conservative oxygen therapy maintaining  $SpO_2$  between 94% and 98% (or  $PaO_2$  between 70 and 100 mmHg) reduced intensive care unit (ICU) death (absolute risk reduction 8.6%, 95% confidence interval [CI] 1.7–15%;  $P = 0.01$ ) and episodes of shock, liver failure and bacteraemia [9]. Interestingly, the subgroup analysis among patients presenting with respiratory failure at admission ( $n = 250$ ) showed an absolute risk reduction in ICU death of 12.8% (95% CI 2.3–23.0).

Cardiovascular hyperoxia consequences have been evaluated in small groups of healthy individuals and patients with chronic heart failure. Hyperoxia induced vasoconstriction, reduced cardiac output by decreasing systolic ejection volume, increased peripheral vascular resistance and increased filling pressure [10-15].

Lastly, a recent systematic review and meta-analysis showed that too much supplemental oxygen increased mortality for medical patients in hospital [4], but no study has evaluated the effect of hyperoxia on the outcome of patients presenting with pulmonary congestion caused by AHF. The main objective of our study was to evaluate the impact of early hyperoxia exposure on patients with AHF hospitalized for pulmonary congestion.

## **Methods**

### **Study design**

This was a retrospective, single-centre, observational study conducted in the ICU of the Hôpital Européen Georges Pompidou, in Paris, over a 2-year period (2015–2016). Data collection and analyses were conducted in accordance with the French national guidelines. All patients (or proxies) admitted to the ICU were informed that medical data might be used for research; no opposition to using data for research was expressed by the patients (or proxies).

### **Patients**

All adult patients admitted to the ICU at the Hôpital Européen Georges Pompidou between 1 January 2015 and 31 December 2016 for acute respiratory distress caused by AHF were assessed. Patients presenting with pulmonary congestion caused by AHF (defined by clinical presentation of AHF with acute pulmonary oedema and at least one of these objective findings of AHF: B-type natriuretic peptide [BNP] > 400 pg/mL or N-terminal prohormone of BNP > 1200 pg/mL or pulmonary echography or chest X-ray showing pulmonary vascular congestion signs or echocardiography showing structural and/or functional alterations of the heart) were included.

Patients who presented with an out-of-hospital cardiac arrest, severe chronic obstructive pulmonary disease or long-term oxygen therapy, and those who had received oxygen therapy in the previous month or who died in the first 24 hours following admission were not included.

### **Data**

Clinical and biological data were collected prospectively in the computer database routinely used for clinical purposes.

All arterial blood gases collected in the ICU during the first day were analysed. Venous blood gases were not taken into account.

Data on baseline characteristics, patient medications, oxygen therapy with the fraction of inspired oxygen ( $FiO_2$ ), use of mechanical ventilation (invasive and non-invasive), occurrence of infection during ICU stay, ICU length of stay, hospital length of stay, alive/dead status at discharge and at 30 days and unplanned hospital readmission at 30 days were collected.

## **Endpoints**

The primary endpoint was all-cause death at 30 days. The 30-day time frame was chosen as a shorter time frame would not catch recurrence and morbidity, and a longer time frame would catch events more likely linked to chronic morbidity than to the AHF syndrome [16, 17].

The secondary endpoints were prevalence of hyperoxia (defined as at least one arterial blood gas with a  $PaO_2 > 100$  mmHg), unplanned hospital readmission within the first 30 days, occurrence of pneumonia and bacteraemia, hypoxic events, ICU length of stay and total length of stay. Hypoxic events were defined as  $SpO_2 \leq 88\%$  for longer than 2 minutes and requiring therapeutic action.

## **Patient groups**

Patients with AHF were divided into two groups: the hyperoxia group, including patients with at least one arterial blood gas with a  $PaO_2 > 100$  mmHg in the first 24 hours; and the control group, including patients in whom the  $PaO_2$  was  $\leq 100$  mmHg for all arterial blood gases. Hyperoxia was defined as a  $PaO_2$  strictly  $> 100$  mmHg in an arterial blood gas.

## **Statistical analyses**

The results are presented as medians (interquartile ranges) for quantitative variables, and as numbers (proportions) for qualitative variables. Baseline characteristics and outcomes were compared between the two groups of patients (the hyperoxia group and the control group). Non-parametric tests were used. Binary logistic regression multivariable analysis was performed to determine if hyperoxia was an independent risk factor for 30-day outcome. The covariables used in the model were age, male sex and sequential organ failure assessment (SOFA) score [18].



All statistical tests were two-tailed, with a significance threshold of 0.05. Analyses were performed with R (version 3.2.4).

## Results

### Patient characteristics

From 1 January 2015 to 31 December 2016, 96 patients were admitted to the ICU for acute pulmonary oedema; 75 met the inclusion criteria and were included in the analysis.

The main characteristics of the population are reported in [Table 1](#). The median age was 76 (68–83) years, and there were 38 men (51%). The median SOFA score was 5 (4–6). Among the 40 patients requiring mechanical ventilation, 28 (37%) were treated by non-invasive ventilation and 12 (16%) needed orotracheal intubation. Eleven patients (15%) received catecholamines, 59 (79%) received diuretics and 26 (35%) received vasodilator agents.

The median length of stay in hospital was 15 (12–18) days and the median length of stay in the ICU was 5 (4–6) days.

### Prevalence of hyperoxia

During the first 24 hours, 43 patients (57.3%) presented at least one arterial blood gas with a  $\text{PaO}_2 > 100$  mmHg, whereas 32 patients (42.7%) did not. Of note, hyperoxia was already present at admission in 17 patients (23%) ([Table 2](#)).

The admission clinical and biological data for the two groups are described in [Table 1](#).

### Primary and secondary endpoints

At 30 days, the mortality rate did not differ between the two groups: six patients died in the hyperoxia group (14.0%) compared with six in the control group (18.8%) ( $P = 0.85$ ) ([Table 3](#) and [Fig. 1](#)).

The 30-day hospital readmission rate did not differ between groups (14.0% in the hyperoxia group compared with 9.3% in the control group;  $P = 0.21$ ) ([Table 3](#) and [Fig. 1](#)).

The ICU lengths of stay, hospital lengths of stay and rates of infection were not significantly different between the two groups. The incidence of hypoxic events was higher in the control group compared with in the hyperoxia group (34.9% vs 68.8%;  $P < 0.001$ ) ([Table 3](#)).

## Factors associated with 30-day mortality

After adjustment for age and other confounders, hyperoxia was not associated with death at 30 days (odds ratio 0.77, 95% CI 0.24–2.41).

## Discussion

To our knowledge, this is the first study assessing the prevalence and potential effects of hyperoxia in patients admitted to an ICU for acute pulmonary oedema resulting from AHF. Our first finding was that at least some periods of hyperoxia are frequent in patients with AHF managed in the ICU. In addition, hyperoxia was not associated with increased 30-day death. Of note, the 30-day hospital readmission rate did not differ between groups.

In our study, only a few patients presented with hyperoxia at the time of admission to the ICU. However, once admitted, the majority of patients experienced hyperoxia, underlying the crucial role of physicians in generating phases of hyperoxia, and thus the possibility to avoid them. This point raises the question of the benefit/risk balance in the administration of high amounts of oxygen to critically ill patients, considering the risk of harmful effects of hyperoxia, as the endothelial production of free radicals induces cerebral, systemic, coronary vasoconstriction and deleterious haemodynamic effects, as described previously.

Our results did not confirm those of studies published recently. Indeed, these studies demonstrated harmful effects of hyperoxia in patients with different acute diseases, such as cardiac arrest or myocardial infarction [3, 6, 7].

The 30-day death rate in our study was higher than in previous studies assessing patients with AHF [16, 17, 19], which reported 30-day mortality rates of around 6–8%. Compared with previous studies conducted in cardiac ICUs, ours was conducted in a general ICU admitting more severe patients. During their hospitalization, almost half of the patients (53.3%) needed mechanical ventilation, a high number had an endotracheal intubation and 15% had inotropic drugs. In the French OFICA study, assessing 631 patients with AHF with pulmonary oedema, and in the 581 patients from the EuroHeart Failure Survey II, 15.4% and 31.5% of patients, respectively, required non-invasive ventilation [17, 19]. Also, our population included many patients with co-morbidities, with one-third having kidney failure.

## **Study limitations**

Because of the low number of patients included, our study suffered from a lack of power to draw definite conclusions about the consequences of hyperoxia. Moreover, the study was carried out in a single centre, and was observational and retrospective, which applies additional limitations to its findings. Of note, we assessed neither the duration nor the level of hyperoxia. There were selection biases because of the heterogeneity and severity of our population, making it hard to prove the harmful effect of hyperoxia on patient outcome. We are currently designing a multicentre randomized controlled clinical trial to compare a conservative oxygen therapy strategy with a liberal oxygen therapy strategy, to provide a definitive answer about the consequences of hyperoxia in a larger population of patients with acute pulmonary oedema.

## **Conclusion**

In this preliminary study assessing patients referred to an ICU for acute pulmonary oedema, we did not identify any difference in outcomes between patients with phases of hyperoxia and patients without hyperoxia.

## **Sources of funding**

None.

## **Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

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## Figure legend

**Figure 1.** Outcomes, according to oxygenation group.

**Table 1** Baseline characteristics.

	All patients ( <i>n</i> = 75)	Hyperoxia group ( <i>n</i> = 43)	Control group ( <i>n</i> = 32)	<i>P</i>
Age (years)	76 (68–83)	74 (64–85)	76.5 (65–88)	0.30
Male sex	38 (51)	25 (58)	13 (41)	0.9
Supraventricular arrhythmia	42 (56)	20 (47)	22 (69)	0.42
Chronic lung disease	14 (19)	3 (7)	11 (34)	< 0.001
Chronic kidney failure	23 (31)	11 (26)	12 (38)	0.78
Ischaemic cardiomyopathy	33 (44)	23 (54)	10 (31)	0.69
Ejection fraction (%)	50 (47–54)	49 (44–53)	49 (44–53)	0.11
SOFA score	5 (4–6)	4 (3–7)	5 (3–7)	0.20
Mechanical ventilation	40 (53)	23 (53)	17 (53)	0.96
Non-invasive ventilation	28 (37)	13 (30)	15 (47)	
Invasive ventilation	12 (16)	10 (23)	2 (6)	0.59
Mechanical ventilation duration (days)	2 (1–3)	2 (1–3)	2 (0.6–3.4)	0.37
Medication				
Catecholamines	11 (15)	9 (21)	2 (6)	< 0.01
Diuretics	59 (79)	35 (81)	24 (75)	0.90
Vasodilators	26 (35)	16 (37)	10 (31)	0.92
Renal support	7 (9)	3 (7)	4 (13)	0.76

Data are expressed as median (interquartile range) or number (%). SOFA: sequential organ failure assessment.

**Table 2** Blood gas analysis at admission and at 24 hours, according to oxygenation group.

	Hyperoxia group	Control group	<i>P</i>
Patients presenting at least one PaO <sub>2</sub> > 100 mmHg	43	32	
Blood gas analysis at admission			
pH	7.21 (7.10–7.43)	7.24 (7.20–7.40)	0.41
PaO <sub>2</sub>	119 (76–158)	70 (66–80)	< 0.001
PaCO <sub>2</sub>	41 (36–52)	46 (37–58)	0.16
Lactate	2.0 (1.5–2.6)	1.9 (1.5–2.9)	0.42
Blood gas analysis at 24 hours			
pH	7.40 (7.40–7.50)	7.50 (7.50–7.50)	
PaO <sub>2</sub>	101 (80–136)	72 (65–80)	0.12
PaCO <sub>2</sub>	37 (41–43)	43 (37–48)	0.009
Lactate	1.40 (1.1–2.2)	1.7 (1.5–2.3)	0.07

Data are expressed as number or median (interquartile range). PaCO<sub>2</sub>: partial pressure of carbon dioxide; PaO<sub>2</sub>: partial pressure of oxygen.



**Table 3** Outcomes, according to oxygenation group.

	Hyperoxia group ( <i>n</i> = 43)	Control group ( <i>n</i> = 32)	<i>P</i>
Infection occurrence	6 (14.0)	6 (18.8)	0.12
Hypoxic events	15 (34.9)	22 (68.8)	< 0.001
Length of stay in ICU (days)	3.3 (2.0–6.9)	4.5 (3.4–7.8)	0.16
Length of stay in hospital (days)	12.2 (7.5–16.3)	12.1 (8.3–17.6)	0.20
Death at 30 days	6 (14.0)	6 (18.8)	0.85
Unplanned hospital readmission at 30 days	6 (14.0)	3 (9.3)	0.21

Data are expressed as number (%) or median (interquartile range). ICU: intensive care unit.

