Effect of preoxygenation using non-invasive ventilation before intubation on subsequent organ failures in hypoxaemic patients: a randomised clinical trial

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Abstract

Background: Previous data showed that non-invasive ventilation (NIV) applied for 3 min before tracheal intubation ensured better oxygenation compared with using a non-rebreather bag-valve-mask. We aimed to determine whether preoxygenation using NIV is effective in reducing the incidence of organ dysfunction in hypoxaemic, critically ill patients in intensive care.

Methods: A multicentre, randomised, open-label trial evaluating 100% FiO_2 administered with NIV (99 patients) *vs* with face mask (102 patients) for 3 min before tracheal intubation. The primary endpoint was the maximal value of Sequential Organ Failure Assessment score within 7 days after intubation.

Results: The median (inter-quartile range) values of the maximal value of the Sequential Organ Failure Assessment score within 7 days post-intubation were not significantly different between the two randomised groups: nine (6–12) in the NIV group *vs* 10 (6–12) in the face mask group (P=0.65). In patients treated by NIV prior to the randomisation, there was a significant increase in the occurrence in adverse events in patients randomised to face mask [odds ratio=5.23 (1.61;16.99), P=0.0059].

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Conclusions: This study failed to demonstrate any benefits of using NIV as a preoxygenation method to reduce organ dysfunction compared with usual preoxygenation in hypoxaemic, critically ill patients requiring tracheal intubation for invasive ventilation. NIV should not be discontinued for preoxygenation in the cases of patients treated by NIV before the decision to intubate.
Clinical trial registration: NCT00472160.

- Preoxygenation of the lungs using non-invasive ventilation (NIV) has been shown to reduce hypoxaemia compared to using a face mask before tracheal intubation.
- The effect of NIV on outcomes in the critically ill is not known.
- In this randomised trial, hypoxaemia occurred during intubation in both groups but the incidence was higher in patients whose lungs were preoxygenated using a face mask.
- This was more marked in patients who had been receiving NIV treatment previously.
- There was no effect on the development of organ failure or other clinical outcomes, but the study may have been underpowered to detect some differences.

Airway management in hypoxaemic critically ill patients requiring tracheal intubation and invasive ventilation is still a matter of concern. Difficult tracheal intubation has been observed in at least 10% of these patients and is associated with profound oxyhaemoglobin desaturation (SpO_2<80%) in 25% of cases.[1] Preoxygenation is important; the ultimate goal is to avoid or at least reduce the length and severity of hypoxaemia during laryngoscopy and intubation because of its potential deleterious consequences. The rate of oxyhaemoglobin desaturation mainly depends on the amount of stored oxygen at the onset of apnoea. We have previously evaluated non-invasive ventilation (NIV) as a novel approach to preoxygenation.[2] In acute respiratory failure, NIV improves oxygenation by delivering high oxygen concentration, by unloading respiratory muscle, by recruiting alveoli, and by increasing lung volumes. NIV applied for 3 min before intubation ensured better SpO_2 and PaO_2 values during intubation compared with the usual preoxygenation method—a non-rebreathing bag-valve-mask.[2] However, it is uncertain whether this approach improves clinical outcomes. To date, only one study has examined the benefits of NIV as one of a 10-point intubation management protocol.[3] The authors showed that implementation of such management reduced both severe hypoxaemia and collapse during intubation and within the first hour following the intubation of critically ill patients.

Our aim was to ascertain whether NIV is a more effective preoxygenation method for the reduction of organ dysfunction than usual preoxygenation in hypoxaemic, critically ill patients requiring tracheal intubation for invasive ventilation in the intensive care unit (ICU).

Methods

The study was a multicentre, randomised, open-label trial evaluating 100% FiO_2 administered with NIV *vs* with face mask during 3 min preceding intubation. The study was undertaken according to the Declaration of Helsinki and in keeping with French regulations. The protocol was approved by the national ethical review board (CPP:2006/69). Data were gathered using electronic case report forms by the Clinical Research Unit Lariboisière St-Louis, University Paris Diderot which independently undertook all statistical analyses.

Participants

Patients were enrolled at six sites. All patients more than 18 yr old with hypoxaemic acute respiratory failure requiring intubation were eligible for the study. Main exclusion criteria were intubation for encephalopathy or coma, decompensation of chronic respiratory failure, cardiopulmonary resuscitation, and pregnancy.

Randomisation

Patients were assigned via an interactive voice response system at the central randomisation centre, in a 1:1 ratio. Randomisation was stratified according to centre and condition of ventilation at the time of randomisation (oxygen supplementation alone or non-invasive respiratory support). We used the standard operating procedure of the clinical research department to avoid any knowledge of the randomisation list by the participants of the trial.

Data collection

The following data were collected: patient's characteristics; reason for admission; preadmission functional status was assessed using the Knaus scale (A, prior good health, no functional limitation; B, mild to moderate limitation of activity because of a chronic disease; C, serious but not incapacitating restriction of activity; and D, severe restriction of activity, including persons bedridden or institutionalized).[4] The general ICU-specific score (Simplified Acute Physiology Score II) was calculated on Day 1.[5] Organ failure-specific scores [Sequential Organ Failure Assessment (SOFA) and the number of organ failures] were calculated on Day 1 and within the first 7 days post-intubation (i.e. on each of the 7 days after intubation). An organ failure was defined as SOFA score of $\geq$3 points for the concerned organ (need for vasopressor, mechanical ventilation with PaO_2/FiO_2 ratio of <200, Glasgow Coma Scale score of <9, serum bilirubin of >100 μmol litre^{-1}, serum creatinine of >300 μmol litre^{-1} or oliguria lasting for >24 h, platelet count of <50 000 mm^3).[6]

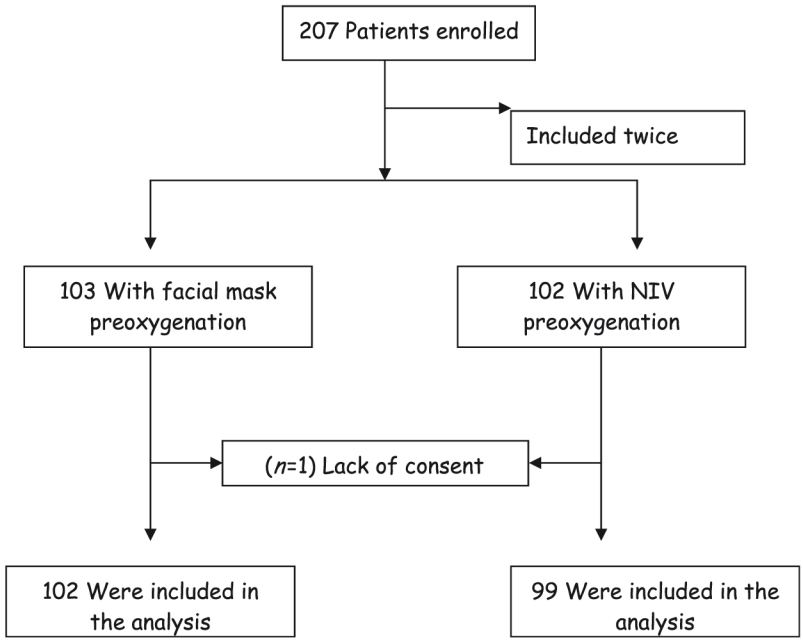

Fig 1. Flow chart. NIV, non-invasive ventilation.

Intervention

Preoxygenation was performed for a 3-min period before a standardized rapid sequence intubation. For the control group, preoxygenation used a non-rebreathing bag-valve-mask with an oxygen reservoir driven by 15 litre min^{-1} oxygen. Patients were allowed to breathe spontaneously with occasional assists (usual the preoxygenation method). For the NIV group, pressure support mode was delivered by an ICU ventilator through a face mask adjusted to obtain an expired tidal volume of 6–8 ml kg^{-1}. The fraction of inspired oxygen (FiO_2) was 100% and we used a Positive End Expiratory Pressure (PEEP) of 5 cm H_2O. Standardized rapid-sequence intubation was performed by a senior physician (etomidate, 0.3 mg kg^{-1}; succinylcholine, 1 mg kg^{-1}; laryngoscopy with a Macintosh size 3 or 4 blade, and cricoid pressure to secure the airway). After oral intubation, the patient was mechanically ventilated, with a tidal volume of 6–8 ml kg^{-1}, a respiratory rate of 20 bpm, a PEEP of 5 cm H_2O, and an FiO2 of 100%. Pulse oximetry (SpO_2) was continuously monitored throughout the procedure. Arterial blood gases were sampled before preoxygenation and after intubation (within 30–60 min). The intubation conditions were reported using the intubation difficulty scale.[7]

Endpoints

The primary endpoint of the trial was the maximal value of SOFA score within the first 7 days post-intubation.

The secondary endpoints were the following: 1. preoxygenation failure, i.e. requirement for an early stop of preoxygenation and immediate intubation because of absence of improvement or deterioration in SpO_2; 2. adverse event during preoxygenation or intubation defined as occurrence of arrhythmia with haemodynamic failure, and/or occurrence of regurgitation (presence of gastric content seen during laryngoscopy), severe O_2 desaturation (SpO_2<80%), *de novo* myocardial ischemia (myocardial repolarization and/or elevated serum troponin sampled between 4 and 8 hr after intubation); 3. number of organ failures in the ICU within the first 7 days post-intubation; 4. duration of stay in the ICU calculated as the number of days alive out of ICU within 28 days; 5. duration of ventilation calculated as the number of days alive free of ventilation (invasive or non-invasive) within 28 days; and 6. percentage of death in the ICU within 28 days.

Statistical analysis

A sample size of 100 patients per group was fixed on the basis of a standard deviation for SOFA score around 5 (calculated from data by Moreno and colleagues[8]), and the requirement of an 80% power to detect a difference at least equal to two between the two types of preoxygenation by analysis of variance (ANOVA) at a 5% two-sided alpha value. All analyses included the intention-to-treat population (all patients randomly assigned to treatment groups, analysed as randomised). Decision for intubation can occur in patients receiving or not an NIV; this is the reason why the present study was stratified according to the type of ventilation before randomisation. All quantitative variables were analysed using analysis of covariance (ANCOVA). Group of randomisation, centres and strata (i.e. the type of ventilation before randomisation) were included in the model as effects. The baseline value of SOFA score was included as covariate. When the quantitative variables were not Gaussian non-parametric, ANCOVA was used. Binary variables were analysed using multivariate logistic regression. The number of organ failures (ordinal variables with a limited number of categories) was studied using multivariate polychotomous regression. Group of randomisation, centres, and strata were included in the multivariate regression models. Frequencies of

patients with at least one adverse event were compared by the Chi-square test. Frequency of adverse events were compared using generalized estimating equations since several adverse events can occur in the same patient. All tests were two-sided with a 5% significance level. All analyses were made using SAS Version 9.2 (from SAS Institute, Cary, North Carolina, USA).

Results

Between July, 2007 and January, 2010, 201 patients were randomly assigned to receive preoxygenation by NIV (99 patients) or face mask (102 patients) before intubation. We excluded six patients (Fig 1). Baseline characteristics were very similar between the two randomisation groups at the admission (Table 1), before preoxygenation (Table 2), during and after intubation (Table 3). Among patients randomised, 91 (45%) were already oxygenated via NIV (Table 2). Preoxygenation failure, i.e. requirement for an early stop of preoxygenation and immediate intubation, was observed in five patients and only in the face mask group (Table 3).

Primary criterion: SOFA max

The median (inter-quartile range) values of the maximal value of the SOFA score within the first 7 days post-intubation were not significantly different between the two randomised groups; nine (six to 12) in the NIV group *vs* 10 (six to 12) in the face mask group ($P = 0.65$) (Table 4). No significant differences between centres or interactions between strata or centre and randomised procedure were found.

Table 1 Baseline characteristics of the 201 studied patients. Data are presented as *n* (%) or median (interquartile). ICU, intensive care unit; NIV, non-invasive ventilation; SOFA, Sequential Organ Failure Assessment Score

Variables	Preoxygenation NIV *n*=99	Preoxygenation face mask *n*=102
Age (yr)	65 (57–74)	62 (53–74)
Weight (kg)	67 (60–80)	72 (63–84)
Height (cm)	170 (162–175)	170 (163–175)
Body mass index	24 (22–27)	25 (22–30)
Male	66 (67%)	69 (68%)
Main reason for ICU admission		
Acute respiratory failure	40 (40%)	44 (43%)
Sepsis	12 (10%)	11 (11%)
Postoperative	14 (14%)	15 (15%)
Simplified Acute Physiology Score II	48 (38–60)	46 (37–58)
Knaus scale,		
No functional limitation	46 (47%)	32 (31%)
Mild to moderate limitation	34 (35%)	47 (46%)
Serious limitation	16 (16%)	22 (22%)
Severe limitation	2 (2%)	1 (1%)
SOFA	6 (4–9)	7 (5–9)
Number of organ failures	1 (1–2)	1 (1–2)

Table 2 Characteristics of patients before preoxygenation. Data are presented as *n* (%) or median (interquartile). NIV, non-invasive ventilation

Variables	Preoxygenation NIV *n*=99	Preoxygenation face mask *n*=102
NIV before preoxygenation	45 (46%)	46 (45%)
Systolic arterial pressure (mm Hg)	131 (110–149)	130 (113–150)
Heart rate (beats min^{-1})	109 (92–120)	110 (98–129)
Pulse oximetry (SpO_2), %	93 (88–98)	93 (90–98)
FiO_2 (%)	70 (48–90)	70 (48–70)
Blood gases		
PaO_2 (pKa)	9.7 (7.9–14)	10.9 (8.1–13.2)
$PaCO_2$ (pKa)	5.5 (4.4–6.8)	4.8 (3.9–6.3)
pH	7.4 (7.3–7.4)	7.4 (7.3–7.5)
BE (mmol $litre^{-1}$)	24 (21–27)	22 (18–25)
SaO_2 (%)	94 (90–97)	95 (91–98)
PaO_2/FiO_2	132 (80–175)	126 (95–207)

Secondary criteria

Number of organ failures

Statistical distribution of number of organ failures in the two groups is shown in Table 4. These distributions were not significantly different between the two randomised groups ($P = 0.34$). The effect of baseline value of SOFA was significant ($P < 0.001$) whereas the effect of strata was at the limit of significance ($P = 0.0504$). No significant differences between centres or interaction between strata or centre and randomised procedure were found.

Adverse events during preoxygenation or intubation

The percentage of adverse events was 21.4% in the NIV group *vs* 28.7% in the face mask group, $P = 0.24$ (Table 3).

Since for this parameter, the interaction between the randomised procedure and strata was significant, we analysed the randomised procedure for each strata. In patients treated by face mask prior to the randomisation, there was no significant difference between the two randomised groups [odds ratio=0.678 (0.257;1.773), P=0.43] whereas in patients treated by NIV prior to the randomisation, there was a significant increase in the occurrence of adverse events in patients randomised to face mask [odds ratio=5.23 (1.61;16.99), P=0.0059] (Table 5). No significant effects of baseline value of SOFA or centres were found.

Duration of ventilation or stay in ICU

The median (inter-quartile range) values of days alive free of ventilation within 28 days post-intubation were not significantly different between the two randomised groups (Table 4). Similar conclusions were found regarding the number of days alive outside the ICU, four (zero to 17) in the NIV group *vs* three (zero to 12) in the face mask group ($P = 0.14$).

Table 3 Characteristics of patients during and after intubation. Data are presented as *n* (%) or median (interquartile). NIV, non-invasive ventilation

Variables	Preoxygenation NIV *n*=99	Preoxygenation face mask *n*=102	*P*
Rapid sequence intubation, *n* (%)	90 (91.8%)	91 (90.1%)	0.67
Intubation difficulty scale	0 (0–2)	1 (0–2)	0.21
Systolic arterial pressure (mm Hg)*	119 (91–142)	115 (90–145)	0.67
Heart rate (beats min^{-1})*	102 (90–120)	112 (99–130)	0.01
Pulse oximetry (SpO_2), %*	92 (84–98)	88 (79–95)	0.12
FiO_2	100 (70–100)	100 (70–100)	0.62
Blood gases†			
PaO_2 (pKa)	15.6 (10.7–23.9)	13.7 (10.8–26.4)	0.99
$PaCO_2$ (pKa)	6 (5.2–7.2)	5.9 (5.1–6.4)	0.12
pH	7.33 (7.26–7.40)	7.32 (7.24–7.40)	0.74
BE (mEq $litre^{-1}$)	24 (21–27)	23 (18–27)	0.06
SaO_2 (%)	98 (95–99)	98 (95–99)	0.75
Rapport PaO_2/FiO_2	154 (89–220)	150 (97–232)	0.90
Patients with at least one adverse	21 (21.4%)	29 (28.7%)	0.24
event during preoxygenation or intubation	18 (18.4%)	28 (27.7%)	0.10
SpO_2<80%	1 (1%)	2 (2%)	
Arrhythmia with haemodynamic failure Regurgitation	1 (1%)	2 (2%)	
Myocardial ischaemia	3 (3.1%)	1 (1%)	
Preoxygenation failure‡	0 (0%)	5 (5.3%)	
Total number of adverse events	23	38	

* The minimal value.
† Arterial blood gases measurement were performed 30–60 min after intubation.
‡ Preoxygenation failure was defined as absence of improvement or deterioration in SpO_2.

Table 4 Outcome. Data are presented as *n* (%) or median (interquartile). NIV, non-invasive ventilation, SOFA, sequential organ failure assessment score

Variables	Preoxygenation NIV *n*=99	Preoxygenation face mask *n*=102	*P*
Maximal SOFA value*	9 (6–12)	10 (6–12)	0.65
Number of organ failures:			
0	8 (8.2%)	3 (3.1%)	0.34
1	23 (23.5%)	27 (27.6%)	
2	34 (34.7%)	26 (26.5%)	
3	20 (20.4%)	26 (26.5%)	
4	9 (9.2%)	11 (11.2%)	
5	4 (4.1%)	5 (5.1%)	
Death†	31 (31.3%)	38 (37.3%)	0.76
Duration of stay in ICU‡	4 (0–17)	3 (0–12)	0.14
Duration of ventilation¶	9 (1–21)	5.5 (1–21)	0.37
Duration of invasive ventilation¶	13 (1–23)	9 (1–21)	0.40
Duration of non-invasive ventilation¶	27 (18–28)	26 (14.5–28)	0.85

* Maximal value of the SOFA score within 7 days post-intubations.
† Percentage of death in intensive care unit within 28 days.
‡ Duration of stay in intensive care unit (ICU) calculated as the number of days alive out of ICU within 28 days.
¶ Duration of ventilation calculated as the number of days alive free of ventilation (invasive/non-invasive) within 28 days.

Death

The percentage of death was not significantly different among the two groups; 31.3% in the NIV group *vs* 37.3% in the face mask group ($P = 0.76$). The effect of baseline value of SOFA was significant ($P < 0.0001$). No significant effect of strata centres or interaction between strata or centre and randomised procedures were found.

Discussion

This study failed to demonstrate any benefits of using NIV as a preoxygenation method to reduce organ dysfunction assessed by the maximal value of the SOFA score within 7 days following intubation compared with the usual preoxygenation in hypoxaemic, critically ill patients requiring tracheal intubation for invasive ventilation in the ICU. However, the results emphasized that NIV should not be discontinued for preoxygenation in the cases of patients treated by NIV before the decision to intubate, as there was a significant increase in adverse events when face mask preoxygenation was used in patients previously receiving NIV.

We had put forward the hypothesis that NIV may reduce organ dysfunction. Profound oxyhaemoglobin desaturation has been shown to increase morbidity and mortality in a specific population. We have previously shown that NIV is a safe preoxygenation method which is more effective in preventing arterial oxyhaemoglobin desaturation than the usual method of preoxygenation during tracheal intubation in critically ill patients.[2] The present randomised and multicentric study does not confirm this advantage. Indeed, despite the use of NIV for preoxygenation, up to 18.4% (SpO_2 <80%) of the patients experienced arterial oxyhaemoglobin desaturation during intuba-

Table 5 Adverse events in patients with non-invasive, NIV, respiratory support at the time of randomisation (prior to intervention), n=91. Data are presented as n (%) or median (interquartile). NIV, non-invasive ventilation; SOFA, sequential organ failure assessment score

Variables	Preoxygenation NIV n=45	Preoxygenation face mask n=46	OR	P
Patients with at least one adverse event during preoxygenation or intubation	8 (17.8%)	19 (41.3%)	5.2 (1.6–17)	0.006
SpO_2<80%	7 (16.6%)	19 (41.3%)		0.002
Arrhythmia with haemodynamic failure	0 (0%)	2 (4.3%)		
Regurgitation	0 (0%)	1 (2.2%)		
Myocardial ischaemia	1 (2.2%)	0 (0%)		
Preoxygenation failure	0 (0%)	5 (10.8%)		
Total number of adverse events	8	27		
Maximal SOFA value*	9.5 (6–13)	9.5 (7–12)		0.59
Number of organ failures:	2 (2–3)	2 (1–4)		0.68
0	1 (2.2%)	2 (4.3%)		
1	10 (22.2%)	10 (21.7%)		
2	15 (33.3%)	13 (28.3%)		
3	9 (20.0%)	8 (17.4%)		
4	6 (13.3%)	10 (21.7%)		
5	4 (8.9%)	3 (6.5%)		
Death†	15 (33%)	16 (35%)	1.2 (0.46–3.14)	0.70

* Maximal value of the SOFA score within 7 days post-intubations.
† Percentage of death in ICU within 28 days.

tion. Although the PaO_2/FiO_2 ratios were similar for the two groups, the median PaO_2 in those receiving preoxygenation by face mask was 12% higher than those given NIV as preoxygenation (median 82 *vs* 73 mm Hg) (Table 2). Although this difference is not statistically different, it may be clinically relevant and might help to explain why no difference was found between the groups in subsequent organ failures. Adverse events during preoxygenation and intubation were not found to be statistically different between the two groups, although there was a trend to reduce preoxygenation failure when NIV was used as compared with the usual method, $P = 0.06$ (Table 3). Also, the patients were found to be less hypoxaemic (PaO_2 >9.33 kPa) and less hypercapnic ($PaCO_2$ ≤5.47 kPa) than the participants of the previous study (PaO_2 <9.33 kPa and $PaCO_2$ ≥6.53 kPa).[2] In the control group, SpO_2 <80% during intubation occurred in 27.7% of the patients. This incidence is much lower than those observed in the previous study (46%), but complies with the findings of a French prospective multiple-centre study.[3] This could at least partly explain why preoxygenation with the usual method was not associated with higher arterial oxyhaemoglobin desaturation events than with NIV. Finally, it is not surprising to observe that NIV does not reduce organ dysfunctions, because there was no more oxyhaemoglobin desaturation as compared with using a usual preoxygenation method. The most relevant serious adverse event with a major impact on the primary outcome chosen here would be a hypoxic cardiac arrest, which is obviously a rare situation. Despite the inclusion of about 200 patients, the study might still be underpowered to detect these rare scenarios.

The decision to use intubation can occur in patients treated with NIV. This is why the present study was stratified according to the type of ventilation before randomisation. In this group, when NIV was moved to a non-rebreather bag-valve-mask for the preoxygenation, there was a significant increase in the occurrence of adverse events (odds ratio = 5.23, Table 5).

Recent surveys show that NIV is being increasingly used as first-line ventilatory therapy for acute hypoxaemic respiratory failure.[9] To date, NIV is initiated in up to 20–30% of the patients as a trial ventilatory support instead of invasive ventilation for acute respiratory syndrome.[10,11] NIV reduces the rate of intubation and subsequent invasive ventilation in a selected population with acute hypoxaemic respiratory failure such as surgical or immunosuppressed patients.[12–14] As a consequence, NIV is gaining in popularity among intensivists. In our study, among randomised patients, 91 (45%) were already oxygenated using NIV before the decision to intubate.

Miguel-Montanes and colleagues[15] reported for the first time on the use of high-flow nasal cannula oxygen as an alternative preoxygenation technique. This device can be used to deliver up to 60 litre min^{-1} oxygen with the ability to reach 100% FiO_2. In this pivotal before-after study, the authors showed that as a preoxygenation method, high-flow nasal cannula oxygen significantly reduced hypoxaemia during intubation as compared with a non-rebreather bag-valve-mask. One of the main advantages of this approach is the possibility to oxygenate (apneic oxygenation) the patient during the whole intubation procedure. However, despite this theoretical advantage, two recent multicentre randomised studies did not confirm the benefit of this approach.[16,17]

Conclusions

This multicentre, randomised study failed to demonstrate that NIV is more effective as a preoxygenation method in reducing organ dysfunction than usual preoxygenation in hypoxaemic, critically ill patients requiring tracheal intubation. However, in patients treated by NIV before the decision to intubate, NIV should be pursued for preoxygenation, as it enables the reduction of severe hypoxaemia as compared with using non-rebreather bag-valve-mask.

Authors' contributions

Conception and design of the work, data analysis, writing paper: C.B., S.J.
Acquisition of data: G.P., B.J., E.F., J.Y.L., F.V., A.H.

New-onset atrial fibrillation in critically ill patients and its association with mortality: A report from the FROG-ICU study

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A B S T R A C T

Background: Atrial fibrillation (AFib) is associated with adverse outcome in critical illness, but whether this effect is independent from other risk factors remains uncertain. New-onset AFib during critical illness may be independently associated with increased in-hospital and long-term risk of death.
Methods: FROG-ICU was a prospective, observational, multi-centre cohort study designed to investigate the outcome of critically ill patients. Inclusion criteria were invasive mechanical ventilation and/or treatment with a positive inotropic agent for >24 h. Heart rhythm was assessed at inclusion and during ICU stay with digital ECG recordings. Among patients who had AFib during ICU stay, new-onset and recurrent AFib were diagnosed in patients without and with previous history of AFib, respectively. Primary endpoint was in-hospital mortality; secondary endpoint was 1-year mortality among ICU survivors.
Results: The study included 1841 critically ill patients. During ICU stay, AFib occurred in 343 patients (19%). New-onset AFib (n = 212) had higher in-hospital mortality compared to no AFib (47 vs. 23%, $P < 0.001$) or recurrent AFib (34%, $P = 0.032$). New-onset AFib showed increased risk of in-hospital death after multivariable adjustment compared to no AFib (OR 1.6, $P = 0.003$) or recurrent AFib (OR 1.8, $P = 0.02$). Among the 1464 ICU-survivors, new-onset AFib during ICU stay showed higher post-ICU risk of death compared to no AFib (HR 2.2, $P < 0.001$). After multivariable adjustment, new-onset AFib showed higher post-ICU risk of death compared to no AFib (HR 1.6, $P = 0.03$).
Conclusion: New-onset AFib is independently associated with in-hospital and post-ICU risk of death in critically ill patients.

Keywords:
Atrial fibrillation
ICU
Critical illness
Outcome
Mortality

1. Introduction

Atrial fibrillation (AFib) is the most common arrhythmia in critically ill patients with incidence up to 25% in non-cardio-surgical intensive care units (ICUs) [1,2]. In critically ill patients, AFib may precipitate acute heart failure and thromboembolic complications [3–5]. Critical illness may induce the development of AFib in patients without previous history of arrhythmia (new-onset AFib) or precipitate relapses in patients with history of paroxysmal AFib (recurrent AFib). The underlying mechanisms include fluid and electrolyte imbalance, inflammation, ischemia and adrenergic overstimulation [2], which impair efficacy of treatments and promote early relapses [6].

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[1] MA and SI equally contributed to this project.
[2] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Several studies reported increased short-term mortality and longer hospital stay associated with development of AFib during critical illness [7,8], however, there is still uncertainty whether new-onset AFib is merely a marker of disease severity or independently contributes to unfavorable outcome. Two very recent studies provided opposing results. Gupta et al. failed to show independent association between the presence of AFib (new-onset or recurrent) during critical illness and in-hospital mortality [9]. By contrast, Shaver et al. described increased in-hospital mortality associated with new-onset or recurrent AFib, independently from the severity of critical illness or underlying cardiac risk factors [10].

Moreover, little is known about the impact of AFib, in particular new-onset forms, on outcome after recovery from critical illness. Neither Gupta et al. nor Shaver et al. reported on the long-term outcomes of their patients. Chen et al. recently identified new-onset AFib as independent predictor of 60-day mortality in medical ICU patients [11]. Previously, Meierhenrich et al. failed to show a difference in long-term mortality associated with AFib in septic shock patients [12].

The primary aim of this French and euROpean Outcome reGistry in Intensive Care Unit (FROG-ICU) sub-study was to test the hypothesis that new-onset AFib during critical illness is independently associated with in-hospital and post-ICU mortality.

2. Methods

2.1. Study design

The FROG-ICU study was a prospective, observational, multi-centre cohort study designed to investigate long-term mortality of critically ill adult patients [13]. All consecutive patients admitted to any of the 28 participating medical, surgical or mixed ICUs in 19 hospitals in France and Belgium were screened for eligibility. Inclusion criteria were invasive mechanical ventilation and/or treatment with a positive inotropic agent for >24 h. Exclusion criteria were age <18 years, severe head injury, brain death or persistent vegetative state, pregnancy or breastfeeding, organ transplantation in the last 12 months and/or lack of social security coverage.

Heart rhythm was assessed continuously at the patient's monitor by the investigators and documented by digital 12-lead ECG at inclusion, during the first 3 days of ICU stay, twice a week thereafter and at ICU discharge. Concomitantly, patient characteristics including medical history, hemodynamic parameters and medical treatment were recorded. Details about study design have been previously published [13]. Patients with lacking information about heart rhythm were excluded from this sub-study. Fig. 1 shows the flowchart of the study population.

Among patients who had any episode of AFib during ICU stay, new-onset and recurrent AFib were diagnosed in patients without and with previous history of AFib, respectively. Patients who remained in sinus rhythm were defined as "no AFib".

Primary endpoint was in-hospital mortality. Secondary endpoint was 1-year mortality among ICU survivors.

The study was performed in accordance with Good Clinical Practice and the Declaration of Helsinki 2002, validated by the corresponding ethical committees and registered on ClinicalTrials.gov (NCT01367093).

2.2. Statistical analysis

Continuous variables are expressed as median (interquartile range), nominal variables are expressed as number (percentages). Differences between independent groups were assessed with Wilcoxon rank sum test, Mann Whitney *U* test and Fisher's exact test, as appropriate. Adjusted *P*-values for multiple comparisons are reported, if appropriate. Unadjusted and covariate adjusted logistic regression models were used to determine the association between AFib and in-hospital mortality. Using step-by-step backward regression, 7 independent covariates of in-hospital mortality (age, gender, Simplified Acute Physiology Score (SAPS II), treatment with inotropes or vasopressors at inclusion, serum lactate level at inclusion, high-sensitive troponin I at inclusion, B-type natriuretic peptide (BNP) at inclusion) were selected among 15 clinical variables with prognostic value on short-term outcome (age, gender, SAPS II, history of congestive heart failure, history of coronary artery disease, history of hypertension, history of diabetes, septic shock at inclusion, neurological disease at inclusion, treatment with inotropes or vasopressors at inclusion, serum lactate level at inclusion, serum creatinine at inclusion, BNP at inclusion, high-sensitive troponin I at inclusion, C-reactive protein (CRP) at inclusion). Risk of in-hospital mortality is expressed as odds ratio (OR) and 95% confidence interval (CI). Long-term survival was plotted with the Kaplan-Meier curve and difference between groups was tested with the log-rank test. Unadjusted and covariate adjusted Cox proportional hazards models were used to evaluate the association between AFib and one-year mortality in ICU survivors. Adjustments were performed for the previously identified 14 independent predictors of one-year post-ICU survival (age, Charlson comorbidity index, loss of autonomy, severe valve disease or prior valve surgery, chronic renal disease, peripheral vascular disease, recent malignant tumors, red blood cell transfusion during ICU stay, length of ICU stay > 20 days, systolic blood pressure at ICU discharge, body temperature at ICU discharge < 37 °C, leucocytes at ICU discharge > 20 G/L, platelets at ICU discharge < 10 G/L, total serum protein at ICU discharge < 60 g/L) [14]. Risk of one-year mortality is expressed as hazard ratio (HR) and 95% CI. The null hypothesis was rejected with an adjusted two-sided *P*-value < 0.05. All statistical analyses were performed using R statistical software (The "R" Foundation for Statistical Computing, Vienna, Austria).

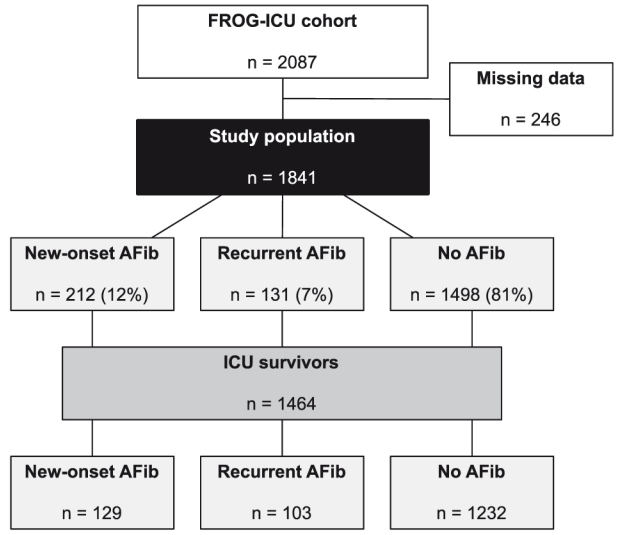

Fig. 1. Flowchart of the study population. Legend: AFib atrial fibrillation, ICU intensive care unit.

3. Results

3.1. Study population and outcome

A total of 2087 patients were included in the FROG-ICU cohort from July 2011 to December 2013.

Two-hundred and forty-six patients (12%) were excluded from the analysis because of lacking data about heart rhythm. The study population consisted of 1841 critically ill patients with a median Simplified Acute Physiology Score (SAPS II) of 49 (35–63) points (Fig. 1). Supplemental Table 1 summarizes baseline characteristics of the study population. The median delays between ICU admission and study inclusion was 3 (2–5) days. The median ICU length of stay was 13 (7–22) days. The ICU and in-hospital mortality were 20% and 26%, respectively.

3.2. Incidence of arrhythmia during ICU stay

AFib was documented in 343 patients (19%) during the ICU stay. By contrast, 1498 patients (81%) remained in sinus rhythm (no AFib). New-onset AFib and recurrent AFib were diagnosed in 212 and 131 patients, respectively. As depicted in Fig. 2, the first episode of AFib mostly occurred the day of study inclusion, with decreasing incidence in the following days. Of the 1464 ICU survivors, ECG at discharge was available for 922 patients. AFib was documented in 90 patients (9.8%).

3.3. In-hospital outcome of patients with new-onset AFib

Patients with new-onset AFib had higher in-hospital mortality (47%) compared to patients with no AFib (23%, $P < 0.001$) and recurrent AFib (34%, $P = 0.032$), as illustrated in Fig. 3. New-onset AFib and recurrent AFib were both associated with increased risk of in-hospital death compared to no AFib (OR 3.0 (95% CI 2.2–4.0), $P < 0.001$) and

(OR 1.8 (95% CI 1.2–2.6), $P = 0.004$), respectively. New-onset AFib was associated with higher risk of in-hospital death compared to recurrent AFib (OR 1.7 (95% CI 1.1–2.6), $P = 0.024$).

Patients with new-onset AFib showed several notable differences in clinical and disease characteristics (Supplementary Table 1). After adjustment for 7 independent covariates of in-hospital mortality, new-onset AFib was independently associated with higher in-hospital risk of death compared to no AFib (OR 1.6 (95% CI 1.2–2.2), $P = 0.003$) and to recurrent AFib (OR 1.3 (95% CI 1.01–1.8), $P = 0.04$). Conversely, recurrent AFib showed similar risk of in-hospital death compared to no AFib, after adjustment for clinical confounders (OR 0.9 (95% CI 0.6–1.4), $P = 0.70$), Fig. 3.

Furthermore, median length of ICU stay of patients with new-onset AFib (15 (9–28) days) was longer compared to those of patients with no AFib (12 (7–21) days) or recurrent AFib (12 (8–21) days), $P = 0.009$. Among ICU survivors, patients with new-onset AFib (14 (9–23) days) had still longer ICU stay compared to those with no AFib (12 (7–21) days) or recurrent AFib (12 (8–21) days), although the difference was not significant, $P = 0.28$.

3.4. Post-ICU mortality of patients with new-onset AFib

A total of 1464 patients were discharged alive from ICU. As shown in Fig. 4, ICU survivors with new-onset AFib during ICU stay (n = 129) showed higher 1-year mortality compared to ICU survivors with no AFib (n = 1232, paired log-rank $P < 0.001$), but similar to ICU survivors with recurrent AFib (n = 103, paired log-rank $P = 0.40$).

After multivariable adjustment for 14 independent predictors of one-year post-ICU survival, ICU survivors with new-onset AFib showed higher 1-year risk of death compared to patients with no AFib (HR 1.6 (95% CI 1.1–2.4), $P = 0.030$). Recurrent AFib was associated with no significant association with increased risk of death compared to patients with no AFib (HR 1.4 (95% CI 0.9–2.1), $P = 0.23$), Fig. 4.

4. Discussion

The present study shows that new-onset AFib is an independent predictor of in-hospital and long-term mortality in a large, international, multi-centre ICU population.

The management of critically ill patients developing AFib is challenging. Indeed, AFib may impair the ventricular filling and precipitate acute heart failure [3–5], on the other hand, management of AFib in ICU patients is particularly difficult, because many antiarrhythmic treatments are either contraindicated or their efficacy is reduced, predisposing to early relapses [6,15,16]. Understanding whether AFib independently contributes to worse outcome of critically ill patients or is merely a marker of disease severity is therefore of crucial importance. In fact, depending on whether AFib independently contributes to worse outcome (or not), further research may be needed to find strategies for reducing the burden of AFib in critically ill patients.

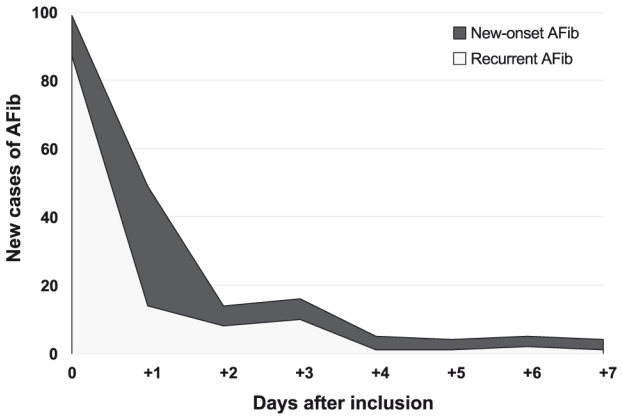

Fig. 2. Incidence of new cases of atrial fibrillation after study inclusion. Legend: AFib atrial fibrillation.

Our study confirmed a high prevalence of AFib in critically ill patients, previously shown in medical, surgical and cardio-surgical ICU settings [8,12,17–19]. Our data also confirmed that the incidence of AFib during ICU stay is particularly high in the first days of acute illness [7,8,18].

Our study showed that critically ill patients developing AFib during ICU stay, and in particular those with new-onset AFib, had higher in-hospital mortality compared to patients without AFib. This observation is in line with previous data, showing worse short-term outcome in ICU patients with new-onset AFib compared to patients without or with recurrent AFib [7]. By adjusting for clinical confounders, the present study clearly shows the independent association of AFib with increased risk of in-hospital death. These results are in contrast with data from a retrospective single-centre study by Gupta et al. and a prospective multi-centre study by Annane et al., which both failed to show independent association of AFib with increased in-hospital mortality [8,9].

Multiple explanations exist for these contrasting results. First, both studies did not separately analyze new-onset and recurrent forms of AFib. Second, the study by Gupta et al. included a population of less severely ill patients compared to FROG-ICU with significantly lower physiologic derangements and in-hospital mortality. This may have reduced the detrimental effect of AFib on short-term mortality. Third, the study by Annane et al. did no distinction between AFib and other forms of supraventricular tachycardia. Furthermore, the relatively low number of events and the high number of covariates used for adjustment may have impaired the ability to see relevant associations between arrhythmias and in-hospital outcome.

Conversely, a recent prospective single-centre study by Shaver et al. identified AFib (either new-onset or recurrent) as independent predictor of in-hospital mortality in critically ill patients, as reported in our study [10]. In addition, our study showed an even higher risk of in-hospital death in patients with new-onset compared to those with recurrent AFib, regardless of illness severity. The reasons for this difference are unknown, but one might speculate that both the hemodynamic consequences and mortality associated with the presence of AFib during critical illness might be more dramatic in patients not “adapted” to the arrhythmia.

The present study further addressed the association of AFib during ICU stay and long-term risk of death. Raw survival data indicated that ICU survivors with either new-onset or recurrent AFib had higher long-term mortality compared to patients without AFib. However, only the presence of new-onset AFib during ICU stay did independently predict worse long-term outcome, while recurrent forms did not. This observation adds an important piece in the puzzle of knowledge about AFib during critical illness. Indeed, it delimitates the detrimental effect of AFib on survival of critically ill patients to the new-onset forms. A retrospective single-centre study by Chen et al. identified new-onset AFib as independent predictor of 60-day mortality in a medical ICU population [11]. A single-centre study by Meierhenrich et al. including septic shock patients and a single-centre study by Topaz et including acute myocardial infarction patients, showed a trend toward higher long-term mortality in new-onset AFib compared to patients without AFib, although the differences were not statistically significant because of an underpowered studies [12,20]. The present study, using an international, multi-centre design and including a very large, tough well characterized, mixed ICU population describes new-onset AFib as an independent predictor of long-term risk of death in ICU patients, while recurrent AFib is rather a marker of comorbidity burden and secondarily to worse long-term outcome without independent association with increased long-term risk of death.

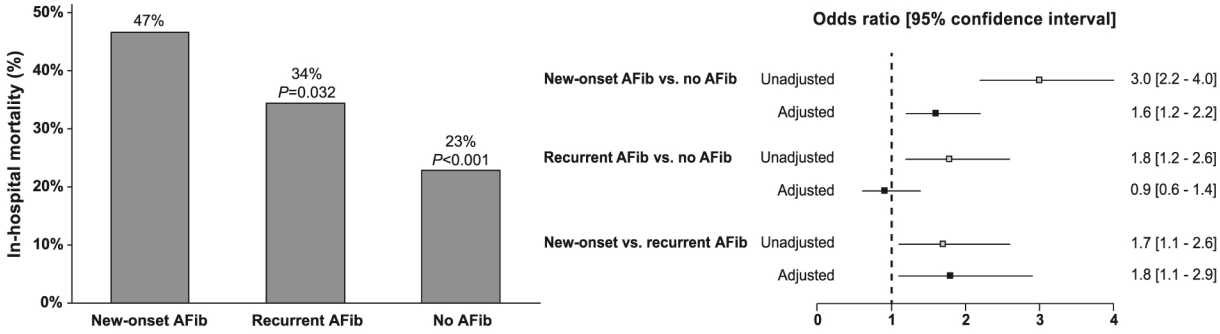

Fig. 3. In-hospital mortality according to occurrence of AFib during ICU stay. Legend: Reported *P*-values refer to comparisons with the new-onset AFib group. Adjustment performed for age, gender, SAPS II, treatment with inotropes or vasopressors at inclusion, serum lactate level at inclusion, high-sensitive troponin I at inclusion, BNP at inclusion. AFib atrial fibrillation - BNP B-type natriuretic peptide - SAPS simplified acute physiology score.

5. Limitations

Our study has several limitations that deserve to be acknowledged. Firstly, the study included adult critically ill patients in predominantly non-cardiac ICUs, and therefore the results may not be generalized to the paediatric and cardiac ICU population. Secondly, the presence of AFib was assessed by reviewing patient's chart and digitally recorded ECGs. Using this technique, although being standard in clinical practice, short and asymptomatic episodes of AFib might have been missed compared to using continuous Holter-ECG recordings [18]. Nevertheless, the prevalence of AFib in our cohort is in line with other studies, including those who used other techniques of detection [21]. However, misclassification of some AFib patients in the no-AFib group would have weakened our results, which conversely are strong and consistent. Moreover, study inclusion occurred after ICU admission. As a consequence, since ECG recordings prior ICU admission are not available, the group of patients with recurrent AFib includes patients with history of AFib developing AFib during hospital stay and those with pre-existing persistent or permanent AFib. Thirdly, due to the observational study design, management of patients with or without AFib, in particular concerning cardioversion and antiarrhythmic treatments, is not controlled and whether AFib itself or its treatment has led to the observed differences in outcome, is unknown. A recent study by Balik et al. showed that restoration of sinus rhythm was associated with better one-year outcome in univariate analysis, but restoration of sinus rhythm was not independently associated with better one-year outcome after multivariable adjustment, suggesting that successful restoration of sinus rhythm might be rather a "marker" of more favorable prognosis [22]. Moreover, since the majority of patients in our study were in sinus rhythm at ICU discharge, differences in outcomes cannot be attributed to lack of conversion in sinus rhythm. Additional studies to assess the impact of preventive strategies or antiarrhythmic therapies on incidence of AFib and in-hospital outcome of critically ill patients are needed.

Fourthly, despite careful identification and selection of co-variables to adjust the risk of death associated with AFib, other hidden variables not included in the models may interfere with our results.

6. Conclusion

New-onset AFib, but not recurrent AFib, is independently associated with increased risk of in-hospital death and one-year outcome of ICU survivors in critically ill patients.

Disclosures

AR received lecture fees from Amomed Pharma GmbH and Orpha Swiss GmbH, which both distribute esmolol and vernakalant.

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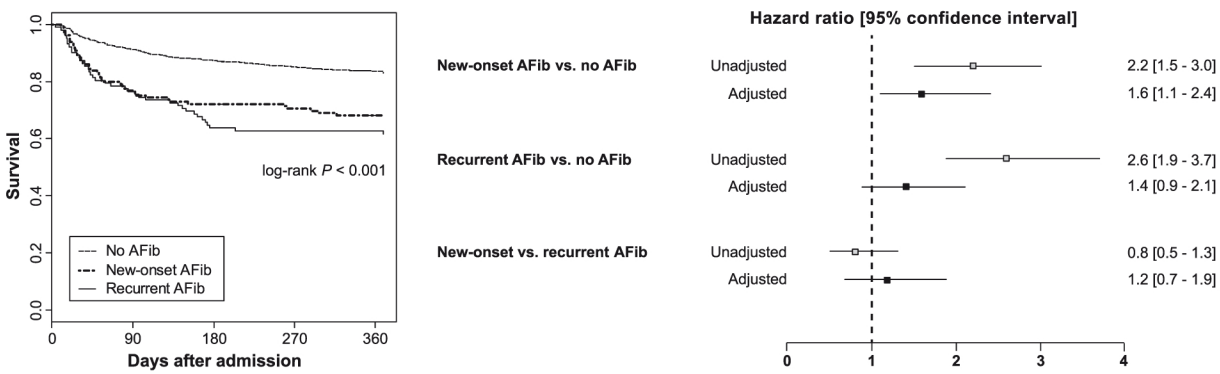

Fig. 4. Long-term outcome of ICU survivors (n = 1464) according to occurrence of AFib during ICU stay. Legend: Adjustment performed for age, Charlson comorbidity index, loss of autonomy, severe valve disease or prior valve surgery, chronic renal disease, peripheral vascular disease, recent malignant tumors, red blood cell transfusion during ICU stay, length of ICU stay > 20 days, systolic blood pressure at ICU discharge, body temperature at ICU discharge < 37 °C, leucocytes at ICU discharge > 20 G/L, platelets at ICU discharge < 10 G/L, total serum protein at ICU discharge < 60 g/L. AFib atrial fibrillation - CRP C-reactive protein - ICU intensive care unit.

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