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# **A randomized controlled trial of the intraoperative use of noninvasive ventilation versus supplemental oxygen by face mask for procedural sedation in an electrophysiology laboratory**

## **Une étude randomisée contrôlée sur l'utilisation peropératoire de la ventilation non invasive par rapport à la supplémentation en oxygène par masque facial pour la sédation procédurale dans un laboratoire d'électrophysiologie**

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### **Enregistrement de l'étude**

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### **Keywords**

Airway, apnea , cardiology , mechanical ventilation , noninvasive ventilation , sedation

# Abstract

## Purpose

The efficacy of noninvasive ventilation (NIV) during procedures that require sedation and analgesia has not been established. We evaluated whether NIV reduces the incidence of respiratory events.

## Methods

In this randomized controlled trial, we included 195 patients with an American Society of Anesthesiologists Physical Status of III or IV during electrophysiology laboratory procedures. We compared NIV with face mask oxygen therapy for patients under sedation. The primary outcome was the incidence of respiratory events determined by a computer-driven blinded analysis and defined by hypoxemia (peripheral oxygen saturation  $<90\%$ ) or apnea/hypopnea (absence of breathing for 20 sec on capnography). Secondary outcomes included hemodynamic variables, sedation, patient safety (composite scores of major or minor adverse events), and adverse outcomes at day 7.

## Results

A respiratory event occurred in 89/98 (95%) patients in the NIV group and in 69/97 (73%) patients with face masks (risk ratio [RR], 1.29; 95% confidence interval [CI], 1.13 to 1.47;  $P<0.001$ ). Hypoxemia occurred in 40 (42%) patients in the NIV group and in 33 (34%) patients with face masks (RR, 1.21; 95% CI, 0.84 to 1.74;  $P = 0.30$ ). Apnea/hypopnea occurred in 83 patients (92%) in the NIV group vs 65 patients (70%) with face masks (RR, 1.32; 95% CI, 1.14 to 1.53;  $P<0.001$ ). Hemodynamic variables, sedation, major or minor safety events, and patient outcomes were not different between the groups.

## Conclusions

Respiratory events were more frequent among patients receiving NIV without any safety or outcome impairment. These results do not support the routine use of NIV intraoperatively.

Study registration [ClinicalTrials.gov \(NCT02779998\)](https://clinicaltrials.gov/ct2/show/study/NCT02779998);

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# Résumé

## Objectif

L'efficacité de la ventilation non invasive (VNI) pendant les interventions nécessitant une sédation et une analgésie n'a pas été établie. Nous avons évalué si la VNI réduisait l'incidence des complications respiratoires.

## Méthode

Dans cette étude randomisée contrôlée, nous avons inclus 195 patients de statut physique III ou IV selon l'American Society of Anesthesiologists pendant des interventions en laboratoire d'électrophysiologie. Nous avons comparé la VNI à l'oxygénothérapie par masque facial pour les patients sous sédation. Le critère d'évaluation principal était l'incidence des complications respiratoires déterminée par une analyse en aveugle assistée par ordinateur et définie par une hypoxémie (saturation périphérique en oxygène  $\leq 90\%$ ) ou une apnée/hypopnée (absence de respiration pendant 20 secondes à la capnographie). Les critères d'évaluation secondaires comprenaient les variables hémodynamiques, la sédation, la sécurité des patientes (scores composites des événements indésirables majeurs ou mineurs) et les issues indésirables au jour 7.

## Résultats

Un événement respiratoire est survenu chez 89/98 (95 %) patients du groupe VNI et chez 69/97 (73%) patients ayant un masque facial (risque relatif [RR], 1,29; intervalle de confiance [IC] à 95 %, 1,13 à 1,47;  $P < 0,001$ ). Une hypoxémie est survenue chez 40 (42 %) patients du groupe VNI et chez 33 (34 %) patients ayant un masque facial (RR, 1,21 ; IC à 95 %, 0,84 à 1,74;  $P = 0,30$ ). Une hypoxémie est survenue chez 40 (42 %) patients du groupe VNI et chez 33 (34 %) patients ayant un masque facial (RR, 1,21; IC 95 %, 0,84 à 1,74;  $P = 0,30$ ). Les variables hémodynamiques, la sédation, les événements de sécurité majeurs ou mineurs et les issues pour les patients n'étaient pas différents entre les groupes.

## Conclusion

Les complications respiratoires étaient plus fréquentes chez les patients recevant une VNI sans aucun impact sur la sécurité ou les issues. Ces résultats n'appuient pas l'utilisation systématique de la VNI en peropératoire.

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Noninvasive ventilation (NIV) is known to treat acute respiratory failure during postoperative complications and in critically ill patients.<sup>1,2</sup> The mechanisms of its benefit include mechanical support, which mitigates the exaggerated workload of acute respiratory failure, and positive end-expiratory pressure, which counteracts alveolar flooding secondary to acute pulmonary edema. This benefit has been shown in patients with cardiothoracic diseases.<sup>3–5</sup> It is recommended that patients treated with NIV should be conscious; nevertheless, an increasing number of procedures requiring sedation and NIV support have been reported in the intensive care unit (ICU) setting.<sup>6,7</sup> Reports of patients who were sedated for surgery and were treated with NIV exist in the literature.<sup>8,9</sup> The pitfalls of such data reside in the weakness of the signal reported, such as transient hypoxemia assessed by an external observer. Challenges reside in direct measurements of the respiratory variables and independent analysis that allow robust reporting.

The number of procedures in electrophysiology laboratories has greatly increased in recent years. In a previous study, we reported a high incidence of respiratory events in this specific population.<sup>10</sup> A small number of studies have investigated the use of NIV during cardiothoracic procedures performed under procedural sedation and have reported beneficial results mainly in case reports, but none of them were randomized controlled trials (RCTs).<sup>8</sup>

We hypothesized that NIV would decrease the number of respiratory events during cardiothoracic procedures performed under procedural sedation compared with standard oxygen face mask use. Our primary goal was to decrease the number of respiratory events, defined by a composite outcome based on an independent direct measurement of physiologic variables from the patient monitor. Hence, we used a computerized blinded analysis that consisted of variable collection via patient monitoring measurements with independent software reporting and a blinded analysis of apnea/hypopnea or hypoxemia. We designed this RCT to continuously evaluate the efficacy of NIV to standard oxygen supplementation during procedural sedation through a computerized blinded analysis.

## Methods

### Ethics

This single-centre RCT was approved before the start of the study by the Comité de Protection des Personnes Sud- Est V on 4 November 2015 (Chairperson: Dr Charley; Grenoble, France, RCB: 2015-A01594-45). The ClinicalTrials.gov identifier is NCT02779998 (registered 4 November 2015). This study was designed as a Prospective Randomized Open with Blinded Evaluation (PROBE) study. Written informed consent was obtained from all patients before inclusion in this study.

### Study population and setting

The two groups were defined according to the ventilator strategy: the noninvasive ventilation group (NIV group) and the usual clinical care with the face mask (Capnomask<sup>®</sup>, A202MX, Mediplus, High Wycombe, UK) oxygen therapy group (or the standard face mask group).

Patients were eligible for the trial if they were outpatients or hospitalized awaiting a procedure in an electrophysiology laboratory (i.e., cardioverter defibrillator or pacemaker implantation or replacement) and if they had an American Society of Anesthesiologists (ASA) Physical Status of III or IV. This was informed by the higher incidence of respiratory events in ASA III or IV patients compared with low-risk patients observed in a previously published study from our institution.<sup>10</sup> The exclusion criteria for enrolment were as follows: age  $\geq$  18 yr; ASA Physical Status of I and II; current treatment for obstructive sleep apnea syndrome with continuous positive airway pressure (CPAP) or NIV devices; and contraindications to the use of NIV. As part of our standard of care, patients who were already being treated with CPAP or NIV devices received specific treatment during the procedure and the immediate postoperative period. Consequently, we elected not to include these patients to limit/minimize bias as this specific population was already educated regarding the devices.

The intervention was conducted under the supervision of a senior consultant anesthesiologist and intensivist. A trained nurse anesthetist was the principal operator, was present throughout the entire operation, and was able to freely adjust the drugs given and the airway management and initiate emergency procedures. The randomization was computer-generated using centralized web-based blocks of a random size that were produced by the Clinical Investigation Centre of Grenoble without stratification before the first patient was included. Allocation concealment according to the randomization was preserved during the computer acquisition. A research fellow independent from the procedure management was responsible for the computer acquisition of physiologic data from the patient monitor during the procedure and database management. To this point, the software analysis of the respiratory events was registered. Then, the computerized results were kept blinded and analyzed by an independent adjudication committee for a final validation of the respiratory event quotations to minimize measurement bias due to inaccurate wave signals. To separate registration and randomization from the analysis period, processing from the database to the adjudication committee was performed by a senior anesthesiologist independent of the randomization and the surgical procedure. None of the participants in the adjudication committee were members of the cardiovascular department.

## Interventions

Noninvasive ventilation was administered with the dedicated medical device, “Élysée<sup>TM</sup> 150” (RESMED Ltd., Bella Vista, NSW, Australia). The NIV protocol was specific and allowed patients to be ventilated using CPAP and pressure support ventilation (PSV) in response to changes in the respiratory pattern needing different mechanical ventilation settings.<sup>2</sup> The fraction of inspired oxygen ( $F_{iO_2}$ ) was titrated to target a peripheral oxygen saturation ( $SpO_2$ )  $\geq$  94%. We used a double-limb respiratory circuit (Intersurgical<sup>®</sup> Fontenay sous Bois, France). The patients did not have the opportunity to try NIV preoperatively. Patients allocated to the NIV group had to be ventilated with a titrated positive end-expiratory pressure level from 5 to 10 cm H<sub>2</sub>O. Pressure support ventilation was not compulsory. Patients could be ventilated with CPAP if needed. The target tidal volume was  $8 \text{ mL} \leq \text{kg}^{-1}$  (ideally  $6 \text{ mL} \leq \text{kg}^{-1}$ ) of the ideal body weight. The PSV was set to achieve this target and maintained below a 20 cm H<sub>2</sub>O threshold. The inspiratory trigger was set as sensitive as possible in the auto-triggering threshold limit. A full description of the NIV protocol is given in the Electronic Supplementary Material (ESM) eAppendix and eFig. 1.

In the usual care standard face mask group, a Capnomask<sup>®</sup> (A202 MX, Mediplus, High Wycombe, UK) was used as our standard of care to continuously monitor capnography (see

ESM eFig. 2). This device is a face mask with a port to enable attachment of a CO<sub>2</sub> sampling line. At the beginning of sedation, the initial oxygen flow was set at 4 L·min<sup>-1</sup>. This flow was titrated to obtain an SpO<sub>2</sub> greater than 94%, with a maximum of 15 L·min<sup>-1</sup>.

In both groups, only if required were maneuvers to maintain the airway applied, such as the use of an oropharyngeal airway (“Guedel cannula”), mandibular subluxation, and the use of face mask ventilation as a rescue intervention. The protocol included the use of intravenous titration of nalbuphine and sedation with a continuous intravenous infusion of propofol administered via a syringe pump. The Bispectral Index<sup>TM</sup> (BISTM; Medtronic/Covidien, Minneapolis, MN, USA) was continuously recorded, which is not the standard procedure at our institution. Hence, we decided to keep the personnel blinded to the BIS during the procedure to avoid biasing sedation management. All procedures were conducted with patients in the supine position. Ropivacaine was used to provide local anesthesia in the infra-clavicular region.

## Endpoints

The primary endpoint was the incidence of respiratory events, defined by a composite score of the occurrence of hypoxemia or apnea/hypopnea. Hypoxemia was defined by a decrease in SpO<sub>2</sub> < 90%, and apnea/hypopnea was defined by an absence of a breathing cycle for 20 sec on the capnogram (CO<sub>2</sub>20s).

Our secondary endpoints were the stability of the intraoperative physiologic variables, sedation, overall patient safety (composite scores of major or minor adverse events), safety of NIV use during sedation in the operating room, and adverse outcomes at day 7. We also compared the number of episodes of hypoxemia and apnea/hypopnea as continuous variables between groups in patients who had at least one episode.

Regarding safety, we compared the two groups in the incidence of major and minor adverse events and adverse outcomes at day 7. A major adverse event was defined as a composite of the following events: pneumothorax, intubation or laryngeal mask airway insertion, any surgical complication requiring a revision procedure, pericardial effusion or cardiac tamponade requiring a surgical procedure, and cardiopulmonary resuscitation. A minor adverse event was defined as the occurrence of any of the following: oropharyngeal airway insertion, mandibular subluxation, manual face mask ventilation, mask-related skin or nasal injury, and nausea or vomiting. Rescue therapy with crossover to NIV and standard face mask oxygen was considered if needed as well as manual face mask ventilation and intubation. All aspiration events were also recorded.

The adverse outcomes at day 7 were defined as a composite of the occurrence of any of the following: death, pulmonary edema, myocardial infarction, acute respiratory failure, and pneumonia. We also noted hospital and ICU length of stay.



## Measurements

The primary endpoint was based on a computer analysis using RECAN<sup>®</sup> software (Alpha-2<sup>®</sup>, Lyon, France) with physiologic variable extraction from Philips<sup>™</sup> monitoring (Amsterdam, Netherlands) (see ESM eFigs 3–5). The software acquisition was performed by a research fellow who was not involved in the clinical management of the patients. Disconnections due to technical issues were noted and not taken into account in the final analysis. The results from the software acquisitions were then analyzed by the independent adjudication committee blinded to the patients' group allocation to validate the calculations based on the SpO<sub>2</sub> and capnogram waveforms on each real-time monitor tracing.

The stability of the intraoperative physiologic variables was assessed through the same computer extraction process. The two components of the primary endpoint were separately analyzed as continuous variables. Low blood pressure or bradycardia was defined by the need for catecholamine drugs or volume resuscitation. The oxygen flow rate and fraction of inspired oxygen were noted. The variables from the ventilator measurements were gathered through continuous software monitoring (ResScan<sup>™</sup> 3.16 software, RESMED Ltd., Bella Vista, NSW, Australia). A full description of the NIV measurements is given in the ESM eAppendix.

## Statistical analysis

The statistical analyses were independently carried out by the Clinical Investigation Center of Grenoble with Stata<sup>®</sup> version 13 software (Stata Corporation, College Station, TX, USA). The analyses were performed on an intent-to-treat basis after the usual procedures of data management and database freezing.

The sample size calculation was based on a previously published clinical observational study.<sup>10</sup> We expected a 40% incidence of respiratory events in the control group (standard face mask group). Our hypothesis was that there would be a 50% reduction in the NIV group. With an alpha of 5% and a statistical power of 80%, 82 patients per group were required, and a total sample size of 200 patients was planned.

The descriptive analyses concerned all the variables that were collected, and the data are described as number and percentage for qualitative variables and mean and standard deviation (SD) or median and interquartile range [IQR] for continuous variables, according to the distribution. A missing data replacement procedure was defined for the primary endpoint.

The statistical tests were performed with alpha = 0.05. The primary endpoint and qualitative secondary endpoints were compared with the Chi square test if the validity conditions were met; otherwise, they were compared with Fisher's exact test. The continuous secondary endpoints were compared with Student's t test or the Mann–Whitney U test according to the data distribution. The additional statistics usual used for therapeutic trials were also presented (the relative risk and 95% confidence interval [CI], the relative risk reduction and 95% CI, the odds ratio and 95% CI, and the number of patients needed).

# Results

## Patients

From 19 January 2017 to December 2018, 1,369 patients underwent a procedure in the electrophysiology laboratory and were screened for inclusion; of these, 200 were included, and 195 underwent randomization. The mean (SD) age of the patients was 72 (12) yr and 28% of the patients were women (Figure, flow chart). Five patients were excluded before randomization; three met the exclusion criteria, one withdrew his consent, and one did not meet the inclusion criteria (ASA II). There were 98 patients in the NIV group and 97 patients in the standard face mask group.

Respiratory curves were not interpretable for seven (4%) of the patients removed after randomization (four in the NIV group and three in the standard face mask group). This percentage was below the limit of 5% predefined for imputation of missing data, and statistical analysis of the primary outcome was performed using data from all the remaining patients ( $n = 188$ ). The secondary outcomes were analyzed using the available data for each endpoint.

The characteristics of the patients at baseline were similar in the two groups (Table 1). The mean left ventricular ejection fraction was 44% (14) in the overall studied population, and there was a high incidence of associated comorbidities (diabetes, 24%; hypertension, 41%; chronic heart failure, 26%; coronary artery disease, 36%; and history of cardiac surgery, 12%).

The procedures were mainly represented by dual chamber pacemaker implantation (32%), cardioverterdefibrillator implantation (23%), and implantable device replacement (23%). The median [IQR] duration of the interventions was 66 [50–80] min (Table 2).

The intraoperative sedative, analgesic (Table 2) or hemodynamic support (Table 3) did not vary according to the randomization group.

## Trial treatment

Among the 98 patients allocated to the NIV group, four patients had an early failure of NIV, two refused the device, and four had uninterpretable curve signals. In the standard face mask group, two patients had an early failure of the face mask, and three patients had no interpretable signal. Rescue therapy was possible in each group using the alternative treatment. Consequently, seven patients were eventually treated with the standard face mask, and two patients had NIV as a rescue therapy in response to deep and/or repeated hypoxemia despite their original allocation group.

The maximum  $F_{iO_2}$  in the NIV population was 87% [75–97], and the median  $O_2$  maximal flow was 6 L·min<sup>-1</sup> [6–8]. Among the NIV patients, 30 patients received CPAP alone, 29 received PSV alone, and 39 patients had a mix of both settings. The NIV ventilator results are described in the ESM eAppendix.

## Primary outcomes

A respiratory event (hypoxemia or apnea/hypopnea) was observed in 89 patients in the NIV group (94.7%; 95% CI, 88 to 98) and in 69 patients in the usual care standard face mask group (73.4%; 95% CI, 63 to 82) (risk ratio [RR], 1.29; 95% CI, 1.13 to 1.47;  $P < 0.0001$ ; Chi square test) (Table 2).

## Secondary outcomes

A hypoxemia event occurred in 40/96 patients in the NIV group (42%; 95% CI, 32 to 52) and in 33/96 patients in the standard face mask group (34%; 95% CI, 25 to 45) (RR, 1.21; 95% CI, 0.84 to 1.74; Chi square test,  $P = 0.33$ ). In patients who presented at least one hypoxemia event, the median [IQR] number of episodes was 2 [1–2.5] per procedure in the NIV group (ESM eFigs. 6 and 7) and 2 [1–4] per procedure in the standard face mask group ( $P = 0.54$ , Mann–Whitney). Apnea/hypopnea occurred in 83 patients (92%; 95% CI, 85 to 97) in the NIV group and in 65 patients (69.9%; 95% CI, 59 to 79) in the standard face mask group (RR, 1.32; 95% CI, 1.14 to 1.53;  $P < 0.001$ , Chi squared test). In patients who presented at least one apnea/hypopnea event, the median [IQR] number of episodes was 10 [7–15] per procedure in the NIV group (ESM eFigs. 8 and 9) and 3 [1–5] per procedure in the standard face mask group ( $P < 0.001$ , Mann–Whitney).

The hemodynamic variables were similar in both groups (Table 3). The use of sedation and analgesic drugs did not differ between the groups (Table 1). The BIS index was 71 (95% CI, 58 to 76) in the NIV group and 69 (95% CI, 61 to 76) in the standard face mask group ( $P = 0.82$ , Mann–Whitney) and was below a threshold of 60 during 16% (95% CI, 3 to 67) of the time in the NIV group and during 17% (95% CI, 1 to 58) of the time in the standard face mask group.

Regarding the safety endpoint assessments (Table 4), the occurrence of a major adverse event was reported in two patients in the NIV group vs one patient in the standard face mask group: one patient had a pneumothorax, and one patient had a procedural complication in the NIV group vs one patient needing cardiopulmonary resuscitation in the standard face mask group. One patient needed medical intervention (for sedation purposes) in the standard face mask group. Aspiration during the procedure was reported in one patient in the NIV group. A minor adverse event was reported in 62/98 patients in the NIV group (63%; 95% CI, 53 to 73) and in 63/97 patients in the standard face mask group (65%; 95% CI, 55 to 74), mainly represented by the need for mandibular subluxation 60% (95% CI, 50 to 70) in the NIV group vs 44% (95% CI, 34 to 55) in the standard face mask group ( $P = 0.03$ ; Chi square) (Table 4). The median leakage percentage during NIV was 69 [52–85]% (ESM eTable).

A day 7 outcome defined by the composite endpoint of the occurrence of death, pulmonary edema, myocardial infarction, acute respiratory failure and pneumonia occurred in three NIV recipient patients, while none were observed in the standard face mask group. The length of hospital stay, length of ICU stay, and mortality rate were not significantly different between the two groups (Table 5).

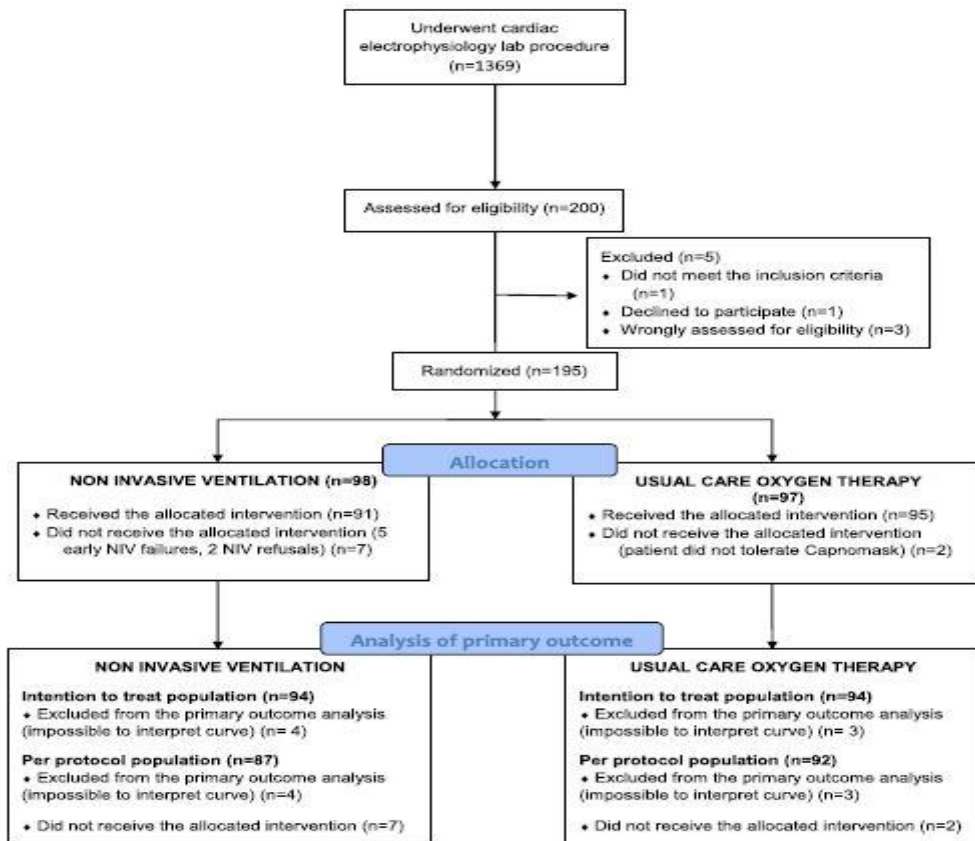


Figure Study flow chart

**Table 1** Patient characteristics

	Noninvasive ventilation <i>N</i> = 98	Standard face mask <i>N</i> = 97
Age (yr)	73 (12)	72 (12)
Male	78/98 (80%)	70/97 (72%)
Weight (kg)	76 (12)	76 (17)
Height (cm)	170 (8)	169 (9)
BMI (kg·m <sup>-2</sup> )	26 (4)	26 (5.0)
ASA Physical Status III	89/98 (91%)	88/97 (91%)
ASA Physical Status IV	9/98 (9%)	9/97 (9%)
Hospitalization		
Cardiology ward	85/98 (87%)	86/97 (89%)
Cardiac surgery ward	9/98 (9%)	10/97 (10%)
ICU	4/98 (4%)	1/97 (1%)
Left ventricular ejection fraction (%)	43.5 (14)	43.6 (14)
Cardiovascular comorbidities		
Diabetes	21/98 (21%)	25/97 (26%)
Hypertension	37/98 (38%)	44/97 (45%)
Chronic heart failure	27/98 (28%)	25/97 (26%)
Coronary artery disease	41/98 (42%)	30/97 (30%)
Cardiac surgery	15/98 (15%)	9/97 (9%)
Respiratory comorbidities		
Nontreated sleep apnea	7/98 (7%)	6/97 (6%)
COPD	6/98 (6%)	3/97 (3%)
Chronic respiratory failure	2/98 (2%)	3/97 (3%)
Oxygen therapy	4/98 (4%)	-
NYHA		
I	15/98 (15%)	15/97 (15%)
II	31/98 (32%)	25/97 (26%)
III	21/98 (21%)	18/97 (19%)
IV	5/98 (5%)	1/97 (1%)
Missing	26/98 (26%)	38/97 (39%)

Numbers are *n*/total *N* (%) for qualitative variables and mean (standard deviation) for continuous variables

ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; NYHA = New York Heart Association

**Table 2** Procedure and sedation characteristics

	Noninvasive ventilation <i>N</i> = 98	Standard face mask <i>N</i> = 97
Procedure		
Single-chamber pacemaker	13/98 (13%)	6/97 (6%)
Dual-chamber pacemaker	34/98 (35%)	28/97 (29%)
Triple-chamber pacemaker	7/98 (7%)	7/97 (7%)
Defibrillator	21/98 (21%)	24/97 (25%)
Device replacement	20/98 (20%)	25/97 (26%)
Lead insertion	3/98 (3%)	3/97 (3%)
Other	-	4/97 (4%)
Duration of intervention (min)	65 [51–80]	66 [50–80]
Sedation		
Propofol	97/98 (99%)	96/97 (99%)
Propofol dose (mg) ( <i>n</i> = 189)	255 [164–370]	250 [170–345]
Other sedative*	3/98 (3%)	-
Analgesia		
Nalbuphine	96/98 (98%)	97/97 (100%)
Nalbuphine dose (mg) ( <i>n</i> = 191)	8 [6–10]	7 [5–10]
Paracetamol	85/98 (87%)	86/97 (89%)
Paracetamol dose (g) ( <i>n</i> = 170)	1 [1–1]	1 [1–1]
Other analgesic†	-	1/97 (1%)

Numbers are *n*/total *N* (%) for qualitative variables and mean (standard deviation) or median [interquartile range] for continuous variables according to the data distribution

\*Other sedative: ketamine 30 mg, midazolam 2.5 mg, ketamine 15 mg

†Other analgesic: nefopam

## Discussion

The main result of our study was that routine use of NIV in the electrophysiology laboratory was associated with an increase in respiratory events. This increase in respiratory events was mainly represented by an excess in the number of absent breathing cycles for 20 sec detected on the capnogram to evaluate apnea/hypopnea. The use of NIV did not prevent the patients' desaturation.

Literature reports have described inconsistent effects of NIV. A benefit of NIV was reported for acute exacerbation of chronic obstructive pulmonary disease, but studies in postextubation respiratory failure showed that NIV did not improve mortality or the need for reintubation in the ICU setting.<sup>1,11</sup> Moreover, positive effects on mortality or reintubation rate have been reported in the treatment of acute respiratory failure in the perioperative setting.<sup>2,12,13</sup>

Nevertheless, NIV trials remained inconsistent and failed in other specific perioperative conditions to significantly prevent postoperative pulmonary complications such as pneumonia, reintubation, and death.<sup>14,15</sup> We expected a preventive effect on respiratory events, as the number of patients who underwent cardiac surgery was high in our study, and this surgery is known to cause diaphragmatic dysfunction.<sup>16</sup> Moreover, the use of NIV with CPAP or pressure support is recommended in postoperative hypoxemic cardiac surgery patients.<sup>17</sup> The main difference between such ICU patients and the patients in this study is that very few of them were acutely ill, resulting in the absence of an impaired balance between respiratory workload and demand. Concerning the comparison with surgical patients, most of the postoperative studies reporting positive results were conducted during major surgeries when the thoracic and pulmonary mechanics were affected, notably with atelectasis, whereas patients in the present study were only affected by a wound in the upper chest wall.<sup>18</sup> Finally, all patients underwent the procedure in the supine position because venous access was needed. This position is known to worsen sleep apnea disorders and might similarly predispose to functional airway obstruction in sedated patients.<sup>19</sup> Overall, we may conclude that NIV, while potentially beneficial in a selected ICU population,<sup>6,20</sup> did not prove to be an appropriate solution for this study population.

**Table 3** Primary outcome and intraoperative variables

	Noninvasive ventilation N = 94	Standard face mask N = 94	Relative risk (95% CI)	P value
<b>Primary outcome</b>				
Intention-to-treat population (n = 188)				
Rate of respiratory events: hypoxemia and/or apnea/hypopnea	89/94 (95%)	69/94 (73%)	1.29 (1.13 to 1.47)	< 0.001*
Per-protocol population (n = 179)				
Rate of respiratory events: hypoxemia and/or apnea/hypopnea	84/87 (97%)	68/92 (73%)	1.33 (1.16 to 1.51)	< 0.001*
	N = 87	N = 92		
<b>Physiologic variable stability</b>				
Hypoxemia (n = 192)	40/96 (42%)	33/96 (34%)	1.21 (0.84 to 1.74)	0.33*
Apnea/hypopnea (n = 183)	83/90 (92%)	65/93 (70%)	1.32 (1.14 to 1.53)	< 0.001*
Low blood pressure or bradycardia requiring the use of catecholamine drugs or volume expansion (n = 195)	28/98 (29%)	29/97 (30%)	0.96 (0.62 to 1.48)	0.84*

Numbers are n/total N (%) for qualitative variables and mean (standard deviation) or median [interquartile range] for continuous variables according to the data distribution

\*Chi square test

CI = confidence interval

**Table 4** Patient safety

	Noninvasive ventilation N = 98	Usual care Oxygen therapy N = 97	Relative risk (95% CI)	P value
<b>Safety of ventilation</b>				
Incidence of major adverse events	2/98 (2%)	1/97 (1%)	0.99 (0.14 to 6.89)	0.50†
Pneumothorax	1/98 (1%)	0/97 (0%)	NA	1†
Intubation or laryngeal mask airway insertion	0/98 (0%)	0/97 (0%)	NA	NA
Surgical complication	1/98 (1%)	0/97 (0%)	NA	1†
Pericardial effusion requiring surgical drainage	0/98 (0%)	0/97 (0%)	NA	NA
Cardiopulmonary resuscitation	0/98 (0%)	1/97 (1%)	NA	0.50†
Incidence of minor adverse events	62/98 (63%)	63/97 (65%)		0.81*
Mask-related skin and nasal injuries	0/98 (0%)	0/97 (0%)	NA	0.62*
Nausea or vomiting	0/98 (0%)	0/97 (0%)	NA	NA
Manual face mask ventilation	0/98 (0%)	1/97 (1%)	NA	0.50†
Oropharyngeal airway insertion	41/98 (42%)	44/97 (45%)	0.92 (0.67 to 1.27)	0.62*
Mandibular subluxation	59/98 (60%)	43/97 (44%)	1.36 (1.03 to 1.79)	0.03*

Numbers are n/total N (%) for qualitative variables or mean (standard deviation) or median [interquartile range] for continuous variables according to the data distribution.

\*Chi square test

†Fisher's exact test

CI = confidence interval; NA = not applicable

**Table 5** Patient outcomes on day 7

	Noninvasive ventilation <i>N</i> = 98	Usual care Oxygen therapy <i>N</i> = 97	<i>P</i> value
Composite endpoint of main respiratory and cardiac complications, <i>n</i> /total <i>N</i> (%)	3/98 (3%)	0/97 (0%)	0.25†
Death	1/98 (1%)	0/97 (0%)	1.00 †
Acute pulmonary edema	1/98 (1%)	0/97 (0%)	1.00†
Myocardial infarction	0/98 (0%)	0/97 (0%)	NA
Acute respiratory failure*	1/98 (1%)	0/97 (0%)	1.00†
Pneumonia	0/98 (0%)	0/97 (0%)	NA
Length of hospital and ICU stay, median [IQR]			
Length of hospital stay (days)	1 [1–4] ( <i>n</i> = 98)	1 [1–4] ( <i>n</i> = 97)	0.98‡
Length of ICU stay (days)	2 [0–27]	0 [0–4]	0.50‡

Numbers are *n*/total *N* (%) for qualitative variables and median [IQR] for continuous variables according to the data distribution

\*Acute respiratory failure was defined as a respiratory rate  $\geq 25$  breaths per minute with  $\text{SpO}_2 \leq 92\%$  or  $\text{PaO}_2/\text{F}_i\text{O}_2 \leq 300$  during oxygen therapy  $\geq 10 \text{ L}\cdot\text{min}^{-1}$  for a minimum of 15 min

†Fisher's exact test

‡Mann–Whitney test

CI = confidence interval;  $\text{F}_i\text{O}_2$  = inspiratory fraction of oxygen; ICU = intensive care unit; IQR = interquartile range;  $\text{PaO}_2$  = arterial partial pressure of oxygen;  $\text{SpO}_2$  = peripheral oxygen saturation

The experimental approach of this study may provide answers to the issues of intraoperative NIV. Oxygen titration was possible in both groups using two different methods. Nevertheless, oxygenation titration did not reduce the incidence of hypoxemia. Oxygen delivery may have not been the key issue. As a consequence, the exploratory data from the airway management and respiratory pattern with NIV during sedation might be more relevant. The occurrence of apnea/hypopnea events emphasizes the importance of an appropriate interface for airway management. Hence, we cannot exclude the possibility that some patients would have benefited from different interface types, such as nasal masks or helmets. Another important point is the high incidence of interventions necessary to maintain patency of the upper airway tract in patients undergoing this degree of sedation. Mandibular subluxation was needed for most of the patients in the NIV group. Despite this maneuver, the measured expiratory volume and pressure reported were low because of leaks. Therefore, we hypothesize that individualized airway management with an appropriate and wider choice of interfaces might be essential for patients under sedation and NIV. One type of NIV mask with three sizes was insufficient to address each patient's specific need. We also observed that the quantity or depth of sedation or analgesia did not vary between the two groups. Bispectral Index values, total drug use, and achievement of clinical goals were similar in both groups. Nevertheless, as respiratory patterns change with the ventilation modes, the same sedation strategy may not produce the same outcomes. We hypothesize that patients at this level of sedation may benefit from intermittent positive pressure ventilation, while a patient with lighter sedation would benefit more from PSV.

There are several strengths to this study, including the randomized design, the selected population, the blinded analysis of the endpoints through a computer-driven approach, the explicit criteria for respiratory events, the postoperative pulmonary complications, and the patient outcomes with a seven-day follow-up period. Additionally, the safety of NIV, as shown in this randomized controlled trial, is encouraging. Our results showed a low incidence of intraoperative and early postoperative complications and an absence of impaired prognosis at day 7 post intervention. Moreover, our experimental approach provided responses to the challenges of intraoperative NIV.



Our findings are subject to several limitations. First, we designed this study based on the incidence of respiratory events reported in a previous study that only used clinical assessment and not an independent analysis from continuous monitoring.<sup>10</sup> Consequently, we may have underestimated the number of respiratory events compared with a computer-based analysis in the sample size calculation. Additionally, we may have overestimated respiratory events with some unrelated clinical meaning for the clinician. Although this fact might be true for apnea/hypopnea events, the number of hypoxemia events remained comparable in the control group (34%) to the historical cohort.<sup>10</sup>

Second, our primary endpoint was a composite endpoint of hypoxemia and the absence of breathing cycles for 20 sec detected on the capnogram as surrogate criteria for apnea/hypopnea. Capnography is efficient for evaluating the respiratory rate and is sensitive to upper airway closure.<sup>21</sup> Despite its potential usefulness, respiratory rate measurement by the impedance method was inaccurate because of the surgical draping during pacemaker implantation that does not provide an appropriate location. Nevertheless, to limit the measurement bias, the primary endpoint assessment was made by a computer driven analysis that was reviewed by an independent adjudication committee and that was blinded to the randomization groups.

Third, the present study was not designed to show a significant decrease in the number of adverse patient outcomes in the NIV group. The lack of significance is mainly due to the low incidence of adverse events in this stable medico-surgical population who had scheduled procedures.

Fourth, our choice was to include patients in the electrophysiology laboratory for pacemaker implantation. Such interventions are minimally invasive in terms of respiratory mechanics. Our conclusion may not be applicable to other types of procedures.

Fifth, careful registration of monitoring curves and reading from the adjudication committee may not be sufficient to avoid measurement bias due to NIV disconnections or CO<sub>2</sub> washout due to high oxygen flow. Although the respiratory rate measured by capnometry with a face mask was efficient at high flows, the absolute values of end-tidal CO<sub>2</sub> were lower as the flow increased.<sup>21</sup>

Sixth, the study was a single-centre study, so the generalizability of the results is limited by a single-centre effect.

Among patients undergoing a procedure in a stimulation laboratory with moderate to deep procedural sedation, NIV was associated with the occurrence of more respiratory events than with the use of standard face mask oxygen supplementation. Although the present study supports the safety of NIV, the patient outcomes were not improved. Overall, these findings do not support the routine use of NIV in this setting.

### **Author contributions**

Pierre-Henri Moury, Flora Greco, and Pierre Albaladejo designed the study; Pierre-Henri Moury, Valentin Pasquier, Flora Greco, Jean-Lionel Arvieux, Silvia Alves-Macedo, Marion Richard, and Myriam Casez-Brasseur enrolled the patients; Pierre-Henri Moury, Jean-Lionel Arvieux, Silvia Alves-Macedo, Damien Bedague, Michel Durand, and Marion Richard conducted the study; Kristina Skaare and Jean-Luc Bosson analyzed the data; Pierre-Henri

Moury, Valentin Pasquier, Jean-Luc Bosson, and Pierre Albaladejo analyzed all the data; Pierre-Henri Moury and Valentin Pasquier interpreted the results; Pierre-Henri Moury and Valentin Pasquier drafted the manuscript; all authors had full access to all of the study data, contributed to drafting of the manuscript or critically revised it for important intellectual content, and took responsibility for the integrity of the data and the accuracy of the data analysis.

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There are no conflicts of interest to disclose related to the subject of the article.

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