Assessment of preoperative noninvasive ventilation before lung cancer surgery: The preOVNI randomized controlled study

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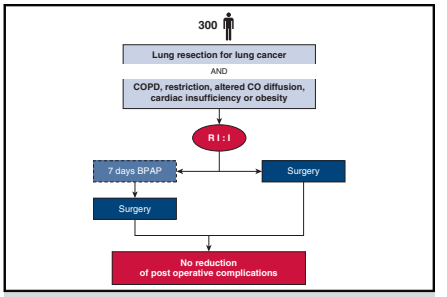
ABSTRACT

Objectives: The preOVNI study was a randomized, controlled, open-label study that investigated whether preoperative noninvasive ventilation (NIV) could reduce postoperative complications after lung cancer surgery.

Methods: Adult patients with planned lung cancer resection and with at least 1 cardiac or respiratory comorbidity were included and randomly assigned to preoperative NIV (at least 7 days and 4 h/day) or no NIV. The primary endpoint was the rate of postoperative protocol-defined complications.

Results: Three hundred patients were included. In the NIV group, the median NIV duration was 8 days. No difference of postoperative complication rates was evidenced: 42.6% in NIV group and 44.8% in no-NIV group ($P = .75$). The rate of pneumonia was greater in no-NIV group compared with the NIV group, but statistical significance was not achieved (28.0 vs 37.7%, respectively; $P = .08$). The type of surgery (open or minimally invasive) did not impact these results after multivariable analysis.

Conclusions: No benefit was evidenced for preoperative NIV before lung cancer surgery. Further studies should determine the optimal perioperative management to decrease the rate of postoperative complications. (J Thorac Cardiovasc Surg 2020;160:1050-9)



Randomized groups and main result of the study.

CENTRAL MESSAGE

In this randomized controlled study, preoperative NIV before lung cancer surgery did not reduce postoperative complications.

PERSPECTIVE

NIV alone failed to reduce postoperative complications but, in the NIV group, a nonsignificant lower rate of postoperative pneumopathies was observed. Further studies should focus on specific comorbidities (such as COPD or cardiac insufficiency). The effect of NIV associated with other procedures such as preoperative pulmonary rehabilitation or physiotherapy could be evaluated for fragile patients.

See Commentaries on pages 1060 and 1062.

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Abbreviations and Acronyms

AHI = apnea–hypopnea index
CI = confidence interval
COPD = chronic obstructive pulmonary disease
FEV1 = forced expiratory volume in 1 second
FVC = forced vital capacity
ITT = intention-to-treat
NIV = noninvasive ventilation
NSCLC = non–small cell lung cancer
PaO_2 = partial pressure of oxygen
SD = standard deviation
TLco/AV = diffusion coefficient of carbon monoxide per unit alveolar volume

Scanning this QR code will take you to the article title page to access supplementary information.

Surgery is the recommended treatment for localized non–small cell lung cancer (NSCLC), achieving a 5-year survival >50% for stages I to II.[1,2] The complication rate is 24% to 42% (mainly persistent air leak, pneumonia, acute respiratory insufficiency, and atelectasis) and 38% for patients with chronic obstructive pulmonary disease (COPD).[3,4] The main risk factors for complications are impaired respiratory function, general health, general anesthesia, surgery-related diaphragmatic trauma, and surgery duration >80 minutes.[4,5] The relative risk of death related to pulmonary complications is 14.9 (95% confidence interval [CI], 4.76-26.9), mainly related to the most serious respiratory complications.[4,6-8] Therefore, guidelines of the European Respiratory Society and the American Thoracic Society recommend preoperative assessment of the respiratory function before lung cancer surgery.[9,10]

Preoperative noninvasive ventilation (NIV) seems to improve functional parameters when realized during induction of anesthesia.[11-14] The pathophysiology remains unclear, but improvement in bronchial drainage and respiratory flow and volume could explain these improved functional parameters. Preoperative NIV could also acclimate the patient to this procedure if NIV is necessary after surgery. Regarding cardiac insufficiency, positive expiratory pressure is known to favor alveolar recruitment and to decrease alveolar edema.[15] A preliminary prospective clinical trial studied pre- and postoperative NIV (bilevel positive airway pressure) to prevent postoperative pulmonary function impairment.[16] Thirty-two patients with forced expiratory volume in 1 second (FEV1) <70% were randomly assigned to NIV from D-7 to D+3 versus no NIV. Patients receiving NIV had significantly improved respiratory parameters (partial pressure of oxygen [PaO_2], forced vital capacity [FVC], and FEV1) immediately after surgery, suggesting an effect of preoperative treatment.

The POPVNI trial assessed systematic postoperative prophylactic NIV on acute respiratory events after major lung resection in patients with COPD with no reduction of acute respiratory events.[17] Given the conflicting results of previous randomized studies, we sought to clarify the role of NIV before lung cancer surgery. We tested the hypothesis that preoperative NIV with bilevel positive airway pressure would reduce the rate of postoperative complications in high-risk patients after lung cancer surgery.

METHODS

Study Design

The preOVNI study was a randomized, controlled, open-label multicentric trial performed from 2012 to 2017 in 19 French centers. The primary objective was to demonstrate that preoperative NIV reduced the rates of postoperative complications in high-risk patients after lung cancer surgery. The secondary objectives were to identify subgroups of patients who benefited the most from preoperative NIV and to evaluate the safety of NIV.

The protocol was conducted in accordance with the Declaration of Helsinki statement and was approved by an independent ethics committee (''Ouest VI''). Written informed consent was obtained from each patient. This study is registered with the ClinicalTrials.gov identifier NCT01685580 (IDRCB: 2011-A00939-32). The protocol of this study has been previously published (Table E1).[18]

Patient Selection and Inclusion Criteria

Patients ≥18 years were included if scheduled for lung resection (lobectomy or segmentectomy) for NSCLC or suspicion. In addition, they should have at least 1 of the following criteria: obstructive lung disease (FEV1/FVC <70% and predicted FEV1 <80%); restrictive lung disease (FVC <80% or total lung capacity <80%); ratio diffusion coefficient of carbon monoxide per unit alveolar volume (TL_{CO}/AV) <60%; history of hypercapnic respiratory failure within the previous year; long-term oxygen therapy; heart failure; history of acute cardiogenic pulmonary edema; or obesity (>30 kg/m^2). These criteria were chosen to include high-risk patients for postoperative complications. The cardiac insufficiency criteria were chosen to select a ''real-life population'' and because cardiac insufficiency is strongly associated with postoperative complications.[4]

Main exclusion criteria were planned pneumonectomy, patients refusing surgery or with unresectable or inoperable tumors; contraindication to NIV (lack of technical understanding, facial malformation, tight stenosis of the upper airway, uncontrollable vomiting, unable to remove the mask); cognitive impairment or severe psychiatric disorders; patient already on invasive ventilation or NIV; and pregnancy.

Study Conduct

Visits and procedures of the study are described in Figure 1. Patients signed a written consent form and were randomized at visit V1 (D-30 to D-7 before surgery). During visit V2 (consultation or day hospital D-15 to D-7), clinical examination, spirometry and blood gas analyses were performed and NIV was started under the supervision of a pneumologist. The device was VPAP ST ventilator (ResMed, San Diego, Calif). The following pressures were proposed: from 3 to 6 cm H_2O for positive expiratory pressure and from 10 to 14 cm H_2O for inspiratory pressure,

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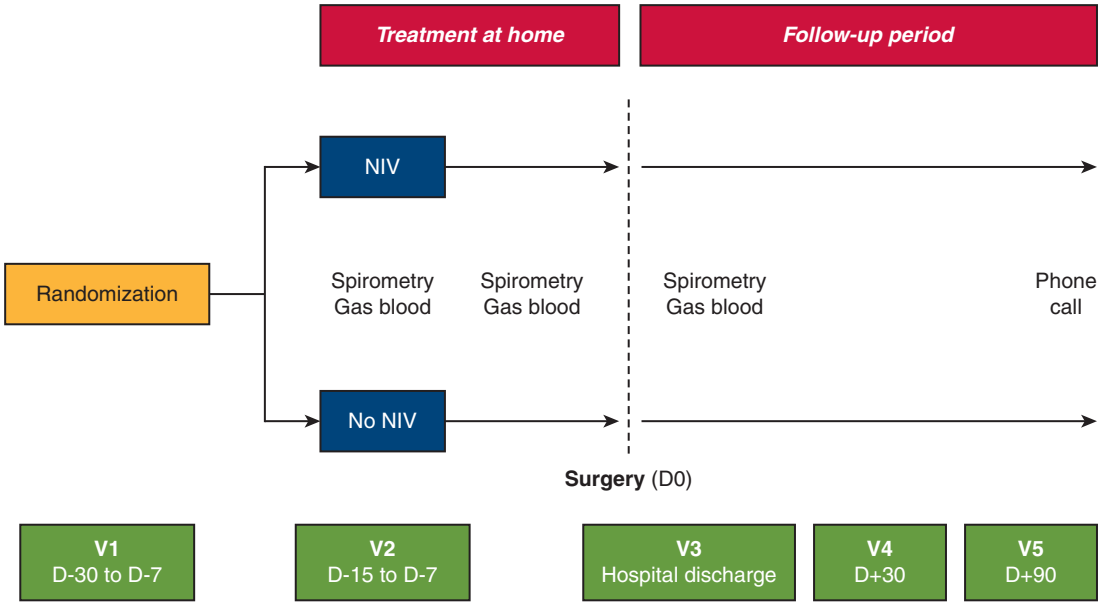

FIGURE 1. Visits and procedures during the preOVNI study. Patients were randomized at visit V1. During visit V2, clinical examination, spirometry, and blood gas analyses were performed and NIV was started under the supervision of a pneumologist. Three visits were scheduled after surgery: at hospital discharge (for clinical examination, record of complications during hospitalization, spirometric tests, blood gas analysis), 1 month after surgery (for clinical examination and record of complications), and after 3 months (telephone call for late post-operative complications). *NIV*, Noninvasive ventilation; *V*, visit; *D*, day.

but investigators could modify them. These parameters were proposed but were not mandatory because patients had very different comorbidities, sometimes associated. Indeed, parameters of NIV are very different for obstructive or restrictive lung disorders or in case of cardiac insufficiency. Parameters could be modified in case of poor tolerance. To detect sleep apneas, a record was performed in the NIV group under continuous pressure of 4 cm H_2O for the first night only (SHAM CPAP). The SHAM CPAP is not the gold standard for the diagnosis of obstructive sleep apnea. It was used because observational studies showed no decrease of apnea–hypopnea index (AHI) with 4 cm H_2O and airflow limitations are correlated to AHI. Unlike previous study, NIV was stopped after the last night before surgery since the objective was to specifically evaluate the preoperative effect of NIV.[16]

At home, an accredited provider was responsible for NIV use. The provider came to the patient's home once during the NIV period and provided one phone call. In case of nonadherence or safety event, the investigators were contacted. Compliance was precisely assessed with the memory card of the device. The recommended daily duration of NIV was at least 6 hours, either continuously or discontinuously. It was thus proposed to perform NIV for 3 hours after lunch and in the evening; if NIV was well-tolerated during sleep, it could be prolonged throughout the night. The provider completed a form on patient's compliance. Preoperative physiotherapy was accepted if prescribed before randomization.

Postoperative NIV was allowed only in case of complications. Three visits were scheduled after surgery: at hospital discharge (for clinical examination, record of complications during hospitalization, spirometric tests, blood gas analysis), 1 month after surgery (for clinical examination and record of complications), and after 3 months (telephone call for late postoperative complications).

Spirometric tests were performed for all patients at visit V2 (NIV initiation for NIV group), just before surgery, and at hospital discharge, using a Piko-6 spirometer (nSpire Health, Longmont, Colo). Blood gas were analyzed at visit V2, just before and after surgery, and at hospital discharge.

Statistical Analysis

The primary endpoint was the rate of cardiorespiratory complications within 1 month after surgery, defined as pneumonia or lower respiratory tract infection, prolongation of postoperative intubation >24 hours, hypoxemic and/or hypercapnic acute respiratory insufficiency, atelectasis, de novo atrial fibrillation, acute heart failure, or death. Each complication was precisely defined in the previously published protocol, stratified on Common Terminology Criteria for Adverse Events scale V3 and blindly adjudicated by the scientific committee.[18] For example, pneumonia was considered in case of rapid onset of radiologic findings (>72 hours) with fever >38°C or inflammatory syndrome or antibiotherapy. The primary analysis was intention-to-treat (ITT). A per-protocol analysis was also performed with patients without major protocol deviations.

Secondary endpoints were all separate items of the primary endpoint, duration of stay at hospital and in the intensive care unit, NIV safety (mask tolerance, facial cutaneous lesions, air leakage duration) and adherence, respiratory and blood–gas parameters, myocardial infarction, bronchial fistula, acute myocardial ischemia, confused postoperative state, postoperative venous thromboembolism, pneumothorax, pneumomediastinum, subcutaneous emphysema, and pleurisy.

Considering a rate of expected postoperative respiratory and cardiovascular complications (primary endpoint) of 30% in control group and 15% in NIV group, 150 patients in each group were necessary (bilateral alpha risk, 5%: power 83%; lost to follow-up 5%). Patients were randomized 1:1 with block size of 4 and with stratification on centers.

Categorical variables were compared by χ^2 test (or Fisher exact test) and continuous variables by 2-sided Student *t* test (or Wilcoxon test). Tests were 2-sided, and a *P* value lower than .05 was considered to be statistically significant.

The primary endpoint was adjusted on clinically relevant variables, which are recognized as predictive factors for postoperative complications: type of surgery (open or thoracoscopy because there was significantly more thoracoscopies in the no-NIV group), COPD, and carbon monoxide

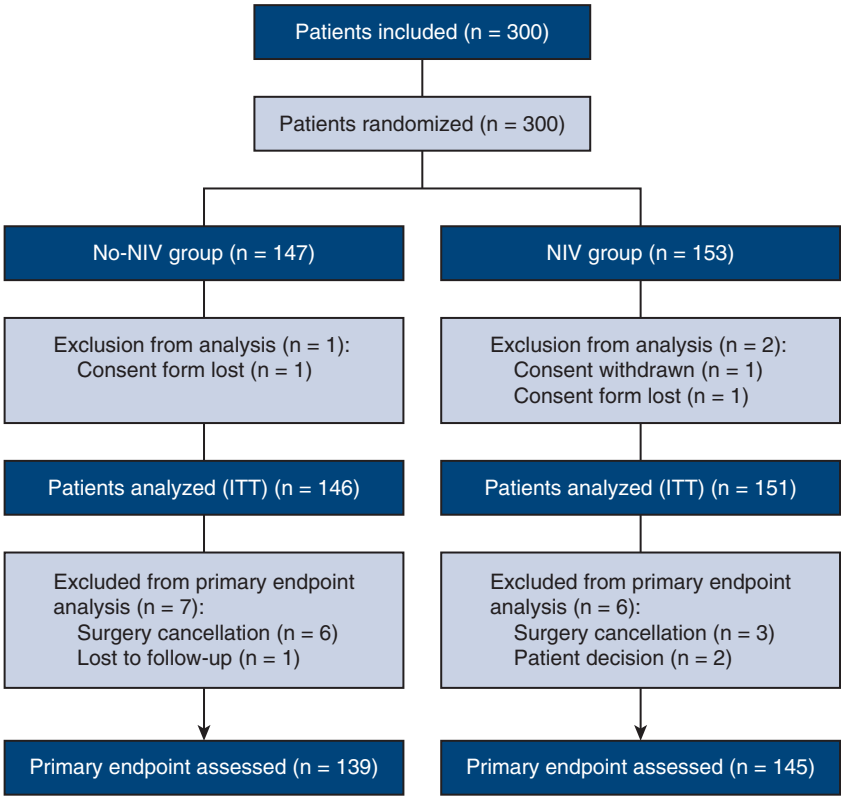

FIGURE 2. Consolidated Standards of Reporting Trials flow diagram of the preOVNI study. From 2012 to 2017, 300 adult patients scheduled for lung resection (lobectomy or segmentectomy) for NSCLC or suspicion were randomized: 153 in NIV group and 147 in no-NIV group; 297 were included in ITT analysis. *NIV*, Noninvasive ventilation; *ITT*, intention-to-treat.

transfer (this was performed using logistic regression). The analyses were performed using SAS, version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Patients Characteristics

From 2012 to 2017, 300 patients were randomized: 153 in NIV group and 147 in no-NIV group; 297 were included in ITT analysis (withdrawn/loss of consent for 3 patients) (Figure 2). The study centers were opened between 2012 and 2015. The objective was 15 active centers, and 1 center was closed because of low accrual. Seven centers included the majority of patients. All centers were chosen because NIV-trained investigators were available.

There were 86 major deviations in ITT population (inclusion/exclusion criteria, n = 7; lost to follow-up or patient decision, n = 3; surgery cancellation, n = 9; NIV $\leq$4 hours per day or missing data, n = 67). Per-protocol population included 211 patients: 135 in no-NIV group and 76 in NIV group. Early study discontinuation occurred for 15 patients in each group. The primary endpoint was assessed in 139 patients in the no-NIV group and 145 patients in the NIV group of ITT population and in all patients of per-protocol population.

Patient characteristics in the ITT population were as follows: mean (standard deviation [SD]) age 64.3 (8.8) years, male 70.7%, current smokers 32.2% and former smokers 63.7%, mean body mass index 25.6 (5.1) kg/m^2 (Table 1). Inclusion in the study was mainly due to obstructive lung disease (47.1%), heart failure (27.9%), TL_{CO}/AV <60% (22.1%), and obesity (17.3%). Other comorbidities were history of cancer (14.5%), diabetes (11.4%), and hypertension (14.1%). Lung cancers were mainly adenocarcinoma (55.2%) and squamous cell carcinoma (34.5%) at stage I to II (89.1%) (Table 2).

Perioperative Management

At visit V1, median FEV1 was 2080 mL, median FVC was 3170 mL, and median FEV1/FVC was 0.7. Preoperative examinations performed were echocardiography (n = 212 patients, abnormal 69.3%), electrocardiogram (n = 241, abnormal 91.3%), TLco/AV (n = 183, mean 66.0%), ventilation/perfusion lung scan (n = 28), maximal oxygen consumption (n = 35), and 6-minute walk test (n = 28). Median PaO_2 was 78.0 mm Hg (n = 232 patients) at V2 and 81.0 mm Hg (n = 167) before

TABLE 1. Characteristics of patients at inclusion in the preOVNI study

	No-NIV group (n = 146)	NIV group (n = 151)	*P* value
Age, y, mean (SD)	64.3 (8.9)	64.3 (8.8)	.9780
Male, n (%)	100 (68.5)	110 (72.8)	.4097
Body mass index, kg/m^2, mean (SD)	25.8 (5.3)	25.5 (4.9)	.5939
Inclusion criteria, n (%)			
Obstructive lung disease	73 (50.0)	67 (44.4)	.3313
Restrictive lung disease	13 (9.0)	19 (12.8)	.2973
TL_{CO}/VA <60%	34 (23.4)	31 (20.8)	.5851
History of hypercapnic respiratory failure	1 (0.7)	3 (2.0)	.6226
Long-term oxygen therapy	1 (0.3)	1 (0.7)	.4932
Heart failure	38 (26.2)	44 (29.5)	.5253
History of acute cardiogenic pulmonary edema	3 (2.1)	5 (3.4)	.7230
Obesity	25 (17.2)	26 (17.4)	.9624
COPD*	82 (56.9)	75 (50.0)	.2328
Score of dyspnea (MRC), n (%)			
0	69 (50.7)	74 (52.1)	.1899
1	51 (37.5)	44 (31.0)	
≥2	16 (11.8)	24 (16.9)	
Performance status (ECOG), n (%)			
0	83 (59.3)	87 (60.0)	.6222
1	52 (37.1)	48 (33.1)	
≥2	5 (3.5)	10 (6.9)	
Epworth score, n (%)			
≤8	119 (90.2)	109 (80.1)	.0304
9-14	13 (9.8)	26 (19.1)	
≥15	0	1 (0.7)	
Smoking, n (%)			
Current smoker	47 (32.2)	38 (25.2)	.0639
Former smoker	93 (63.7)	97 (64.2)	
Never smoker	6 (4.1)	16 (10.1)	

The NIV and no-NIV groups had similar presentations. *NIV*, Noninvasive ventilation; *SD*, standard deviation; TL_{CO}, transfer factor of the lung for carbon monoxide; *VA*, alveolar volume; *COPD*, chronic obstructive pulmonary disease; *MRC*, Medical Research Council; *ECOG*, Eastern Cooperative Oncology Group. *Defined as forced expiratory volume in 1 second (FEV1) divided by forced vital capacity (FVC) <70%.

surgery; the corresponding values for $PaCO_2$ were 38.0 (n = 231) and 39.0 mm Hg (n = 167).

Patients underwent NIV for a mean (SD) of 9.8 (5.1) days and 6.9 (4.9) h/day (Table 3). The mean percentage of days with NIV ≥4 hours was 68.1%. The compliance varied according to the study centers: a median NIV use ≥4 hours per day was reported in 57.1% to 100% of patients in centers that included 2 or more patients (Table E2). The mean (SD) initial expiratory and inspiratory positive airway pressures were 5.1 (1.4) mm Hg and 11.3 (2.3) mm Hg, respectively. During the first night, the mean (SD) residual AHI was 3.7 (6.0) per hour and sleep apnea syndrome was suspected for 22.9% of patients. A total of 11.1% (15/135) of patients in the no-NIV group and 19.0% in the NIV group (27/142) underwent preoperative respiratory physiotherapy ($P = .067$).

Surgery was more frequently thoracoscopy in the no-NIV group compared with the NIV group (26.4% vs 14.4%; $P = .013$) (Table 2). Locoregional anesthesia was performed in 16.7% of cases and peridural anesthesia in 54.4%. The surgical procedure was most frequently lobectomy (80.0%). Mean (SD) duration of surgery was 132 (65) minutes with no difference according to treatment groups.

Postoperative Complications

The overall rates of postoperative cardiorespiratory complications within 1 month after surgery (main criteria) were 44.6% (62/139) in the no-NIV group and 42.8% (62/145) in the NIV group for ITT analysis ($P = .75$) (Table 4).

The rate of pneumonia was greater in the no-NIV group compared with the NIV group, but statistical significance was not achieved (37.7% vs 28.0%, respectively; $P = .08$). The other components of the primary endpoint were comparable in the no-NIV and NIV groups; the most frequent were hypoxemic and/or hypercapnic acute respiratory insufficiency (15.3 vs 14.1%, respectively), atelectasis

TABLE 2. Characteristics of lung cancer and surgery in the preOVNI study

	No-NIV group (n = 146)	NIV group (n = 151)
Lung cancer histology, n (%)*		
Adenocarcinoma	46 (54.1)	45 (56.3)
Squamous cell carcinoma	26 (30.6)	31 (38.8)
Small cell cancer	3 (3.5)	1 (1.3)
Carcinoid cancer	6 (7.1)	1 (1.3)
Other	4 (4.7)	2 (2.5)
Missing	132	61
Cancer stage (cTNM) at inclusion, n (%)		
I	84 (67.2)	83 (68.0)
II	29 (23.2)	24 (19.7)
III	10 (8.0)	14 (11.5)
IV	2 (1.6)	1 (0.8)
Missing	21	29
Type of surgery, n (%)†		
Thoracotomy	103 (73.6)	125 (85.6)
Thoracoscopy	37 (26.4)	21 (14.4)
Surgical procedure, n (%)		
Lobectomy	107 (78.1)	119 (83.8)
Pneumonectomy (unscheduled)	6 (4.4)	4 (2.8)
Segmentectomy	5 (3.6)	6 (4.2)
Wedge resection	19 (13.9)	13 (9.2)
Duration (min) from incision to closure, mean (SD)	128 (60)	136 (68)
Locoregional anesthesia, n (%)	21 (15.8)	25 (17.6)
Peridural anesthesia, n (%)	71 (53.0)	78 (55.7)

No difference was noticed in terms of type of cancers, staging, anesthesia. More thoracoscopies were performed in the no-NIV group. *NIV*, Noninvasive ventilation; *cTNM*, clinical Tumor, Node, Metastasis; *SD*, standard deviation. *$P = .2487$ for lung cancer histology. †$P = .013$ for comparison of rates of thoracotomy vs thoracoscopy.

TABLE 3. Characteristics of noninvasive ventilation

	NIV group (n = 151)
Initial parameters of NIV (visit 2), mean (SD)	
Expiratory positive airway pressure, mm Hg	5.1 (1.4)
Inspiratory positive airway pressure, mm Hg	11.3 (2.3)
Minimal frequency (per min)	10.1 (2.4)
Compliance with preoperative NIV	
Number of days with NIV, mean (SD)	9.8 (5.1)
Days with NIV ≥4 h, n (%)	6.9 (4.9)
Percentage of days with NIV ≥4 h, mean (SD)	68.1 (33.7)
Residual apnea-hypopnea index (per h), mean (SD)	3.7 (6.0)
Suspicion of sleep apnea syndrome during the first night, n (%)*	
No	74 (77.1)
Slight	11 (11.5)
Moderate	6 (6.2)
Severe	5 (5.2)

The observance was >4 h/day for 68.1% of patients; 22.9% of patients presented with suspected sleep apnea syndrome. *NIV*, Noninvasive ventilation; *SD*, standard deviation. *With continuous positive airway pressure 4 cm H_2O.

(13.2 vs 12.3%), and de novo atrial fibrillation (10.3 vs 13.1%). No difference was evidenced for the rates of complications with severity grade ≥3.

Subgroup analyses did not evidence categories of patients who could benefit from NIV. There was no decrease of the complication rate with NIV in the COPD subgroup patients. The complication rate in each group was adjusted on the type of surgery (open vs minimally invasive), COPD, and carbon monoxide transfer <60%: the adjusted odd ratio (NIV vs no NIV) was 0.86 (95% CI, 0.53-1.38; $P = .52$). Subgroup analyses did not evidence categories of patients who could benefit from NIV. Concerning the greater rate of thoracoscopies in the no-NIV group, the odds ratio for postoperative complications (NIV vs no NIV) was 0.94 (95% CI, 0.71-1.24) in the thoracotomy group and 0.75 (95% CI, 0.31-1.82) in the thoracoscopy group. Therefore, there is no treatment effect heterogeneity associated with the type of surgery (Table 5). In per-protocol analysis, the overall rates of complications were 45.2% for no-NIV versus 42.1% for NIV ($P = .67$).

The rates of the other complications were also comparable in the no-NIV and NIV groups; the most frequent were pneumothorax (12.6 vs 10.9%, respectively), subcutaneous emphysema (9.6 vs 12.4%), and pleurisy (4.4 vs 5.8%).

Mean (SD) duration of stay at the hospital was 11.6 (6.4) days for the no-NIV group and 11.9 (8.7) days for the NIV group ($P = .43$); mean durations of stay in the intensive care unit were 6.3 (6.6) and 5.9 (7.0) days, respectively ($P = .45$). Mean duration of postoperative air leakage was 3.1 (4.0) days in the no-NIV group and 2.3 (3.5) days in the NIV group ($P = .26$).

The day after surgery, median PaO_2 and $PaCO_2$ were 79.0 and 42.0 mm Hg (n = 77 and n = 78) in the no-NIV group and 79.0 and 40.0 mm Hg (n = 80) in the NIV group, respectively. At hospital discharge, median PaO_2 and $PaCO_2$ were 72.5 and 38.0 mm Hg (n = 70) in the no-NIV group and 72.5 and 38.5 mm Hg (n = 70) in the NIV group.

A total of 94.8% (127/134) of patients in the no-NIV group and 89.7% (130/145) in the NIV group underwent postoperative respiratory physiotherapy ($P = .11$). A total of 22.9% (32/140) of patients in the no-NIV group and 28.1% (41/146) in the NIV group underwent postoperative NIV ($P = .31$) for a mean duration of 4.0 (3.5) and 5.9 (5.4) days, respectively ($P = .096$). Postoperative NIV was realized only in case of complication.

Safety

Adverse events were comparable in both groups: 37.0% (54/146) in the no-NIV group versus 39.0% (59/

TABLE 4. Primary endpoint: postoperative cardiorespiratory complications within 1 month after surgery in the preOVNI study

	No-NIV group (n = 146)	NIV group (n = 151)	*P* value*
Primary endpoint			
Postoperative cardiorespiratory complications, n (%)	62 (44.6)	62 (42.8)	.75
Missing	8	8	
Components of the composite primary endpoint, n (%)			
Pneumonia or lower respiratory tract infection	52 (37.7)	40 (28.0)	.08
Atelectasis	18 (13.2)	17 (12.3)	.82
Hypoxemic and/or hypercapnic acute respiratory insufficiency	21 (15.3)	20 (14.1)	.77
Prolongation of postoperative intubation >24 h	2 (1.5)	0 (0)	.25
Acute heart failure	3 (2.2)	8 (5.7)	.14
De novo atrial fibrillation	14 (10.3)	18 (13.1)	.47
Death	4 (2.9)	7 (4.8)	.39
Other complications			
Myocardial infarction	1 (0.7)	2 (1.4)	1.00
Bronchial fistula	0	1 (0.7)	1.00
Acute myocardial ischemia	3 (2.2)	8 (5.7)	.14
Confused postoperative state	9 (6.7)	5 (3.6)	.25
Postoperative venous thromboembolism	0 (0)	1 (0.7)	1.0
Pneumothorax	17 (12.6)	15 (10.9)	.66
Pneumomediastinum	1 (0.7)	1 (0.7)	1.00
Subcutaneous emphysema	13 (9.6)	17 (12.4)	.46
Pleurisy	6 (4.4)	8 (5.8)	.59
Hospital stay, d	11.5 (6.4)	11.9 (8.7)	.44
ICU stay, d	6.3 (6.6)	5.9 (7.0)	.45
Air leak duration, d	2.7 (3.8)	2.3 (3.5)	.26

No difference was found for the primary endpoint and the secondary endpoints. *NIV*, Noninvasive ventilation; *ICU*, intensive care unit. *χ^2 test.

151) in the NIV group, including postoperative air leakage: 3.1 (4.0) days versus 2.3 (3.5) days ($P = .26$). Serious adverse events were 17.8% (26/146) versus 17.2% (26/151), respectively. Facial cutaneous lesions were reported in 1.6% (2/151) of patients receiving NIV. NIV was discontinued by 13.4% (17/151) of patients (mask intolerance, n = 1; intolerance to pressure levels, n = 3: other, n = 13).

TABLE 5. Subgroup analysis evaluating the effect of NIV vs no-NIV

	Univariate analysis		Logistic regression analysis	
	Odds ratios (95% CI) for postoperative complications (NIV vs no-NIV)	*P* value	Odds ratios (95% CI) for postoperative complications (NIV vs no-NIV)	*P* value
NIV	0.93 (0.58-1.48)	.75		
Age >60 y	1.05 (0.60-1.83)	.87		
Male sex	0.75 (0.43-1.30)	.3		
BMI >30 kg/m^2	2.13 (0.71-6.37)	.17		
Active smoker	0.86 (0.36-2.09)	.74		
Previous cardiovascular disease	0.94 (0.38-2.34)	.9		
Previous COPD	1.26 (0.57-2.80)	.57	0.91 (0.57-1.48)*	.72
Previous stroke	0.71 (0.14-3.58)	.68		
Previous cancer or hemopathy	0.75 (0.20-2.85)	.68		
TLCO <60%	0.44 (0.16-1.23)	.54	0.87 (0.47-1.59)†	.65
Thoracoscopy	0.67 (0.20-2.27)	.52	0.85 (0.53-1.37)‡	.5
Loco-regional anesthesia	1.30 (0.40-4.20)	.66		
Peridural anesthesia	0.66 (0.34-1.26)	.2		

Logistic regression analysis was performed as planned only for "previous COPD," "TLCO <60%," and "type of surgery." *NIV*, Noninvasive ventilation; *CI*, confidence interval; *BMI*, body mass index; *COPD*, chronic obstructive pulmonary disease; *TLCO*, carbon monoxide– free transfer. *COPD vs no COPD. †TLCO < 60% vs ≥ 60%. ‡Open vs thoracoscopy.

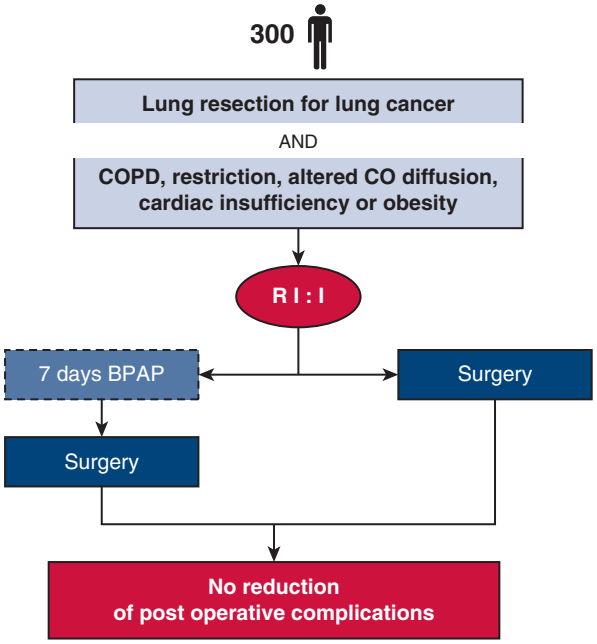

FIGURE 3. The preOVNI study. The preOVNI study was a randomized controlled study evaluating preoperative bilevel positive airway pressure (*BPAP*) before lung cancer surgery; 300 patients were 1:1 randomized. There was no difference in terms of postoperative complications between the two groups. *COPD*, Chronic obstructive pulmonary disease; *CO*, carbon monoxide; *R*, randomization.

DISCUSSION

In this randomized, controlled, open-label trial, preoperative NIV did not decrease the postoperative complication rate after lung cancer surgery (Figure 3 and Video 1). However, the generalization of these results to other countries cannot be taken for granted due to differences in patient care practices (for example, length of stay was longer than in other databases and was dependent on centers). A multivariable analysis adjusted on type of surgery, COPD, and diffusion alteration did not change this result. Per-protocol analysis confirmed the ITT analysis. There was only a nonsignificant decreased rate of pneumonia in the NIV group, one of the items of the composite endpoint (37.7% vs 28.0%; $P = .08$). There is a discrepancy regarding the results of preliminary studies. Beside the positive effects of preoperative NIV on functional parameters in thoracic surgery,[16] NIV seemed to decrease postoperative complications after aortic surgery. Thus, in an open-label monocentric study, 30 patients with COPD were randomized to receive NIV 15 days before and after surgery.[19] Patients with NIV experienced less pulmonary complications (0% vs 33%; $P = .004$) and shorter duration of intensive care unit stay (2.5 vs 6.5 days, $P < .001$). Although these results were promising, sample sizes were small and protocols for NIV administration were heterogenous.

The strengths of our trial are the large sample size and the high rate of randomized patients analyzed for the primary endpoint (94.7%). These strengths reinforce the conclusion of an absence of effect of NIV in this population of patients. These results raise some questions:

The rate of cardiorespiratory complications in the control group was greater than expected (44.8% vs 30%). The initial 30% rate was the basis for the calculation of the sample size. The objective of a decrease of 50% of postoperative complications seems too ambitious. Even though a greater sample size could achieve statistical significance, we have no guarantee, however, for a clinically significant difference. Nevertheless, the result concerning the most frequent postoperative complication (pneumonia) is promising.

Another limitation is the open-label nature of the trial. The trial was not blinded for evident reasons. Nevertheless, each cardiorespiratory complication was blindly adjudicated by the scientific committee. Anyway, the limitations of open-label studies are rather questioned when a difference between groups is observed.

The choice of the components of a composite endpoint is always difficult and the risk is to mask a specific signal among too many individual components generating high background noise. Therefore, we chose the most frequent and serious postoperative cardiorespiratory complications.

The NIV pressure levels were proposed to the investigators, but they decided the final level, thus complicating comparisons with other studies. These parameters were deliberately low because we wanted to enhance compliance (patients had no other reason than surgery to undergo NIV). Even with these parameters and individual adjustments by trained investigators, adherence was low, thus suggesting that this regimen was difficult to follow for these patients. We could not assess whether patients with poor compliance were those with a higher risk of complications.

We selected patients on the basis of their high risk not on a single at-risk condition (obesity or COPD, for example), which is another source of heterogeneity. The effects of NIV could have been diluted, but no subgroup of patients seemed to benefit from NIV. About 30% of patients were included because of cardiac insufficiency, and NIV seemed to have absolutely no effect regarding postoperative cardiovascular complications. Thus, it is possible that the choice of the inclusion criteria and the main judgment criteria had an impact on the overall results. Moreover, surgery type (open or VATS) may have also diluted the effect of NIV. Patients without NIV underwent more preoperative physiotherapy ($P = .067$). Even considering this result as nonsignificant, it could impact the result of the study.

The effects of NIV on functional respiratory parameters, including FEV1 and FVC, and the high level of complications in patients with COPD are rationale for an effect in patients with COPD. This treatment could be

VIDEO 1. Presentation of the preOVNI study, Dr Nicolas Paleiron, MD. Video available at: https://www.jtcvs.org/article/S0022-5223(19)33106-X/fulltext.

combined with smoking cessation, respiratory physiotherapy, and improvement of nutritional status; indeed, malnutrition is associated with increased postoperative ventilation and increased length of hospital stay in patients with COPD undergoing lung-reduction surgery.[20-22]

In recent years, noninvasive procedures such as stereotaxic radiotherapy or radiofrequency have been developed for the most fragile patients. Moreover, thoracic surgery has been improved: in France, 40% of patients actually benefit from video-assisted thoracoscopy or robot-assisted surgery, resulting in shorter hospital stay and a decrease of complication rates. This point should be considered for future studies, as the rate of thoracoscopies may have biased our results.[23-27]

CONCLUSIONS

In this large-scale, randomized study, no benefit was evidenced for preoperative NIV before NSCLC surgery (Figure 3). Decreasing the rate of postoperative complications remains a public health concern. Further studies should focus on particularly at-risk patients, excluding those with cardiac insufficiency who are not reliable for noninvasive treatment of localized NSCLC; stratification according to the type of surgery and the presence of obstructive sleep apnea must be performed.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: noninvasive ventilation, lung cancer surgery, postoperative complications, randomized controlled trial

TABLE E1. PreOVNI Study Protocol (Summary of the protocol in French)

Primary Objective

The main objective of the preOVNI study is to demonstrate that bilevel positive airway pressure at home during the 7 days preceding lung cancer surgery (lobectomy or segmentectomy) reduces postoperative pulmonary and cardiovascular complications in patients with obstructive or restrictive ventilatory disorder, obesity, or chronic heart failure. The secondary objective is to determine the subgroups of patients who benefited most from preoperative noninvasive ventilation and the tolerance of this technique.

Type of Study

This is a French, open-label, multicenter, randomized controlled trial comparing preoperative noninvasive ventilation with standard care.

Inclusion Criteria

Patient >18 years of age scheduled to undergo a planned lung cancer surgery (lobectomy or segmentectomy) for primary bronchial cancer and:

- Obstructive ventilatory disorder (forced expiratory volume in 1 second [FEV1]/forced vital capacity <70% and FEV1 <80% of the theoretical) or restrictive (forced expiratory volume <80% or total lung capacity <80%) or decreased diffusion coefficient of carbon monoxide per unit alveolar volume <60% or previous history of hypercapnic respiratory decompensation with carbon dioxide partial pressure > 45 mm Hg in the year before surgery
- Or heart failure (precise definition given in the protocol)
- Or obesity (body mass index >30 kg/m^2)

All patients included in the study must have benefited before the inclusion of the following exams:

- Cardiac ultrasound with evaluation of left ventricular ejection fraction, filling pressures, pulmonary arterial pressure on tricuspid insufficiency, aortic, mitral, pulmonary, and tricuspid valve function
- 12-lead electrocardiogram
- Respiratory function tests: spirometry (FEV1, forced vital capacity, distal expiratory flow (DEM) 25, DEM50, DEM75), diffusing capacity of the lungs for carbon monoxide and diffusing capacity of the lungs for carbon monoxide/alveolar volume measurement, plethysmography (VR, CPT, VR/CPT)
- Performing a ventilation/perfusion scintigraphy and maximal oxygen consumption measurement to assess operability is at the discretion of the investigator, as recommended by the European Respiratory Society.

Criteria for Noninclusion

The criteria for noninclusion are the impossibility to consent, contraindications to noninvasive ventilation (poor understanding of the technique, facial malformation, tight stenosis of the upper airways, uncontrollable vomiting, inability to remove the mask, disorders cognitive or psychiatric severe compromising adherence to noninvasive ventilation), patients without health insurance or already undergoing invasive or noninvasive ventilation. The planned pneumonectomy is a criterion of noninclusion because the complications are rather different and a priori little influenced by the realization of preoperative noninvasive ventilation sessions.

Criteria for Judgment

The primary endpoint is a combined endpoint comprising the following postoperative cardiorespiratory complications: pneumonitis, hypoxemic and/or hypercapnic acute respiratory failure, segmental, lobar or pulmonary atelectasis, cardiac insufficiency, atrial fibrillation.

The secondary criteria are mortality, length of stay in hospital, tolerance of noninvasive ventilation on the number of hours of use and local complications, changes in functional respiratory parameters and hematosis, duration of postoperative bubbling, bronchial fistulas, pneumothorax, pneumomediastinum, extensive subcutaneous emphysema, pleurisy, venous thromboembolic events, postoperative confusion syndromes, and all items of the primary endpoint, taken individually. Postoperative respiratory and cardiac complications have been precisely defined in the protocol. Their severity is measured by the Common Terminology Criteria for Adverse Events scale.

Practical Arrangements

Noninvasive ventilation will be started in the hospital (in consultation or day hospital, at the discretion of the principal investigator of the center), 7 to 15 days before surgery, under the supervision of a pulmonologist. The device used in this study is the S9 VPAP ST (ResMed, San Diego, Calif). It will be performed at home by an accredited provider with experience of this type of treatment. To ensure good compliance, the provider will commit to come to the patient the day after the start of treatment, then ensure at least 1 telephone contact before surgery. The provider will communicate the compliance of noninvasive ventilation to the investigator by completing a standardized form. Noninvasive ventilation may be continued after surgery at the discretion of the investigator. The interface will be a naso-oral mask or nasal or oral. The following parameters will be used to initiate ventilation, and may be modified by the investigator depending on the patient's tolerance:

- Inspiratory added pressure: 10 to 14 cm H_2O,
- Expiratory pressure: 3 to 10 cm H_2O,
- Minimum frequency: 7 to 15/min,
- Slope: 150 ms.

The recommended daily duration will be 6 hours a day, recommending 1 session of 3 hours a day, and a session of 3 hours in the evening. If the patient supports it, noninvasive ventilation may be continued overnight.

(Continued)

TABLE E1. Continued

Following the surgical procedure, the patient will be able to benefit from noninvasive ventilation sessions (regardless of his or her randomization arm) in case of complications. The indication, the ventilatory mode, the interface, the daily duration, and the number of sessions will be indicated in the CRF. Postoperative "systematic" noninvasive ventilation is not allowed.
Statistical Analysis
Descriptive Statistics
Calculation of frequencies and 95% confidence intervals for categorical variables; calculation of means and standard deviations after verification of a normal distribution for continuous variables.
A flowchart will be realized. The sample will be described using the usual statistical parameters.
Analytical Statistics
The main analysis will be done as "intent to treat"; a secondary analysis, "per protocol," will be realized
Univariate Analysis
The analysis of the primary endpoint will be performed by comparing the frequencies of patients with complication (primary endpoint) in both arms, using a χ^2 test.
Regarding the secondary criteria, the 2 arms will be compared:
• using a Student test for quantitative variables (or a Wilcoxon test in case of non-normality of the distribution of the variable considered)
• using a χ^2 test for qualitative variables (or a Fisher test if necessary)
• using a log-rank test for survival data type variables
Multivariate Analysis
Multivariate analyzes will complement the previously defined univariate analyzes, in order to obtain an adjustment for possible confounding factors on the one hand, and to look for possible interactions on the other. The models used will be logistic regression, linear regression, and Cox model.

TABLE E2. Adherence data for noninvasive ventilation in each center

	Centers															
	All (N = 151)	**C1 (N = 16)**	**C2 (N = 50)**	**C3 (N = 9)**	**C4 (N = 9)**	**C5 (N = 4)**	**C6 (N = 1)**	**C7 (N = 2)**	**C8 (N = 34)**	**C9 (N = 2)**	**C10 (N = 9)**	**C12 (N = 2)**	**C13 (N = 1)**	**C15 (N = 3)**	**C16 (N = 8)**	**C17 (N = 1)**
NIV adherence (median use >4 h/d)																
NA	36	2	4	9	2	2	0	2	2	0	7	1	0	3	1	1
	(23.8%)	(12.5%)	(8%)	(100%)	(22.2%)	(50%)	(0%)	(100%)	(5.9%)	(0%)	(77.8%)	(50%)	(0%)	(100%)	(12.5%)	(100%)
No	39	6	15	0	0	0	0	0	12	1	2	0	1	0	2	0
	(33.9%)	(42.9%)	(32.6%)	(0%)	(0%)	(0%)	(0%)	(0%)	(37.5%)	(50%)	(100%)	(0%)	(100%)	(0%)	(28.6%)	(0%)
Yes	76	8	31	0	7	2	1	0	20	1	0	1	0	0	5	0
	(66.1%)	(57.1%)	(67.4%)	(0%)	(100%)	(100%)	(100%)	(0%)	(62.5%)	(50%)	(0%)	(100%)	(0%)	(0%)	(71.4%)	(0%)

NIV, Noninvasive ventilation; *C1*, CHRU de Brest; *C2*, HIA Clermont-Tonnerre; *C3*, HIA Clamart; *C4*, HIA Saint-Anne; *C5*, CHI Créteil; *C6*, Hôpital Pasteur CHU de Nice; *C7*, Centre Hospitalier Victor Dupouy; *C8*, Clinique du Grand Large; *C9*, Hôpital Pontchaillou; *C10*, Hôpital de Boisguillaume; *C11*, HIA Laveran; *C12*, Hôpital Nord Ouest; *C13*, Centre hospitalier du Pays d'Aix; *C14*, CHG Roanne; *C15*, CHU Angers; *C16*, CHU Limoges; *C17*, CHU Saint-Etienne; *NA*, not available.