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Inspiratory effort assessment by esophageal manometry early predicts noninvasive ventilation outcome in de novo respiratory failure: a pilot study

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Key words: *acute respiratory distress syndrome, respiratory failure, non-invasive mechanical ventilation, transpulmonary pressure, esophageal pressure swings*

Abbreviations: ARDS, acute respiratory distress syndrome; ARFCCI, chronic critical illness; MV, invasive mechanical ventilation; NIV, non-invasive mechanical ventilation

At a Glance Commentary

Scientific Knowledge on the Subject. Non-invasive mechanical ventilation (NIV) is becoming increasingly used to assist spontaneous breathing during acute hypoxic de novo respiratory failure (AHRF), even though its potential therapeutic effect in this setting is controversial. Reported data show that NIV is used in 15% of patients with acute respiratory distress syndrome (ARDS) irrespective of the severity of respiratory failure and it seems to be associated with higher mortality in the case of failure. Several predictors of NIV failure in AHRF have been investigated but were found to be insufficient to aid the timing of endotracheal intubation. Thus, there is a need for an early robust predictor of NIV failure to avoid intubation delay.

What This Study Adds To The Field. Our exploratory study shows that, in patients with moderate to severe AHRF who were candidates for a 24-hour NIV trial, the magnitude of inspiratory effort relief was an early and accurate predictor of NIV failure. Our study suggests that monitoring of esophageal pressure might assist clinicians in the timing of intubation for patients with AHRF undergoing a NIV trial.

Abstract

Rationale

The role of inspiratory effort has still to be determined as a potential predictors of non-invasive mechanical ventilation (NIV) failure in acute hypoxic de novo respiratory failure (AHRF).

Objectives

We explore the hypothesis that inspiratory effort might be a major determinant of NIV failure in these patients.

Methods

Thirty consecutive patients with AHRF admitted to a single center and candidates for a 24-hour NIV trial were enrolled. Clinical features, tidal changes in esophageal (ΔP_{es}) and dynamic transpulmonary pressure (ΔP_L), expiratory tidal volume, and respiratory rate were recorded on admission and 2-4-12-24 hours after NIV start, and were tested for correlation with outcomes.

Measurements and Main Results

ΔP_{es} and $\Delta P_{es}/\Delta P_L$ were significantly lower 2 hours after NIV start in patients who successfully completed the NIV trial (n=18) compared to those who needed endotracheal intubation (n=12) [median=11 (IQR=8–15) cmH_2O vs 31.5 (30–36) cmH_2O, p<0.0001] while other variables differed later. ΔP_{es} was not related to other predictors of NIV failure at baseline. NIV-induced reduction in ΔP_{es} of 10 cmH_2O or more after 2 hours of treatment was strongly associated to avoidance of intubation, and represented the most accurate predictor of treatment success (OR=15, 95%CI 2.8-110, p=0.001, AUC=0.97, 95%CI 0.91–1, p<0.0001).

Conclusions

The magnitude of inspiratory effort relief as assessed by ΔP_{es} variation within the first 2 hours of NIV was an early and accurate predictor of NIV outcome at 24 hours.

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Key words: *acute respiratory distress syndrome, respiratory failure, non-invasive mechanical ventilation, transpulmonary pressure, esophageal pressure swings*

Introduction

The role of assisted spontaneous breathing (SB) in patients with acute hypoxic de novo respiratory failure (AHRF) is still controversial. When acute lung injury is mild, SB is desirable to preserve respiratory muscle function, improve the ventilation/perfusion ratio and regional ventilation (1), and reduce sedation and days of invasive mechanical ventilation (MV) (2). On the other hand, recent studies have suggested that SB might be a potential mechanism for lung damage if acute respiratory distress is severe (3). In recent years, non-invasive mechanical ventilation (NIV) has been increasingly used to assist SB in the intensive care setting, even though its potential therapeutic effect in AHRF is still debated. It has been reported that NIV is used in 15% of patients with acute respiratory distress syndrome (ARDS) irrespective of the severity of respiratory failure and it seems to be associated with higher mortality when PaO_2/FiO_2 is lower than 150 mmHg (4). Moreover, some studies have shown that NIV failure is associated with increased mortality in patients with AHRF (4,5); however, when NIV treatment is successful, it might considerably reduce the risk of death and length of ICU stay in this subset of patients (5).

Despite the fact that several potential factors associated with NIV failure have been investigated in hypoxic patients, there are no robust predictors that might alert the intensivist to the need for endotracheal intubation (ETI) within the very first hours of ventilation (6). Although the mechanisms behind the association between NIV failure and poorer survival remain unclear, a potential role for SB might be hypothesized. When SB is preserved during AHRF, the intensity of inspiratory effort may follow a critical increase in respiratory drive thus producing uncontrolled swings in transpulmonary pressure (P_L) that would increase the risk of injury to the dependent lung and predispose the patient to the onset of self-inflicted lung injury (SILI) (6). The underlying mechanisms of SILI are heterogeneous and include the pendelluft phenomenon, increased transvascular pressure gradient aggravating alveolar damage, excessive diaphragmatic loading with impaired systemic oxygen

delivery, and muscle injury (3,7–9).

In this study, we explore the hypothesis that, in patients with moderate or severe AHRF undergoing a NIV trial, the excessive spontaneous effort of the patients, measured with esophageal pressure swings (ΔP_{es}), may be a major determinant of NIV failure at 24 hours.

Methods

Study population

This prospective observational cohort study was carried out in a single eight-bed Respiratory Intensive Care Unit (RICU) at the University Hospital of Modena (I) following approval from the Ethics Committee "Area Vasta Emilia Nord" (registered protocol number 4485/C.E., document 266/16). After testing our study hypothesis in 4 patients (pilot data not included in the analysis) during the period October 2016 to December 2018, the study has been registered retrospectively on ClinicalTrial.gov (ID NCT03826797). Thirty consecutive patients were then enrolled in between February and October 2019. Written informed consent to participate in the study and to analyze and divulgate clinical data was obtained from all patients admitted.

Inclusion criteria were age > 18 years and the presence of AHRF with PaO_2/FiO_2 ratio < 200 mmHg despite high-flow nasal oxygen with flow set at 60 L/min, and a candidate to receive a NIV trial according to the attending RICU staff, whose decision was taken upon clinical conditions blinded to the purpose of the study. Patients were excluded in the case of a previously established diagnosis of chronic obstructive pulmonary disease; diagnosed pulmonary embolism; neuromuscular disease; cardiogenic acute pulmonary edema; interstitial lung disease; chest wall deformities; the need for immediate endotracheal intubation (ETI) as represented by any of the following: cardiopulmonary arrest; respiratory arrest; loss of consciousness with respiratory pauses; psychomotor agitation requiring sedation; pH less than 7.20; neurological deterioration or massive secretions;

hemodynamic instability or major electrocardiographic abnormalities; pregnancy; intolerance to NIV; hypercapnic respiratory failure of any etiology ($PaCO_2$ > 45 mmHg); home long-term oxygen therapy; denied informed consent.

General measures

Demographics and relevant comorbidities were assessed on admission. Clinical severity as assessed by the Kelly Scale, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, the Simplified Acute Physiology Score (SAPS II), the Subsequent Organ Failure Assessment (SOFA) score and the Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate (HACOR) score were assessed and recorded on admission and after 2, 4, 12, and 24 hours. Arterial blood gases (PaO_2-$PaCO_2$), pH, PaO_2/FiO_2 ratio, respiratory rate (RR), and blood lactate values were recorded before NIV start and 2, 4, 12, and 24 hours later. A chest X-ray was taken on admission and 24 hours after NIV start.

Physiological measurements

A multifunctional nasogastric tube with a dedicated pressure transducer (NutriVent™, SIDAM, Mirandola, Italy) was placed before starting NIV. The nasogastric tube was connected to a dedicated monitoring system (OptiVent™, SIDAM, Mirandola, Italy) to record swings in esophageal (P_{es}) and dynamic transpulmonary (P_L) pressures. In order to avoid using absolute values for P_{es} and P_L, we always refer to ΔP_{es} and ΔP_L from the end-expiratory level, respectively (10). Appropriate catheter position was confirmed by visualization of cardiac artifacts on P_{es} traces and radiopaque markers on chest X-rays, and validation of esophageal pressure measurements was obtained through dynamic occlusion tests (11,12). ΔP_{es} was calculated as the negative deflection of P_{es} from the onset of inspiratory effort. ΔP_L was as the tidal change in transpulmonary pressure, calculated as airway pressure (P_{aw}) minus P_{es} (10).

ΔP_{es}, ΔP_L, and $\Delta P_{es}/\Delta P_L$ ratios were assessed on admission and 2, 4, 12, and 24 hours after NIV start. Initial measurements were performed at each pre-specified time point while the patient was breathing spontaneously through the ventilator circuit. Data were sampled at 100 Hz and processed on a dedicated data acquisition system (OptiVent™, SIDAM, Mirandola, Italy) (12). Data sampling was numerically stored and downloaded via USB stick at each time of assessment. Offline breath-by-breath analysis was then performed for each measurement then averaged by a specific software (Flux View Respiratory Mechanics Monitor (NBMED- Medical Graphics, Milano, Italy). For all the measurements the beginning of the inspiratory phase was identified at the instant of P_{es} initial decay while the end of inspiration considered at the point of P_{es} that elapsed 25% of time from its maximum deflection to return to baseline.

Respiratory flow was measured by an external heated Fleisch No. 2 pneumotachograph (Fleisch, Lausanne, Switzerland) inserted between the patient's oronasal facemask (Bluestar™, KOO Medical Equipment, Shanghai, PRC) and a connector with a side port for mechanical measurement. Expiratory tidal volume (Vte) was obtained by numerical integration of the flow signal. Vte was then adjusted to the predicted body weight (PBW) to derive Vte/kg of PBW. Vte/kg of PBW was assessed on admission and 2, 4, 12 and 24 hours after NIV start. Minute ventilation (VE) was calculated as the product of Vte and RR and assessed on admission and 2, 4, 12 and 24 hours after NIV start. $Vte/\Delta P_L$ was further measured at each pre-defined time point.

Leaks from the oronasal facemask were computed using dedicated ventilator-integrated software (GE Healthcare Engstrom Carestation™, GE Healthcare, Finland) based on the equation: leaks (L/min) = (inspiratory Vt – expiratory Vt) x RR.

All measurements were performed during a stable spontaneous breathing pattern of 5 minutes and results were averaged for each assessment step.

NIV treatment

After Nutrivent™ placement, NIV was started and set by a respiratory physician with expertise in Respiratory Intensive Care. Patients were connected via a conventional circuit with an appropriately sized oronasal facemask equipped with a dedicated output for probes (Bluestar™, KOO Medical Equipment, Shanghai, PRC) to a high-performance ventilator (GE Healthcare Engstrom Carestation™, GE Healthcare, Finland) in pressure support pre-set mode. Heat and moisture exchanger (HME) (HYGROBAC, DAR, Mirandola, Italy) was placed to the ventilator circuit's Y-piece. Positive end expiratory pressure (PEEP) was initially set at 6 cmH2O, and subsequently fine-tuned (4–8 cmH2O) in order to target a SatO2 > 92% with a delivered FiO2 less than 70%. Pressure support (PS) was set at 10 cmH_2O, and then progressively modified, according to tidal volume (Vte/kg of PBW), in order to target a Vte/kg of PBW lower than 9.5 ml/kg of PBW and a RR lower than 30 breaths/min. The oronasal facemask was finely adjusted to target a leak flow lower than 20 L/min. The inspiratory trigger was set at 3 L/min and respiratory cycling was set at 25% of the inspiratory peak flow. Great care was taken by the nurses in charge of NIV, and who were blinded to the protocol, to avoid any possible air leaks. The inspiratory fraction of oxygen delivered (FiO_2) was increased to target a transcutaneous oxyhemoglobin saturation of 88–94%. Setting was adjusted by the attending physician blinded to the study purpose and based on blood gases and/or continuous oxymetry assessment. Patients receiving NIV treatment were not sedated. The decision as to whether to proceed to ETI at 24 hours after NIV start was taken according to best clinical practice by the attending RICU staff, blinded to the results of the physiological assessment acquired through the Optivent™ monitor only at each pre-defined time point. NIV failure was defined by the onset of the need for ETI or by death. Criteria for ETI included: (a) PaO_2/FiO_2 ratio unchanged or worsened or below 150 mmHg, (b) the need to protect airways due to neurological deterioration or massive secretions, (c) hemodynamic instability or major electrocardiographic abnormalities, (d) unchanged

or worsened dyspnea and persistence of respiratory distress (RR > 35 bpm, gasping for air, psychomotor agitation requiring sedation, abdominal paradox).

Outcome measures

The influence of ΔP_{es} on NIV failure or success at 24 hours was pre-specified as a primary outcome. The impact of ΔP_L, $\Delta P_{es}/\Delta P_L$ ratio, PaO_2/FiO_2 ratio, RR, Vte/kg of PBW, $Vte/\Delta P_L$, VE and the HACOR score on NIV outcome at 24 hours and the correlation between ΔP_{es} and radiographic changes on chest X-ray within the first 24 hours after NIV start were assessed as secondary outcomes. Radiographic changes on chest X-ray within the first 24 hours after admission were assessed by a radiologist with expertise in chest X-ray and blinded to the purpose of the study. Changes were classified as follows: relevant worsening, worsening, mild worsening, unmodified, relevant improvement, improvement, mild improvement.

Statistical analysis

The statistical package GraphPad Prism 8.0 (GraphPad Software, Inc., La Jolla, CA, USA) was used for statistical analysis. Due to the exploratory nature of the study, no sample size calculation was performed. Descriptive statistics was used to characterize the study population as a whole and according to primary outcome. The nonparametric Mann–Whitney and Student *t* test were used for the comparison of continuous variables. Comparison between dichotomous variables was performed by the χ^2 test or Fisher's exact test, where appropriate. The time course of ΔP_{es}, ΔP_L, $\Delta P_{es}/\Delta P_L$ ratio, PaO_2/FiO_2 ratio, Vte/kg of PBW, $Vte/\Delta P_L$, RR, VE and HACOR score according to NIV outcome within the first 24 hours of treatment was assessed through ANOVA analysis. Then a post-hoc Bonferroni-Dunn's multiple test was used to perform the pairwise comparison of means for each analyzed variable at the prespecified time points. The correlation between baseline values of ΔP_{es} and PaO_2/FiO_2, Vte, RR, HACOR score, $Vte/\Delta P_L$ and the chest X-ray radiographic categories was assessed through Pearson's correlation coefficient. The impact of ΔP_{es} change within 2 hours after

NIV start and baseline value of $Vte/\Delta P_L$ on NIV outcome was assessed through a logistic regression model. A receiver operating characteristic (ROC) analysis was then performed to identify the best predictive cut-off for ΔP_{es} change within 2 hours after NIV start and for baseline $Vte/\Delta P_L$. The association between the best cut-off value of ΔP_{es} change after 2 hours of NIV and baseline $Vte/\Delta P_L$, Vte > 9.5 ml/kg of PBW, RR > 30 bpm, PaO_2/FiO_2 ratio < 150 mmHg and HACOR score > 5 within 2 hours after NIV start on NIV failure at 24 hours was then tested through univariate logistic regression analysis. ROC analysis was used to assess the accuracy in predicting NIV failure at 24 hours for all the analyzed variables at pre-specified cut offs. Then, at 30 days, survival analysis was performed through a log-rank test for ΔP_{es} change within 2 hours after NIV start. A p-value less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

Over the study period, 30 out of 86 consecutive patients admitted for AHRF to the RICU of the University Hospital of Modena (Italy) and who were candidates to receive a NIV trial were enrolled in this study. Of these, 12 patients (40%) experienced NIV failure within 24 hours after NIV start. Those patients for which the need for ETI was defined at 24 hours as the "alert" criterion of our internal guideline, were thereafter intubated by the RICU staff. Of those who were successful in the 24-hour trial (60%), none were further intubated during their RICU stay. The flow chart for patients in this study is shown in Figure 1.

The general features and clinical characteristics of the whole population at baseline and according to NIV outcome at 24 hours are presented in Table 1. None of the features assessed were significantly different between the two groups of patients (NIV failure vs NIV success) at baseline. In particular, the overall population presented an average value of PaO_2/FiO_2 of 125 (interquartile

range [IQR] 101–170) mmHg, which did not differ significantly according to NIV outcome at 24 hours (100 [118–141] mmHg and 111 [132–173]) mmHg, respectively, p=0.5). All patients with ARDS (n=15) presented pulmonary ARDS. In 10 patients, the etiology was identified as infectious (bacterial n=4, fungal n=2, viral n=4) while for 5 patients, no etiological diagnosis was made. Patients with pneumonia had unilateral lung consolidation and 9 of them presented a bacterial infectious cause (*Streptococcus pneumoniae* n=4, intracellular pathogens n=4, *Hemophilus influenzae* n=1). The presence of pneumonia and ARDS was equally distributed between the two groups (42% vs 44% p>0.9, 58% vs 44% p=0.7, respectively).

Physiological measurements and NIV outcome

Table 2 shows the physiological dynamic respiratory mechanics for the whole population at baseline and in the NIV outcome subgroups at baseline and after 2 hours of NIV. At baseline, the median value of ΔP_{es} was 34 (26–40) cmH_2O. Of note, none of the physiological features analyzed were significantly different at baseline between the two groups. After 2 hours of NIV, the median value of ΔP_{es} was significantly lower for those patients who were successful in the 24-hour NIV trial compared to patients who failed (11 [8–15] cmH_2O vs 31.5 [30–36] cmH_2O, p<0.0001). Moreover, these latter patients presented a significantly increased value of ΔP_L once NIV had started compared to patients who experienced NIV success at 24 hours (39.5 [37.5–42-3] cmH_2O vs 30.5 [28–43.5] cmH_2O, p=0.04).

Figure 2, panel A shows ΔP_{es} changes from baseline within the first 2 hours of NIV for the whole population and according to NIV outcome at 24 hours. ΔP_{es} decreased significantly after 2 hours of NIV for the whole population and for those patients who were successful in the NIV trial, whereas it did not change for patients who experienced NIV failure. Moreover, only these latter patients presented a significant increase in ΔP_L after 2 hours of NIV (Figure 2, panel B).

Waveform analysis of ΔP_L and ΔP_{es} swings 2 hours after NIV start is displayed in Figure 3, for a patient who failed the 24-hour NIV trial (panels A and C) and for a patient who succeeded (panels B and D). The time course of the physiological and clinical variables (ΔP_{es}, ΔP_L, $\Delta P_{es}/\Delta P_L$, RR, PaO_2/FiO_2 ratio, HACOR score, Vte/kg of PBW, $Vte/\Delta P_L$, and VE) in the two categories of patients according to NIV outcome showed a significant improvement over time in patients who were successful in the NIV trial. Moreover, only ΔP_{es} significantly decreased earlier (2 hours after NIV start) in those patients who were successful in the NIV trial compared to those who failed ($p<0.0001$, Figure E1A, supplementary material). The ratio between ΔP_{es} and ΔP_L was significantly different 2 hours after NIV start between the two groups ($p<0.0001$, Figure E1C, supplementary material), while ΔP_L ($p=0.04$, Figure E1B, supplementary material), Vte/kg of PBW, VE, $Vte/\Delta P_L$ ($p=0.01$, $p=0.01$, and $p=0.001$, Figure E2, panel A, B, C, respectively, supplementary material), RR, PaO_2/FiO_2, HACOR score ($p=0.02$, $p<0.0001$, and $p=0.03$, Figure E3, panel A, B, C, respectively, supplementary material) were all significantly different more than 2 hours after NIV start.

Significant inverse correlation was found between baseline ΔP_{es} and $Vte/\Delta P_L$ ($r=-077$, $p<0.0001$, Figure E4 supplementary material). No significant correlation was found between baseline ΔP_{es} and PaO_2/FiO_2 ratio ($r=–0.01$, $p=0.9$, Figure E5, panel A supplementary material), RR ($r=0.23$, $p=0.2$, Figure E5, panel B supplementary material), HACOR score ($r=0.05$, $p=0.8$, Figure E5, panel C supplementary material), and Vte/kg of PBW ($r=–0.05$, $p=0.8$, Figure E5, panel D supplementary material).

Radiological changes and inspiratory effort

The correlation analysis performed for radiographic changes showed that patients with a greater reduction in ΔP_{es} 2 hours after NIV start experienced more consistent improvements on chest X-ray at 24 hours, whereas patients with a limited reduction of ΔP_{es} were those who showed a deterioration on chest X-ray (Figure E6, supplementary material).

Inspiratory effort and clinical outcome

In the logistic regression model, ΔP_{es} changes within the first 2 hours of NIV showed a significant association with NIV failure at 24 hours (odds ratio [OR]=1.7, 95%CI 1.2–3, p=0.01) while baseline Vte/ΔP_L was not significantly associated with NIV outcome (p=.03). From ROC analysis, ΔP_{es} changes < 10 cmH_2O gave the most accurate cut-off value for prediction of NIV failure (sensitivity 0.91 95%CI 0.65–1, specificity 0.83 95%CI 0.61–0.94, likelihood ratio=5.5, positive predictive value=0.79, 95%CI 0.52–0.92, negative predictive value=0.94 95%CI 0.72–1, Table E1, supplementary material); Vte/ΔP_L < 0.33 ml/Kg/cmH2O showed the best cut-off value for prediction of NIV failure (sensitivity 0.67 95%CI 0.40–0.86, specificity 0.5 95%CI 0.29–0.71, likelihood ratio=1.3, positive predictive value=0.47, 95%CI 0.26–0.7, negative predictive value=0.7 95%CI 0.42–87, Table E2, supplementary material. When univariate logistic regression was applied to the pre-specified potential predictors of NIV failure, ΔP_{es} changes < 10 cmH_2O showed the highest association with NIV failure at 24 hours (OR=15 95%CI 2.8–110, p=0.001). Among the other predictors tested, Vte > 9.5 ml/kg of PBW and HACOR > 5 after 2 hours of NIV were significantly associated with NIV failure at 24 h (OR=7.9 95%CI 1.5–72, p=0.02 and OR=6.3 95%CI 0.9–49, p=0.046, respectively) while RR > 30 bpm, PaO_2/FiO_2 ratio < 150 mmHg and Vte/ΔP_L < 0.33 ml/Kg/cmH2O, although strongly associated, did not reach statistical significance (Table 3). From ROC analysis, ΔPes changes < 10 cmH_2O within the first 2 hours after NIV start showed higher accuracy in predicting NIV failure (AUC=0.97 95%CI 0.91–1, p<0.0001) (Figure 4) than baseline Vte > 9.5 ml/kg of PBW, HACOR score > 5, RR > 30 bpm, PaO_2/FiO_2 ratio < 150 mmHg and Vte/ΔP_L < 0.33 ml/Kg/cmH2O (AUC=0.88 95%CI 0.76–0.99, p=0.0005, AUC=0.85 95%CI 0.71–0.99, p=0.00, AUC=0.83 95%CI 0.67–0.98, p=0.003, AUC=0.74 95%CI 0.56–0.92, p=0.03, AUC= 0.58 95%CI 0.37-0.8, p=0.44, respectively).

Kaplan–Meier curves showed a significant increase in 30-day mortality among patients with ΔP_{es} reduction < 10 cmH_2O within the first 2 hours after NIV start compared to patients with a more

consistent early improvement (HR=4.5 95%CI 1.01–17.9, p=0.048, Figure E7 supplementary material).

Discussion

In this exploratory study, patients with moderate to severe AHRF undergoing a NIV trial presented a median baseline value for ΔP_{es} of 34 cmH_2O that was significantly reduced within the first 2 hours of ventilation in patients who were successful in the NIV trial, while those patients failing NIV did not have a significantly reduced ΔP_{es}. This study therefore shows that a significant ΔP_{es} reduction within the first 2 hours of NIV start was an early and accurate predictor of NIV outcome and was significantly correlated with radiographic changes after 1 day of NIV. Moreover, the magnitude of inspiratory effort at baseline did not show a significant correlation with the severity of respiratory failure, tidal volume, RR, and HACOR score on admission.

Physiological measurements and NIV outcome

Early prediction of NIV failure in AHRF

The application of NIV in treating patients with AHRF is a controversial issue and it is currently used in clinical practice irrespective of the severity of PaO_2/FiO_2. Despite the initial promising results on the effectiveness of NIV in patients with hypoxic respiratory failure (13,14), more recent studies focusing on patients with AHRF and excluding underlying chronic respiratory diseases or cardiogenic pulmonary edema warn of the increased mortality rates once ETI is delayed (5,15,16). Despite the fact that failure rates can exceed 60% in patients with more severe AHRF, successful application of NIV is independently associated with survival and shorter length of ICU stay (5). Giving these assumptions, it seems of critical interest to identify early predictors of NIV failure in order to avoid deleterious intubation delay in this subset of patients.

Previous studies have shown that several factors (i.e. higher severity score on admission, older age,

ARDS or pneumonia as the etiology for acute respiratory failure, or a lack of improvement in blood gas exchange within 1 hour of treatment) are associated with NIV failure in patients with AHRF, although these were insufficient to influence ETI timing (17). In our study, all of these factors were not different in patients who failed the 24-hour NIV compared to patients who were successful in the trial. In a recent single-center study, Duan and coworkers developed and validated the HACOR score for prediction of NIV failure in patients with AHRF, showing that patients with a HACOR score greater than 5 after the first hour of NIV were at greater risk for NIV failure and, if switched to invasive mechanical ventilation (MV) within the first 12 hours, presented reduced in-hospital mortality (18). In our study, the HACOR score was significantly associated with increased NIV failure but not as early as ΔP_{es}. Moreover, both groups of patients presented a HACOR score greater than 5 after the first 2 hours of NIV. Two recent studies have demonstrated that moderate-to-severe hypoxemia significantly affects NIV outcome in patients with ARDS-induced AHRF (19,20). Our study presented a carefully selected population of patients with moderate to severe AHRF, whose average PaO_2/FiO_2 was 132 mmHg and in whom significant differences between those who were successful in the NIV trial compared to those who were subjected to ETI did not become evident until 12 hours after the start of NIV. Of interest, the inspiratory effort at baseline as expressed by ΔP_{es} did not show a significant correlation with the severity of respiratory failure. These findings are in line with data reported in a recent physiological study by Grieco et al. where ΔP_e was unrelated to oxygenation impairment during helmet NIV and high flow oxygen treatment (21). Our data further underline the inability of PaO_2/FiO_2 ratio alone to identify patients with harmful respiratory drive.

In a recent trial, Carteaux and coworkers showed that a Vte value greater than 9.5 mL/kg was independently associated with NIV failure in patients with AHRF (22) suggesting a role of high Vte as a potential predictor of NIV failure in this setting (19). The results from our study are in line with their reported data although significant differences in Vte between patients who failed the NIV

treatment and those who were successful became evident 12 hours after NIV start. Moreover, the magnitude of inspiratory effort was not correlated with average Vte at baseline. Considering these data, the inability to apply protective ventilation should be considered a critical mechanism of NIV failure in this subset of patients.

The main result from our study was that a change in ΔP_{es} less than 10 cmH_2O within the first 2 hours after NIV start was an early and accurate predictor of NIV failure at 24 hours when compared to other variables, such as PaO_2/FiO_2, Vte, HACOR, and RR. From a clinical point of view, these data might suggest that, in patients with moderate to severe AHRF, the effectiveness of a NIV trial should be related to the reduction in the patient's inspiratory effort, quantifiable through esophageal manometry. The consequences of this reduction translate into a subsequent significant reduction of Vte, a decrease in RR, and an improvement in PaO_2/FiO_2 with a few hours latency. Moreover, the correlation analysis showed that ΔP_{es} on admission was not associated with the baseline value of other predictors of NIV failure.

Radiological changes and inspiratory effort

Inspiratory effort and self-inflicted lung injury during NIV

Our results showed a significant correlation between ΔP_{es} changes within the first 2 hours of NIV and radiographic progression at 24 hours. Despite being less accurate than a computed tomography scan, chest X-ray showed good sensitivity in detecting lung alteration in patients with ARDS (23) and might be considered reliable in the evaluation of the extent and distribution of lung opacities, once a diagnosis has already been made (24).

The results of our study support the hypothesis that inspiratory effort might be a potential mechanism of lung damage enhancement if acute respiratory distress is severe. Although data from animal models indicate ΔP_L as a major determinant of SILI, experimental studies conducted on normal trained subjects during exhausting endurance exercise demonstrated that potentially

injurious values of ΔP_L (up to 52 cmH_2O) did not translate into lung mechanical changes (25,26). To understand this, we have to consider that, in normal fluid-like lung, the inspiratory swing in pleural pressure produced by inspiratory effort is homogeneously distributed across the pleural surface. In contrast, in injured solid-like lung, the inspiratory pleural swing is not uniformly dissipated, resulting in a more negative deflection in the dependent lung zones with tidal over-recruitment and local overstretch (6). More recently, two trials investigating the role of assisted SB in mechanically ventilated patients showed that SB was not associated with poorer outcome when compared to controlled MV (27,28), but they lacked assessment of the inspiratory effort. Our results might suggest that a major determinant in generating lung stress lies in the dynamic component of the inspiratory effort rather than in the absolute value of the pressure generated. Interestingly, within the first 2 hours of NIV, $\Delta P_{es}/\Delta P_L$ was different in those who were successful in the NIV trial compared to those who failed it. This ratio might express to what extent dynamic ΔP_L is affected by the patient's respiratory drive and might introduce a new insight in the understanding of SILI. In particular, for the same value of ΔP_L, patients who presented higher values of ΔP_{es} experienced a higher NIV failure rate. This mechanism alongside a Vt of more than 6 ml, high breathing frequency and elevated mechanical power should be considered critical for SILI. These results highlight the potential role of the pendelluft phenomenon and negative pressure alveolar edema in determining SILI. Recently, in a rat model of acute lung injury, Henzler and coworkers showed that ΔP_L was more important than inspiratory effort in generating ventilatory associated lung injury during partial ventilatory support (29). These results are apparently contradictory to those reported in our study, but some issue might have influenced the conclusions. First, the experimental PEEP was set at 5 cmH_2O which, in a murine model, is comparable to higher levels in larger animals, producing a sort of recruitment favoring a fluid-like behavior of the lung and reducing the harmful role of SB (25). Second, the animals ventilated with a lower level of support presented hypercapnic acidosis that

might have mitigated the ventilatory-associated lung injury. Furthermore, in our study we have assessed the $Vte/\Delta P_L$ as a surrogate of lung compliance in order to explore the concept of baby lung during NIV. Data show an inverse linear correlation between $Vte/\Delta P_L$ and inspiratory effort (Figure E4, supplementary material). Moreover, the time course of this index resulted different between those who succeeded the 24 hours NIV trial as compared to those who failed (Figure E2, panel C, supplementary material). Thus, this might justify the discrepancies in the behavior of Vte and inspiratory effort. Although not significantly associated with NIV failure this index deserves further investigations in larger physiological trials.

Limitations of the study

Our study has several limitations. First, the number of patients might have underpowered the results obtained. In particular, the value of ΔP_{es} changes < 10 cmH_2O should be confirmed in larger trials. Second, our study population was highly selected influencing the generalization of our results. In particular, none of the patients who were successful in the 24-hour trial required further intubation thus indicating that patients were enrolled very early in the course of the disease. Third, we did not carry out any assessment of inflammatory biomarkers. The determination of cytokine levels might clarify the role of vigorous inspiratory effort in exaggerating lung injury. Moreover, as patients were studied during spontaneous breathing, what we measured was dynamic P_L, thus the influence of the inspiratory and expiratory resistances on the measured pressures should be considered. Furthermore, we did not perform gastric pressure assessment, so ΔP_{es} values may have been overestimated in the case of expiratory muscle recruitment. Finally, despite the fact that our study identifies ΔP_{es} changes as the major and early physiological predictor of NIV failure, the evaluation of a composite parameter that takes into account the various components of the respiratory drive (including minute ventilation, respiratory rate, inspiratory flow rate and P0.1) as a bundle, might be of relevant clinical importance and should be assessed in further multicenter trials.

At this time, we believe that this technique produces highly reliable data if managed in centers with expertise in esophageal manometry. Notwithstanding this, an increase in its use should raise the level of confidence in daily clinical practice.

Conclusion

Even with the limitations described, our study highlights new concepts which can be summarized as follows: 1) patients with severe AHRF undergoing NIV may achieve harmful dynamic transpulmonary pressure levels, 2) the magnitude of inspiratory effort during NIV is the earliest and most accurate parameter that predicts failure, 3) the amount of inspiratory effort is not correlated with oxygenation, therefore PaO_2/FiO_2 ratio cannot be used as a surrogate of ΔP_{es}, 4) the significant correlation between ΔP_{es} changes within the first 2 hours of NIV and radiographic progression at 24 hours suggest that SILI might be a potential mechanism of lung damage in these patients.

In the hypothesis of SILI as a critical factor affecting NIV failure in patients with AHRF, we found that the magnitude of inspiratory effort as assessed by ΔP_{es} variation within the first 2 hours of NIV treatment is an early and accurate predictor of outcome at 24 hours. The clinical implications of our study suggest that monitoring esophageal pressure might help clinicians in the making decision process (airway intubation) for patients with AHRF undergoing a NIV trial. Due to the exploratory nature of this study, findings should be confirmed in multicenter clinical trials.

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Figure legends

Fig. 1. Flow chart for patients in this study.

Fig. 2. (A) ΔP_{es} changes from baseline within the first 2 hours of NIV for the whole population and according to NIV outcome at 24 hours. (B) ΔP_{L} changes from baseline within the first 2 hours of NIV for the whole population and according to NIV outcome at 24 hours.

Fig. 3. Graphical representation of ΔP_{L} and ΔP_{es} waveform swings after 2 hours of NIV for a patient who failed the NIV trial at 24 hours (panels A and C) and for a patient who was successful (panels B and D). The beginning of the inspiratory phase was identified at the time of P_{es} initial decay, while the end of inspiration was considered at the point of P_{es} that elapsed 25% of time from its maximum deflection to return to baseline.

Fig. 4. Receiver operating characteristic (ROC) analysis. ΔP_{es} changes < 10 cmH_2O within the first 2 hours of NIV showed a high accuracy in predicting NIV failure (AUC=0.97, $p<0.0001$).

Tables

Table 1. Baseline features of the study population presented as a whole or as NIV outcome at 24 hours

Feature	Overall	NIV failure	NIV success	p
Number of patients	30	12	18	
Age, years (IQR)	71 (66–81)	69 (62–80)	71 (68–81)	0.7
Male, n (%)	20 (67)	8 (67)	12 (67)	>0.9
BMI, kg/m^2 (IQR)	23 (19–27)	22.5 (18–26)	24 (21–27)	0.3
Charlson index, score (IQR)	4 (3–5.5)	4 (3–5)	4.5 (3–6)	0.6
Pneumonia, n (%)	13 (23)	5 (42)	8 (44)	>0.9
ARDS, n (%)	15 (50)	7 (58)	8 (44)	0.7
Kelly scale, score (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	0.4
APACHE II, score (IQR)	27 (21–38)	24.5 (19–45)	28 (25–37)	0.8
SAPS II, score (IQR)	36 (26–41)	36 (31–38)	36 (25–44)	0.6
SOFA, score (IQR)	6 (4–8.8)	5.5 (3–8)	6.5 (4–9)	0.6
PaO_2/FiO_2, mmHg (IQR)	125 (101–170)	118 (100–141)	133 (111–144)	0.5
pH, value (IQR)	7.48 (7.44–7.51)	7.49 (7.46–7.52)	7.48 (7.44–7.5)	0.2
$PaCO_2$, mmHg (IQR)	35 (30–40)	34 (30–37)	36 (30–42)	0.2
Blood lactate, mg/dl (IQR)	27 (14–40)	30 (18–40)	25 (12–40)	0.7
Serum creatinine, mg/dl (IQR)	0.68 (0.5–0.9)	0.6 (0.5–0.7)	0.8 (0.65–0.8)	0.4
PEEP, cmH_2O (IQR)	8 (6.5–10)	8 (7.5–10)	8 (6–10)	0.7
PS, cmH_2O (IQR)	10 (10–14)	11 (10–12)	11 (10–14)	0.3

Data are presented as number (n) and percentage (%) for dichotomous values or median and interquartile range (IQR) for continuous values.

APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; BMI, body mass index; HACOR, Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate; NIV, non-invasive mechanical ventilation; PEEP, positive end expiratory pressure; PS, pressure support; SAPS II, Simplified Acute Physiology Score; SOFA, Subsequent Organ Failure Assessment.

Table 2. Clinical and physiological features of the study population at baseline and after 2 hours of NIV

Feature	Overall	NIV failure	NIV success	p
Baseline RR, bpm (IQR)	36 (27–44))	34 (27–42)	36 (27–45)	0.8
RR after 2 hours of NIV, bpm (IQR)	30 (24–37)	31 (25–37)	30 (24–37)	0.6
Baseline ΔP_L (ΔP_{es}), cmH_2O (IQR)	35 (26–40)	38 (32–42)	32.5 (24–39)	0.1
ΔP_{es} after 2 hours of NIV, cmH_2O (IQR)	19.5 (12–5–31)	31.5 (30–36)	11 (8–15)	<0.0001
ΔP_L after 2 hours of NIV, cmH_2O (IQR)	37 (30–43)	39.5 (37.5–42.3)	30.5 (28–43.5)	0.04
Baseline VE, L/min (IQR)	28.1 (25.6–34.7)	28.3 (25.8–32.3)	27.4 (22.2–28.9)	0.6
VE after 2 hours of NIV, L/min (IQR)	23.3 (18.2–27.3)	27.2 (25–27.8)	19.8 (16.5–25)	0.07
Baseline Vte, ml/kg of PBW (IQR)	11 (9–12)	11 (9.5–12.3)	10.9 (9–11.2)	0.7
Vte after 2 hours of NIV, ml/kg of PBW (IQR)	11 (10–12)	11 (10–12.3)	10.8 (8.5–12)	0.5
Baseline Vte/ΔP_L, ml/Kg/cmH2O (IQR)	0.32 (0-28-0.57)	0.31 (0.29-0.57)	0.33 (0.27-0.4)	0.3
Vte/ΔP_L after 2 hours of NIV, ml/Kg/cmH2O (IQR)	0.31 (0.25-0.39)	0.36 (0.21-0.44)	0.29 (0.26-0.31)	0.1
HACOR score (IQR)	6 (5–8)	6.5 (4.8–8)	6 (6–7)	0.5
HACOR score after 2 hours of NIV (IQR)	6 (5–6)	6 (4.8–6.5)	5.5 (4–6)	0.4

Data are presented as number and percentage for dichotomous values or median and interquartile range (IQR) for continuous values.

HACOR, Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate; NIV, non-invasive mechanical ventilation; PBW, predicted body weight; ΔP_{es}, change in esophageal pressure; ΔP_L, change in dynamic transpulmonary pressure; RR, respiratory rate; VE, minute ventilation; Vte, expiratory tidal volume, Vte/ΔP_L, expiratory tidal volume on transpulmonary pressure ratio.

Table 3. Association between physiological and clinical variables and NIV failure at 24 hours

Feature	OR	95%CI	p
ΔP_{es} < 10 cmH_2O post 2h NIV	15	2.8–110	0.001
Vte > 9.5 ml/kg of PBW	7.9	1.5–72	0.02
HACOR score > 5 post 2h NIV	6.3	0.9–49	0.046
RR > 30 bpm	5.5	0.8–112	0.14
PaO_2/FiO_2 < 150 mmHg	2	0.5–9.8	0.4
Vte/ΔP_L < 0.33 ml/Kg/cmH2O	2	0.4-9.8	0.36

Data are presented as odds ratio and 95%CI.

OR, odds ratio; NIV, non-invasive mechanical ventilation; PBW, predicted body weight; ΔP_{es}, change in esophageal pressure; RR, respiratory rate; Vte, expiratory tidal volume, Vte/ΔP_L, expiratory tidal volume on transpulmonary pressure ratio.

Supplementary material

Figure E1. Time course assessment through ANOVA analysis of ΔP_{es} (panel A), ΔP_L (panel B), and $\Delta P_{es}/\Delta P_L$ (panel C) for patients who failed and who were successful in the 24-hour NIV trial.

Figure E2. Time course assessment through ANOVA analysis of Vte/kg of PBW (panel A), VE (panel B), and Vte/ΔP_L panel C) for patients who failed and who were successful in the 24-hour NIV trial .

Figure E3. Time course assessment through ANOVA analysis of RR (panel A), PaO_2/FiO_2 ratio (panel B), and HACOR score (panel C) for patients who failed and who were successful in the 24-hour NIV trial.

Figure E4. Correlation between ΔP_{es} and Vte/ΔP_L values on admission (r=-0.77, p<0.0001).

Figure E5. Correlation between ΔP_{es} and PaO_2/FiO_2 ratio (panel A, r=–0.01, p=0.9), RR (panel B, r=0.23, p=0.2), HACOR score (panel C, r=0.05, p=0.8), and Vte/kg of PBW (panel D, r=–0.05, p=0.8) on admission.

Figure E6. Correlation assessed through Pearson's correlation coefficient between ΔP_{es} changes 2 hours after NIV start and radiographic changes on chest X-ray assessed at 24 hours. Colored panels correspond to categories of radiographic change as assessed by the radiologist (from left to right: relevant worsening, worsening, mild worsening, unmodified, mild improvement, improvement, relevant improvement).

Figure E7. Probability to die at 30 days from admission according to the reduction of ΔP_{es} within the first 2 hours after NIV start.

Table E1. Sensitivity and specificity table derived from ROC analysis of ΔP_{es} changes after 2 hours of NIV on NIV failure.

Table E2. Sensitivity and specificity table derived from ROC analysis of baseline $Vte/\Delta P_L$ on NIV failure.

Inspiratory effort assessment by esophageal manometry early predicts noninvasive ventilation outcome in de novo respiratory failure: a pilot study

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Key words: *acute respiratory distress syndrome, respiratory failure, non-invasive mechanical ventilation, transpulmonary pressure, esophageal pressure swings*

Abbreviations: ARDS, acute respiratory distress syndrome; ARFCCI, chronic critical illness; MV, invasive mechanical ventilation; NIV, non-invasive mechanical ventilation

At a Glance Commentary

Scientific Knowledge on the Subject. Non-invasive mechanical ventilation (NIV) is becoming increasingly used to assist spontaneous breathing during acute hypoxic de novo respiratory failure (AHRF), even though its potential therapeutic effect in this setting is controversial. Reported data show that NIV is used in 15% of patients with acute respiratory distress syndrome (ARDS) irrespective of the severity of respiratory failure and it seems to be associated with higher mortality in the case of failure. Several predictors of NIV failure in AHRF have been investigated but were found to be insufficient to aid the timing of endotracheal intubation. Thus, there is a need for an early robust predictor of NIV failure to avoid intubation delay.

What This Study Adds To The Field. Our exploratory study shows that, in patients with moderate to severe AHRF who were candidates for a 24-hour NIV trial, the magnitude of inspiratory effort relief was an early and accurate predictor of NIV failure. Our study suggests that monitoring of esophageal pressure might assist clinicians in the timing of intubation for patients with AHRF undergoing a NIV trial.

Abstract

Rationale

The role of inspiratory effort has still to be determined as~~Among the~~ a potential predictors of non-invasive mechanical ventilation (NIV) failure in acute hypoxic de novo respiratory failure (AHRF)~~, the precise role of inspiratory effort has to be determined~~.

Objectives

We explore the hypothesis that~~, in patients with AHRF undergoing a NIV trial,~~ inspiratory effort might be a major determinant of NIV failure in these patients.

Methods

Thirty consecutive patients with AHRF admitted to ~~the Respiratory Intensive Care Unit of a~~a single center and candidates for a 24-hour NIV trial were enrolled ~~in this study~~. Clinical features, tidal changes in esophageal (ΔP_{es}) and dynamic transpulmonary pressure (ΔP_L), expiratory tidal volume, and respiratory rate were recorded on admission and 2~~, ~~4~~, ~~12~~, and ~~24 hours after NIV start, and were tested for correlation with ~~NIV outcome and chest X-ray at 24 hours~~outcomes.

Measurements and Main Results

ΔP_{es} and $\Delta P_{es}/\Delta P_L$ ~~ratios~~ were significantly lower 2 hours after NIV start in ~~those~~ patients who successfully completed the NIV trial (n=18) compared to those who ~~failed~~ needed endotracheal intubation (n=12) [median=11 (IQR=8–15) cmH_2O vs 31.5 (30–36) cmH_2O, p<0.0001 ~~and 0.71 (0.78–0.86) vs 0.35 (0.43–0.50), p<0.0001, respectively~~] while other variables differed later. ΔP_{es} was not related to other predictors of NIV failure at baseline. ~~A significant correlation was found between ΔP_{es} variation within the first 2 hours of NIV and chest X-ray worsening (p=0.0035).~~ NIV-induced reduction in ΔP_{es} ~~changes <~~of 10 cmH_2O or more ~~within the first~~after 2 hours of ~~NIV were~~treatment was ~~stronger~~ strongly associated to avoidance of intubation, and represented the most accurate

predictor of treatment success~~and more accurate predictors of NIV failure among those tested~~ (OR=15, 95%CI 2.8-110, p=0.001, AUC=0.97, 95%CI 0.91–1, p<0.0001).

Conclusions

The magnitude of inspiratory effort relief as assessed by ΔP_{es} variation within the first 2 hours of NIV was an early and accurate predictor of NIV outcome at 24 hours.

Number of words in Abstract: ~~280~~232

Key words: *acute respiratory distress syndrome, respiratory failure, non-invasive mechanical ventilation, transpulmonary pressure, esophageal pressure swings*

Introduction

The role of assisted spontaneous breathing (SB) in patients with acute hypoxic de novo respiratory failure (AHRF) is still controversial. When acute lung injury is mild, SB is desirable to preserve respiratory muscle function, improve the ventilation/perfusion ratio and regional ventilation (1), and reduce sedation and days of invasive mechanical ventilation (MV) (2). On the other hand, recent studies have suggested that SB might be a potential mechanism for lung damage if acute respiratory distress is severe (3). In recent years, non-invasive mechanical ventilation (NIV) has been increasingly used to assist SB in the intensive care setting, even though its potential therapeutic effect in AHRF is still debated. It has been reported that NIV is used in 15% of patients with acute respiratory distress syndrome (ARDS) irrespective of the severity of respiratory failure and it seems to be associated with higher mortality when PaO_2/FiO_2 is lower than 150 mmHg (4). Moreover, some studies have shown that NIV failure is associated with increased mortality in patients with AHRF (4,5); however, when NIV treatment is successful, it might considerably reduce the risk of death and length of ICU stay in this subset of patients (5).

Despite the fact that several potential factors associated with NIV failure have been investigated in hypoxic patients, there are no robust predictors that might alert the intensivist to the need for endotracheal intubation (ETI) within the very first hours of ventilation (6). Although the mechanisms behind the association between NIV failure and poorer survival remain unclear, a potential role for SB might be hypothesized. When SB is preserved during AHRF, the intensity of inspiratory effort may follow a critical increase in respiratory drive thus producing uncontrolled swings in transpulmonary pressure (P_L) that would increase the risk of injury to the dependent lung and predispose the patient to the onset of self-inflicted lung injury (SILI) (6). The underlying mechanisms of SILI are heterogeneous and include the pendelluft phenomenon, increased transvascular pressure gradient aggravating alveolar damage, excessive diaphragmatic loading with impaired systemic oxygen

delivery, and muscle injury (3,7–9).

In this study, we explore the hypothesis that, in patients with moderate or severe AHRF undergoing a NIV trial, the excessive spontaneous effort of the patients, measured with esophageal pressure swings (ΔP_{es}), may be a major determinant of NIV failure at 24 hours.

Methods

Study population

This prospective observational cohort study was carried out in a single eight-bed Respiratory Intensive Care Unit (RICU) at the University Hospital of Modena (I) following approval from the Ethics Committee "Area Vasta Emilia Nord" (registered protocol number 4485/C.E., document 266/16). After testing our study hypothesis in 4 patients (pilot data not included in the analysis) during the period October 2016 to December 2018, the study has been registered retrospectively on ClinicalTrial.gov (ID NCT03826797). Thirty consecutive patients were then enrolled in between February and October 2019. Written informed consent to participate in the study and to analyze and divulgate clinical data was obtained from all patients admitted.

Inclusion criteria were age > 18 years and the presence of AHRF with PaO_2/FiO_2 ratio < 200 mmHg despite high-flow nasal oxygen with flow set at 60 L/min, and a candidate to receive a NIV trial according to the attending RICU staff, whose decision was taken upon clinical conditions blinded to the purpose of the study. Patients were excluded in the case of a previously established diagnosis of chronic obstructive pulmonary disease; diagnosed pulmonary embolism; neuromuscular disease; cardiogenic acute pulmonary edema; interstitial lung disease; chest wall deformities; the need for immediate endotracheal intubation (ETI) as represented by any of the following: cardiopulmonary arrest; respiratory arrest; loss of consciousness with respiratory pauses; psychomotor agitation requiring sedation; pH less than 7.20; neurological deterioration or massive secretions;

hemodynamic instability or major electrocardiographic abnormalities; pregnancy; intolerance to NIV; hypercapnic respiratory failure of any etiology ($PaCO_2$ > 45 mmHg); home long-term oxygen therapy; denied informed consent.

~~Study procedures~~

General measures

Demographics and relevant comorbidities were assessed on admission. Clinical severity as assessed by the Kelly Scale, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, the Simplified Acute Physiology Score (SAPS II), the Subsequent Organ Failure Assessment (SOFA) score and the Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate (HACOR) score were assessed and recorded on admission and after 2, 4, 12, and 24 hours. Arterial blood gases (PaO_2-$PaCO_2$), pH, PaO_2/FiO_2 ratio, respiratory rate (RR), and blood lactate values were recorded before NIV start and 2, 4, 12, and 24 hours later. A chest X-ray was taken on admission and 24 hours after NIV start.

Physiological measurements

A multifunctional nasogastric tube with a dedicated pressure transducer (NutriVent™, SIDAM, Mirandola, Italy) was placed before starting NIV. The nasogastric tube was connected to a dedicated monitoring system (OptiVent™, SIDAM, Mirandola, Italy) to record swings in esophageal (P_{es}) and dynamic transpulmonary (P_L) pressures. In order to avoid using absolute values for P_{es} and P_L, we always refer to ΔP_{es} and ΔP_L from the end-expiratory level, respectively (10). Appropriate catheter position was confirmed by visualization of cardiac artifacts on P_{es} traces and radiopaque markers on chest X-rays, and validation of esophageal pressure measurements was obtained through dynamic occlusion tests (11,12). ΔP_{es} was calculated as the negative deflection of P_{es} from the onset of

inspiratory effort. ΔP_L was as the tidal change in transpulmonary pressure, calculated as airway pressure (P_{aw}) minus P_{es} (10).

ΔP_{es}, ΔP_L, and $\Delta P_{es}/\Delta P_L$ ratios were assessed on admission and 2, 4, 12, and 24 hours after NIV start. Initial measurements were performed at each pre-specified time point while the patient was breathing spontaneously through the ventilator circuit. Data were sampled at 100 Hz and processed on a dedicated data acquisition system (OptiVent™, SIDAM, Mirandola, Italy) (12). Data sampling was numerically stored and downloaded via USB stick at each time of assessment. Offline breath-by-breath analysis was then performed for each measurement then averaged by a specific software (Flux View Respiratory Mechanics Monitor (NBMED- Medical Graphics, Milano, Italy). For all the measurements the beginning of the inspiratory phase was identified at the instant of P_{es} initial decay while the end of inspiration considered at the point of P_{es} that elapsed 25% of time from its maximum deflection to return to baseline.

Respiratory flow was measured by an external heated Fleisch No. 2 pneumotachograph (Fleisch, Lausanne, Switzerland) inserted between the patient's oronasal facemask (Bluestar™, KOO Medical Equipment, Shanghai, PRC) and a connector with a side port for mechanical measurement. Expiratory tidal volume (Vte) was obtained by numerical integration of the flow signal. Vte was then adjusted to the predicted body weight (PBW) to derive Vte/kg of PBW. Vte/kg of PBW was assessed on admission and 2, 4, 12 and 24 hours after NIV start. Minute ventilation (VE) was calculated as the product of Vte and RR and assessed on admission and 2, 4, 12 and 24 hours after NIV start. $Vte/\Delta P_L$ was further measured at each pre-defined time point.

Leaks from the oronasal facemask were computed using dedicated ventilator-integrated software (GE Healthcare Engstrom Carestation™, GE Healthcare, Finland) based on the equation: leaks (L/min) = (inspiratory Vt – expiratory Vt) x RR.

All measurements were performed during a stable spontaneous breathing pattern of 5 minutes and results were averaged for each assessment step.

NIV treatment

After Nutrivent™ placement, NIV was started and set by a respiratory physician with expertise in Respiratory Intensive Care. Patients were connected via a conventional circuit with an appropriately sized oronasal facemask equipped with a dedicated output for probes (Bluestar™, KOO Medical Equipment, Shanghai, PRC) to a high-performance ventilator (GE Healthcare Engstrom Carestation™, GE Healthcare, Finland) in pressure support pre-set mode. Heat and moisture exchanger (HME) (HYGROBAC, DAR, Mirandola, Italy) was placed to the ventilator circuit's Y-piece. Positive end expiratory pressure (PEEP) was initially set at 6 cmH2O, and subsequently fine-tuned (4–8 cmH2O) in order to target a SatO2 > 92% with a delivered FiO2 less than 70%. Pressure support (PS) was set at 10 cmH_2O, and then progressively modified, according to tidal volume (Vte/kg of PBW), in order to target a Vte/kg of PBW lower than 9.5 ml/kg of PBW and a RR lower than 30 breaths/min. The oronasal facemask was finely adjusted to target a leak flow lower than 20 L/min. The inspiratory trigger was set at 3 L/min and respiratory cycling was set at 25% of the inspiratory peak flow. Great care was taken by the nurses in charge of NIV, and who were blinded to the protocol, to avoid any possible air leaks. The inspiratory fraction of oxygen delivered (FiO_2) was increased to target a transcutaneous oxyhemoglobin saturation of 88–94%. Setting was adjusted by the attending physician blinded to the study purpose and based on blood gases and/or continuous oxymetry assessment. Patients receiving NIV treatment were not sedated. The decision as to whether to proceed to ETI at 24 hours after NIV start was taken according to best clinical practice by the attending RICU staff, blinded to the results of the physiological assessment acquired through the Optivent™ monitor only at each pre-defined time point. NIV failure was defined by the onset of

the need for ETI or by death. Criteria for ETI included: (a) PaO_2/FiO_2 ratio unchanged or worsened or below 150 mmHg, (b) the need to protect airways due to neurological deterioration or massive secretions, (c) hemodynamic instability or major electrocardiographic abnormalities, (d) unchanged or worsened dyspnea and persistence of respiratory distress (RR > 35 bpm, gasping for air, psychomotor agitation requiring sedation, abdominal paradox).

Outcome measures

The influence of ΔP_{es} on NIV failure or success at 24 hours was pre-specified as a primary outcome. The impact of ΔP_L, $\Delta P_{es}/\Delta P_L$ ratio, PaO_2/FiO_2 ratio, RR, Vte/kg of PBW, $Vte/\Delta P_L$, VE and the HACOR score on NIV outcome at 24 hours and the correlation between ΔP_{es} and radiographic changes on chest X-ray within the first 24 hours after NIV start were assessed as secondary outcomes. Radiographic changes on chest X-ray within the first 24 hours after admission were assessed by a radiologist with expertise in chest X-ray and blinded to the purpose of the study. Changes were classified as follows: relevant worsening, worsening, mild worsening, unmodified, relevant improvement, improvement, mild improvement.

Statistical analysis

The statistical package GraphPad Prism 8.0 (GraphPad Software, Inc., La Jolla, CA, USA) was used for statistical analysis. Due to the exploratory nature of the study, no sample size calculation was performed. Descriptive statistics was used to characterize the study population as a whole and according to primary outcome. The nonparametric Mann–Whitney and Student *t* test were used for the comparison of continuous variables. Comparison between dichotomous variables was

performed by the χ^2 test or Fisher's exact test, where appropriate. The time course of ΔP_{es}, ΔP_L, $\Delta P_{es}/\Delta P_L$ ratio, PaO_2/FiO_2 ratio, Vte/kg of PBW, $Vte/\Delta P_L$, RR, VE and HACOR score according to NIV outcome within the first 24 hours of treatment was assessed through ANOVA analysis. Then a post-hoc Bonferroni-Dunn's multiple test was used to perform the pairwise comparison of means for each analyzed variable at the prespecified time points. The correlation between baseline values of ΔP_{es} and PaO_2/FiO_2, Vte, RR, HACOR score, $Vte/\Delta P_L$ and the chest X-ray radiographic categories was assessed through Pearson's correlation coefficient. The impact of ΔP_{es} change within 2 hours after NIV start and baseline value of $Vte/\Delta P_L$ on NIV outcome was assessed through a logistic regression model. A receiver operating characteristic (ROC) analysis was then performed to identify the best predictive cut-off for ΔP_{es} change within 2 hours after NIV start and for baseline $Vte/\Delta P_L$. The association between the best cut-off value of ΔP_{es} change after 2 hours of NIV and baseline $Vte/\Delta P_L$, Vte > 9.5 ml/kg of PBW, RR > 30 bpm, PaO_2/FiO_2 ratio < 150 mmHg and HACOR score > 5 within 2 hours after NIV start on NIV failure at 24 hours was then tested through univariate logistic regression analysis. ROC analysis was used to assess the accuracy in predicting NIV failure at 24 hours for all the analyzed variables at pre-specified cut offs. Then, at 30 days, survival analysis was performed through a log-rank test for ΔP_{es} change within 2 hours after NIV start. A p-value less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

Over the study period, 30 out of 86 consecutive patients admitted for AHRF to the RICU of the University Hospital of Modena (Italy) and who were candidates to receive a NIV trial were enrolled in this study. Of these, 12 patients (40%) experienced NIV failure within 24 hours after NIV start. Those patients for which the need for ETI was defined at 24 hours as the "alert" criterion of our

internal guideline, were thereafter intubated by the RICU staff. Of those who were successful in the 24-hour trial (60%), none were further intubated during their RICU stay. The flow chart for patients in this study is shown in Figure 1.

The general features and clinical characteristics of the whole population at baseline and according to NIV outcome at 24 hours are presented in Table 1. None of the features assessed were significantly different between the two groups of patients (NIV failure vs NIV success) at baseline. In particular, the overall population presented an average value of PaO_2/FiO_2 of 125 (interquartile range [IQR] 101–170) mmHg, which did not differ significantly according to NIV outcome at 24 hours (100 [118–141] mmHg and 111 [132–173]) mmHg, respectively, p=0.5). All patients with ARDS (n=15) presented pulmonary ARDS. In 10 patients, the etiology was identified as infectious (bacterial n=4, fungal n=2, viral n=4) while for 5 patients, no etiological diagnosis was made. Patients with pneumonia had unilateral lung consolidation and 9 of them presented a bacterial infectious cause (*Streptococcus pneumoniae* n=4, intracellular pathogens n=4, *Hemophilus influenzae* n=1). The presence of pneumonia and ARDS was equally distributed between the two groups (42% vs 44% p>0.9, 58% vs 44% p=0.7, respectively).

Physiological measurements and NIV outcome

Table 2 shows the physiological dynamic respiratory mechanics for the whole population at baseline and in the NIV outcome subgroups at baseline and after 2 hours of NIV. At baseline, the median value of ΔP_{es} was 34 (26–40) cmH_2O. Of note, none of the physiological features analyzed were significantly different at baseline between the two groups. After 2 hours of NIV, the median value of ΔP_{es} was significantly lower for those patients who were successful in the 24-hour NIV trial compared to patients who failed (11 [8–15] cmH_2O vs 31.5 [30–36] cmH_2O, p<0.0001). Moreover, these latter patients presented a significantly increased value of ΔP_L once NIV had started compared

to patients who experienced NIV success at 24 hours (39.5 [37.5–42-3] cmH_2O vs 30.5 [28–43.5] cmH_2O, p=0.04).

Figure 2, panel A shows ΔP_{es} changes from baseline within the first 2 hours of NIV for the whole population and according to NIV outcome at 24 hours. ΔP_{es} decreased significantly after 2 hours of NIV for the whole population and for those patients who were successful in the NIV trial, whereas it did not change for patients who experienced NIV failure. Moreover, only these latter patients presented a significant increase in ΔP_L after 2 hours of NIV (Figure 2, panel B).

Waveform analysis of ΔP_L and ΔP_{es} swings 2 hours after NIV start is displayed in Figure 3, for a patient who failed the 24-hour NIV trial (panels A and C) and for a patient who succeeded (panels B and D). The time course of the physiological and clinical variables (ΔP_{es}, ΔP_L, $\Delta P_{es}/\Delta P_L$, RR, PaO_2/FiO_2 ratio, HACOR score, Vte/kg of PBW, $Vte/\Delta P_L$, and VE) in the two categories of patients according to NIV outcome showed a significant improvement over time in patients who were successful in the NIV trial. Moreover, only ΔP_{es} significantly decreased earlier (2 hours after NIV start) in those patients who were successful in the NIV trial compared to those who failed (p<0.0001, Figure E1A, supplementary material). The ratio between ΔP_{es} and ΔP_L was significantly different 2 hours after NIV start between the two groups (p<0.0001, Figure E1C, supplementary material), while ΔP_L (p=0.04, Figure E1B, supplementary material), Vte/kg of PBW, VE, $Vte/\Delta P_L$ (p=0.01, p=0.01, and p=0.001, Figure E2, panel A, B, C, respectively, supplementary material), RR, PaO_2/FiO_2, HACOR score (p=0.02, p<0.0001, and p=0.03, Figure E3, panel A, B, C, respectively, supplementary material) were all significantly different more than 2 hours after NIV start.

Significant inverse correlation was found between baseline ΔP_{es} and $Vte/\Delta P_L$ (r=-077, p<0.0001, Figure E4 supplementary material). No significant correlation was found between baseline ΔP_{es} and PaO_2/FiO_2 ratio (r=–0.01, p=0.9, Figure E5, panel A supplementary material), RR (r=0.23, p=0.2, Figure E5, panel B supplementary material), HACOR score (r=0.05, p=0.8, Figure E5, panel C

supplementary material), and Vte/kg of PBW (r=–0.05, p=0.8, Figure E5, panel D supplementary material).

Radiological changes and inspiratory effort

The correlation analysis performed for radiographic changes showed that patients with a greater reduction in ΔP_{es} 2 hours after NIV start experienced more consistent improvements on chest X-ray at 24 hours, whereas patients with a limited reduction of ΔP_{es} were those who showed a deterioration on chest X-ray (Figure E6, supplementary material).

Inspiratory effort and clinical outcome

In the logistic regression model, ΔP_{es} changes within the first 2 hours of NIV showed a significant association with NIV failure at 24 hours (odds ratio [OR]=1.7, 95%CI 1.2–3, p=0.01) while baseline Vte/ΔP_L was not significantly associated with NIV outcome (p=.03). From ROC analysis, ΔP_{es} changes < 10 cmH_2O gave the most accurate cut-off value for prediction of NIV failure (sensitivity 0.91 95%CI 0.65–1, specificity 0.83 95%CI 0.61–0.94, likelihood ratio=5.5, positive predictive value=0.79, 95%CI 0.52–0.92, negative predictive value=0.94 95%CI 0.72–1, Table E1, supplementary material); Vte/ΔP_L < 0.33 ml/Kg/cmH2O showed the best cut-off value for prediction of NIV failure (sensitivity 0.67 95%CI 0.40–0.86, specificity 0.5 95%CI 0.29–0.71, likelihood ratio=1.3, positive predictive value=0.47, 95%CI 0.26–0.7, negative predictive value=0.7 95%CI 0.42–87, Table E2, supplementary material. When univariate logistic regression was applied to the pre-specified potential predictors of NIV failure, ΔP_{es} changes < 10 cmH_2O showed the highest association with NIV failure at 24 hours (OR=15 95%CI 2.8–110, p=0.001). Among the other predictors tested, Vte > 9.5 ml/kg of PBW and HACOR > 5 after 2 hours of NIV were significantly associated with NIV failure at 24 h (OR=7.9 95%CI 1.5–72, p=0.02 and OR=6.3 95%CI 0.9–49, p=0.046, respectively) while RR > 30 bpm, PaO_2/FiO_2 ratio

< 150 mmHg and Vte/ΔP_L < 0.33 ml/Kg/cmH2O, although strongly associated, did not reach statistical significance (Table 3). From ROC analysis, ΔPes changes < 10 cmH_2O within the first 2 hours after NIV start showed higher accuracy in predicting NIV failure (AUC=0.97 95%CI 0.91–1, p<0.0001) (Figure 4) than baseline Vte > 9.5 ml/kg of PBW, HACOR score > 5, RR > 30 bpm, PaO_2/FiO_2 ratio < 150 mmHg and Vte/ΔP_L < 0.33 ml/Kg/cmH2O (AUC=0.88 95%CI 0.76–0.99, p=0.0005, AUC=0.85 95%CI 0.71–0.99, p=0.00, AUC=0.83 95%CI 0.67–0.98, p=0.003, AUC=0.74 95%CI 0.56–0.92, p=0.03, AUC= 0.58 95%CI 0.37-0.8, p=0.44, respectively).

Kaplan–Meier curves showed a significant increase in 30-day mortality among patients with ΔP_{es} reduction < 10 cmH_2O within the first 2 hours after NIV start compared to patients with a more consistent early improvement (HR=4.5 95%CI 1.01–17.9, p=0.048, Figure E7 supplementary material).

Discussion

In this exploratory study, patients with moderate to severe AHRF undergoing a NIV trial presented a median baseline value for ΔP_{es} of 34 cmH_2O that was significantly reduced within the first 2 hours of ventilation in patients who were successful in the NIV trial, while those patients failing NIV did not have a significantly reduced ΔP_{es}. This study therefore shows that a significant ΔP_{es} reduction within the first 2 hours of NIV start was an early and accurate predictor of NIV outcome and was significantly correlated with radiographic changes after 1 day of NIV. Moreover, the magnitude of inspiratory effort at baseline did not show a significant correlation with the severity of respiratory failure, tidal volume, RR, and HACOR score on admission.

Physiological measurements and NIV outcome

Early prediction of NIV failure in ~~moderate to severe~~ AHRF

The application of NIV in treating patients with AHRF is a controversial issue and it is currently used

in clinical practice irrespective of the severity of PaO_2/FiO_2. Despite the initial promising results on the effectiveness of NIV in patients with hypoxic respiratory failure (13,14), more recent studies focusing on patients with AHRF and excluding underlying chronic respiratory diseases or cardiogenic pulmonary edema warn of the increased mortality rates once ETI is delayed (5,15,16). Despite the fact that failure rates can exceed 60% in patients with more severe AHRF, successful application of NIV is independently associated with survival and shorter length of ICU stay (5). Giving these assumptions, it seems of critical interest to identify early predictors of NIV failure in order to avoid deleterious intubation delay in this subset of patients.

Previous studies have shown that several factors (i.e. higher severity score on admission, older age, ARDS or pneumonia as the etiology for acute respiratory failure, or a lack of improvement in blood gas exchange within 1 hour of treatment) are associated with NIV failure in patients with AHRF, although these were insufficient to influence ETI timing (17). In our study, all of these factors were not different in patients who failed the 24-hour NIV compared to patients who were successful in the trial. In a recent single-center study, Duan and coworkers developed and validated the HACOR score for prediction of NIV failure in patients with AHRF, showing that patients with a HACOR score greater than 5 after the first hour of NIV were at greater risk for NIV failure and, if switched to invasive mechanical ventilation (MV) within the first 12 hours, presented reduced in-hospital mortality (18). In our study, the HACOR score was significantly associated with increased NIV failure but not as early as ΔP_{es}. Moreover, both groups of patients presented a HACOR score greater than 5 after the first 2 hours of NIV. Two recent studies have demonstrated that moderate-to-severe hypoxemia significantly affects NIV outcome in patients with ARDS-induced AHRF (19,20). Our study presented a carefully selected population of patients with moderate to severe AHRF, whose average PaO_2/FiO_2 was 132 mmHg and in whom significant differences between those who were successful in the NIV trial compared to those who were subjected to ETI did not become evident until 12 hours

after the start of NIV. Of interest, the inspiratory effort at baseline as expressed by ΔP_{es} did not show a significant correlation with the severity of respiratory failure. These findings are in line with data reported in a recent physiological study by Grieco et al. where ΔP_e was unrelated to oxygenation impairment during helmet NIV and high flow oxygen treatment (21). Our data further underline the inability of PaO_2/FiO_2 ratio alone to identify patients with harmful respiratory drive.

In a recent trial, Carteaux and coworkers showed that a Vte value greater than 9.5 mL/kg was independently associated with NIV failure in patients with AHRF (22) suggesting a role of high Vte as a potential predictor of NIV failure in this setting (19). The results from our study are in line with their reported data although significant differences in Vte between patients who failed the NIV treatment and those who were successful became evident 12 hours after NIV start. Moreover, the magnitude of inspiratory effort was not correlated with average Vte at baseline. Considering these data, the inability to apply protective ventilation should be considered a critical mechanism of NIV failure in this subset of patients.

The main result from our study was that a change in ΔP_{es} less than 10 cmH_2O within the first 2 hours after NIV start was an early and accurate predictor of NIV failure at 24 hours when compared to other variables, such as PaO_2/FiO_2, Vte, HACOR, and RR. From a clinical point of view, these data might suggest that, in patients with moderate to severe AHRF, the effectiveness of a NIV trial should be related to the reduction in the patient's inspiratory effort, quantifiable through esophageal manometry. The consequences of this reduction translate into a subsequent significant reduction of Vte, a decrease in RR, and an improvement in PaO_2/FiO_2 with a few hours latency. Moreover, the correlation analysis showed that ΔP_{es} on admission was not associated with the baseline value of other predictors of NIV failure.

Radiological changes and inspiratory effort

Inspiratory effort and self-inflicted lung injury during NIV

Our results showed a significant correlation between ΔP_{es} changes within the first 2 hours of NIV and radiographic progression at 24 hours. Despite being less accurate than a computed tomography scan, chest X-ray showed good sensitivity in detecting lung alteration in patients with ARDS (23) and might be considered reliable in the evaluation of the extent and distribution of lung opacities, once a diagnosis has already been made (24).

The results of our study support the hypothesis that inspiratory effort might be a potential mechanism of lung damage enhancement if acute respiratory distress is severe. Although data from animal models indicate ΔP_L as a major determinant of SILI, experimental studies conducted on normal trained subjects during exhausting endurance exercise demonstrated that potentially injurious values of ΔP_L (up to 52 cmH_2O) did not translate into lung mechanical changes (25,26). To understand this, we have to consider that, in normal fluid-like lung, the inspiratory swing in pleural pressure produced by inspiratory effort is homogeneously distributed across the pleural surface. In contrast, in injured solid-like lung, the inspiratory pleural swing is not uniformly dissipated, resulting in a more negative deflection in the dependent lung zones with tidal over-recruitment and local overstretch (6). More recently, two trials investigating the role of assisted SB in mechanically ventilated patients showed that SB was not associated with poorer outcome when compared to controlled MV (27,28), but they lacked assessment of the inspiratory effort. Our results might suggest that a major determinant in generating lung stress lies in the dynamic component of the inspiratory effort rather than in the absolute value of the pressure generated. Interestingly, within the first 2 hours of NIV, $\Delta P_{es}/\Delta P_L$ was different in those who were successful in the NIV trial compared to those who failed it. This ratio might express to what extent dynamic ΔP_L is affected by the patient's respiratory drive and might introduce a new insight in the understanding of SILI. In particular, for the same value of ΔP_L, patients who presented higher values of ΔP_{es} experienced a higher NIV failure rate. This mechanism alongside a Vt of more than 6 ml, high breathing frequency

and elevated mechanical power should be considered critical for SILI. These results highlight the potential role of the pendelluft phenomenon and negative pressure alveolar edema in determining SILI. Recently, in a rat model of acute lung injury, Henzler and coworkers showed that ΔP_L was more important than inspiratory effort in generating ventilatory associated lung injury during partial ventilatory support (29). These results are apparently contradictory to those reported in our study, but some issue might have influenced the conclusions. First, the experimental PEEP was set at 5 cmH_2O which, in a murine model, is comparable to higher levels in larger animals, producing a sort of recruitment favoring a fluid-like behavior of the lung and reducing the harmful role of SB (25). Second, the animals ventilated with a lower level of support presented hypercapnic acidosis that might have mitigated the ventilatory-associated lung injury. Furthermore, in our study we have assessed the $Vte/\Delta P_L$ as a surrogate of lung compliance in order to explore the concept of baby lung during NIV. Data show an inverse linear correlation between $Vte/\Delta P_L$ and inspiratory effort (Figure E4, supplementary material). Moreover, the time course of this index resulted different between those who succeeded the 24 hours NIV trial as compared to those who failed (Figure E2, panel C, supplementary material). Thus, this might justify the discrepancies in the behavior of Vte and inspiratory effort. Although not significantly associated with NIV failure this index deserves further investigations in larger physiological trials.

Limitations of the study

Our study has several limitations. First, the number of patients might have underpowered the results obtained. In particular, the value of ΔP_{es} changes < 10 cmH_2O should be confirmed in larger trials. Second, our study population was highly selected influencing the generalization of our results. In particular, none of the patients who were successful in the 24-hour trial required further intubation thus indicating that patients were enrolled very early in the course of the disease. Third, we did not carry out any assessment of inflammatory biomarkers. The determination of cytokine

levels might clarify the role of vigorous inspiratory effort in exaggerating lung injury. Moreover, as patients were studied during spontaneous breathing, what we measured was dynamic P_L, thus the influence of the inspiratory and expiratory resistances on the measured pressures should be considered. Furthermore, we did not perform gastric pressure assessment, so ΔP_{es} values may have been overestimated in the case of expiratory muscle recruitment. Finally, despite the fact that our study identifies ΔP_{es} changes as the major and early physiological predictor of NIV failure, the evaluation of a composite parameter that takes into account the various components of the respiratory drive (including minute ventilation, respiratory rate, inspiratory flow rate and P0.1) as a bundle, might be of relevant clinical importance and should be assessed in further multicenter trials. At this time, we believe that this technique produces highly reliable data if managed in centers with expertise in esophageal manometry. Notwithstanding this, an increase in its use should raise the level of confidence in daily clinical practice.

~~***Study key messagesConclusion***~~

Even with the limitations described, our study highlights new concepts which can be summarized as follows: 1) patients with severe AHRF undergoing NIV may achieve harmful dynamic transpulmonary pressure levels, 2) the magnitude of inspiratory effort during NIV is the earliest and most accurate parameter that predicts failure, 3) the amount of inspiratory effort is not correlated with oxygenation, therefore PaO_2/FiO_2 ratio cannot be used as a surrogate of ΔP_{es}, 4) the significant correlation between ΔP_{es} changes within the first 2 hours of NIV and radiographic progression at 24 hours suggest that SILI might be a potential mechanism of lung damage in these patients.

~~***Conclusion***~~

In the hypothesis of SILI as a critical factor affecting NIV failure in patients with AHRF, we found that the magnitude of inspiratory effort as assessed by ΔP_{es} variation within the first 2 hours of NIV

treatment is an early and accurate predictor of outcome at 24 hours. The clinical implications of our study suggest that monitoring esophageal pressure might help clinicians in the making decision process (airway intubation) for patients with AHRF undergoing a NIV trial. Due to the exploratory nature of this study, findings should be confirmed in multicenter clinical trials.

Acknowledgments

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Figure legends

Fig. 1. Flow chart for patients in this study.

Fig. 2. (A) ΔP_{es} changes from baseline within the first 2 hours of NIV for the whole population and according to NIV outcome at 24 hours. (B) ΔP_{L} changes from baseline within the first 2 hours of NIV for the whole population and according to NIV outcome at 24 hours.

Fig. 3. Graphical representation of ΔP_{L} and ΔP_{es} waveform swings after 2 hours of NIV for a patient who failed the NIV trial at 24 hours (panels A and C) and for a patient who was successful (panels B and D). The beginning of the inspiratory phase was identified at the time of P_{es} initial decay, while the end of inspiration was considered at the point of P_{es} that elapsed 25% of time from its maximum deflection to return to baseline.

Fig. 4. Receiver operating characteristic (ROC) analysis. ΔP_{es} changes < 10 cmH_2O within the first 2 hours of NIV showed a high accuracy in predicting NIV failure (AUC=0.97, p<0.0001).

Tables

Table 1. Baseline features of the study population presented as a whole or as NIV outcome at 24 hours

Feature	Overall	NIV failure	NIV success	p
Number of patients	30	12	18	
Age, years (IQR)	71 (66–81)	69 (62–80)	71 (68–81)	0.7
Male, n (%)	20 (67)	8 (67)	12 (67)	>0.9
BMI, kg/m^2 (IQR)	23 (19–27)	22.5 (18–26)	24 (21–27)	0.3
Charlson index, score (IQR)	4 (3–5.5)	4 (3–5)	4.5 (3–6)	0.6
Pneumonia, n (%)	13 (23)	5 (42)	8 (44)	>0.9
ARDS, n (%)	15 (50)	7 (58)	8 (44)	0.7
Kelly scale, score (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	0.4
APACHE II, score (IQR)	27 (21–38)	24.5 (19–45)	28 (25–37)	0.8
SAPS II, score (IQR)	36 (26–41)	36 (31–38)	36 (25–44)	0.6
SOFA, score (IQR)	6 (4–8.8)	5.5 (3–8)	6.5 (4–9)	0.6
PaO_2/FiO_2, mmHg (IQR)	125 (101–170)	118 (100–141)	133 (111–144)	0.5
pH, value (IQR)	7.48 (7.44–7.51)	7.49 (7.46–7.52)	7.48 (7.44–7.5)	0.2
$PaCO_2$, mmHg (IQR)	35 (30–40)	34 (30–37)	36 (30–42)	0.2
Blood lactate, mg/dl (IQR)	27 (14–40)	30 (18–40)	25 (12–40)	0.7
Serum creatinine, mg/dl (IQR)	0.68 (0.5–0.9)	0.6 (0.5–0.7)	0.8 (0.65–0.8)	0.4
PEEP, cmH_2O (IQR)	8 (6.5–10)	8 (7.5–10)	8 (6–10)	0.7
PS, cmH_2O (IQR)	10 (10–14)	11 (10–12)	11 (10–14)	0.3

Data are presented as number (n) and percentage (%) for dichotomous values or median and interquartile range (IQR) for continuous values.

APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; BMI, body mass index; HACOR, Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate; NIV, non-invasive mechanical ventilation; PEEP, positive end expiratory pressure; PS, pressure support; SAPS II, Simplified Acute Physiology Score; SOFA, Subsequent Organ Failure Assessment.

Table 2. Clinical and physiological features of the study population at baseline and after 2 hours of NIV

Feature	Overall	NIV failure	NIV success	p
Baseline RR, bpm (IQR)	36 (27–44))	34 (27–42)	36 (27–45)	0.8
RR after 2 hours of NIV, bpm (IQR)	30 (24–37)	31 (25–37)	30 (24–37)	0.6
Baseline ΔP_L (ΔP_{es}), cmH_2O (IQR)	35 (26–40)	38 (32–42)	32.5 (24–39)	0.1
ΔP_{es} after 2 hours of NIV, cmH_2O (IQR)	19.5 (12–5–31)	31.5 (30–36)	11 (8–15)	<0.0001
ΔP_L after 2 hours of NIV, cmH_2O (IQR)	37 (30–43)	39.5 (37.5–42.3)	30.5 (28–43.5)	0.04
Baseline VE, L/min (IQR)	28.1 (25.6–34.7)	28.3 (25.8–32.3)	27.4 (22.2–28.9)	0.6
VE after 2 hours of NIV, L/min (IQR)	23.3 (18.2–27.3)	27.2 (25–27.8)	19.8 (16.5–25)	0.07
Baseline Vte, ml/kg of PBW (IQR)	11 (9–12)	11 (9.5–12.3)	10.9 (9–11.2)	0.7
Vte after 2 hours of NIV, ml/kg of PBW (IQR)	11 (10–12)	11 (10–12.3)	10.8 (8.5–12)	0.5
Baseline $Vte/\Delta P_L$, ml/Kg/cmH2O (IQR)	0.32 (0-28-0.57)	0.31 (0.29-0.57)	0.33 (0.27-0.4)	0.3
$Vte/\Delta P_L$ after 2 hours of NIV, ml/Kg/cmH2O (IQR)	0.31 (0.25-0.39)	0.36 (0.21-0.44)	0.29 (0.26-0.31)	0.1
HACOR score (IQR)	6 (5–8)	6.5 (4.8–8)	6 (6–7)	0.5
HACOR score after 2 hours of NIV (IQR)	6 (5–6)	6 (4.8–6.5)	5.5 (4–6)	0.4

Data are presented as number and percentage for dichotomous values or median and interquartile range (IQR) for continuous values.

HACOR, Heart rate, Acidosis, Consciousness, Oxygenation and Respiratory rate; NIV, non-invasive mechanical ventilation; PBW, predicted body weight; ΔP_{es}, change in esophageal pressure; ΔP_L, change in dynamic transpulmonary pressure; RR, respiratory rate; VE, minute ventilation; Vte, expiratory tidal volume, $Vte/\Delta P_L$, expiratory tidal volume on transpulmonary pressure ratio.

Table 3. Association between physiological and clinical variables and NIV failure at 24 hours

Feature	OR	95%CI	p
ΔP_{es} < 10 cmH_2O post 2h NIV	15	2.8–110	0.001
Vte > 9.5 ml/kg of PBW	7.9	1.5–72	0.02
HACOR score > 5 post 2h NIV	6.3	0.9–49	0.046
RR > 30 bpm	5.5	0.8–112	0.14
PaO_2/FiO_2 < 150 mmHg	2	0.5–9.8	0.4
Vte/ΔP_L < 0.33 ml/Kg/cmH2O	2	0.4-9.8	0.36

Data are presented as odds ratio and 95%CI.

OR, odds ratio; NIV, non-invasive mechanical ventilation; PBW, predicted body weight; ΔP_{es}, change in esophageal pressure; RR, respiratory rate; Vte, expiratory tidal volume, Vte/ΔP_L, expiratory tidal volume on transpulmonary pressure ratio.

Supplementary material

Figure E1. Time course assessment through ANOVA analysis of ΔP_{es} (panel A), ΔP_L (panel B), and $\Delta P_{es}/\Delta P_L$ (panel C) for patients who failed and who were successful in the 24-hour NIV trial.

Figure E2. Time course assessment through ANOVA analysis of Vte/kg of PBW (panel A), VE (panel B), and Vte/ΔP_L panel C) for patients who failed and who were successful in the 24-hour NIV trial .

Figure E3. Time course assessment through ANOVA analysis of RR (panel A), PaO_2/FiO_2 ratio (panel B), and HACOR score (panel C) for patients who failed and who were successful in the 24-hour NIV trial.

Figure E4. Correlation between ΔP_{es} and Vte/ΔP_L values on admission (r=-0.77, p<0.0001).

Figure E5. Correlation between ΔP_{es} and PaO_2/FiO_2 ratio (panel A, r=–0.01, p=0.9), RR (panel B, r=0.23, p=0.2), HACOR score (panel C, r=0.05, p=0.8), and Vte/kg of PBW (panel D, r=–0.05, p=0.8) on admission.

Figure E6. Correlation assessed through Pearson's correlation coefficient between ΔP_{es} changes 2 hours after NIV start and radiographic changes on chest X-ray assessed at 24 hours. Colored panels correspond to categories of radiographic change as assessed by the radiologist (from left to right: relevant worsening, worsening, mild worsening, unmodified, mild improvement, improvement, relevant improvement).

Figure E7. Probability to die at 30 days from admission according to the reduction of ΔP_{es} within the first 2 hours after NIV start.

Table E1. Sensitivity and specificity table derived from ROC analysis of ΔP_{es} changes after 2 hours of NIV on NIV failure.

Table E2. Sensitivity and specificity table derived from ROC analysis of baseline $Vte/\Delta P_L$ on NIV failure.

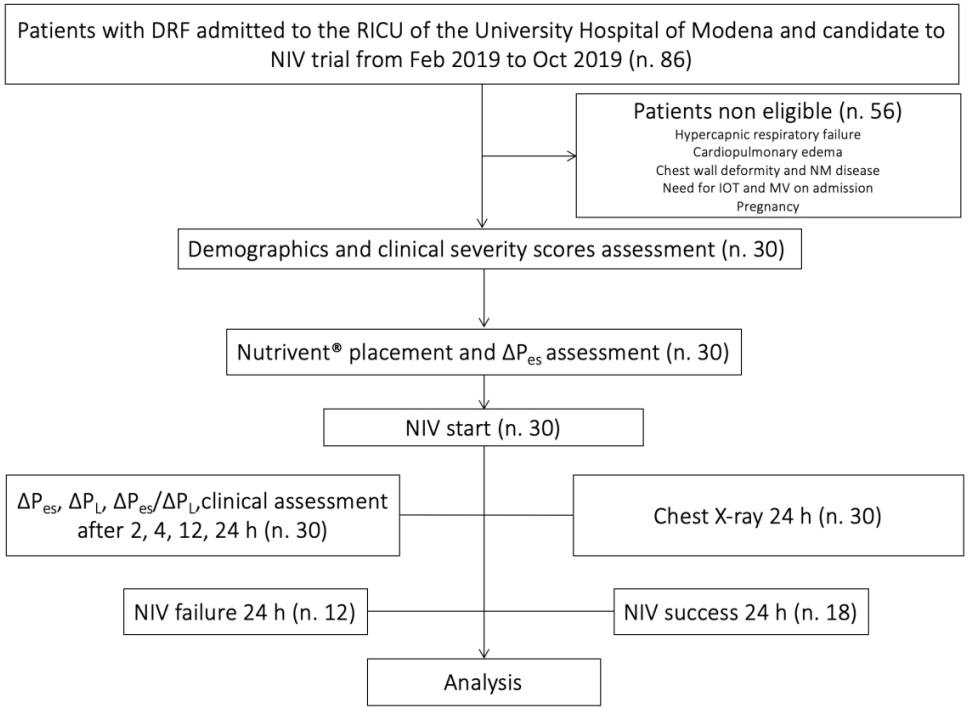
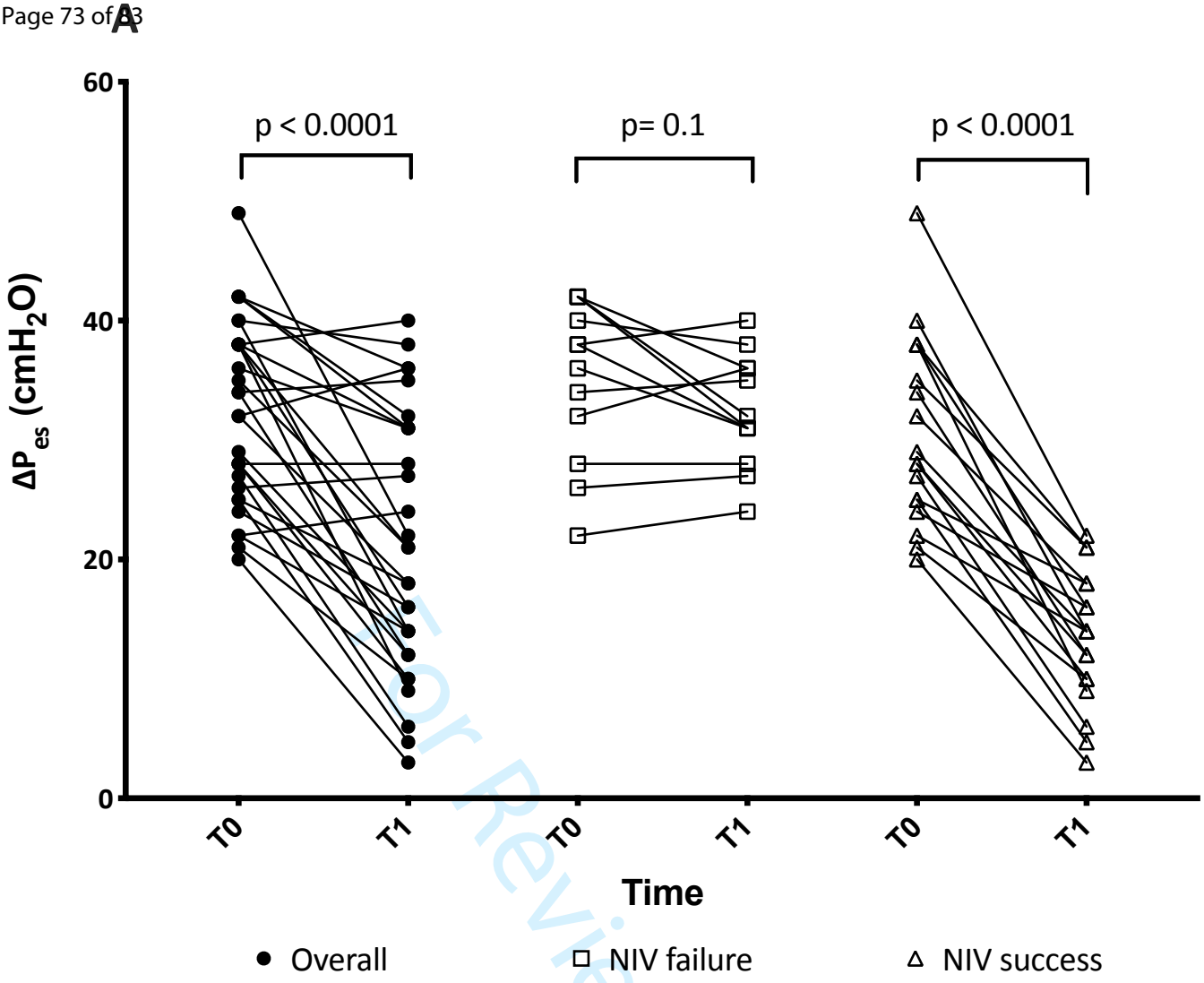
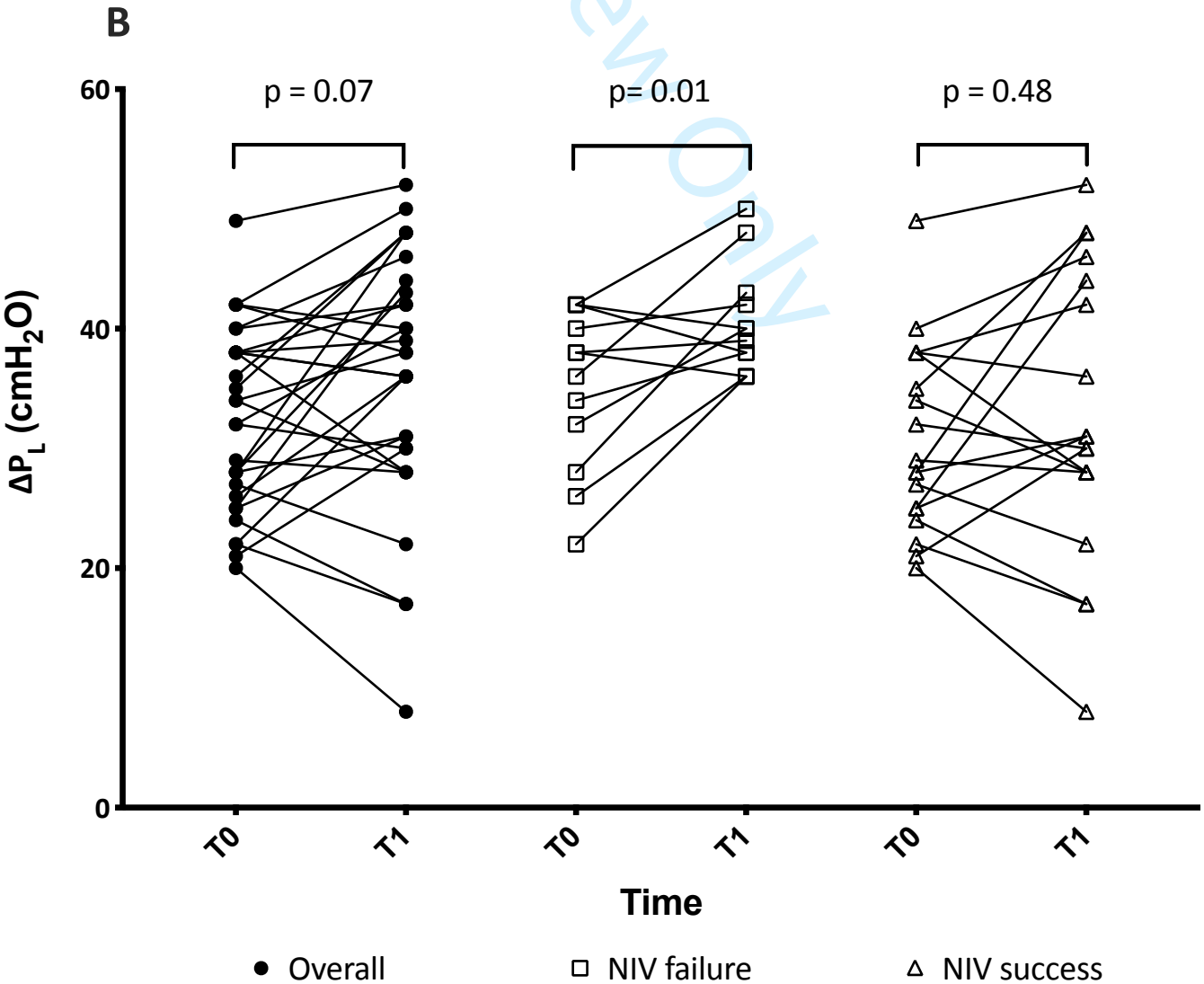
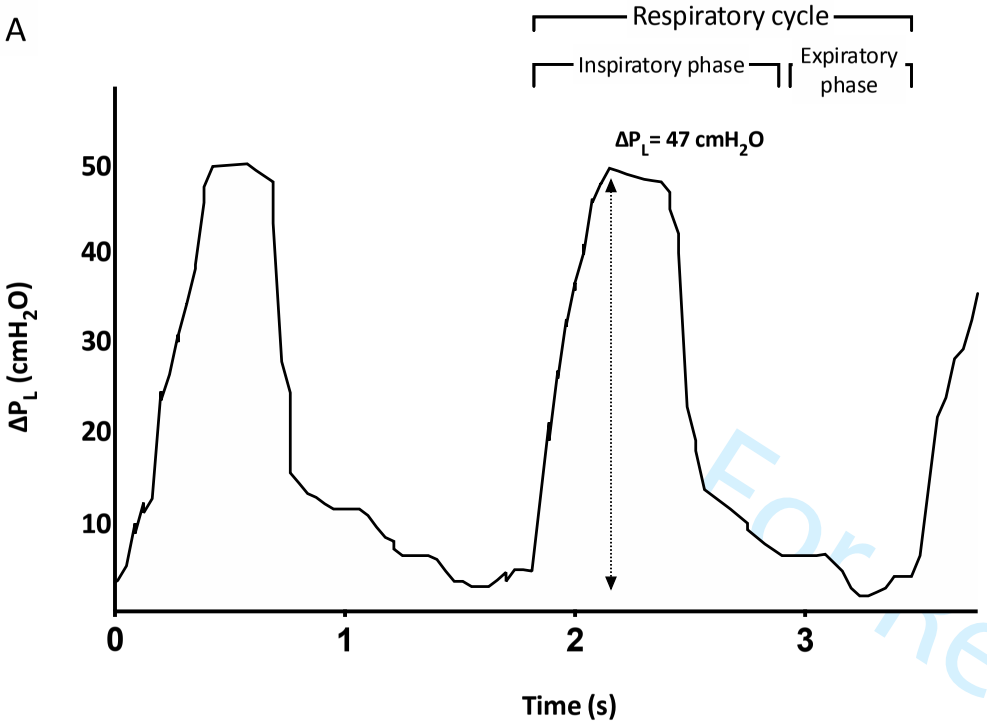
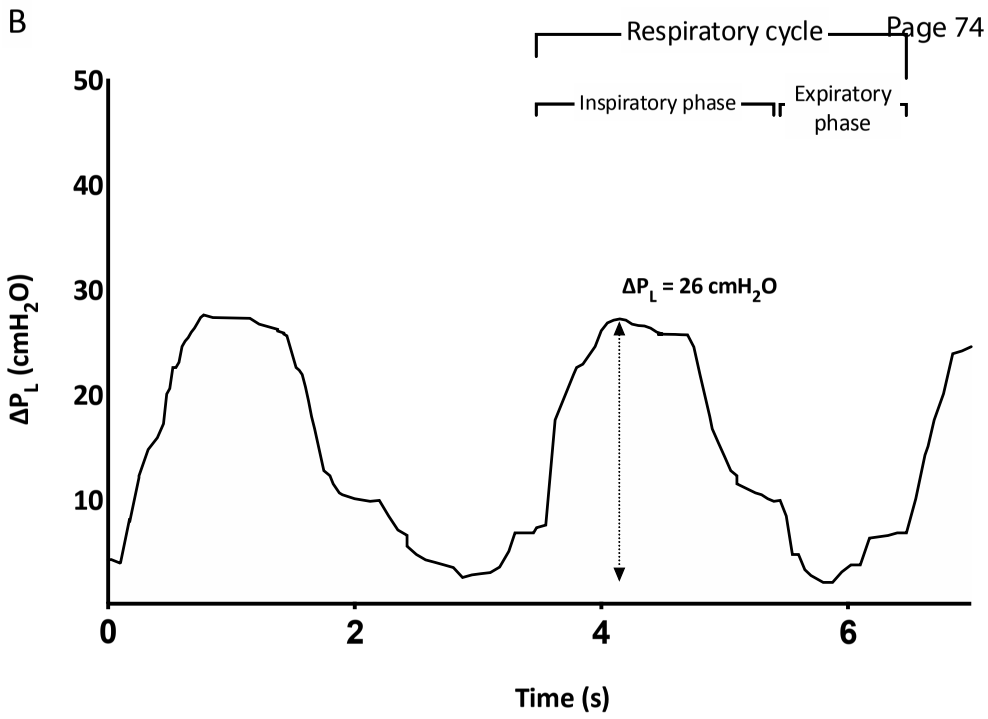


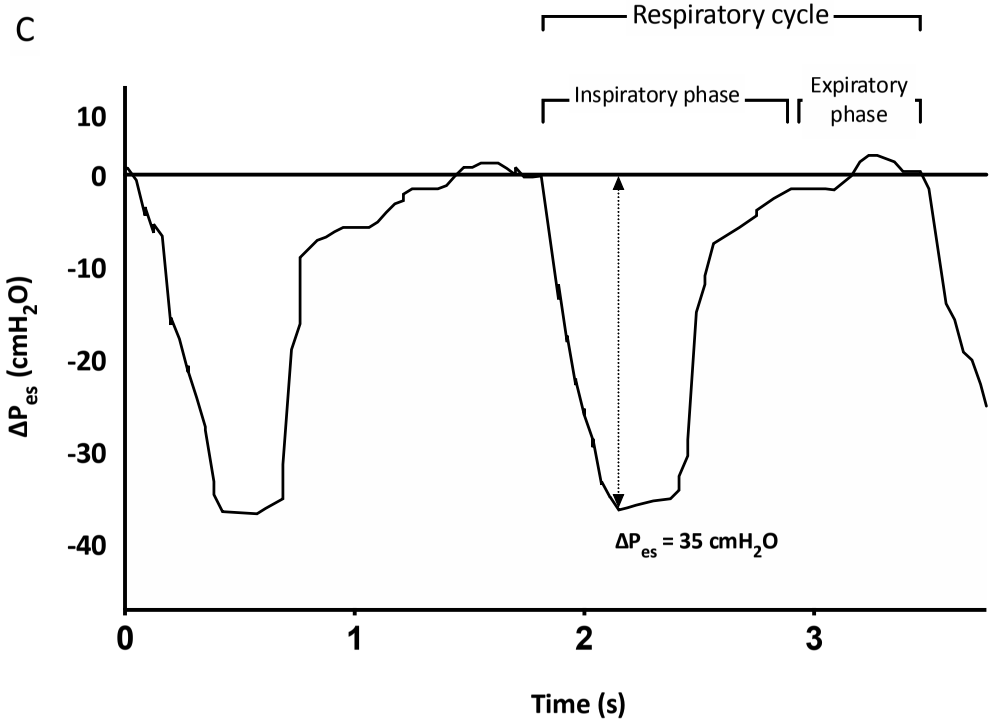
Fig. 1. Flow chart for patients in this study.

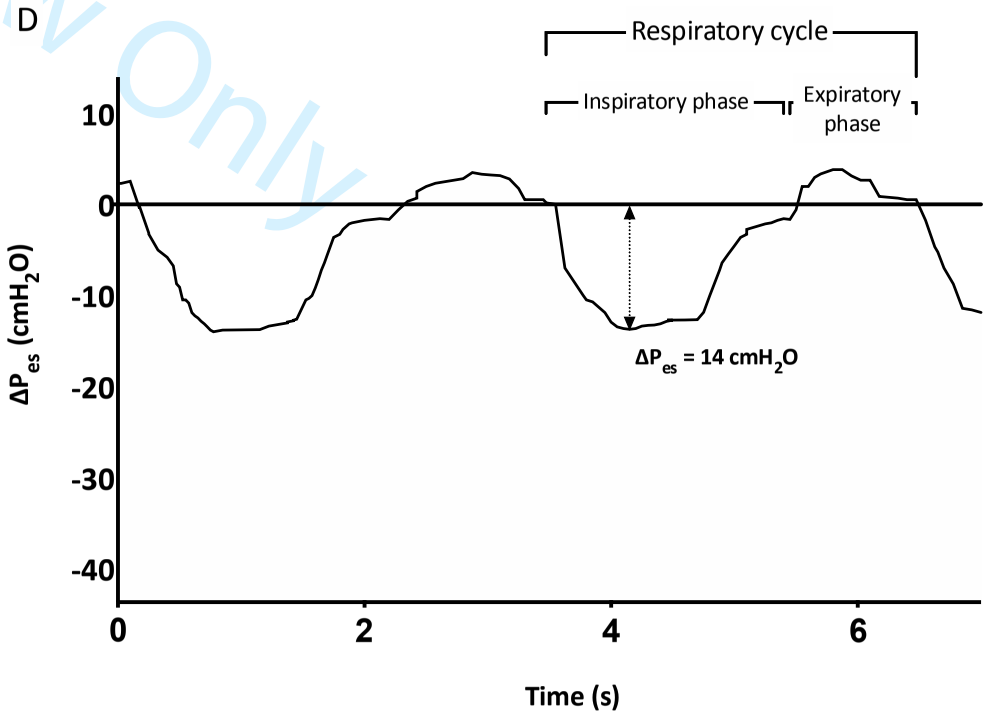


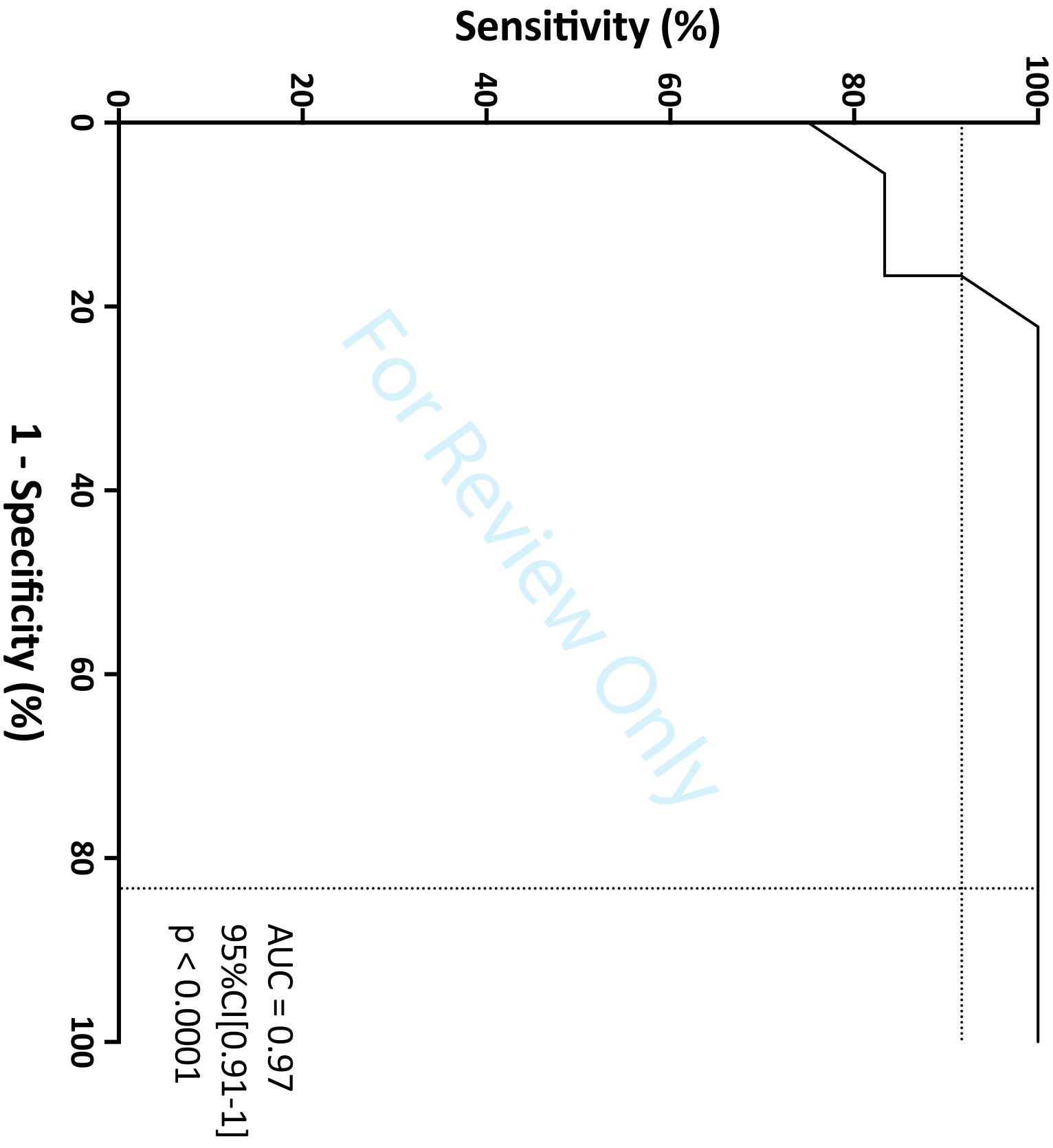




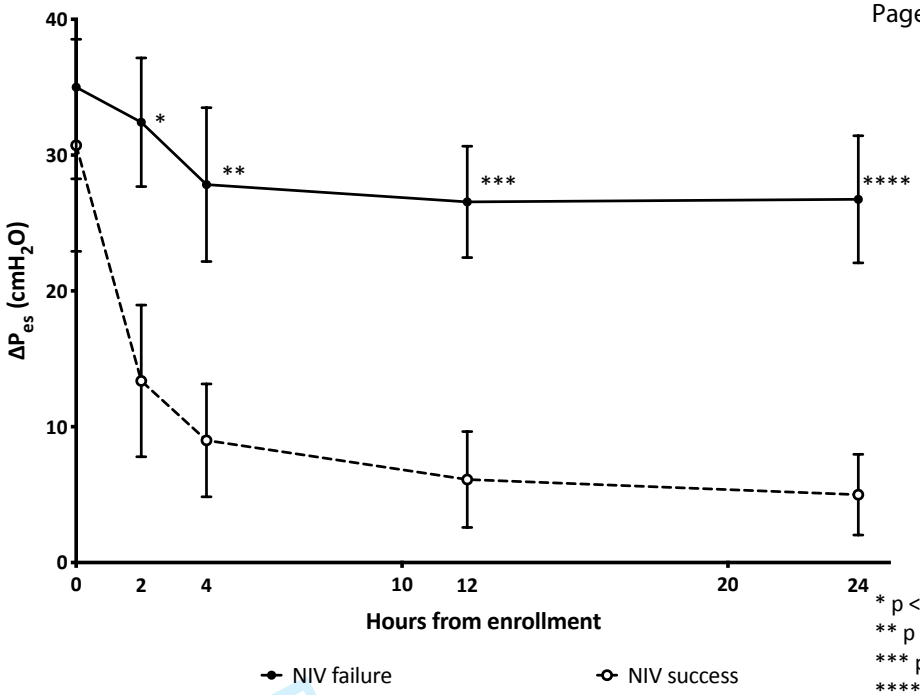






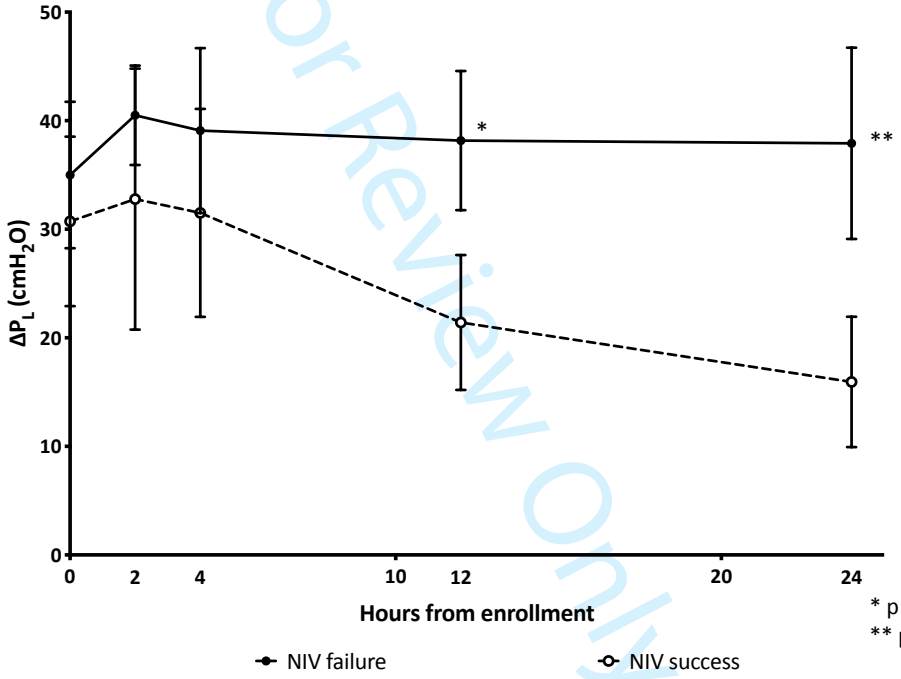


A



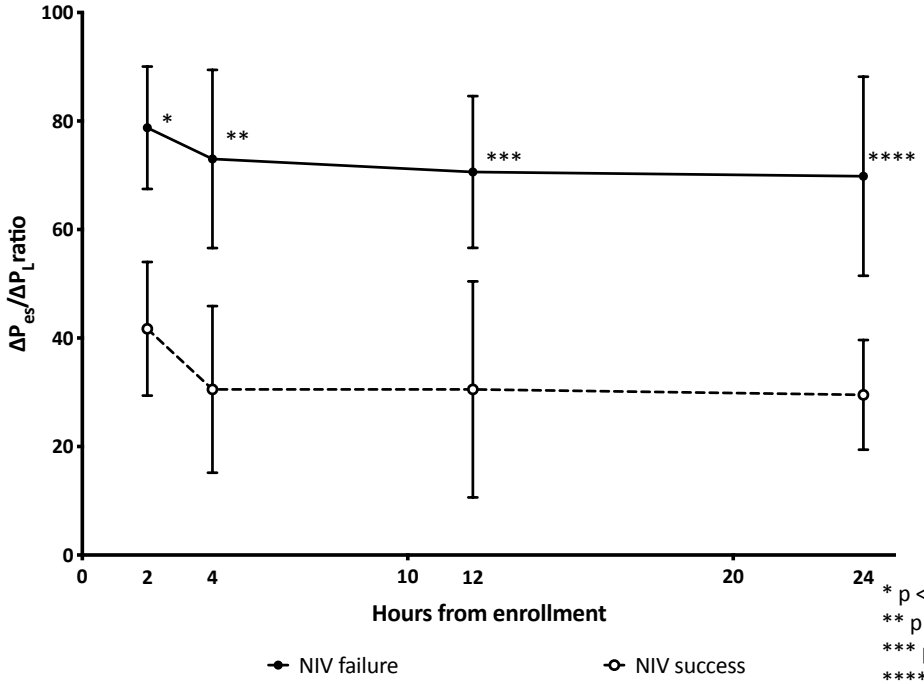
* p < 0.0001
** p < 0.0001
*** p < 0.0001
**** p < 0.0001

B



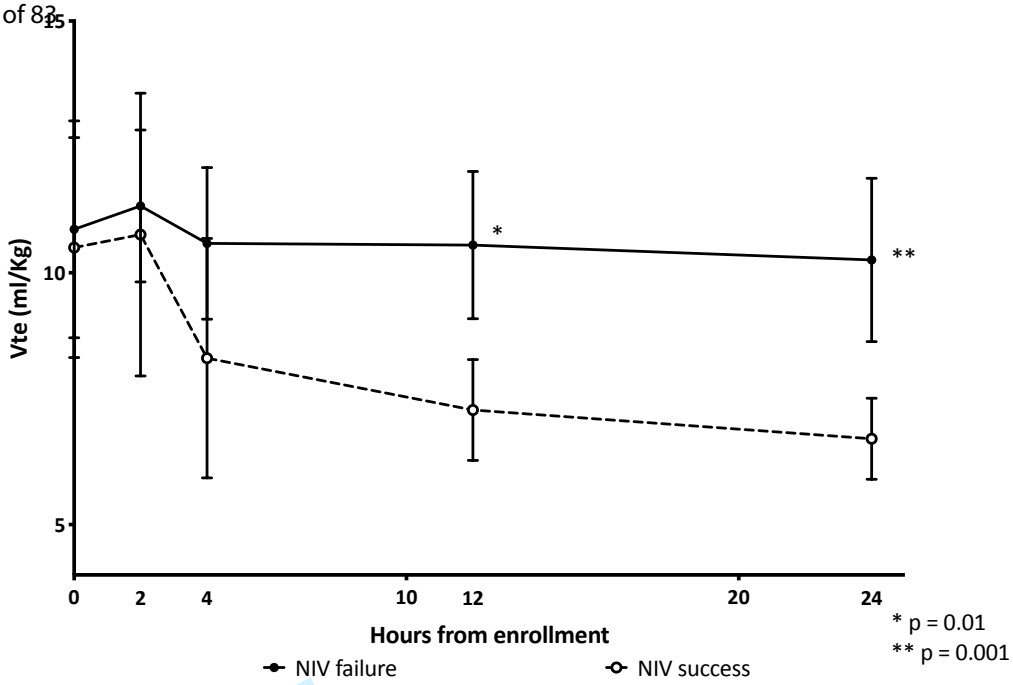
* p = 0.04
** p = 0.008

C



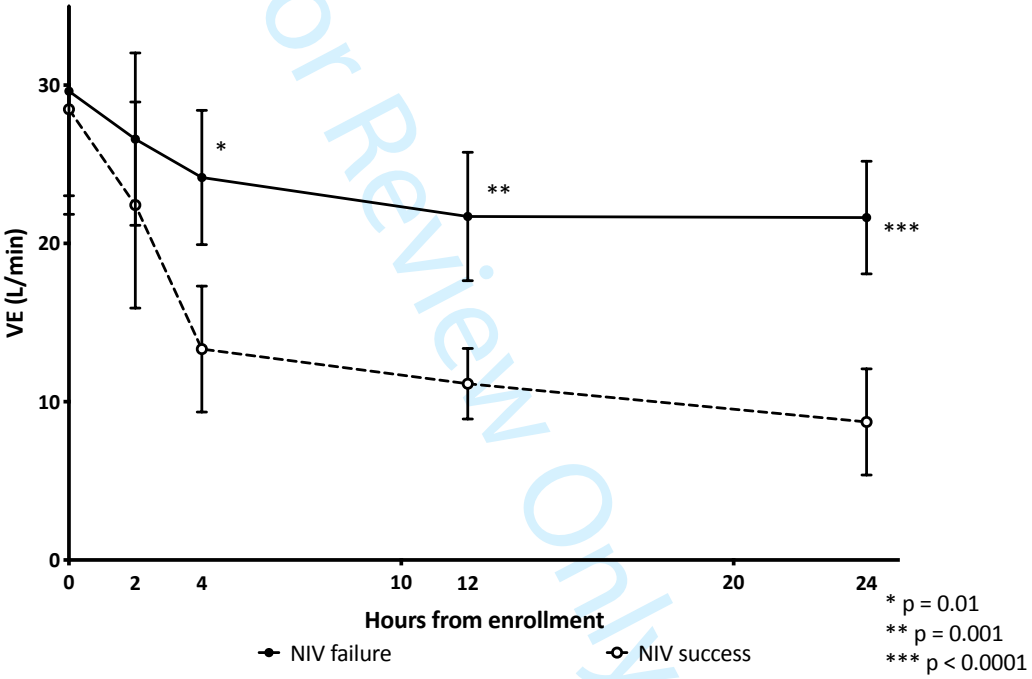
* p < 0.0001
** p = 0.0005
*** p < 0.0001
**** p = 0.015

A



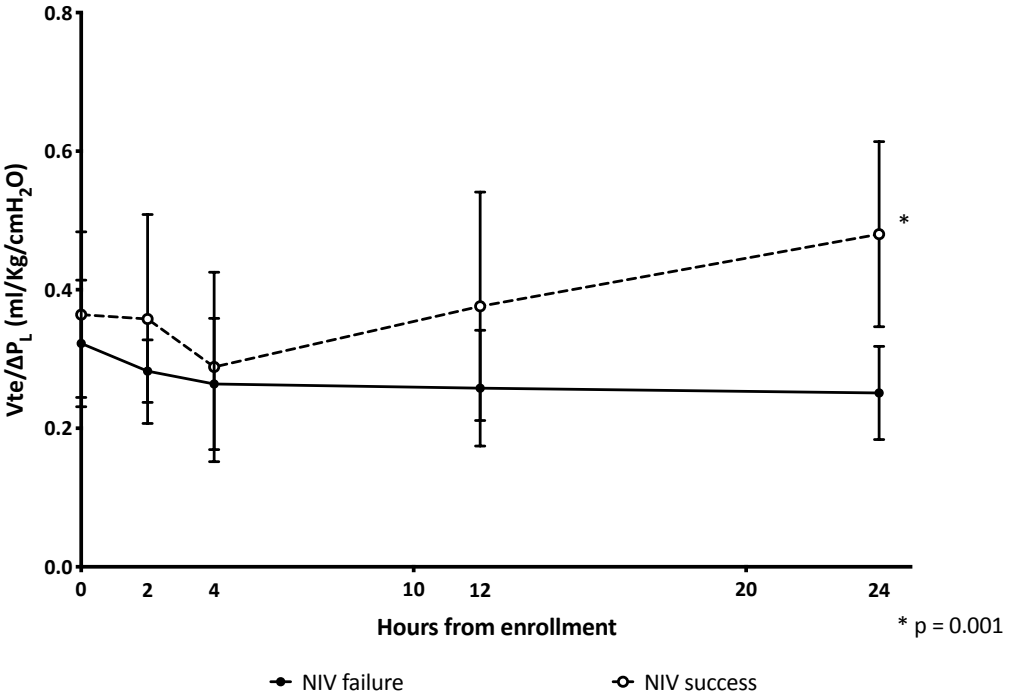
* p = 0.01
** p = 0.001

B



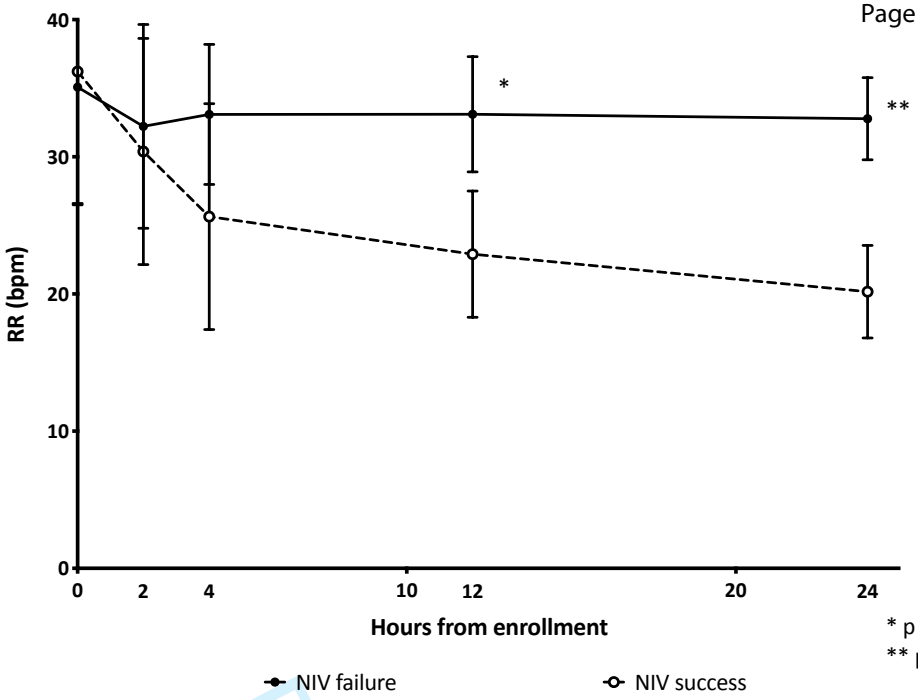
* p = 0.01
** p = 0.001
*** p < 0.0001

C



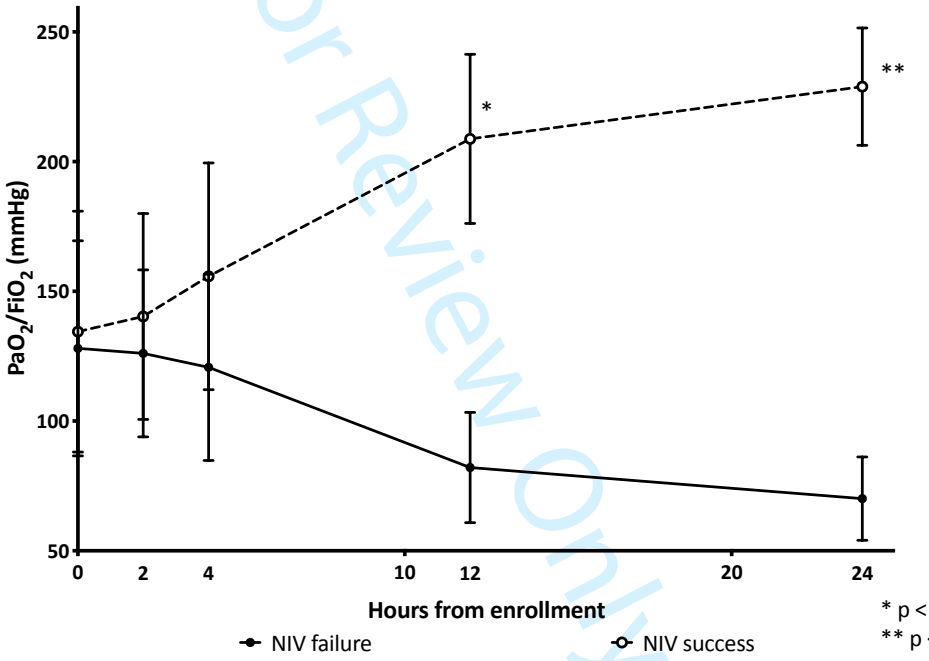
* p = 0.001

A



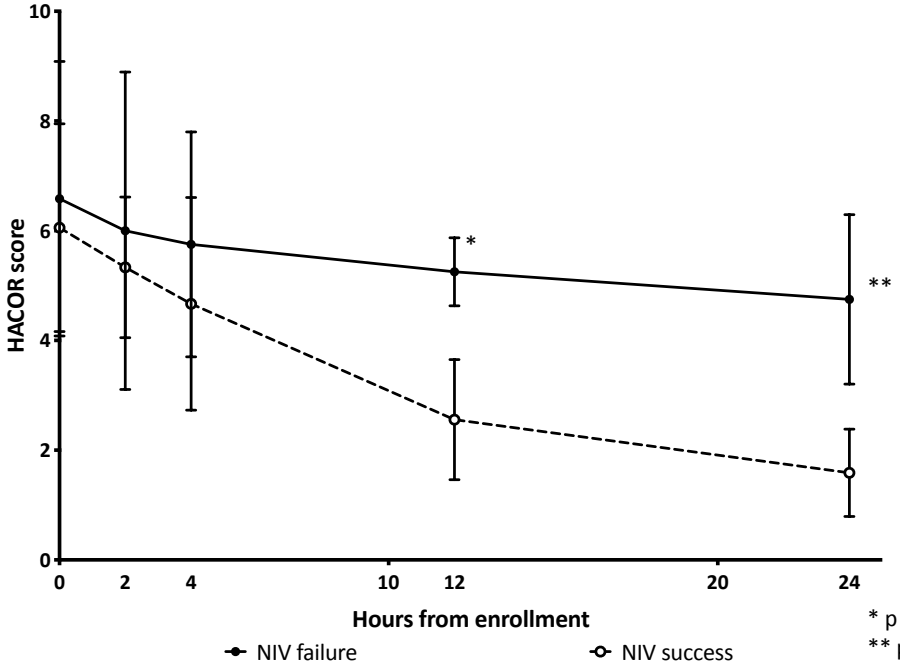
* p = 0.02
** p < 0.0001

B

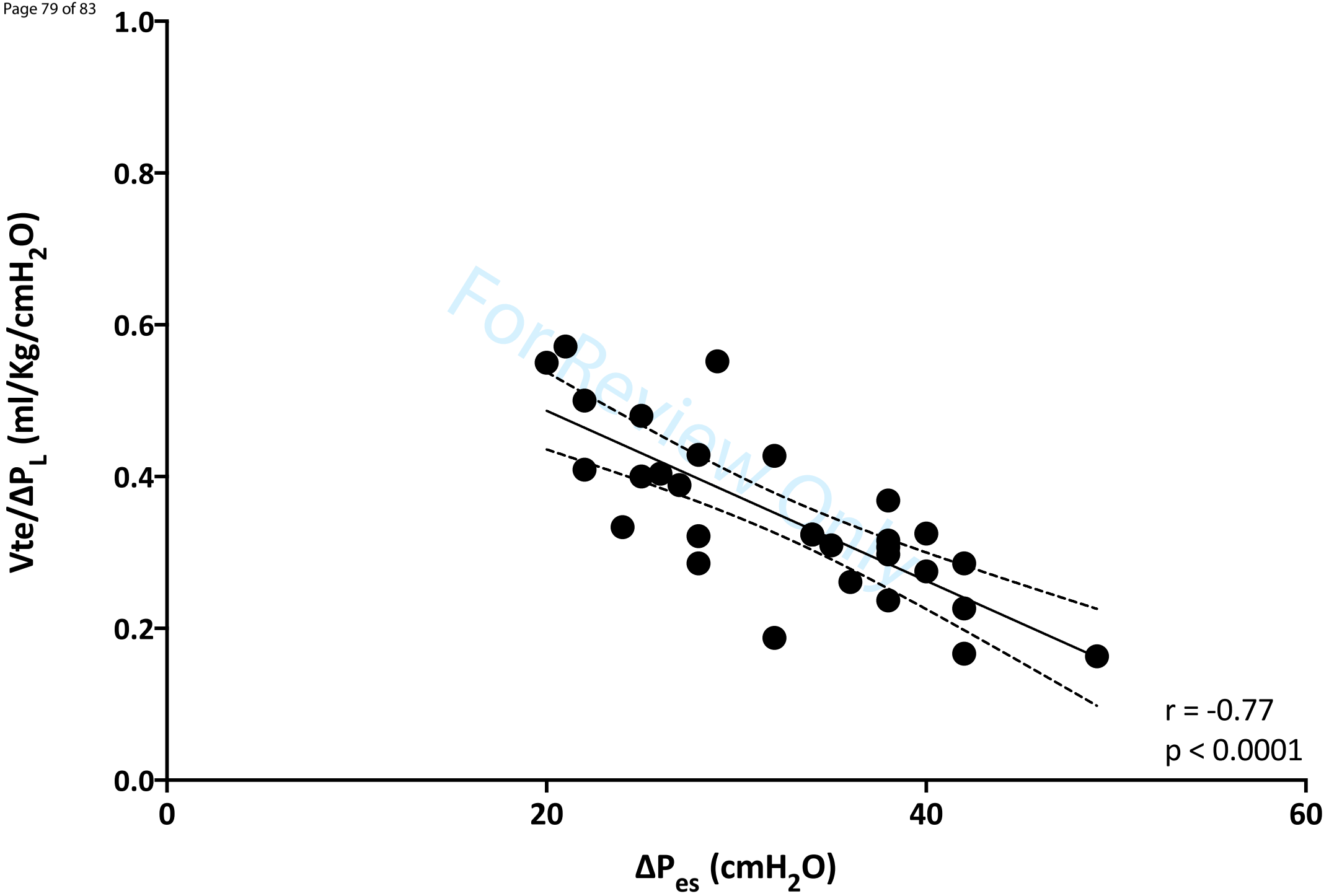


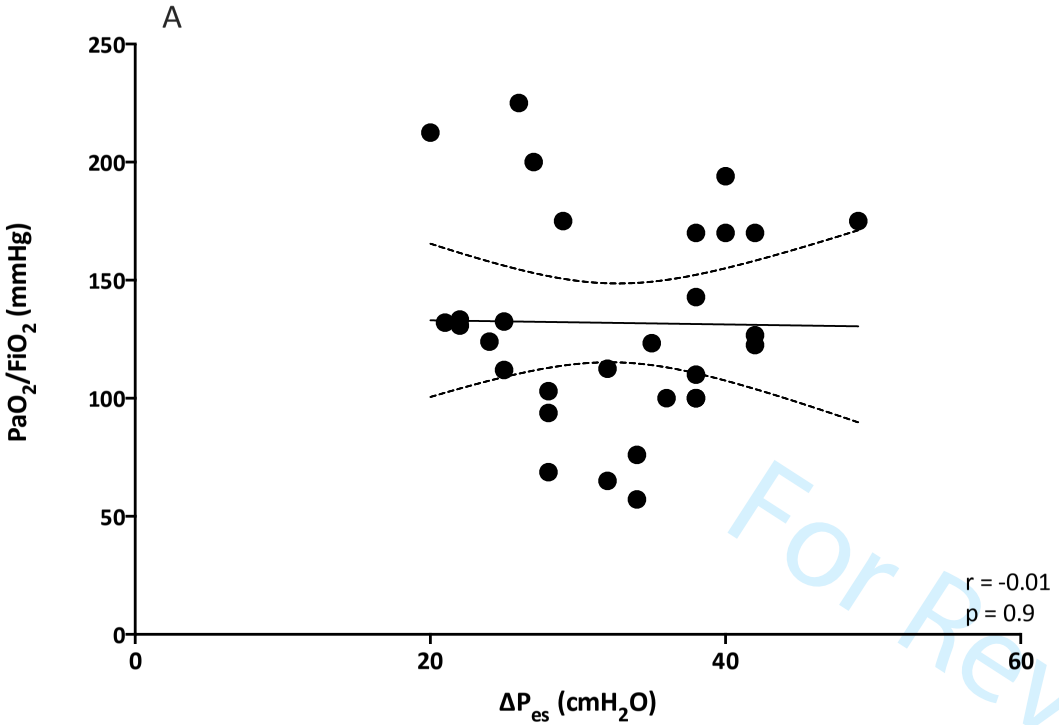
* p < 0.0001
** p < 0.0001

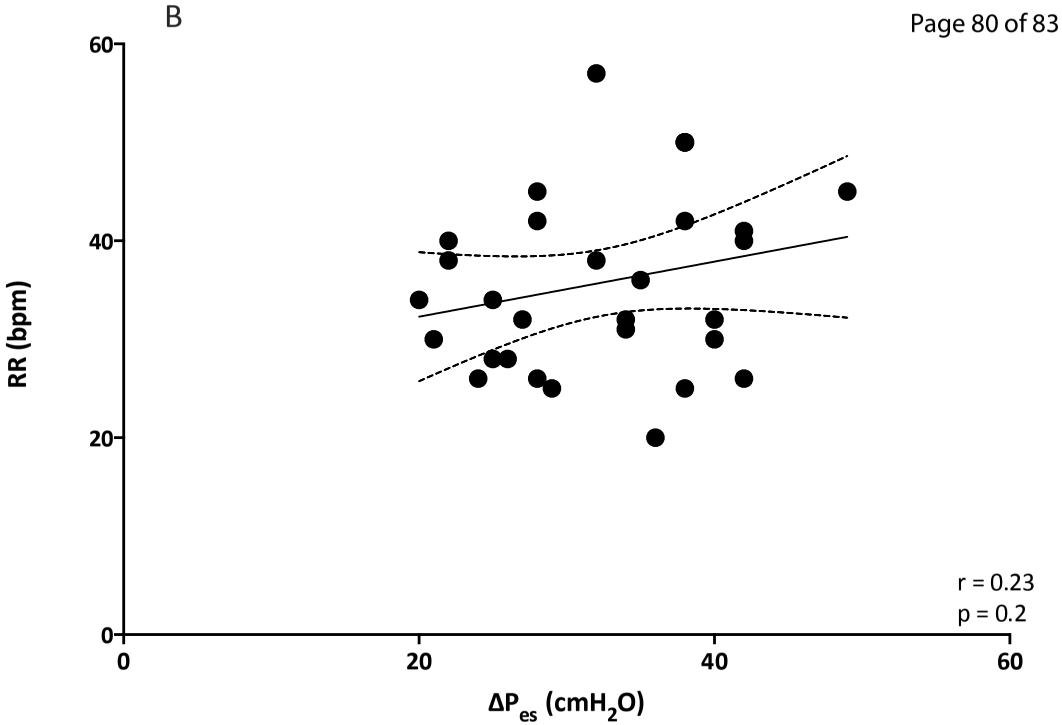
C

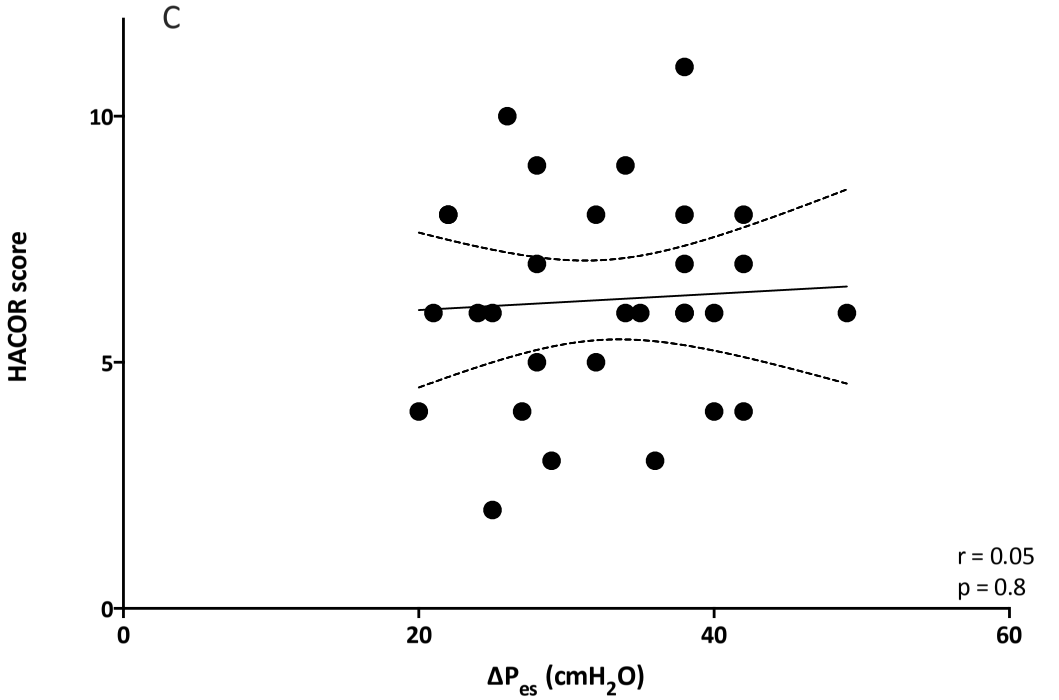


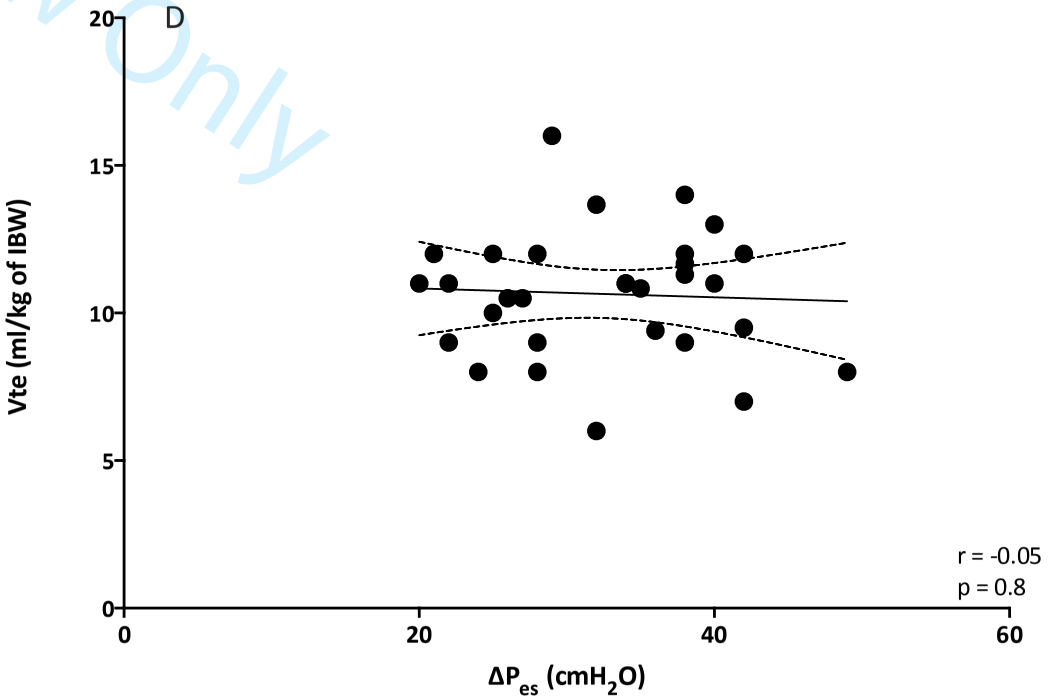
* p = 0.03
** p < 0.0001

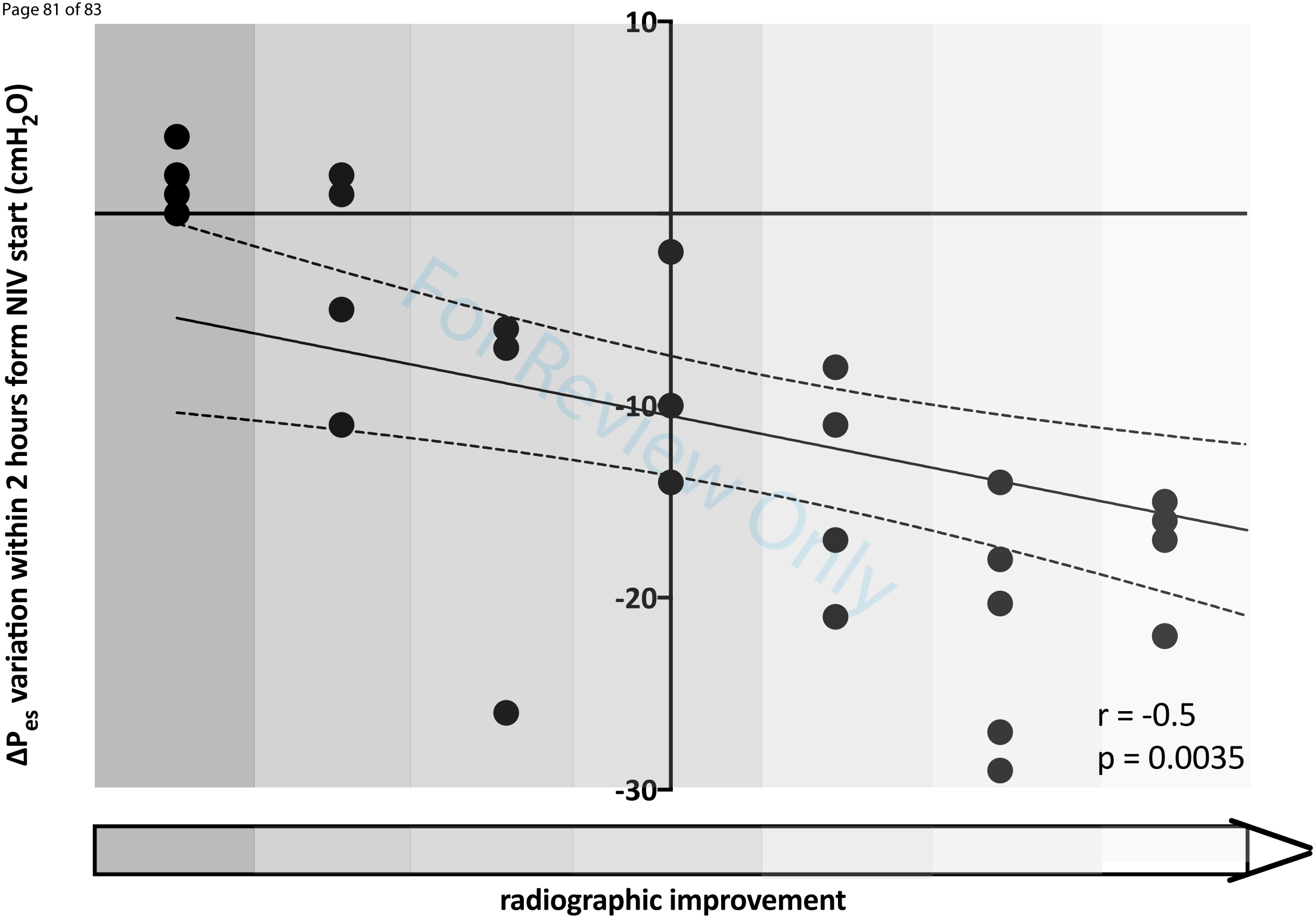


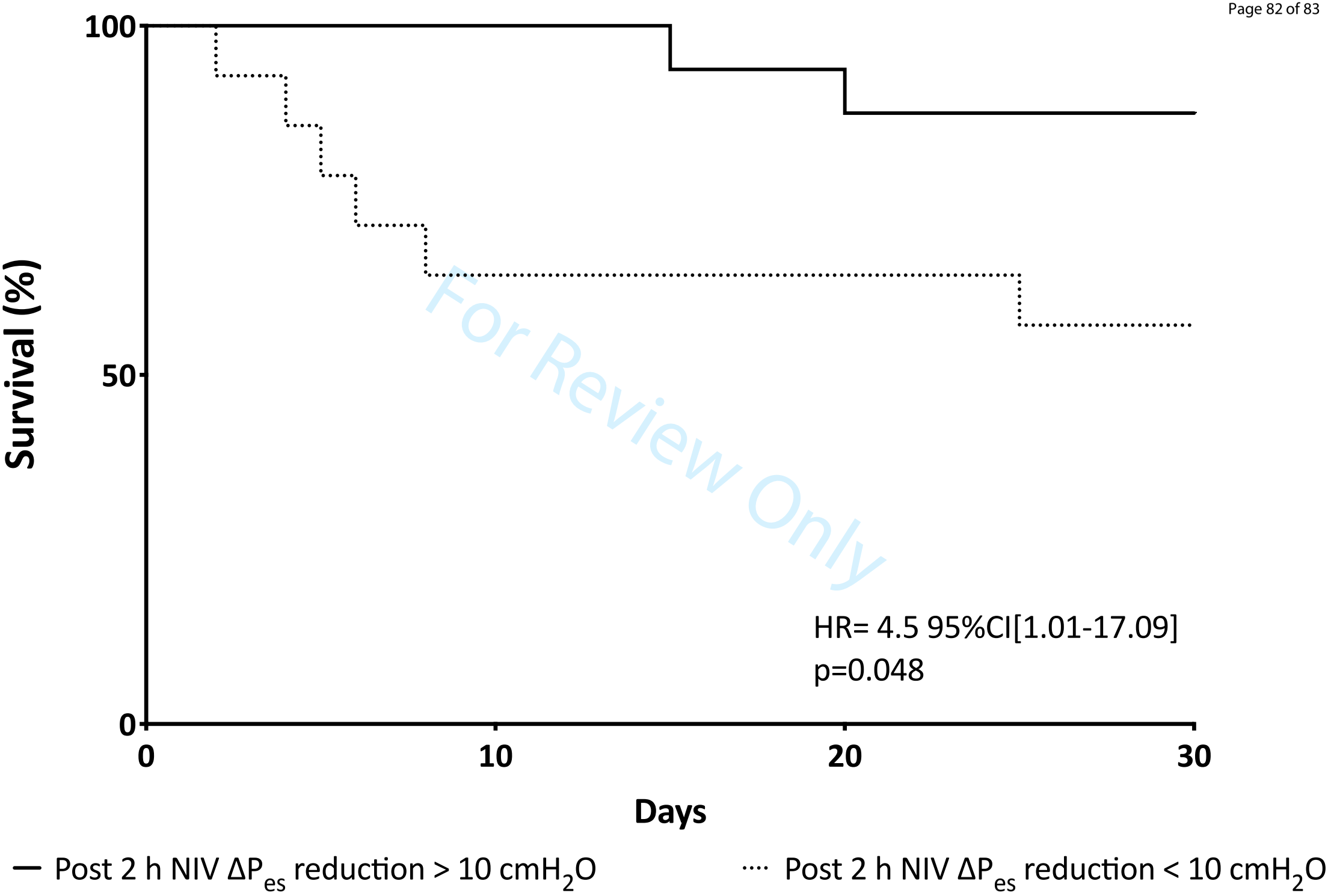












	Sensitivity%	95% CI	Specificity%	95% CI	Likelihood ratio
> -28.00	100,0	75,75% to 100,0%	5,556	0,2850% to 25,76%	1,059
> -26.50	100,0	75,75% to 100,0%	11,11	1,974% to 32,80%	1,125
> -24.00	100,0	75,75% to 100,0%	16,67	5,837% to 39,22%	1,200
> -21.50	100,0	75,75% to 100,0%	27,78	12,50% to 50,87%	1,385
> -20.65	100,0	75,75% to 100,0%	33,33	16,28% to 56,25%	1,500
> -19.15	100,0	75,75% to 100,0%	38,89	20,31% to 61,38%	1,636
> -17.50	100,0	75,75% to 100,0%	44,44	24,56% to 66,28%	1,800
> -16.50	100,0	75,75% to 100,0%	55,56	33,72% to 75,44%	2,250
> -15.50	100,0	75,75% to 100,0%	61,11	38,62% to 79,69%	2,571
> -14.50	100,0	75,75% to 100,0%	66,67	43,75% to 83,72%	3,000
> -12.50	100,0	75,75% to 100,0%	77,78	54,79% to 91,00%	4,500
> -10.00	91,67	64,61% to 99,57%	83,33	60,78% to 94,16%	5,500
> -9.000	83,33	55,20% to 97,04%	83,33	60,78% to 94,16%	5,000
> -7.500	83,33	55,20% to 97,04%	94,44	74,24% to 99,72%	15,00
> -6.500	75,00	46,77% to 91,11%	100,0	82,41% to 100,0%	
> -5.500	66,67	39,06% to 86,19%	100,0	82,41% to 100,0%	
> -3.500	58,33	31,95% to 80,67%	100,0	82,41% to 100,0%	
> -1.000	50,00	25,38% to 74,62%	100,0	82,41% to 100,0%	
> 0.5000	41,67	19,33% to 68,05%	100,0	82,41% to 100,0%	
> 1.500	25,00	8,894% to 53,23%	100,0	82,41% to 100,0%	
> 3.000	8,333	0,4274% to 35,39%	100,0	82,41% to 100,0%	

	Sensitivity%	*"95% CI"*	*Specificity%*	*"95% CI"*	*"Likelihood ratio"*
"< 0.1650"	0,000	"0.000% to 24.25%"	94,44	"74.24% to 99.72%"	0,000
"< 0.1771"	8,333	"0.4274% to 35.39%"	94,44	"74.24% to 99.72%"	1,500
"< 0.2068"	8,333	"0.4274% to 35.39%"	88,89	"67.20% to 98.03%"	0,7500
"< 0.2315"	16,67	"2.961% to 44.80%"	88,89	"67.20% to 98.03%"	1,500
"< 0.2490"	16,67	"2.961% to 44.80%"	83,33	"60.78% to 94.16%"	1,000
"< 0.2681"	25,00	"8.894% to 53.23%"	83,33	"60.78% to 94.16%"	1,500
"< 0.2804"	25,00	"8.894% to 53.23%"	77,78	"54.79% to 91.00%"	1,125
"< 0.2915"	41,67	"19.33% to 68.05%"	77,78	"54.79% to 91.00%"	1,875
"< 0.3022"	50,00	"25.38% to 74.62%"	77,78	"54.79% to 91.00%"	2,250
"< 0.3083"	50,00	"25.38% to 74.62%"	72,22	"49.13% to 87.50%"	1,800
"< 0.3126"	50,00	"25.38% to 74.62%"	66,67	"43.75% to 83.72%"	1,500
"< 0.3186"	50,00	"25.38% to 74.62%"	61,11	"38.62% to 79.69%"	1,286
"< 0.3225"	50,00	"25.38% to 74.62%"	55,56	"33.72% to 75.44%"	1,125
"< 0.3243"	58,33	"31.95% to 80.67%"	50,00	"29.03% to 70.97%"	1,167
"< 0.3292"	66,67	"39.06% to 86.19%"	50,00	"29.03% to 70.97%"	1,333
"< 0.3509"	66,67	"39.06% to 86.19%"	44,44	"24.56% to 66.28%"	1,200
"< 0.3787"	75,00	"46.77% to 91.11%"	44,44	"24.56% to 66.28%"	1,350
"< 0.3944"	75,00	"46.77% to 91.11%"	38,89	"20.31% to 61.38%"	1,227
"< 0.4019"	75,00	"46.77% to 91.11%"	33,33	"16.28% to 56.25%"	1,125
"< 0.4065"	83,33	"55.20% to 97.04%"	33,33	"16.28% to 56.25%"	1,250
"< 0.4181"	83,33	"55.20% to 97.04%"	27,78	"12.50% to 50.87%"	1,154