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Director: Prof. Giuseppe Biagini

QUANTIFICATION AND PHYSIOPATHOLOGICAL ROLE OF INSPIRATORY EFFORT IN THE DEVELOPMENT OF SELF-INFLICTED LUNG INJURY IN SPONTANEOUSLY BREATHING PATIENTS WITH ACUTE HYPOXIC RESPIRATORY FAILURE: A CLINICAL MODEL OF ACUTE LUNG DAMAGE

PhD candidate: Dr. Ivana Castaniere

Supervisor: Prof. Enrico M. Clini

Co-supervisor: Dr. Alessandro Marchioni

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Index

Abstract……**1**

Sinossi……**3**

General introduction……**5**

Early inspiratory effort assessment by esophageal manometry predicts noninvasive ventilation outcome in de novo respiratory failure: a pilot study ……**9**

Inspiratory effort and lung mechanics in spontaneously breathing patients with acute respiratory failure due to COVID-19: a matched control study……**43**

Nasal pressure swings as the measure of inspiratory effort in spontaneously breathing patients with COVID-19-associated acute respiratory failure……**65**

General discussion……**83**

Abstract

The role of spontaneous breathing (SB) in patients with acute hypoxic respiratory failure (ARF) is still controversial. With mild ARF, it is important to maintain SB in order to preserve respiratory muscle function, to improve the ventilation/perfusion ratio, and to reduce sedation and days of invasive mechanical ventilation (MV). However, recent evidence has suggested that SB might be a potential mechanism for lung damage when ARF is severe. According to this hypothesis, the intensity of inspiratory effort may follow a critical increase of respiratory drive thus producing uncontrolled swings in transpulmonary pressure that would increase the risk of lung damage and worsened clinical outcome, just following the onset of a "self-inflicted lung injury" (SILI).

Several methods to measure the inspiratory effort have been proposed to implement respiratory monitoring in patients with ARF and prompt clinicians to non-invasive (NIV) or invasive ventilator support. Esophageal manometry is a reliable method to estimate the magnitude of inspiratory effort, although procedural issues significantly reduce its use in daily clinical practice. With this project, we aimed both at quantifying the inspiratory effort of patients with ARF under SB, and at investigating its role as a potential mechanism inducing SILI and the associated clinical outcomes.

The research question has been addressed by means of 3 different clinical studies hold at the Respiratory Intensive Care Unit of the University Hospital of Modena between 2016 and 2021. In the first prospective investigation we estimated the intensity of spontaneous breathing effort in 30 patients with ARF by esophageal manometry during the first 24 hours of NIV and tested the hypothesis that vigorous spontaneous effort may be related to lung injury (estimated by chest X-ray) and NIV failure. We found that vigorous effort was present in patients with ARF before starting NIV and that its persistency after starting NIV was associated with worsening lung injury; moreover, it was the earliest and most accurate parameter to predict NIV failure. In the second prospective observational trial we investigated the inspiratory effort of spontaneously breathing patients with COVID-19 pneumonia as compared to a matched cohort of patients with ARDS. We reported that early after onset, COVID-19 induced ARF shows a relatively lower inspiratory effort then ARDS, thus probably lowering the risk of SILI and suggesting a different mechanism behind hypoxemia. In the third physiological study we aimed at describing the correlation between and esophageal (ΔPes) and nasal pressure (ΔPnos) as a potential measure of inspiratory effort in patients with COVID-19-associated ARF under SB. We found that ΔPnos was highly correlated with ΔPes, showing persistency over time and low inter-patient variability regardless the application of different type of non-invasive respiratory support.

Overall, with this project, we gave clinical evidence to evolve the concept of SILI induced by excessive inspiratory effort in patients with ARF under SB. Data have suggested that, with increased inspiratory effort, the risk of lung damage is higher, and it is associated with higher risk of failing non-invasive respiratory supports. Furthermore, we have provided preliminary data for evolving an innovative and clinically applicable method to measure and monitor inspiratory effort in patients developing ARF.

Abbreviations: SB, spontaneous breathing; ARF, acute respiratory failure; SILI, self-inflicted lung injury; COVID-19, SARS-CoV-2 induced disease; MV, invasive mechanical ventilation; NIV, non-invasive mechanical ventilation; ΔP_{es}, change in esophageal pressure; ΔP_{nos}, change in nasal pressure.

Sinossi

Il ruolo del respiro spontaneo (RS) nei pazienti con insufficienza respiratoria acuta ipossiemica (IRA) è controverso. Quando il danno polmonare è lieve, mantenere il RS è auspicabile per preservare il funzionamento muscolare, migliorare il rapporto ventilo/perfusivo, ridurre la sedazione e i giorni di ventilazione meccanica invasiva (VMI). Tuttavia, evidenze recenti suggeriscono come il RS possa essere un potenziale meccanismo di danno polmonare in caso di distress respiratorio. In relazione a questa ipotesi, l'intensità dello sforzo inspiratorio può provocare un aumento critico del drive respiratorio, producendo così un'oscillazione della pressione transpolmonare che incrementerebbe il rischio di danno polmonare, e peggioramento degli esiti clinici, per insorgenza del cosiddetto "danno polmonare auto-indotto (DPAI)".

Sono stati proposti vari metodi per quantificare e monitorare lo sforzo inspiratorio nei pazienti con IRA e fornire indicazioni cliniche sul corretto timing per adozione di tecniche ventilatorie non invasive (VMNI) e invasive. Un metodo affidabile per quantificare lo sforzo inspiratorio è la manometria esofagea benché la difficoltosa applicazione clinica ne riduca l'impiego nella pratica quotidiana.

Lo scopo di questo progetto sviluppato su un percorso di ricerca triennale è stato quello di quantificare lo sforzo inspiratorio nel paziente con IRA in RS e indagarne il ruolo come potenziale meccanismo responsabile del DPAI, valutare gli esiti clinici.

La ricerca è stata sviluppata mediante tre successivi studi clinici effettuati presso la Terapia Intensiva Respiratoria del Policlinico Universitario di Modena tra il 2016 e il 2021. Nel primo studio prospettico è stata stimata l'entità dello sforzo inspiratorio mediante manometria esofagea in 30 pazienti in RS con IRA nelle prime 24 ore di VMNI ed è stata correlata con il danno polmonare, valutato tramite radiografia toracica, e l'esito (fallimento della VMNI). È stato rilevato come la persistenza di eccessivo sforzo inspiratorio dopo l'applicazione della VMNI fosse associata ad un peggioramento del danno polmonare, risultando questo il parametro più precoce ed accurato per predire il fallimento del trattamento ventilatorio. Nel secondo studio prospettico abbiamo indagato lo sforzo inspiratorio nei pazienti in RS con polmonite COVID-19 confrontati con una coorte di pazienti con sindrome da distress respiratorio acuto (ARDS). Abbiamo evidenziato che, nelle fasi precoci di insorgenza, l'IRA indotta dalla malattia COVID-19 induceva uno sforzo inspiratorio inferiore rispetto ad ARDS, con rischio minore di DPAI, e suggeriva un diverso meccanismo sottostante l'ipossiemia. Nel terzo studio fisiologico è stata studiata la correlazione tra pressione esofagea (ΔPes) e pressione

nasale (ΔPnos) come potenziale indicatore dello sforzo respiratorio in pazienti in RS con IRA conseguente a malattia COVID-19. È stata documentata una forte correlazione tra ΔPnos e ΔPes, persistente nel tempo e con una bassa variabilità inter-paziente nonostante l'applicazione di diverse tipologie di supporto respiratorio non-invasivo.

Nel suo complesso, con questo progetto abbiamo cercato di fornire evidenze sperimentali di tipo clinico al fine di approfondire il concetto di danno polmonare indotto da eccessivo sforzo inspiratorio. I dati hanno suggerito che, quando lo sforzo inspiratorio è elevato, il rischio di danno polmonare è maggiore e si associa a un più elevato rischio di fallimento dei supporti di respirazione non invasiva. Inoltre, abbiamo prodotto dati iniziali per lo sviluppo di un sistema innovativo per quantificare e monitorizzare clinicamente lo sforzo inspiratorio dei pazienti in corso di IRA.

Abbreviazioni: RS, respiro spontaneo; IRA, insufficienza respiratoria acuta; DPAI, danno polmonare auto-indotto; VMI, ventilazione meccanica invasive; VMNI, ventilazione meccanica non invasive; COVID-19, malattia indotta da SARS-CoV-2; ΔP_{es}, variazione della pressione esofagea; ΔP_{nos}, variazione della pressione nasale.

General introduction

Keeping spontaneous breathing (SB) preserved over time during acute hypoxic respiratory failure (ARF) of different etiology still represents a controversial matter among intensivists. On one hand, the maintenance of SB is important to preserve respiratory muscle function, to improve the ventilation/perfusion ratio, and to prevent deep sedation and days of invasive mechanical ventilation (MV) (1). On the other, a highly stimulated respiratory drive might enhance lung damage when ARF is severe (2,3). According to this hypothesis, the intensity of inspiratory effort may follow a critical increase of respiratory drive thus producing uncontrolled swings in transpulmonary pressure, just following the onset of a "self-inflicted lung injury" (SILI), that could increase the risk of lung damage and worsen the clinical outcome (4). The underlying mechanisms of SILI are heterogeneous and include pendelluft phenomenon, increased trans-vascular pressure gradient aggravating alveolar damage, excessive diaphragmatic loading with impaired systemic oxygen delivery, and muscle injury (2,3,5). Non-invasive respiratory support (including high flow nasal cannulae [HFNC] and non-invasive mechanical ventilation [NIV]) is becoming increasingly used to assist SB during ARF, even though its potential therapeutic effect in this setting is still debated. 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 (5). Conversely, successful application of NIV is independently associated with survival and shorter length of ICU stay (6). Giving these assumptions, it seems of critical interest to identify early predictors of NIV failure in order to avoid intubation delay in this subset of patients. Several predictors of NIV failure in ARF have been investigated but were found to be insufficient to aid the timing of endotracheal intubation and mechanical ventilation (MV) start (3).

In the hypothesis of SILI as a major component of lung damage enhancement during ARF it seems of major importance to explore the role of inspiratory effort in affecting clinical outcomes of spontaneously breathing patients with ARF. Further, optimizing the inspiratory effort monitoring as reliable predictors of non-invasive respiratory support failure might assist clinicians in the managing of these patients with the aim to safely keep SB preserved and to avoid deleterious delays in endotracheal intubation. Several methods to measure the inspiratory effort have been proposed to implement respiratory monitoring in patients with ARF and prompt clinicians the best type of

ventilator support (3, 7). Esophageal manometry is a reliable method to estimate the magnitude of inspiratory effort, although procedural issues significantly reduce its use in daily clinical practice (8).

The aim of this project developed over a 3-years period was 1) to quantify the inspiratory effort of patients with ARF of different etiology under SB, 2) to investigate its role as a potential mechanism inducing SILI and the associated clinical outcomes, and 3) to optimize its monitoring technique to obtain a reliable ad non-invasive tool for the clinical management of patients with ARF.

The research question has been addressed by means of 3 different clinical studies hold at the Respiratory Intensive Care Unit of the University Hospital of Modena between 2016 and 2021.

In the first prospective investigation we estimated the intensity of spontaneous breathing effort in 30 patients with ARF by esophageal manometry during the first 24 hours of NIV and tested the hypothesis that vigorous spontaneous effort may be related to lung injury (estimated by chest X-ray) and NIV failure. We found that vigorous effort was present in patients with ARF before starting NIV and that its persistency after starting NIV was associated with worsening lung injury; moreover, it was the earliest and most accurate parameter to predict NIV failure (9).

In the second prospective observational trial we investigated the inspiratory effort of spontaneously breathing patients with COVID-19 pneumonia as compared to a matched cohort of patients with ARDS. We reported that early after onset, COVID-19 induced ARF shows a relatively lower inspiratory effort then ARDS, thus probably lowering the risk of SILI and suggesting a different mechanism behind hypoxemia (10).

In the third physiological study we aimed at describing the correlation between and esophageal (ΔPes) and nasal pressure (ΔPnos) as a potential measure of inspiratory effort in patients with COVID-19-associated ARF under SB. We found that Δpnos was highly correlated with ΔPes, showing persistency over time and low inter-patient variability regardless the application of different type of non-invasive respiratory support for caring.

Overall, with this project, we contributed with clinical evidences to the evolving concept of SILI, as induced by excessive or uncontrolled inspiratory effort in patients with ARF and breathing spontaneously, even if assisted non-invasively.

Data have suggested that, with increased inspiratory effort, the risk of lung damage is higher, and it is associated with higher risk of failing non-invasive respiratory supports (8,9). Furthermore, we have provided preliminary data for an innovative and clinically applicable surrogate method to measure and to monitor inspiratory effort in patients developing ARF.

Abbreviations: SB, spontaneous breathing; ARF, acute respiratory failure; SILI, self-inflicted lung injury; ARDS, acute respiratory distress syndrome; COVID-19, SARS-CoV-2 induced disease; ARDS, acute respiratory distress syndrome; MV, invasive mechanical ventilation; HFNC, high flow nasal cannulae; NIV, non-invasive mechanical ventilation; ICU, intensive care unit; ΔP_{es}, change in esophageal pressure; ΔP_L, change in nasal pressure.

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

Tonelli R, Fantini R, Tabbì L, Castaniere I, Pisani L, Pellegrino MR, Della Casa G, D'Amico R, Girardis M, Nava S, Clini EM, Marchioni A. Early Inspiratory Effort Assessment by Esophageal Manometry Predicts Noninvasive Ventilation Outcome in De Novo Respiratory Failure. A Pilot Study. Am J Respir Crit Care Med. 2020 Aug 15;202(4):558-567. doi: 10.1164/rccm.201912-2512OC. PMID: 32325004; PMCID: PMC7427381.

Abstract

Background

Non-invasive mechanical ventilation (NIV) is becoming increasingly used to assist spontaneous breathing during acute hypoxic de novo respiratory failure (ARF). The role of inspiratory effort has still to be determined as a potential predictor of NIV failure in acute hypoxic de novo respiratory failure (ARF). With this study, we explored the hypothesis that inspiratory effort might be a major determinant of NIV failure in these patients.

Methods

Thirty consecutive patients with ARF 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.

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.

Abbreviations: SB, spontaneous breathing; ARF, acute respiratory failure; ETI, endotracheal intubation; SILI, self-inflicted lung injury; ARDS, acute respiratory distress syndrome; MV, invasive mechanical ventilation; NIV, non-invasive mechanical ventilation; 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; 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; OR, odds ratio.

Introduction

The role of assisted spontaneous breathing (SB) in patients with acute hypoxic de novo respiratory failure (ARF) 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 ARF 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 ARF (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 ARF, 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 ARF 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 ARF 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, diagnosis, clinical features 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 ARF 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.

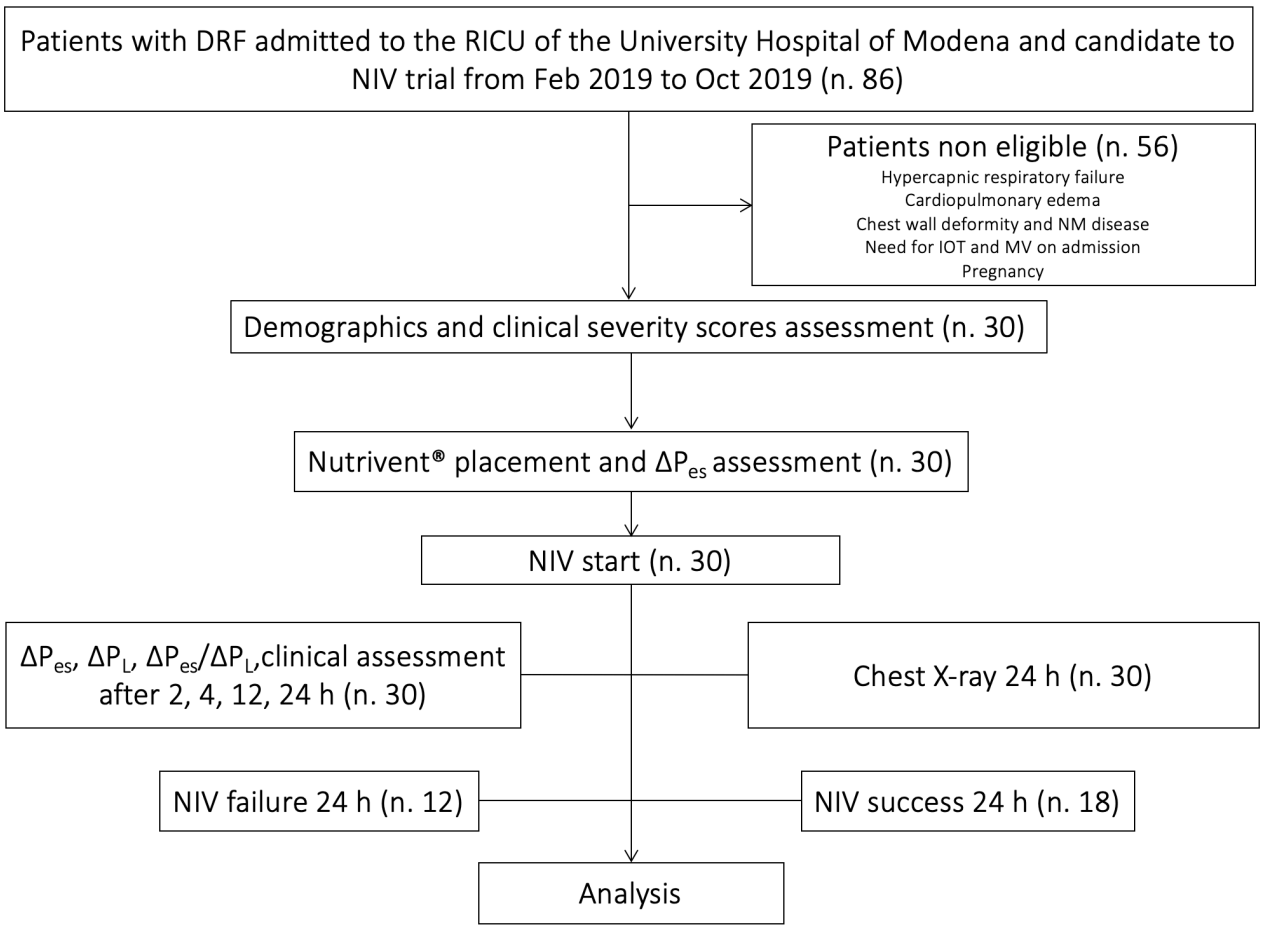

Figure 1

Flow chart for patients in the study.

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.

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

Table 1

Baseline features of the study population presented as a whole or as NIV outcome at 24 hours. Data are presented as number (n) and percentage (%) for dichotomous values or median and interquartile range (IQR) for continuous values. The nonparametric Mann–Whitney and Student t test were used for the comparison of continuous variables. Comparison between dichotomous variables was performed by the χ2 test or Fisher's exact test, where appropriate. Significance was set for p value < 0.05.

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.

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

Table 2

Clinical and physiological features of the study population at baseline and after 2 hours of NIV. Data are presented as median and interquartile range (IQR). The nonparametric Mann–Whitney and Student t test were used for the comparison. Significance was set for p value < 0.05.

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, $p=0.04$).

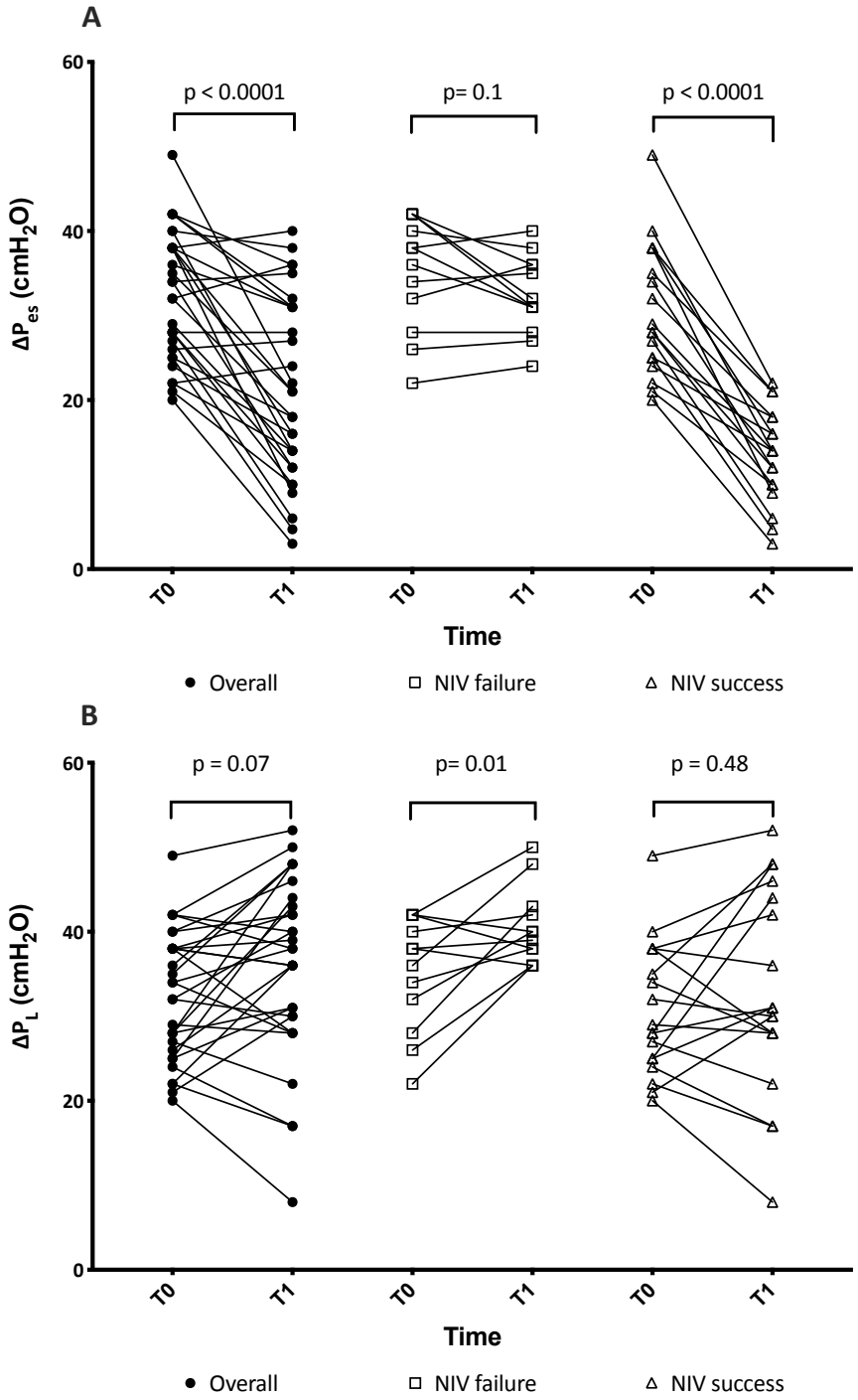

Figure 2

Panel A. ΔP_{es} changes from baseline within the first 2 hours of NIV for the whole population and according to NIV outcome at 24 hours. Panel 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. The Student t test was used for the comparison. Significance was set for p value < 0.05.

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).

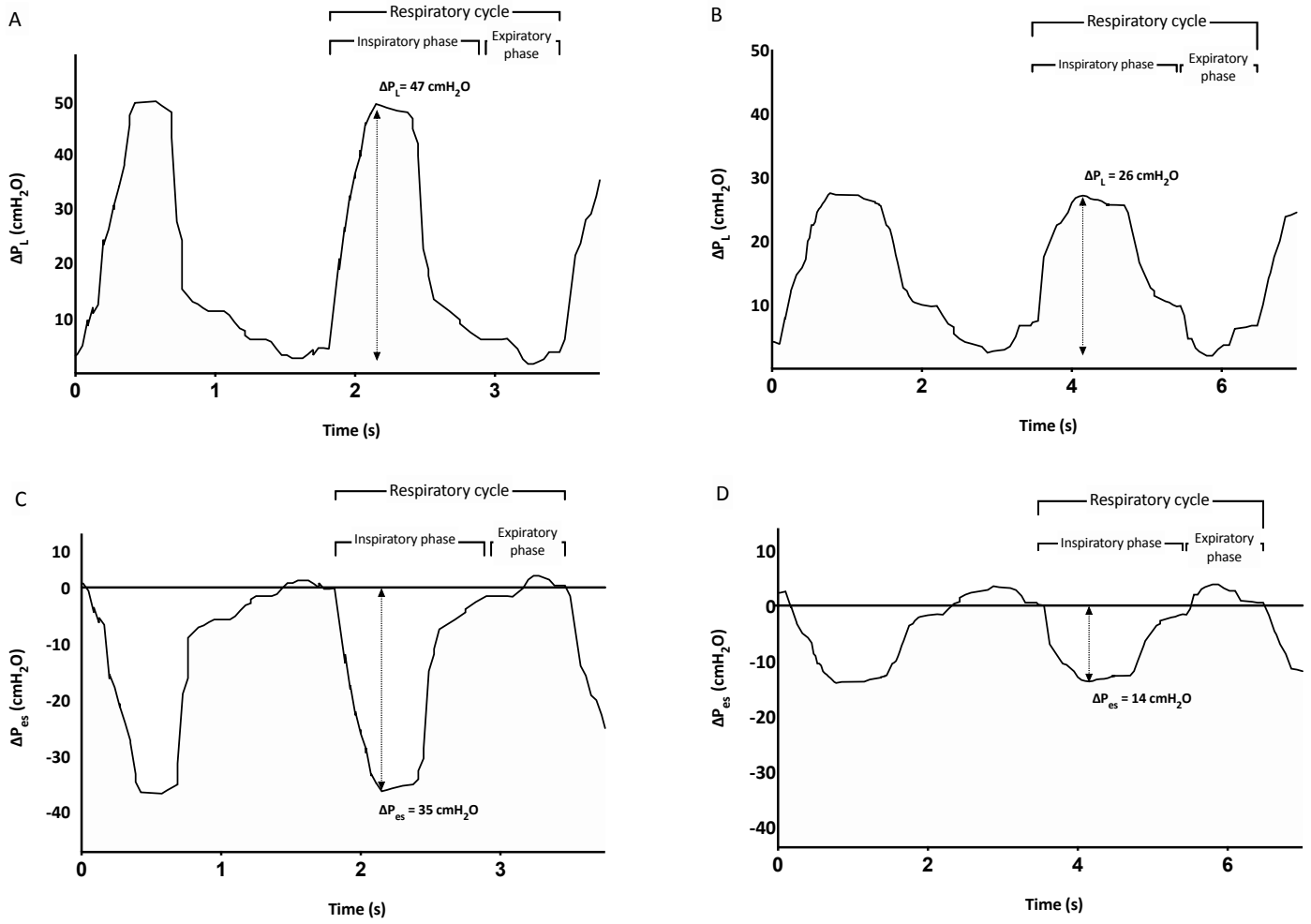

Figure 3

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.

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 4, panel A). The ratio between ΔP_{es} and ΔP_L was significantly different 2 hours after NIV start between the two groups ($p<0.0001$, Figure 4, panel C), while ΔP_L ($p=0.04$, Figure 4 panel B), Vte/kg of PBW, VE, $Vte/\Delta P_L$ ($p=0.01$, $p=0.01$, and $p=0.001$, Figure 5, panel A, B, C, respectively), RR, PaO_2/FiO_2, HACOR score ($p=0.02$, $p<0.0001$, and $p=0.03$, Figure 6, panel A, B, C, respectively) were all significantly different more than 2 hours after NIV start.

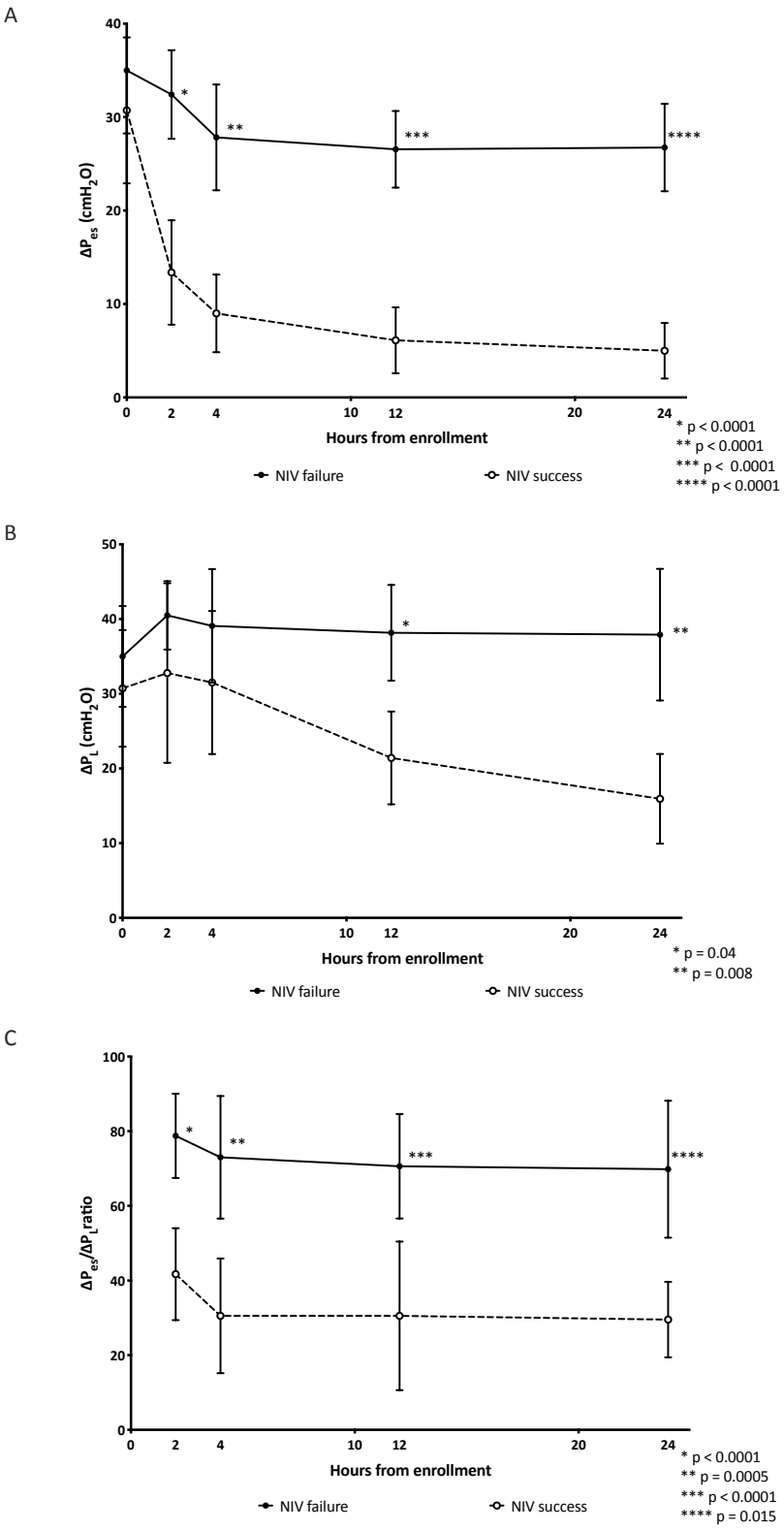

Figure 4

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. 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. Significance was set for p value < 0.05.

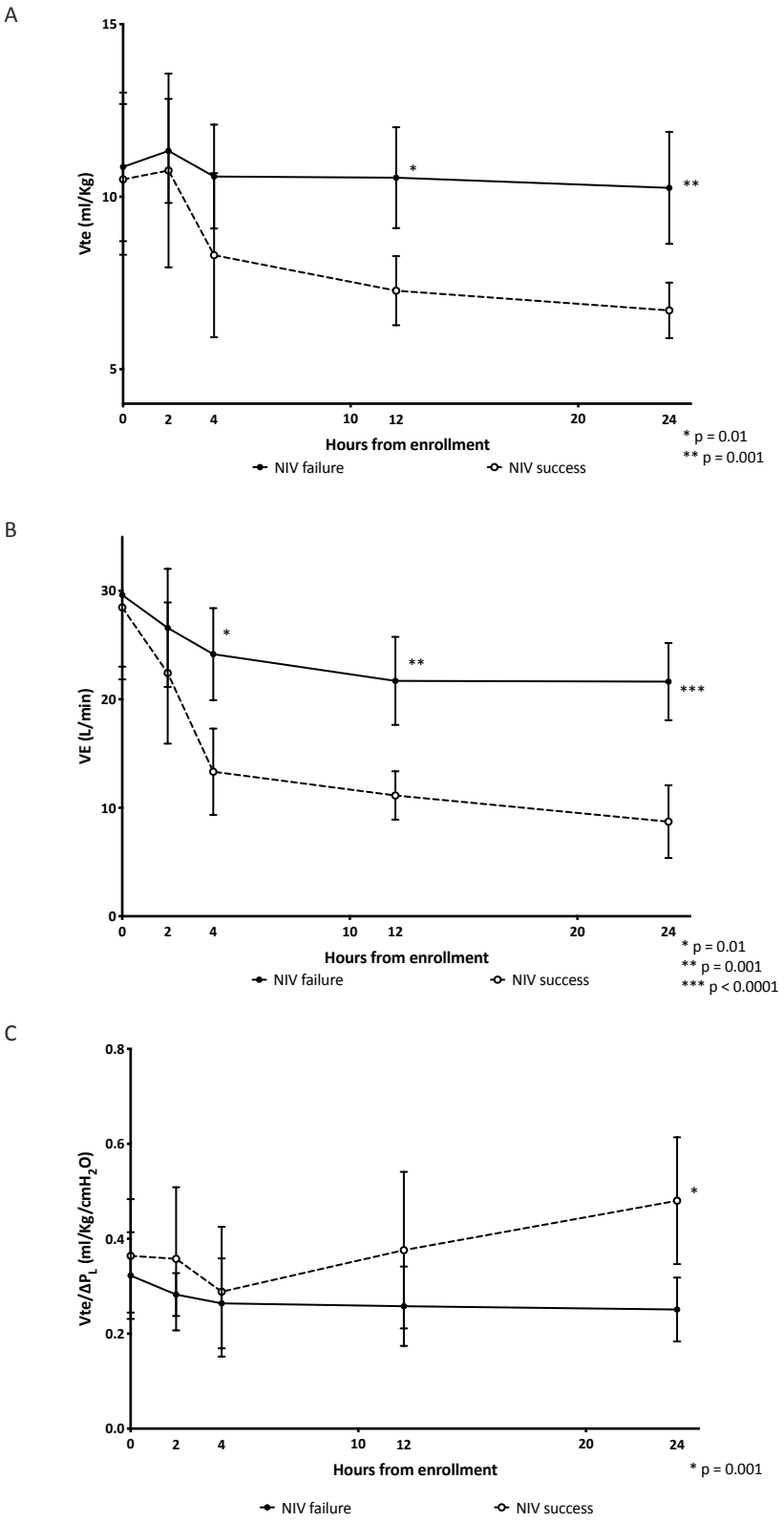

Figure 5

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. 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. Significance was set for p value < 0.05.

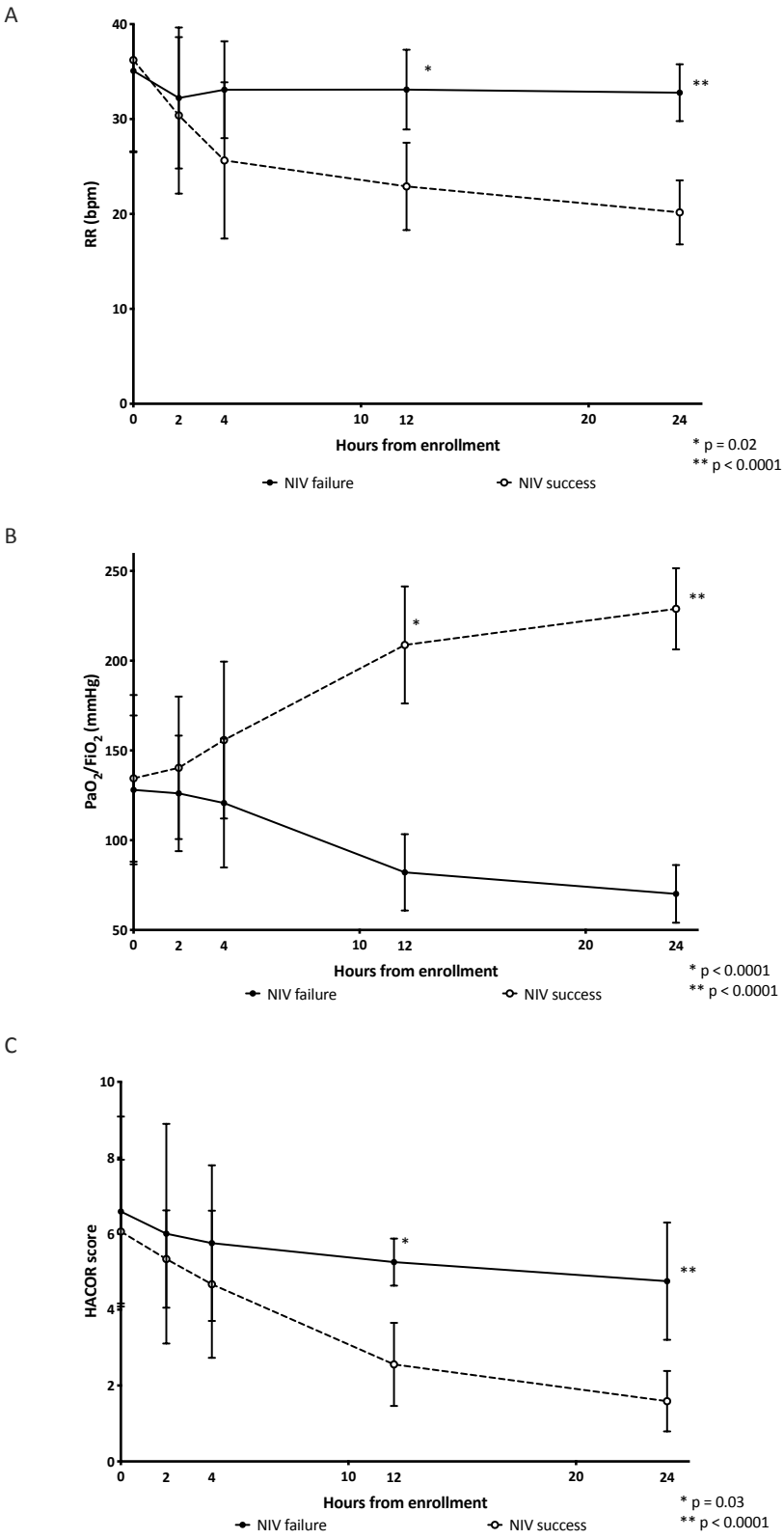

Figure 6

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. 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. Significance was set for p value < 0.05.

Significant inverse correlation was found between baseline ΔP_{es} and $Vte/\Delta P_L$ (r=-077, p<0.0001, Figure 7).

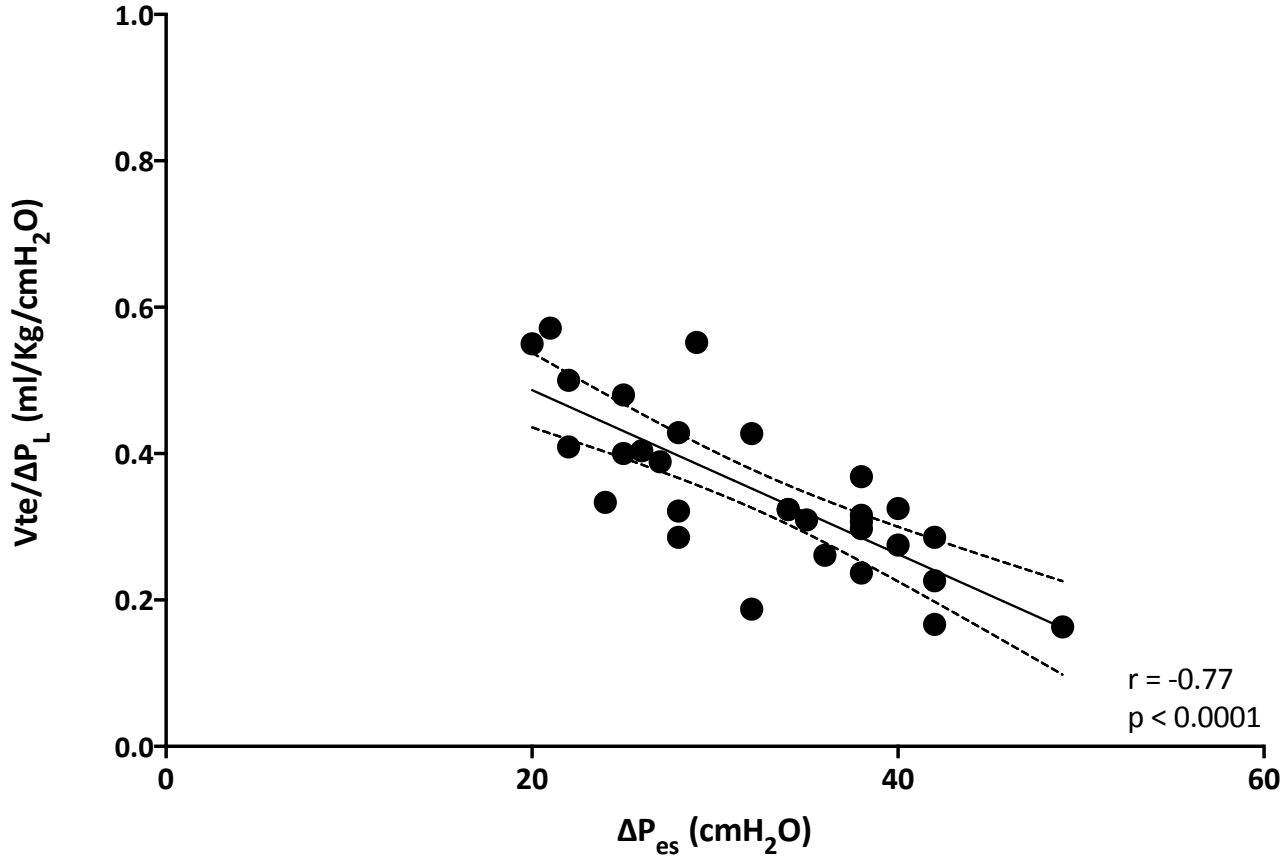

Figure 7

Correlation between ΔP_{es} and $Vte/\Delta P_L$ values on admission assessed by means of Pearson's correlation coefficient and showed through linear regression (r=-0.77, p<0.0001). Significance was set for p value < 0.05.

No significant correlation was found between baseline ΔP_{es} and PaO_2/FiO_2 ratio (r=–0.01, p=0.9, Figure 8, panel A), RR (r=0.23, p=0.2, Figure 8, panel B), HACOR score (r=0.05, p=0.8, Figure 8, panel C), and Vte/kg of PBW (r=–0.05, p=0.8, Figure 8, panel D).

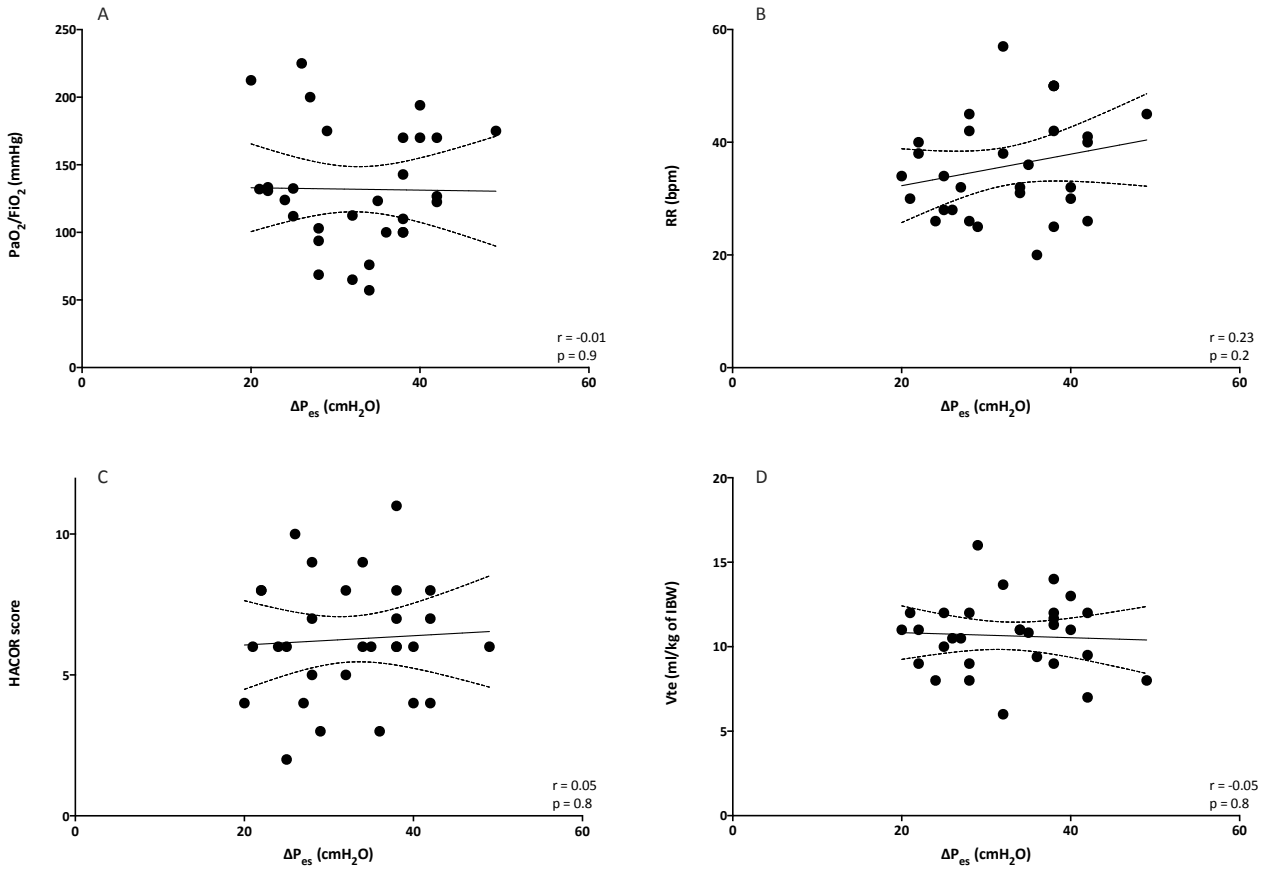

Figure 8

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. Correlation was sought by means of Pearson's correlation coefficient and showed through linear regression. Significance was set for p value < 0.05.

<u>Radiological changes and inspiratory effort</u>

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 9).

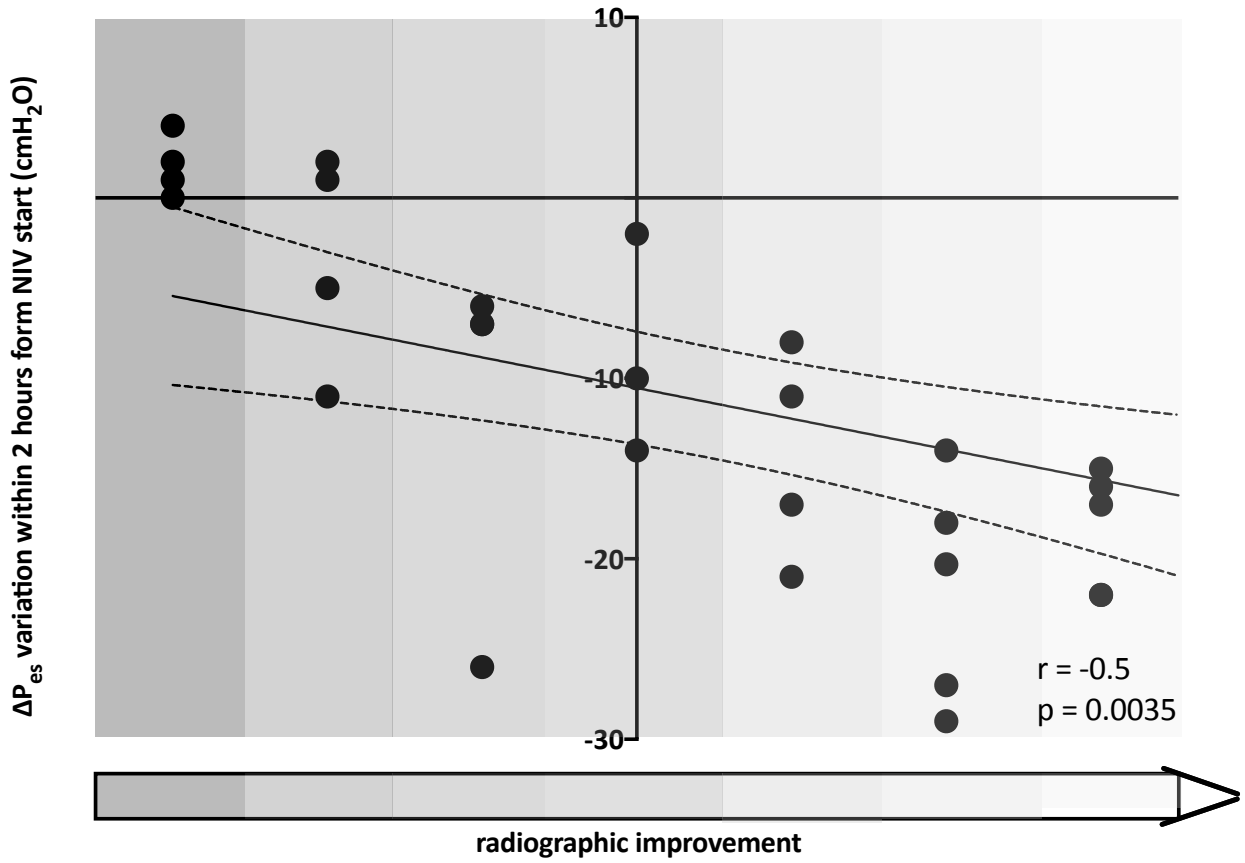

Figure 9

Correlation assessed through Pearson's correlation coefficient and showed by means of linear regression 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). Significance was set for p value < 0.05.

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 $Vte/\Delta P_L$ 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 3); $Vte/\Delta P_L$ < 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 4).

	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%	

Table 3

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

	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

Table 4

Sensitivity and specificity table derived from ROC analysis of baseline Vte/ΔP_L on NIV failure.

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 5).

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

Table 5.

Association between physiological and clinical variables and NIV failure at 24 hours assessed through a logistic regression model. Significance was set for p value < 0.05. Data are presented as odds ratio and 95%CI.

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 10) 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).

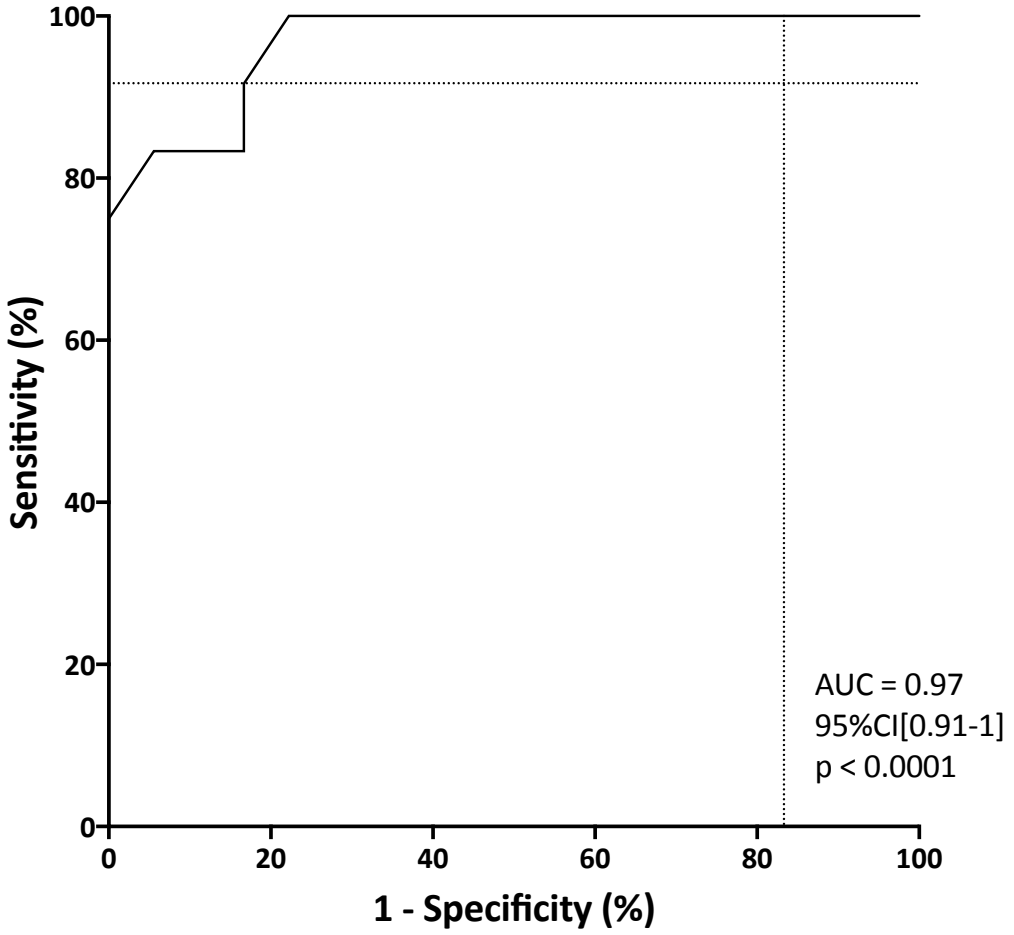

Figure 10

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). Significance was set for p value < 0.05

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 11).

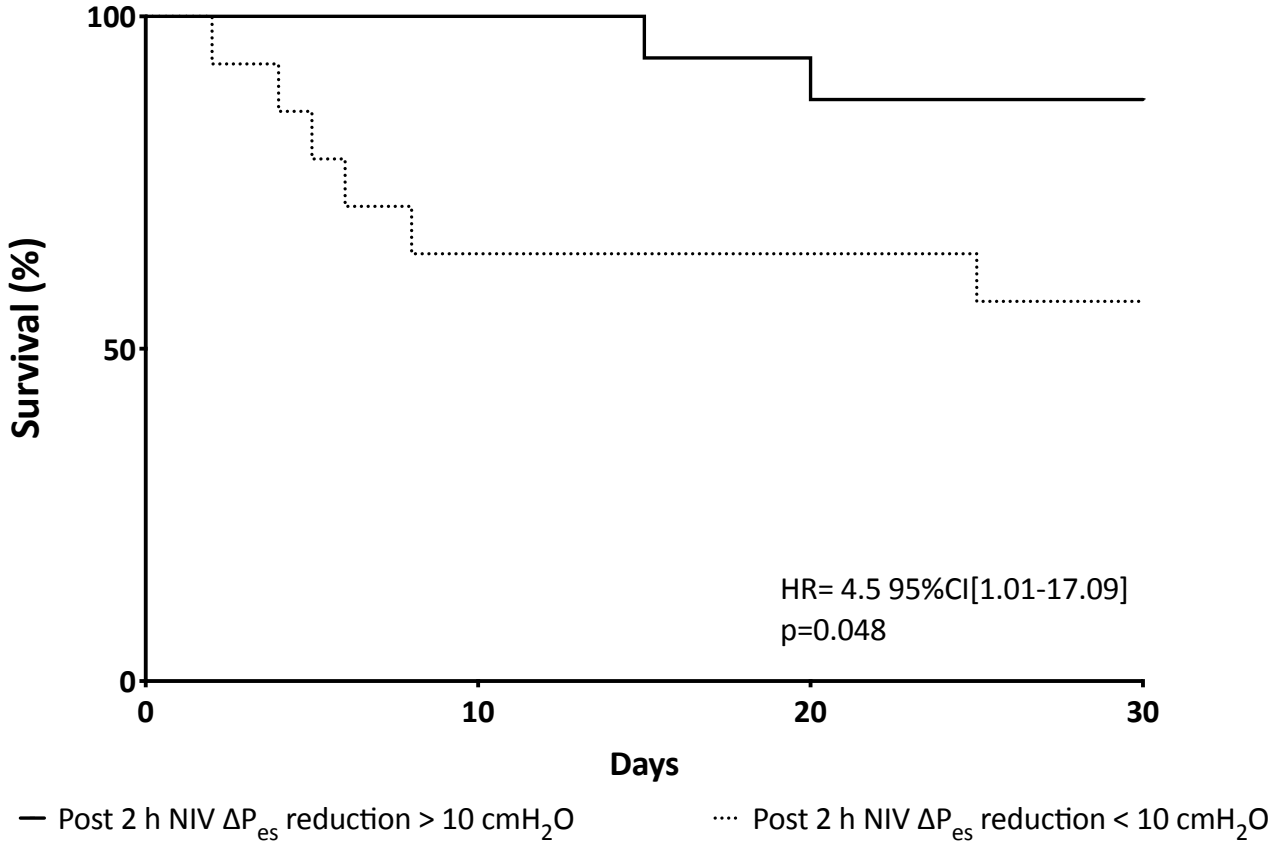

Figure 11

Probability to die at 30 days from admission according to the reduction of ΔP_{es} within the first 2 hours after NIV start expressed through hazard ratio (log-rank) and showed by means of Kaplan-Meier survival curve. Significance was set for p value < 0.05.

Discussion

In this exploratory study, patients with moderate to severe ARF 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.

Early prediction of NIV failure in ARF

The application of NIV in treating patients with ARF 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 ARF 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 ARF, 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 ARF, 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 ARF, 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 ARF (19,20). Our study presented a carefully selected population of patients with moderate to severe ARF, 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 ARF (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 ARF, 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.

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.

Conclusions

Even with the limitations described, our study highlights new concepts which can be summarized as follows: 1) patients with severe ARF 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 ARF, 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 ARF undergoing a NIV trial. Due to the exploratory nature of this study, findings should be confirmed in multicenter clinical trials.

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Inspiratory effort and lung mechanics in spontaneously breathing patients with acute respiratory failure due to COVID-19: a matched control study

Tonelli R, Busani S, Tabbì L, Fantini R, Castaniere I, Biagioni E, Mussini C, Girardis M, Clini E, Marchioni A. Inspiratory Effort and Lung Mechanics in Spontaneously Breathing Patients with Acute Respiratory Failure due to COVID-19: A Matched Control Study. Am J Respir Crit Care Med. 2021 Sep 15;204(6):725-728. doi: 10.1164/rccm.202104-1029LE. PMID: 34214009; PMCID: PMC8521698.

Abstract

Background

The respiratory mechanics of patients with COVID-19 pneumonia developing acute respiratory distress syndrome (CARDS) are still subject to debate, and probably represent a model of lung injury different from typical acute respiratory distress syndrome (ARDS). In particular, data regarding the lung mechanical behavior of CARDS in the early phase of its onset are lacking. The aim of the present study was to investigate the pathophysiological characteristics of spontaneously breathing CARDS patients in the early phase of acute respiratory failure.

Methods

Thirty-five consecutive, spontaneously breathing CARDS patients undergoing a non-invasive mechanical ventilation (NIV) trial were compared with a historic cohort of ARDS patients 1:1 matched by PaO_2/FiO_2 level. In the two groups, respiratory mechanics and respiratory drive were recorded at baseline and 2 hours after the start of NIV. Correlations between positive end-expiratory pressure (PEEP) levels and changes in lung mechanics and PaO_2/FiO_2 ratios were also assessed.

Results

At baseline, CARDS patients presented significantly lower respiratory drive activation than ARDS patients. Moreover, dynamic compliance was higher while dynamic mechanical power was lower in CARDS compared with ARDS. Two hours after starting NIV, percent variation in transpulmonary pressure and dynamic mechanical power was higher in CARDS than in ARDS. PEEP levels were inversely correlated with both dynamic compliance and PaO_2/FiO_2 ratio in CARDS, while a direct positive association with the same variables was found in ARDS.

Conclusions

In the early phase of its onset, patients with CARDS present atypical physiopathological characteristics, with a resultant mechanical behavior that is different from comparable forms of typical ARDS.

Abbreviations: ARDS, acute respiratory distress syndrome; SARS-CoV-2, severe acute respiratory syndrome CoronaVirus 2; COVID-19, coronavirus disease 2019; ARF, acute respiratory failure; bpm, breaths per minute; CARDS, coronavirus disease 2019 acute respiratory distress syndrome; IMV, invasive mechanical ventilation; ETI, endotracheal intubation; NIV, non-invasive mechanical ventilation; PEEP, positive end-expiratory pressure; PBW, predicted body weight; PSV, pressure support; SILI, self-inflicted lung injury; SOFA, subsequent organ failure assessment; RICU, Respiratory Intensive Care Unit; ICU, Intensive Care Unit; RT–PCR; real-time–polymerase chain reaction; ΔP_{es}, change in esophageal pressure; ΔP_L, change in dynamic transpulmonary pressure; RR, respiratory rate; VE, minute ventilation; VILI, ventilator-induced lung injury; Vte, expiratory tidal volume; $Vte/\Delta P_L$, expiratory tidal volume/transpulmonary pressure ratio

Introduction

Since the onset of the COVID-19 pandemic, there has been a great deal of debate as to whether acute respiratory failure (ARF) induced by CoronaVirus (SARS-CoV-2) infection should be classified as a classic form of Acute Respiratory Distress Syndrome (ARDS), or constitute a subtype of lung injury with different pathophysiological characteristics (1). Several physiological studies in COVID-19 ARDS (CARDS) have reported an overlap with the mechanical properties of the respiratory system previously found in typical ARDS but their results have been inconsistent (2–6). Recent data on physiological and radiological features in CARDS showed a lack of correlation between venous admixture and PaO_2/FiO_2 with the fraction of non-aerated lung, suggesting a different mechanism behind hypoxemia (7). Moreover, the disparity between hypoxia and lung mechanical derangement alongside a relatively spared lung compliance may indicate an unusual involvement in thrombotic lung microangiopathy (7–9). Although these observations may sound discordant, the data reported do refer to heterogeneous populations of CARDS patients undergoing invasive mechanical ventilation (IMV) with different timings of endotracheal intubation (ETI). It has been hypothesized that several physical and biological mechanisms can drive progression between the different phases of acute lung injury due to SARS-CoV-2 infection, thus modifying the mechanical properties and behavior of CARDS over time (10). Data on mechanical properties of CARDS in the early phase of its onset, when spontaneous breathing is still preserved, are still lacking. Recently, in a cohort of non-COVID-19 patients with ARF undergoing a trial of non-invasive mechanical ventilation (NIV), the magnitude of inspiratory effort was strongly correlated with the need to switch to IMV, suggesting that self-inflicted lung injury (SILI) could play a key role in lung damage progression (11). To investigate the pathophysiological characteristics in the early phase, we compared the respiratory mechanics and physiological features of spontaneously breathing CARDS patients with a historically matched cohort of ARDS patients who were candidates for a NIV trial.

Materials and methods

Study population

Patients with COVID-19 pneumonia developing CARDS consecutively admitted to the Respiratory Intensive Care Unit and the Intensive Care Unit of the University Hospital of Modena over the period between August 1st, 2020 and March 15th, 2021 were prospectively considered eligible for enrollment. This study was conducted in accordance with the pre-existing Ethics Committee "Area Vasta Emilia Nord" approval (registered protocol number 4485/C.E., document 266/16) and in the context of a previously registered protocol (*ClinicalTrial.gov: ID NCT03826797*). Informed consent to participate in the study and to allow their clinical data to be analyzed and published were obtained from participants.

Inclusion criteria were as follows: documented SARS-CoV-2 positive real-time–polymerase chain reaction (RT–PCR) on a nasal or pharyngeal swab; bilateral infiltrates documented by chest X-ray; age > 18 years; presence of ARF with PaO_2/FiO_2 ratio < 200 mmHg despite high-flow nasal oxygen (set with at least 60 L/min and FiO_2 higher than 0.6); candidates for a NIV trial according to the attending staff; and consent to receive esophageal manometry assessment.

Exclusion criteria were: cardiogenic acute pulmonary edema or concomitant hypercapnic respiratory failure ($PaCO_2$ > 45 mmHg) of any etiology; previously established diagnosis of chronic obstructive pulmonary disease, neuromuscular disease or chest wall deformities; interstitial lung disease; home long-term oxygen therapy; need for immediate ETI (11); and intolerance to NIV.

This CARDS population was 1:1 propensity score-matched (by PaO_2/FiO_2 ratio, age, body mass index [BMI] and sequential organ failure assessment score [SOFA]) with non-COVID-19 ARF extracted from our dataset (treated between 2016 and 2021). The logit of the score was taken with a caliper of 0.2 in order to maximize the number of patients without comprising the match. All patients were in a similar phase from onset of ARF, with preserved spontaneous breathing but unable to maintain SaO2> 92% despite optimized high flow oxygen (HFO), thus candidate to receive a NIV trial according to local protocol

General measurements

Demographics and clinical characteristics, arterial blood gases, PaO_2/FiO_2 ratio, respiratory rate (RR), blood lactate level, and clinical severity as assessed by the Subsequent Organ Failure Assessment (SOFA) score were recorded on admission.

Physiological measurements

A multifunctional nasogastric tube with a pressure transducer (NutriVent™, SIDAM, Mirandola, Italy) connected to a dedicated monitoring system (OptiVent™, SIDAM, Mirandola, Italy) to record swings in esophageal (P_{es}) and dynamic transpulmonary (P_L) pressures was placed before starting NIV as previously reported (11) and according to the recommended calibration protocol (12,13). 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, calculated as recommended (14). For all of the measurements, the beginning of the inspiratory phase was identified at the instant of P_{es} initial decay while the end of inspiration was considered to be the value of P_{es} where 25% of the time had elapsed from maximum deflection to returning to baseline. The respiratory flow was measured by an external heated pneumotachograph (Fleisch No.2, 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. Minute ventilation (VE) was calculated as the product of Vte and RR. $Vte/\Delta P_L$ was further measured as a surrogate for lung compliance and named "dynamic compliance". A simplified surrogate of mechanical power (defined as "dynamic mechanical power") was then calculated as 0.098 * RR * Vte * (ΔP_L + Positive end-expiratory pressure [PEEP]) (15). 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. In every single patient (in both the CARDS and ARDS groups), each measurement was recorded under standardized conditions over five consecutive minutes of spontaneous breathing, initially without ventilatory assistance, then 2 hours after starting NIV. Data were numerically stored and downloaded from a USB stick at each time point.

NIV trial

NIV was started and set by a skilled respiratory physician. 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. A heat and moisture exchanger (HME) (HYGROBAC, DAR, Mirandola, Italy) was attached

to the ventilator circuit's Y-piece. PEEP was initially set at 8 cmH_2O and subsequently fine-tuned to target a peripheral oxygen saturation (SpO_2) > 92% with a delivered inspiratory fraction of oxygen (FiO_2) less than 0.7. Pressure support (PS) was set at 10 cmH_2O, and then progressively modified, according to tidal volume (Vte/kg of PBW), to target a Vte/kg of PBW < 9.5 mL/kg of PBW and a RR < 30 breaths/min. The inspiratory trigger was set at 3 L/min and respiratory cycling was set at 25% of the inspiratory peak flow. The delivered FiO_2 was increased to target a SpO_2 of 88–94%. The oronasal facemask was tightened to target a leak flow lower than 20 L/min. All patients under NIV treatment did not receive any kind of sedation.

Statistical analysis

To build the ARDS group, a one-to-one matching procedure was performed with the nearest-neighbor method without replacement. Data are displayed as median and IQR (interquartile range). The Student's t-test assessed the difference between group means when data were distributed normally; otherwise, the Mann-Whitney U test was used. Comparison between dichotomous variables was performed with the $\chi 2$ test or Fisher's exact test, where appropriate. ANOVA was used to test as an interaction for whether the change in physiological variables 2-hour after starting NIV was different between groups. The relationship between PEEP and relative change in dynamic compliance and PaO_2/FiO_2 ratio 2 hours after starting NIV was tested with the Pearson correlation coefficient and assessed through linear regression. Statistical analyses were performed using SPSS version 25.0 with PSMATCHING3 R Extension command (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.0 (GraphPad Software, Inc., La Jolla, Ca, USA) unless otherwise indicated.

Results

Patient characteristics

CARDS (n=30) and PaO_2/FiO_2-matched ARDS groups had similar baseline characteristics, except for a lower value of blood lactate (1 vs 1.7 mmol/L, p=0.001), and a higher D-Dimer level (1310 vs 815 mg/dL, p=0.01). No differences were found between pressure values set during the NIV trial in the two groups (Table 1).

Parameter	CARDS (n=30)	ARDS (N=30)	p value
Clinical variables			
Age, years (IQR)	68 (57-77)	68 (57-78)	0.9
Male, n (%)	23 (77)	22 (73)	0.9
BMI, kg/m^2 (IQR)	24 (21-27)	24 (20-26)	0.9
Charlson index, score (IQR)	3 (2-4)	4 (2-5)	0.1
Kelly scale, score (IQR)	1 (1-1)	1 (1-1)	0.9
SOFA, score (IQR)	3 (3-4)	3 (3-4)	0.9
†PaO_2/FiO_2, mmHg (IQR)	127 (100-138)	124 (100-133)	0.9
PaO_2/FiO_2 2 hours post NIV, mmHg (IQR)	133 (118-155)	139 (119-158)	0.4
pH, value (IQR)	7.48 (7.46-7.5)	7.48 (7.44-7.5)	0.7
pH post NIV, value (IQR)	7.45 (7.44-7.46)	7.46 (7.43-7.48)	0.5
$PaCO_2$, mmHg (IQR)	33 (30-38)	34 (30-40)	0.7
$PaCO_2$ post NIV, value (IQR)	35 (32-37)	35 (32-36)	0.7
Blood lactate, mmol/L (IQR)	1 (0.7-1.2)	1.7 (1-2.2)	0.001
Serum creatinine, mg/dL (IQR)	0.7 (0.6-0.9)	0.7 (0.5-0.9)	0.8
D-dimer, mg/dL (IQR)	1310 (862-9400)	815 (540-1233)	0.01
* PEEP, cmH_2O (IQR)	10 (8-10)	10 (8-11)	0.7
* PSV, cmH_2O (IQR)	12 (10-12)	12 (10-16)	0.2
ETI, n (%)	9 (30)	11 (37)	0.8
28-day mortality, n (%)	6 (20)	5 (17)	0.9

Table 1

Characteristics of the study groups at inclusion, ventilatory settings and clinical outcome. Data are presented as number (n) and percentage for dichotomous values or median and interquartile ranges (IQR)) for continuous values. The nonparametric Mann–Whitney and Student t test were used for the comparison of continuous variables. Comparison between dichotomous variables was performed by the χ2 test or Fisher's exact test, where appropriate. Significance was set for p value < 0.05. PEEP and PSV values reported were those measured during the first 2 hours of NIV. † The values of PaO_2/FiO_2 ratio used for matching these groups as well as pH and PCO_2 values were those measured during HFNC before starting NIV.*

Physiological measurements

At baseline, the median value of ΔP_{es} was significantly lower in the CARDS group compared with ARDS patients (12 vs 34 cmH_2O, p<0.0001) (Figure 1).

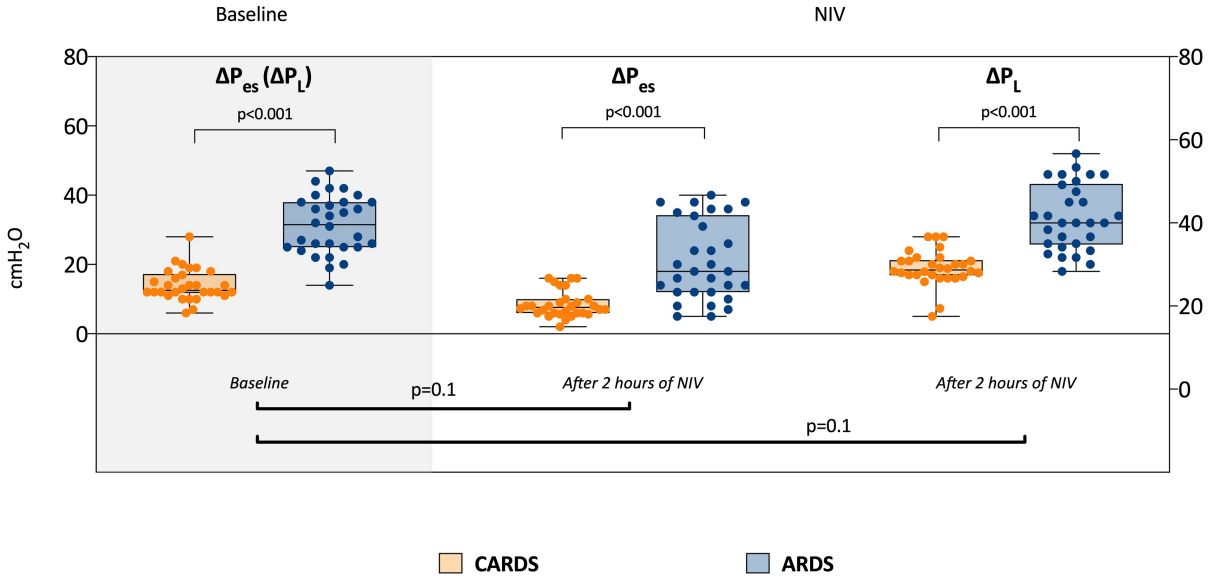

Figure 1

Measured individual values of ΔP_{es} and ΔP_L in the matched study groups either at baseline and 2-hour after initiating NIV. The Student's t-test assessed the difference between group means. ANOVA was used to test as an interaction for whether the change in physiological variables 2-hour after starting NIV was different between groups. Significance was set for p value < 0.05. No statistical difference was found when testing as an interaction for whether the change of ΔP_{es} and ΔP_L 2 hours after starting NIV was different between CARDS and ARDS (p=0.1 and p=0.1 respectively).*

All values of lung mechanics, RR, VE, Vte and dynamic mechanical power at baseline and 2-hour after starting NIV are resumed in Table 2. At baseline, CARDS patients showed lower value of RR (p<0.001), Vte (p=0.003), VE (p<0.001), dynamic mechanical power (p<0.001) and higher dynamic

compliance (p<0.001) as compared to ARDS. A significant reduction in ΔPes and RR and a significant increase in dynamic mechanical power was reported for both groups, while no change was noted in either dynamic compliance or Vte 2-hour after starting NIV.

Parameter	**CARDS (n=30)**			**ARDS (N=30)**			**p value**
Mechanical variables	**Baseline**	**2 hours post NIV**	**p value**	**Baseline**	**2 hours post NIV**	**p value**	**ANOVA**
ΔP_{es}, cmH_2O (IQR)	12.5 (11.8-17.3)	7.6 (6-10)	<0.0001	32 (25-38)	18 (12-34)	<0.001	0.1
ΔP_L, cmH_2O (IQR)	12.5 (11.8-17.3)	18.4 (17- 21)	<0.0001	32 (25-38)	32 (26-43)	0.5	0.1
RR, bpm (IQR)	28 (25–30)	24 (21–26)	<0.0001	35 (30–41)	31 (24–38)	0.01	0.1
VE, L/min (IQR)	20 (17–23)	18 (15–22)	0.1	27 (23–32)	24 (20–28)	0.004	0.6
Vte, mL/kg of PBW (IQR)	9.2 (8.1–10.3)	10.1 (9–11.2)	0.2	11 (9–12)	10.2 (10–12)	0.4	0.6
Dyn compliance, mL/cmH_2O (IQR)	55 (40-69)	41 (31-52)	0.1	25 (19-31)	21 (16-34)	0.9	0.2
*Dyn mechanical power, J/min (IQR)	27 (19-40)	56 (41-60)	<0.0001	95 (68-107)	102 (66-130)	0.1	0.2

Table 2

*Mechanical variables before and after NIV of the study groups at inclusion. Data are presented as median and interquartile ranges (IQR)) for continuous values. The nonparametric Mann–Whitney and Student t test were used for the comparison of continuous variables. Significance was set for p value < 0.05. *Dyn mechanical power = ΔP_L * 98 x Vte * 10^{-6} x RR/60.*

Despite no interaction was found between groups and changes in the physiological variables after NIV, ΔPL showed a statistically significant increase in patients with COVID-19. In this group the baseline value of dynamic mechanical power was considerably lower than in non-COVID-19 (27 vs 95 J/min, p<0.0001). After NIV, the dynamic mechanical power showed a statistically significant increase in COVID-19. More specifically, CARDS patients showed a significant reduction in ΔP_{es} and RR (Figure 2, panel A and D), a significant increase in ΔP_L and dynamic mechanical power (Figure 2, panel B and F), while no change was noted in either dynamic compliance or Vte (Figure 2, panel C and E). On the other hand, 2 hours after starting NIV, there was a significant reduction in ΔP_{es} and RR (Figure 3, panel A and D) in ARDS patients, but no changes in any other recordings (Figure 3, panels B, C, E, and F).

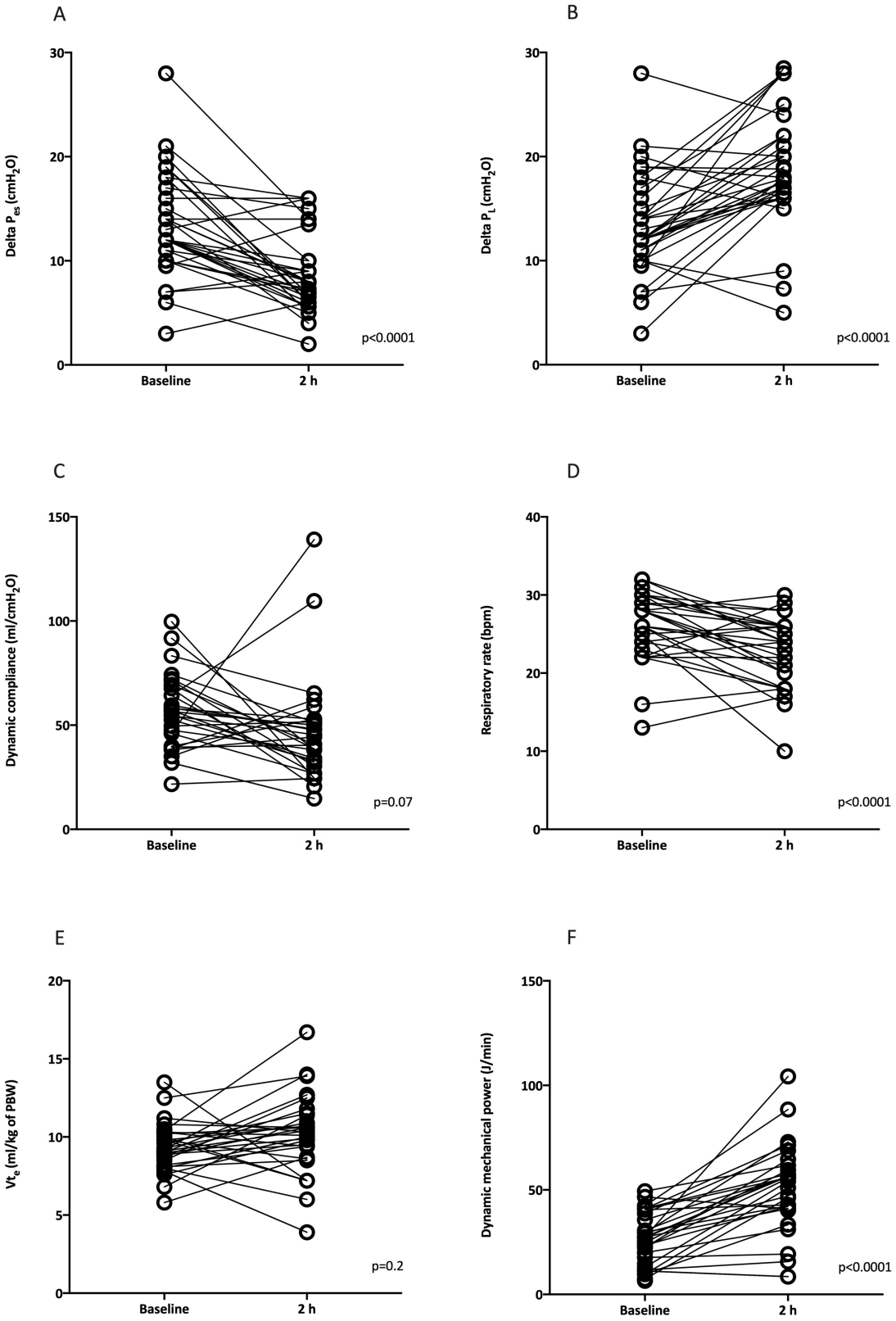

Figure 2

Physiological effect of NIV application in CARDS patients displaying individual changes in ΔP_{es} (panel A), ΔP_L (panel B), dynamic compliance (panel C), respiratory rate (panel D), Vte (panel E), and dynamic mechanical power (panel F). The Student t test for paied varibales was used for the comparison. Significance was set for p value < 0.05

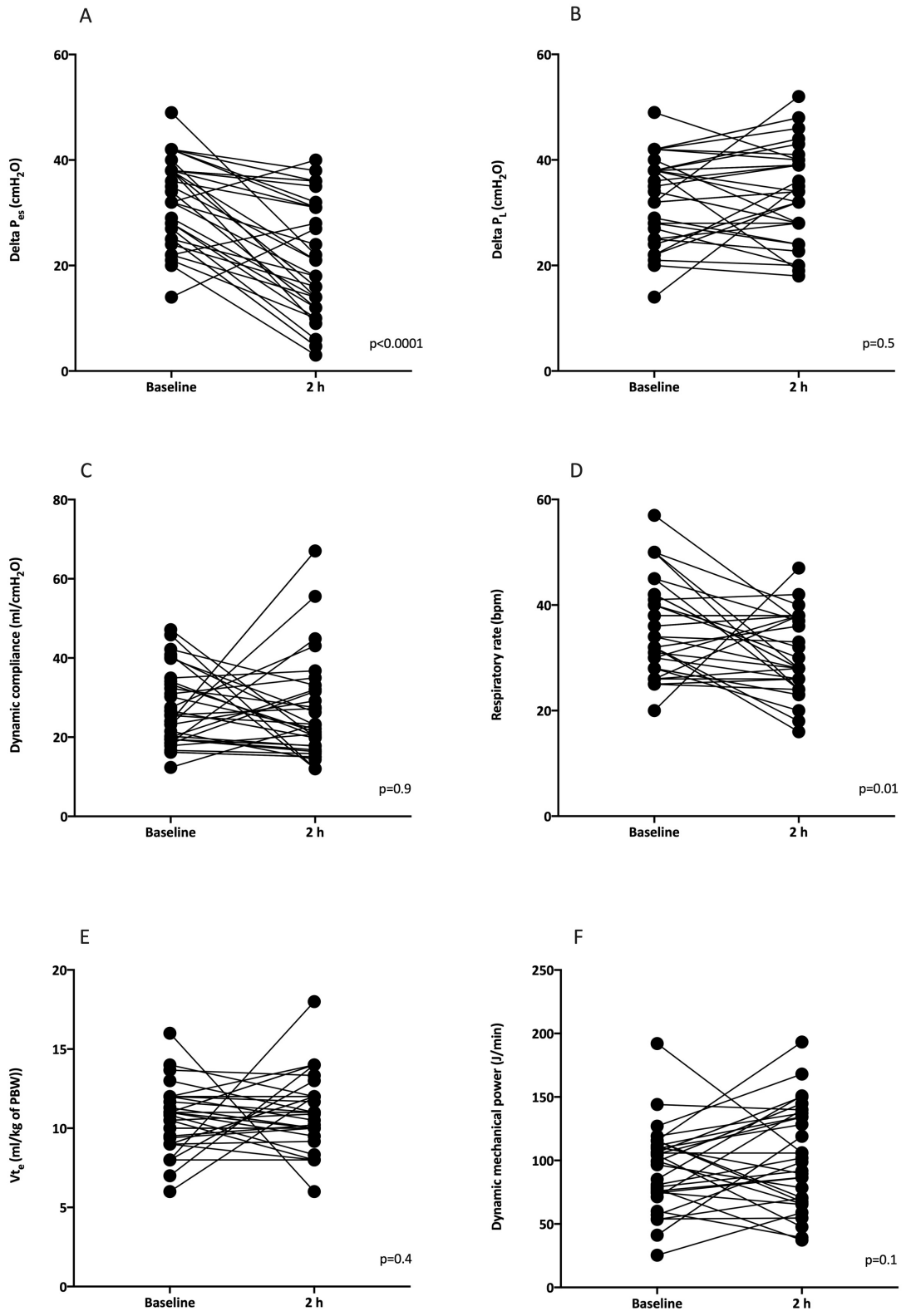

Figure 3

Physiological effect of NIV application in ARDS patients displaying individual changes in ΔP_{es} (panel A), ΔP_L (panel B), dynamic compliance (panel C), respiratory rate (panel D), Vte (panel E), and dynamic mechanical power (panel F). The Student t test for paied varibales was used for the comparison. Significance was set for p value < 0.05

Two hours after starting NIV, PEEP levels were inversely correlated with dynamic compliance variation in CARDS (r=–0.41, p=0.01 see Figure 4, panel A), while a direct positive association was found in ARDS patients (r=0.45, p=0.01, see Figure 4, panel B). Similarly, PEEP levels were inversely (r=–0.08, p=0.7, panel C, Figure 4) and directly (r=0.3, p=0.06, panel D, Figure 4) correlated with PaO_2/FiO_2 ratio variation in CARDS and ARDS patients, respectively, although statistical significance was not achieved.

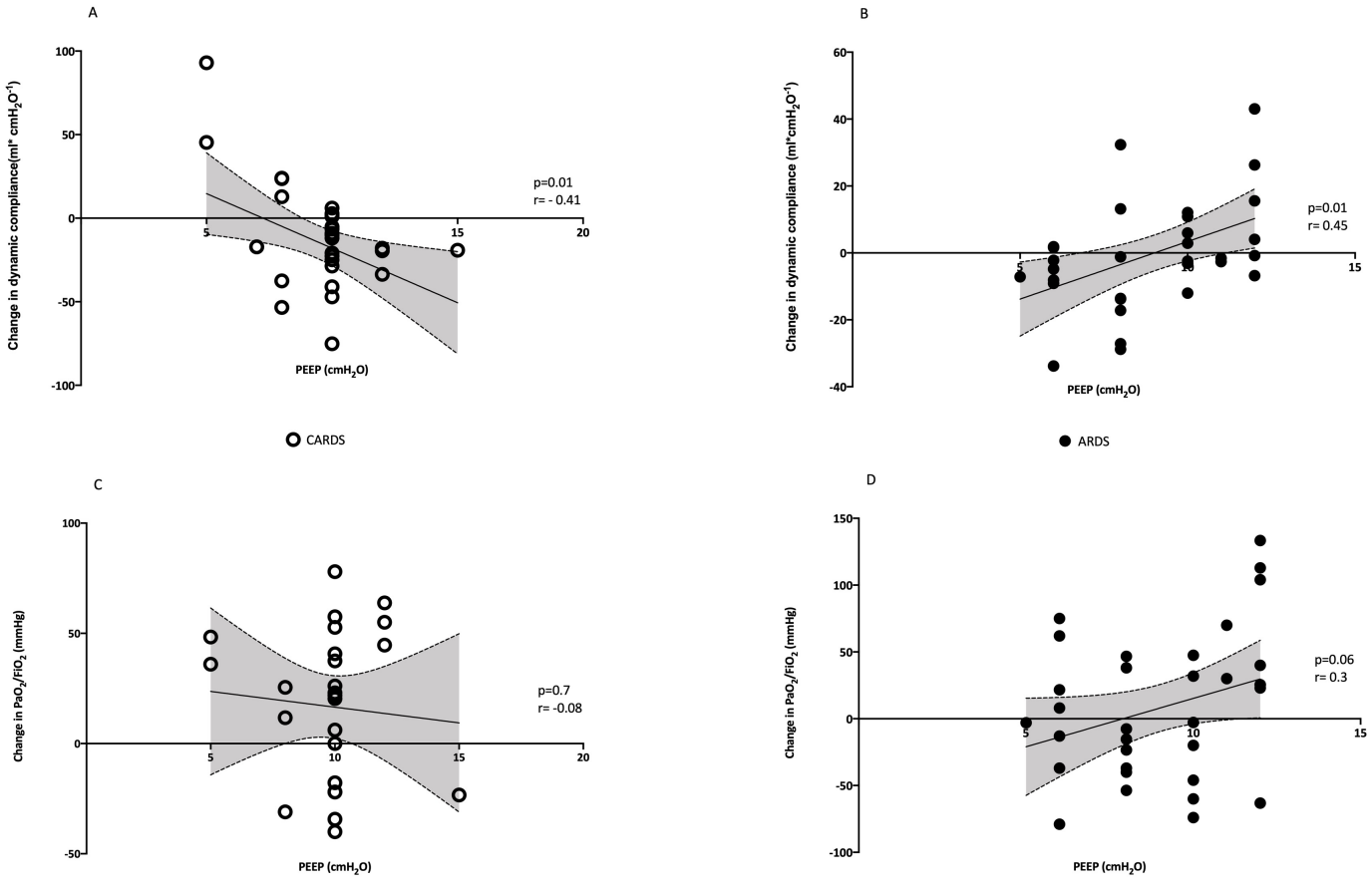

Figure 4

Correlation assessed through Pearson's correlation coefficient and showed by means of linear regression between PEEP values and change in both dynamic compliance and PaO_2/FiO_2 ratio in CARDS (panel A and C, respectively) and ARDS (panel B and D, respectively) groups. Significance was set for p value < 0.05

Discussion

Our physiological investigation demonstrated that in the early phase of severe ARF, when requiring NIV, patients with COVID-19 pneumonia (CARDS) behave with different mechanical characteristics and respiratory drive activation when compared with typical ARDS. To our knowledge, this is the first report assessing respiratory mechanics and inspiratory effort in spontaneously breathing patients with COVID-19 pneumonia, while other authors have partially reported some of these characteristics in patients already under IMV (16,17).

In the early phase of the outbreaks, some observations identified COVID-19 pneumonia as a heterogenous disease, whose distinctive features were severe impairment of gas exchange associated with relatively spared respiratory system compliance (18). Further studies exploring the mechanical characteristics of mechanically ventilated CARDS patients, found a significant overlap with the classic form of ARDS, with a median respiratory system compliance ranging from 27 to 41 mL/cmH_2O. These data have led us to recommend similar ventilatory strategies in ARDS patients with the same mechanical and clinical characteristics, without regard to whether they present respiratory failure after COVID-19 pneumonia or no-COVID underlying conditions (3–5,19–21). Notwithstanding, the data available refers to cohorts undergoing IMV. Moreover, since the timing of ETI was not standardized and, mainly in early pandemic waves, often relied on the availability of ICU resources, patients were presumably screened at different stages of the disease. This may justify the heterogenous findings reported, likely due to the time in which the patients were subjected to IMV. On the other hand, our study showed that, in the early phase of ARF, when spontaneous breathing is preserved, the dynamic compliance of the respiratory system is twice as high in CARDS patients as in those with typical ARDS (57 vs 24 mL/cmH_2O), at comparable P/F ratio. This observation reinforces the concept that, in the initial stage of its onset, CARDS is a specific disease, whose main feature is a gap between the severity of hypoxia and respiratory mechanics derangement. Furthermore, the abnormally elevated mean value of D-Dimer found in patients with COVID-19 pneumonia (Table 1), is likely to suggest the role of microvasculature involvement in the mechanism of CARDS.

Recently, it has also been speculated that the progression across CARDS may be triggered by excessive inspiratory drive activation (10,22). A growing body of evidence from experimental studies suggests that, in patients with ARDS, a vigorous respiratory effort could worsen regional lung damage, introducing the concept of self-induced lung injury (SILI) (23–25). A clinical experiment by our group recently found that patients with moderate to severe ARF undergoing NIV exhibited very

high respiratory drive activation (median esophageal pressure swing 34 cmH_2O), and this remained high during the early phase of non-invasive ventilation and was associated with unfavorable outcomes, thus reinforcing the idea of SILI during assisted spontaneous breathing (11). Data in the present study showed a relatively low activation of respiratory drive in patients with moderate to severe CARDS during the early phase of NIV support (median ΔP_{es} 12 cmH_2O, RR 23 bpm, Vte 9.1 mL/kg of PBW), which is in line with the clinical concept of "happy hypoxemia" (26) and underlines the mismatch between central drive activation and moderate to severe hypoxia, at variance with the typical form of ARDS. Moreover, at least theoretically, the present data suggest that, in the very early phase of assisted spontaneous breathing, the role of SILI in determining lung damage in CARDS does not seem as crucial as in typical ARDS. Nevertheless, even if respiratory drive was under less stress compared with ARDS, the application of NIV in CARDS resulted in an even better percent reduction in inspiratory effort and respiratory rate (see Figure 2 and Figure 3, panel A and D).

Another debated issue in the ventilatory management of CARDS is the role of alveolar recruitment in improving lung mechanics (27). A very recent study in patients with severe CARDS undergoing IMV reported that a higher PEEP setting resulted in limited alveolar recruitment as assessed by computed tomography (CT) lung weight quantification (28). Those authors speculated that, unlike ARDS, PEEP might improve oxygenation by ameliorating the ventilation to perfusion (V/Q) matching in lung regions with low V/Q, rather than through alveolar recruitment. In another series of 10 CARDS patients receiving lung-protective ventilation, using high PEEP was associated with worsening of lung compliance with no beneficial effects on gas exchange (29). These findings were recently confirmed by Coppola et al. who showed that, in 23 critically ill patients with CARDS, increasing PEEP from a low (5 cmH_2O) to a higher (15 cmH_2O) level led to a significant deterioration in lung mechanics (30). In our cohort of CARDS patients, dynamic compliance showed a trend to reduction 2 hours after starting NIV (Figure 2, panel C). Moreover, even though our study was not designed to obtain information on lung behavior according to PEEP levels, we have noted that elevated values of PEEP were inversely correlated with the relative change of PaO_2/FiO_2 ratio and dynamic lung compliance after NIV. In contrast, typical ARDS patients showed a favorable association between PEEP values, respiratory mechanics, and gas exchange 2 hours after starting NIV, suggesting a different behavior in response to recruitment (Figure 4).

The concept of mechanical power has recently been developed to explore the interaction between ventilatory support and lung damage. In particular, the degree of ventilator-induced lung injury (VILI) has been related to the amount of energy transferred from the mechanical ventilator to the

respiratory system (31). Assuming that the amount of energy to which the lung is subjected may be crucial, even during assisted spontaneous breathing, thus influencing SILI development, we derived a simple surrogate of mechanical power replacing the change in airway pressure during inspiration with dynamic transpulmonary pressure (15). In our CARDS group, the baseline value of dynamic mechanical power was considerably lower than in ARDS (27 vs 99 J/min, $p<0.0001$). After the NIV trial, the dynamic mechanical power showed a significant increase in CARDS patients alone. This may suggest an unfavorable interaction between potential and kinetic energy transferred from the respiratory muscles and the mechanical ventilator to the lungs of these patients, at least in the early phase of NIV. Nevertheless, the absolute value of dynamic mechanical power in CARDS was significantly lower than in patients with ARDS, even after NIV, with a resultant low risk of NIV-induced lung injury.

Clinical implications

The present findings have potentially new clinical implications. First, given the low respiratory drive activation – also reflected in low dynamic mechanical power – alongside a relatively unchanged dynamic compliance found in the early stages of CARDS, great caution should be taken when considering early ETI to anticipate protective MV in these individuals (32). Indeed, ventilatory management might account for the extremely broad mortality range across patients with similar disease severity (20–80%) (33). Notably, comparing intubation rates between pandemic waves, it has been shown that a 41.9% decrease in ETI rate was associated with a 20.9% decrease in 28-day mortality (34). Second, given the low recruitability of early CARDS, we suggest a low PEEP setting under non-invasive ventilatory assistance to minimize the mechanical disadvantage due to local parenchymal overdistension. This is in line with a growing body of evidence that highlights the efficacy of the high-flow nasal cannula (HFNC) in reducing the endotracheal intubation rate (35–37). Lastly, continuous monitoring of a patient's inspiratory effort associated with dynamic respiratory mechanics, could indicate the transition from a lung with fluid-like lung behavior to a lung with solid-like mechanical properties (i.e. similar to a typical form of ARDS). Therefore, we believe that assessing ΔP_{es} over time might assist intensivists in answering the "*intubate or not intubate*" dilemma. Moreover, based on our data, we can suggest more tailored ventilation strategies according to ΔP_{es} monitoring.

Limitations

Our study suffers from several limitations. First, it represents an exploratory analysis with no sample size assessment, limited number of patients and monocentric design. Second, the higher baseline blood lactate value in non-COVID-19 group may reflect a difference in terms of balance from oxygen delivery to tissue metabolic needs, with potential influence on the breathing pattern. An elevated value of lactic anions, even in the absence of blood acidosis, might have boosted the ventilatory response, configuring a non-mechanical factor influencing the different behavior between COVID-19 and non-COVID-19 patients. Third, the observational nature of the study design does not allow to draw firm conclusions on respiratory response to NIV application. Fourth, major concerns should be raised with regard to the dynamic mechanical power measured here as a surrogate marker for mechanical power to analyze respiratory mechanics in spontaneously breathing non-intubated patients. Our calculation is derived from the simplified equation by Becher et al. (15), whose assumption was an ideal "square wave" P_{aw} during inspiration, which is not reproducible during spontaneous or assisted breathing (i.e. NIV). Despite these approximations, we do believe that this index may represent a reliable estimate of the amount of energy transferred from respiratory muscle and ventilatory assistance to the lung during assisted spontaneous breathing. Finally, we limited our analysis to a 2-hour snapshot during the NIV trial, and did not explore changes over a longer period. Notwithstanding, we believe that this preliminary observation supports implementation of continuous monitoring of the patient's inspiratory effort during episodes of hypoxemic ARF. At difference with ARDS, results in CARDS indicate a limited inspiratory effort in the early phase of ARF thus suggesting caution when considering early ETI to anticipate protective MV in these individuals.

Conclusions

This study indicates that, in the early phase of its onset, CARDS presents atypical physiopathological characteristics, with a resultant different mechanical behavior (i.e. better compliance and lower respiratory drive activation) when compared with typical ARDS, thus making lungs less prone to SILI development. At this stage of the disease, the relatively spared compliance may justify the limited beneficial effect of PEEP in alveolar recruitment. Further studies should focus on assessment of the mechanical properties of CARDS over disease stages, assuming a dynamic progression of lung damage.

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Nasal pressure swings as the measure of inspiratory effort in spontaneously breathing patients with COVID-19-associated acute respiratory failure

Abstract

Background

Exaggerated inspiratory effort could translate into self-inflicted lung injury (SILI), thus worsening clinical outcomes of patients with acute respiratory failure of different etiology undergoing noninvasive respiratory support Although esophageal manometry is a reliable method to estimate the magnitude of inspiratory effort and the risk of SILI in patients with acute respiratory failure (ARF), procedural issues significantly limit its use in daily clinical practice. The aim of this proof-of-concept physiological study was to describe the correlation between nasal (ΔP_{nos}) and esophageal pressure swings (ΔP_{es}) as a potential measure of inspiratory effort in spontaneously breathing patients with COVID-19-associated ARF.

Methods

From January 1st, 2021 to April 1st, 2021, 51 consecutive patients with ARF admitted to the Respiratory Intensive Care Unit (RICU) of the University Hospital of Modena (Italy) and candidate to escalation of non-invasive respiratory support (NRS) were enrolled. Clinical features and tidal changes in esophageal and nasal pressure were recorded on RICU admission and 24h after NRS start. Correlation between ΔP_{es} and ΔP_{nos} served as primary outcome while their associations with NRS outcome at 72h were further assessed as secondary outcomes.

Results

ΔP_{es} and ΔP_{nos} showed high correlation at baseline (R^2=0.92, p<0.001), with all patients under high flow nasal cannula (HFNC), and at 24 hours (R^2=0.96, p<0.001), with most patients receiving non-invasive ventilation (NIV). The correlations between ΔP_{es} and ΔP_{nos} at 24 hours remained significant after splitting the study population according to the NRS (HFNC or NIV) received. At 24h, patients who were further intubated had both higher ΔP_{es} (14 [12–18] versus 6 [5–8] cmH_2O, p<0.001) and ΔP_{nos} (7.5 [5.6–8] versus 2.9 [2–3.2] cmH_2O, p<0.001) as compared with those who succeeded NRS.

Conclusions

In patients with COVID-19-associated ARF, ΔP_{es} and ΔP_{nos} are highly correlated during assisted and non-assisted spontaneous tidal breathing.

Abbreviations: ARF, acute respiratory failure; NRS, non-invasive respiratory support; NIV, non-invasive mechanical ventilation; HFNC, high flow nasal cannula; P_L transpulmonary pressure; ΔP_{es}, esophageal pressure swings; ΔP_{nos}, nasal pressure swings; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus-2; COVID-19, SARS-CoV-2 induced Disease; RICU, Respiratory Intensive Care Unit; RR, respiratory rate; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation; SAPS II Simplified Acute Physiology Score; PEEP, Positive end-expiratory pressure; PS, pressure support; RT-PCR real-time–polymerase chain reaction; BPM, breaths per minute; IQR, interquartile range; FiO_2, fraction of oxygen; ETI, endotracheal intubation; ROC, receiver operating characteristic; SNIP, Sniff Nasal Inspiratory Pressure; ΔP_{aw}, airway pressure swings.

Introduction

Inspiratory effort producing excessive transpulmonary pressure (P_L) has a key role in lung damage progression during acute respiratory failure (ARF) of different etiology (1), including severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) induced disease (COVID-19) (2). Negative alveolar pressure, *pendelluft* phenomenon, local overstretch of dependent lung zones and asymmetrical distribution of P_L applied to inhomogeneous lung parenchyma have been hypothesized as potential mechanisms of injury (3, 4). These mechanisms could translate into self-inflicted lung injury (SILI) and worsen clinical outcomes of spontaneously breathing patients with ARF (3, 4). Esophageal pressure swings (ΔP_{es}) mirror P_L during non-assisted spontaneous breathing, thus esophageal manometry may be a reliable estimate of the magnitude of inspiratory effort (5) and could predict failure of non-invasive positive pressure ventilation (NIV) (4, 6).

However, esophageal manometry is not easy to implement at the bedside (7), especially in unstable patients with respiratory distress and severe impairment of gas exchange (8, 9). Notwithstanding, respiratory monitoring of patients with ARF would be useful in all patients at risk of SILI (8). The recent COVID-19 pandemic has increased the number of patients with ARF breathing spontaneously and requiring non-invasive respiratory support (NRS), especially outside the intensive care setting (10). These patients are at risk of deterioration and could benefit from continuous monitoring of inspiratory effort (11). Early physiological studies comparing ΔP_{es} with nasal (ΔP_{nos}) and mouth pressure swings, showed no phase difference between pressure waveforms during incremental inspiratory effort (12) and correlation between ΔP_{es} and airway pressure swings (ΔP_{aw}) during inspiratory effort test performed with an occlusion maneuver (13, 14).

The primary aim of this proof-of-concept physiological study was to describe the correlation between ΔP_{es} and ΔP_{aw} captured by ΔP_{nos} in a cohort of spontaneously breathing patients with COVID-19-associated ARF candidate to receive non-invasive respiratory support (HFNC or NIV). We hypothesized that ΔP_{es} and ΔP_{nos} were correlated. The correlation between ΔP_{es} and ΔP_{nos} in patients during different types of NRS and the association with NRS outcome at 72 hours served as secondary outcomes.

Materials and methods

Study cohort

Patients with COVID-19 pneumonia developing ARF admitted to the Respiratory Intensive Care Unit (RICU) of the University Hospital of Modena between January 1st, 2021 and April 1st, 2021 were prospectively considered eligible for enrollment. This was a pre-planned sub-study of a previously registered protocol (ClinicalTrial.gov: ID NCT03826797). The local Ethics Committee (Comitato Etico Area Vasta Emilia Nord) approved the study approval (protocol number 4485/C.E., document 266/16). Written informed consent was obtained from all participants.

Inclusion criteria were documented severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) positive real-time–polymerase chain reaction (RT–PCR) on a nasal or pharyngeal swab; bilateral infiltrates documented by chest X-ray; age > 18 years; presence of ARF with a peripheral oxygen saturation (SpO_2) < 90% under conventional oxygen supply through Venturi mask with an inspiratory oxygen fraction (FiO_2) of 0.5, candidate to escalation of respiratory assistance to HFNC; and consent to receive esophageal and nasal manometry assessment. Exclusion criteria were cardiogenic acute pulmonary edema or concomitant hypercapnic respiratory failure ($PaCO_2$ > 45 mmHg) of any etiology; previously established diagnosis of chronic obstructive pulmonary disease, neuromuscular diseases, significant anatomical alterations of the nasal tract, or chest wall deformities; interstitial lung disease; home long-term oxygen therapy and need for immediate endotracheal intubation.

Measurements

Demographics and clinical characteristics, arterial blood gases, PaO_2/FiO_2 ratio, respiratory rate (RR), blood lactate level, and clinical severity as assessed by the Sequential Organ Failure Assessment (SOFA) score, the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II and the Simplified Acute Physiology Score (SAPS) II were collected at admission.

Once admitted to the RICU and enrolled all patients received HFNC. The escalation from HFNC to NIV was made upon clinical decision by the attending staff blinded to the study purposes. All patients underwent two subsequent assessments of ΔP_{es} and ΔP_{nos}: the first (baseline assessment) was performed soon after RICU admission on HFNC; the second (24 h assessment) was performed after 24 hours, with the NRS (HFNC or NIV) set by the RICU staff at that time.

The P_{es} swing was measured by means of a multifunctional nasogastric tube (NutriVent™, SIDAM, Mirandola, Italy) according to a standardized protocol (4). The P_{nos} swing was measured through a

plug allocated in the nostril where the nasogastric tube was placed during spontaneous breathing while the contralateral nostril was kept patent, both during HFNC and NIV. The plug was made of one hypoallergenic foam ear plug (3M Company, Saint Paul, Minnesota (MN), USA) with inserted a 16 Gauge polyurethane intravenous cannula. The esophageal balloon and the nasal plug were connected to two pressure transducers included in a dedicated monitoring system (OptiVent^{TM}, SIDAM, Mirandola, Italy) via two identical 100-cm polyurethane catheters. ΔP_{es} and ΔP_{nos} were assessed simultaneously (Figure 1).

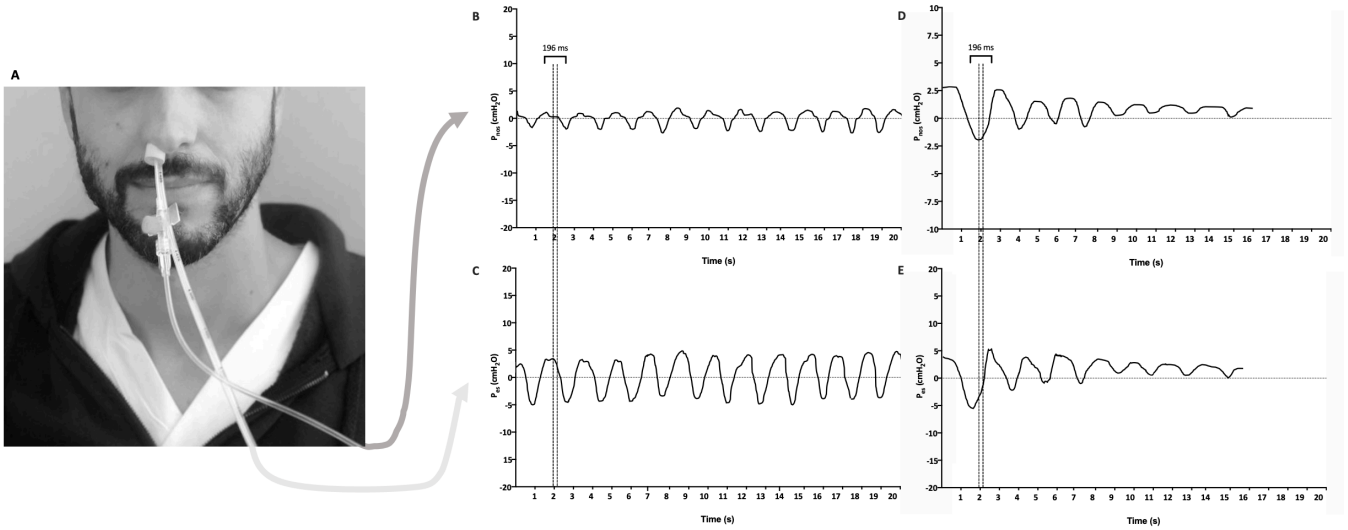

Figure 1

Panel A. Simultaneous positioning of esophageal catheter for ΔP_{es} assessment and nasal plug made of hypoallergenic foam ear plug equipped with a 16 Gauge polyurethane intravenous cannula for ΔP_{nos} measurements. The contralateral nostril was kept open. Panel B and C. Simultaneous assessment of ΔP_{nos} and ΔP_{es} during unsupported spontaneous breathing, showing in phase waveforms with a 196 ms time latency of ΔP_{nos} over the onset of inspiratory effort captured by ΔP_{es}. Panel D and E. Simultaneous assessment of ΔP_{nos} and ΔP_{es}, showing decremental inspiratory effort after NIV placement.

Measurements were taken while in the sitting position and breathing through the patent nostril with the mouth closed. Data were sampled at 100 Hz and processed on a dedicated data acquisition system (OptiVentTM, SIDAM, Mirandola, Italy). Data sampling was stored on a USB stick and processed *a posteriori*. All measurements were recorded after a stable spontaneous breathing pattern (5 minutes during unassisted breathing and further under HFNC or NIV) was reached. The average value of 3 subsequent breaths was considered for analysis. Measurements were performed during spontaneous breathing assisted with HFNC at baseline and during spontaneous breathing assisted with HFNC or NIV at 24 hours.

Noninvasive respiratory support

HFNC was delivered with a high flow device (Optiflow™and AIRVO™, Fisher & Paykel Healthcare Ltd, Auckland, New Zealand) through appropriately sized nasal cannulas. Flow delivery was initially set at 60 L/min and temperature at 37°C then adjusted according to the patient's tolerance; oxygen fraction was set as appropriate.

NIV was prescribed and set by a skilled respiratory physician. Patients were connected via a conventional circuit with an appropriately sized total face mask equipped with a dedicated output for probes (DiMax zero™, Dimar, Medolla, Italy) to a high-performance ventilator (GE Healthcare Engstrom Carestation™, GE Healthcare, Finland) in pressure support mode (PS). A heat and moisture exchanger (HME) with antimicrobial properties (Hygrobac, DAR, Mirandola, Italy) was connected after the Y-piece. Positive end-expiratory pressure (PEEP) was initially set to 8 cmH_2O and subsequently titrated to target a SpO_2)> 92% with a delivered inspiratory fraction of oxygen (FiO_2) below 0.7. Pressure support (PS) was set to 10 cmH_2O, and then progressively adjusted targeting a tidal volume below 9.5 mL/kg of predicted body weight and a RR < 30 bpm. The inspiratory trigger was set at 3 L/min and respiratory cycling at 25% of the inspiratory peak flow. The delivered FiO_2 was increased to target a SpO_2 of 88–94%. The facemask was fitted to a leak flow below 20 L/min. Patients did not receive sedation during HFNC or NIV.

The decision to proceed to endotracheal intubation was taken according to local protocols by the attending staff, blinded to the results of the physiological parameters; criteria included: a) PaO_2/FiO_2 ratio unchanged or worsened or below 150 mmHg, b) worsening dyspnea persistence of RR >35 bpm, c) the need to protect airways due to neurological deterioration or massive secretions, d) hemodynamic instability or major electrocardiographic abnormalities, e) gasping for air, psychomotor agitation requiring sedation, abdominal paradox movements.

Statistical analysis

The correlation between ΔP_{es} and ΔP_{nos} at baseline (on HFNC) and at 24 hours (on HFNC or NIV according to clinical condition) was pre-specified as the primary outcome. The distribution of the ratio between ΔP_{es} and ΔP_{nos} at baseline and after 24 hours was described. Normality of data was assessed with visual inspection of quantile-quantile plots, and data are reported as median [interquartile range, IQR], if not stated otherwise. Correlations were sought using Pearson's R, between-groups differences with the Fisher's and Wilcoxon tests, as appropriate. A sample size of

at least 37 patients would have provided 90% power (1-β) to detect a correlation with R > 0.5 at an α level of 0.05. In a sensitivity analysis, we compared the agreement between ΔP_{es} and estimated based on ΔP_{nos} using the Bland-Altman method, to assess whether ΔP_{nos} could serve as a surrogate of ΔP_{es}. $\Delta P_{es,estimated}$ was computed as $k \cdot \Delta P_{nos}$, where k is the average ratio of ΔP_{es} to ΔP_{nos} measured at baseline. In a secondary sensitivity analysis, the differences of ΔP_{es} and ΔP_{nos} in patients that required endotracheal intubation versus those who were still under NIV or HFNC at 3 days from inclusion were assessed. Statistics were performed using R (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was assumed with two-tailed $p<0.05$.

Results

Patient characteristics

Fifty-one out of 100 consecutive patients admitted for COVID-19 induced ARF to the RICU of the University Hospital of Modena (Italy) and candidate to receive HFNC were enrolled in this study. Excluded patients showed either: presence of chronic respiratory disease of any etiology (N=18), unavailability of research staff (N=18), refusal to undergo esophageal manometry (N=13). Of these, 41 patients (80.4%) escalated from HFNC to NIV within 24 hours. Nine (17.6%) patients underwent ETI at day 3. The clinical characteristics of the study population at baseline are presented in Table 1.

Variable	**CARDS**
Age, years [IQR]	70 [56 - 78]
Sex, n [%]	68,6%
SOFA, score, [IQR]	3 [3 - 3]
SAPSII score, [IQR]	28 [23 - 33]
APACHEII score, [IQR]	11 [7 - 14]
Admission PaO_2/FiO_2, mmHg [IQR]	129 [100 - 150]
Admission respiratory rate, bpm [IQR]	26 [24 - 29]
Admission ΔP_{es}, cmH_2O [IQR]	12 [9.5 - 15]
Admission ΔP_{nos}, cmH_2O [IQR]	5.6 [4.2 - 8]
24 hours PaO_2/FiO_2, mmHg [IQR]	143 [112 - 163]
24 hours respiratory rate, bpm [IQR]	22 [20 - 25]

Table 1.

General and clinical characteristics of the study population. Data are presented as number (n) and percentage for dichotomous values or median and interquartile ranges (IQR)) for continuous values.

Correlation between ΔP_{es} and ΔP_{nos}

At baseline, mean ΔP_{es} and ΔP_{nos} were 12.0 [9.5 - 15.0] and 5.6 [4.2 - 8] cmH_2O respectively. At 24 hours, mean ΔP_{es} and ΔP_{nos} were 6.5 [5.0 - 10.0] and 3.0 [2.1 - 4.6] cmH_2O.

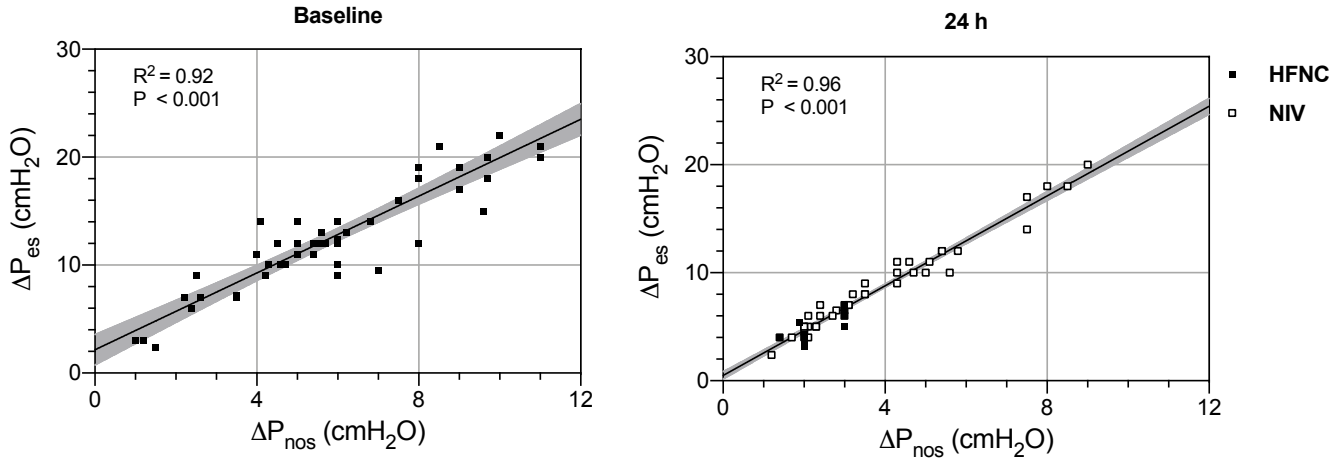

Figure 2

Pearson's R^2 showing correlation between ΔP_{es} and ΔP_{nos} at baseline (Panel A), when all patients were assisted with HFNC (R^2=0.92, p<0.001), and at 24 hours (Panel B, R^2=0.96, p<0.001), with most patients receiving NIV. At both time points ΔP_{es} and ΔP_{nos} showed strong correlation. Significance was set for p value < 0.05

Figure 2 shows the correlation between ΔP_{es} and ΔP_{nos} at baseline (Panel A), with all patients under HFNC (R^2=0.92, p<0.001), and at 24 hours (Panel B, R^2=0.96, p<0.001), with most patients receiving NIV. The correlations between ΔP_{es} and ΔP_{nos} at 24 hours remained significant after splitting the study population according to the NRS (HFNC or NIV) used (Figure 3).

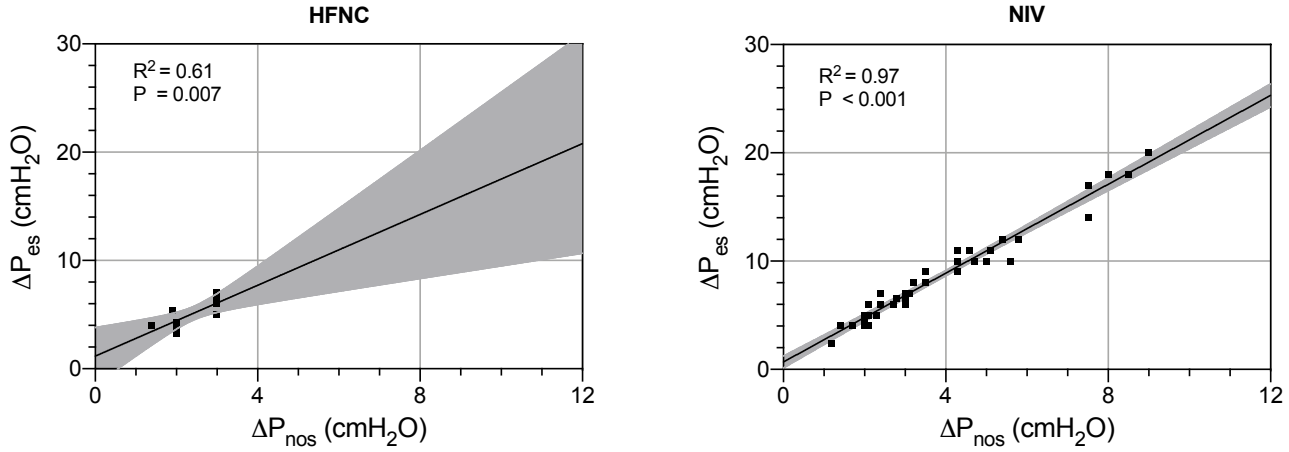

Figure 3

Pearson's R showing correlations between ΔPes and ΔPnos at 24 hours after splitting the study population according to the NRS received. Significance was set for p value < 0.05

ΔP_{es} to ΔP_{nos} ratio

The baseline $\Delta P_{es}/\Delta P_{nos}$ ratio was 2.14 [2.04 – 2.47] and 2.22 [2.09 – 2.38] at baseline and 24h, respectively. As illustrated in Figure 4, the distribution of $\Delta P_{es}/\Delta P_{nos}$ ratio at baseline and at 24 hours was similar (p=0.41) and also did not differ in patients receiving HFNC or NIV at 24h (2.13 [1.85 – 2.33] versus 2.26 [2.13 – 2.38], p = 0.154).

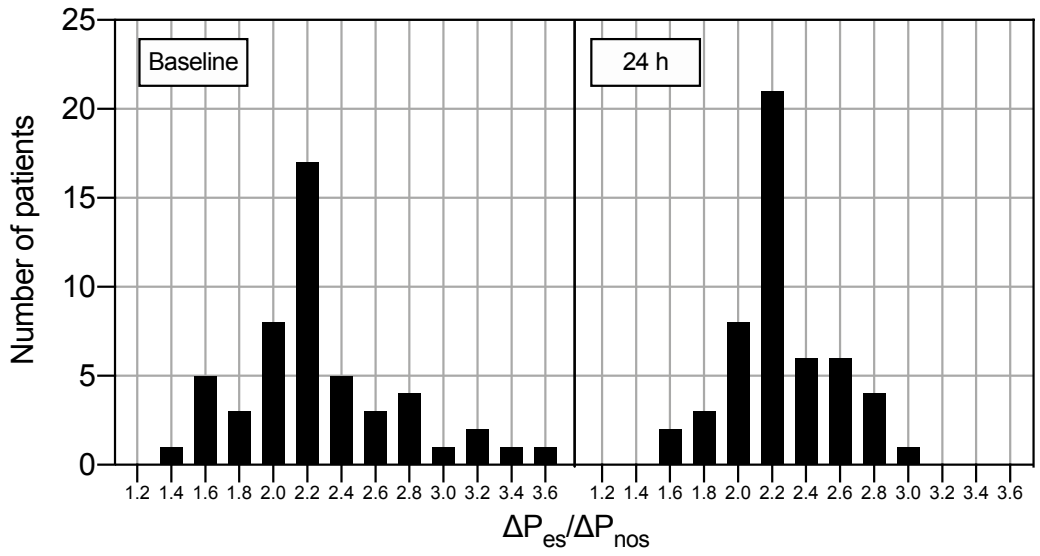

Figure 4

Histogram bars illustrating the distribution of $\Delta P_{es}/\Delta P_{nos}$ ratio at baseline and at 24 hours. Comparison was sought by means of Student t test. Significance was set for p value < 0.05. The ratio was not different between baseline and 24 hours (p=0.41).

Sensitivity analyses

The mean $\Delta P_{es}/\Delta P_{nos}$ ratio at baseline (2.25) was the value used as multiplication factor to compute $\Delta P_{es,estimated}$ from ΔP_{nos}. Bland-Altman method showed a bias of 0.6 cmH_2O and 95% limits of agreement from -4.1 to 5.3 cmH_2O, while at 24 h the bias was 0.1 cmH_2O and the 95% limits of agreement from -1.6 to 1.9 cmH_2O (Figure 5).

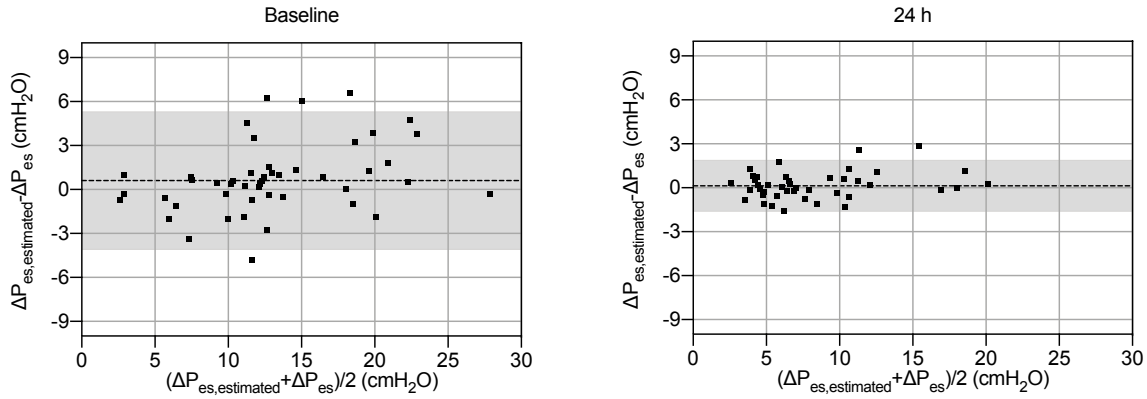

Figure 5

Bland-Altman analysis assessing the agreement between ΔPes measured with esophageal manometry and estimated based on ΔPnos (ΔPes,estimated) and computed as k· ΔPnos, where k is the average ratio of ΔPes to ΔPnos measured at baseline. At baseline a bias of 0.6 cmH2O and 95% limits of agreement from -4.1 to 5.3 cmH2O was found, while at 24 h the bias was 0.1 cmH2O and the 95% limits of agreement from -1.6 to 1.9 cmH2O.

Characteristics of patients who were intubated versus those still on NRS at day 3 are displayed in **Table 2**: ΔP_{es} was 14.0 [9.5 – 17.0] and 12.0 [10.0 - 14.0] cmH_2O (p = 0.706), while ΔP_{nos} was 6.0 [4.1 – 8.0] and 5.6 [4.3 - 7.5] cmH_2O (p = 0.990), respectively. At 24h, patients who were further intubated had both higher ΔP_{es} (14.0 [12.0 – 18.0] versus 6.0 [5.0 – 8.0] cmH_2O, p < 0.001) and ΔP_{nos} (7.5 [5.6 – 8.0] versus 2.9 [2.0 – 3.2] cmH_2O, p < 0.001) as compared with those still under NRS.

Variable	Still on non-invasive at day 3 (n=42)	Intubated at day 3 (n=9)	p value
Age, years [IQR]	**68 [56 - 75]**	**73 [56 - 78]**	**0.5**
Sex, n [%]	**64.3%**	**88.9%**	**0.2**
SOFA, score, [IQR]	**3 [3 - 3]**	**3 [3 - 3]**	**0.7**
SAPSII score, [IQR]	**29 [23 - 33]**	**27 [24 - 33]**	**0.8**
APACHEII score, [IQR]	**11 [7 - 15]**	**11 [7 - 13]**	**0.5**
Admission PaO_2/FiO_2, mmHg [IQR]	**132 [99 - 151]**	**109 [100 - 120]**	**0.1**
Admission RR, bpm [IQR]	**26 [24 - 29]**	**26 [24 - 29]**	**0.9**
Admission ΔP_{es}, cmH_2O [IQR]	**12 [10 - 14]**	**14 [9,5 - 17]**	**0.7**
Admission ΔP_{nos}, cmH_2O [IQR]	**5.6 [4.3 – 7.5]**	**6 [4,1 - 8]**	**0.9**
HFNC, n [%]	**23.8%**	**0,0%**	**---**
NIV, n [%]	**76.2%**	**0,0%**	**---**

24 hours PaO_2/FiO_2, mmHg [IQR]	**144 [131 - 173]**	**112 [85 - 152]**	**0.1**
24 hours RR, bpm [IQR]	**21 [20 - 24]**	**28 [24 - 30]**	**0.002**
24 hours ΔP_{es}, cmH_2O [IQR]	**6 [5 - 8]**	**14 [12 - 18]**	**<0.001**
24 hours ΔP_{nos}, cmH_2O [IQR]	**2,9 [2 - 3,2]**	**7,5 [5,6 - 8]**	**<0.001**

Table 2

General and clinical characteristics of the study population according to respiratory support at day 3. Data are presented as number (n) and percentage for dichotomous values or median and interquartile ranges (IQR)) for continuous values. The nonparametric Mann–Whitney and Student t test were used for the comparison of continuous variables. Comparison between dichotomous variables was performed by the χ2 test or Fisher's exact test, where appropriate. Significance was set for p value < 0.05.

Discussion

The main findings of this study are that, in a population of patients with COVID-19 induced ARF, ΔP_{nos} measured with closed mouth was highly correlated with ΔP_{es} during non-assisted and assisted spontaneous breathing. The correlation between these two physiological variables showed persistency over time and low inter-patient variability regardless the application of different type of NRS (HFNC or NIV). Moreover, ΔP_{nos} and ΔP_{es} after 24 hours from NRS start resulted significantly higher in those patients that were subsequently intubated.

To our knowledge, this is the first study assessing the correlation between tidal changes of esophageal and nasal pressure during spontaneous breathing in a specific subset of patients with ARF. Previous physiological studies already reported that P_{es} could be estimated by nasal pressure during a sniff test (12). However, sniff represents a ballistic maneuver characterized by an acute increase in lung volume associated with a distortion of the chest wall, far from an isometric contraction (15). Moreover, during volitional maximal inspiratory effort, the nasal valve of the patent nostril collapses, thus behaving as a Starling resistor. The pressure measured beyond the collapsed segment was found to closely reflect esophageal pressure with an average ratio P_{es} /P_{nos} of 1.05 during maximal sniff and of 1.09 during submaximal sniff, being P_{nos} always less than P_{es}. During tidal spontaneous breathing, instead, the posterior nasal valve remains open. When P_{nos} and P_{es} are measured during spontaneous breathing without the collapse of the posterior nasal valve, simultaneous pressure waveforms do not show phase difference, though the pressure ratio increased (12). Based on these assumptions, P_{nos} swing is likely to mirror variation of P_{es} during spontaneous breathing. Indeed, our study confirmed that ΔP_{nos} was highly correlated with ΔP_{es} with a narrow range of ratio between the two values.

The distribution of $\Delta P_{es}/\Delta P_{nos}$ ratio across our patient cohort was relatively consistent showing low inter-patient variability over time and under different type of support (Figure 2 and 3, Supplementary materials). Given that ΔP_{nos} reflects the P_{aw} variation during tidal breathing, a potential interference in ΔP_{nos} and $\Delta P_{es}/\Delta P_{nos}$ ratio assessment following the application of positive inspiratory pressure could have been hypothesized. However our results showed that these measurements are not affected by the onset of positive pressure support ventilation. This might be due to the effect of the nasal plug that makes the nostril cavity an isolated anatomical structure not influenced by external pressure. This mechanism could explain why the $\Delta P_{es}/\Delta P_{nos}$ ratio remains constant over time regardless of the application of NIV. If confirmed on an heterogenous populations of patients with ARF, these preliminary data might suggest monitoring ΔP_{nos} as a non-

invasive and easy-to-perform surrogate measure of ΔP_{es} to monitor the patient's inspiratory effort during both assisted and not assisted spontaneous breathing.

Our data showed that in patients with COVID-19 induced ARF with moderate to severe gas exchange impairment, the magnitude of inspiratory effort as assessed by esophageal manometry was not very high. A clinical study by our group recently showed that non-COVID-19 patients undergoing NIV presented extremely marked respiratory drive activation. This remained high during the early phase of assisted ventilation and was associated with unfavorable outcomes, thus reinforcing the idea of SILI during assisted spontaneous breathing (4). Notwithstanding the limited inspiratory effort observed during tidal breathing, patients with COVID-19 induced ARF still showed value of ΔP_{es} above physiological ranges (16, 17). Given the association between ΔP_{es} (and ΔP_{nos}) even with the need for endotracheal intubation, one could speculate a role of SILI in affecting the outcome of NRS. Although this study was not designed to explore clinical outcomes, ΔP_{es} and ΔP_{nos} showed comparable accuracy in predicting need for endotracheal intubation, thus suggesting the use of ΔP_{nos} as a surrogate of ΔP_{es} in monitoring patients with ARF candidate to assisted breathing and impending risk for intubation.

Although, our study reported high correlation between ΔP_{es} and ΔP_{nos} in spontaneously breathing patients with COVID-19 induced ARF, this technique may suffer from several physiological limitations that deserve discussion. First, previous studies regarding Sniff Nasal Inspiratory Pressure (SNIP) test showed that the transmission of pressure changes from the alveoli to the upper airways is altered in case of airflow limitation (18). Moreover, SNIP was found to underestimate sniff ΔP_{es} on average by 14% in patients with acute asthma and by 19% in patients with stable COPD (19, 20). Despite ΔP_{nos} and SNIP exhibit different physiological behaviors, dynamic hyperinflation may affect $\Delta P_{es}/\Delta P_{nos}$ ratio also during spontaneous breathing. As we have excluded patients with hypercapnic respiratory failure and chronic obstructive respiratory disease, the results of our study should not be extended to patients affected by significant dynamic intrinsic positive end expiratory pressure. Second, the measurement of ΔP_{nos} during spontaneous breathing may be affected by the collapse of the posterior nasal valve induced by exaggerated respiratory drive (15, 21). In this circumstance, tidal inspiratory breathing may become similar to an inspiratory effort against a closed airway, thus amplifying the pressure variation captured in the nostril. In this line, a device able to maintain the posterior nasal valve open could be useful to obtain reliable value of ΔP_{nos}. Third, all the measurements were performed with patients asked to keep the mouth closed for the entire evaluation time. This task may be difficult to accomplish in certain clinical conditions (e.g. elevated

respiratory drive, intense shortness of breath, lack of collaboration). Further limitation of this physiological measurement is represented by severe nasal congestion or anatomical alterations of the nostrils.

Conclusions

With this proof-of-concept physiological study we have showed that nasal pressure swing during spontaneous tidal breathing was highly correlated with esophageal pressure swing in patients with COVID-19-associated ARF. The ratio between these variables showed persistency over time and low inter-patient variability regardless the application of NIV. Furthermore, ΔP_{nos} mimicked ΔP_{es} accuracy in predicting the risk of intubation in this cohort. Should data be confirmed on larger studies and in heterogenous populations with ARF ΔP_{nos} could be extended in different setting of care, given the noninvasive and easy-to-use measurement, thus implementing the respiratory monitoring of patients with acute respiratory failure and impending risk for intubation.

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General discussion

Spontaneous breathing and lung damage in acute respiratory failure

Keeping spontaneous breathing preserved in patients with acute respiratory failure (ARF) under non-invasive respiratory assistance may represent a risky gamble when hypoxemia is severe. On one hand, several positive physiological effects have been described including the avoidance of deep sedation and/or myorelaxants drugs, the prevention of muscle mass loss, the spare of diaphragmic function and the reduction of delirium onset (1). A growing body of evidence derived from animal models and clinical investigations on classical ARDS has strengthened the hypothesis that the presence of intense respiratory effort producing excessive negative pleural pressure swings (P_{pl}) plays a critical role in the onset and progression of lung and diaphragm damage, especially when lung impairment is severe (2-5). This unfavorable mechanical condition predisposes to the so-called patient's self-inflicted lung injury (P-SILI), whose underlying mechanisms differentiate from those sustaining the well-known model of ventilatory induced lung injury (VILI). When lungs are healthy, the transpulmonary pressure (P_L) generated by the diaphragmatic contraction is uniformly distributed over the entire lung surface. The elastic response of the lung follows a "liquid-like" behavior without local alveolar over-distention (6). When acute lung injury occurs, local inflammation and alveolar edema make lung tissue inhomogeneous. The transmission of the forces applied to pulmonary parenchyma during spontaneous breathing becomes asymmetrical and the elastic response of the lung follows a "solid-like" behavior. In particular, the negative swing in pleural pressure generated during active inspiration is not uniformly distributed, being magnified in dependent regions and alongside the diaphragmatic interface, where high values of P_L are concentrated (7). The unbalanced application of physical forces during spontaneous breathing causes a pressure gradient between nondependent and dependent lung zones, resulting in a disproportionate distribution of tidal volume with unsafe local stretch of the dependent lung (pendelluft phenomenon) (3, 7). Furthermore, a significant drop in intrathoracic pressure due to intense inspiratory effort can result in negative changes in alveolar pressure. The following increase in transmural vascular pressures in pulmonary capillaries predisposes to the development of pulmonary edema (8). Moreover, disparate radial traction forces applied in the corner vessels adjacent to stress raisers, may generate a siphoning effect of blood towards areas of higher P_L (pendelblut phenomenon) (9). Finally, load-induced diaphragm injury can occur during intense

spontaneous breathing, as suggested by the radiological signs of muscle edema (5) and the histological evidence of fiber disruption, sarcomeric derangement and amplified inflammation (10). These biophysical insults related to the magnitude of inspiratory effort and to the following lung parenchymal stretch, alveolar edema and diaphragmatic overload can result in a pattern of progression from the initial lung damage, worsening ventilatory and clinical outcomes (3). Figure 1 illustrates the mechanism of P-SILI.

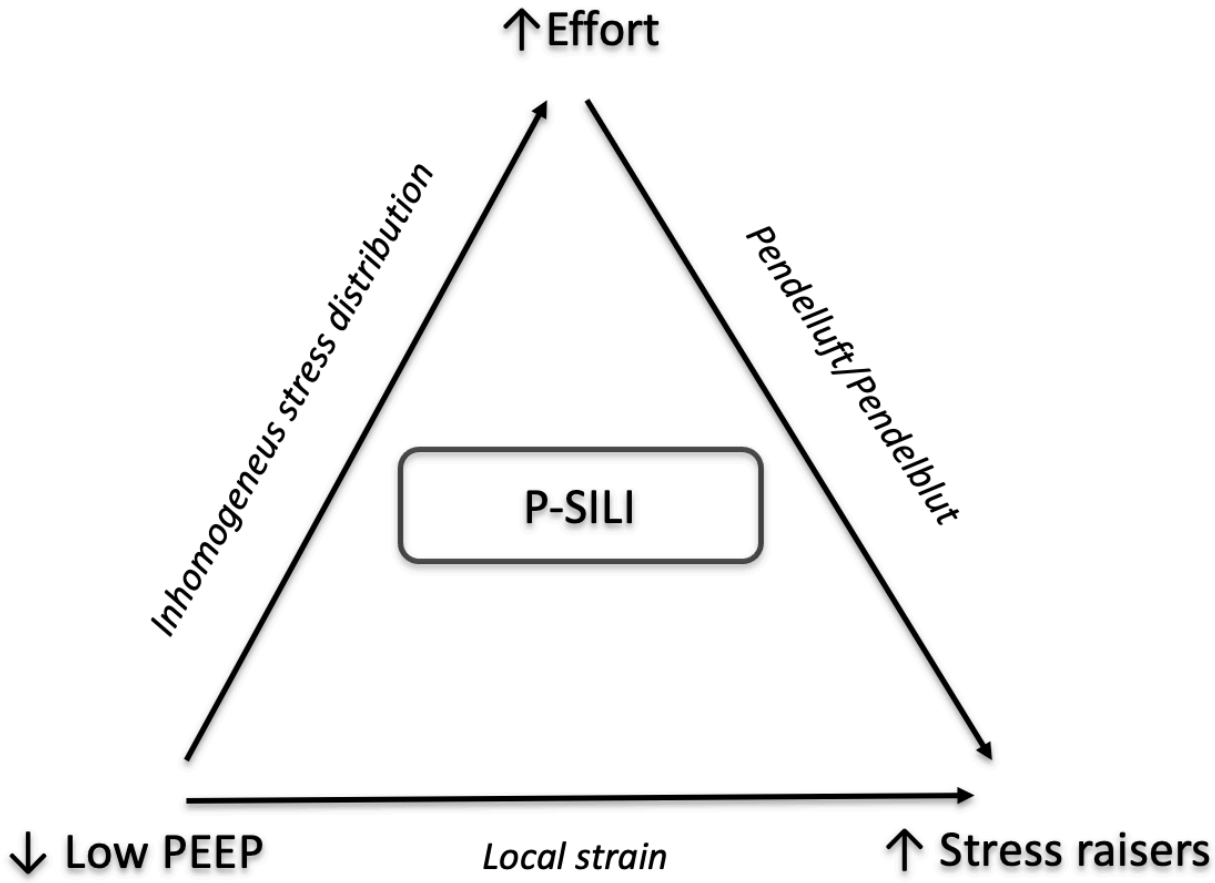

Figure 1

Pathophysiology and mutual interaction of the mechanisms of self-inflicted lung injury.

Spontaneous breathing and lung damage in acute respiratory failure due to COVID-19

The characteristics of respiratory drive activation along with the mechanical and clinical consequence of spontaneous breathing in COVID-19 patients have become matter of investigation, giving the peculiar pathophysiological features of this unforeseen form of ARF (11). Since the onset

of the pandemic, several clinical observations have pointed out that a considerable number of patients experiencing COVID-19 pneumonia in the early phase do not present subjective dyspnea despite severe hypoxemia, being this condition defined as “happy hypoxia” (12-14). Although, the mechanisms beyond the limited shortness of breath are not fully understood, it has been hypothesized that a damage of the C-pulmonary afferent fibers driven by the inflammatory cascade or by direct viral involvement may affect the coupling between bio-mechanical stimuli and respiratory drive activation (15). A recently published matched study comparing COVID-19 receiving non-invasive respiratory support with moderate to severe ARF with classical ARDS (16), showed a relatively low activation of respiratory drive in COVID-19 patients during the early phase (median ΔP_{es} 12.5 cmH_2O, RR 28 bpm, Vte 9.2 mL/kg of predicted body weight [PBW] versus ΔP_{es} 32 cmH_2O, RR 35 bpm, Vte 10.9 mL/kg of PBW), which is in line with the aforementioned concept of “happy hypoxemia” (14) and underlines the mismatch between central drive activation and moderate to severe hypoxia, at variance with the typical form of ARDS. At least theoretically these data seem to suggest that, in the very early phase of assisted spontaneous breathing, the role of SILI in determining further lung damage in early COVID-19 ARF does not seem as crucial as in typical forms of ARDS. Nevertheless, even if respiratory drive resulted in less stress as compared with ARDS, the application of non-invasive mechanical ventilation (NIV) in these patients determined a significant reduction of inspiratory effort with values of ΔP_{es} close to physiological ranges (6-10 cmH_2O). Further, at the early stage of the disease, the reported dynamic compliance of the respiratory system was twice as high in COVID-19 patients as in those with typical ARDS (55 vs 25 mL/cmH2O), at comparable P/F ratio. Moreover, investigations on lung behavior during spontaneous breathing according to different PEEP levels in this cohort (unpublished data) showed that, elevated values of PEEP were inversely correlated with the relative change of PaO2/FiO2 ratio and dynamic lung compliance after NIV (Figure 2). In contrast, typical ARDS patients showed a favorable association between PEEP values and gas exchange 2 hours after starting NIV, suggesting a different behavior in response to recruitment. These findings are in line with those reported by Coppola et al. who showed that, in 23 critically ill patients with COVID-19 pneumonia, increasing PEEP from a low (5 cmH2O) to a higher (15 cmH2O) level led to a significant deterioration in lung mechanics as assessed via esophageal manometry (17).

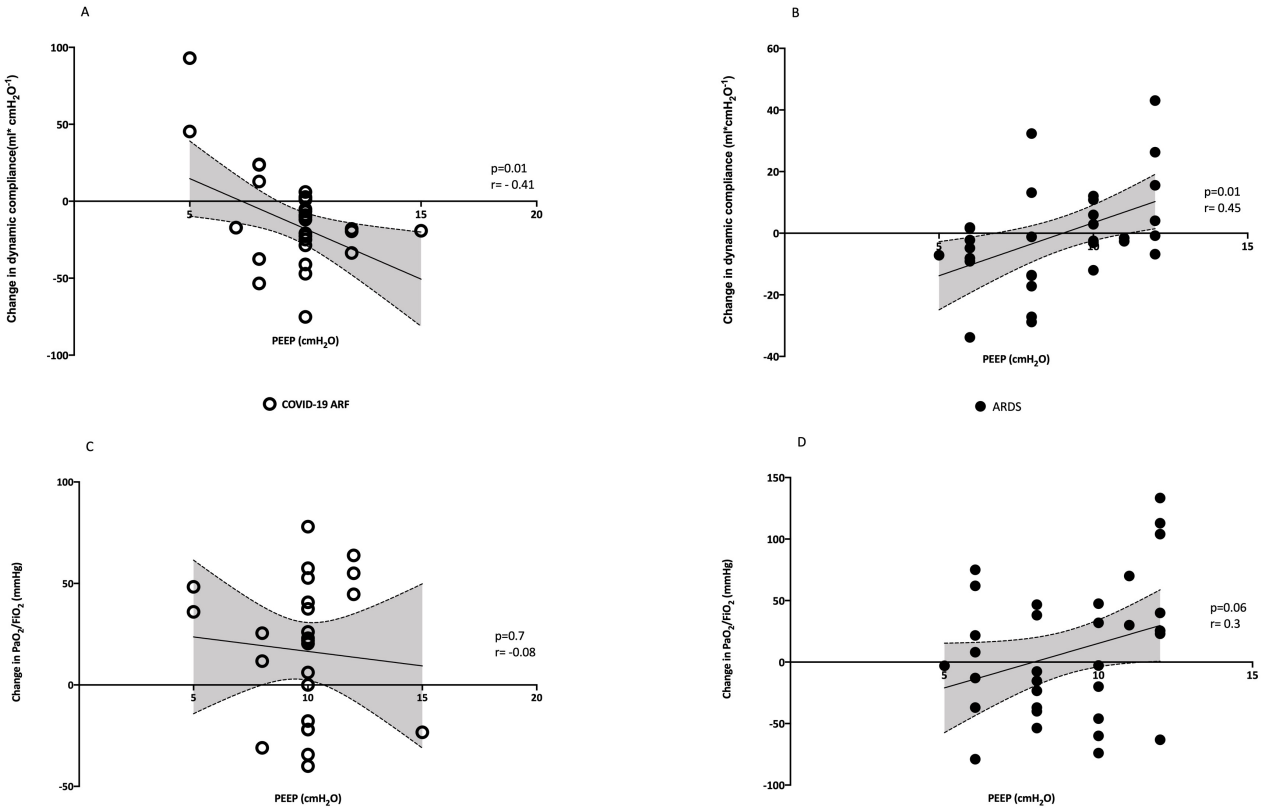

Figure 2

Correlation between PEEP values and change in both dynamic compliance and PaO2/FiO2 ratio in COVID-19 pneumonia (panel A and C, respectively) and ARDS (panel B and D, respectively) patients.

The concept of mechanical power has recently been developed to explore the interaction between ventilatory support and lung damage. In particular, the degree of VILI has been related to the amount of energy transferred from the mechanical ventilator to the respiratory system (18). Assuming that the amount of energy to which the lung is subjected may be crucial, even during assisted spontaneous breathing, thus influencing SILI development, a simple surrogate of mechanical power may be derived by replacing the change in airway pressure during inspiration with dynamic transpulmonary pressure (19). In patients with COVID-19, the baseline value of dynamic mechanical power was considerably lower than in ARDS (27 vs 95 J/min, $p<0.0001$). After a 2 hours NIV trial, the dynamic mechanical power showed a significant increase in COVID-19 patients alone. This may suggest an unfavorable interaction between potential and kinetic energy transferred from the respiratory muscles and the mechanical ventilator to the lungs of these patients, at least in the early phase of the disease when respiratory drive is still preserved.

In more advanced stages of COVID-19 pneumonia, following the phenotype transition with increase in lung weight and relative drop in lung compliance, an increase in respiratory drive has been

documented and correlated with worsening of respiratory function during attempts to wean patients from mechanical ventilation (20). A recent computational study has shown how, in a model correlated to COVID-19 patients, when intense inspiratory effort (namely pleural pressure swing) is reached, the physical forces produced were comparable with those associated with VILI during mechanical ventilation (21). The authors concluded that inspiratory effort in these patients should be carefully monitored and controlled to reduce the risk of lung injury.

Clinical significance of inspiratory effort monitoring in spontaneously breathing COVID-19

Given that esophageal pressure swings mirror P_{pl} during spontaneous breathing, esophageal manometry by means of an esophageal balloon catheter is considered a reliable method to quantify the magnitude of inspiratory effort (22). If in typical ARDS an intense inspiratory effort as documented by high ΔP_{es} values was associated with unfavorable ventilatory outcomes (5), a pressure threshold to be considered harmful and predisposing to the onset of SILI in COVID-19 patients is still to be defined. However, the continuous monitoring of inspiratory effort through esophageal manometry may allow the following physiological evaluations on patient's respiratory drive, assessing the impact of non-invasive respiratory support and improving the ventilatory management of spontaneous breathing patients with severe COVID-19:

1) The quantification of inspiratory effort allows a precise characterization of respiratory drive, whose hyperactivation requires immediate intervention, irrespective on the severity of gas exchange impairment (23). If respiratory drive is not attenuated, the increase in lung tissue stress and the raise in pulmonary trans-vascular pressures, sustained by vigorous breathing effort, may worsen every stage of COVID-19 pneumonia (24).
2) Assessing changes in ΔP_{es} following the application of non-invasive respiratory support may help in early discriminating between good and low responders to respiratory assistance, avoiding the use of positive pressure when unneeded. Further, in patients who fail to reduce the inspiratory effort within the first hours of HFNC or NIV application, an upgrade in the intensity of respiratory support should be promptly considered (Figure 3).

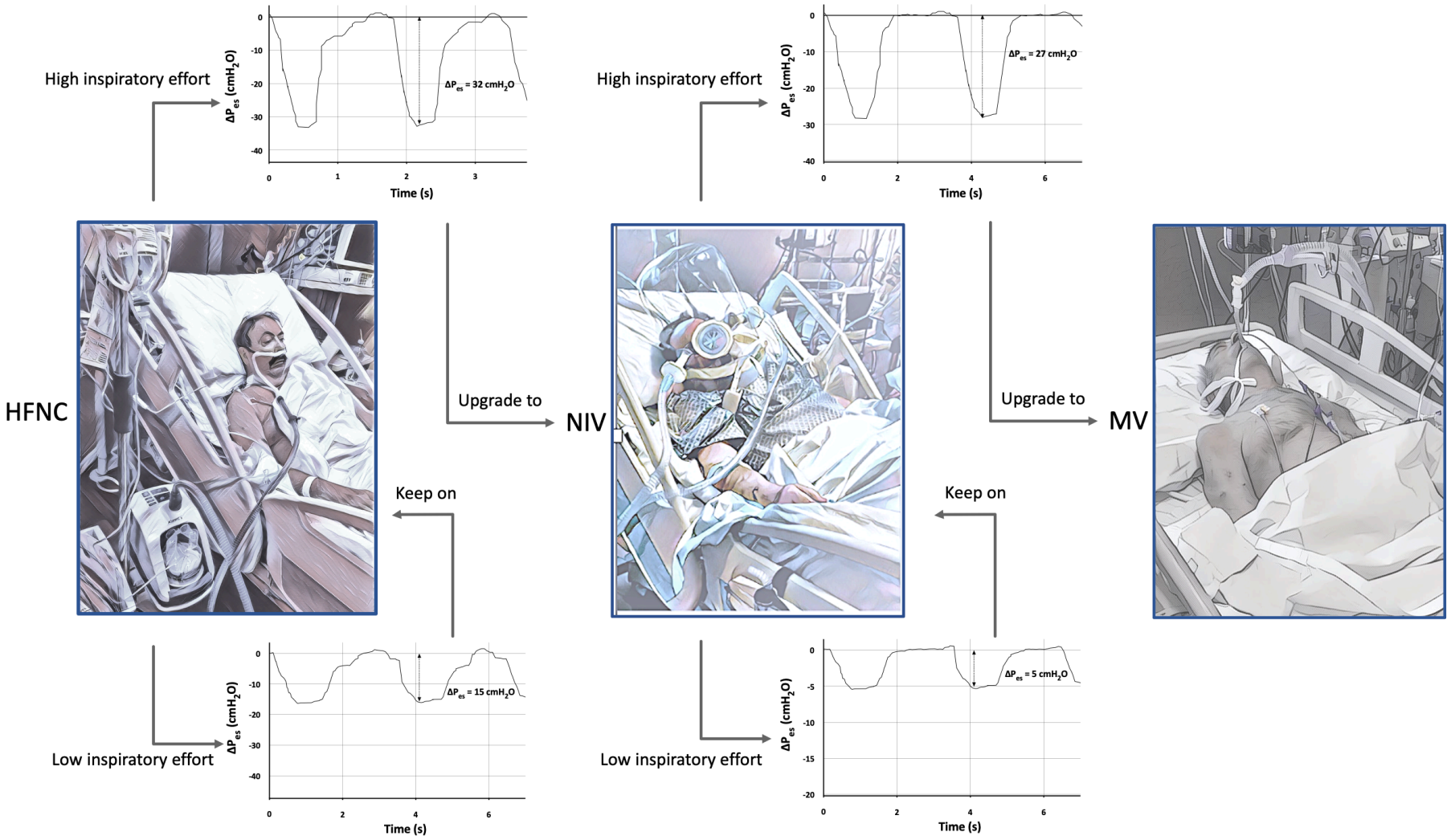
High inspiratory effort
ΔP_es (cmH2O)
ΔP_es = 32 cmH2O
Time (s)
High inspiratory effort
ΔP_es (cmH2O)
ΔP_es = 27 cmH2O
Time (s)
HFNC
Upgrade to
NIV
Upgrade to
MV
Keep on
Keep on
Low inspiratory effort
ΔP_es (cmH2O)
ΔP_es = 15 cmH2O
Time (s)
Low inspiratory effort
ΔP_es (cmH2O)
ΔP_es = 5 cmH2O
Time (s)

Figure 3

Practical flow-chart of respiratory assistance for patients with COVID-19 acute respiratory failure based on inspiratory effort assessment. A HFNC trial might be started with close monitoring of inspiratory effort. If low values of ΔP_{es} are detected, HFNC should be kept with close monitoring of esophageal pressure swings and gas exchange. In case of high inspiratory effort, non-invasive respiratory assistance should be upgraded to NIV. If ΔP_{es} is reduced by positive pressure application, NIV might be continued with continuous monitoring of inspiratory effort. In case NIV fails to reduce inspiratory effort, a rapid switch to MV should be considered.

3) A continuous monitoring of respiratory effort may inform on the changes in the respiratory mechanics of the patient. In particular, an abrupt increase in ΔP_{es} may suggest a rapid derangement of respiratory system compliance, mirroring the transition from a lung with fluid-like behavior to parenchymal solid-like elastic properties.
4) Esophageal manometry could be useful to obtain information on lungs mechanical features and the relative response to positive pressure application on respiratory system. A surrogate of lung compliance, namely dynamic compliance, can be derived comparing the values of P_L with expiratory tidal volume (Vte). Further, a simplified surrogate of mechanical power, defined as dynamic mechanical power can be calculated as 0.098 * RR * Vte * (ΔPL + positive end-expiratory pressure [PEEP]) (25). Although approximate, this index may represent a reliable estimate of the amount of energy transferred from respiratory muscle and ventilatory assistance to the lung during assisted spontaneous breathing. All these physiological variables may inform the clinician on lung recruitability at bedside, allowing a PEEP optimization during non-invasive respiratory assistance. Further, un unfavorable change in dynamic compliance and mechanical power following PEEP application, may suggest a limited lung recruitability forecasting the risk of local overdistension.

Despite systematic assessment of inspiratory effort by means of esophageal monitoring is certainly appealing, this technique seems not easy to implement in everyday clinical practice (26). This is partially due to technical issue such as the correct insertion and proper placement of the probe that influences the accuracy and interpretation of measurements. Moreover, the procedure itself could result difficult when respiratory drive is markedly activated, as it may happen in wakeful patients with respiratory distress and severe gas exchange impairment. (27). Finally, another limitation is represented by the invasive nature of the maneuver that may cause discomfort and potential side effects in wakeful patients with ARF (28). Notwithstanding an advanced respiratory monitoring of patients with ARF should be recommended every time there is risk of an injurious (spontaneous or

assisted) ventilation. Physiological and clinical evidence often showed an uncertain time course of COVID-19 induced ARF, with a rapid transition from mild scenarios to more severe atypical and typical form of ARDS (29). Ideally, given this unpredictable behavior, an advanced respiratory monitoring including inspiratory effort assessment should be provided.

A more feasible method for measuring inspiratory effort without the technical issue of esophageal manometry could implement SILI monitoring in all clinical setting with the aim to predict patients' respiratory deterioration. Thus, research on non-invasive methods to surrogate the magnitude of inspiratory effort in order to optimize the ventilatory management of patients with ARF of different etiology (including COVID-1), inside or outside ICU, is fairly welcomed.

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