# Bedside imaging monitoring techniques in invasively ventilated patients

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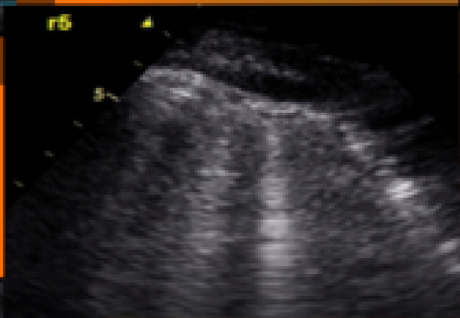

# Bedside Imaging Techniques in Invasively Ventilated patients

# BEDSIDE IMAGING MONITORING TECHNIQUES IN INVASIVELY VENTILATED PATIENTS

Charalampos Pierrakos

Bedside imaging monitoring techniques in invasively ventilated patients

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# Bedside imaging monitoring techniques in invasively ventilated patients

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door Charalampos Pierrakos
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Faculteit der Geneeskunde

*.....to the memory of all my patients who have left this world during the COVID-19 pandemic*

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# Chapter 1: General Introduction and Outline of the Thesis

*Charalampos Pierrakos, Markus W. Hollman ,Marcus J. Schultz, Frederique Paulus and Lieuwe D. Bos*

## Introduction

Invasive mechanical ventilation is a life-sustaining modality routinely used to support the respiratory function of critically ill patients. Even though mechanical ventilation for supporting respiratory function was invented in the 19th century, positive pressure ventilation was introduced in clinical practice only in the 1950s[1]. Since then, ventilators have improved considerably due to technological progress, allowing for better interaction between physician, ventilator, and patient. Awareness around invasive ventilation has increased due to the ongoing Coronavirus disease 2019 (COVID–19) pandemic due to an impending shortage of intensive care unit (ICU) capacity and mechanical ventilators.

The positive pressure applied by mechanical ventilators to the conducting airways and alveoli can damage the lung tissue ('barotrauma')[2] and can have significant hemodynamic effects by increasing intrathoracic pressures[3]. On the other hand, when insufficient pressure is used, the alveolus closes at the end of expiration resulting in cycling opening and close of lung units, which may also cause injury ('atelectotrauma')[4]. Furthermore, closed or filled alveoli cause inhomogeneity of gas distribution in the lung, resulting in local overdistention of open units leading to further injury ('volutrauma')[5]. Recognition of these processes has led to the introduction of 'protective ventilation' with lower tidal volumes and low airways pressure, which has improved outcomes considerably. This effect is most profound in patients with acute respiratory distress syndrome (ARDS), a form of acute exsudative pulmonary edema that results in a consolidated and stiffened lung[6,7]. There is much more debate about selecting the positive end-expiratory pressure (PEEP) at the bedside[8]. There does not seem to be a single adequate setting for all invasively ventilated patients. Mechanical ventilation, therefore, is personalized to the patients' needs, which requires close monitoring[9].

Important progress has been made in monitoring intra-thoracic pressures, e.g., by esophageal pressure measurements, and these can be used to guide invasive ventilation[10,11]. However, investigating lung mechanics is arduous, particularly in not deeply sedated spontaneously breathing patients, and separation of different components of respiratory compliance, i.e., compliance of the lung and chest wall and intraabdominal pressure, is not evident in clinical practice[12,13]. Therefore, there is an increasing interest in using image techniques aiming to visualize lung morphology and evaluate lung aeration in invasively ventilated patients[14]. These tools can be used to prognostically enrich studies by including patients with more severe forms of lung injury who are more likely to reach the primary endpoint (such as mortality) or can be used for predictive enrichment by selecting those patients who are more likely to benefit from an intervention[15].

Chest X-ray has been the go-to option for monitoring lung aeration of critically ill patients at the bedside[16]. However, the cost-effectiveness of routine chest X-ray use has been challenged in the contemporary ICU[17]. Furthermore, the capacity of chest X-rays for the evaluation of lung edema in patients with ARDS is limited[18,19]. Thoracic computed tomography (CT) is a more advanced image technique. It is considered the gold standard technique for the accurate evaluation of the gas distribution volume and aeration of lung tissue[20]. In invasively ventilated patients. CT has been proved helpful for lung morphology identification in patients with ARDS[21], recruitment maneuver effect and lung overdistention[22]. Nevertheless, this technique shares important limitations. The need to transfer the patient to another department for chest imaging yields this technique unsuitable for monitoring as it cannot be easily repeated[23]. Image analysis is also laborious and expertise that is not routinely available is needed to make quantitative judgements[24]. Furthermore, it is a technique that may not be available in resource-limited settings. Hence, there is an urgent need for evaluation alternative imaging techniques readily available at the bedside[23].

*Lung ultrasound*

Lung ultrasound (LUS) is a noninvasive imaging technique that can be used at the bedside. It can be used to estimate lung aeration, which makes it an attractive alternative technique in settings where resources are restricted, or assessment needs to be repeated[25]. Even though the air is an obstacle to the passage of ultrasound, the artifacts produced by pleura can be used to distinguish between normal and pathological lung aeration[26]. The interest in lung ultrasound has grown in recent years as a systematic examination of critically ill patients' thorax permits to diagnose pathologic conditions related to respiratory failure and monitor lung aeration [27]. One frequently used tool to quantify the extent of pulmonary pathologies is the so-called global LUS score, in which LUS patterns across 12 lung regions are caught in a numerical score[28]. An 'A–pattern' (i.e., repeating horizontal (A–)lines parallel to the pleural line, suggesting normal aeration) is scored '0', a 'B–pattern' (i.e., 3 or more vertical (B–)lines starting from the pleural line and reaching the bottom of the screen, suggesting partial loss of aeration) is scored '1' if they cover ≤ 50% of the pleural line and '2' if lines cover >50% of the pleural line, and a 'C–pattern' (i.e., consolidation, suggesting near-complete to complete loss of aeration) is scored '3'. The individual scores per region are summed into a global LUS aeration score, which thus ranges from '0' (normal aeration in all regions) to '36' (severe abnormal aeration in all regions).

*Electrical impedance tomography*

Electrical impedance tomography (EIT) is another promising noninvasive, radiation-free technique that can continuously evaluate local and global lung aeration and function at the bedside. EIT is based on the principle that tissues have a good electrical conductivity, whereas air is an excellent insulator. Given that there is a tidal entrance and exit of air into the thorax during inspiration and expiration, a tidal variation of thoracic resistances is expected. EIT measures electrical activity at the thorax surface after a rotating high-frequency and low-intensity current injection. With the help of software, resistance is calculated for the thorax, and their changes compared to a reference are reconstructed to an image. Obtained images can be analyzed either in real-time or off-line[29]. The validity and reproducibility of EIT findings are derived from several experimental and clinical studies comparing EIT with reference techniques like computed tomography, positron emission tomography[29]. Of note, EIT can give information for the global lung ventilation homogeneity, i.e., lung overdistention, and local mechanics and function[30].

*Transthoracic echocardiography*

Lung-heart interaction is a well-known phenomenon that occurs because the heart is encased within the rigid chest encompassed by the lungs[31]. The repetitive increase in intrathoracic pressure due to invasive ventilation decreases heart preload and increases pulmonary vascular resistances, affecting the systolic and diastolic function of the right ventricle (RV)[32]. The visual assessment of RV function with transthoracic echocardiography is challenging because of its complex structure, contraction pattern and retrosternal position[33]. Nevertheless, parameters obtained through transthoracic echocardiography such as comparing right to left ventricular surface, tricuspid annulus propagation excursion (TAPSE) and tricuspid systolic maximal velocity can be helpful to identify severe right ventricular dysfunction at the bedside indirectly[34]. Furthermore, the RV myocardial performance index (RV-MPI) derived from echocardiographic measuring isovolumetric, and ejection intervals measure both systolic and diastolic RV performance, which is to a certain degree fluid status–independent[35].

**Aims and hypothesis**

This thesis is a collection of investigations focusing on evaluating lung and heart function through bedside available imaging technics, including LUS, EIT and transthoracic echocardiography, in invasively ventilated critically ill patients.

The specific aims were:

1. to determine the accuracy of LUS in identifying lung morphology in invasively ventilated patients;
2. to determine the association of the global LUS score with outcome in invasively ventilated patients with COVID-19 related ARDS;
3. to study changes in lung aeration evaluated through EIT parameters during prone position in invasively ventilated patients with COVID−19 related ARDS;
4. to determine the association of RV-MPI derived through transthoracic echocardiography and clinical outcomes in invasively ventilated patients; and
5. to study the differences in RV-MPI derived through transthoracic echocardiography in patients ventilated with low or higher PEEP.

We hypothesized:

1. that LUS can reliably classify lung morphology into ‘focal’ and ‘not-focal’;
2. that a higher global LUS score indicative of decreased lung aeration is associated with worse clinical outcomes in invasively ventilated COVID-19 patients, independent of ARDS severity;

3. that prone positioning decreases the inhomogeneity of aeration and recruits collapsed lung tissue as measured by EIT in invasively ventilated COVID–19 patients;
4. that RV dysfunction evaluated with transthoracic echocardiography is associated with worse clinical outcomes in invasively ventilated patients; and
5. that RV function evaluated with transthoracic echocardiography is affected by the chosen PEEP strategy.

**Outline of this thesis**

In **Chapter 2**, we describe the results of a systematic review of the literature aimed to identify morphological, anatomical and functional imaging characteristics that predict lung recruitability in the invasively ventilated patient. For each included study, we collected data related to patient characteristics, type of recruitment manoeuver, criteria for a 'responder' to recruitment and the baseline characteristics to identify factors that differentiate between 'responders' and 'non-responders'. The study's main findings regarding heterogeneity in recruitment response and differences between "responders" and "non-responders" were shown in a table. We further synthesized the current evidence for heterogeneity and prediction of recruitment response in an overview table, stratified per imaging method used. Finally, we attempted to link the physiological and morphological characteristics of responders and non-responders in an overview figure.

In **Chapter 3**, we present the results of a posthoc analysis on two prospective studies that enrolled invasively ventilated patients with ARDS examined with LUS and chest CT scanning at the same time[25,36]. Two participating centers (Amsterdam University Medical Centers, location 'Academic Medical Center' (AMC) Amsterdam, The Netherlands and Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy ) separately developed two LUS methods for classifying lung morphology into 'focal' and 'not−focal' morphology. Either of these methods (Amsterdam and Lombardy method) was based on a stepwise approach starting with evaluating the anterior LUS score. Moreover, a previously developed LUS method was tested based on anterior LUS scores (Piedmont method)[37]. The sensitivity and specificity of all three LUS methods were assessed in the cohort of the other centre(s) by using CT as the gold standard for classifying lung morphology. We hypothesized that LUS can reliably classify lung morphology into 'focal' and 'not-focal' compared to gold standard chest CT. The Amsterdam and Lombardy cohorts consisted of 32 and 19 ARDS patients.

**Chapter 4** reports the results of a retrospective international multicenter study that evaluated patients with COVID-19 related ARDS with at least one LUS study within 5 days after invasive mechanical ventilation initiation. LUS studies were performed as part of routine practice using the 12-region technique[28]. Subpleural consolidations and abnormal pleural line were also assessed offline in each field using saved ultrasound clips. The association of LUS with outcomes was analyzed with multi-state, competing risk proportional hazard models. Two sensitivity analyses were performed for the following predefined subgroups: (a) severity of ARDS according to $PaO_2/FiO_2$ based on cutoffs described in the Berlin definition for ARDS, and (b) days of invasive ventilation before LUS examination, on day 0, day 1, day 2 to 3, and day 4 to 5. The primary outcomes were the risks for successful liberation from invasive ventilation and intensive care mortality up to 28 days. 137 patients were included in the study. We hypothesized that a higher global LUS score indicative of decreased lung aeration is associated with worse clinical outcomes in invasively ventilated COVID-19 patients independent of ARDS severity.

**Chapter 5** describes the results of a prospective observational study enrolled invasively ventilated patients with COVID−19 severe ARDS receiving prone position for refractory hypoxemia. Changes in lung aeration by EIT were studied from before to after placing a patient prone and back to supine. Linear mixed-effects models were used to evaluate changes in lung aeration. Endpoints were global inhomogeneity and changes in local compliance, end-expiratory lung impedance (EELI), and poorly ventilated areas ('silent spaces'). Recruitment of lung tissue was considered to occur if compliance, EELI and 'silent spaces' was improved. We included 15 spontaneously breathing invasively ventilated. We hypothesized that prone positioning decreases the inhomogeneity of aeration and recruits collapsed lung tissue as measured by EIT in invasively ventilated COVID-19 patients.

**Chapter 6** presents the results of a posthoc analysis of patients included in two multicenter randomized clinical trials of invasive ventilation—in one study, named 'Protective Ventilation in Patients Without ARDS' (PReVENT) [39], ventilation with a low tidal volume ($V_T$) was compared with ventilation with an intermediate $V_T$; in the other study, named 'REstricted versus Liberal positive end-expiratory pressure in patients without ARDS' (RELAx), ventilation with lower PEEP was compared to ventilation with higher PEEP [38]. Echocardiography was performed as part of two substudies that focused on the effects of the tested ventilation strategies on cardiac function and enrolled patients in only one center, the Amsterdam UMC, location 'AMC', Amsterdam, The Netherlands. To investigate the prognostic capacity of RV−MPI in invasively ventilated critically ill patients without ARDS, we used multistate, competing risk proportional hazard models. The primary outcome was successful liberation from invasive ventilation and secondary outcome mortality at 28 days. Of 81 patients enrolled in the PReVENT and RELAx substudies, 73 patients could be included in the posthoc analysis. We hypothesized that RV dysfunction evaluated with transthoracic echocardiography is associated with worse clinical outcomes in invasively ventilated patients.

**Chapter 7** presents the findings of RELAx echo substudy. Patients were randomized to a ventilation strategy with lower PEEP, in which PEEP was titrated from 5 $cmH_2O$ to the lowest level at which oxygenation remained satisfactory, versus a ventilation strategy with higher PEEP, in which PEEP was set at 8 $cmH_2O$. According to the study protocol, in RELAx echo substudy, patients without severe hemodynamic instability ventilated for 24 to 48 hours were examined with transthoracic echocardiography. To investigate the effects of PEEP levels on heart function, we compared the echocardiographic derived parameters in the group of patients randomized to high or low PEEP strategy. The right ventricular myocardial performance index was the primary endpoint of the study. Of 146 patients enrolled in the RELAx trial in our center, 44 patients could be included in the substudy. We hypothesized that RV function evaluated with transthoracic echocardiography is affected by PEEP strategy.

**Chapter 8** provides a summary of the findings of the studies mentioned above. **Chapter 9** consists of a General Discussion and discusses the Future Perspectives. Finally, **Chapter 10** is a summary in Dutch.

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# Chapter 2: Assessment of the effect of recruitment maneuver on lung aeration through imaging analysis in invasively ventilated patients: a systematic review.

*Charalampos Pierrakos , Marry R Smit, Laura A Hagens, Nanon F L Heijnen, Markus W Hollmann, Marcus J Schultz, Frederique Paulus , Lieuwe D.J. Bos*

*Front Physiol. 2021;12:666941.*

## Abstract

### Background

Recruitment maneuvers (RMs) have heterogeneous effects on lung aeration and have adverse side effects. We aimed to identify morphological, anatomical and functional imaging characteristics that might be used to predict the of RMs on lung aeration in invasively ventilated patients.

### Methods

We performed a systemic review. Studies including invasively ventilated patients who received a RM and in whom re-aeration was examined with chest computed tomography (CT), electrical impedance tomography (EIT), and lung ultrasound (LUS) were included.

### Results

20 studies were identified. Different types of RMs were applied. The amount of re-aerated lung tissue after a RM was highly variable between patients in all studies, irrespective of the used imaging technique and the type of patients (ARDS, non-ARDS). Imaging findings suggesting a non-focal morphology (i.e., radiologic findings consistent with attenuations with diffuse or patchy loss of aeration) were associated with a higher likelihood of recruitment and lower chance of overdistention than a focal morphology (i.e.,, radiological findings suggestive of lobar or segmental loss of aeration). This was independent of the used imaging technique but only observed in patients with ARDS. In patients without ARDS, the results were inconclusive.

### Conclusions

ARDS patients with imaging findings suggestive of non-focal morphology show most re-aeration of previously consolidated lung tissue after RMs. The role of imaging techniques in predicting the effect of RMs on re-aeration in patients without ARDS remains uncertain.


## Introduction

A lung recruitment maneuver (RM) is a dynamic and transient increase in transpulmonary pressure aiming at (re-)opening collapsed lung parts and increasing end-expiratory lung volume [1]. In theory, the opening of collapsed or ‘non-aerated’ lung areas decreases shunt, improving both oxygenation and removal of $CO_2$[2,3]. Furthermore, atelectatic areas might cause stress on, or deformation of, aerated regions, resulting in the additional injury of lung parenchyma[4]. Accordingly, decreasing atelectatic areas with RM could protect the lungs, a strategy often referred to as the ‘open lung concept[5].

The value of RMs without the use of any imaging monitoring is disputed, as so far, clinical studies have failed to show benefit with regard to patient-centered outcomes - and even suggest harm[6]. The absence of net benefit might be explained by the heterogeneity and unpredictable effects of RMs on lung aeration [7,8]. The pressure threshold that should be overpassed during RMs to open atelectatic lung units is multifactorial and cannot be calculated precisely[8,9]. Furthermore, any increase in airways pressure will result in higher pressures in all lung parts, also those that are 'open', and these areas might be harmed by overdistention[9]. Thus, the benefit of RMs needs to be balanced between re-aeration and overdistention.

Changes in lung morphology indicative of re-aeration or overdistention can be estimated using lung imaging[10] Various imaging techniques like chest computed tomography (CT), electrical impedance tomography (EIT), and lung ultrasound (LUS) have been suggested to be useful to evaluate lung morphology and function in an individual patient[11]. We performed a systematic review to describe imaging-based methods to assess re-aeration after RMs in patients receiving invasively ventilation at the intensive care unit or the operating room. In this review, we focus on the variability of imaging based methods definitions and the clinical utility of baseline imaging characteristics.

## Methods

This protocol was designed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[12]. The study protocol has been registered on PROSPERO (CRD42020188056)

*Eligibility Criteria*

The PICO used to define eligibility criteria: 1) **P** (population): invasive mechanical ventilation either in the intensive care unit (ICU) or the operating room (OR) with or without ARDS, 2) **I** (intervention) : recruitment maneuver of any sort, 3) **C** (comparison) : LUS and/or EIT and/or CT was used to evaluate re-aeration of previously consolidated lung tissue, 4) **O**: baseline image characteristics were reported and evaluated for their predictive value of recruitment . Original studies written in English were only included whereas animal studies, case reports, comments, letters and studies whom enrolled pediatric patients were not included.

*Information sources and Search:*

We searched EMBASE using PubMed on 15 December 2020 using the following key words: *((“diagnostic imaging”[Subheading] OR (“diagnostic”[All Fields] AND “imaging”[All Fields]) OR “diagnostic imaging”[All Fields] OR “ultrasound”[All Fields] OR “ultrasonography”[MeSH Terms] OR “ultrasonography”[All Fields] OR “ultrasound”[All Fields] OR “ultrasonics”[MeSH Terms] OR “ultrasonics”[All Fields]) OR “ct”[All Fields]) OR “computed tomography”[All Fields]) OR ((“IEEE Int Conf Electro Inf Technol”[Journal] OR “eit”[All Fields]) OR “electrical impedance tomography”[All Fields])) AND ((“positive-pressure respiration”[MeSH Terms] OR (“positive-pressure”[All Fields] AND “respiration”[All Fields]) OR “positive-pressure respiration”[All Fields] OR “peep”[All Fields]) AND Recruitment[All Fields]).*

*Study selection*

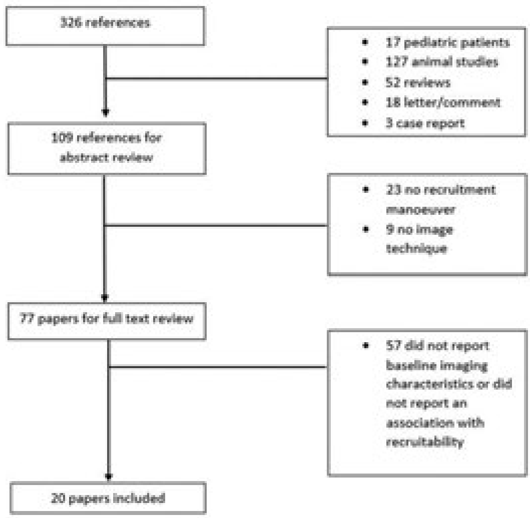
The identified studies were assessed for inclusion criteria based on title and then on abstract. For all selected papers, the full text was read and discussed between two authors

(CP and LDB). Studies that fulfilled the inclusion criteria were included in this review.

*Data collection*

For each included study, we collected data related to patient characteristics and whether they referred to ARDS patients or not. The type of recruitment maneuver that was used was categorised as: a) sustained inflation, b) sigh c) pressure-control ventilation and d) variable ventilation[13]. We recorded the criteria that were used to define a 'responder' to recruitment and the baseline characteristics to identify factors that differentiate between 'responders' and 'non-responders'. For those studies including patients with ARDS, we documented whether authors classified patients as having 'focal' (*i.e.* radiological attenuations with lobar or segmental distributions) or 'non-focal' (*i.e.* radiological attenuation with diffuse or patchy distribution) abnormal lung morphology.

**Figure 1.** Flow diagram of the studies selection




*Bias assessment*

The Quality Assessment of Diagnostic Accuracy Studies-2 ( QUADAS-2) was used for the assessment of the methodologic quality of selected studies[14]. The four recommended domains (*i.e.* patient selection, index test, reference standard and flow/timing) were assessed for low, high or unclear risk of bias. As for the reference standard domain, CT was considered the "gold standard" for assessing lung re-aeration. Given the insufficient evidence to classify LUS or EIT as adequate reference tests to asses lung aeration we considered the risk of bias to be high. Concerns regarding applicability for the first three domains were also assessed and scored as low, high or unclear.

*Synthesis of results*

The following data were combined into a table: patient group that was studied, number of patients, type of recruitment and maximal airway pressure reached, assessment of re-aeration of lung tissue, criteria to define "responder". The main findings of the study regarding heterogeneity in re-aerated lung tissue and differences between "responders" and "non-responders" were also shown. We further synthesized the current evidence for heterogeneity and prediction of recruitment response in an overview table, stratified per imaging method that was used. Finally, we linked the morphological characteristics derived from different imaging techniques of responders and non-responders in an overview figure.

## Results

### *Included studies*

The described search resulted in 326 articles, of which 249 were excluded based on the title and abstract review. Twenty out of the remaining 77 studies were included in this review based on a full-text review (**Fiure 1**), summarized in **Table 1**. 17 studies included deeply sedated patients, while sedation level was not mentioned in the other 3 studies. In all patients in the included studies were in the supine position during RM. In the majority of the included studies enrolled ARDS patients exclusively (14 studies ,70%). Three studies (15%) included a mixed population of intensive care unit patients and in three studies (15%), patients undergoing elective operation were included. Three studies had the primary goal of quantification of potential for lung recruitment [15,16] or recruitment prediction[17]. Regarding lung imaging techniques, most of the studies (10 studies, 50%) assessed chest CT scan, followed by LUS (5 studies, 25%) and EIT (5 studies, 25%). Notably, chest CT was only used in studies that included patients with ARDS.

**Table 1**. Studies included in this review.

| Study | Patients | N | RM | Pmax | Imaging modality | Recruitment definition method | Outcome |
|---|---|---|---|---|---|---|---|
| He et al 2020 [42] | ICU (deeply sedated) | 30 | PC | NG | EIT | Ratio overdistended to recruited pixels | RM resulted in a high variability of the changes in the ration of overdistended to recruited pixels measured with EIT. No differences in the EELI and GI between responders and not responders to RM. |
| Genereux et al 2019 [24] | OR (deeply sedated) | 45 | SI | 30 cm$H_2O$ | LUS | 12 areas derived LUS score | RM did not result in a significant improvement of LUS score. |
| Karsten et al 2019 [23] | ICU (NM) | 15 | Sigh | 40 cm$H_2O$ | EIT | Local compliance (ODCL index) | RM resulted in the complete disappearance of collapsed units (ODCLindex) in all studied patients, but there was a high variation of the over-distention extension (19±17 %). After RM, the proportion of collapsed units was highly variable (0%–50%), independently of the selected PEEP (5-13 cm$H_2O$). |
| Zhao et al 2019 [43] | ARDS (deeply sedated) | 3 | Sigh | 35 cm$H_2O$ | EIT | Increase in ventilation in dependent areas | Those with ventilation distribution predominantly in the most dependent regions are likely not-responders to RM. |
| Camporota et al 2019 [16] | ARDS (sedation level not mentioned) | 47 | SI | 45 cm$H_2O$ | CT | Proportion of re-aerated lung tissue compared to the total lung weight | RM resulted in a variable change in aerated lung tissue with a mean of 24.3% (-2-76). All patients were on ECMO and had a very high percentage of non-aerated lung tissue. Non-recruitable tissue varied between 50% and 80% of total lung weight. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Eichler et al 2018 [19] | OR (deeply sedated) | 37 | Sigh | 40 cm$H_2O$ | EIT | EELI slope | A downward course of EELI may indicate the need for RM ($EELI_{30sec}$ /$EELI_{0sec}$ <1) . This pattern of EELI inversed after RM and PEEP increase. |
| Tang et al 2017 [44] | ARDS (deeply sedated) | 40 | PC | 35 cm$H_2O$ | LUS | Regasification score | RM resulted in significant changes in aeration in the anterior and lateral areas, but not in the posterior areas. |
| Longo et al 2017[18] | OR (deeply sedated) | 40 | Sigh | 35 cm$H_2O$ | LUS | Resolution of atelectasis | RM resolved atelectasis in all but 2/20 (10%) of the patients. The RM effect was assessed with TOE. |
| Eronia et al 2017 [25] | ICU (deeply sedated) | 16 | SI | 40 cm$H_2O$ | EIT | EELI slope | A downward course of end-expiratory lung impedance may indicate the need for RM (10min delta EELI >10%). This pattern of EELI inversed after RM and PEEP increase. |
| Chiumello et al 2016 [36] | ARDS (sedation level not mentioned) | 22 | Sigh | NG | CT | Proportion of re-aerated lung tissu compared to the total lung weight | Responders to RM (increase in tissue >-100 HU) had higher amount of non-inflated tissue at PEEP 5cm$H_2O$ ($r^2$ =0.44). This relation disappears when responders are defined by increase in tissue >-500 HU ($r^2$=0.002). |
| *Caironi et al 2015 [20] | ARDS (deeply sedated) | 14 | PC | 45 cm$H_2O$ | CT | Proportion of re-aerated lung tissu compared to the total lung weight | Responders to RM had higher total lung weights. RM results in a highly variable recruitment of non-aerated lung tissue. This is independent of the severity of disease and baseline PEEP. |
| de Matos et al 2012 [37] | ARDS (deeply sedated) | 51 | PC | 60 cm$H_2O$ | CT | Sectional lung weight re-aerated | RM resulted in variable aeration of previously non-aerated lung tissue: 45% (25 – 53). Responders to RM did not have a higher initial amount of non-aerated tissue (PEEP 10 cm$H_2O$; $r^2$= 0.03). |
| Rode et al 2012 [45] | ARDS (deeply sedated) | 17 | Sigh | 30 cm$H_2O$ | LUS | Crater like consolidations' borders leveling and abutting pleural line | RM resolved most (92%) of crater-like subpleural consolidations visible during ZEEP. |
| Bouhemad et al 2011 [46] | ARDS (deeply sedated) | 40 | SI | 40 cm$H_2O$ | LUS | Increase lung re-aeration score | RM was unlikely to affect consolidations in posterior and caudal regions. RM responders were more likely to have non-focal rather than focal lung morphology. |
| Constantin et al 2010 [17] | ARDS (deeply sedated) | 19 | SI | 40 cm$H_2O$ | CT | Proportion of re-aerated lung volume compared to the total lung volume | RM responders were more likely to have non-focal than focal lung morphology at ZEEP. Hyperinflation during RM is predicted by the lung volume between -800 and -900HU in ZEEP ($r^2$=0.77). |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Caironi et al 2010 [47] | ARDS (deeply sedated) | 68 | PC | 45 cm-$H_2O$ | CT | Proportion of re-aerated lung tissue compared to the total lung weight | RM responders had more opening and closing lung tissue at PEEP 5 cm$H_2O$. RM responders had a homogeneous cephalo-caudal distribution of non-aerated areas while non-responders had a linear cephalo-caudal increase of non-aerated areas. |
| Gattinoni et al 2006 [15] | ARDS (sedation level not mentioned) | 68 | PC | 45cm-$H_2O$ | CT | Proportion of re-aerated lung tissue compared to the total lung weight | RM had a variable effect on opening of lung tissue (Median 9% Range -10% – 60%). RM response was predicted by recruitment of lung tissue after increase of PEEP from 5-15 cm$H_2O$ ($r^2$ =0.72). RM response was predicted by the amount of non-aerated tissue at PEEP 5cm$H_2O$. |
| Borges et al 2006 [21] | ARDS (deeply sedated) | 26 | PC | 60 cm-$H_2O$ | CT | Proportion of re-aerated lung tissue compared to the total lung weight and proportion of re-aerated lung volume compared to the total lung volume | RM shows different responses with variation of lung opening pressures. RM at 40 cmH2O resulted in response in less than 50%, while this increased to 93% at 60 cm$H_2O$. |
| *Nieszkowska et al 2004 [48] | ARDS (sedation level not mentioned) | 32 | Sigh | NG | CT | Volume increase in non-aerated or poorly aerated areas | RM responders more frequently had non-focal morphology rather than focal (lobar) morphology (recruited volume: 572 ± 25 ml vs 249 ±159 ml). RM did not result in over-inflation in patients with a diffuse morphology. |
| Vieira et al 1999 [22] | ARDS (sedation level not mentioned) | 14 | Sigh | 45 cm-$H_2O$ | CT | Total lung volume increases | RM responders more frequently had a non-focal morphology. RM responders more frequently had a biphasic lung density histogram with a peak at -700 to -900 HU > 50ml at ZEEP is related to a higher amount of over-inflation with RM. |

*OR: Operating room , N: number of enrolled patients, Pmax: Maximum pressure used for recruitment maneuver, RM: Lung recruitment maneuver, SI: Sustained inflation, PC : Pressure-Control , LUS : Lung ultrasound, EIT : electrical impedance tomography, CT : Computed tomography, ODCL: Overdistention collapse index, PEEP: Positive end-expiratory pressure, ZEEP: Zero end-expiratory pressure , EELI: End expiratory lung impedance , LIL: left inferior lobe, TOE: transoesophageal echocardiography, HU: Hounsfield units, COPD: Chronic obstructive pulmonary disease, *: Retrospective study*

Quality characteristics of included studies, in relation to the aim of this systematic review, are presented in Table S1. In two studies there was a high concern regarding applicability of population selection. These two studies included a highly selective population, i.e., patients after cardiac surgery[18] or patients who underwent tracheostomy[19].

*Recruitment methodology and identification of 'responders'*

In eight studies (42%) a sigh, in six studies (31%) a pressure-control method, and in five studies (26%) a sustained inflation was used for the RM (Table 1). Applied maximum

**Table 2** Findings related to the assessment of recruitment after recruitment maneuver application

| Imaging modality | Definition of "recruitment" | Base-line PEEP | Maximum applied pressure (mean & range) |
|---|---|---|---|
| **LUS** | Decrease 4 points in LUS score[24]<br>Maximum increase of regasification score [44]<br>Disappearance of atelectasis or B-lines [18,45,46] | ZEEP [24,44,45,46]<br>6 $cmH_2O$[18] | 34 $cmH_2O$ [30-40] |
| **EIT** | Any decrease in ODCLindex (23)<br>Reverse of EELI ratio from <1 to >1 [25,43]<br>Changes of the pixel ratio of overdistention to recruitment > 15% (42) | ZEEP [23,42]<br>5-8 $cmH_2O$ [43] ,<br>PEEP/$FiO_2$ table PEEP[25],<br>8 $cmH_2O$[19] | 39 $cmH_2O$ [35-40] |
| **CT** | Decrease in non-aerated weight of lung (>-100HU) [15,16,20,21,36,37,47]<br>Decrease in non-aerated and poorly aerated weight of lung (>-500HU) [36]<br>Increase in the volume of gas penetrating in non-aerated areas (>-500HU) [21]<br>Increase in the volume of gas penetrating in non-aerated and poorly aerated areas (>-500HU) [17,22,48] | ZEEP [17,22,48]<br>5 $cmH_2O$ [15,16,17,20,36]<br>10 $cmH_2O$ [37],<br>5-10 $cmH_2O$ [21] | 48 $cmH_2O$ [40-60] |

*PEEP: positive end-expiratory pressure, ZEEP : zero end-expiratory pressure, LUS: Lung ultrasound, EIT : electrical impedance tomography, CT : computed tomography, EELI: End expiratory lung impedance, HU: Hounsfield units, ODCL: Overdistention collapse index,*

airway pressure varied widely, between 30 and 60cm $H_2O$. Classification of responders depended on the imaging technique used (**Table 2**). None of the studies defined the criteria to identify 'responders' beforehand. Patients were classified *post hoc* as 'responders' and 'non-responders' based on the median value of the study population in studies that quantified re-aeration by CT imaging. Recruitment 'responders' generally had an increase in aeration of non-aerated lung tissue of more than 20% (**Figure 2**).

*Heterogeneity in re-aeration and prediction of positive response to RM*

Re-aeration after RM varied widely between studies, independent of the used image technique (**Table 3**). Unsurprisingly, most CT imaging studies showed that around 50% of patients are 'non-responders' to recruitment because the median value was used as cut-off value[15,16,20-22]. Studies that used other imaging techniques did not mention the proportion of 'non-responders', though recruitment was described as 'highly variable'[23,24].

Imaging findings related to the amount of re-aerated lung tissue in patients with ARDS were the extent of lost aeration before RM, the distribution of non-aerated areas (craniocaudal and anteroposterior distribution), the morphology of non-aerated areas (e.g. crater-like consolidation), and functional lung characteristics related to tidal recruitment (tidal opening/ closing tissue) (**Table 3**). Findings that are more likely to resemble a diffuse or patchy loss of aeration (*i.e.* non-focal morphology) were suggestive for an increased likelihood of positive response to RMs (**Figure 3**). This was independent of the image technique employed.

**Table 3.** Observed recruitment maneuver re-aeration effect and findings related to potential for lung re-aeration after recruitment maneuver according the imaging module and the presence or not ARDS.

| | ARDS | Non-ARDS |
|---|---|---|
| **Observed lung re-aeration with imaging analysis** | | |
| LUS | 8% of evaluated consolidations did not respond to RM [45] | No change of LUS score after RM[24] |
| | 27% of patients had a re-aeration score ≥ 8 and an increase in lung volume more than 600ml after RM [46] | 10% of patients do not respond to RM[18] |
| EIT | Extremely high variability in changes of the ration between overdistention and collapsed ration [42] | Variable* compromise between the extension of lung collapse and over-distention after RM[23] |
| CT | High variability* of potential recruitment tissue [20] | |
| | Potential recruitable tissue: 45% (range 5-75) [37] | |
| | Potential recruitable tissue: 9%(range -10-60) [15] | |
| | Potential recruitable tissue: 24.3% (range -2-76)[16] t | |
| | High variability of opening lung pressures [20] | |
| **Findings that predicted more lung re-aeration** | | |
| LUS | Anterior located consolidations [44,46] | |
| | Crater-like sub-pleural consolidations [45] | |
| EIT | Predominant ventilation in non-dependent areas [43] | Decreasing pattern of EELI (delta EELI >10% or EELI index <1) [19,25] |
| CT | Not aerated tissue (>-100 HU) >25-30% of total lung tissue [15,36] | |
| | Non-focal lung morphology [17,48] | |
| | Homogeneous cephalo-caudal distribution of 40-50% non-aeration area [47] | |
| | Opening and closing lung tissue (141±81g) [47] | |

Only one study addressed the prediction of response to RM in patients in the operating room. A decreasing pattern of end-expiratory lung impedance (EELI) evaluated with EIT was found to be related to the amount of re-aerated lung tissue[19] (**Table 3**).

*Overdistention*

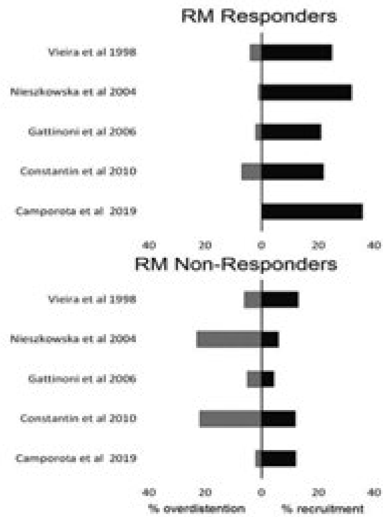
Overdistention was assessed in studies that used CT or EIT only, as LUS cannot be used for this purpose. Studies employing CT imaging showed the average percentage of overdistended lung volume to vary between 0% to 20% (**Figure 2**). EIT studies revealed the average overdistention secondary to RMs across patients to range between 5% to 30% [23]. Nevertheless, local overdistention in non-dependent areas may exceed 60% of that area[25]. ‘Non-Responders’ identified by CT had a higher increase in hyperinflated lung tissue compared to ‘responders’ (**Figure 2**).

## Discussion

The results of this systematic review can be summarized as follows: a) data that quantify the potential for lung recruitment based on imaging are limited, b) the definition of positive response to RMs was highly variable and c) patients with imaging characteristics suggestive for a non-focal morphology of ARDS seemed to show more re-aeration at RMs with moderate inspiratory pressures.

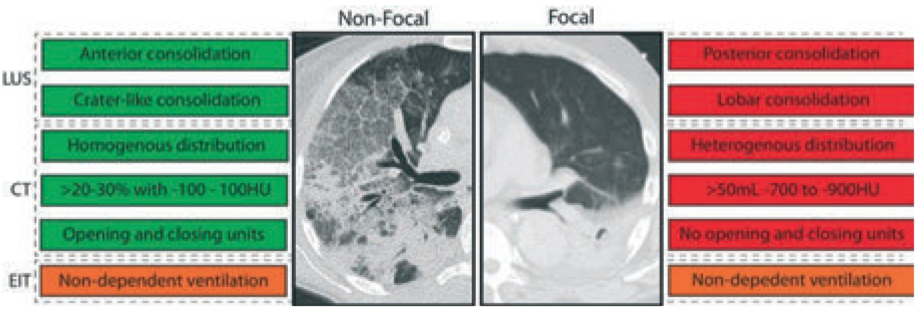
The included studies used a wide range of maximum airway pressures to recruit lung tissue. Most collapsed areas can be opened, but frequently only at very high airway pressures[26]. Borges et al. found opening pressures of 60 $cmH_2O$ in patients with ARDS to be common, with coexistence of areas opening at lower and higher pressures in the majority of patients [21]. In clinical practice, maximum airway pressure is often selected based on the hemodynamic fragility of the patient rather than the expected pressure needed for lung recruitment[27]. This might explain why CT compared to LUS and EIT studies revealed higher recruitment pressures as transfer for CT imaging requires more hemodynamically stable patients[28]. Recent RCTs suggest airway pressure above 50 $cmH_2O$ to be associated with serious adverse events, even when the patient is exposed to it for a short period of time [6,29]. As the different components that attribute to the compliance of the respiratory system (compliance of the lung and chest wall as well as intraabdominal pressure) cannot be easily separated in clinical practice[30] assessing the RMs effect with imaging techniques is important in clinical practice. Rather than defining the pressure at which the lung can be opened, it is more important to determine whether recruitment can be achieved with moderate airway pressures. In other words, when comparing patients with a similar expected risk of side-effects due to a transient increase in inspiratory pressures, a patient who responds to the RM with reaeration of previously collapsed lung tissue may still benefit, but a patient without this response may not.

**Figure 2.** The proportions of lung recruitment and lung overdistention in patients who were characterized responders or not responders to lung recruitment maneuvers (RM) based on computed tomography findings.




This review also revealed several challenges associated with the quantification of lung *re-aeration* with image technics: there is poor agreement between imaging techniques and there is no universal definition of recruitment response. Chiumello et al. found poor agreement between CT and LUS with respect to assessment of re-aeration, not unexpected since LUS is a semi-quantitative method assessing only the sub-pleural areas[31]. Furthermore, the role of LUS for assessing overdistention is currently unknown[32]. Pleural line displacement identified with LUS, as well the number of A-lines are relevant indexes which are currently being studied [33,34]. EIT quantifies collapsed lung units based on local changes in compliance [35]. However, compliance might be more related to the improvement or deterioration of already ventilated lung units than the real recruitment of atelectatic lung units[36]. Even though CT is considered the gold standard for detecting lung recruitment defining the degree of re-aeration remains challenging. Potentially recruitable lung tissue, determined by CT, is mainly expressed as percentage of total lung volume since absolute values depend on lung dimensions. However, expressing recruitment as percentage implies mathematical coupling with the total atelectatic volume, which is at least debatable[37]. Gattinoni et al. introduced the terms "high" and "low" recruitment responders based on the median percentage of potentially recruitable lung tissue determined by CT[15]. Worth mentioning, different median percentages of potentially recruitable tissue were reported in later studies [16,37], probably due to heterogeneity in inclusion characteristics and application of various maximum airway pressures. Given that recruitment is a continuous spectrum that depends on applied airway pressure and several imaging characteristics, speaking about "responders" from "non-responders" is a false dichotomization.

**Figure 3**. Imaging abnormalities that predicted response to recruitment maneuvers (RM) stratified per morphology. LUS: lung ultrasound, EIT: electrical impedance tomography, CT: computed tomography, HU: Houndsfield units. Green: imaging abnormality in line with responder to RM, Red: imaging abnormality in line with non-responder to RM, Orange: imaging abnormality in line with responder with high uncertainty. Text-boxes on the left: consistent with non-focal morphology. Text-boxes on the right: consistent with focal morphology.




We set out to determine the role of imaging techniques in predicting the lung response to RM. The main strength of this review is the systematic and integrative approach. We excluded studies that based assessment of recruitment on mechanical or oxygenation variables as those can be influenced by factors other than recruitment of lung tissue, which is also known as the recruitment paradox[38]. We also acknowledge several limitations. First, we had to perform secondary analyses of many included studies as they were not intended to quantify potential for lung re-aeration, limiting statistical comparisons between groups. Second, we did directly not compare imaging techniques. Each method has intrinsic limitations, such as visualisation of the subpleural region only for LUS and the need for patient transport for CT, that justify preferential use of one technique over another in specific situations. Of note, the definition and method of recruitment varied between studies even when the same image technique was used, which made direct comparisons impossible. Third, given the undefined role of LUS and EIT in the assessment of recruitment, a significant number of trials had an unclear risk of bias.

All features predictive for increased lung re-aeration after RM are consistent with a non-focal morphology of ARDS. Patients with focal ARDS lack, by definition, ventral consolidations not limited to the subpleural space and show a heterogeneous distribution of consolidation with less opening and closing, what renders them very unlikely to be recruitable. In line with this notion, patients with non-focal morphology were typically recruitable while patients with focal morphology were not [17,39]. Notably, atelectasis is usually located in dorsal lung areas in patients without lung injury requiring invasive mechanical ventilation [18,40] implying a 'focal' morphology. This may explain the lack of RMs efficiency to increase lung aeration in invasively ventilated patients in the operating room [24]. Although the results of this review are not conclusive for patients without ARDS, it stresses the need for further research into lung morphology and its relation to lung re-aeration with robust imaging technics in these patients.

By integrating data from multiple studies to morphological classifications, we present a framework used to better design and interpret future studies. We have to acknowledge that this classification is imperfect, as one EIT study that only included three patients suggested that predominant ventilation in the non-dependent areas predicted recruitment, while this is not a feature that is consistent with non-focal morphology of ARDS. The relation between re-aeration and improvement in ventilation perfusion mismatch and heart function was not evaluated in this review[41]. Furthermore, in this review we investigated the imaging techniques role in predicting RMs effects in deeply sedated patients without considering the optimal level of PEEP that would be required after recruitment to keep the lung open. Rather than a final classification, we suggest that the morphological classification is a good starting point to further improve from, with the addition of other predictors. Furthermore, more attention should be drawn to the quantification of overdistention rather than measurement of re-aeration alone. Balancing the assessment of negative and positive effects may improve our understanding as to what patients may or may not benefit from RMs.

## Conclusions

We conclude that defining positive response to RMs using imaging techniques is challenging and not yet well elucidated. Variations in RM method, population selection as well as different imaging techniques should be taken into consideration in future studies. Given the adverse events associated with high maximum airway pressures, only the lungs of specific patients can be re-aerated with moderate maximum airway pressures. Lung ultrasound and CT characteristics consistent with non-focal morphology of ARDS are predictive of more re-aeration in response to recruitment maneuver. The morphological characteristics related to successful response to RMs in patients without ARDS have not been studied to date.

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# Chapter 3: Lung Ultrasound Assessment of Focal and Non-Focal Lung Morphology in Patients with Acute Respiratory Distress Syndrome

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## Abstract

### Background

The identification of phenotypes based on lung morphology can be helpful to better target mechanical ventilation of individual patients with acute respiratory distress syndrome (ARDS). We aimed to assess the accuracy of lung ultrasound (LUS) methods for classification of lung morphology in critically ill ARDS patients under mechanical ventilation.

### Methods

This was a post-hoc analysis on two prospective studies that performed LUS and chest computed tomography (CT) scanning at the same time. Expert panels from the two participating centres separately developed two LUS methods for classifying lung morphology based on LUS aeration scores from a 12-region exam (Amsterdam and Lombardy method). Moreover, a previously developed LUS method based on anterior LUS scores was tested (Piedmont method). Sensitivity and specificity of all three LUS methods was assessed in the cohort of the other centre(s) by using CT as the gold standard for classification of lung morphology.

### Results

The Amsterdam and Lombardy cohorts consisted of 32 and 19 ARDS patients respectively. From these patients, 23 (45%) had focal lung morphology while others had non-focal lung morphology. The Amsterdam method could classify focal lung morphology with a sensitivity of 77% and a specificity of 100%, while the Lombardy method had a sensitivity and specificity of 100% and 61%. The Piedmont method had a sensitivity and specificity of 91% and 75% when tested on both cohorts. With both the Amsterdam and Lombardy method, most patients could be classified based on the anterior regions alone.

### Conclusions

LUS-based methods can accurately classify lung morphology in invasively ventilated ARDS patients compared to gold standard chest CT. The anterior LUS regions showed to be the most discriminant between focal and non-focal lung morphology, although accuracy increased moderately when lateral and posterior LUS regions were integrated in the method.

## Introduction

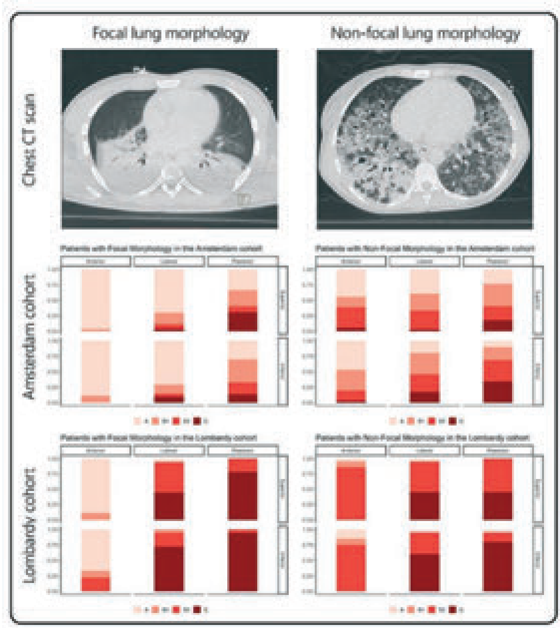
Acute respiratory distress syndrome (ARDS) is a frequent cause of hypoxemic respiratory failure and is characterized by protein rich pulmonary edema[1]. Diagnosis is based on a set of clinical and radiological criteria[2,3], resulting in remarkable physiological, radiological and biological heterogeneity[4-7]. The notion that there is no 'typical' ARDS may explain the failure of large clinical trials to demonstrate beneficial effects of unselective application of therapeutic interventions[5].

The identification of ARDS phenotypes can be helpful to better target treatment of individual patients with ARDS [1]. Lung imaging with computed tomography (CT) has been used to differentiate two distinct phenotypes of ARDS based on lung morphology. Lungs with diffuse and patchy loss of aeration (non-focal phenotype) generally respond well to recruitment while lungs with predominant dorso-inferior consolidations (focal phenotype) respond better to prone positioning[8]. Misclassification of these two different phenotypes results in misaligned ventilation strategies and is related to a substantial increase in mortality[9]. Therefore, it is pivotal to accurately recognize morphological phenotypes before a personalised strategy can be applied.

While CT scan remains the gold standard for lung assessment, it has several inherent limitations. It requires transportation to radiology department, which can be at high risk for critically ill patients, and requires moderate doses of radiation yielding it unsuitable as a monitoring tool. Furthermore, interpretation of morphology requires considerable expertise, which is pivotal in avoiding misclassification[9]. Chest X-rays are commonly performed in the intensive care unit (ICU), but recognition of focal and non-focal ARDS phenotypes remains challenging in these images [9]. Therefore, a bedside, simple and easily repeatable imaging tool would ideally provide useful information to manage ARDS patients in everyday practice.

Lung ultrasound (LUS) is a bed-side imaging technique that has been used to evaluate critically ill patients with acute respiratory failure[10]. LUS has potential in both diagnosis and monitoring of ARDS and showed a good correlation with chest CT in estimating lung aeration[11-14]. A previously performed study showed promising results for LUS as a tool to classify lung morphology, but the percentage of patients with focal lung morphology was exceptionally low in this population and moreover the method lacks external validation[15]. We aimed to assess the accuracy of LUS methods for classification of lung morphology in critically ill ARDS patients under mechanical ventilation. We

**Figure 1.** Overview of LUS patterns present per lung region for the Amsterdam and Lombardy cohorts The upper images show examples of CT images from patients with focal and non-focal lung morphology. The middle and lower figures show the distribution of LUS patterns (A-pattern (score 0), B-patterns (score 1 & 2) and C-patterns (score 3)) for the anterior, lateral and posterior lung regions stratified for lung morphology as assessed by CT and cohort. LUS: Lung ultrasound, CT: Computed tomography.



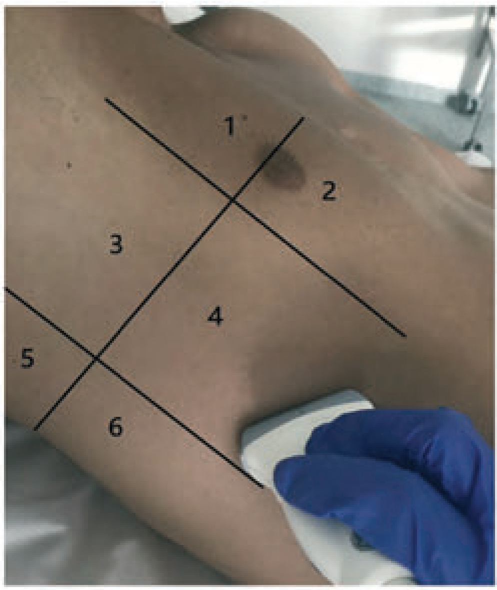
hypothesized that LUS can reliably assess lung morphology compared to gold standard chest CT[16].

## Materials and Methods

### *Study design and ethical concerns*

We performed a post-hoc analysis on two prospective studies that performed LUS and chest CT scanning at the same time. The Amsterdam cohort consisted of invasively ventilated patients included in prospective observational study performed in the ICU of the Amsterdam University Medical Centers, location 'Academic Medical Center' (AMC), Amsterdam, The Netherlands[17]. The study protocol was approved by the institutional review board (IRB) of the AMC (2017_312#B201859). Patients in this study were analysed if they fulfilled the Berlin criteria of ARDS[3]. The Lombardy cohort consisted of patients from a study in invasively ventilated ARDS patients performed at the ICU of the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy. This study was approved by the hospitals' IRB[12].

**Figure 2:** Lung regions scanned in a 12-region LUS exam shown for one hemithorax LUS images were acquired using a linear transducer and a transversal approach. Zone 1 and 2 are anterior LUS regions, zone 3 and 4 are lateral LUS regions and zone 5 and 6 are posterior LUS regions. LUS: Lung ultrasound



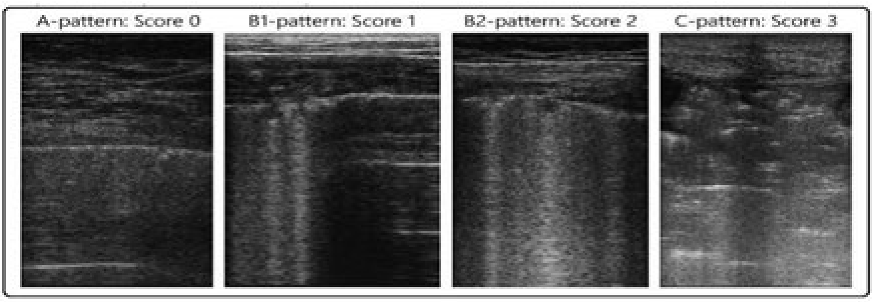

### *Definitions*

Focal morphology was defined as isolated consolidations with an infero-dorsal dominance as assessed with CT. Non-focal morphology was defined as presence of diffuse or patchy opacifications, with or without dorsal consolidations (**Figure 1** and Supplemental Figure 1).

### *Lung morphology assessed with CT*

Chest CT scans of both studies were evaluated and characterized as focal or non-focal by at least two investigators. In case of disagreement, the scans were discussed in a panel of at least three investigators until a consensus was reached. This classification was performed while blinded for the results of the LUS exam and were used as the reference standard in all subsequent analysis. Evaluation of LUS and CT images in the Amsterdam and Lombardy cohort was performed independently by researchers from the respected centres.

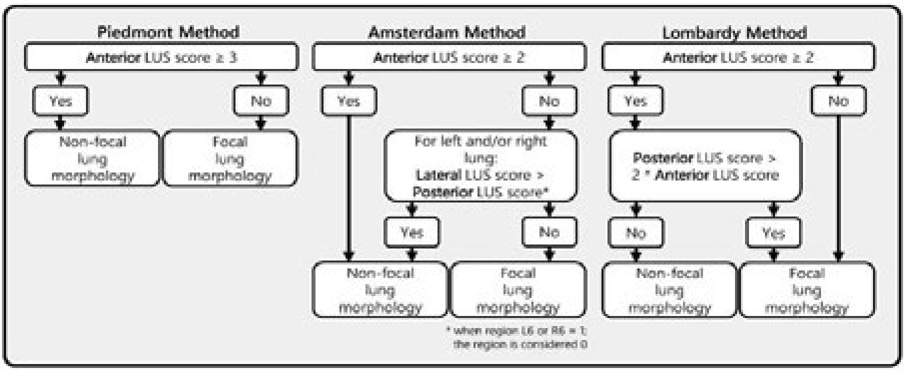
**Figure 3:** Lung ultrasound images for all LUS patterns and scores Each LUS image was scored with the LUS aeration score: An ‘A-pattern’ (i.e., repeating horizontal A-lines parallel to the pleural line) was scored ‘0’, a ‘B-pattern’ (i.e., ≥3 vertical B-lines starting from the pleural line and reaching the bottom of the screen) was scored ‘1’ if B-lines are well-spaced and cover ≤50% of the pleural line, and ‘2’ if B-lines cover ≥50% of the pleural line, and a ‘C-pattern’ (i.e., consolidation) was scored ‘3’. The global LUS score is the sum of all 12 lung regions and reaches from 0-36 and the anterior, lateral and posterior LUS score are the sum of 4 lung regions and reach from 0-12. LUS: Lung ultrasound




*LUS examination*

In the Lombardy cohort, LUS was performed immediately before or after the CT examination with the same ventilator and using identical settings; the original protocol assessed patients at positive end-expiratory pressure (PEEP) of 5 and 15 $cmH_2O$, but only the CT and LUS exams at a PEEP level of 5 $cmH_2O$ were analysed for the present study[12]. In the Amsterdam cohort, LUS was performed in the ICU just before transport to the CT scanner with the patient connected to the transport ventilator. The PEEP level in the Amsterdam cohort remained at the clinical PEEP level as set by the treating physician and was equal during LUS and CT. In both studies the LUS exam was performed using an identical 12-region protocol with patients in semi-recumbent position. Each hemithorax was divided into 6 regions: anterior, lateral and posterior fields were identified by sternum, anterior and posterior axillary lines; each field was further divided into superior and inferior regions (**Figure 2**). The regions were scanned with a transversal approach – *i.e.,* the probe aligned with the intercostal space – to maximize lung exposition and minimize rib related shadowing; the scanning area was centred in the region of interest (**Figure 3** and Supplemental Figure 2). LUS videos were stored and scored off-line by sonographers with extensive expertise in LUS blinded for the findings on the chest CT scan. A regional score was computed according to the visualized artefacts: (1) An ‘A-pattern’ (i.e., repeating horizontal A-lines parallel to the pleural line, suggesting normal aeration) was scored ‘0’, (2) a ‘B-pattern’ (i.e., 3 or more vertical B-lines starting from the pleural line and reaching the bottom of the screen, suggesting partial loss of aeration) was scored ‘1’ if B-lines are well-spaced and cover ≤50% of the pleural line, and ‘2’ if B-lines cover ≥50% of the pleural line, and (3) a ‘C-pattern’ (i.e., consolidation, suggest-

**Figure 4:** Ultrasound lung morphology assessment methods This figure presents three LUS morphology assessment methods that were designed and/or evaluated in this study. All three methods classify focal or non-focal lung morphology based on LUS aeration scores from a 12-region LUS exam. The anterior, lateral and posterior LUS scores were defined as the sum of the LUS aeration score in the four anterior, lateral and posterior regions, respectively. The Piedmont method was previously proposed in a study from Costamagna et al15. The Amsterdam and Lombardy method were developed for the purpose of this study by two expert panels from the corresponding regions. *LUS: Lung ultrasound*.




ing near-complete to complete loss of aeration) was scored ‘3’[18-20] (**Figure 3**). Examples of LUS clips are added as supplemental video’s 1-6. Missing LUS images were complemented by the mean LUS aeration score of the other available LUS images in the concerning region (anterior, lateral or posterior region). The global LUS aeration score was defined as the sum of LUS aeration scores from all 12 images; anterior, lateral and posterior LUS scores were computed as the sum of anterior, lateral and posterior regions respectively.

*Derivation of the LUS-based method*

Lung morphology assessment through LUS was assessed with three different methods. One previously published method by Costamagna et al. (Piedmont method) and two methods that were developed by expert panels in Amsterdam and Lombardy. The Piedmont method considered lung morphology as non-focal when patients had an anterior LUS score larger or equal than 3, and remaining patients as having focal lung morphology[15]. The Amsterdam and Lombardy method were independently developed based on the LUS and CT data from the corresponding cohort (Amsterdam and Lombardy cohorts). Both of these methods were based on a stepwise approach starting with the evaluation of the anterior LUS score. In the second step, the posterior LUS score was either compared with the lateral LUS score (Amsterdam method) or with the anterior LUS score (Lombardy method) (**Figure 4**).

*Validation of the LUS-based methods*

Performance of the three LUS methods was assessed by using the methods to classify lung morphology in the cohort of the other centre(s). No further changes were allowed to the methods during the validation phase.

*Endpoints*

The primary endpoint of the study was the sensitivity and specificity of the LUS-based methods (index test) for lung morphology based on the CT scan (reference test). The secondary endpoints were (1) the comparison of anterior, lateral and posterior LUS scores, all stratified for focal and non-focal lung morphology, (2) comparison of the three LUS-based methods when applied to both cohorts combined, and (3) identification of best cut off point for the anterior LUS score in both cohorts combined.

*Statistical analysis*

Demographic and clinical variables were presented as percentages for categorical variables and as medians with interquartile ranges (IQR) for continuous variables. Categorical variables were compared with the Chi-squared test and continuous variables were compared with the Mann-Whitney U test. Based on the lung morphology classifications of LUS and CT, contingency tables were generated to characterize the sensitivity and specificity of the method with respect to the reference standard. Sensitivity, specificity, disease prevalence, positive predictive value (PPV) and negative predictive value (NPV) as well as accuracy were calculated and expressed as percentages. Moreover, the F1-score and Matthews correlation coefficients were calculated. No formal power calculation was performed. Differences in classification accuracy between the LUS methods were assessed by comparing receiver operating characteristic (ROC) curves and calculating the categorical net-reclassification index (NRI) and integrated discrimination index (IDI) using R (R Development Core Team, 2011) through the R-studio interface (Version 1.2.1335) using data of both the Amsterdam and Lombardy cohort.

## Results

*Patient population*

The Amsterdam and Lombardy cohort consisted of 32 and 19 patients respectively. Patient characteristics are presented in **Table 1**. 14 patients (44%) had focal morphology in the Amsterdam cohort and 9 (47%) in the Lombardy cohort ($p=0.84$). LUS scores per region for both cohorts and a CT example of focal and non-focal lung morphology is presented in Figure 1. Patients in the Amsterdam cohort had a lower global LUS score compared to patients in the Lombardy cohort (13 [7-17] vs 25 [23-29], $p < 0.01$). The global LUS score was also lower in the Amsterdam cohort compared to the Lombardy cohort in patients with mild ARDS (11 [4-16] vs 24 [20-24], $p < 0.01$) and moderate ARDS (15 [8-17] vs 25 [23-29], $p <0.01$). Only one patient in the Amsterdam cohort had severe ARDS.

**Table 1.** Characteristics of the patients included in the Amsterdam and Lombardy cohorts examined with lung ultrasound and computed tomography. *ARDS: Acute respiratory distress syndrome. IQR: Inter-quartile range. LUS: Lung ultrasound. ICU: Intensive Care Unit. $PaO_2$: Partial pressure of oxygen. $FiO_2$: Fraction of inspired oxygen.*

| Characteristic | Amsterdam cohort | | Lombardy cohort | |
|---|---|---|---|---|
| | Focal ARDS N=14 | Non-Focal ARDS N=18 | Focal ARDS N=9 | Non-Focal ARDS N=10 |
| **Age, median (IQR), years** | 57 (37-67) | 59 (56-68) | 59 (47-75) | 55 (45-73) |
| **Female, No. (%)** | 3 (21) | 5 (28) | 4 (44) | 3 (30) |
| **Duration of invasive ventilation before enrolment, , days** | 4 (2-8) | 4 (1-6) | 2 (2-4) | 5 (2-10) |
| **ICU mortality, No. (%)** | 6 (43) | 6 (33) | 6 (67) | 5 (71)[a] |
| **Global LUS score** | 7 (2-9) | 16 (12-18) | 24 (22-25) | 28 (25-31) |
| **ARDS severity** | | | | |
| **Mild, No. (%)** | 8 (57) | 8 (44) | 3 (33) | 2 (20) |
| **Moderate, No. (%)** | 5 (36) | 10 (56) | 5 (56) | 6 (60) |
| **Severe, No. (%)** | 1 (7) | 0 | 1 (11) | 2 (20) |
| **Respiratory measures, median (IQR)** | | | | |
| **$PaO_2$ to $FiO_2$ ratio** | 255 (135-289) | 199 (138-233) | 176 (113-225) | 152 (103-180) |
| **$FiO_2$, %** | 50 (40-60) | 60 (50-65) | 50 (40-59) | 50 (50-65) |
| **Tidal volume, mL** | 503 (411-551) | 433 (349-582) | 450 (340-520) | 450 (325-550) |
| **Positive end-expiratory pressure, cm $H_2O$** | 7 (5-8) | 10 (8-12) | 5 (5-5) | 5 (5-5) |
| **Respiratory rate, breaths/min** | 22 (16-25) | 26 (17-35) | 18 (16-25) | 15 (10-16) |

[a]Data available in 7 out of 10 patients

In the Amsterdam cohort, 46 out of 384 (12%) LUS images were missing due to chest tubes, subcutaneous emphysema or morbid obesity (median of 1 [0-2] regions per patient). From the missing LUS images, 1, 12 and 33 images were missing in the anterior, lateral and posterior region, respectively. The Lombardy cohort did not have missing LUS images. Additionally, the PEEP level was 8 [5-11] $cmH_2O$ in the Amsterdam cohort and 5 [5-5] $cmH_2O$ in the Lombardy cohort ($p < 0.01$).

*Diagnostic performance*

The diagnostic performance of the three methods for detecting focal morphology is presented in **Table 2**. The performance of the Piedmont method was moderate to good when tested on data of the Amsterdam and Lombardy cohort combined with a sensitivity of 91% and a specificity of 75%, for detecting focal lung morphology. The Amsterdam method had a good performance when tested on data of the Lombardy cohort with a sensitivity of 77% and specificity of 100% for the detection of focal lung morphology. The Lombardy method had a moderate performance when tested on data of the Amsterdam cohort with a sensitivity of 100% and a specificity of 61% for the detection of focal lung morphology.

The Amsterdam method performed significantly better than the Piedmont method (NRI: 0.179 [CI: 0.037–0.320], IDI: 0.179 [CI: 0.034–0.323], p = 0.015). The Amsterdam method was not significantly better than the Lombardy method (NRI: 0.127 [CI: -0.063–

0.318], IDI: 0.127 [CI: -0.067–0.322], p= 0.199). There was no difference in classification between the Lombardy and Piedmont method (NRI: 0.051 [CI: -0.083–0.185], IDI: 0.051 [-0.086–0.188], p= 0.463). ROC curves for the three LUS methods are presented in **Figure 5**.

For the Amsterdam method, 13 out of 18 patients in the Amsterdam cohort and 10 out of 10 patients in the Lombardy cohort could be classified as non-focal lung morphology solely based on the anterior LUS score. For the Lombardy method, 14 out of 14 patients in the Amsterdam cohort and in 7 out of 9 patients in the Lombardy cohort could be classified as focal lung morphology solely based on the anterior LUS score. Additional data on routes towards classification for the Amsterdam and Lombardy method is presented in the supplemental results.

*Regional LUS differences between morphologies*

Anterior LUS scores were higher in patients with non-focal morphology compared to patients with focal morphology in both the Amsterdam (3 [1-5] vs 0 [0-1], p<0.001) and the Lombardy cohort (8 [5-8] vs 1 [0-2], p<0.001). An ROC curve for the anterior LUS score is

**Table 2.** Distribution of examined patients according to their lung morphology determined with LUS-based method in comparison to CT findings. LUS: Lung ultrasound. CT: Computed tomography. PPV: Positive predictive value. NPV: Negative predictive value. MCC Matthews correlation coefficient

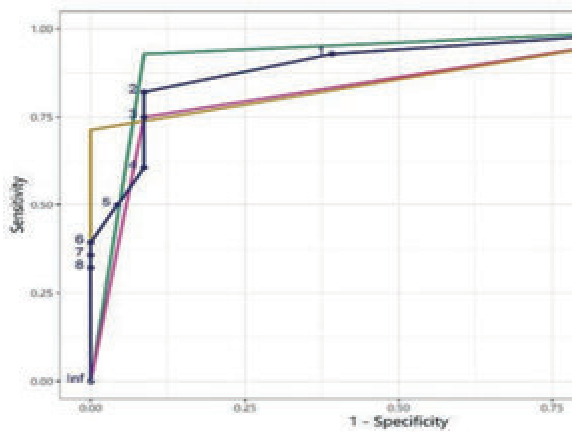
| | | | Cross tabulation LUS and CT | | Test characteristics | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Method** | **Cohort** | | CT: Focal | CT: Non-focal | Sensitivity | Specificity | PPV | NPV | Accuracy | F1-score | MCC |
| **Piedmont** | Validation Amsterdam (N=32) | LUS: Focal | 14 | 7 | 100% | 61% | 67% | 100% | 78% | 0.8 | 0.64 |
| | | LUS: Non-Focal | 0 | 11 | | | | | | | |
| | Validation Lombardy (N=19) | LUS: Focal | 7 | 0 | 78% | 100% | 100% | 83% | 89% | 0.88 | 0.81 |
| | | LUS: Non-Focal | 2 | 10 | | | | | | | |
| **Amsterdam** | Derivation Amsterdam (N=32) | LUS: Focal | 14 | 2 | 100% | 89% | 88% | 100% | 94% | 0.94 | 0.88 |
| | | LUS: Non-Focal | 0 | 16 | | | | | | | |
| | Validation Lombardy (N=19) | LUS: Focal | 7 | 0 | 78% | 100% | 100% | 83% | 89% | 0.88 | 0.81 |
| | | LUS: Non-Focal | 2 | 10 | | | | | | | |
| **Lombardy** | Validation Amsterdam (N=32) | LUS: Focal | 14 | 7 | 100% | 61% | 67% | 100% | 78% | 0.8 | 0.64 |
| | | LUS: Non-Focal | 0 | 11 | | | | | | | |
| | Derivation Lombardy (N=19) | LUS: Focal | 9 | 1 | 100% | 90% | 90% | 100% | 94% | 0.95 | 0.9 |
| | | LUS: Non-Focal | 0 | 9 | | | | | | | |

presented in Figure 5, showing that an anterior LUS score ≤ 2 is the most discriminant cut-off for classification of non-focal lung morphology in the Amsterdam and Lombardy cohort combined. The lateral LUS score was higher in patients with non-focal morphology compared to patients with focal morphology in the Amsterdam cohort (5 [3-7] vs 1 [0-3], p= 0.012) but not in the Lombardy cohort (10 [8-12] vs 10 [9-12], p=0.803). The posterior LUS score was not different between patients with non-focal morphology and patients with focal morphology in both the Amsterdam cohort (7 [5-9] vs 4 [3-8], p=0.166) and the Lombardy cohort (11 [10-11] vs 12 [11-12], p=0.054) (**Figure 1**).

## Discussion

The main findings of this study can be summarized as follows: (1) LUS-based methods can accurately classify lung morphology in invasively ventilated patients with ARDS, and (2) an anterior LUS score equal or larger than 2 was strongly related with a non-focal lung morphology.

**Figure 5**. ROC curves for the LUS methods and the anterior LUS score in predicting non-focal lung morphology ROC curves for the Piedmont, Amsterdam and Lombardy method and for the anterior LUS score regarding classification of non-focal lung morphology when applied to both the Amsterdam and Lombardy cohort. The area under the ROC curve was: 0.83 for the Piedmont method, 0.92 for the Amsterdam method, 0.86 for the Lombardy method and 0.90 for the anterior LUS score. As the output of the LUS methods for lung morphology classification is dichotomous, only one cut-off can be presented for the corresponding ROC curves. LUS: Lung ultrasound, ROC: Receiver operating characteristic




Personalized ventilation based on lung morphology has great potential to improve treatment of individual ARDS patients, but only if lung morphology is correctly classified[9]. Chest CT is the gold standard for classification of lung morphology, but is commonly not feasible due to risky transport and CT can also be complex to interpret[1]. Therefore, there is a strong need for an accurate alternative to chest CT, that is available bedside and accessible for all ICU physicians. LUS can fill this implementation gap as LUS-based methods are objective and easy to apply in clinical practice as they rely on a well-defined and validated scoring system[21]. For example, previously implemented LUS methods with comparable complexity were reproducible between operators after limited training[22-25]. Moreover, LUS is one of the tools that is also suitable for diagnosis and management of ARDS patients in limited resource settings[11,26].

Because there was uncertainty on the best approach towards estimating lung morphology with LUS we considered and studied several methods. The ‘AzuRea’ group described a LUS method for assessment of lung morphology to evaluate changes in oxygenation following prone position[27]. However, this method did not capture lung morphology accurately and was not considered applicable to our population. Costamagna et al. proposed a LUS method based on anterior LUS scores for classification of lung morphology and validated the method with gold standard chest CT (Piedmont method)[15]. This method performed excellent in the original study but the performance decreased substantially when applied to the Amsterdam and Lombardy cohorts. A possible explanation could be selection bias in the Piedmont study because only 23% of patients were classified as having focal lung morphology, which is substantially lower compared to other cohorts[8,9]. Another second reason could be the different approach in scoring B-patterns between the Piedmont study and the cohorts used in the present study.

The present study confirms that the anterior LUS scores are most important in classification of lung morphology. The fact that anterior LUS regions had the largest influence in classifying lung morphology enhances the applicability of LUS in clinical practice, as these regions are easy and quick to assess. As a misaligned ventilation strategy is probably worst for patients with focal lung morphology ventilated as a patient with non-focal lung morphology[9] a low anterior LUS score could be an indication of low PEEP and prone position rather than alveolar recruitment manoeuvre. But although the anterior LUS score is most important, the posterior LUS score when compared to the lateral LUS score (Amsterdam method) or anterior LUS score (Lombardy method) should not be neglected. Incorporating these ratios in a two-step approach can significantly improve the performance of LUS methods and therefore avoid harmful misclassifications. Moreover, a complete 12-region LUS exam can be performed within 10 minutes by an experienced sonographer[24].

The Amsterdam and Lombardy methods performed best when using data from the centre they were derived from. Both methods had a high accuracy for lung morphology in their respected validation cohorts as well, with the Amsterdam method seemingly outperforming the Lombardy method. The major difference between these methods lies in the diagnostic approach: in the Amsterdam method a high anterior LUS score was used to confirm non-focal morphology whereas in Lombardy method a low anterior LUS score was used to confirm focal morphology. Both the Lombardy and Amsterdam method showed decreased performance during external validation. A possible explanation for this decrease is the significant difference in LUS scores between cohorts. The higher LUS scores in the Lombardy cohort might be the result of the lower PEEP settings or higher disease severity in this particular cohort. The original study where the Lombardy cohort was derived from showed that the global LUS score lowered with 4 points when PEEP was changed from 5 $cmH_2O$ to 15 $cmH_2O$[12]. The difference in PEEP of 10 $cmH_2O$ in this previous study was however much larger than the difference in median PEEP of 3 $cmH_2O$ between the Amsterdam and Lombardy cohorts. It is therefore likely that the higher mortality and disease severity in the Lombardy cohort largely contributed to the higher LUS scores as well. Subsequently, patients with non-focal morphology and a low anterior LUS score were only found in the Amsterdam cohort where a higher clinically used PEEP was applied in patients with a low-moderate global LUS score. Patients with focal morphology and a high anterior LUS score were only identified in the Lombardy cohort where the global LUS score was higher and PEEP was fixed at 5 cm$H_2O$ per protocol.

The level of PEEP during assessment of lung morphology is important, as changes in PEEP alter lung aeration that is measured with lung imaging[21]. It should be noted that previous studies assessed lung morphology at zero PEEP, but this was not done in both cohorts of this study[8]. This is unpractical, unethical and subsequent studies used a PEEP of 5 cm$H_2O$[8], which is in line with the PEEP used in the Lombardy cohort where patients were studied at PEEP of 5 cm$H_2O$ per protocol. Future studies should investigate at what PEEP level lung morphology should be assessed with LUS and then modify the LUS method accordingly.

This study has several strengths. The external validity of the study is high as we used two different cohorts of ARDS patients treated in different centres for development and validation of LUS-based methods for identification of lung morphology. LUS examination was identical in the two cohorts and the patients were examined almost simultaneously with CT examination. The validity of LUS to evaluate lung morphology was assessed at different levels of PEEP, with a varying level of PEEP in the Amsterdam cohort that reflects clinical practice in this institution. Nevertheless, this study also has several limitations. First, the validity of using the difference between lateral and posterior LUS scores in the Amsterdam method was not fully assessed as all the patients with non-focal morphology in the Lombardy cohort were classified solely based on the anterior LUS regions. Second, the sample size of both cohorts was small due to the limited availability of paired LUS and CT images using standardized protocols at the same PEEP settings. Therefore, prospective validation of the LUS methods is advised. Third, both cohorts did not include any patients with COVID-19 related ARDS, thus we cannot translate our findings to this prevalent disease.

In conclusion, LUS-based methods can accurately classify lung morphology in invasively ventilated ARDS patients compared to gold standard chest CT. The anterior LUS regions showed to be the most discriminant between focal and non-focal lung morphology, although accuracy increased moderately when lateral and posterior LUS regions were integrated in the method.

## SUPPLEMENTARY MATERIAL TO:

**Lung Ultrasound Assessment of Focal and Non-Focal Lung Morphology in Patients with Acute Respiratory Distress Syndrome**

### Route towards classification using the Amsterdam and Lombardy methods

For the Amsterdam method, the majority of patients with non-focal lung morphology could be classified solely based on the anterior LUS score (13 out of 18 patients in the Amsterdam cohort and 10 out of 10 patients in the Lombardy cohort). In patients from the Amsterdam cohort with non-focal lung morphology that were not classified based on the anterior LUS score, 3 out of 5 patients were correctly classified based on a lateral LUS score that was higher than the posterior LUS score in at least one hemithorax. The other two patients with non-focal lung morphology from the Amsterdam cohort could not be classified based on the anterior LUS score or the ratio between lateral and posterior LUS scores, and were misclassified. In the Lombardy cohort, two patients with focal lung morphology were misclassified as having non-focal lung morphology by the Amsterdam method due to an anterior LUS score ≥ 2.

For the Lombardy method, most patients with focal lung morphology were correctly classified solely based on anterior LUS scores (14 out of 14 patients in the Amsterdam cohort and in 7 out of 9 patients in the Lombardy cohort). Using the Lombardy method, 7 out of 18 patients in the Amsterdam cohort with non-focal lung morphology were misclassified as having focal lung morphology, all explained by the presence of an anterior LUS score ≤ 2. In patients from the Lombardy cohort, 1 out of 10 patients with non-focal lung morphology was misclassified by the Lombardy method because the posterior LUS score was higher than two times the anterior LUS score.

## Supplemental figures

**Figure 1.** Examples of ARDS lung morphology categorized as ‘focal’ or ‘non focal: a) Consolidations isolated in the dorsal areas (focal morphology), b) Diffuse patchy loss in ventral and/or dorsal areas without any consolidations (non-focal morphology), c) Consolidations in the dorsal areas and diffuse patchy loss in ventral areas (non-focal morphology), d) Consolidations in one lung at dorsal areas and diffuse patchy loss with or without consolidation in the other lung (non-focal morphology)

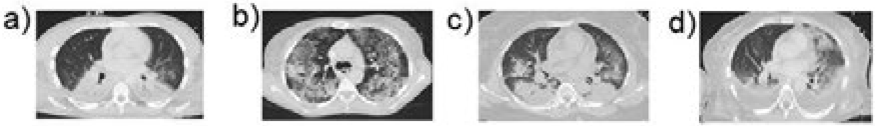
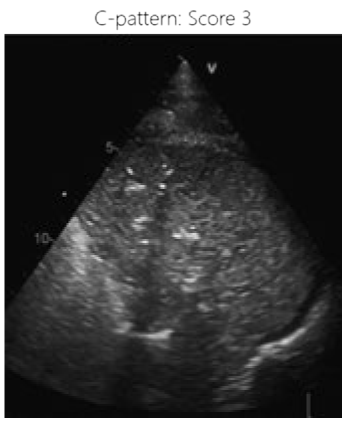



**Figure 2.** Lung ultrasound image of a consolidated lung ultrasound pattern using a phased array transducer.



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# Chapter 4: A lower global lung ultrasound score is associated with higher likelihood of successful extubation in invasively ventilated COVID-19 patients

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**Abstract**

Lung ultrasound (LUS) can be used to assess loss of aeration, which is associated with outcome in patients with COVID-19 presenting to the emergency room. We hypothesized that LUS scores are associated with outcome in critically ill COVID-19 patients receiving invasive ventilation. This retrospective international multicenter study evaluated patients with COVID–19 related ARDS with at least one LUS study within 5 days after invasive mechanical ventilation initiation. The global LUS score was calculated by summing the 12 regional scores (range 0 to 36). Pleural line abnormalities and subpleural consolidations were also scored. The outcomes were successful liberation from the ventilator and intensive care mortality within 28 days, analyzed with multi-state, competing risk proportional hazard models. 137 patients with COVID-19 related ARDS were included in our study. The global LUS score was associated with successful liberation from mechanical ventilation (hazard ratio (HR), 0.91 [95%–CI 0.87–0.96]; P=0.0007), independently of the ARDS severity, but not with 28 days mortality (HR: 1.03 [95%–CI 0.97–1.08]; P=0.36). Subpleural consolidation and pleural line abnormalities did not add to the prognostic value of the global LUS score. Examinations within 24 hours of intubation showed no prognostic value. To conclude, a lower global LUS score 24 hours after invasive ventilation initiation is associated with increased probability of liberation from the mechanical ventilator COVID–19 ARDS patients, independently of the ARDS severity.

*Trial registration: Clinicaltrials.gov identifier: NCT04487769*

**Introduction**

Coronavirus disease 2019 (COVID–19) is responsible for hundreds of thousands of deaths worldwide, and this number is still rapidly increasing[1]. Respiratory failure is the most common and severe complication of COVID–19, and bilateral and multi–lobar infiltrates can progress rapidly over the first few days of illness[2]. Approximately 5% of hospitalized patients require admission to an intensive care unit (ICU), mainly for invasive mechanical ventilation[3]. There is a high variability in the reported mortality across invasively ventilated COVID–19 patients[4-6]. The severity of loss of aeration, typically assessed by chest CT scan, has been related to outcomes in hospitalized COVID-19 patients[7-9], but CT-scan capacity is limited and may even not be available in a resource limited setting.

Lung ultrasound is a bedside, radiation–free, low–cost diagnostic imaging tool that can be used for assessing lung aeration and parenchymal abnormalities[10]. The global lung ultrasound score (LUS) quantifies lung aeration by translating LUS patterns into a numerical score across 12 lung regions and summing the results[11-12]. Previous studies have shown a correlation between LUS and severity of acute respiratory distress syndrome (ARDS)[13], and with mortality in invasively ventilated critically ill patients[14]. LUS has previously been performed in a general population of COVID-19 patients outside the hospital[15], presenting to the emergency room[16-18] and on the general wards[19-26] and has been found to be related to adverse outcomes including the need of invasive ventilation. Nevertheless, the role of LUS in evaluating the severity of patients after initiation of invasive ventilation is much less certain[27]. Evaluating lung disease severity with LUS may be important for ICU resource planning, especially in settings where resources are restricted, as well as for personalized ventilatory approach[28].

The aim of this study is to assess the association between global LUS score and outcome, specifically defined as liberation from the ventilator and survival in critically ill COVID-19 patients under invasive ventilation. We hypothesized the global LUS score to have prognostic value in invasively ventilated COVID–19 patients independently of ARDS severity.

## Methods

*Design*

This is an international multicenter cohort study. We retrospectively reviewed patients with reverse transcriptase polymerase chain reaction (RT–PCR) confirmed COVID–19 under invasive ventilation in ICUs of four hospitals in three countries: the Brugmann University Hospital Brussels (Brussel, Belgium), the Miulli Regional Hospital (Acquaviva delle Fonti, Italy) and the Amsterdam University Medical Centres, locations AMC and VUMC between February 2020 and 31 December 2020. LUS studies were performed as part of routine practice, and were executed by experienced ultrasonographers (n=10) who performed at least 50 systematic lung ultrasound exams before.

*Ethics*

Ethical approval for this study was provided by the ethical committees of each hospital (Brugmann University Hospital N° CE 2020/136; Azienda Ospedaliero-Universitaria Policlinico di Bari 0030638/22/04/2020; Amsterdam UMC location AMC W18_311; Amsterdam UMC location VUMC 2020.011).

*Patients*

Patients were included if they received a LUS within first 5 days after invasive ventilation initiation but before extubation. Patients who received a LUS while supported with extracorporeal membrane oxygenation (ECMO) were excluded. Only the first available examination of LUS was used for the analysis.

*Data collected*

The following data was extracted from chart: demographic characteristics, APACHE II and SOFA score on admission, vital signs, and ventilator and blood gas parameters on the day of LUS examination.

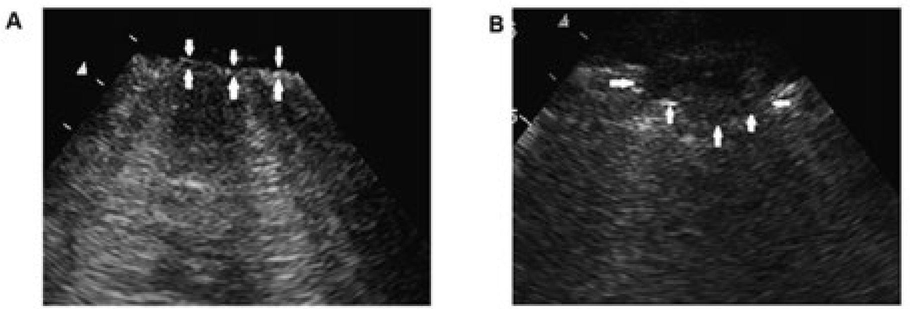
*The protocol for LUS*

Lung ultrasound examination was performed with the available equipment at the

COVID ICUs of the participating hospitals. The following machines were available: MyLab™ Five ultrasound machine with a convex probe (Esaote Spa, Genova, Italy), a Vivid S5 with curvilinear probe (General Electric Healthcare, Chicago, USA), a LOGIQ E with a linear probe (GE Healthcare, Milwaukee, US) and a Sonosite Edge II (Fujifilm Sonosite, Bothell, Washington, United States).

The 12–region technique was used in all examinations in which ultrasound was performed on six areas on each side of the chest, i.e., two ventral regions, two lateral regions, and two postero–lateral regions[29]. The aeration pattern observed in each region was scored from 0 to 3 according to the LUS aeration score as follows: '0', A–pattern with ≤ 2 B–lines; '1', more than 2 separated B–lines that cover ≤50% of the pleural line; '2', B–lines that cover >50% of the pleural line; or '3', lung consolidation. In theory, the global LUS score can range

**Figure 1.** Pleural line abnormalities (A) and subpleural consolidation (B) identified with lung ultrasound in patient with COVID–19 infection.




tion from the normally appearing thin, smooth and continuous hyperechoic line[29]. Subpleural consolidations were defined as one or more echo poor regions juxtaposed to the pleural line, which were not large enough to be scored as a tissue-like pattern or "Lobar consolidation" in the lung aeration score[30].

*Outcomes*

The primary outcomes were the risks for successful liberation from invasive ventilation and intensive care mortality up to 28 days.

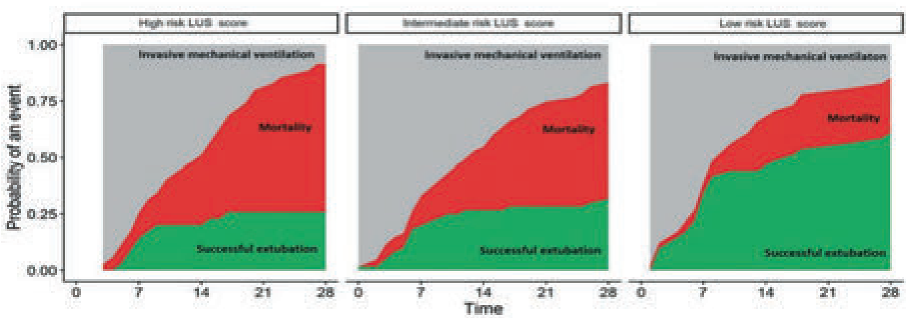
*Statistical analysis*

No formal power analysis was performed for this exploratory analysis. Rather, all patients that fulfilled the inclusion and exclusion criteria were included. Demographic, clinical, and outcome variables were presented as percentages for categorical variables and as medians with interquartile ranges (IQR) for continuous variables.

The association of LUS with outcomes was analyzed with multi-state, competing risk proportional hazard models as described in the *survival* package via the *compete* function in *R*. Risks were estimated for successful extubation and mortality and compared to persistent intubation (reference category). Follow-up was censored after 28 days. Two sensitivity analysis were performed for the following predefined subgroups: (a) severity of ARDS according to $PaO_2/FiO_2$ based on cutoffs described in the Berlin definition[31] and (b) days of invasive ventilation before LUS examination (exam on day 0, day 1, day 2-3, day 4-5).

Receiver operating characteristic (ROC) curve analysis was used to derive the prognostic discriminatory performance of global LUS in determining successful liberation from invasive ventilation and mortality at day 28. Based on the calculated area under the ROC curve (AUROCC) the prognostic accuracy was interpreted as follows: excellent between 0.9–1, good between 0.8–0.89, fair between 0.7–0.79, poor between 0.6–0.69 and very poor between 0.5–0.59[32]. AUROCCs were compared using the DeLong test. Two cut-offs were defined: one with a high sensitivity of above 80% for poor outcome (composite of persistent mechanical ventilation at day 28 or mortality; selecting for a good negative predictive value) and one with a high specificity of above 80% for poor outcome (selecting for a good positive predictive value). The analysis was repeated using the three categories resulting from these cut-offs. All analyses were performed in R through the R-studio interface (www.r-project.org, R version 3.3.1). A *P*-value below 0.05 was considered significant.

**Figure 2.** Three categories of global LUS score and cumulative incidence of outcomes. X-axis: days since intubations. Y-axis: probability of an event (extubation or death) in the population. The three facets show the risk for patients with a high risk global LUS score (left), intermediate risk (middle) and low risk global LUS score (right). Red area show the patients who died. Green area shows the patients who were successfully extubated.




## Results

### *Patients*

A total of 137 patients were studied. Patient characteristics are presented in **Table 1.** At day 28, 53 patients (38%) were successfully extubated, while 64 patients (47%) had died and 20 patients (15%) were still receiving invasive mechanical ventilation. Compared to the patients who failed to be extubated within 28 days, patients who were successfully extubated had a higher $PaO_2/FiO_2$ of 148 mmHg (IQR: 115–173) versus 113 mmHg (IQR: 98–153, P=0.013) and a lower global LUS score of 18 (IQR: 15−23) versus 21 points (IQR: 18−24, P=0.005).

**Table 1.** Characteristics of patients with COVID-19 disease examined with lung ultrasound.

| | Successful liberation of mechanical ventilation and alive at 28 days | Still intubated or deceased at 28 days | P value |
|---|---|---|---|
| Number of patients | 53 | 84 | |
| Day of LUS | 1 (0–2) | 1 (0–2) | 0.71 |
| Demographics | | | |
| Age, years | 61 (54-68) | 71 (62–76) | <0.01 |
| Sex, female | 32 (61) | 46 (54) | 0.59 |
| APACHE II | 13 (12–17) | 14 (12–22) | 0.21 |
| SOFA score | 7 (5-8) | 8 (5-10) | 0.06 |
| Global LUS score | 18 (15−23) | 21(18−24) | <0.01 |
| Subpleural consolidations, fields per patient | 3 (1−5) | 5 (2−6) | 0.01 |
| Pleural line abnormalities, fields per patient | 3 (1− 5) | 3 (1−5) | 0.91 |
| Biology | | | |
| D-dimers, ng/ml | 1440 (873–3875) | 2326 (1720–4063) | 0.03 |
| CRP, µg/ml | 77 (40–159) | 108 (21–172) | 0.81 |
| Ventilation parameters | | | |
| Ventilation mode | | | |
| Volume controlled | 20 (38) | 36 (42) | 0.59 |
| Pressure controlled | 17 (32) | 30 (36) | 0.71 |
| Pressure support | 16 (30) | 18 (22) | 0.31 |
| Tidal volume, ml | 425 (378-484) | 418 (390-460) | 0.71 |
| Tidal volume, ml/kg PBW | 6.3 (5.8-6.9) | 6.3 (5.6-6.5) | 0.75 |
| PEEP set, cm $H_2O$ | 10 (8-12) | 10 (8-12) | 0.81 |
| Pplat, cm $H_2O$ | 22 (19–26) | 24 (20–27) | 0.21 |
| Driving Pressure | 12 (11−17) | 14 (10−17) | 0.55 |
| Static Compliance | 35 (26−44) | 31 (24−44) | 0.55 |
| $SpO_2$, % | 94 (93–96) | 95 (94–97) | 0.83 |
| $FiO_2$ | 55 (50-70) | 64 (55-80) | <0.01 |
| $PaO_2/FiO_2$ | 148 (115–173) | 113 (98–153) | 0.01 |
| Complications/procedures | | | |
| VAP | 11(21) | 59 (71) | <0.01 |
| ECMO | 0 (0) | 4 (5) | 0.15 |
| Tracheostomy | 5 (9) | 19 (22) | 0.06 |
| Death (28 days) | 0 (0) | 64 (76) | |

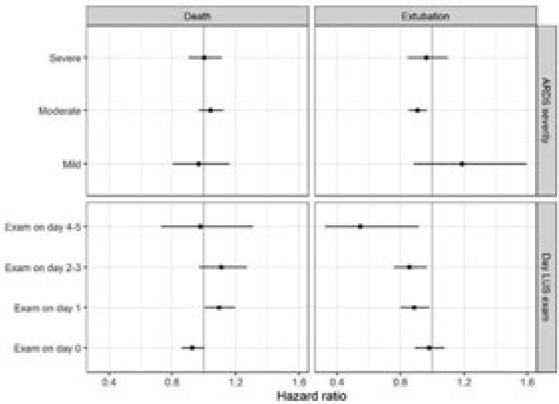
*Data are presented as mean(± standard deviation) median (interquartile range) or number (%). APACHE, Acute Physiology and chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; PBW, predicted body weight; PEEP, positive end–expiratory pressure; Pplat, plateau pressure; SpO2, peripheral pulse oxymetric saturation; FiO2, fraction of inspired oxygen; PaO2, arterial oxygen tension; VAP, ventilator associated pneumonia; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit*

*Association between global LUS score and outcome*

The global LUS score was associated with successful liberation from invasive ventilation (hazard ratio (HR): 0.91 [95%–CI: 0.87–0.96]; P=0.0007) but not with 28 days mortality (HR: 1.03 [95%–CI: 0.97–1.08]; P=0.36) in competing risk analysis.

However, the prognostic capacity of the global LUS sore for successful liberation from the ventilator at day 28 and mortality was poor (AUROCC of 0.65 [95%–CI 0.54–0.74], AUROCC of 0.63 [95%–CI 0.53–0.72], respectively). The optimal cutoff for > 80% sensitivity for the combined endpoint of persistent mechanical ventilation or death at day 28 was 17, while it was 24 for > 80% specificity (Table 3). The corresponding hazard ratios for the probability of being liberated from the ventilator compared to a score of 17 or below (low risk group, n=41), were 0.47 (95%-CI: 0.26-0.85; P=0.01) for the patients with LUS score 18−24 (intermediate risk group, n=71) and 0.37 (95%-CI: 0.17-0.79; P=0.01) for the patients with LUS above 24 (high risk group, n=25; **Figure 2).**

**Figure 3.** Forest plot of global LUS score association with probability of successful liberation of invasive ventilation and death at 28 days according to ARDS severity and the day of examination after start invasive ventilation. X-axis: Hazard ratio for increase of global LUS score for mortality (left) and extubation (right) based on competing risk analysis. The dots provide the point estimate and the lines the 95% confidence interval for estimated associations, stratified for predefined subgroups.




Only patients with a global LUS score of 24 and above had an increased probability of death (HR: 2.3; 95%-CI: 1.08-4.8; P=0.03) compared to a score of 17 or below. Adding subpleural consolidations or pleural line abnormalities did not improve the prognostic capacity for successful extubation or mortality at day 28 (**Table 2**).

*Subgroup analyses*

When patients were classified according to ARDS severity, 11 patients (9%) had mild, 85 patients (68%) had moderate and 29 (23%) had severe ARDS. For twelve patients $PaO_2/FiO_2$ was missing. The global LUS score was associated with the probability of being liberated from the ventilator while alive at 28 days after intubation independently of ARDS severity **(Figure 3)**. There was no evidence for variation of global LUS association with outcome according to the categories of $P_aO_2/FiO_2$ (no interaction; P=0.49).

The majority of the patients were examined within 24 hours after invasive ventilation initiation (61 patients, 44%) whereas 39 patients (28%) were examined between 24 and 48 hours, 24 patients (17%) between 48 and 96 hours and 13 patients (9%) between 96-120 hours after start of invasive ventilation. There was evidence variation of global LUS score according to the time of examination (interaction term, P=0.036). When the examination was performed within 24 hours after intubation, the global LUS score was not associated with the probability of successful extubation in the first 28 days **(Figure 3)**.

**Discussion**

The results of this study can be summarized as follows: (1) an increasing global LUS score indicative of parenchymal damage and loss of aeration is associated with a lower likelihood of mechanical ventilation liberation during the first 28 days of invasive mechanical ventilation but not with mortality, (2) this association was independent from ARDS severity but not from timing of examination and (3) additional LUS findings such as subpleural consolidations and pleural line abnormalities do not significantly improve the prognostic value.

LUS is attractive method for evaluation the severity of COVID-19 patients because ultrasound machines are widely available and thereby the technique can be used even in resource–limited settings. Furthermore, LUS examination at the bedside can potentially decrease or eliminate the need for transport to the radiology department, which is helpful particularly in the context of invasively ventilated patients. Increasing global LUS scores were associated with a higher probability of requiring invasive ventilation for at least 28 days.

Severity assessment of severe COVID-19 early after invasive ventilation initiation is challenging as ventilator management can moderate the prognostic value of easily derived parameters such as the $P_aO_2/FiO_2$ [33]. Simultaneously, the compliance of the respiratory system is low in most of these patients and has little prognostic value[34]. In our study, patients who successfully extubated had a similarly low respiratory system compliance compared to patients who were not successfully extubated. The loss of aeration estimation with LUS was associated with successful extubation independent of the $P_aO_2/FiO_2$ categories, which are used in clinical practice for ARDS severity assessment. Hence, based on these results we think LUS can be used as an additional tool to clinical and laboratory parameters for the severity appreciation on invasively ventilated patients with COVID-19 ARDS.

We did not confirm the results of a previous study in non-COVID-19 related ARDS patients that showed that a global LUS score of 16.5 was predictive for mortality[35]. As rapid extubation is predicted by less extensive parenchymal involvement, reflective of a lower degree of lung injury, we may speculate that mortality is mainly driven by the occurrence of ICU-acquired complications such as pneumonia, pulmonary embolism and ICU acquired weakness and the ability to endure prolonged duration of mechanical ventilation that is frequently needed for COVID-19 related ARDS. This finding is in line with a previous study that showed no association between decreased volume of well-aerated lung tissue as assessed by chest computed tomography and 30-day mortality in critically ill patients with COVID-19 ARDS[36]. Of note, that study also showed that global LUS score was a better predictor of outcome than the CT severity score[36]. In non-COVID-19 related ARDS, the relationship be-

**Table 2.** Prognostic values of global lung ultrasound (LUS) score alone and with the addition of number of areas with subpleural consolidations or pleural line abnormalities

| Outcome | Score | AUROCC (95%CI) | Cut-off | | Poor outcome | Good outcome |
|---|---|---|---|---|---|---|
| Mortality at day 28 | **Global LUS score** | 0.63 (0.53 – 0.72) | 17 | >=17 | 54 | 42 |
| | | | | <17 | 10 | 31 |
| | | | | | ***Sensitivity:84*** | ***Specificity:37*** |
| | | | 24 | >=24 | 23 | 12 |
| | | | | <24 | 41 | 61 |
| | | | | | Sensitivity: 35 | Specificity: 83 |
| | **+ Subpleural con-solidations** | 0.61 (0.51 – 0.71) | 19 | >=19 | 46 | 45 |
| | | | | <19 | 10 | 22 |
| | | | | | ***Sensitivity:82*** | ***Specificity:32*** |
| | | | 28 | >=28 | 19 | 13 |
| | | | | <28 | 37 | 54 |
| | | | | | ***Sensitivity: 33*** | ***Specificity: 81*** |
| | **+ Pleural line ab-normalities** | 0.58 (0.47 – 0.68) | 18 | >=18 | 46 | 47 |
| | | | | <18 | 10 | 20 |
| | | | | | Sensitivity:82 | Specificity:30 |
| | | | 28 | >=28 | 19 | 11 |
| | | | | <28 | 37 | 56 |
| | | | | | ***Sensitivity:33*** | ***Specificity: 83*** |

| Outcome | Score | AUROCC (95%CI) | Cut-off | | Poor outcome | Good outcome |
|---|---|---|---|---|---|---|
| **Successful liberation from mechanical ventilation while alive at day 28** | **Global LUS score** | 0.65 (0.54 – 0.74) | | ≥17 | 68 | 28 |
| | | | 17 | <17 | 16 | 25 |
| | | | | | ***Sensitivity: 81*** | ***Specificity: 47*** |
| | | | | >=24 | 26 | 9 |
| | | | 24 | <24 | 58 | 44 |
| | | | | | ***Sensitivity: 31*** | ***Specificity: 83*** |
| | **+ Subpleural consolidations** | 0.65 (0.55 – 0.75) | | >=19 | 62 | 29 |
| | | | 19 | <19 | 12 | 20 |
| | | | | | ***Sensitivity:84*** | ***Specificity:41*** |
| | | | | >=28 | 25 | 7 |
| | | | 28 | <28 | 49 | 42 |
| | | | | | ***Sensitivity: 32*** | ***Specificity: 86*** |
| | **+ Pleural line abnormalities** | 0.61 (0.51 – 0.71) | | >=18 | 61 | 32 |
| | | | 18 | <18 | 13 | 17 |
| | | | | | Sensitivity:82 | Specificity:35 |
| | | | | >=28 | 13 | 17 |
| | | | 28 | <28 | 53 | 40 |
| | | | | | ***Sensitivity: 28*** | ***Specificity: 82*** |

tween mortality rates and the amount of not aerated areas in invasively ventilated patients is not clear either[37-40]. Even though the limited duration of follow-up of one month may have obscured associations with longer term mortality[41], we conclude that the extent of parenchymal involvement is a poor predictor of outcome when applied to a cohort of critically ill patients requiring invasive mechanical ventilation.

We aimed to facilitate bedside estimation for the risk of adverse outcomes by identifying a cut-off for the global LUS score that could predict mortality or liberation of invasive ventilation in COVID-19 related ARDS patients. In contrast to previous studies that evaluated patients who did not receive invasive mechanical ventilation[17,19,23-25], we were unable to provide a single LUS value that was highly predictive of outcome. However, liberation of mechanical ventilation at 28 days was much more likely in patients with a global LUS lower than 17, while this was very unlikely in patients with a global LUS score higher than 24. Importantly, these cutoffs are not to replace the continuous value and are arbitrary. We prespecified a sensitivity and specificity of 80% for successful extubation, but one could argue that higher certainties are needed for clinical decision making.

Global LUS scores obtained from exams that were performed on the first day of invasive ventilation showed to have less prognostic value compared to LUS exams that were performed after the first day. We postulate that the association between global LUS scores and outcomes are influenced bythe  response to invasive mechanical ventilation and/or corticosteroid treatment. In our cohort, patients examined on the first day after invasive ventilation initiation had a median LUS score of 22. This score is consistent with the results of previous study in which patients with COVID-19 in the ED who required invasive ventilation had a median LUS score of 22[19]. Assessment of lung re-aeration as response by computed tomography in COVID-19 patients has shown conflicting results[42-43]. Assessment of the influence of ventilator management on association between global LUS scores and outcomes should be a topic for future studies.

Subpleural consolidations and pleural line abnormalities are commonly used to distinguish ARDS from cardiogenic pulmonary edema[44] and are also frequently reported in patients with COVID–19 related ARDS[45-48]. In theory, both of these findings can be related to the severity of COVID-19 disease. Additionally, the presence of subpleural consolidations might also indicate a pulmonary embolism[49]. In terms of prognostication, both subpleural consolidations and pleural line abnormalities were found to be associated with the prognosis in COVID-19 patients outside15  and inside the hospital[19]. We found more regions with subpleural consolidations in patients with a poor outcome but not more pleural line abnormalities. Nevertheless, the extent of subpleural consolidations or pleural line abnormalities were not quantitatively related to liberation of ventilation or mortality in the subset of COVID-19 patients who require intubation and mechanical ventilation. As the global LUS score was associated with the extent of subpleural consolidations, we reason that subpleural consolidations are more related to the degree of lung aeration loss rather than to a distinct predictor of mortality or liberation of invasive ventilation.

The main strength of this study is that the global LUS score was assessed by an identical and systematic method by multiple investigators in patients that were treated in four different centers in three different countries. Moreover, we included only COVID-19 patients with severe respiratory failure undergoing invasive ventilation, a homogeneous group of patients that has been underrepresented in COVID-19 LUS cohorts. We accounted for competing risks and were able to distill an association with liberation of ventilation when accounting for the occurrence of mortality during the first 28 days of invasive ventilation. This study also has limitations. First, this is a retrospective study and the indication and time point for a lung ultrasound exam was not prescribed in a protocol. Lung ultrasound exams were done as part of routine clinical practice and all performed within 5 days after start of invasive ventilation. Second, we could not assess the prognostic value of the changes in the LUS score over time as LUS exams were not performed repeatedly in the participating centers. Dynamic changes in LUS scores should be studied further as monitoring tool for re-aeration of lung tissue[50]. Additional studies should focus on LUS as it is an excellent technique to use in a resource-limited setting as alternative for chest radiography or chest CT[51].

## Conclusions

The global LUS score is associated with successful liberation from invasive ventilation, but not with mortality during the first four weeks of invasive ventilation. In patients with a low global LUS score, extubation can be expected in the first weeks of mechanical ventilation while this is uncommon in patients with a high global LUS score. The extend of subpleural consolidations or pleural line abnormalities does not add prognostic value to the global LUS score in invasively ventilated patients.

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# Chapter 5: Prone Positioning Decreases Inhomogeneity and Improves Dorsal Compliance in Invasively Ventilated Spontaneously Breathing COVID–19 Patients––a study using electrical impedance tomography

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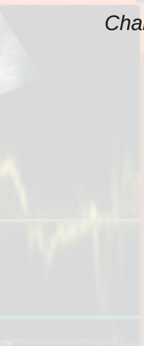


*Submitted*

## Abstract

### Background
We studied prone positioning effects on lung aeration by electrical impedance tomography (EIT) in spontaneously breathing invasively ventilated patients with acute hypoxemic respiratory failure caused by coronavirus disease 2019 (COVID–19).

### Methods
This was a single-center prospective observational study. Changes in lung aeration by EIT were studied from before to after placing a patient prone and back to supine, in COVID–19 patients planned for prone positioning for refractory hypoxemia. Endpoints were global inhomogeneity and changes in local compliance, end–expiratory lung impedance (EELI), and poorly ventilated areas ('silent spaces'). Linear mixed–effects models were used to evaluate changes in lung aeration.

### Results
Fifteen patients were enrolled, with a median $PaO_2/FiO_2$ of 82 [54 to 115] mmHg before prone positioning. Patients remained prone for median of 19 [17 to 21] hours. At 2 hours after initiation of prone positioning, there was no change in the global inhomogeneity index; at 16 hours the global inhomogeneity index was lower. At 2 hours, there were neither changes in dorsal and ventral compliance nor in dorsal EELI; ventral EELI was increased ($\beta_{FE}$, +333 [95%– confidence interval (CI) 129 to 536]), after 16 hours, dorsal compliance was improved ($\beta_{FE}$, +18.9 [95%–CI 9.1 to 28.8]) and dorsal EELI was increased ($\beta_{FE}$, +252 [95%–CI 13 to 496]); at 2 and 16 hours, dorsal 'silent spaces' was unchanged ($\beta_{FE}$, –4.6 [95%–CI –12.3 to +3.2]), while ventral 'silent spaces' was increased ($\beta_{FE}$, +7.9 [95%–CI +0.2 to +15.6]). The observed changes induced by prone positioning disappeared after turning patients back to supine.

### Conclusions
In this cohort of spontaneously breathing invasively ventilated COVID–19 patients, prone positioning decreased inhomogeneity, increased lung volumes, and improved dorsal compliance. Prone positioning did not result in recruitment of collapsed lung tissue, and most other changes were temporal.


## Introduction

Prone positioning can improve oxygenation in acute respiratory distress syndrome (ARDS) patients with severe hypoxemia[1-4]. Most investigations that focused on changes in lung aeration induced by prone positioning have been performed in deeply sedated and paralyzed patients.

Prone positioning is widely used in patients with ARDS related to coronavirus disease 2019 (COVID–19)[5]. In our experience, most of these patients could be placed in the prone position without receiving neuromuscular blocking agents. In fact, we did hardly use extra sedation in these patients, and consequently these patients remained spontaneously breathing while in the prone position[6].

We assessed the effects of prone positioning on global and local changes in lung aeration in critically ill COVID–19 patients that were placed in the prone position while spontaneously breathing. We hypothesized that prone positioning would decrease the inhomogeneity of aeration and recruit collapsed lung tissue. We therefore assessed several aeration parameters by electric impendence tomography (EIT), early and late after placing patients in the prone position, and also determined the effects of placing a patient back into the supine position.

## Methods

*Design and setting*

This was a single center prospective observational study in invasively ventilated COVID–19 patients admitted to the intensive care unit (ICU) in the Amsterdam University Medical Centers, locations 'AMC', Amsterdam, the Netherlands, during the second wave of the national outbreak. The Local Ethics Committee approved the study (W20_545#20.605), and informed consent was waived as in our ICU both prone positioning and EIT monitoring was part of the standard care.

*Inclusion and exclusion criteria*

Patients with were eligible if (1) COVID–19 pneumonia was proven by means of RT–PCR for the SARS–CoV–2; (2) receiving invasive ventilation with a spontaneous breathing mode, and (3) when planned for prone position because of refractory hypoxemia. Exclusion criteria were the presence of a pacemaker, or of one or more thoracic tube. For practical reasons we also excluded patients that were contaminated or had an infection with one or more multi–resistant bacteria, and when there was no EIT monitor available.

*Data collected*

Baseline demographics were captured for each patient. The extent and density of alveolar opacities on chest X–ray within the last day before the prone positioning session were scored using the 'Radiographic Assessment of Lung Edema (RALE) score[7]. Dead space was calculated using the Enghoff modification of the Bohr equation. Dynamic global compliance was calculated by dividing $V_T$ with the difference between maximum total respiratory system pressure and positive end–expiratory pressure (PEEP).

EIT images were collected 1 hour before initiation of prone positioning, 2 and 16 hours after initiation of prone positioning, and 2 hours after return to the supine position. Vital signs, ventilator parameters and blood gas analysis results were collected 1 hour before prone positioning, at 2 and 16 hours after initiation of prone positioning, and after 2 hours in the supine position.

*Electrical impedance tomography*

A silicone electrical impedance tomography belt with 16 electrodes connected to a

PulmoVista® 500 EIT monitor (Dräger Medical GmbH, Lübeck, Germany) was placed around the chest at the 4th intercostal space, and a reference electrode was placed in the abdominal area. The belt remained attached during the whole prone positioning session, and thereafter at 2 hours in the supine position, without any further adjustments.

EIT images were recorded at 40 Hz. Images were digitally filtered using a low–pass filter with a cutoff of 40/min. EIT–images were analyzed in line using the EITdiag software® (Dräger Medical GmbH). The following parameters were calculated:

- Global inhomogeneity index (GI) – calculated as the ratio of the sum of absolute differences between the median value of tidal variation and every single pixel value to the sum of all impedance values—a higher GI means more inhomogeneous distribution of the $V_T$;
- Local dynamic compliance – calculated by dividing the local proportion of total tidal impedance variation calibrated to $V_T$ to the difference between maximum total respiratory system pressure and PEEP;
- End–expiratory lung impedance (EELI) – by comparing lung impedance at the end of expiration to the impedance at the end of expiration before prone positioning;
- 'Silent spaces' – defined as the number of pixels with minimal impedance variation less than 10% to maximal impedance and a correlation coefficient > 40% of the maximum linear correlation coefficient with the global impedance waveform; and
- Center of ventilation – calculated by dividing the ventral and the dorsal lung regions in equal impedance changes, and expressed in percent of the dorsal-to-ventral thorax diameter—a percentage > 50% represents a more ventral ventilation distribution

*Study endpoints*

The main endpoints were the global homogeneity index, and ventral and dorsal local compliance, EELI and 'silent spaces'.

*Analysis plan*

Demographic, clinical, and outcome variables were presented as percentages for categorical variables and as medians with interquartile ranges (IQR) for continuous variables.

Dorsal and ventral regions of interest (ROIs) were symmetrical and were defined by divid-

**Table 1.** Patients characteristics.

| Variables | |
|---|---|
| Number of patients | 15 |
| Age, *years* (IQR) | 62 (56–71) |
| Sex, *female* (%) | 7 (46) |
| Time after intubation, *days* (IQR) | 4 (3–6) |
| Duration of Prone position, hours (IQR) | 19 (17–21) |
| Tidal volume, *mL* (IQR) | 438 (395–512) |
| Tidal volume, *mL/kg PBW* (IQR) | 7.6 (5.7–9.7) |
| PEEP, $cmH_2O$ (IQR) | 10 (9–13) |
| $PaO_2/FiO_2$, *mmHg* (IQR) | 82 (54–115) |
| $spO_2/FiO_2$ (IQR) | 118 (94–153) |
| Compliance, $mL/cmH_2O$ (IQR) | 45 (30–59) |
| Mechanical Power, *J/min* (IQR) | 22.9 (13.6−26.3) |
| RALE score (IQR) | 25 (23−35) |

PBW: per predictive body weight, PEEP: positive end expiratory pressure, PaO2 : Partial arterial pressure of oxygen, $FiO_2$: Fraction of inspired oxygen, $spO_2$: Saturation of peripheral oxygen, RALE: Radiographic Assessment of Lung Edema.

ing lung images. We used linear mixed model analysis using the R package lme4 to quantify the changes in aeration during and after prone positioning. Herein, measurement before initiation of prone positioning were used as a reference for all successive measurements, i.e., at 2 and 16 hours after initiation of prone positioning and at 2 hours after the patient was placed back in the supine position. A random intercept was used for each patient to account for variation in the baseline values. Fixed effects were estimated and reported with the 95%–confidence intervals (CI). Recruitment of lung tissue was considered to occur if compliance, EELI and 'silent spaces' was improved.

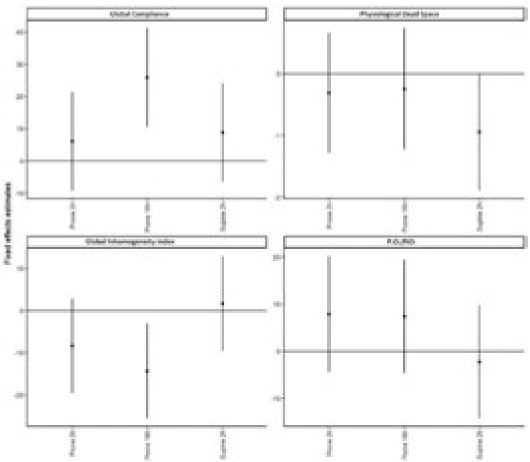
All analyses were performed in R through the R–studio interface (www.r-project.org, R version 3.3.1). A P–values < 0.05 was considered significant.

## Results

*Patients and prone positioning*

We included 15 spontaneously breathing invasively ventilated COVID–19 patients, all with severe ARDS. Baseline characteristics and respiratory parameters before prone positioning are presented in **Table 1**. Patients were invasively ventilated with pressure support ventilation. Prone positioning was initiated median 4 [3 to 6] days after start of ventilation. In one patient, prone positioning was stopped at 3 hours because of a technical problem with the central venous line. In the other patients, duration of the first prone positioning session lasted median 19 [17 to 21] hours. The level of PEEP (PEEP) was left unchanged. No significant changes in $PaO_2/FiO_2$ and dead space were observed (**Figure 1**).

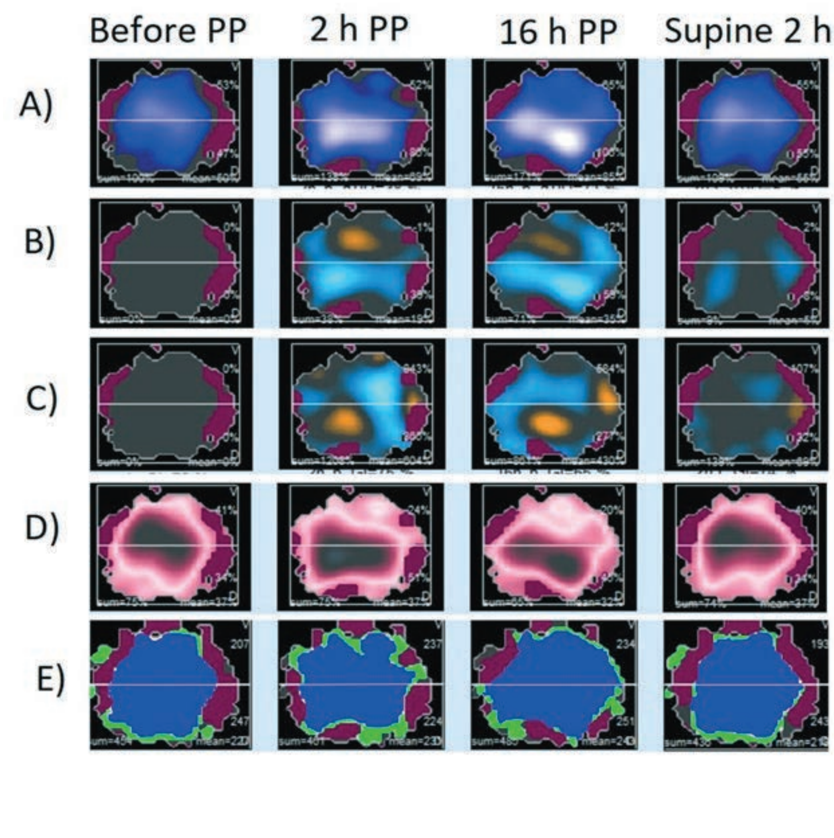
**Figure 1.** The dynamic effect of prone position (PP) on global ventilatory parameters. Values before PP were considered as reference values. The regression coefficients and 95% confidence intervals are reported.



*Prone positioning–induced EIT changes*

Ventilation distribution was predominately dorsal with the median center of ventilation at 47.8 [46.1 to 51.2] %. **Figure 2** shows representative changes in EIT parameters during and after prone position. Global compliance was unchanged at 2 hours after initiation of prone position but increased at 16 hours (**Figure 1**). Global inhomogeneity index was unchanged at 2 hours after initiation prone position but decreased at 16 hours (**Figure 1**). Lo-

**Figure 2.** Regional electrical impedance derived parameters during the different study phases in a representative patient. Panel A: Impedance map; Panel B: Impedance changes distribution compared to values before prone position (PP), increases are presented with blue color and decreases with orange ; Panel C: End expiratory impedance changes distribution compared to values before PP, increases are presented with blue color and decreases with orange; Panel D: Global inhomogeneity index map. The bigger the difference between the tidal variation and the median tidal, the darker the color turns. Panel E: Map of well-ventilated pixels (blue color) poorly ventilated pixels (green color) and not ventilated pixels (red color).

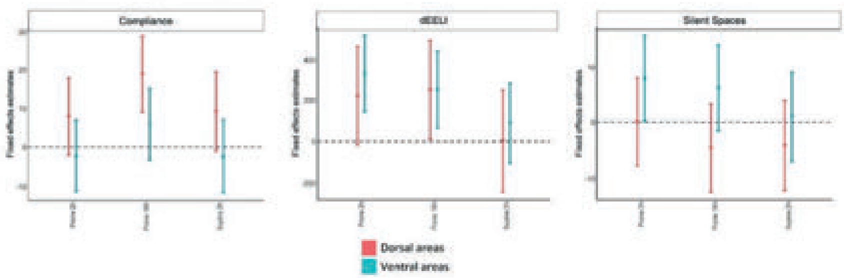


cal compliances were unchanged at 2 hours after initiation of prone positioning. At 16 hours after initiation of prone position dorsal compliance increased whereas ventral compliance was unchanged (**Figure 3**). EELI increased only in ventral areas at 2 hours after initation of prone positioning. At 16 hours after initiation of prone position either the dorsal and ventral EELI increased (**Figure 3**). ‘Silent spaces’ increased in ventral areas and were unchanged at 2 hours after initiation of prone position. At 16 hours after initiation of prone position ‘silent spaces’ in either ventral and dorsal areas were unchanged (**Figure 3**).

*Supine positioning–induced EIT changes*

Global compliance returned to baseline when patients were placed back into the supine position (**Figure 1**). Global inhomogeneity index returned to baseline values when patients were placed back (**Figure 1**). Local compliances returned to baseline when patients were placed back into the supine position (**Figure 3**). EELI in either dorsal and ventral areas returned to baseline when patients were placed back into the supine position (**Figure 3**). ‘Silent spaces’ were unchanged in either ventral and dorsal areas when patients were placed back into the supine position (**Figure 3**).

**Figure 3.** The dynamic effect of prone position (PP) on local compliance, changes in end-expiratory lung impedance, and silent spaces. Values before PP were considered as reference values. The regression coefficients and 95% confidence intervals are reported.




## Discussion

The findings of this study in spontaneously breathing invasively ventilated COVID–19 patients with severe ARDS provide evidence that that prone position decreases ventilation inhomogeneity without causing evident recruitment of lung tissue, and that aeration of dorsal lung areas improves progressively during prone position but recede to baseline values early after return to the supine position.

COVID–19 ARDS is characterized by a diffuse loss of aeration that is not dominant in the dependent lung areas[8]. Patients with this lung morphology could benefit less from prone positioning[9]. During prone positioning, we observed an improvement in the compliance of dorsal areas associated with an increase in the EELV, which implies that the aeration of ventral areas improved. However, we did not find any decrease in silent spaces, which suggests that atelectasis in dorsal areas did not dissappear[10,11]. Accordingly, the improvement of the aeration should be attributed to an improved aeration of already open lung units, and not recruitment of closed areas. Compliance decreased in ventral areas despite increase in EELV. As silent pixels of ventral areas also increased[10], overdistention of ventral areas is the most likely explanation for this finding[12]. Thus prone positioning has an effect in the aeration improvement of dorsal areas, but this benefit should be weighed against the risk of increased ventral overdistention.

Our findings are in line with findings in previous studies in patients with ARDS due to another cause[13-16]. However, opposite to those studies, in our study ventilation was predominant present in the dorsal areas before proning. This difference may be explained by the fact that patients our study had an active and functioning diaphragm while patients in the other studies received controlled ventilation under deep sedation and muscle paralysis.

Predominant dorsal ventilation before prone positioning could negatively moderate recruitment effects of prone positioning[13,14]. While diaphragmatic function is expected to decrease in the prone position[17], we observed an improved aeration and compliance of the dorsal areas, which was accompanied by a decreased global inhomogeneity. Hence, prone positioning can still improve ventilation homogeneity in patients with diaphragmatic activity.

In our cohort of patients, we did neither observe significant changes in $PaO_2/FiO_2$ nor in dead space. In previous studies, the response of $PaO_2/FiO_2$ to prone positioning had no association with its effect on outcome[18,19]. An improvement in dead space, however, is associated with a lower mortality[20]. Prone positioning could confer benefit by preventing or minimizing ventilator–associated lung injury. Our findings fit into this idea. The improved homogeneity and compliance are indicative for better, more lung protective, mechanical ventilation. However, the increase in 'silent spaces' in ventral lung parts may suggest harm in these areas by prone positioning.

The main strength of this study was the systematic evaluation of the aeration changes in spontaneously breathing invasively ventilated patients. Early spontaneously breathing is increasingly used, and the benefits of muscle paralysis are increasingly questioned[21] ,also in COVID–19 patients[22]. We investigated prone positioning–induced temporal changes in lung aeration longitudinally, including before and after the episode patients were in a prone position. In our study, prone positioning was standard of care, and the team was very well used with accepting spontaneous breathing in these patients. Also, patients received no other interventions that could have affected lung aeration, like changes in PEEP or recruitment maneuvers.

There are also some limitations. The sample size was small, albeit comparable to previous studies[13,15,16]. Changes in aeration, however, were compared within each patient. We did not measure transpulmonary pressures, since esophagus catheters are not standardly used in our unit. Finally, time between initiation of ventilation and start of this study differed between patients, because prone positioning was only applied in case refractory hypoxemia developed. Also, we exclusively included spontaneously breathing patients, and appearance of spontaneous breathing was also variable.

## Conclusions

In this cohort of spontaneously breathing invasively ventilated COVID–19 patients with severe ARDS, prone positioning resulted in decreased inhomogeneity, increased aeration, and improved dorsal compliance. Prone positioning, however, did not result in recruitment of collapsed lung tissue, and the effects of were largely reversed after placing patients back into a supine position.

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# Chapter 6: The Right Ventricular–Myocardial Performance Index is not Associated with Outcomes in Invasively Ventilated ICU Patients––Posthoc Analysis of Two Randomized Clinical Trials

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*Submitted*

## Abstract

### Background

The objective of the study was to determine the prognostic capacity of the right ventricular (RV) myocardial performance index (MPI) for successful liberation from the ventilator and death within 28 days.

### Methods

Posthoc analysis of 2 ventilation studies in invasively ventilated patients not having ARDS. RV–MPI was collected through transthoracic echocardiography within 24 to 48 hours from start of invasive ventilation according to the study protocols. RV–MPI ≤ 0.54 was considered normal. The primary endpoint was successful liberation from the ventilator < 28 days; the secondary endpoint was 28–day mortality.

### Results

81 patients underwent transthoracic echocardiography at median 30 (24–42) hours after start of ventilation—in 73 (90%) patients the RV–MPI could be collected. 56 (77%) patients were successfully liberated from the ventilator < 28 days; 22 (30%) patients had died before or at day 28. 18 (25%) patients had an abnormal RV–MPI. RV–MPI was neither associated with successful liberation from the ventilator within 28 days (HR, 2.2 [95%–CI 0.47–10.6]; P = 0.31) nor with 28–day mortality (HR, 1.56 [95% CI 0.07–34.27]; P=0.778).

### Conclusions

In invasively ventilated critically ill patients not having ARDS, RV–MPI has no prognostic capacity for successful liberation from invasive ventilation.


## Introduction

Acute right ventricular (RV) dysfunction is a common complication in critically ill patients and is associated with higher morbidity and mortality[1]. RV function is affected by the change from negative to positive intrathoracic pressure in patients who receive invasive ventilation, by decrease in venous return and increase in RV afterload[2]. Acute RV failure in invasively ventilated patients can cause life–threatening hemodynamic instability and delay liberation from the ventilator[3,4]. Accordingly, monitoring RV function could be important for fluid optimization, vasopressor strategy, and respiratory support in these patients[3,5].

The RV myocardial performance index (MPI) is an easy-to-obtain variable through transthoracic echocardiography[6]. RV–MPI is a measure of both systolic and diastolic RV performance, which is which is to a certain degree fluid status–independent[7]. RV–MPI has a predictive capacity for mortality in various patient groups, including patients with primary pulmonary hypertension[8] and patients with chronic heart failure[9]. RV–MPI also has predictive capacity for mortality in critically ill patients, such as patients after cardiac surgery[10], patients with acute pulmonary embolism[11], patients after myocardial infarction[12] and in patients with sepsis[13], or acute respiratory distress syndrome (ARDS)[14]. In the latter group, RV–MPI has been shown to have predictive capacity for liberation from the ventilator[14].

It is uncertain whether RV–MPI also holds prognostic capacity in invasively ventilated critically ill patients without ARDS. To test the hypothesis that an abnormal RV function is associated with and has prognostic capacity for duration of ventilation in these patients, we collected RV–MPI in patients who underwent transthoracic echocardiography in two studies on invasive ventilation.

## Methods

*Design*

This is a posthoc analysis of patients included in two multicenter randomized clinical trials of invasive ventilation—in one study, ventilation with a low tidal volume (VT) was compared with ventilation with an intermediate VT (the 'Protective Ventilation in Patients Without ARDS' (PReVENT) study)[15]; in the other study, ventilation with lower PEEP was compared to ventilation with higher PEEP (the 'REstricted versus Liberal positive end-expiratory pressure in patients without ARDS' (RELAx) study)[16]. The results of the substudy with the PReVENT study have been published in part before[17]. Echocardiography was performed as part of two substudies that focused on the effects of the tested ventilation strategies on cardiac function, and enrolled patients in only one center, the Amsterdam UMC, location 'AMC', Amsterdam, The Netherlands, from 4 November 2014, to 20 August 2017 (in the PReVENT study) and from 26 October 2017, to 17 December 2019 (in the RELAx study).

*Ethics*

Ethical approval for the two parent studies (Ethical Committee number: 2014_075#B2014424ENG and Ethical Committee number 2017_074#C2017635), was provided by Medical Ethics Review Committee of AMC on September 19, 2014, and, June 28, 2018. Ethical approval for the two substudies (Ethical Committee number W14_2992017_074, and Ethical Committee number #B2018435) was provided by Medical Ethics Review Committee of AMC on November 4, 2014 and July 18, 2018. Patients or relatives had to provide written informed consent before participation in the parent study, as well as the substudy.

*Study registration*

The studies were registered at clinicaltrials.gov (NCT02153294, June 3, 2014; NCT03167580, May 13, 2017).

*Patients*

The PReVENT and RELAx studies had identical inclusion and exclusion criteria, and enrolled patients who received invasive ventilation shortly before and not longer than one hour after admission to the intensive care unit (ICU) and who were expected not to be extubated within 24 h of randomization. The exclusion criteria were age < 18 years, presence of ARDS according to the current definition of ARDS[18] known chronic obstructive pulmonary disease (COPD), pregnancy, increased and un-controllable intracranial pressure, history of pulmonary disease, and new pulmonary thromboembolism. Patients were excluded from participation in the substudies if known poor left ventricular function, with left ventricular ejection fraction less than or equal to 30%, and severe shock, requiring norepinephrine ≥ 0.5 µg/kg/min.

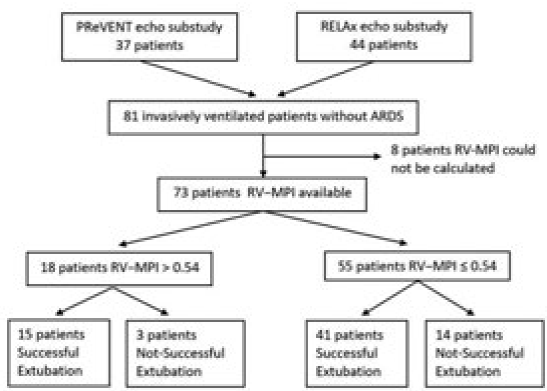
*Data collected*

Patient demographics, disease severity scores, and reasons for intubation and invasive ventilation were collected at baseline. Ventilator settings and parameters, fluid status, and inotropic and vasopressor use were collected at the time of transthoracic echocardiography.

*Transthoracic echocardiography*

Transthoracic echocardiography was performed by physicians trained in cardiac ultrasound in critically ill patients using a Vivid 9 Dimension Ultrasound System (GE Healthcare, Hoevelaken, The Netherlands). Transthoracic echocardiography was performed in the supine position without any major mobilization 24 to 48 hours after invasive ventilation initiation. A comprehensive transthoracic echocardiogram was performed, and the right and left heart were assessed using parasternal, apical, and subcostal sonographic windows. Continuous cardiac rhythm was recorded. Images and videos were stored digitally and analyzed blindly using automated function imaging software (EchoPAC®, GE Vingmed, Norway). For the analysis of echocardiographic variables, the median values of three or five cardiac cycles were calculated for sinus rhythm and atrial fibrillation, respectively.

**Figure 1.** Flow chart of the patients enrolled in the study.




Pulsatile and continuous wave Doppler was used to assess blood velocities. Tissue Doppler imaging (TDI) and motion mode (M–mode) synchronized with electrocardiogram readings were used to assess mitral and tricuspid valve annulus motion. Isovolumetric contraction time, isovolumetric relaxation time, and ejection time were calculated from the TDI trace. MPI was calculated as the ratio between the sum of the isovolumetric contraction and relaxation time to the ejection time. Two–dimensional speckle tracking for the right and left ventricle was calculated from the 4–chamber apical view after tracing the endocardial borders of the left and right ventricles. Regions of interest (ROIs) were automatically generated and manually corrected when necessary. The global longitudinal strain was calculated for the left ventricle. For the RV, the free wall was automatically divided into three segments, that is, basal, mid, and apical, and the means of the strain values were calculated for each segment.

*Outcomes*

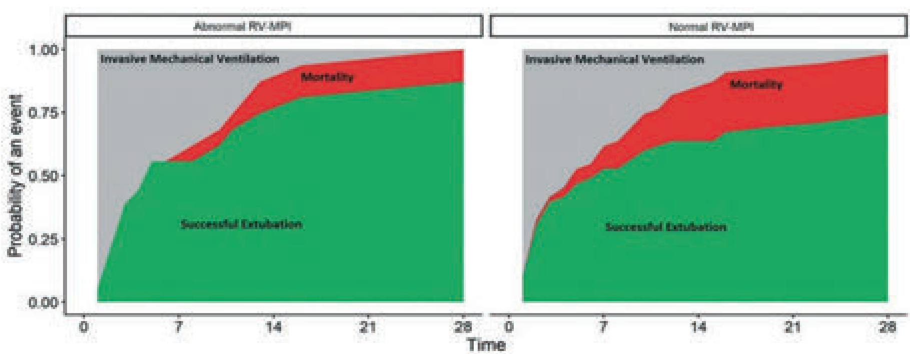
The primary outcome of this post hoc analysis was successful liberation from invasive ventilation within 28 days, in which successful liberation was defined as no requirement for tracheal intubation within a 48–hour period following extubation and alive. The secondary outcome was the 28–day mortality.

*Statistical analysis*

The number of available patients in the substudies of the two randomized clinical trials served as the sample size for this analysis.

Demographic, clinical, echocardiographic, and outcome variables were presented as percentages for categorical variables and as medians with interquartile ranges (IQR) for continuous variables, and compared using the Mann–Whitney U test or Chi square test, as

**Figure 2.** Abnormal right ventricular myocardial performance index (RV−MPI > 0.54) and normal RV−MPI ( ≤ 0.54) and cumu-lative incidence of outcomes. X-axis: days since intubations. Y-axis: probability of an event (extubation or death) in the population. The two facets show the risk for patients with an abnormal RV-MPI (left) and normal RV-MPI (right). Red areas show the patients who died. Green area shows the patients who were successfully extubated.




appropriate. Patients were classified as having a normal or an abnormal RV–MPI based on a previously defined cutoff (RV–MPI ≤ 0.54, normal)[19].

The association of RV–MPI with outcomes was analyzed with multistate, competing risk proportional hazard models as described in the survival package via the compete func-

**Table 1.** Demographic and clinical characteristics according to normal or abnormal right ventricular myocardial performance index (RV−MPI).

| Variables | Abnormal RV−MPI (n = 18) | Normal RV−MPI (n = 55) | p value |
|---|---|---|---|
| **Age, years, median (IQR)** | 68 (56–73) | 64 (54–70) | 0.29 |
| **Female gender, No. (%)** | 5 (27) | 30 (54) | 0.06 |
| **Height, cm, median (IQR)** | 175 (170–183) | 173 (168–178) | 0.27 |
| **Weight, kg, median (IQR)** | 79 (72–88) | 75 (66–71) | 0.81 |
| **SOFA score, median (IQR) *** | 9.5 (6.5–13) | 9.0 (7.0–11.0) | 0.47 |
| **APACHE II score, median (IQR) *** | 25 (23−29) | 22 (17−27) | 0.34 |
| **PaO2/FiO2, median (IQR)** | 354 (219–375) | 284 (220–370) | 0.53 |
| **Medical reasons for admission (%)** | 14 (77) | 40 (72) | 0.76 |
| **Reason of intubation, No. (%)** | | | |
| **Respiratory failure** | 6 (33) | 11 (20) | 0.17 |
| **Cardiac arrest** | 2 (11) | 8 (15) | 0.99 |
| **Depressed level of consciousness** | 4 (22) | 12 (22) | 0.73 |
| **Planned postoperative ventilation** | 5 (28) | 19 (34) | 0.98 |
| **Airway protection** | 1 (6) | 5 (9) | 0.99 |
| **Ventilatory mode, No. (%) *** | | | |
| **Pressure Controlled ventilation** | 3 (17) | 23 (42) | 0.08 |
| **Volume Controlled Ventilation** | 5 (27) | 1 (2) | <0.01 |
| **Pressure support ventilation** | 10 (55) | 31(56) | 0.98 |
| **Vasopressor use *** | | | |
| **Norepinephrine, No (%)** | 10 (55) | 19 (34) | 0.09 |
| **Norepinephrine dose, µg/kg/min, median (IQR)** | 0.16 (0.10–0.27) | 0.11 (0.09–0.17) | 0.11 |
| **Sinus rhythm, No (%)*** | 16 (88) | 49 (89) | 0.99 |
| **ICU LOS** | 9.5 (5.0−15.5) | 4.5 (3.0−13.5) | 0.29 |
| **Successfully extubated 28 days** | 15 (83) | 41 (74) | 0.53 |
| **Mortality 28 days** | 3 (16) | 13 (23) | 0.23 |

tion in R. Risks were estimated for successful extubation and mortality and compared to persistent intubation (reference category). Follow–up was censored after 28 days. Patients who died and received a follow–up of less than 28 days with no events were not censored to eliminate bias through censoring by mortality. This analysis was repeated for other parameters of RV dysfunction.

Moderation of the association of RV–MPI with outcomes by VT or PEEP was evaluated by adding an interaction term to the above-mentioned models. Hazard ratios (HR) with 95%confidence intervals (CI) were calculated for each outcome.

**Table 2.** Echocardiographic variables of left and right ventricle of invasively ventilated patients examined within 48 h after mechanical ventilation initiation according to normal or abnormal right ventricular myocardial performance index (RV−MPI).

| **Variables** | **Abnormal RV−MPI** (n = 18) | **Normal RV−MPI** (n = 55) | **p value** |
|---|---|---|---|
| **Right Ventricular function** | | | |
| ***Systolic parameters*** | | | |
| Myocardial performance index | 0.71 (0.61–0.75) | 0.36 (0.29–0.41) | <0.01 |
| Tricuspid annular plane systolic excretion (mm) | 16 (15–19) | 22 (18–26) | <0.01 |
| Global longitudinal strain, % | −12 (−18–−10) | −19 (−24–−16) | <0.01 |
| Isovolumetric acceleration, m/sec | 2.1 (1.4–2.7) | 3.1 (2.1–4.7) | <0.01 |
| Systolic maximal velocity, cm/s | 11 (8–12) | 13 (11–16) | 0.02 |
| ***Diastolic parameters*** | | | |
| Early I/Atrial velocity ratio | 1.1 (0.8–1.4) | 1.1 (0.8–1.2) | 0.29 |
| Early maximal diastolic velocity (E') , cm/s | 10 (8–12) | 12 (10–15) | 0.07 |
| E/E' | 4.7 (3.1–5.4) | 4.1 (3.2–5.4) | 0.61 |
| ***General parameters*** | | | |
| Pulmonary acceleration time ($m/s^2$) | 8.2 (7.1−8.8) | 10.5 (7.1−12.5) | 0.25 |
| Right ventricle/Left Ventricle diameter | 0.81 (0.73–0.87) | 0.79 (0.65–0.89) | 0.37 |
| **Left Ventricular function** | | | |
| ***Systolic parameters*** | | | |
| Myocardial performance index | 0.58 (0.44–0.68) | 0.42 (0.38–0.52) | <0.01 |
| Systolic parameters | | | |
| Ejection fraction, % | 43 (37–53) | 55 (47–61) | <0.01 |
| Global longitudinal strain, % | −12 (−14–−10) | −14 (−18–−10) | 0.09 |
| Isovolumetric acceleration, m/sec | 1.5 (1.1–2.8) | 2.5 (1.7–4.1) | 0.01 |
| Systolic maximal velocity, cm/s | 7.5 (6.0–10.0) | 8.7 (7.0–10.0) | 0.21 |
| ***Diastolic parameters*** | | | |
| Early I /Atrial velocity ratio | 0.9 (0.7–1.2) | 1.0 (0.7–1.2) | 0.91 |
| Early maximal diastolic velocity (E') , cm/s | 8.0 (7.0–10.0) | 8.5(6.5–11.0) | 0.62 |
| E/E' | 6.9 (5.7–10.1) | 8.2 (6.2–10.8) | 0.32 |
| ***General parameters*** | | | |
| Cardiac index, L/min/m2 | 2.00 (1.63–2.92) | 2.57 (1.93–3.36) | 0.06 |
| Eccentricity index | 1.00 (0.85–1.26) | 0.92 (0.81–1.05) | 0.23 |

All analyses were performed in R using the R–Studio interface (www.r-project.org, R version 3.3.1 (accessed on 08/05/2022). Statistical significance was set at $p < 0.05$.

## Results

*Patients*

A total of 81 patients were enrolled in the two substudies. We excluded four pa-tients from the cohort of patients enrolled in the substudy of the PReVENT study, be-cause outcomes of interest were missing for these patients. Thus, we had 73 patients left for the current analysis (**Figure 1**). Patient characteristics are presented in **Table 1**. Eighteen patients (25%) had abnormal RV–MPI. Patients with a normal RV–MPI did not differ from patients with an abnormal RV–MPI, neither with regards to disease severity nor to oxygenation disturbances. There were neither differences in noradrenaline use nor in the applied dosages. Echocardiography findings, including RV–MPI, are presented in **Table 2**.

**Table 3.** The association of right ventricular parameters obtained with transthoracic echocardiography with the prob-ability of successful liberation from invasive ventilation and death at 28 days

| Variables | Hazard Ratio (95% CI) | p value |
|---|---|---|
| Endpoint: Successful Extubation | | |
| Myocardial performance index | 2.2 (0.47–10.63) | 0.30 |
| Tricuspid annular plane systolic excretion | 0.9 (0.95−1.04) | 0.93 |
| Systolic maximal velocity | 1.0 (0.94−1.06) | 0.91 |
| Global longitudinal strain | 1.1 (0.99−1.08) | 0.10 |
| Right ventricle/Left Ventricle diameter | 0.6 (0.21−2.11) | 0.48 |
| Endpoint: Mortality | | |
| Myocardial performance index | 1.6 (0.07–34.27) | 0.77 |
| Tricuspid annular plane systolic excretion | 1.1 (0.93−1.12) | 0.59 |
| Systolic maximal velocity | 1.1 (0.87−1.09) | 0.67 |
| Global longitudinal strain | 0.9 (0.86−1.01) | 0.09 |
| Right ventricle/Left Ventricle diameter | 0.5 (0.22−14.33) | 0.58 |

*Association of RV–MPI with liberation form invasive ventilation*

The RV–MPI, used as a continuous variable, was not associated with successful liberation from invasive ventilation before day 28 (HR, 2.2 [95% CI 0.47–10.63]; P = 0.306). RV–MPI > 0.54 was also not associated with a lower probability of successful liberation from mechanical ventilation (HR, 0.89 [95% CI 0.49 –1.62]; P= 0.72) (**Figure 2**).

*Association of RV−MPI with mortality*

The RV–MPI was not associated with 28–day mortality (HR, 1.56 [95% CI 0.07–34.27]; P=0.778). An RV–MPI > 0.54 was also not associated with mortality (HR, 2.1[95% CI 0.46–9.17]; P= 0.34) (**Figure 2**).

*Associations of other echocardiography–derived parameters for RV function with outcomes*

Other echocardiography-derived parameters for RV function were not associated with successful liberation from invasive ventilation before day 28 (**Table 3**).

**Table 4.** Respiratory and hemodynamic variables at the time of transthoracic echocardiography according to normal or abnormal right ventricular myocardial performance index (RV−MPI).

| Variables | Abnormal RV−MPI (n = 18) | Normal RV−MPI (n = 55) | p value |
|---|---|---|---|
| ***Respiration*** | | | |
| Tidal Volume, ml/kg PBW, median (IQR) | 8.55 (7.47–9.72) | 7.3 (5.7–8.6) | 0.02 |
| PEEP, cm $H_2O$, median (IQR) | 5 (5–7) | 8 (1–8) | 0.56 |
| $FiO_2$, %, median (IQR) | 25 (22–33) | 30 (25–35) | 0.51 |
| $SpO_2$, median (IQR) | 95 (94–96) | 97 (94–98) | 0.39 |
| RR, breaths/min, median (IQR) | 17 (14–21) | 19 (15–24) | 0.27 |
| ***Laboratory*** | | | |
| Ph, median (IQR) | 7.43 (7.40–7.48) | 7.44 (7.40–7.46) | 0.97 |
| $P_aCO_2$, kPa, median (IQR) | 4.9 (4.21–5.75) | 5.0 (4.5–5.4) | 0.67 |
| $P_aO_2$, kPa, median (IQR) | 10.8 (10.2–11.7) | 10.6 (9.7–11.9) | 0.81 |
| ***Hemodynamics*** | | | |
| Heart Rate, mmHg, median (IQR) | 90 (79–103) | 80 (67–99) | 0.18 |
| Systolic Blood Pressure, mmHg, median (IQR) | 118 (104–141) | 130 (109–163) | 0.29 |
| Diastolic Blood Pressure, mmHg, median (IQR) | 67 (57–79) | 65 (56–72) | 0.48 |
| Mean Arterial Pressure, mmHg, median (IQR) | 86 (73–92) | 85 (76–102) | 0.82 |

*PBW: Per predicted body weight, PEEP: Positive end expiratory pressure, $FiO_2$: Fraction inspired oxygen, $SpO_2$: Peripheral oxygen saturation, RR: respiratory rate, $P_aCO_2$: partial pressure of carbon dioxide in the arterial blood, $P_aO_2$: partial pressure of carbon dioxide in the arterial blood,*

*Subgroup analyses*

PEEP levels were not different between patients with normal RV–MPI and those with abnormal RV–MPI (**Table 4**), and there was no evidence of moderation by PEEP of the associations of RV–MPI with outcome (P = 0.81). VT was higher in patients with RV–MPI ≤ 0.54 (**Table 4**), but there was no evidence Table 1. Demographic and clinical characteristics according to normal or abnormal right ventricular myocardial performance index (RV−MPI). of moderation by VT of the association of RV–MPI with outcome (P = 0.35).

## Discussion

The findings of this study can be summarized as follows: 1) RV–MPI is abnormal in a substantial number of patients that receive invasive ventilation for reasons other than ARDS; 2) in these patients, RV–MPI is neither associated with successful liberation from the ventilator within 28 days; 3) nor with 28–day mortality.

The findings of our study are in contrast with results of one previous study [14]. Indeed, in that study RV–MPI was strongly associated with duration of ventilation. Several difference between our study and that previous study should be mentioned, though. First, that study enrolled patients with ARDS, while we restricted enrollment to patients not having ARDS. Second, and probably as a consequence of this, patients in the previous study were ventilated with higher PEEP than in our study. The results of the current study add to our understanding of the association of RV–MPI with liberation of mechanical ventilation and mortality in critically ill patients, by showing that the prognostic value of RV–MPI may depend on presence of ARDS, and maybe also the level of PEEP.

The findings of our study are in line with the results of several other studies[20-22] and one meta-analysis[23], Indeed, these investigations did not find an association of right ventricular dysfunction with successful liberation from invasive ventilation. Of note, associations of diastolic left ventricular function with successful liberation from invasive ventilation have been reported before [23.] An abnormal right ventricular function could be associated with an abnormal systolic or diastolic left ventricular function[24-26]. However, only left ventricular diastolic dysfunction, and not systolic dysfunction, has been found to have an association with successful extubation[23], and in our cohort we did find only systolic, and not diastolic dysfunction of the left ventricle.

RV–MPI is, at least in part preload–dependent, and the size of VT and level of PEEP could affect preload of the right ventricle in invasively ventilated patients. Thus, RV–MPI could change with variations in these ventilatory settings. In our cohort, patients were ventilated with higher or lower VT[15], and with higher or lower PEEP[16], as per the study protocols of the two parent studies. In this analysis, however, the association of the RV–MPI with the outcomes of interest was neither affected by VT size nor by PEEP level.

The results of this study can be used to decide on whether RV–MPI should be monitored with transthoracic echocardiography in invasively ventilated patients without ARDS. One could hypothesize that right ventricular dysfunction is in part caused by higher intrathoracic pressures, as patients randomized to ventilation with higher VT, and patients randomized to ventilation with higher PEEP more often had an abnormal RV–MPI. While we show that RV–MPI has no predictive validity, we cannot exclude that RV–MPI may be useful in guiding fluid and inotrope therapy in these patients.

Of note, while RV–MPI seems a relatively easy to collect index, in 8 out of 81 patients we were not able to capture it. However, other parameters are usually more difficult to collect—for instance, right ventricular global longitudinal strain, another parameter for right ventricular function could not be measured in more than a quarter of these patients.

The strength of this study was the systematic evaluation of the prognostic validity of RV function in a homogeneous population of critically ill patients without ARDS, by far the largest population in most ICUs. Patients were examined soon after the start of invasive ventilation, thereby reducing the risk of the effects of other strategies, as well as selection bias due to early death. We also excluded patients with pre-existing heart failure. Echocardiographic parameters were evaluated in a blind fashion, and only in a small portion of patients, the RV–MPI could not be collected.

This study also has limitations. First, although the sample size was larger than that in most other studies on this topic, the confidence intervals were wide suggesting that we may have been underpowered to reject the tested hypotheses. Seen the lack of previous studies on associations of RV–MPI with outcome in this specific group of critically ill patients we were not able to perform a proper sample size calculation. Second, patients were evaluated only once in the acute phase, and we cannot exclude the possibility that some patients developed right ventricular dysfunction at later timepoints in the course of their disease or in response to certain treatments, like the administration of fluid, or the use of inotropes and vasopressors.

### Conclusions

In this posthoc analysis of two studies in invasively ventilated critically ill patients without ARDS, RV–MPI had no prognostic capacity for successful liberation from invasive ventilation or death. The prognostic capacity of RV–MPI should be further studied in prospective investigations that have a larger sample size.

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# Chapter 7: Myocardial Function during Ventilation with Lower versus Higher Positive End–expiratory Pressure in Patients without ARDS

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## Abstract

### Background
The effect of positive end–expiratory pressure (PEEP) on myocardial function is uncertain among intensive care unit patients without acute respiratory distress syndrome (ARDS). This study investigated whether lower PEEP has beneficial effects on myocardial systolic and diastolic function compared to higher PEEP.

### Methods
Forty–four ventilated patients without ARDS underwent transthoracic echocardiography between 24−48 hours after start of invasive ventilation according to the 'REstricted versus Liberal positive end-expiratory pressure in patients without ARDS (RELAx) trial' comparing lower *versus* higher PEEP. The primary outcome was right ventricular myocardial performance index, a measure of combined systolic and diastolic function, with a lower value indicating a better myocardial function. Secondary outcomes were left ventricular myocardial performance index and specific systolic and diastolic function parameters.

### Results
Twenty patients were ventilated with lower PEEP (mean ± SD, 0 ± 1 cm$H_2O$), 24 patients with higher PEEP (8 ± 1 cm$H_2O$) (mean difference, −8 cm$H_2O$; 95% CI −8.1 to −7.9 cm$H_2O$; *P* = 0.01). Tidal volume size was low in both groups (median [IQR], 7.2 [6.3 to 8.1] *versus* 7.0 [5.3 to 9.1] ml/kg predicted body weight; *P* = 0.97). The median right ventricular myocardial performance index was 0.32 [IQR, 0.26 to 0.39] in the lower PEEP group *versus* 0.38 [0.32 to 0.41] in the higher PEEP group; median difference, –0.03, 95% CI −0.11 to 0.03; *P* = 0.33. Median left ventricular myocardial performance index was 0.41 [0.37 to 0.49] in the lower PEEP group *versus* 0.45 [0.39 to 0.54] in the higher PEEP group; median difference, –0.02; 95% CI −0.09 to 0.04; *P* = 0.35). Other systolic and diastolic parameters were similar between the PEEP groups.

### Conclusions
In patients without ARDS ventilated with a low tidal volume, lower PEEP had no beneficial effects on right ventricle myocardial performance index compared to higher PEEP.


## Introduction

Mechanical ventilation, the most frequently applied strategies in the intensive care unit (ICU) is a potentially harmful intervention[1]. Protective ventilation, a strategy aiming at reducing the intensity of mechanical stimulation on lung tissue is often used to mitigate the detrimental effects of mechanical ventilation[2]. While the protective role of a lower tidal volume ($V_T$) is well defined, uncertainty remains regarding the protective effects of the positive end-expiratory pressure (PEEP), particularly in patients without acute respiratory distress syndrome (ARDS)[3]. Therefore, the REstricted versus Liberal positive end-expiratory pressure in patients without ARDS (RELAx) trial investigated the impact of using lower PEEP (lowest possible PEEP level between 0 to 5 $cmH_2O$) compared with using higher PEEP (8 $cmH_2O$) in patients without ARDS[4].

PEEP is well–known to cause significant hemodynamic changes that could lead to decreased cardiac index[5]. Higher PEEP may increase intrathoracic pressure leading to an increase of the right ventricular afterload, decreased venous return and decreased left and right ventricular contractility[6]. Clinical studies that evaluated the effects of PEEP on right heart preload[7,8] and on right ventricle contractility and afterload[9-11] showed an heterogeneous response depending on global heart function and the levels of PEEP applied. Importantly, these studies investigated the effects of PEEP levels well above 10 $cmH_2O$, a level that is usually not applied in patients without ARDS. Experimental studies in different animal models without ARDS showed ventilation with higher PEEP to have a negative effect on cardiac output compared to ventilation with lower PEEP[12-14]. However, these investigations were heterogeneous in their design and outcomes[14].

This study was conducted to compare lower versus higher PEEP on right and left ventricular function in patients without ARDS, assessed by echocardiography between 24 and 48 hours after start of invasive ventilation. We hypothesized that lower PEEP has beneficial effects on right ventricular systolic and diastolic function compared to higher PEEP with use of low tidal volumes.

## Material and methods

*Study design and setting*

The RELAx trial (clinicaltrials.gov, trial number NCT03167580) was a national, multicenter, randomized clinical trial in invasively ventilated ICU patients without ARDS[4]. Patients were randomized to a ventilation strategy with lower PEEP, in which PEEP was titrated from 5 $cmH_2O$ to the lowest level at which oxygenation remained satisfactory, versus a ventilation strategy with higher PEEP, in which PEEP was set at 8 $cmH_2O$. In the recently published RELAx trial, a lower PEEP strategy was noninferior to a higher PEEP strategy with regard to the number of ventilator-free days at day 28, these findings supported the use of lower PEEP in patients without ARDS.

We performed a single–center transthoracic echocardiography substudy of RELAx patients enrolled in Amsterdam University Medical Center, location AMC, who were mechanically ventilated for 24 to 48 hours according to the study protocol. Within this timeframe we assessed and compared changes in cardiac function as measured by transthoracic echocardiography in response to the compared ventilation strategies. The institutional review board of the Amsterdam University Medical Center approved this substudy (2017_074#B2018435, July 18, 2018, Amsterdam, The Netherlands), and deferred informed consent was obtained from a legal representative for this substudy, as part of the parent study RELAx.

Exclusion criteria were a known poor left ventricular function (ejection fraction less than or equal to 30%), severe shock requiring norepinephrine greater than or equal to 0.5 μg/kg/minute, and ventilation with PEEP greater than 2 $cmH_2O$ in the lower PEEP group and less than 7 $cmH_2O$ in the higher PEEP group.

Transthoracic echocardiography images were recorded using the GE Healthcare Vivid 9 Dimension Ultrasound System with a 2-5 MHz sector probe. Images were continuously and digitally stored according to local standard protocol.

*Study Protocol*

Full details of the study methods, including the ventilation strategies, have been described previously[15]. Briefly, within 1 hour of initiation of ventilation in the ICU, the patients were randomized in a 1:1 ratio to a ventilation strategy using lower or higher PEEP. The local investigators randomized patients using a central, dedicated, password-protected, encrypted, web-based automated randomization system (SSL–encrypted website with ALEA software, TenALEA Consortium, Amsterdam, The Netherlands). Randomization was conducted using random block sizes with a maximum of 8 patients. The attending nurses and physicians were not blinded to the intervention. Patients randomized to the lower PEEP group started with 5 $cmH_2O$ and every 15 minutes the PEEP was down–titrated by 1 $cmH_2O$ to a minimum of 0 $cmH_2O$. For patients assigned to the higher PEEP group, PEEP was set to 8 $cmH_2O$. If $SpO_2$ or $PaO_2$ dropped below 92%, or below 60 mm Hg for more than 5 minutes, $FiO_2$ was increased to maximal 0.6 before PEEP was increased in steps of 1 $cmH_2O$ up to 5 $cmH_2O$ (lower PEEP group) or up to more than 8 $cmH_2O$ (higher PEEP group).

Before the transthoracic echocardiography, hemodynamic and respiratory data of patients were recorded. All ventilator settings and drug doses remained unaltered during the approximately 30 minutes required for transthoracic echocardiography. If arterial blood gas data were collected within 4 hours of the transthoracic echocardiography, these data were obtained from the electronic patient data system. Skin electrodes were attached to generate a continuous cardiac rhythm on the echocardiogram with a minimum recording of three cardiac cycles in case of sinus rhythm, or five cardiac cycles in case of atrial fibrillation according to guidelines[16].

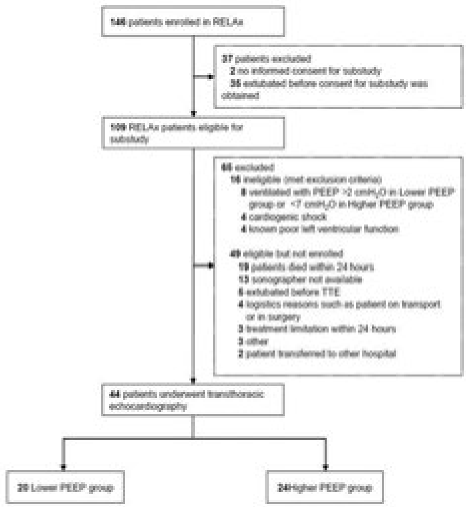
The right ventricular myocardial performance index was the primary endpoint of the study. The myocardial performance index was calculated from tissue Doppler imaging by adding the isovolumetric contraction time to the isovolumetric relaxation time and then dividing the sum by the ejection time. Secondary endpoints included the left ventricular myocardial performance index, and various systolic and diastolic echocardiographic parameters.

The images were obtained by physicians trained in ultrasound procedures in critically ill patients (CZ, MB, LP, AA, CP) and were analyzed offline using automated function imaging software (EchoPAC; GE Vingmed, Norway) by an observer who was blinded for the randomization group assignment.

*Statistical Analysis*

Based on the results of a recent study in a comparable patient cohortv[17], we expected that 18 patients per PEEP group would be sufficient to achieve a power of 80% with a two–sided significance level of 0.05 to detect a 0.12 difference in the myocardial performance index of the right heart. the sample size was increased by 20% to correct for dropouts (i.e. if myocardial performance index could not be determined from transthoracic echocardiography due to insufficient windows), meaning that a total of 44 patients were required.

**Figure 1.** Flow of patients




Continuous variables were compared between the PEEP groups using the independent–samples t–test in case of a normal distribution; otherwise, the Mann–Whitney U test was used. Categorical variables were compared between the PEEP groups using the chi–square test. Categorical data are reported as numbers with percentages in parentheses. Continuous data are reported as means with their standard deviation (SD) in case of a normal distribution; otherwise, medians with their interquartile range (IQR) are provided. Comparisons are shown with the mean difference and the 95% confidence interval (CI) from the independent-samples t–test in normally distributed cases; otherwise, the Hodges–Lehmann estimate of the median difference and 95% CI was used.

All analyses were performed in R through the R–studio interface (www.r-project.org, R version 3.3.1). A two–sided p value under 0.05 was considered statistically significant.

**Results**

From July 2018 through December 2019, 146 patients were enrolled in the RELAx trial in our center. After exclusion of patients not eligible for this substudy,109 patients remained suitable for participation. Of these 65 patients were excluded (16 met exclusion criteria, and 49 were eligible but not enrolled) leaving 44 patients who underwent a transthoracic echocardiography examination. Data of the 44 patients, 20 patients allocated to lower PEEP and 24 patients allocated to higher PEEP, was analyzed (**Figure 1**).

*Baseline characteristics*

Baseline characteristics are presented in **Table 1.** From the enrolled patients, 75% were admitted to the ICU for a medical reason. The most frequent reason for invasive ventilation was respiratory failure (29.5%). The majority of patients were ventilated in pressure

**Table 1.** Baseline Characteristics of the Patients

| | Lower PEEP (*n* = 20) | Higher PEEP (*n* = 24) | *P value* |
|---|---|---|---|
| Age, y, median (IQR) | 64 (56–72) | 65(59–70) | 0.93 |
| Female gender, No. (%) | 10 (50) | 8(33) | 0.34 |
| Height, cm, mean ± SD | 172 ± 10 | 175 ± 7 | 0.25 |
| Weight, cm, mean ± SD | 76 ± 16 | 83 ± 16 | 0.15 |
| SOFA score, mean ± SD a | 10.1 ± 2.9 | 9.6 ± 3.7 | 0.69 |
| Reason of ICU admission, No. (%) | | | |
| Elective surgery | 4(20) | 0(0) | 0.03 |
| Urgent surgery | 3(15) | 4(16) | 0.99 |
| Medical | 13(65) | 20(84) | 0.18 |
| Reason of intubation, No. (%) | | | |
| Respiratory failure | 6(30) | 7(29) | 0.28 |
| Cardiac arrest | 1(5) | 5(21) | 0.19 |
| Planned postoperative ventilation | 7(35) | 3(12) | 0.14 |
| Depressed level of consciousness | 5(25) | 6 (25) | 0.99 |
| Airway protection | 1 (5) | 3 (12) | 0.61 |
| Ventilatory mode, No. (%) | | | |
| Pressure-controlled | 5 (25) | 6 (25) | 0.99 |
| Pressure support | 15 (75) | 15 (63) | 0.51 |
| Adaptive support ventilation | 0 | 3 (12) | 0.23 |
| Sedation, No (%) | 5 (25) | 13 (54) | 0.09 |
| Propofol | 5(25) | 12(50) | 0.17 |
| Midazolam | 2(10) | 2(8) | 1.00 |
| RASS, median (IQR) [b] | -3 (-3 – -1) | -4 (-5 – -3) | 0.06 |
| Vasopressors | | | |
| Norepinephrine, No (%) | 5 (25) | 7 (29) | 0.98 |
| Norepinephrine dose, µg $kg^{-1}$ $min^{-1}$, mean ± SD | 0.12 ± 0.11 | 0.13 ± 0.08 | 0.78 |
| Sinus rhythm, No (%) | 17 (85) | 22(85) | 0.83 |
| Fluid balance, ml, median (IQR) | 304 (-604–928) | 1215 (-89–1944) | 0.04 |

*Data are given as median ± SD when normally distributed, otherwise median (IQR) is used. Numbers are presented with (%).* [a] *SOFA score ranges from 0 to 24, with higher values indicating a more severe condition* [b] *RASS scores ranges from -5 to +4. Abbreviations: SD, standard deviation; ICU, Intensive Care Unit; IQR, interquartile range; PEEP, positive end-expiratory pressure; RASS, Richmond Agitation-Sedation Scale; SOFA, Sequential Organ Failure Assessment* support ventilation upon transthoracic echocardiography examination. All but 5 patients were in sinus rhythm, with 3 patients in atrial fibrillation in the lower PEEP group and 2 patients in atrial fibrillation in the higher PEEP group. The majority of the patients in both groups were hemodynamically stable. More than one–third of patients received sedation. The fluid balance on the day of transthoracic echocardiography examination was higher in the higher PEEP group.

*Respiratory and Hemodynamic parameters*

The respiratory and hemodynamic parameters are presented in **Table 2**. Patients were invasively ventilated according to the study protocol for a median of 36 [27 to 46] hours at the moment of transthoracic echocardiography examination. Patients in the lower PEEP group received a mean PEEP of 0 ± 1 $cmH_2O$, and patients in the higher PEEP group re-

**Table 2** Respiratory and Hemodynamic Parameters at Transthoracic Echocardiographic Examination

| | Lower PEEP (*n* = 20) | Higher PEEP (*n* = 24) | Point Estimate of the Difference (95% CI) | *P* value |
|---|---|---|---|---|
| Time, h, median (IQR)[a] | 36(27–46) | 36(27–46) | 0(-7– 9) | 0.76 |
| Respiration | | | | |
| PEEP, cm $H_2O$, mean ± SD | 0 ± 1 | 8 ± 1 | -8(-8.1—-7.9) | <0.01 |
| Pmax, cm $H_2O$ , mean ± SD | 11.7 ± 4.1 | 20.1 ± 4.7 | -8.4 (-11.1—-5.6) | <0.01 |
| $FiO_2$, %, median (IQR) | 27(24−35) | 30(24−34) | -3(-4—4) | 0.91 |
| $SpO_2$, median (IQR) | 97(96−99) | 98(95−99) | -1(-0.9—1.9) | 0.45 |
| $V_T$ / predicted body weight, ml/kg, median (IQR)[b] | 7.22(6.3−8.1) | 7.02(5.3−9.1) | 0.20( -1.4—1.2) | 0.97 |
| RR, breaths/min, mean ± SD | 19 ± 6 | 22 ± 6 | -3(-6—1) | 0.12 |
| Minute volume, l/min, median (IQR) | 9.5(8.1−10.8) | 10.2(8.7−13.1) | -0.5(-3.5—0.3) | 0.14 |
| Laboratory | | | | |
| pH, median (IQR) | 7.46 ± 0.05 | 7.42 ± 0.04 | 0.04(0.01—0.07) | 0.01 |
| $PaCO_2$, kPa, median (IQR) | 4.6(4.1−5.2) | 5.1(4.7−5.5) | -0.5(-0.9—0.1) | 0.07 |
| $PaO_2$, kPa, median (IQR) | 10.8(10.4−12.6) | 11.0(10.1−12.0) | -0.2(-1.1—1.1) | 0.82 |
| Hemoglobin, mmol/l, mean ± SD | 6.3 ± 0.05 | 7.3 ± 0.04 | -1(-1.9— -0.2) | 0.01 |
| Hemodynamics | | | | |
| HR, beats/min, median (IQR) | 81(67−100) | 82(66−105) | -1(-18—10.9) | 0.65 |
| SBP, mmHg, mean ± SD | 138 ± 26 | 125 ± 29 | 13(-4—29) | 0.15 |
| DBP, mmHg, mean ± SD | 63 ± 11 | 61 ± 12 | 2(-4—9) | 0.51 |
| MAP, mmHg, mean ± SD | 88 ± 15 | 82 ± 15 | 6(-2—15) | 0.17 |

*Data are given as median ± SD when normally distributed, otherwise median (IQR) is used. Comparisons are shown with the point estimate of the mean or median difference, 95% CI and two sided P value; [a] Time after randomization to the lower PEEP or higher PEEP strategy according to the RELAx trial. ; [b] Predicted body weight was calculated as 50+ 0.91 x (height [cm] – 152.4) for men and 45.5+0.91 (height [cm] – 152.4) for women.Abbreviations: DBP, diastolic blood pressure; $FiO_2$, fraction of inspired oxygen; Hb, hemoglobin; HR, heart rate; ICU, Intensive Care Unit; IQR, interquartile range; MAP, mean arterial pressure, $PaCO_2$, partial pressure of carbon dioxide; $PaO_2$, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure; Pmax, maximal airway pressure; RASS, Richmond Agitation-Sedation Scale; RR, Respiratory rate; SBP, systolic blood pressure; SD, standard deviation; SOFA, Sequential Organ Failure Assessment; $SpO_2$ oxygen saturation as measured by pulse oximetry and $V_T$, tidal volume.*

ceived a mean PEEP of 8 ± 1 $cmH_2O$ (mean difference, –8 $cmH_2O$; 95% CI, –8 to –8 $cmH_2O$; $P < 0.01$). Accordingly, the maximum airway pressure was lower in patients ventilated with lower PEEP compared with those ventilated with higher PEEP (12 ± 4 versus 20 ± 4 $cmH_2O$; mean difference –8 $cmH_2O$; 95% CI, –11 to –6 $cmH_2O$; $P < 0.01$). Tidal volumes were similar for the two PEEP groups. The mean pH was higher in the lower PEEP group; the mean hemoglobin was higher in the higher PEEP group. Hemodynamic parameters did not differ between the two PEEP groups.

*Echocardiographic evaluation*

Mitral or aortic valvopathy was present in none of the patients. There were no differences in the mean diameter of the vena cava inferior or in distensibility index (1.6 ± 0.5 versus 1.9 ± 0.6 cm ($P = 0.22$), and 32 [17 to 160] % versus 23 [7 to 49] % ($P = 0.21$) in the lower and higher PEEP group, respectively).

*Right and left ventricular systolic and diastolic function*

Ventricular systolic and diastolic function parameters are presented in **Table 3**. Indicators of increased right ventricular pressure and volume overload were not different between the groups, with no differences in right ventricular afterload as well.

The primary endpoint, the right ventricular myocardial performance index could not be acquired in 5 patients, in 4 patients from the higher PEEP group and in 1 patient from the lower PEEP group. The left ventricular myocardial performance index was obtained in all 44 patients. The median right ventricular myocardial performance index was 0.32 [IQR, 0.26 to 0.39] in the lower PEEP group versus 0.38 [0.32 to 0.41] in the higher PEEP group; median difference, –0.03; 95% CI, –0.11 to 0.03; $P = 0.33$. The median left ventricular myocardial performance index 0.41 [IQR, 0.37 to 0.49] in patients ventilated with lower PEEP versus 0.45 [0.39 to 0.54] in patients ventilated with higher PEEP; median difference, –0.02; 95% CI, –0.09 to 0.04; $P = 0.35$. No differences were found in any parameter for systolic and diastolic function of the left or right ventricular between the PEEP groups (**Table 3**).

## Discussion

This study shows that mechanical ventilation with lower PEEP in ICU patients without ARDS does not affect the right ventricular myocardial performance index compared to higher PEEP. The left ventricular myocardial performance index and other systolic and diastolic echocardiographic parameters were also not different between the two PEEP groups.

The detrimental effects of PEEP on the heart has been assessed extensively in patients with ARDS[8,18-20]. However, the effects of PEEP levels on cardiac function has not been assessed thoroughly in patients without ARDS, and this clinical study adds information on whether ventilation with a lower PEEP improves cardiac function. Increasing pressure at the end of expiration can affect heart function by changing lung volume and intrathoracic pressure independently of ARDS presence[6]. Nevertheless, several pathophysiological factors can amplify detrimental PEEP effects on cardiac function in patients with ARDS such as decreased lung compliance, hypoxia and hypercapnia[21], which are not often present in patients without ARDS. In the current study, patients in both PEEP groups had $PaCO_2$ values

**Table 3.** Right and Left Ventricular Systolic and Diastolic Function

| Right Ventricular Variables | Lower PEEP (*n* = 20) | Higher PEEP (*n* = 24) | *p* value | Left Ventricular Variables | Lower PEEP (*n* = 20) | Higher PEEP (*n* = 24) | *p value* |
|---|---|---|---|---|---|---|---|
| Myocardial performance index, median (IQR) | 0.32 (0.26 − 0.39) | 0.38 (0.32 − 0.41) | *0.33* | Myocardial performance index, median (IQR) | 0.41 (0.37 − 0.49) | 0.45 (0.39 − 0.54) | *0.35* |
| Tricuspid annular plane systolic excursion (mm) , median (IQR) | 22 (17 − 25) | 20 (18 − 22) | *0.75* | Ejection fraction, %, median (IQR) | 55 (49− 58) | 59 (51− 65) | *0.23* |
| Global longitudinal strain, %, median (IQR) | −18 (−20 to -11) | −22 (-24 to −16) | *0.17* | Global longitudinal strain, %, median (IQR) | −12 (−19 to −8) | −12 (−15 to 10) | *0.92* |
| Isovolumetric acceleration, m/sec, median (IQR) | 3.3 (3.1−4.1) | 3.1 (2.5−4.9) | *0.41* | Isovolumetric acceleration, m/sec, median (IQR) | 3.2(2.1− 4.7) | 3.4 (2.1− 5.9) | *0.49* |
| Systolic maximal velocity, cm/s, mean ± SD | 12.4 ± 3 | 12.5 ± 4 | *0.91* | Systolic maximal velocity, cm/s, mean ± SD | 8.3 ± 2.2 | 8.3 ± 2.3 | *0.92* |
| Early/Atrial velocity ratio, median (IQR) | 1.1 (0.8−1.2) | 0.9 (0.8−1.1) | *0.53* | Early/Atrial velocity ratio, median (IQR) | 0.9 (0.72−1.1) | 1.0 (0.66−1.3) | *0.81* |
| Early maximal diastolic velocity, cm/s, mean ± SD | 11.1 ± 3 | 12.7 ± 4 | *0.21* | Early maximal diastolic velocity, cm/s, mean ± SD | 8.7 ± 3.4 | 8.7 ± 3.1 | *0.95* |
| E/E’, median (IQR) | 4.1 (3.3−5.6) | 4.1 (3.3−5.6) | *0.28* | E/E’, median (IQR) | 8.3 (6.1−11.6) | 8.6 (6.4− 10.8) | *0.82* |
| Pulmonary acceleration time m/s$^2$ , mean ± SD | 9.1 ± 4 | 8.9 ± 3 | *0.93* | Cardiac index, l min$^{-1}$ m$^{2\ -1}$, mean ± SD | 2.8 ± 0.9 | 2.5 ± 0.7 | *0.24* |
| Right ventricle/Left Ventricle diameter, median (IQR) [a] | 0.72 (0.61 – 0.81) | 0.74 (0.61 – 0.93) | *0.75* | Eccentricity index, mean ± SD | 1 (0.8 – 1.1) | 0.9 (0.8 – 1.0) | *0.39* |

within the normal range, no hypoxia was observed, and the respiratory system was within normal ranges. In addition, there was sufficient time for correction of a possible preload decrease in the higher PEEP group as illustrated by the higher fluid balance. In this study, we observed that decreasing PEEP in hemodynamically stable patients without ARDS has minor effects on right heart afterload and right – and left systolic and diastolic function.

The effects of PEEP on cardiac function in this study should be seen within the context of ventilation with a lower tidal volume. In one recent study, performed in a comparable group of patients, right ventricular myocardial performance index was lower during ventilation with a lower tidal volume versus a higher tidal volumes (0.41 vs 0.64) [17]. In that study, PEEP was 5 $cmH_2O$ in the two study arms. The findings of the current study add to our understanding of the effects of positive pressure ventilation on the right ventricle by showing that a ventilation strategy that has the potential to increase lung strain (i.e., ventilation with a higher tidal volume and higher PEEP from the previous study) results in a higher myocardial performance index compared to a ventilation strategy that causes less lung strain (i.e., ventilation with a lower tidal volume and lower PEEP from the current study) (0.32 versus 0.64)[17]. This could mean that the negative effects of an increase in tidal volume may have a bigger effect on right ventricle functioning than an increase in PEEP, or that the negative effects of higher PEEP are nullified by the use of a lower tidal volume. This should be evaluated in future studies.

The myocardial performance index, obtained using tissue Doppler imaging, was chosen in this study to assess right heart function for several reasons. First, myocardial performance index is a straightforward, reproducible, indicator of both systolic and diastolic function[22]. The results of this study confirm that right ventricle myocardial performance index is easily obtained parameter in the context of critically ill invasively ventilated patients; in only 5 patients it was not possible to obtain myocardial performance index, which was accounted for with the 20% increase in sample size. Second, in this study we searched for mild changes in systolic and diastolic right ventricle function and not for acute cor pulmonale which is characterized by well-defined echocardiographic criterium. In this context, myocardial performance index has been proven in previous studies as a strong predictor of survival[7,23]. Third, myocardial performance index is a preload-independent echocardiographic measure[22]. Pseudo–normalization of the right ventricular myocardial performance index has been reported only when right atrial pressures are higher than 15 mmHg[24]. However, in our cohort patients are unlikely to have such a high atrial pressure because the inferior vena cava diameter was less than 2.1 cm in both PEEP groups[25].

Strengths of this study are that the effects of PEEP were evaluated in a heterogeneous population of ICU patients without ARDS, who were randomly divided into two PEEP groups. The protocol this study was pre–published, and the transthoracic echocardiography data were analyzed by a blinded physician. Patients in both groups were well equilibrated and specifically, there was no difference in the tidal volume in both PEEP groups. This is the first clinical study to assess the effects of decreasing PEEP to the lowest possible level on cardiac function in invasively ventilated patients not having ARDS. This study also has some limitations. First, we only used transthoracic echocardiography to evaluate cardiac function. While transthoracic echocardiography was performed in a stable setting, future studies should include additional parameters of cardiac function to strengthen the current findings. Second, we did not perform serial transthoracic echocardiographies. Certainly, right ventricular function in patients requiring prolonged ventilation can be affected by several other factors (e.g., sepsis, ARDS). On the other hand, 24 to 48 hours of mechanical ventilation is sufficiently long to study the effects of PEEP without the risk of such confounders. Third, we did not measure intrathoracic pressure, and therefore we cannot determine the effects of intrathoracic pressures between the patients ventilated with lower or higher PEEP. Measuring intrathoracic pressure, however, is challenging in patients with spontaneous ventilation. Furthermore, the distribution of pressures across the pericardium and lungs is highly variable and not easily defined. Fourth, we assessed the effects of PEEP in hemodynamically stable patients without significant right ventricular dysfunction. However, another study suggests that the effects of PEEP on the right ventricle is dependent on the baseline heart function[26].

**Conclusion**

In patients without ARDS ventilated with low tidal volume, ventilation with lower PEEP had no beneficial effects on the right ventricle myocardial performance index when compared to ventilation with higher PEEP.

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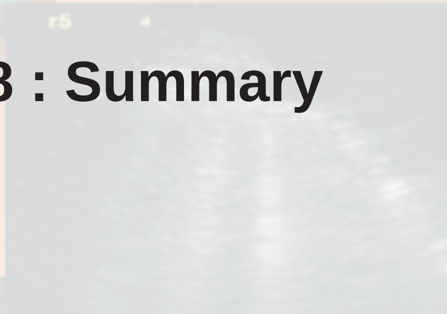

# Chapter 8 : Summary




*Charalampos Pierrakos, Markus W. Hollman ,Marcus J. Schultz, Frederique Paulus and Lieuwe D. Bos*

This thesis is a collection of investigations focusing on evaluating lung and heart function through bedside available imaging technics, including lung ultrasound (LUS), electric impedance tomography (EIT) and transthoracic echocardiography, in invasively ventilated critically ill patients. This chapter summarizes the findings and discusses the future perspectives.

The specific aims were:

1. to determine the accuracy of LUS in identifying lung morphology in invasively ventilated patients;
2. to determine the association of the global LUS score with outcome in invasively ventilated patients with COVID–19 related acute respiratory distress syndrome (ARDS);
3. to study changes in lung aeration evaluated through EIT parameters during prone position in invasively ventilated patients with COVID–19 related ARDS;
4. to determine the association of right ventricle–myocardial performance index (RV–MPI) derived through transthoracic echocardiography and clinical outcomes in invasively ventilated patients; and
5. to study the differences in RV–MPI derived through transthoracic echocardiography in patients ventilated with low or higher positive end–expiratory pressure (PEEP).

The overarching hypothesizes were:

1. that LUS can reliably classify lung morphology into ‘focal’ and ‘non–focal’ phenotypes;
2. that a higher global LUS score indicative of decreased lung aeration is associated with worse clinical outcomes in invasively ventilated COVID–19 patients, independent of ARDS severity;
3. that prone positioning decreases the inhomogeneity of aeration and recruits collapsed lung tissue as measured by EIT in invasively ventilated COVID–19 patients;
4. that right ventricular (RV)–function evaluated with transthoracic echocardiography is associated with worse clinical outcomes in invasively ventilated patients; and
5. that RV–function evaluated with transthoracic echocardiography is affected by the chosen PEEP strategy.

**Chapter 2** describes the results of a systematic review of the literature aimed to identify morphological, anatomical and functional imaging characteristics that predict lung recruitability in the invasively ventilated patient. For each included study, we collected data related to patient characteristics, type of recruitment manoeuver (RM), criteria for a ‘responder' to recruitment and the baseline characteristics to identify factors that differentiate between 'responders' and 'non–responders'. Twenty studies were identified, including invasively ventilated patients who received a RM and in whom re-aeration was examined with chest computed tomography (CT), EIT and LUS. Different types of RMs were applied and the amount of re-aerated lung tissue after a RM was highly variable between patients in all studies. In patients with ARDS, imaging findings suggesting a non–focal morphology ,i.e., radiologic findings consistent with attenuations with diffuse or patchy loss of aeration were associated with a higher likelihood of recruitment and lower chance of overdistention than a focal morphology, i.e., radiological findings suggestive of lobar or segmental loss of aeration, independently of the used imaging technique. In contrast, the results were inconclusive in patients without ARDS. We concluded that LUS and CT characteristics consistent with the non-focal morphology of ARDS are predictive of more re-aeration in response to recruitment maneuvers. The role of imaging techniques in predicting the effect of RMs on re-aeration in patients without ARDS remains uncertain.

In **Chapter 3,** we present the results of a posthoc analysis on two prospective[1,2] studies that enrolled invasively ventilated patients with ARDS examined with LUS and chest CT scanning at the same time. Two participating centers (Amsterdam University Medical Centers, location 'Academic Medical Center' (AMC) Amsterdam, The Netherlands and Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy) separately developed two LUS methods for classifying lung morphology into 'focal' and 'not−focal' morphology. Additionally, a previously developed LUS method based on anterior LUS scores (Piedmont method) was evaluated[3]. We hypothesized that LUS can reliably classify lung morphology into 'focal' and 'not-focal' compared to gold standard chest CT. The study's primary endpoint was the sensitivity and specificity of the LUS-based methods (index test) for lung morphology based on the CT scan (reference test). We concluded that LUS–based methods could accurately classify lung morphology in invasively ventilated ARDS patients compared to gold standard chest CT. The anterior LUS regions showed to be the most discriminant between focal and non-focal lung morphology. However, accuracy increased moderately when lateral and posterior LUS regions were integrated into the method.

In **Chapter 4** and **Chapter 5,** we present the results of two observational studies in COVID–19 patients with acute respiratory failure. In **Chapter 4**, we included 137 COVID–19 invasively ventilated patients treated in 4 independent ICUs who were examined with LUS within 5 days after invasive ventilation initiation. We hypothesized that a higher global LUS score indicative of decreased lung aeration is associated with worse clinical outcomes in invasively ventilated COVID–19 patients, independent of ARDS severity. The outcomes were successful liberation from the ventilator and intensive care mortality within 28 days, analyzed with multistate, competing risk proportional hazard models. We concluded that a lower global LUS score 24 hours after invasive ventilation initiation is associated with an increased probability of liberation from the mechanical ventilator COVID–19 ARDS patients, independently of the ARDS severity. This indicates that there a subgroup of patients with less non-aerated lung tissue who recover more rapidly resulting in shorter duration of mechanical ventilation.

In **Chapter 5,** we included 15 spontaneously breathing invasively ventilated patients with COVID–19 patients placed in prone position for refractory hypoxemia. We hypothesized that prone positioning decreases the inhomogeneity of aeration and recruits collapsed lung tissue as measured by EIT in invasively ventilated COVID–19 patients. Changes in lung aeration were studied by EIT from before to after placing a patient prone and back to supine. Endpoints were global inhomogeneity and changes in local compliance, end-expiratory lung impedance (EELI), and poorly ventilated areas ('silent spaces'). Using linear mixed-effects models, we identified an increase in EELI and compliance in dorsal areas associated with a decrease in the global inhomogeneity index. However, we did not observe any decrease in poorly ventilated areas. We concluded that in spontaneously breathing invasively ventilated COVID–19 patients, prone positioning decreased inhomogeneity, increased lung volumes, and improved dorsal compliance without recruitment of collapsed lung tissue.

In **Chapter 6** and **Chapter 7,** we present the results of two studies evaluating right heart function using the RV–MPI obtained with transthoracic echocardiography in invasively ventilated patients without ARDS. The enrolled patients were included in two multicenter randomized clinical trials of invasive ventilation and hospitalized in the ICU of Amsterdam University Medical Center, location AMC—in one study, named the 'Protective Ventilation in Patients Without ARDS' (PReVENT), ventilation with a low tidal volume ($V_T$) was compared with ventilation with an intermediate $V_T$ in ; in the other study, named 'REstricted versus Liberal positive end-expiratory pressure in patients without ARDS' (RELAx), ventilation with lower PEEP was compared to ventilation with higher PEEP. The patients were examined with transthoracic echocardiography within 24 to 48 hours after invasive ventilation initiation. In **Chapter 6,** we present the results of the posthoc analysis including the patients of the RELAx and PReVENT substudies. We hypothesized that RV dysfunction evaluated with transthoracic echocardiography is associated with worse clinical outcomes in invasively ventilated patients. A substantial number of invasively ventilated patients without ARDS had an abnormal RV-MPI, but it was neither associated with successful liberation from the ventilator within 28 days nor with 28–day mortality. We concluded that in invasively ventilated critically ill patients without ARDS, RV–MPI had no prognostic capacity for successful liberation from invasive ventilation or death. RV–MPI's prognostic capacity should be further studied in prospective investigations that have a larger sample size. **Chapter 7** showed the results of another analysis of the substudy of RELAx. In RELAx, patients were randomized to a ventilation strategy with lower PEEP (5 $cmH_2O$) or higher PEEP (8 $cmH_2O$) and examined transthoracic echocardiography within 24 to 48 hours. We hypothesized that RV function evaluated with transthoracic echocardiography is affected by the chosen PEEP strategy. We found that mechanical ventilation with lower PEEP in ICU patients without ARDS does not affect the RV–MPI compared to higher PEEP. We concluded that in patients without ARDS ventilated with low tidal volume, ventilation with lower PEEP had no beneficial effects on the right ventricle myocardial performance index compared to ventilation with higher PEEP.

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# Chapter 9: General discussion and future prospective

The main findings of the research described in this thesis can be summarized as follows: 1) Lung morphology in patients with acute respiratory distress syndrome (ARDS) can predict the effect of recruitment manoeuver (RM) on lung aeration, and lung ultrasound (LUS) can be used to classify lung morphology at the bedside in invasively ventilated patients, 2) LUS can be used to evaluate the severity of lung aeration decrease in ARDS patients, and electrical impedance tomography (EIT) can be used for evaluation of lung aeration changes and homogeneity of ventilation during position changes in invasively ventilated patients with ARDS and 3) right ventricular (RV) dysfunction assessed by transthoracic echocardiography in invasively ventilated patients without ARDS is not influenced by positive end-expiratory pressure (PEEP) strategy and is not associated with outcomes in this patient category.

The introduction of imaging techniques could help to tailor mechanical ventilation to the patients' personal needs of the patients[1]. Nevertheless, imaging monitoring lung and heart function in invasively ventilated patients is challenging for several reasons, namely: 1) the patients are not easily mobilized and the quality of the image is several times not optimal, 2) ventilatory parameters can affect the visibility of lung and heart and 3) there is a lack of a consistent framework for the interpretation of the findings. The results of the studies presented in this thesis deal with the challenges and provide an overview of what imaging techniques could be useful under what circumstances. The different techniques are discussed separately below.

*Lung ultrasound*

The results of several studies have suggested that LUS can provide reliable information about lung aeration and that this can be used in the diagnosis of ARDS[2-5]. The findings described in this thesis further point to the use of LUS to identify lung morphology and as a tool to identify the severity of lung involvement. In **Chapter 3**, we demonstrated that LUS findings could be used to identify 'focal' or 'non–focal' lung morphology in ARDS, which (in **Chapter 2)** was found to be associated with recruitment maneuver results. Additionally, findings in **Chapter 4** imply that LUS can be used to assess the severity of lung aeration decrease in invasively ventilated patients with COVID–19 ARDS independently of oxygenation parameters. Therefore, the results of this thesis suggest that LUS can be used as a tool to identify subgroups of patients with different responses to treatment and distinct prognostic profiles.

Previous studies have demonstrated a remarkable loss of aeration in anterior areas in patients with ARDS and 'non-focal' lung morphology but not in those with 'focal'[6,7]. Furthermore, global LUS has been associated with the severity of lung involvement in patients with ARDS[3,7]. Therefore, the results of this thesis confirm the previous investigations as we also found that many individual patients were classified only by examination of anterior regions with LUS and a global LUS higher than 17 was associated with a worse outcome. In addition, our study validated these results in an independent cohort of patients treated in different centers evaluating the LUS score obtained by an identical and systematic method by multiple investigators in invasively ventilated patients.

*Electrical impedance tomography*

EIT can be used for PEEP titration in invasively ventilated patients with ARDS and has therefore been introduced into clinical practice in several centers[7]. In **Chapter 5**, we evaluated changes in aeration caused by prone position in invasively ventilated patients with COVID–19 using the EIT. Prone positioning is widely used in patients with ARDS, particularly in patients with coronavirus disease 2019 (COVID–19) and refractory hypoxemia[8]. Of note, prone position effects cannot be evaluated through LUS as it is impossible to score, and thus compare, the chest regions that are scored in the supine position. Additionally, today hyperinflation cannot be detected with LUS. The results of our research demonstrate that the beneficial effects of prone position on lung aeration are progressive over time and that 16-hour periods of prone position ventilation are likely also needed in this group. Besides improvement in respiratory system compliance, we also observed evidence for overdistention of the anterior areas, which can lead to ventilator-induced lung injury. Hence, the results of this study revealed that changes in aeration monitored by EIT can be used to monitor patients put into prone position.

In contrast to previous studies[9-12], we evaluated the EIT imaging technique in lightly sedated spontaneously breathing invasively ventilated patients with COVID–19 ARDS. We evaluated patients in pragmatic conditions as prone position was standard care and patients received no other interventions that could have affected lung aeration. Using parameters typically derived from EIT examination such as Global Inhomogeneity Index[13], end–expiratory lung impedance changes and ‘silent spaces’[14], we assessed local volume changes and evaluated the recruitment of collapsed lung tissue or hyperinflation. Given that early spontaneously breathing is increasingly used even in prone position[15], and the benefits of muscle paralysis are increasingly questioned[16], the results of our thesis extend our knowledge in using EIT monitoring in patients who are not deeply sedated.

*Transthoracic echocardiography*

In this thesis, we investigated the evaluation of RV function through transthoracic echocardiography in invasively ventilated patients. RV myocardial performance index (RV−MPI) was used as the primary indicator for RV function since it has been suggested as an, at least in part, preload–independent and easily derived index of systolic and diastolic and systolic performance of the right heart[17]. Even though we could not capture RV–MPI in 8 out of 81 patients enrolled in the posthoc analysis presented in **Chapter 6,** other ultrasound−derived parameters of RV function are usually even more difficult to collect. For instance, the right ventricular global longitudinal strain could not be measured in more than a quarter of these patients. RV–MPI is therefore likely the most clinically appropriate method to monitoring right heart systolic function in invasively ventilated patients as it is relatively easy to be obtained and is not affected by ventilatory parameters.

However, we also demonstrated that the clinical utility of assessing right heart function should be further evaluated. In **Chapter 6**, we did not find RV-MPI association with outcome in invasively ventilated patients. Besides, in **Chapter 7,** we found that RV−MPI is not different in patients randomized to high or low PEEP. One could hypothesize that higher intrathoracic pressures in part cause right ventricular dysfunction. In a previous study, patients randomized to ventilation with higher $V_T$ had an abnormal RV−MPI[18]. Patients randomized to high or low PEEP in the study presented in **Chapter 6** were all ventilated with low tidal volume. Therefore, the differences in RV−MPI were subtler than expected and no statistically significant difference was found with the predetermined sample size. All the patients of the two substudies did not have ARDS and were ventilated with very low or moderate PEEP levels (0 to 8 cm $H_2O$), which implies no substantial increases in vascular resistance. Therefore, the results of this thesis add to our knowledge in the interpretation of right ventricular function in invasively ventilated patients without ARDS. While we show that RV−MPI has no predictive validity, we cannot exclude that RV−MPI may be useful in guiding ventilatory or fluid and inotrope therapy in invasively ventilated patients. Monitoring of RV function might have most added value in patients with ARDS or known pulmonary hypertension.

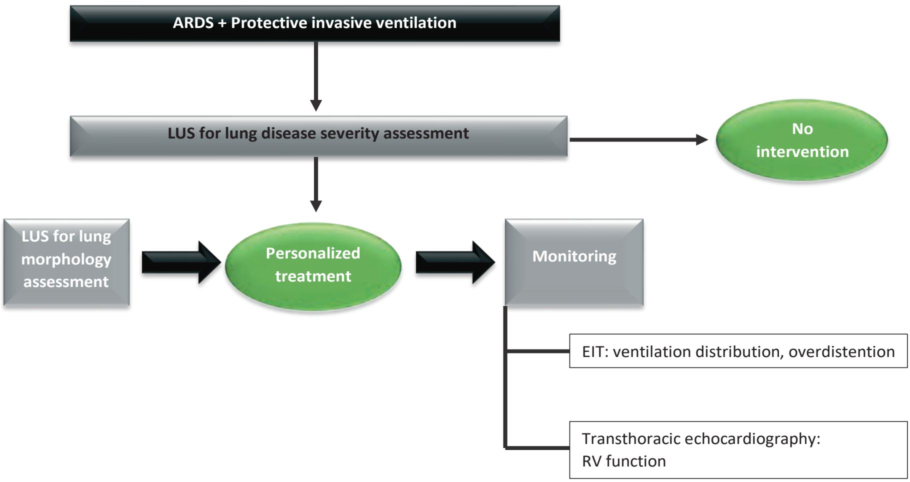
**Future perspectives**

The ultimate aim of personalized medicine is to improve patient outcomes by applying treatments that are tuned to the needs of the individual patient. The here described imaging techniques could facilitate better tailoring of invasive ventilation strategies. However, a previous study that evaluated personalized treatment of the ARDS patient based on imaging technics, i.e., chest X−Ray or chest computed tomography, failed to show any benefit[19]. Misdiagnosis of the lung morphology mainly on chest X−rays by local investigators led to the misclassification and resulted in applying the wrong treatment strategy. These were the patients who were harmed by the intervention, which clearly identifies the need for an objective and careful evaluation of the added value of imaging−guided personalized ventilation. Therefore, the translation from results obtained in observational studies to positive trial results followed by clinical application is not straightforward.

A better estimation of the risk for outcomes, for example, based on the extent of pulmonary edema or right ventricular dysfunction, could facilitate the inclusion of patients with a higher probability of reaching the primary endpoint. Previous studies have found a correlation between global LUS[20] or RV−MPI[21] and mortality in invasively ventilated patients. However, in **Chapter 4,** we showed that a higher global LUS score, indicative of more pulmonary edema, was not associated with increased mortality. In **Chapter 7,** we showed that transthoracic echocardiography−derived parameters of RV function were not associated with outcomes in invasively ventilated patients without ARDS. The differences in the results can be explained by the fact that we used imaging technics in different populations compared to previous studies. In **Chapter 4** we assessed invasively ventilated patients with COVID−19 related ARDS who frequently need prolonged duration and mortality in this population can be mainly driven by the occurrence of ICU−acquired complications or the ability to endure prolonged duration of mechanical ventilation[22]. Besides, in **Chapter 7** we used transthoracic echocardiography to evaluate patients without ARDS and subsequently less lung oedema and considerable less important heart-lung interactions. Therefore, evaluation of either one alone pulmonary edema or right ventricular dysfunction will likely result in a too simplistic view of the physiological changes that inform personalized ventilation strategy; future studies should evaluate a more holistic strategy incorporating the findings of multiple bedside imaging technics.

Within such a holistic view, LUS can be used for multiple purposes in invasively ventilated patients with ARDS. First, LUS can reliably identify patients with pulmonary edema and possibly discriminate between cardiopulmonary edema and ARDS[23]. Second, we and others have shown that the extent of the edema is associated with outcomes and patients with a low global LUS score are very likely to be extubated soon and might there be excluded from intervention studies. Last, LUS can be used to classify the lung morphology of

**Figure 1.** Example utility of  bedside imaging techniques for the management of invasively ventilated patients.




ARDS patients and thereby identify patients with a higher probability of positive response to recruitment or prone positioning. EIT and  RV-MPI can be used for monitoring invasively ventilated ARDS patients' lung and RV function before, during and after intervention (Figure 1). This will ensure that invasive ventilation is delivered without detrimental effects to the lung (overdistention captured with EIT) and the heart (right heart failure captured with RV-MPI).  Using such an approach can limit the harmful effects of delivering the wrong personalized intervention due to misclassifications.

Despite the above-described perspective for patients with ARDS, the role of bedside imaging technics for the treatment of patients without ARDS remains much more obscure. LUS utility as a tool for severity disease assessment as well as for selecting patients for specific treatment in patients without ARDS should be further evaluated. The combination of EIT and LUS for monitoring patients without ARDS is still not thoroughly evaluated. The role of transthoracic echocardiography for heart−lung interactions monitoring and its clinical value, particularly in hemodynamically unstable patients or with preexisting heart disease, should be part of the next research.

## Conclusions

The results of this thesis show that three commonly available bedside imaging technics can be used to identify patients with different lung morphologies, assess pulmonary edema, which is related to patient outcomes and can be used to evaluate overdistention and RV failure during invasive ventilation. Each could earn a place in clinical practice when applied in the right patient category and combined with an easily applicable and consistent system of interpreting results. In patients with ARDS, LUS can be used to identify lung morphology and severity of lung aeration decrease. EIT is suitable for monitoring aeration changes and homogeneity of ventilation, particularly when patients are placed in prone position. RV–MPI obtained through transthoracic echocardiography can be used for monitoring right heart function in invasively ventilated patients. Findings of this thesis can be used for the design of future studies related to invasive ventilation.

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# Chapter 10: Nederlandse samenvatting

Dit proefschrift is een verzameling onderzoeken die gericht zijn op het evalueren van de long- en hartfunctie door middel van beeldvormende technieken aan het bed, waaronder longechografie (LUS), elektrische impedantietomografie (EIT) en transthoracale echocardiografie bij invasief beademde, ernstig zieke patiënten. Dit hoofdstuk geeft een samenvatting van de bevindingen en bespreekt de toekomstperspectieven.

De specifieke doelen waren:

1. om de nauwkeurigheid van LUS te bepalen bij het identificeren van longmorfologie bij invasief beademde patiënten;
2. om de associatie van de globale LUS-score met de uitkomst te bepalen bij invasief beademde patiënten met aan COVID-19 gerelateerd acuut, ademnoodsyndroom (ARDS);
3. om veranderingen in longbeluchting te bestuderen, geëvalueerd door EIT-parameters tijdens de buikligging bij invasief beademde patiënten met COVID-19 gerelateerde ARDS;
4. om het verband te bepalen van de rechterventrikel-myocardiale prestatie-index (RV-MPI) afgeleid door transthoracale echocardiografie en klinische resultaten bij invasief beademde patiënten; en
5. om de verschillen in RV-MPI te bestuderen die zijn afgeleid door transthoracale echocardiografie bij patiënten die worden beademd met een lage of hogere positieve eind-expiratoire druk (PEEP).

De overkoepelende hypothesen waren:

1. dat LUS longmorfologie betrouwbaar kan classificeren in ‘focale’ en ‘niet-focale’ fenotypes;
2. dat een hogere globale LUS-score die wijst op verminderde longbeluchting geassocieerd is met slechtere klinische resultaten bij invasief beademde COVID-19-patiënten, onafhankelijk van de ernst van ARDS;
3. dat buikligging de inhomogeniteit van beluchting vermindert en samengevallen longweefsel rekruteert, zoals gemeten door EIT bij invasief geventileerde COVID-19-patiënten;
4. dat de rechterventrikelfunctie (RV), geëvalueerd met transthoracale echocardiografie, geassocieerd is met slechtere klinische resultaten bij invasief beademde patiënten; en
5. dat de RV-functie geëvalueerd met transthoracale echocardiografie wordt beïnvloed door de gekozen PEEP-strategie.

**Hoofdstuk 2** beschrijft de resultaten van een systematisch literatuuroverzicht met als doel morfologische, anatomische en functionele beeldvormingskenmerken te identificeren die de recruteerbaarheid van longen voorspellen bij de invasief beademde patiënt. Voor elk opgenomen onderzoek verzamelden we gegevens met betrekking tot patiëntkenmerken, het type rekruteringsmanoeuvre (RM), criteria voor een 'responder' op rekrutering en de basiskenmerken om factoren te identificeren die onderscheid maken tussen 'responders' en 'non-responders'. Er werden twintig studies geïdentificeerd, waaronder bij invasief beademde patiënten die een RM kregen en bij wie herbeluchting werd onderzocht met thorax-computertomografie (CT), EIT en LUS. Er werden verschillende soorten RM's toegepast en de hoeveelheid opnieuw belucht longweefsel na een RM was in alle onderzoeken zeer variabel tussen patiënten. Bij patiënten met ARDS waren beeldvormingsbevindingen die een niet-focale morfologie suggereren, d.w.z. radiologische bevindingen die consistent zijn met diffuus of fragmentarisch verlies van beluchting, geassocieerd met een grotere kans op rekrutering en een lagere kans op overdistentie dan een focale morfologie, d.w.z. radiologische bevindingen wijzend op lobair of segmentaal verlies van beluchting, onafhankelijk van de gebruikte beeldvormingstechniek. Daarentegen waren de resultaten niet overtuigend bij patiënten zonder ARDS. We concludeerden dat LUS- en CT-kenmerken die consistent zijn met de niet-focale morfologie van ARDS voorspellend zijn voor meer herbeluchting als reactie op rekruteringsmanoeuvres. De rol van beeldvormingstechnieken bij het voorspellen van het effect van RM's op herbeluchting bij patiënten zonder ARDS blijft onzeker.

In **Hoofdstuk 3** presenteren we de resultaten van een post-hoc analyse van twee prospectieve studies waarin invasief beademde patiënten met ARDS deelnamen, die tegelijkertijd werden onderzocht met LUS en CT-scan op de borst. Twee deelnemende centra (Amsterdam Universitaire Medische Centra, locatie 'Academisch Medisch Centrum' (AMC) Amsterdam, Nederland en Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milaan, Italië) ontwikkelden afzonderlijk twee LUS-methoden voor het classificeren van longmorfologie in 'focaal' en ' niet-focale' morfologie. Daarnaast werd een eerder ontwikkelde LUS-methode op basis van anterieure LUS-scores (Piedmont-methode) geëvalueerd We veronderstelden dat LUS de longmorfologie betrouwbaar kan classificeren in 'focaal' en 'niet-focaal' in vergelijking met gouden standaard CT-thorax. Het primaire eindpunt van de studie was de gevoeligheid en specificiteit van de op LUS gebaseerde methoden (indextest) voor longmorfologie op basis van de CT-scan (referentietest). We concludeerden dat op LUS gebaseerde methoden de longmorfologie nauwkeurig konden classificeren bij invasief beademde ARDS-patiënten in vergelijking met gouden standaard CT-thorax. De anterieure LUS-regio's bleken het meest discriminerend te zijn tussen focale en niet-focale longmorfologie. De nauwkeurigheid nam echter matig toe wanneer laterale en posterieure LUS-regio's in de methode werden geïntegreerd.

In **Hoofdstuk 4** en **Hoofdstuk 5** presenteren we de resultaten van twee observationele onderzoeken bij COVID-19-patiënten met acuut respiratoir falen. In **Hoofdstuk 4** hebben we 137 COVID-19 invasief beademde patiënten geanalyseerd die werden behandeld in 4 onafhankelijke IC's en die binnen 5 dagen na aanvang van de invasieve beademing werden onderzocht met LUS. We veronderstelden dat een hogere globale LUS-score die wijst op verminderde longbeluchting geassocieerd is met slechtere klinische resultaten bij invasief beademde COVID-19-patiënten, onafhankelijk van de ernst van ARDS. De resultaten waren een succesvolle bevrijding van de ventilator en sterfte op de intensive care binnen 28 dagen, geanalyseerd met multistate, concurrerende risico-proportionele risicomodellen. We concludeerden dat een lagere globale LUS-score 24 uur na het starten van invasieve beademing geassocieerd is met een verhoogde kans op bevrijding van de mechanische ventilator in COVID-19 ARDS-patiënten, onafhankelijk van de ernst van de ARDS. Dit geeft aan dat er een subgroep van patiënten met minder niet-belucht longweefsel is die sneller herstelt, wat resulteert in een kortere duur van de beademing. In **Hoofdstuk 5** hebben we 15 spontaan ademende, invasief beademde patiënten geïncludeerd met COVID-19-patiënten in buikligging voor refractaire hypoxemie. We veronderstelden dat buikligging de inhomogeniteit van beluchting vermindert en samengevallen longweefsel rekruteert, zoals gemeten door EIT bij invasief beademde COVID-19-patiënten. Veranderingen in longbeluchting werden bestudeerd door EIT van voor tot na het plaatsen van een patiënt in buikligging en terug in rugligging. Eindpunten waren globale inhomogeniteit en veranderingen in lokale compliantie, eind-expiratoire longimpedantie (EELI) en slecht geventileerde ruimtes (‘stille ruimtes’). Met behulp van lineaire mixed-effects-modellen identificeerden we een toename in EELI en compliance in dorsale gebieden geassocieerd met een afname van de wereldwijde inhomogeniteitsindex. In slecht geventileerde ruimtes zagen we echter geen afname. We concludeerden dat bij spontaan ademende, invasief beademde COVID-19-patiënten, buikligging voor verminderde inhomogeniteit, verhoogde longvolumes en verbeterde dorsale compliantie zorgt zonder rekrutering van samengevallen longweefsel.

In **Hoofdstuk 6** en **Hoofdstuk 7** presenteren we de resultaten van twee studies die de functie van het rechter hart evalueren met behulp van de RV-MPI verkregen met transthoracale echocardiografie bij invasief beademde patiënten zonder ARDS. De ingeschreven patiënten werden opgenomen in twee multicenter gerandomiseerde klinische onderzoeken naar invasieve beademing en opgenomen in de ICU van het Amsterdam Universitair Medisch Centrum, locatie AMC – in één onderzoek, genaamd de ‘Beschermende Ventilatie bij Patiënten Zonder ARDS’ (PReVENT), werd beademing met een laag ademvolume ($V_T$) vergeleken met ventilatie met een tussenliggende $V_T$; in het andere onderzoek, genaamd ‘REstricted versus Liberal positive end-expiratory pressure bij patiënten zonder ARDS’ (RELax), werd beademing met lagere PEEP vergeleken met beademing met hogere PEEP. De patiënten werden binnen 24 tot 48 uur na aanvang van invasieve beademing onderzocht met transthoracale echocardiografie. In **Hoofdstuk 6** presenteren we de resultaten van de posthoc analyse, inclusief de patiënten van de RELAx en PReVENT substudies. Onze hypothese was dat RV-disfunctie geëvalueerd met transthoracale echocardiografie geassocieerd is met slechtere klinische resultaten bij invasief beademde patiënten. Een aanzienlijk aantal invasief beademde patiënten zonder ARDS had een abnormale RV-MPI, maar dit was niet geassocieerd met een succesvolle bevrijding van de beademing binnen 28 dagen, noch met een mortaliteit na 28 dagen. We concludeerden dat bij invasief beademde ernstig zieke patiënten zonder ARDS, RV-MPI geen prognostische capaciteit had voor succesvolle bevrijding van invasieve beademing of overlijden. De prognostische capaciteit van RV-MPI moet verder worden bestudeerd in prospectieve onderzoeken met een grotere steekproefomvang. **Hoofdstuk 7** liet de resultaten zien van een andere analyse van de substudie van RELAx. In RELAx werden patiënten gerandomiseerd naar een beademingsstrategie met lagere PEEP (5cm$H_2O$) of hogere PEEP (8 cm$H_2O$) en onderzochten ze binnen 24 tot 48 uur transthoracale echocardiografie. We veronderstelden dat de RV-functie die wordt geëvalueerd met transthoracale echocardiografie wordt beïnvloed door de gekozen PEEP-strategie. We vonden dat mechanische ventilatie met lagere PEEP bij IC-patiënten zonder ARDS geen invloed heeft op de RV-MPI in vergelijking met hogere PEEP. We concludeerden dat bij patiënten zonder ARDS die werden beademd met een laag ademvolume, beademing met een lagere PEEP geen gunstige effecten had op de myocardiale prestatie-index van de rechter ventrikel in vergelijking met beademing met een hogere PEEP.

# Appendices

**PhD Portfolio**

PhD student: C. Pierrakos

PhD period: 2020−2022

PhD supervisors : Pr. M.J.Schultz, Pr. M.W.Hollman, F. Paulus, L.D.Bos

| | Year | ECTS |
|---|---|---|
| **General Courses** | | |
| European Diploma in advanced critical care EchoCardiography | 2018-2019 | 70.4 |
| Data analysis in MATLAB | 2020 | 3 |
| Research Pathway - Level 1 | 2022 | 1.3 |
| **Presentations** | | |
| Oral presentation at European Respiratory Society international congress: ‘Lung Ultrasound Score for Prognostication in invasively ventilated COVID-19 patients’ | 2021 | 1 |
| **Attended Conferences** | | |
| e-Days Hemodynamic Monitoring | 2021 | 0.67 |
| 40th ISICEM, Brussels, Belgium | 2021 | 1.6 |
| ERS International Congress | 2021 | 1.6 |
| 32nd Annual ELSO Virtual Conference | 2021 | 1.6 |
| **Other activities** | | |
| Intensive care research meeting (weekly) | 2019-2021 | 1 |
| Intensive care journal club (mounthly) | 2020-2021 | 0.6 |
| Review papers submitted to the journals “Critical Care”, “Journal of translational Medicine” and “PloS one” | 2019-2022 | 9.6 |

**List of Publications**

**Update list available on:** https://pubmed.ncbi.nlm.nih.gov/?term=Pierrakos+C&sort=date

*A) Original peer-reviewed papers*


1. Pierrakos C, Lieveld A, Pisani L, Smit MR, Heldeweg M, Hagens LA, Smit J, Haaksma M, Veldhuis L, Schmidt RW, Errico G, Marinelli V, Attou R, David CE, Zimatore C, Murgolo F, Grasso S, Mirabella L, Cinnella G, De Bels D, Schultz MJ, Tuinman PR, Bos LD. A Lower Global Lung Ultrasound Score Is Associated with Higher Likelihood of Successful Extubation in Invasively Ventilated COVID-19 Patients. Am J Trop Med Hyg. 2021 Oct 18;105(6):1490-1497.
2. Pierrakos C, Smit MR, Pisani L, Paulus F, Schultz MJ, Constantin JM, Chiumello D, Mojoli F, Mongodi S, Bos LDJ. Lung Ultrasound Assessment of Focal and Non-focal Lung Morphology in Patients With Acute Respiratory Distress Syndrome. Front Physiol. 2021 Sep 14;12:730857.
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9. Pierrakos C, Velissaris D, Scolletta S, Heenen S, De Backer D, Vincent JL. Can changes in arterial pressure be used to detect changes in cardiac index during fluid challenge in patients with septic shock? Intensive Care Med. 2012 Mar;38(3):422-8.

10. Pierrakos C, Vincent JL. The changing pattern of acute respiratory distress syndrome over time: a comparison of two periods. Eur Respir J. 2012 Sep;40(3):589-95.

11. Pierrakos C, Bonios M, Drakos S, Charitos E, Tsolakis E, Ntalianis A , Nanas S, Charitos C, Nanas J, Terrovitis J. Mechanical assistance by intra-aortic balloon pump counter-pulsation during reperfusion increases coronary blood flow and mitigates the no-reflow phenomenon. Experimental study Artif Organs. 2011;35(9):867-874.

*B) Review articles*

1. Pierrakos C, Smit MR, Hagens LA, Heijnen NFL, Hollmann MW, Schultz MJ, Paulus F, Bos LDJ. Assessment of the Effect of Recruitment Maneuver on Lung Aeration Through Imaging Analysis in Invasively Ventilated Patients: A Systematic Review.Front Physiol. 2021 Jun 4;12:666941.

2. Pierrakos C, Velissaris D, Bisdorff M, Marshall JC, Vincent JL. Biomarkers of sepsis: time for a reappraisal. Crit Care. 2020 Jun 5;24(1):287.

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5. Pierrakos C, Karanikolas M, Scolletta S, Karamouzos V, Velissaris D. Acute respiratory distress syndrome: pathophysiology and therapeutic options. J Clin Med Res. 2012 Feb;4(1):7-16.

6. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. Critical Care. 2010; 14(1):R15

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# Aknowledgments

‘ὡς ἐμεγαλύνθη τὰ ἔργα σου, Κύριε· πάντα ἐν σοφίᾳ ἐποίησας’

Brussels 15 Avril 2022,

Writing down these words, meaning the end of this precious experience, I feel like Odysseus after arriving in Ithaka, contemplating the sea he had traversed. Without any doubt, this project proved to be an exciting journey in the mysterious world of research which made me wiser and 'so full of experience' to 'understand by then what this Ithaca means'. But, what most important comes to my mind is that this project would have never been possible without the aid and support of so many people that I am grateful to them.

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