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Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico
Regione Lombardia

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REcruitment **MA**neuvers and Mechanical **V**entilation guided by **EIT** in pediatric Acute Respiratory Distress Syndrome (pARDS)

Acronym:

REMAV-EIT

Unique ID Protocol 1170_2021

Version and date: Version 1.0 – Date 11.11.2021.

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LIST OF ABBREVIATIONS

ALI = Acute Lung Injury

ANOVA = ANalysis Of VAriance

CI = Confidential Interval

CCW= Chest Wall Compliance

Crs= Compliance Respiratory System

Cl= Compliance Lung

cmH_2O = centimetres of water

DP= Driving Pressure

EC = Ethics Committee

ECG = Electrocardiogram

EIT = Electrical Impedance Tomography

FiO2 = Fraction of inspired Oxygen

GC = Geometric Centre

GI = Global Inhomogeneity Index

HR = Heart Rate

IC = Informed Consent

ICU = Intensive Care Unit

LIP= Lower Inflection Point

mmHg = millimetres of mercury

NIBP = Non-Invasive Blood Pressure

pARDS=pediatric Acute Respiratory Distress Syndrome

PEEP = Positive End Expiratory Pressure

PIM2= Pediatric Index of Mortality

PELOD= Paediatric Logistic Organ Dysfunction score

Plung= Transpulmonary pressure

ROI = Region Of Interest

RVD = Regional Ventilation Delay

SpO_2 = peripheral oxygen saturation

SRM = Stepwise Recruitment Maneuver

TID = Tidal Impedance Distribution

CE: Ethical Committee

CI: informed Consent

CRF: Case Report Form

GCP: Good Clinical Practice

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1. INTRODUCTION

1.1 Background and rational

There is evidence from randomized controlled trials in adult patients with Acute Respiratory Distress Syndrome (ARDS) suggesting that delivering small tidal volumes with adequate levels of Positive End-Expiratory Pressure (PEEP) and a restrictive fluid strategy could improve outcome (1–3). However, there is also evidence that there is a dichotomy in outcome in patients with ARDS and not all patients respond uniformly (4–8). Concurrent with these data and with the common bedside experience that individual patients may or may not respond to interventions, such as escalation of PEEP or positional changes, there may be a role for a more personalized ventilator strategy. This strategy could account for the unique individual morphology of lung disease, such as the amount of atelectasis and overdistension as a percentage of total lung tissue, the exact location of atelectasis, and whether positional changes or elevation of PEEP produce lung recruitment or overdistension.

Recruitment is the dynamic process of opening previously collapsed lung units by increasing transpulmonary pressure. Lung units can be kept open by airway pressures that are lower than those required to open them, leading to the concept of recruitment using periodic higher pressure maneuvers with application of PEEP to maintain alveolar patency. Stepwise Recruitment maneuvers (SRMs) in pARDS improve oxygenation in majority of patients. SRMs should be considered for use on an individualized basis in patients with pARDS should be considered if SpO2 decreases by ≥ 5% within 5 minutes of disconnection during suction or coughing or agitation. If a recruitment maneuver is conducted, a decremental PEEP trial must be done to determine the minimum PEEP that sustains the benefits of the recruitment maneuver.

Electrical impedance tomography (EIT), a bedside monitor to describe regional lung volume changes, displays a real-time cross-sectional image of the lung. Regional volume changes during EIT have been highly correlated with volume changes detected on bedside. EIT is a non-invasive, non-

operator dependent, bedside, radiations-free diagnostic tool, feasible in paediatric patients and repeatable. It allows to study ventilation distribution dividing lungs in four Region Of Interest (ROI). The increase in chest impedance is related to the increased presence of air. Therefore, for each respiratory act, EIT attributes the value of 100% of the current tidal volume to the overall impedance change of the entire chest. Then, it attributes a percentage of the global lung volume to each of the ROI, based on regional impedance changes, thus showing how ventilation is distributed in the areas concerned. ROI can be defined by quadrants or layers distributed in an anteroposterior direction. For the aim of our study, we are going to divide lungs in four dorsoventral ROIs. In addition, EIT measures and calculates other parameters that are related not only to the distribution of ventilation, but also to the homogeneity of ventilation and the response to certain therapeutic maneuvers, such as SRMs or PEEP-application (12-16). The aim of this study is to provide a protocolized strategy to assess optimal recruitment and PEEP setting, tailored on the patients individual response in paediatric Acute Respiratory Distress Syndrome (pARDS).

2. AIM/S OR HYPOTHESIS OF THE STUDY

The primary aim of the study is to assess the Global Index (GI) (as an index of atelectrauma, supra-distention and in general an inhomogeneous ventilation) measured after EIT-guided mechanical ventilation (Staircase Recruitment Maneuver followed by a decremental PEEP trial with the final PEEP value set according with EIT bedside monitoring), compared to the baseline GI value registered during mechanical ventilation set by the physician according to clinical protocolized criteria.

The secondary aim of the study is to describe the followings parameters: differences in Tidal Impedance Distribution, Gravity Centre (GC), Respiratory Mechanics, Blood gases level and physiological parameters (respiratory rate, heart rate, systolic and diastolic blood pressure).

3. STUDY DESIGN

3.1 Study design

Monocentric, non pharmacologic prospective interventional trial

Recruitment method: selective invitation

Eligible patients will be enrolled in the first 48 hours from intubation (17).

3.2 Inclusion criteria

- Intubated and mechanically ventilated children, ageing 1 months-10 years and meeting the PALICC definition for pediatric Acute Respiratory Distress Syndrome (pARDS) (Figure 1.)
- Informed Consent signed

3.3 Exclusion criteria

Patients with one or more of the following characteristics will be excluded:

- Previous barotrauma (pneumothorax, pneumomediastinum or subcutaneous emphysema)
- Signs of intracranial hypertension
- Cyanotic congenital cardiac disease
- Dorso-lumbar pathologies or other bone pathologies associated with restrictive lung disease (such as scoliosis, kyphosis)
- Implantable devices not compatible with EIT (such as pace-makers and implantable cardioverter defibrillator)
- Controindication to positioning the esophageal catheter (surgery, esophageal stenosis)

4. STUDY PROCEDURES

The process for obtaining the informed consent must comply with the regulatory procedures in force. The investigator (or a designated collaborator) and the subject must date and sign the informed consent form before the patient initiates any study procedure. The subject will receive a copy of the IC dated and signed by both parties; the original copy will be kept in the archives designated for the study.

The study flowchart is depicted in Figure 1. Study end points and physiological parameters will be monitored and recorded at T0, T1 and T2 (T0=Enrolment, T1 = EIT guided MV at the end of SRM trial, and T2 = 24 hours with EIT guided MV as depicted in Figure 2).

4.1 Standard of care treatment in pARDS

In our unit, children with pARDS are ventilated with a lung protective strategy, including small tidal volume, high PEEP level and low driving pressure according to ESPNIC guidelines. Baseline ventilation is provided using a cuffed endotracheal tube and a leak test is performed before to start the study. Patients will be ventilated with the Dräger Evita Infinity V500 or the Dräger Evita XL ventilator (Dräger Medical, Lübeck, Germany) and equipped with the inspiratory and expiratory hold pause function. The ventilator will be set in pressure -controlled mode with a target tidal volume of 6 mL/Kg of Ideal Body Weight. The pediatric ventilation circuit will be equipped with an y-flow sensor for the determination of tidal volume in patients < 10 Kg (18).

FIO_2 will be set to maintain a peripheral oxygen saturation 88%-94%. Respiratory rate will be set at 25 breaths min with a fixed I:E ratio 1:1.5 to obtain a pH values ranging from 7.25 to 7.40. Plateau pressure is maintained below 30 cmH_2O during all procedure (19). Inspiratory and expiratory timings are set to obtain return to zero flow at end-expiratory. Driving Pressure will be minimized < 15 cmH_2O to maintain lung protective strategy.

The Acute Respiratory Distress Network (ARDSnet) low-PEEP table will be used as patients' safety guardrail. The patients receive minimally the lowest PEEP from the low-PEEP table and maximally the highest PEEP from the high- PEEP table (Figure 3) (19).

In severe pARDS patients, esophageal pressure will routinely measured with a radio-opaque esophageal balloon (diameter 6 Fr) (CareFusion, Linda, USA) inflated with 0.5–0.8 ml of air connected to a pressure transducer. To ensure the correct position of the catheter, the esophageal balloon will be positioned in the stomach to check the presence of positive deflection. Then, it will be retracted until it reached the lower third of the esophagus; in this position, an inspiratory

occlusion is made to check for concordant changes in airway and esophageal pressure (20-22). During an inspiratory and expiratory pause, the airway and esophageal pressure are measured.
Transpulmonary pressure wil be computed as the difference between airway and esophageal pressure both at end of inspiration and at end of expiration after an inspiratory and expiratory occlusion test respectively.
The respiratory system, lung and chest wall compliance will be computed according to the following formula (24):

Respiratory system compliance (Crs) (ml/cmH_2O) = tidal volume/(airway pressure at end inspiration− airway pressure at PEEP

Respiratory System compliance will be normalized to Ideal Body Weight (pediatric normal value ranging from 1 to 2 ml/cmH_2O/Kg).

Lung compliance (C,l) (ml/cmH_2O) = tidal volume/(transpulmonary pressure at end inspiration− transpulmonary pressure at PEEP)

Chest wall compliance (C, cw) (ml/cmH_2O) = tidal volume/(esophageal pressure at end inspiration − esophageal pressure at PEEP

Airway driving pressure= airway pressure at end inspiration – airway pressure at PEEP

The standard monitoring in pARDS in our unit includes routinely: 1) Respiratory monitoring: FIO2, PEEP, Plateau pressure, Peak Inspiratory Pressure, Mean Airway Pressure, Inspiratory and expiratory tidal volume, Inspiratory and expiratory minute ventilation, sidestream capnography, transpulmonary pressure derived from the positioning of the esophageal catheter and blood gases (arterial or capillary) or transcutaneous gases if is not possible to cannulate radial or femoral artery or if controindications to arterial cannulation are present2) Hemodynamic monitoring: EKG, central

venous pressure, invasive arterial pressure with indwelling arterial catheter, cardiac output monitoring, invasive or noninvasive according to clinical conditions 3) Anesthesia and sedation monitoring (Bispectral Index) (18).

4.3 Intervention of the study

Eligible patients will be enrolled in the study, if inclusion criteria will be still satisfied before 48 hours of mechanical ventilation. At enrolment, mechanical ventilation will be set according to the standard of care criteria mentioned above. EIT parameters, physiological parameters will be computed according to Study Flowchart (T0).
After enrolment, Intervention of the study will include: EIT measurement, Staircase Recruitment Maneuver with EIT guided a decremental PEEP trial; Setting of EIT-guided mechanical ventilation (t1); Reevaluation at 24 hours (t2)

EIT Measurements

EIT measurements in children and infants will be performed using the Dräger PulmoVista500 EIT-device (Dräger Medical GmbH, Lübeck, Germany). The 16-electrode belt will be placed between the 4th and 5th intercostal space with specific belt according to chest diameter of the child. Ventilator data will be continuously recorded by the EIT-device through a serial interface (Medibus, Dräger Medical, Lübeck, Germany) from the ventilator. EIT data will be recorded continuously and recording will be interrupted only for data transmission and processing. All EIT data processing will be performed at the bedside utilizing the EIT easy software application (Dräger Medical GmbH, Lübeck, Germany) according to previous study (24). Will be evaluated: Regional Ventilation Delay (RVD) = Regional inspiratory delay compared to the global, may indicate atelectrauma, supra-distention and in general an inhomogeneous ventilation; Global Inhomogeneity Index (GI) = for every breathing cycle, a so-called tidal image is generated and each pixel of represents the difference in impedance between end-inspiration and end-expiration. The median value of each

tidal image is calculated for the lung area. The sum of the absolute difference between median value and every pixel value is considered to indicate the variation in the tidal volume distribution in the whole lung region and it represent the Global Inhomogeneity Index; Geometric Center (GC) = it is the weighted mean of row sums obtained from TV image and it indicates ventral-to-dorsal shifts in ventilation distribution due to lung opening and closing.

Stepwise Recruitment Maneuver (SRM) with Decremental PEEP trial

Enrolled children with pARDS, will receive SRMs with decremental PEEP trial in presence of:
Reduction in P/F or S/F ratio > 10% compared to baseline MV set according to NIH protocol (19) (due to suctioning, after bronchoscopy or other conditions requiring a transient increase in transpulmonary pressure to restore oxygenation).
SRMs, will be performed in PCV mode with a standardized ventilation protocol. Patient will be sedated, paralyzed and ventilated in PCV mode, FIO_2 to obtain SPO_2> 92%, RR 25, I:E =1:1.5. Alarm of pressure limit will be set at 35 cmH_2O. The ventilator will be equipped with inspiratory and expiratory hold taste. Inspiratory and expiratory occlusion will be held for 5 seconds, data will be stored and analyzed with the EVITA V500 own tool. Partitioning of respiratory system mechanics will then obtained according to definitions above reported.
From baseline clinical ventilation, PEEP will be increased in three steps: 8, 10 and 12 cmH_2O every 20 minutes maintaining the following safety termination criteria: 1) maximum plateau pressure <30 cmH_2O or 2) End Inspiratory Transpulmonary Pressure <28 cmH_2O 3) hemodynamic instability defined as the need of inotropes/vasopressors. During the Staircase Recruitment Maneuver (SRM), the Driving Pressure (DP= plateau pressure - PEEP) will be maintained constant at value < 15 cmH_2O (25,26). After the stepwise SRM, a decremental PEEP trial will be initiated once a plateau pressure of 30 cmH_2O is reached or when end-inspiratory transpulmonary pressure exceeds 28 cmH_2O. After reaching either threshold, PEEP will be reduced in three steps to 12, 10, and finally 8 cmH_2O, with each step lasting 20 minutes, in accordance with previous studies (24,25).

4.4 Measurements

Demographic parameters, comorbidities, factors predisposing to the development of ARDS, Pediatric Index of Mortality 2 (PIM2) score, Paediatric Logistic Organ Dysfunction (PELOD) score, rescue treatments for ARDS (prone position, high frequency oscillatory ventilation and inhaled nitric oxide), 28-day ventilator free days, PICU and Hospital length of stay, PICU and hospital mortality at 3 and 6 months will be recorded on a dedicated electronic database.

Haemodynamics and physiological parameters (EKG, invasive arterial pressure, peripheral oxygen saturation and end tidal carbon dioxide tension) will be continuously monitored and displayed on a multiparametric PICU monitor (Draeger, Lubeck Germany). Blood gases values will be collected from arterial catheter (if in place) or from capillary blood samples. SF ratio and trascutaneous gases will be considered if controindication to arterial catheter positioninig will be present.

Data from ventilator will be collected by a USB driver port and downloaded via Medibus cable connection on the electronic data chart (Digistat, Acerba Italy) (FiO2, PEEP, tidal volume, peak and mean airway pressure). An indwelling arterial catheter will be routinely inserted to obtain arterial blood gas (0.1 mL microsample per measurement) and analyzed in PICU.

5. ENDPOINT

5.1 Primary endpoint

The primary end point of the study will be the Global Index (as an index of atelectrauma, supra-distention and in general an inhomogeneous ventilation)

5.2 Secondary endpoint

The secondary endpoints encompass the followings:

- Differences in Tidal Impedance Distribution (TID) at T0, T1
- Gravity Centre (GC) differences at T0, T1 and
- RVD40% at T0, T1
- Respiratory Mechanics at T0, T1

- Blood gases levels and physiological parameters at T0, T1

6. DURATION/STUDY TIMELINE

The anticipated duration of the study is 2 years (January 2022- January 2024).

Enrolment start: January 2025

Enrolment closure: December 2026

No further in-hospital or follow-up visits are foreseen.

7. STATISTICAL ANALYSIS

7.1 Sample size calculation and statistical analysis

No previous data of similar study are existing, so we calculated the sample size according to clinical data obtained in the last months from EIT application in routine clinical practice.

Considering an α-error = 0.05 and power = 80%, the study would have needed 8 patients to detect a 30% reduction in the primary end point, i.e. GI (mean 40± 4SD). Sample size calculation was performed with MedCalc V19.1.7. software (Ltd, Ostend Belgium).

7.2 Data analysis

Data Analysis from EIT will take place using a MatLab custom-developed program and the Draeger EIT Data Analysis Tool 6.3. Data distribution will be tested with Shapiro Wilk analysis. Primary and secondary endpoints will be then analyzed with parametric or nonparametric ANOVA according to data distribution. Frequencies will be compared with chi-square or Fisher exact test, as appropriate. A p value less than 0.05 will be considered as significant (MedCalc V19.1.7. Ltd, Ostend Belgium).

8. ADVERSE EVENTS / DEVICE DEFICIENCIES

An attending paediatric intensive care physician will always will be present during the study in order to identify, report and treat any adverse event arising during the study.

The protocol will have some determined safety termination criteria aiming to preserve the patients from collateral side effects.

Safety termination criteria includes: Increase in $ETCO_2$ > 10% compared to baseline; Decrease in SPO_2 > 10% compared to baseline; Hemodynamic instability defined as hypotension and need of vasopressors (mean arterial pressure < 20% compared to standard values according to age defined values.

9. RISKS AND BENEFIT EVALUATION

All parts of the study will be performed under the supervision of an experienced paediatric intensive care physician. Any adverse event (see section 8) would be immediately recognized and treated adequately. Adverse events could be related to device malfunction or difficult synchronization between the ventilator and the patient (subject of the present study).

Summarizing, the risks related to the protocol refer to device malfunction, which would be immediately identified and treated by the attending physician. Furthermore, the protocol will allow to identify the ventilatory strategy associated with the best ventilation distribution during MV and this, of course, would be a clear clinical benefit both for the studied patients and for future patients that could benefit from the acquired knowledge.

10. STUDY MANAGEMENT

10.1 Collection and management of data

Information about recruited patients will be entered in a pseudonymised manner into a database managed exclusively by the investigator or designated collaborators and such patients will be identified by unique code. The file that associates the participant's code with the relevant identification data will be stored separately on a password-protected computer. The study database

will be password protected and uploaded to a computer that is also password protected and accessible only to study personnel designated by the principal investigator. The de-identification of the data will take place in such a way that the people who access the database will not be able to trace in any way the identity of the subjects. Only local investigators will be able to trace the identity of the enrolled subjects.

EIT data will be saved on EIT hardware (Drager Pulmovista 500) and on a USB driver anonymously.

10.2 Regulatory aspects and ethical considerations

10.2.1 Approval of the Competent Authority

In accordance with current regulations, the principal investigator must obtain approval from the appropriate Competent Authority before starting the clinical study.

The present study will be conducted in accordance with the rules of the ICH / GCP (International Conference of Harmony / Good Clinical Practice) and all applicable laws, including the Helsinki Declaration of June 1964, amended by the latest World Medical Association General Assembly in Seoul, 2008

10.2.2 Approval of the Ethics Committee

The investigator must ensure that the protocol has been evaluated and approved by the Local Independent Ethics Committee (EC) before starting the study.

The EC must also verify and approve the informed consent form (IC) and all written information that the patient receives before the enrolment in the study

Should the protocol and / or IC need to be changed during the study it will responsibility of the principal investigator to ensure that the changes are reviewed and approved by the EC

The content of these changes will be implemented only after the EC has approved them. Until that time, it will be necessary to refer to the previous version of the document already approved.

10.2.3 Informed consent (IC)

The investigator has the task of informing the patients and parents about all aspects and procedures of the study. In his absence, the following persons will be responsible for informing parents and mature patients about all aspects and procedures of the study.

Dr.ssa Giovanna Chidini, Dr.ssa Cinzia Montani, Dr.ssa Tiziana Marchesi, Dr. Stefano Scalia Catenacci, Dr.ssa Giada Donà, Dr.ssa Ludovica Ughi, Dr.ssa Lucia Orlandi, Dr. Giovanni Babini, dr.ssa Maria Adele Figini.

The process for obtaining the informed consent must comply with the regulatory procedures in force. The investigator (or a designated collaborator) and the subject must date and sign the informed consent form before the patient initiates any study procedure. The subject will receive a copy of the IC dated and signed by both parties; the original copy will be kept in the archives designated for the study. Neither the investigator nor the designated personnel should in any way exercise any coercion or influence on a subject to induce her/him to participate or continue to participate in the study. The decision of a subject to participate in the study must be completely voluntary.

10.3 Duties of the experimenter

According to the local regulations, the investigator must send periodic reports regarding the progress of the study in his centre to the EC and notify the closure of the study. Periodic reports and notification of study closure are part of the investigator's responsibilities

10.4 Study monitoring

According to local regulations and Good Clinical Practice (GCP), the monitor must visit or periodically contact the centre. The duration, nature and frequency of these visits / contacts depend on the recruitment frequency, the quality of the documents held by the centre and from their adherence to the protocol.

Through these contacts, the monitor must:

• monitor and evaluate the progress of the study

• examine the data collected

• conduct verification of the source document

• identify any problems and their solutions

The purposes of the monitoring activity are to verify that:

• the subject's rights and well-being are respected

• the data of the study are accurate, complete and verifiable from the original documents

• the study is conducted in accordance with the protocol and any approved amendments, GCP and applicable regulations.

The experimenter must:

• give the monitor direct access to all relevant documentation

• dedicate part of his time and his staff to the monitor to discuss the monitoring results and any other possible aspects.

The monitor must also contact the centre before the study begins to discuss the protocol and data collection procedures with the staff.

10.5 Quality assurance of the study

As a promoter of the study, IRCCS Ca 'Granda Foundation, Ospedale Maggiore Policlinico can carry out a quality control of the study at its discretion. In this case, the investigator should allow the monitor to access all relevant documentation directly and spend part of her/his time and staff on the auditor to discuss the monitoring results and any other aspects of the study.

Furthermore, the Regulatory Authorities can carry out inspections. In this case, the investigator must authorize the inspector to have direct access to all relevant documentation, and to devote part of her/his time and staff to the inspector himself to discuss the monitoring results and any other aspects of the study.

10.6 Study closure

At study closure, the monitor and the investigator must activate a series of procedures:

• review all the study documentation

• reconcile study data

• reconcile all the clarification reports.

10.7 Archiving of documents

In accordance with current national regulations, the investigator must keep a copy of all the documentation and keep it in a dry and safe place after closing the study.

10.8 Disclosure of information concerning scientific discovery

10.8.1 Confidentiality

The investigator and other personnel involved in the study must process all the information related to the study (including the protocol, data obtained and all the documentation produced during the study) and must not use such information, data or relationships for purposes other than those described in the protocol.

These restrictions do not apply to

1) Information that becomes publicly available, not due to negligence on the part of the investigator or his staff

2) Information requiring the disclosure reserved to EC for the sole purpose of evaluating the study

3) Information that must be disclosed to obtain adequate medical treatment for a study subject

10.8.2 Publications

The IRCCS Ca 'Granda Foundation, Ospedale Maggiore Policlinico is the sole owner of the data.

11. ALLOWANCES AND COMPENSATION FOR DAMAGE

In the event of undesired events or any damage that may result from participation in the research, the Insurance Policy of our Institute is also extended to cover the subjects participating in the research projects

12. PROTOCOL AMENDMENTS

Not applicable to the present study.

13. FINANCIAL AGREEMENTS

Not applicable to the present study.

14. DISCLOSURES ON CONFLICTS OF INTEREST

No conflict of interest related to the present study

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FIGURES

Figure 1. PALICC Criteria for pARDS

Age: Exclude patients with peri-natal related lung disease	Oxygenation		
Timing: Within 7 days of known clinical insult	Non Invasive mechanical ventilation: Full face-mask bi-level ventilation or CPAP ≥5 cm H_2O [2] with PF ratio ≤300 or SF ratio ≤264 [1]		
Origin of Edema: Respiratory failure not fully explained by cardiac failure or fluid overload	Invasive mechanical ventilation		
	Mild	Moderate	Severe
Chest Imaging: Chest imaging findings of new infiltrate(s) consistent with acute pulmonary parenchymal disease	4≤ OI <8 5≤ OSI <7.5[1]	8≤ OI <16 7.5≤ OSI <12.3[1]	OI ≥16 OSI≥12.3[1]
Cyanotic Heart Disease: standard criteria with an acute deterioration in oxygenation not explained by underlying cardiac disease. Chronic Lung Disease: standard criteria with chest imaging consistent with new infiltrate and acute deterioration in oxygenation from baseline. Left Ventricular dysfunction: standard criteria with chest imaging changes and acute deterioration in oxygenation not fully explained by left ventricular dysfunction.			

OI = oxygenation index = (FiO_2* mean airway pressure*100)/ PaO_2
OSI = oxygen saturation index = (FiO_2* mean airway pressure*100) /SpO_2
[1] Use PaO_2 based metric when available. If PaO_2 not available, wean FiO_2 to maintain SpO_2 ≤ 97% to calculate OSI or SF ratio
[2] For non-intubated patients treated with supplemental oxygen or nasal modes of non invasive ventilation see Figure 2 for At Risk Criteria

Figure 2. Study Flowchart

MV Mechanical Ventilation; PEEP Positive End Expiratory Pressure; PCV Pressure Controlled Ventilation ; Crs Respiratory System Compliance; Clung Lung compliance; CCW Chest Wall Compliance, PES Esophageal Pressure; EIT Electro Impedance Tomography; RVD Regional Ventilator Delay; GI Global Inhomogeneity Index; DP Driving Pressure; SRM Stepwise Recruitment Maneuver. T0 Baseline measurement at enrolment; T1 End of SRM trial; T2 End of the study at 24 hours

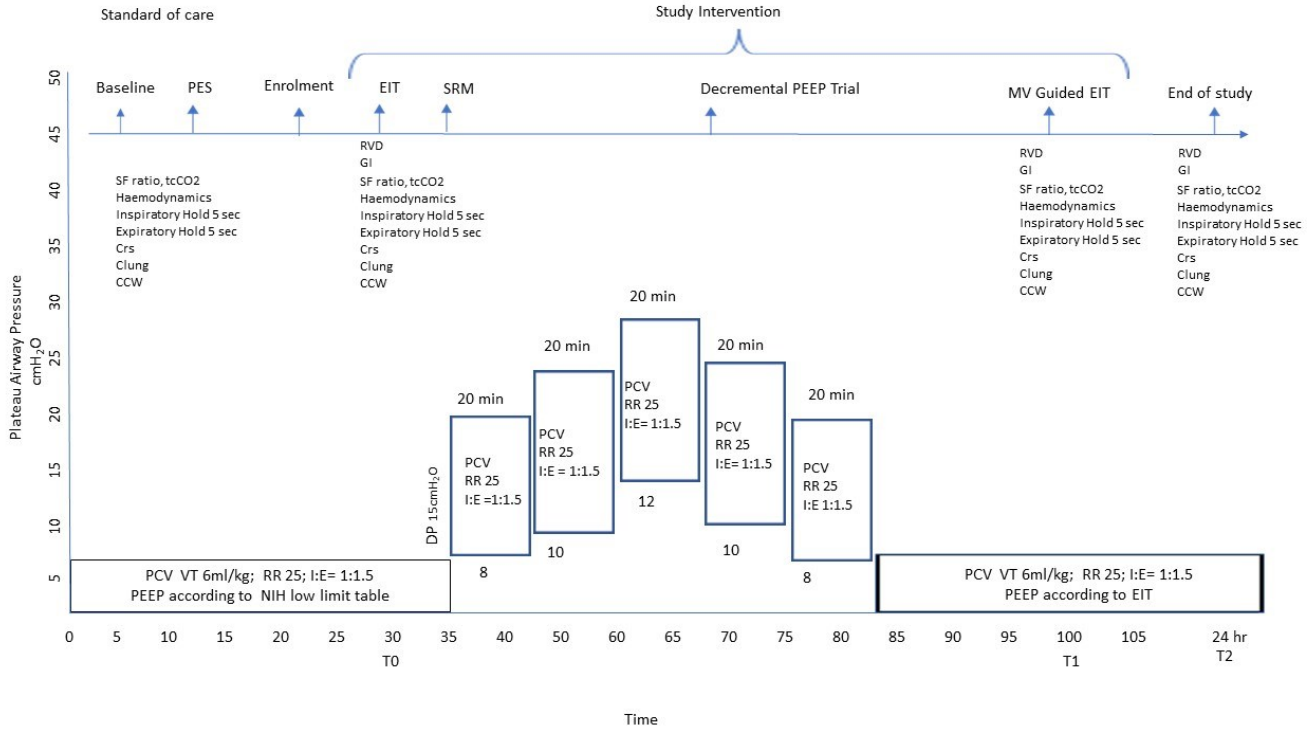

Figure 3. NIH PEEP/FiO_2 Table

Table 1. Summary of Ventilator Procedures in the Lower- and Higher-PEEP Groups.*

Procedure	Value													
Ventilator mode	Volume assist/control													
Tidal-volume goal	6 ml/kg of predicted body weight													
Plateau-pressure goal	≤30 cm of water													
Ventilator rate and pH goal	6–35, adjusted to achieve arterial pH ≥7.30 if possible													
Inspiration:expiration time	1:1–1:3													
Oxygenation goal														
PaO_2	55–80 mm Hg													
SpO_2	88–95%													
Weaning	Weaning attempted by means of pressure support when level of arterial oxygenation acceptable with PEEP ≤8 cm of water and FiO_2 ≤0.40													
Allowable combinations of PEEP and FiO_2†														
Lower-PEEP group														
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24
Higher-PEEP group (before protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0	
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22–24	
Higher-PEEP group (after protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0				
PEEP	12	14	14	16	16	18	20	22	22	22–24				

* Complete ventilator procedures and eligibility criteria are listed in the Supplementary Appendix (available with the full text of this article at www.nejm.org) and at www.ardsnet.org. PaO_2 denotes partial pressure of arterial oxygen, SpO_2 oxyhemoglobin saturation as measured by pulse oximetry, FiO_2 fraction of inspired oxygen, and PEEP positive end-expiratory pressure.

† In both study groups, additional increases in PEEP to 34 cm of water were allowed but not required after the FiO_2 had been increased to 1.0 according to the protocol. The combinations of PEEP and FiO_2 used with PEEP values of less than 12 cm of water were eliminated in the higher-PEEP group after 171 patients had been enrolled in this group.