Universitat Autònoma de Barcelona

EFECTOS FISIOLÓGICOS DE DIFERENTES ESTRATEGIAS VENTILATORIAS EMPLEADAS EN PACIENTES CON INSUFICIENCIA RESPIRATORIA AGUDA SEVERA

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TESIS DOCTORAL

EFECTOS FISIOLÓGICOS DE DIFERENTES ESTRATEGIAS VENTILATORIAS EMPLEADAS EN PACIENTES CON INSUFICIENCIA RESPIRATORIA AGUDA SEVERA

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PRESENTACION

En conformidad a la Normativa académica de la Universidad Autónoma de Barcelona aplicable a los estudio universitarios regulados por el RD 1393/2007 y habiendo sido aprobada la admisión del doctorando en el nuevo programa de doctorado (RD99), la presente tesis se articula por compendio de publicaciones.

Las publicaciones que conforman esta tesis están alineadas en determinar los efectos fisiológicos de dos estrategias habitualmente utilizadas en pacientes en ventilación mecánica con insuficiencia respiratoria aguda severa: el alargamiento de la pausa inspiratoria y la posición en decúbito prono. En estas investigaciones se realiza un razonamiento fisiopatológico de sus efectos en la mecánica respiratoria e intercambio de gases y un análisis de su importancia clínica, justificando su uso y probable influencia en los resultados clínicos.

La relativa sencillez e inocuidad de las maniobras facilita su aplicación en el manejo clínico diario de estos pacientes y la información encontrada puede servir de base para futuros estudios y ampliar su uso en otro tipo de pacientes y patologías.

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A mis fuerzas y mi todo; mi Hijo.

LISTADO DE ABREVIACIONES

CRF: capacidad funcional residual

Crs: compliancia estática del sistema respiratorio

EELV: volumen pulmonar al final de la espiración, *del ingles, end-expiratory Lung Volume*

$EtCO_2$: dióxido de carbono exhalado al final de la espiración

FiO_2: fracción inspirada de oxigeno

FC: frecuencia cardiaca

PaO_2: Presión parcial de oxigeno en sangre arterial

$PaCO_2$: Presión parcial de dióxido de carbono en sangre arterial

PAM: presión arterial media

PBW: Peso Predicho

PEEP: Presión positiva al final de la espiración

PEEPi: Presión positiva intrínseca al final de la espiración

Pmedia: presión media

PP: Posición prono

Ppeak: presión pico

Pplat: presión plateau

$P(a\text{-}et)CO_2$: gradiente de CO_2 entre valor arterial y valor exhalado

Raw: resistencia de vías aéreas

SDRA: Síndrome de distres respiratorio agudo

UCIs: Unidades de Cuidados Intensivos

Vd_{fis}: espacio muerto fisiológico

Vd/Vt: fracción de espacio muerto

VM: Ventilación mecánica

Vrec: volumen pulmonar reclutado inducido por la PEEP, *del ingles, PEEP-induced lung volumen recruitment*

Vt: Volumen corriente

∆Paw: presión de distensión estática del sistema respiratorio.

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1. RESUMEN

Los estudios realizados en la presente tesis están alineadas en determinar los efectos fisiológicos de dos estrategias utilizadas en pacientes en ventilación mecánica con insuficiencia respiratoria aguda severa. Las estrategias analizadas son habitualmente utilizadas en estos pacientes. El primer estudio presentado es sobre el alargamiento de la pausa inspiratoria. En este estudio se ha confirmado que el alargamiento de la pausa inspiratoria disminuye significativamente el espacio muerto y la $PaCO_2$. Con este estudio, se proporciona una aplicación clínica de esta estrategia, ya que, la disminución de la $PaCO_2$ permite disminuir el volumen corriente administrado y ayudar a la ventilación protectiva. El segundo estudio presentado es sobre la variación de los volúmenes pulmonares y el *strain* (deformación del tejido pulmonar causado por el cambio de volumen) con el cambio de posición de supino a prono. Este estudio ha permitido demostrar que los volúmenes pulmonares aumentan significativamente en la posición prono y disminuye significativamente el *strain* dinámico sobre el tejido pulmonar. Estos hallazgos pueden explicar la mejoría de los resultados clínicos con el uso de la posición prono en pacientes con síndrome de distres respiratorio agudo grave. La relativa sencillez e inocuidad de las estrategias estudiadas facilita su aplicación en el manejo clínico diario de estos pacientes y la información encontrada puede servir de base para futuros estudios y ampliar su uso en otro tipo de pacientes y patologías.

2. RESUMEN EN INGLES

The studies described in this thesis are about the physiological effects of two common strategies that are used in mechanically ventilated patients with acute severe respiratory failure. The first study was about the prolongation of inspiratory pause. This study confirmed that the prolongation of inspiratory pause significantly decreased dead space and $PaCO_2$. Indeed, this study provides a clinical application of this strategy, because the decrease of the $PaCO_2$ allows a significant decrease of tidal volume and helps to set the protective ventilation. The second study analysed the variation of lung volumes and *strain* with the change from supine position to prone position. This study showed a significant increase in lung volumes and a significant decrease of *strain* in prone position. These findings could explain the improvement of outcomes with prone position in severe acute respiratory distress syndrome patients. The relative simplicity and safety of these strategies facilitates its application at the bedside. These data could form the basis for future studies in other types of patients and pathologies.

3. INTRODUCCIÓN

La insuficiencia respiratoria aguda es consecuencia de una alteración en el intercambio gaseoso que produce una incapacidad de mantener niveles correctos de presión parcial de oxigeno (PaO_2) y de presión parcial de dióxido de carbono ($PaCO_2$) en sangre arterial.

En los pacientes en los que, a pesar del aporte externo de oxigeno y el tratamiento de la enfermedad desencadenante, persiste la insuficiencia respiratoria y se acompaña con deterioro clínico (apnea, fatiga muscular, alteración de consciencia, disnea extrema, trastornos hemodinámicos, etc) que no permite mantener un equilibrio gasométrico y acido-base adecuado, se debe considerar el inicio de ventilación mecánica (VM).

La VM es uno de los procedimientos más comunes en las unidades de cuidados intensivos. En pacientes con insuficiencia respiratoria aguda la VM se convierte en la base fundamental de su tratamiento. El objetivo inicial de la VM es ayudar en el intercambio gaseoso y reducir el trabajo respiratorio, mientras se resuelva la patología de base que causó la necesidad de su inicio. Sin embargo, su uso por tiempo prolongado se relaciona con complicaciones y peores desenlaces clínicos.

Esteban et al. (1-3) diseñaron 3 estudios de cohortes sobre el uso de la VM y los resultados clínicos de pacientes ingresados en las unidades de cuidados intensivos (UCIs) en los años 1998, 2004 y 2010. Estos estudios evidenciaron un aumento progresivo del uso de la ventilación mecánica no invasiva y el uso de volúmenes corrientes mas pequeños con el paso de los años. El último estudio realizado en el 2010 (3) evidenció que el 35% de pacientes ingresados en las unidades de cuidados necesitaron VM y el 54% de pacientes en VM

desarrollaron al menos una complicación relacionada con VM. En este mismo estudio, se demostró que la modalidad ventilación asistida controlada por volumen es el modo mas utilizado seguido por la ventilación con presión de soporte. Los tres estudios del mismo grupo de investigación (1-3) demostraron una disminución progresiva de la mortalidad de los pacientes en VM siendo del 31% en 1998 al 28% en el año 2010.

La expresión más catastrófica de la insuficiencia respiratoria aguda es el Síndrome de distres respiratorio agudo (SDRA). El SDRA se caracteriza por un edema alveolar a causa de un aumento de la permeabilidad de la membrana alveolo capilar que produce hipoxemia, junto con una disminución del volumen pulmonar y de la compliancia del sistema respiratorio (Crs) (4, 5). Desde su definición inicial realizada por Ashbaugh et al. (6) in 1967, múltiples definiciones han sido publicadas por diferentes consensos de expertos. La definición actual se basa en el último consenso de expertos realizado en el año 2012 (7). Esta definición llamada la "clasificación del SDRA de Berlín" disminuye las limitaciones de anteriores definiciones, que no tenían en cuenta los distintos niveles de gravedad, y añadir como requisito la presencia de parámetros ventilatorios mínimos (PEEP de al menos 5 cmH_2O) para su identificación. La clasificación de Berlín se basa en 4 pilares fundamentales; 1) la presencia de una causa que explique la enfermedad en un periodo de 1 semana, 2) opacidades bilaterales en la radiografía de tórax no explicada por derrames, colapso pulmonar o nódulos, 3) edema alveolar no explicado por falla cardiaca o sobrecarga hídrica y 4) intercambio gasométrico que la subdivide en 3 categorías: SDRA leve con PaO_2/FIO_2 >200 mmHg y ≤ 300 mmHg con presión positiva al final de la espiración (PEEP) ≥ 5 cmH_2O, SDRA moderado con

PaO_2/FIO_2 >100 mmHg y ≤ 200 mmHg con PEEP >5 cmH_2O y SDRA Severo con PaO_2/FIO_2 ≤ 100 mmHg con PEEP >5 cmH_2O.

Recientemente Bellani et al. (8), realizaron un estudio multicéntrico que incluyó a todos los pacientes con ventilación mecánica durante 4 semanas consecutivas en UCIs de todo el mundo. Este estudio evidenció que el 10.4% de los pacientes incluidos cumplieron los criterios de SDRA según la definición de Berlín. La prevalencia fue del 30%, 47% y 23% para SDRA leve, moderado y severo respectivamente. En este estudio la gravedad del SDRA se asoció con un mayor numero de días de VM y de días en las UCIs. De igual manera la mortalidad se asoció con la severidad del SDRA siendo: del 30%, 35% y 43% para el SDRA leve, moderado y severo respectivamente.

El uso de adecuados parámetros ventilatorios y estrategias ventilatorias es fundamental para disminuir el daño pulmonar inducido por la ventilación y mejorar los desenlaces clínicos. En este contexto, la denominada ventilación mecánica protectiva que consiste en el uso de volúmenes corrientes (Vt) bajos y niveles de PEEP moderados-altos se ha relacionado con una disminución de la mortalidad (9, 10). Sin embargo, el uso de Vt bajos puede producir hipercapnia y secundariamente hipertensión pulmonar con disfunción ventricular derecha (11) y eventualmente cor pulmonar agudo (12). El aumento de la frecuencia respiratoria y el uso de humidificadores activos han sido descritos como opciones para disminuir la hipercapnia (13, 14). Otra maniobra que ha demostrado aumentar significativamente la eliminación de la $PaCO_2$ disminuyendo la hipercapnia y el espacio muerto fisiológico es el alargamiento de la pausa inspiratoria (15-20). Estos trabajos sobre el alargamiento de la pausa inspiratoria han estudiado los efectos fisiológicos de ésta maniobra en el

intercambio gaseoso pero no han explorado su potencial uso clínico. De esta manera, la primera estrategia estudiada en la presente tesis es el uso clínico que puede tener el alargamiento de la pausa inspiratoria. Considerando que el alargamiento de la pausa inspiratoria disminuye de la $PaCO_2$, esta estrategia permitiría una disminución del Vt administrado, constituyendo otra herramienta para ayudar en la ventilación mecánica protectiva y con los consecuentes beneficios en la mecánica respiratoria de los pacientes con SDRA.

Otra estrategia que ha demostrado mejorar los desenlaces clínicos en pacientes con SDRA grave es la posición prono (PP) (21). La mejoría en los desenlaces clínicos no parece estar relacionado con la mejoría de la oxigenación (22), sino también a un efecto protector en la lesión inducida por la ventilación (22-24). La PP produce una distribución homogénea del gas inspirado mejorando el índice ventilación perfusión (25) y actúa de manera sinérgica con la PEEP disminuyendo el porcentaje de tejido pulmonar no aireado y pobremente aireado (26-28). La PEEP ayuda también a mantener reclutamiento alveolar (29). El volumen pulmonar reclutado inducido por la PEEP, "*del ingles, PEEP-induced lung volume recruitment* (Vrec)" puede ser medido mediante tomografía axial computarizada (30), curvas de presión volumen (31) o el método de lavado de nitrógeno (32). En la actualidad la información sobre la variación del Vrec con el cambio de posición de supino a prono es escasa.

El uso de la PP ha aumentado con el paso de los años. Bellani et al. (8) en un estudio multicéntrico observacional sobre VM en pacientes con SDRA encontraron un uso de niveles de PEEP de alrededor de 12 cmH_2O y que se utilizó la PP en el 16% de pacientes con SDRA grave. En un estudio mas

reciente realizado por Guerin et al. (33) sobre el uso de PP en pacientes con SDRA evidenció un uso de PP en el 6%, 10% y 33% de pacientes con SDRA leve, moderado y severo respectivamente, una duración de la primera sesión de prono de 18 horas y con un 12% de complicaciones (ulceras, hipoxemia, aumento de presión intracraneal, lesiones oculares y retiro o movilización accidental del tubo endotraqueal).

La PP puede aumentar los volúmenes pulmonares y de esta manera disminuir la tensión excesiva y deformación del tejido pulmonar determinados por el stress (presión transpulmonar) y *strain* (por el cambio de volumen pulmonar) (34, 35). Los dos volúmenes pulmonares que han sido estudiados con el cambio de posición en trabajos previos son el volumen pulmonar al final de la espiración (volumen pulmonar medido con PEEP) "*del ingles, end-expiratory Lung Volume* (EELV)" y la capacidad residual funcional (CRF) (36-40). Sin embargo, la información sobre la variación de los volúmenes en pacientes con SDRA con el cambio de posición es contradictoria. De igual manera, un solo estudio (27) ha analizado la variación del Vrec con el cambio de posición, sin encontrar diferencias del Vrec en ambas posiciones. En este contexto, y considerando que esta información es fundamental para comprender los efectos fisiológicos de la posición prono, la segunda estrategia estudiada en la presente tesis es la variación de los volúmenes pulmonares, del Vrec y del *strain* con el cambio de posición. Estos hallazgos ayudarían a explicar uno de los mecanismos protectores de la PP y su influencia en los desenlaces clínicos.

4. HIPÓTESIS

El análisis de los efectos fisiológicos y la aplicación clínica de las dos estrategias estudiadas pueden facilitar la ventilación mecánica protectiva y explicar la influencia en los desenlaces clínicos de los pacientes con insuficiencia respiratoria aguda severa. El alargamiento de la pausa inspiratoria puede permitir disminuir significativamente el volumen corriente administrado manteniendo los mismos niveles de $PaCO_2$. La posición prono, puede aumentar los volúmenes pulmonares y disminuir el *strain* en el tejido pulmonar constituyendo un mecanismo que podría explicar la mejoría de los desenlaces clínicos.

5. OBJETIVOS

OBJETIVO PRINCIPAL

Analizar los efectos fisiológicos de dos estrategias ventilatorias empleadas en pacientes con insuficiencia respiratoria aguda severa

OBJETIVOS SECUNDARIOS

1. Confirmar que el alargamiento de la pausa inspiratoria disminuye significativamente la $PaCO_2$ y proporcionar una aplicación clínica de esta maniobra al disminuir significativamente el volumen corriente administrado.
2. Estudiar la variación de los volúmenes pulmonares y del *strain* en el tejido pulmonar inducido por el cambio de posición de decúbito supino a decúbito prono.

6. MÉTODOS

Todos los pacientes incluidos en los dos estudios cumplieron los criterios para ADRS según la clasificación de Berlín (7). Fueron excluidos pacientes con <18 años, embarazadas, pacientes con inestabilidad hemodinámica o térmica (variación de temperatura mayor de 0.5ºC en la última hora). Todos los pacientes estuvieron con sedación, analgesia continua y bloqueantes neuromusculares. Los estudios fueron realizados en la UCI del Hospital de la Santa Creu i Sant Pau, Barcelona (España). El comité de ética institucional aprobó los estudios y los pacientes o sus familiares firmaron el consentimiento informado.

En el estudio de alargamiento de la pausa inspiratoria se incluyeron 14 pacientes. Un paciente fue excluido por presentar fiebre, taquipnea e inestabilidad del dióxido de carbono exhalado al final de la espiración ($EtCO_2$). El protocolo del estudio constó de 3 fases consecutivas:

1. Primera fase (Fase basal): Medidas realizadas con parámetros basales pautados por el médico responsable.
2. Segunda fase (Alargamiento de pausa inspiratoria): La pausa inspiratoria fue alargada hasta obtener uno de los siguientes parámetros: a)pausa inspiratoria de 0.7sg, b)PEEP intrínseca ≥ 1cmH_2O o c) Relación inspiración-espiración de 1:1.
3. Tercera Fase (disminución de Vt): Disminución progresiva de Vt (de 30ml en 30ml) hasta obtener una $PaCO_2$ similar a la basal.

Se mantuvo a los pacientes durante 60 minutos en cada fase. Las medidas de mecánica respiratoria, intercambio de gases y hemodinámia fueron recogidas

al final de cada fase. La medición del espacio muerto se realizó mediante la recolección del aire espirado durante 3 minutos en la bolsa de Douglas y fue calculado usando la modificación de Enghoff de la ecuación de Bohr (41): Vd/Vt= (PaCO2 – PeCO2)/PaCO2.

En el estudio de volúmenes pulmonares se incluyeron a 23 pacientes, 1 paciente fue excluido por presentar hipoxemia durante el estudio y 2 pacientes fueron excluidos por problemas técnicos en la medición de los volúmenes pulmonares.

Debido a que en una fase del estudio consiste medidas de volúmenes sin PEEP, para evitar la hipoxemia durante esta fase, los pacientes fueron incluidos cuando tenían una mejoría de su intercambio gaseoso ($FiO_2 \leq 0.6$ and PEEP ≤ 12 cmH_2O) y se incrementó la FiO_2 a 0.8 una hora antes del inicio del estudio.

Los parámetros ventilatorios pautados y la indicación de pronación en estos pacientes fue realizada por el medico responsable y de acuerdo al protocolo del Servicio. Los parámetros ventilatorios, de intercambio gaseoso y hemodinámicos fueron registrados justo antes de empezar el protocolo. El protocolo del estudio constó de 4 pasos consecutivos:

1. Medida del EELV, corresponde al volumen pulmonar con PEEP.
2. Retiro de PEEP.
3. Medida de CRF, corresponde al volumen pulmonar sin PEEP.
4. Medida del Vt necesario para generar una Presión Plateau igual a la PEEP basal (ver Figura 1) (31, 32, 42-44).

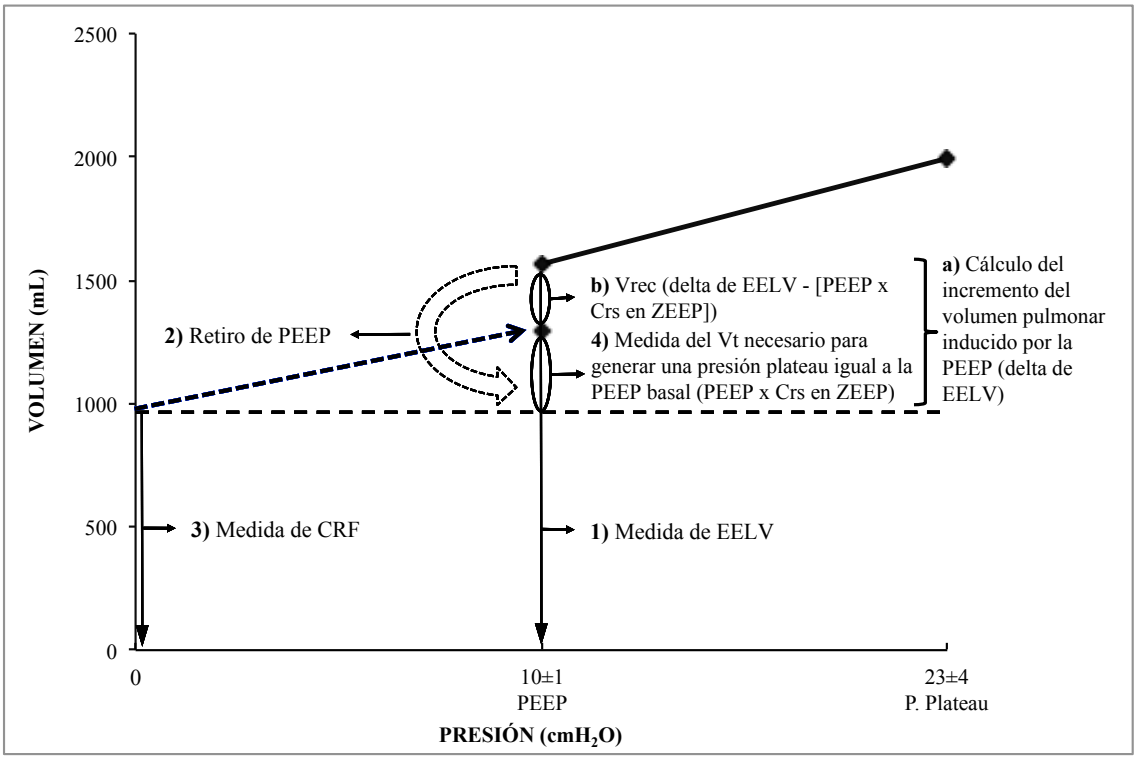
Al finalizar el paso 4, se volvió a pautar la PEEP basal. Estos pasos fueron realizados primero en posición supino, luego el paciente fue colocado en posición prono y una hora después se realizaron los mismo pasos en posición prono.

El resto de volúmenes pulmonares y el *strain* se calcularon con las siguientes ecuaciones (32, 45, 46):

a) Incremento del volumen pulmonar inducido por la PEEP (o delta de EELV) = EELV – CRF.
b) Vrec = Incremento del volumen pulmonar inducido por la PEEP – Vt necesario para generar una Presión Plateau igual a la PEEP (también se puede expresar como delta de EELV – [PEEP x Crs en ZEEP]).
c) *Strain* Dinámico sin PEEP = Vt / CRF.
d) *Strain* Dinámico con PEEP = Vt / (CRF + Vrec).
e) *Strain* Estático con PEEP = (EELV – CRF) / (CRF + Vrec)
f) *Strain* Global con PEEP = (*strain* estático con PEEP + *strain* dinámico) = (EELV – CRF + Vt) / (CRF + Vrec).

Los volúmenes pulmonares fueron medidos con la técnica de lavado de nitrógeno *"washout/washin"* como ha sido descrito previamente (32, 47).

Figura 1. Volúmenes pulmonares, medidas y cálculos realizados en el estudio. Los números de 1 a 4 corresponden a los pasos y medidas realizadas. Las letras a y b corresponden a los cálculos derivados de las medidas realizadas.



7. ARTÍCULOS ORIGINALES ACEPTADOS POR LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO EN MEDICINA E INCLUIDOS EN LA TESIS

PRIMER ARTÍCULO

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End-inspiratory pause prolongation in acute respiratory distress syndrome patients: effects on gas exchange and mechanics

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Abstract

Background: End-inspiratory pause (EIP) prolongation decreases dead space-to-tidal volume ratio (Vd/Vt) and $PaCO_2$. We do not know the physiological benefits of this approach to improve respiratory system mechanics in acute respiratory distress syndrome (ARDS) patients when mild hypercapnia is of no concern.

Methods: The investigation was conducted in an intensive care unit of a university hospital, and 13 ARDS patients were included. The study was designed in three phases. First phase, baseline measurements were taken. Second phase, the EIP was prolonged until one of the following was achieved: (1) EIP of 0.7 s; (2) intrinsic positive end-expiratory pressure $\geq$1 cmH_2O; or (3) inspiratory–expiratory ratio 1:1. Third phase, the Vt was decreased (30 mL every 30 min) until $PaCO_2$ equal to baseline was reached. FiO_2, PEEP, airflow and respiratory rate were kept constant.

Results: EIP was prolonged from 0.12 ± 0.04 to 0.7 s in all patients. This decreased the Vd/Vt and $PaCO_2$ (0.70 ± 0.07 to 0.64 ± 0.08, $p < 0.001$ and 54 ± 9 to 50 ± 8 mmHg, $p = 0.001$, respectively). In the third phase, the decrease in Vt (from 6.3 ± 0.8 to 5.6 ± 0.8 mL/Kg PBW, $p < 0.001$) allowed to decrease plateau pressure and driving pressure (24 ± 3 to 22 ± 3 cmH_2O, $p < 0.001$ and 13.4 ± 3.6 to 10.9 ± 3.1 cmH_2O, $p < 0.001$, respectively) and increased respiratory system compliance from 29 ± 9 to 32 ± 11 mL/cmH_2O ($p = 0.001$). PaO_2 did not significantly change.

Conclusions: Prolonging EIP allowed a significant decrease in Vt without changes in $PaCO_2$ in passively ventilated ARDS patients. This produced a significant decrease in plateau pressure and driving pressure and significantly increased respiratory system compliance, which suggests less overdistension and less dynamic strain.

Keywords: End-inspiratory pause, Dead space, Tidal volume, Acute respiratory distress syndrome, Mechanical ventilation

Background

Mechanical ventilation in patients with acute respiratory distress syndrome (ARDS) must combine both low tidal volumes (Vt) and adequate positive end-expiratory pressure (PEEP) [1, 2]. However, in patients with ARDS, respiratory acidosis and high airway plateau pressures (P_{plat}) may limit management of ventilatory adjustments. In particular, the functional consequences of hypercapnia and respiratory acidosis may differ considerably depending on a patient's condition, and they may involve almost any physiological function [3–6].

Optimization of mechanical ventilation parameters is associated with a reduction in dead space and is a useful strategy to reduce hypercapnia in ARDS patients [7]. Many other strategies have also been developed to decrease hypercapnia at the bedside, such as increases in respiratory rate [8], use of active humidifiers [9] and the tracheal gas insufflation [10] or aspiration of dead space [11]. At bedside, the dead space could be calculated using the Enghoff modification of the Bohr equation. The use of this equation implies the use of $PaCO_2$ as surrogate for

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alveolar carbon dioxide. Therefore, this equation measures a global index of efficiency of gas exchange because it takes also shunt effect into account [12].

Some authors have also shown that prolonging the end-inspiratory pause (EIP) is a feasible maneuver to achieve similar targets [13, 14]. In experimental models [15] and in ARDS patients [14, 16–18], EIP prolongation has proven effective at enhancing CO_2 elimination and decreasing partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and also physiological dead space (Vd_{phys}). Prolonging EIP extends the time available for an enhanced diffusion between inhaled Vt and resident alveolar gas, thus facilitating the transfer of CO_2 from alveoli toward the airways [17, 18].

Although several of the physiological studies described above have reported that EIP prolongation improves gas exchange, none have investigated the potential physiological benefits of this approach in terms of Vt reduction or improved respiratory system mechanics when hypercapnia is of no concern. To address this gap, the objective of our study was to ascertain whether EIP prolongation decreases $PaCO_2$ and whether this effect can be used to decrease Vt while keeping $PaCO_2$ constant. We hypothesized that this approach may have beneficial effects on respiratory system mechanics in ARDS patients.

Methods

The study was performed in the Intensive Care Unit at Hospital de la Santa Creu i Sant Pau, Barcelona (Spain). The institutional ethics committee approved the study (Reference: 10/089), and the patients' relatives gave signed informed consent.

Patients

Fourteen patients who met the criteria for ARDS [19] were included in the study. Exclusion criteria were: age <18 years, pregnancy, hemodynamic or respiratory instability, and variation of more than 0.5 °C in body temperature in the last 12 h before the study was planned [20]. One patient was excluded during the study period (see Results).

All patients were under sedation and analgesia with intravenous perfusion of midazolam and opiates. Neuromuscular blockade was used in all patients to prevent triggering of the ventilator. Careful endotracheal suctioning was performed before the protocol was started. Heated humidifiers (Fisher & Paykel; MR 290 chamber and MR 850 ALU electric heater; Panmure, New Zealand) were used for airway humidification in all patients. These humidifiers were placed in the inspiratory limb of the circuit in accordance with the manufacturer's recommendations. The respiratory rate, FiO_2, inspiratory flow (square pattern) and PEEP were kept constant throughout the study.

Protocol

All patients were in steady state in the 60-min preceding data recording, and all of them were in a semirecumbent position. The study was performed in three consecutive 30-min phases. Measurements in the first phase (baseline phase) were taken under the mechanical ventilation parameters set by the patient's attending physician. In the second phase (EIP prolongation phase), the EIP was prolonged until one of the following parameters was reached: (1) EIP of 0.7 s; (2) intrinsic positive end-expiratory pressure (PEEPi) $\geq$1 cmH_2O; or (3) inspiratory–expiratory ratio (I/E) of 1:1. We chose the EIP prolongation time (0.7 s) based on findings from a previous study by Devaquet et al. [18] in which a 20 % prolongation of the inspiratory time induced a significant decrease in $PaCO_2$ and dead space. In the third phase (Vt reduction phase), the Vt was diminished in steps of 30 mL every 30 min until $PaCO_2$ reached baseline levels.

The following data were collected at inclusion: demographic variables (age, sex, height), simplified acute physiology score II, ARDS etiology and days of mechanical ventilation.

During the last minute of each phase, we collected the following respiratory variables: peak airway pressure, Pplat, mean airway pressure, PEEPi, PEEP, driving airway pressure (ΔPaw), Vt, dead space-to-Vt ratio (Vd/Vt), static compliance of the respiratory system (Crs) and airway resistance. At the same time, we recorded the following gas exchange variables: pH, partial pressure of arterial oxygen (PaO_2), $PaCO_2$ and end-tidal carbon dioxide concentration in the mixed expired gas ($EtCO_2$). PEEPi was measured with a prolonged end-expiratory pause of 4 s, performed using the ventilator expiratory hold button. $EtCO_2$ was measured continuously with a CO_2 mainstream sensor (General Electric Capnostat, Milwaukee, WI, USA). The mean value of the last 10 recorded $EtCO_2$ values in each phase of the study was used for analysis.

Ventilatory settings and airway pressures were recorded directly from the ventilator monitoring system. Plateau pressure was measured during an end-inspiratory pause. Dead space was calculated using the Enghoff modification of the Bohr equation [21]: $Vd/Vt = (PaCO_2 - PeCO_2)/PaCO_2$, being $PeCO_2$ the partial pressure of carbon dioxide in mixed expired gas. Expired gas was measured by collecting gas for 3 min with a Douglas bag (P-341–60; Warren E. Collins Inc., Boston, MA, USA) attached directly to the expiratory port of the ventilator. An automated analyzer (ABL 520; Radiometer A/S, Copenhagen, Denmark) was used to measure expired and arterial gases. Dead space data

were expressed as physiological dead space (Vd_{phys} in mL), defined as the sum of instrumental, anatomic and alveolar dead space [22]. Driving pressure (cmH_2O) was calculated as Pplat-PEEP. Crs (mL/cmH_2O) was calculated as Vt/[Pplat-(PEEP + PEEPi)], and airway resistance ($cmH_2O/L/s$) was calculated as (peak airway pressure − plateau pressure)/Flow. Predicted body weight (PBW) was calculated as follows: 50 + 0.91(height in cm-152.4) for men and 45.5 + 0.91(height in cm-152.4) for women [8]. Arterial to end-tidal CO_2 gradient (P(a-et)CO_2) was calculated in each study phase. We used Puritan Bennett™ 840 (Covidien, Galway, Ireland) and Dräger Evita XL (Dräger Medical, Lübeck, Germany) ventilators. All the ventilators used have a compressible volume compensation system.

Statistical analysis

Data are expressed as mean ± standard deviation. The results were analyzed using one-way analysis of variance for repeated measures (ANOVA) with the Greenhouse–Geisser correction. We performed the Kolmogorov–Smirnov test to confirm normal data distribution. Since the distribution of the data was normal, we used the Student's *t* test and the Pearson linear correlation to compare data and correlations between phases and variables, respectively. A two-tailed *p* value less than 0.05 was considered statistically significant. The SPSS® Statistics (version 20.0, Chicago, IL, USA) statistical software was used for statistical analysis.

Results

One of the 14 patients enrolled in the study was excluded from the analysis due to fever, tachypnea and unstable $EtCO_2$ during the second phase of the study. The study was performed 5 ± 4 days after starting mechanical ventilation. Table 1 shows demographic data at admission, ARDS etiology and baseline characteristics at study day.

Baseline EIP was 0.12 ± 0.04 s, and it was increased to 0.7 ± 0 s in all patients ($p < 0.001$). This EIP change was performed maintaining PEEPi <1 cmH_2O (0.2 ± 0.2 to 0.5 ± 0.4 cmH_2O, $p = 0.06$) and without the I/E inverse ratio ventilation (1:4.7 ± 0:1.3 to 1:1.7 ± 0:0.4, $p = <0.001$). EIP prolongation decreased Vd_{phys} and $PaCO_2$ significantly with respect to basal conditions (267 ± 71 to 244 ± 65 mL and 54 ± 9 to 50 ± 8 mmHg, respectively; $p < 0.001$ for both comparisons). The decrease in $PaCO_2$ levels due to EIP prolongation was correlated with the drop in Vd_{phys} ($r = 0.871$; $p < 0.001$). Individual changes in $PaCO_2$ and in Vd_{phys} are shown in Figs. 1 and 2, respectively.

Between the first and second phase, significant decreases were observed in both the Vd/Vt ratio (0.70 ± 0.07 to 0.64 ± 0.08; $p < 0.001$) and $EtCO_2$ (41 ± 6 to 39 ± 6 mmHg; $p = 0.006$). Basal Vd_{phys} and P(a-et)CO_2 had a close correlation ($r = 0.75$; $p = 0.003$). The change in Vd_{phys} and the change in P(a-et)CO_2 between the first and second phase also showed a close correlation ($r = 0.68$; $p = 0.001$).

In the third phase (EIP prolongation and Vt reduction), the Vt was significantly reduced as compared to previous phases (6.3 ± 0.8 to 5.6 ± 0.8 mL/Kg PBW; $p < 0.001$). In the third phase, as per protocol design, the $PaCO_2$ and pH values were statistically identical to those at baseline (54 ± 9 vs. 54 ± 10 mmHg; $p = 0.90$ and 7.31 ± 0.07 vs. 7.31 ± 0.08; $p = 0.90$, respectively).

The Vd_{phys} decreased progressively and significantly during all phases of the study (267 ± 71 to 244 ± 65 to 216 ± 58 mL; $p < 0.001$). The Vd_{phys} and Vt at baseline were strongly correlated ($r = 0.946$; $p < 0.001$). Additionally, the Vt reduction was tightly correlated with the decrease in Vd_{phys} ($r = 0.894$; $p < 0.001$). Respiratory system mechanics, gas exchange, hemodynamics, and temperature data throughout the study are also given in Table 2.

Discussion

The main finding of our study was that the end-inspiratory pause prolongation allowed to decrease tidal volume while maintaining similar $PaCO_2$ levels. Indeed, the decrease in tidal volume led to a significant decrease in Pplat and ΔPaw, and it also improved the respiratory system compliance.

Several studies have shown that prolongation of EIP enhances CO_2 elimination and decreases dead space and $PaCO_2$ levels [14–18]. Diffusion of CO_2 is time dependent, and EIP prolongation increases the time available for alveolar gas exchange [14, 23, 24]. Devaquet et al. [18] extended inspiratory time from 0.7 ± 0.2 to 1.4 ± 0.3 s by increasing the inspiratory pause time from 0 to 20 % of the total breathing cycle. They observed that this modification significantly decreased both Vd/Vt (around 10 %) and $PaCO_2$ (around 11 %). Despite these beneficial effects of prolonged EIP and the direct relationship between inspiratory time and enhanced CO_2 elimination [16, 18], EIP prolongation may lead to potentially adverse effects such as PEEPi production and inversion of the I/E ratio together with increases in mean airway pressure. These effects might also provoke hyperinflation, thus altering cardiac performance [25, 26]. Nevertheless, Devaquet and colleagues [18] showed that EIP could be prolonged without significantly increasing PEEPi (I/E ratio 1:1.5). Not surprisingly, and in spite of a significant increase in EIP, we did not induce any significant increase in PEEPi since the expiratory time was long enough to avoid air trapping at the end of a passive expiration (average expiratory time 1.7 ± 0.3 s). Actually (see Table 2), the average product of three time constants (the time needed to

Table 1 Demographic data at admission and baseline characteristics of patients on the study day

Admission							Study day					
Patient	Age (years)	Gender	SAPS II	PBW (kg)	Measured weight (kg)	ARDS etiology	Days of MV before study	PaO2/FiO2 (mmHg)	FiO2a	PEEP (cmH_2O)[a]	Flow (L/min)[a]	RR (bpm)[a]
1	75	M	59	67.7	58.5	Pneumonia	8	112	0.7	10	70	22
2	52	M	42	68.7	78	Aspiration	13	185	0.65	12	57	20
3	46	F	30	52.4	61	Multiple Trauma	7	118	0.7	12	60	25
4	62	F	69	47.9	55	Pneumonia	5	131	0.6	10	60	25
5	56	F	23	52.4	61.5	Pneumonia	3	100	0.8	12	60	22
6	66	M	40	63.2	72.5	Pneumonia	1	184	0.5	10	60	20
7	57	M	62	69.6	83	Pneumonia	1	147	0.5	8	60	17
8	36	M	24	61.4	90	Pneumonia	4	242	0.5	14	75	23
9	55	M	49	66.8	72	Pneumonia	2	219	0.6	14	70	21
10	51	F	60	43.3	64	Sepsis	12	269	0.4	8	50	21
11	74	F	61	47.9	62.5	Sepsis	1	266	0.5	10	60	21
12	43	M	61	59.6	80.5	Sepsis	3	194	0.7	10	60	22
13	63	M	30	83.1	106	Pneumonia	6	283	0.35	8	60	30
Mean ± SD	57 ± 11		47 ± 16	60.3 ± 11.2	72.6 ± 14.6		5 ± 4	188 ± 64	0.58 ± 0.13	11 ± 2	61 ± 7	22 ± 3

ARDS acute respiratory distress syndrome, FiO_2 fraction of inspired oxygen, *MV* mechanical ventilation, PaO_2/FiO_2 partial pressure of arterial oxygen over fraction of inspired oxygen, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure, *RR* respiratory rate, *SAPS II* simplified acute physiology score II

[a] These settings were kept constant throughout the study

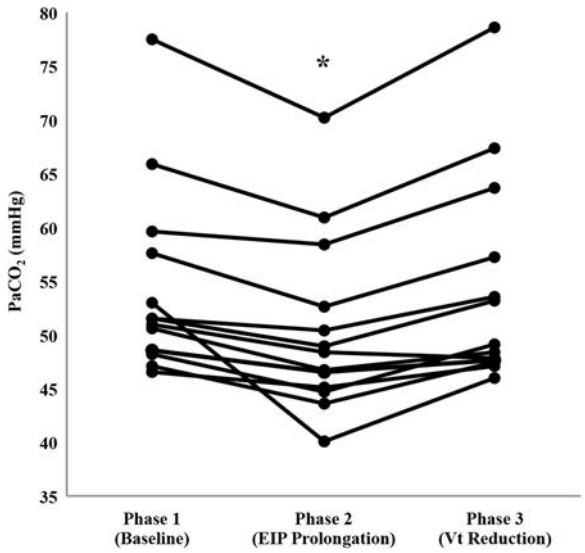

Fig. 1 Individual values for $PaCO_2$ during the study. The *asterisk* denotes statistically significant differences ($p < 0.001$) during prolongation of end-inspiratory pause. *EIP* end-inspiratory pause, *$PaCO_2$* partial pressure of carbon dioxide in arterial blood, *Vt* tidal volume

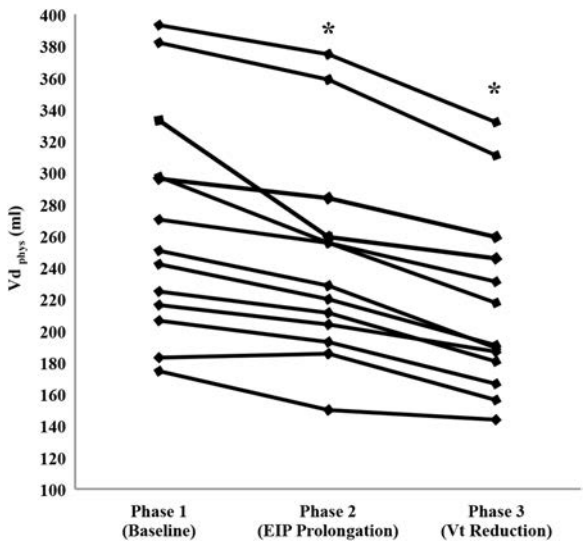

Fig. 2 Individual values for Vd_{phys} during the study. The *asterisks* denote a significant, progressive decrease in Vd_{phys} ($p < 0.001$) during prolongation of end-inspiratory pause (EIP) and during Vt reduction. *EIP* end-inspiratory pause, *Vd_{phys}* physiological dead space, *Vt* tidal volume

passively exhale 96 % of inhaled tidal volume) was in our patients about 1.1 s. ($0.373 \times 3 = 1.1$ s), well below to the average expiratory time.

Prolongation of EIP in our patients caused a significant decrease in dead space and $PaCO_2$ levels that was similar to previously reported [14–18]. When comparing phase 1 (baseline) and phase 2 (isolated EIP prolongation), we found that the decrease in the Vd/Vt correlated well with the drop in $PaCO_2$ ($r = 0.810$; $p < 0.001$). These changes observed in our patients may be explained by the increase on the time available for distribution and diffusion of inspired tidal gas within resident alveolar gas during EIP prolongation [14]. Indeed, total PEEP levels, airflow, respiratory rate, tidal volume and respiratory mechanics were totally unchanged in this phase of our study [14, 27, 28].

Comparing the second (isolated EIP prolongation) and third (EIP prolongation and Vt reduction) phases, our data showed that the Vd/Vt ratio remained unchanged. However, the Vd_{phys}, expressed in mL, decreased significantly between phases 2 and 3. This is explained by the significant reduction in Vt (that also provoked a decrease in Vd_{phys}) during the third phase as compared to the previous phases, and thus Vd/Vt ratio did not change. The fact that the reduction in Vt in the third phase was accompanied by a significant decrease in Vd_{phys} and ΔPaw (with a significant increase in compliance) suggests that some degree of overdistension might be present at baseline.

As previously described, low tidal volume ventilation in ARDS may induce hypercapnia and, secondarily, induce pulmonary artery hypertension that may impair right ventricular function [29] and eventually cause acute cor pulmonale [30]. To reduce hypercapnia in ARDS ventilated patients, active heated humidifiers are often used. These devices significantly decrease dead space, $PaCO_2$ and ventilator mechanical load [9] without increasing airflow resistance [31]. Although active humidification is recommended over heat and moisture exchangers in ARDS patients [32], two studies focussing on the effects of EIP prolongation on gas exchange [16, 17] did not describe the type of humidification used in their patients. A third study used passive or active humidification (10 and 5 patients, respectively) [18]. However, the effects on $PaCO_2$ in all these studies [16–18] were consistently the same, thus suggesting that humidification type per se does not influence the effects of EIP on $PaCO_2$.

Another technique used to decrease hypercapnia is to increase the respiratory rate. However, in ARDS patients, several studies have shown that a high respiratory rate led to gas trapping and induced PEEPi [33, 34]. In addition, experimental models suggested that higher respiratory rates may contribute to the development of ventilator-induced lung injury [35, 36]. Vieillard-Baron et al. [25] compared two respiratory rate strategies, 30 versus 15 breaths/min. They found that the high respiratory rate did not reduce $PaCO_2$ levels but produced dynamic hyperinflation and reduced the cardiac index. In our patients, EIP prolongation was achieved with a relatively

Table 2 Respiratory system mechanics, gas exchange and hemodynamic data during the study

	Phase 1 (baseline)	Phase 2 (EIP prolongation)	Phase 3 (Vt reduction)	Overall *p* value	Intergroup differences
EIP (s)	0.12 ± 0.04	0.7 ± 0	0.7 ± 0	<0.001	a, b
Ppeak (cmH_2O)	38 ± 6	38 ± 6	35 ± 5	<0.001	b, c
Pmean (cmH_2O)	15 ± 3	18 ± 2	17 ± 2	<0.001	a, b, c
Pplat (cmH_2O)	24 ± 3	24 ± 3	22 ± 3	<0.001	b, c
PEEPi (cmH_2O)	0.2 ± 0.2	0.5 ± 0.4	0.5 ± 0.4	0.06	
Vt (mL)	378 ± 73	378 ± 73	336 ± 61	<0.001	b, c
Vt (PBW; mL/Kg)	6.3 ± 0.8	6.3 ± 0.8	5.6 ± 0.8	<0.001	b, c
Vd_{phys} (mL)	267 ± 71	244 ± 65	216 ± 58	<0.001	a, b, c
Vd/Vt	0.70 ± 0.07	0.64 ± 0.08	0.64 ± 0.08	<0.001	a, b
Crs (mL/cmH_2O)	29 ± 9	29 ± 9	32 ± 11	0.001	b, c
Δ Paw (cmH_2O)	13.6 ± 3.6	13.4 ± 3.6	10.9 ± 3.1	<0.001	a, b, c
R_{aw} ($cmH_2O/L/s$)	14 ± 5	13 ± 5	13 ± 4	0.28	
pH	7.31 ± 0.07	7.34 ± 0.09	7.31 ± 0.08	<0.001	a, c
PaO_2 (mmHg)	102 ± 23	98 ± 23	105 ± 29	0.35	
$PaCO_2$ (mmHg)	54 ± 9	50 ± 8	54 ± 10	<0.001	a, c
$EtCO_2$ (mmHg)	41 ± 6	39 ± 6	43 ± 7	0.002	a, c
P(a-et)CO_2 (mmHg)	13 ± 6	12 ± 8	12 ± 9	0.27	
MAP (mmHg)	80 ± 12	76 ± 9	77 ± 12	0.08	
HR (beats/min)	87 ± 19	83 ± 20	86 ± 21	0.14	
Temperature (°C)	36.7 ± 0.9	36.7 ± 0.9	36.6 ± 0.8	0.61	

Data are presented as number (%) or mean ± SD

Intergroup differences ($p < 0.05$): a, phase 1 versus phase 2; b, phase 1 versus phase 3; c, phase 2 versus phase 3

Crs static compliance of the respiratory system, *EIP* end-inspiratory pause, $EtCO_2$ end-tidal carbon dioxide concentration in the expired air, FiO_2 fraction of inspired oxygen, *HR* heart rate, *MAP* mean arterial pressure, PaO_2 partial pressure of oxygen in arterial blood, $PaCO_2$ partial pressure of carbon dioxide in arterial blood, *PBW* predicted body weight, *PEEPi* intrinsic positive end-expiratory pressure, *Pmean* mean airway pressure, *Ppeak* peak airway pressure, *Pplat* plateau airway pressure, P(a-et)CO_2 arterial to end-tidal CO_2 gradient, *Raw* airway resistance, Vd_{phys} physiological dead space, *Vd/Vt* dead space-to-Vt ratio, *Vt* tidal volume, *ΔPaw* driving airway pressure

high inspiratory flow rate (1 L/s), thus avoiding inverse I/E ratio. This was a safe strategy to decrease $PaCO_2$ levels, while keeping respiratory rate constant (22 breaths/min) and not generating PEEPi.

In our study, the reduction in Vt to maintain isocapnia was modest. Should major reductions in Vt were required, then the use of invasive extracorporeal carbon dioxide removal devices had to be considered in order to avoid acute hypercapnia [37].

Studies analyzing the EIP prolongation did not describe changes in PaO_2 [14, 18], except one study by Mercat et al. [16]. This latter study found a slight, but not statistically significant, increase in PaO_2 levels during EIP prolongation. This finding was not confirmed in our study. We speculate that the length of time that patients are maintained with EIP prolongation and the mean airway pressure achieved during extended EIP may have contributed to this finding. Indeed, in Mercat's study [16], EIP prolongation was continued for 1 h with a mean airway pressure of 21 cmH_2O and an I/E ratio 1.1. In contrast, in Devaquet's study [18] and in our own study, EIP prolongation was shorter (30 min in both), mean airway pressure was lower (15 and 17 cmH_2O, respectively), and the I/E ratios achieved were 1:1.5 in Devaquet's study and 1:1.7 in ours.

The main novelty of our study is that prolonging EIP allowed to reduce Vt by 11 % (from 6.3 ± 0.8 to 5.6 ± 0.8 mL/kg of PBW; $p < 0.001$), maintaining $PaCO_2$ levels equal to baseline. These sequential ventilatory changes were accompanied by a reduction in Vd_{phys}. Also, when $PaCO_2$ returned to baseline due to a reduction in Vt, we found a significant decrease in Pplat and an increase in Crs. In addition, these changes in ventilatory mechanics were accompanied by a significant decrease in ΔPaw. All those findings could be explained by a degree of baseline overinflation even though our initial Vt was low [38]. We further support our contention by the tight correlation between Vt and Vd_{phys} at the onset of the study and the tight correlation between the decrease in Vt and Vd_{phys} at the end of the study. Our patients were basally ventilated with parameters similar to those used in previous studies [16–18] in terms of Vt and PEEP, and

Vd/Vt was also similar. Moreover, in our patients, Crs was lower (29 mL/cmH_2O) than in Mercat and Devaquet studies (37 and 50 mL/cmH_2O, respectively). Our findings thus suggest that if $PaCO_2$ is clinically tolerable, EIP prolongation in ARDS provides physiological benefits including a small and consistent decrease in Vt which may help decrease dynamic strain [39].

In our study, a slight but not statistically significant decrease in mean arterial pressure was observed. Such trend could have been the result of complex interactions of $PaCO_2$ and mean airway pressure in cardiovascular system.

We think that EIP prolongation is a feasible maneuver to optimize the consequences of mechanical ventilation in ARDS patients. Physicians may consider using an EIP prolongation in the early phase of ARDS when patients often require sedation and neuromuscular blocking agents. In our study, we have effectively implemented this strategy by using active humidification, relatively high inspiratory flow rates and close monitoring of PEEPi. This bundle decreases $PaCO_2$, which in turn will allow to further decrease Vt and the consequent lung strain when isocapnic conditions are met.

One of the limitations of our study is the relatively small number of patients, the majority with pneumonia, and the fact that the study is short term. Studies with patients with different ARDS etiologies and larger numbers are warranted to confirm our data. Also, we did not measure other parameters such as inflammatory mediators or lung volumes. The calculation of dead space using the Enghoff modification of Bohr equation in patients with large shunt fractions (>20–30 %) could underestimate dead space fraction [12]. In our study, we did not measure intrapulmonary shunt. However, according to the gas exchange values that we obtained, shunt fractions above 30 % are unlikely. Additionally, the EIP prolongation increases the mechanical inflation time and it could extend into neural expiration. Asynchronies may thus develop and cause an inadequate patient–ventilator interaction when the patients are not paralyzed [39–41]. Our results could be dependent on our routine management of mechanical ventilation in ARDS patients, but our findings have been consistent in all patients and we consider they could be extrapolated to other ARDS patients. Finally, the absolute decrease in tidal volume, although statistically significant, is moderate.

Conclusions

In conclusion, our data indicate that EIP prolongation is a simple and feasible strategy to decrease dead space and $PaCO_2$ levels. In addition, when $PaCO_2$ levels are of no clinical concern, EIP prolongation allows us to further decrease tidal volume. This, in turn, decreases plateau airway pressure, driving airway pressure and improves respiratory system compliance, suggesting less overdistension and less risk of dynamic strain and lung injury. Therefore, the use of this simple ventilator maneuver during mechanical ventilation in sedated and paralyzed ARDS patients merits consideration.

Abbreviations

ARDS: acute respiratory distress syndrome; Crs: static compliance of the respiratory system; EIP: end-inspiratory pause; $EtCO_2$: end-tidal carbon dioxide concentration in the mixed expired gas; IE: inspiratory–expiratory ratio; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; PaO_2: partial pressure of arterial oxygen; PBW: predicted body weight; $PeCO_2$: partial pressure of carbon dioxide in mixed expired gas; PEEP: positive end-expiratory pressure; PEEPi: intrinsic positive end-expiratory pressure; P_{plat}: plateau airway pressure; P(a-et)CO_2: arterial to end-tidal CO_2 gradient; Vd/Vt: dead space-to-Vt ratio; Vd_{phys}: physiological dead space; Vt: tidal volume; ΔPaw: driving airway pressure.

Authors' contributions

All authors participated in the study design, data collection and analysis, manuscript writing and final approval. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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RESEARCH

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Lung volumes and lung volume recruitment in ARDS: a comparison between supine and prone position

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Abstract

Background: The use of positive end-expiratory pressure (PEEP) and prone position (PP) is common in the management of severe acute respiratory distress syndrome patients (ARDS). We conducted this study to analyze the variation in lung volumes and PEEP-induced lung volume recruitment with the change from supine position (SP) to PP in ARDS patients.

Methods: The investigation was conducted in a multidisciplinary intensive care unit. Patients who met the clinical criteria of the Berlin definition for ARDS were included. The responsible physician set basal PEEP. To avoid hypoxemia, FiO_2 was increased to 0.8 1 h before starting the protocol. End-expiratory lung volume (EELV) and functional residual capacity (FRC) were measured using the nitrogen washout/washin technique. After the procedures in SP, the patients were turned to PP and 1 h later the same procedures were made in PP.

Results: Twenty-three patients were included in the study, and twenty were analyzed. The change from SP to PP significantly increased FRC (from 965 ± 397 to 1140 ± 490 ml, $p = 0.008$) and EELV (from 1566 ± 476 to 1832 ± 719 ml, $p = 0.008$), but PEEP-induced lung volume recruitment did not significantly change (269 ± 186 ml in SP to 324 ± 188 ml in PP, $p = 0.263$). Dynamic strain at PEEP decreased with the change from SP to PP (0.38 ± 0.14 to 0.33 ± 0.13, $p = 0.040$).

Conclusions: As compared to supine, prone position increases resting lung volumes and decreases dynamic lung strain.

Keywords: ARDS, Lung volumes, Lung strain, Prone, PEEP recruitment, Mechanical ventilation

Background

Acute respiratory distress syndrome (ARDS) is a permeability pulmonary edema, characterized by hypoxemia and a decrease in lung volumes and respiratory system compliance [1, 2]. In patients with ARDS, prone position (PP) produces a more homogeneous distribution of the inspired gas [3] and a better matching between ventilation and perfusion, thereby improving arterial oxygenation [3–5]. Positive end-expiratory pressure (PEEP) and PP have also shown to decrease the percentage of non-aerated and poorly aerated lung tissue and attenuate the regional recruitment–derecruitment phenomena [5–7]. In selected ARDS patients, PP has been proposed to further improve the outcomes [8]. The benefit on survival of PP is not related only to the improvement in gas exchange [9, 10], and the protective effect on ventilator-induced lung injury [3, 9, 11, 12] could also play a role. As compared to supine position (SP), the PP reduces the steep transpulmonary pressure gradient across the vertical axis of the lung, leading to a more homogeneous distribution of pulmonary stress and strain [2, 3, 13].

However, data analyzing the variation in lung volumes with the change from SP to PP in ARDS patients

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are scarce and conflicting [4, 14–17]. We hypothesized that in ARDS patients, PP increases lung volumes (i.e., functional residual capacity and end-expiratory lung volume) and might decrease lung strain [16, 18]. Because the measurement of functional residual capacity (FRC) requires to be made at zero end-expiratory pressure (ZEEP), our study included a lung derecruitment maneuver from baseline PEEP to zero PEEP [19–21] subsequently followed by the reinstitution of the basal PEEP level. These allowed to analyze the variation in lung volumes and to estimate lung volume recruitment and lung strain in both supine and prone positions in patients with ARDS.

Methods

The study was performed in the Intensive Care Department at Hospital de la Santa Creu i Sant Pau, Barcelona (Spain). This study was conducted in accordance with the amended Declaration of Helsinki.

Patients

Patients were considered eligible for the study if they met the Berlin definition criteria for ARDS [22] and had an indication for PP in accordance with our department's protocol (PaO_2/FiO_2 ratio of < 150 mm Hg and FiO_2 of $\geq$ 0.6 with PEEP of at least 5 cm H_2O). We recommend to use protective ventilation with individualized low tidal volume (Vt) and moderate PEEP levels. Essentially, PEEP is titrated according to the gas exchange (Sat O_2, measured by pulse oximeter, around 95%) with end-inspiratory plateau airway pressure (Pplat) not higher than 28 cm H_2O and without hemodynamic instability (mean arterial pressure above 65 mm Hg and no need for fluid replacement). Our detailed ventilatory strategy is included in Additional file 1. Hence, all our patients had been turned in PP before inclusion in the study. To be included, patients had to present an improvement in gas exchange ($FiO_2 \leq 0.6$ and PEEP $\leq$ 12 cm H_2O) in SP in order to avoid severe hypoxemia because of the derecruitment (induced by PEEP withdrawal and ventilation at ZEEP) during the measurement of FRC. Exclusion criteria were: age < 18 years, tracheostomy, pregnancy, major trauma, barotrauma (presence of extra-alveolar air during mechanical ventilation as assessed by daily chest X ray) and hemodynamic instability (systolic blood pressure < 80 or > 160 mm Hg, heart rate < 50 bpm or > 130 bpm or changes in $\pm$ 20% from baseline).

All patients were under continuous sedation and analgesia with intravenous perfusion of midazolam and/or propofol and opioids. During the study period, all patients received neuromuscular blocking agents.

Protocol

The following data were collected: age, height, simplified acute physiology score III at admission, ARDS etiology, days of mechanical ventilation, intensive care unit outcomes, respiratory rate, Vt, PEEP, peak airway pressure, Pplat and arterial blood gases. Respiratory variables were recorded directly from the ventilator.

All patients were ventilated in volume control ventilation using the same ventilator model (Engström Carestation ICU ventilator, General Electric, Madison, WI, USA).

To avoid hypoxemia, defined as oxygen saturation $\leq$ 88% measured through pulse oximetry, we increased the FiO_2 to 0.8 1 h before starting the protocol.

Measurements

Baseline ventilatory and hemodynamic parameters were collected before the protocol to measure lung volumes. The same procedures were carried out in SP and PP and are outlined below (see also Fig. 1):

1. Measurement of end-expiratory lung volume (EELV): EELV is the resting end-expiratory lung volume measured at baseline PEEP.
2. Removal of PEEP and continuation of mechanical ventilation at ZEEP. This derecruitment maneuver

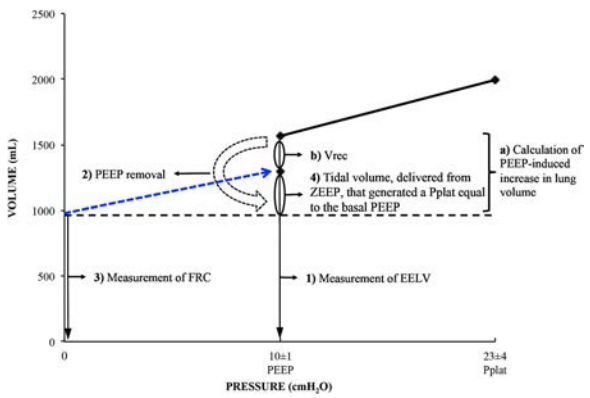

Fig. 1 Lung volumes, measurements and calculations made in the study. The same procedures were carried out in supine and prone positions as follows: (1) measurement of end-expiratory lung volume (EELV): EELV is defined as the resting end-expiratory lung volume at PEEP. (2) Removal of PEEP and continuation of mechanical ventilation at zero end-expiratory pressure (ZEEP). (3) Measurement of functional residual capacity (FRC): FRC is defined as the resting lung volume at ZEEP. (4) Measurement of the tidal volume, delivered from ZEEP, that generated a Pplat equal to the basal PEEP. The same calculations were carried out in supine and prone positions as follows: (a) calculation of PEEP-induced increase in lung volume = EELV minus FRC. (b) Calculation of PEEP-induced lung volume recruitment (Vrec) = PEEP-induced increase in lung volume minus the Vt, delivered from ZEEP, that generated a Pplat equal to the basal PEEP. Blue line represents the compliance at ZEEP

is mandatory to conduct the following step 3, and it is the reason to increase the FiO_2 to 0.8 immediately before starting the protocol (i.e., to avoid hypoxemia).
3. Measurement of functional residual capacity (FRC): FRC is the resting lung volume measured at ZEEP.
4. Measurement of the Vt, delivered from ZEEP, that generated a Pplat equal to the basal PEEP. This step (see Fig. 1) is mandatory to allow a proper estimation of the PEEP-induced lung volume recruitment [19, 20, 23–25].

Once step 4 was completed, the same PEEP that was used at baseline was resumed.

Measurements at ZEEP (FRC and Vt delivered from ZEEP, that generated a Pplat equal to the basal PEEP) included a lung derecruitment maneuver (PEEP removal) that can produce hypoxemia. For the purpose of our investigation, we defined hypoxemia as oxygen saturation $\leq$ 88% measured through pulse oximetry.

The safety limits and contraindications to remove PEEP were:

1. PEEP removal was contraindicated if $FiO_2 > 0.6$ and PEEP > 12 cm H_2O.
2. We increased the FiO_2 to 0.8 1 h before starting the protocol in order to avoid hypoxemia during PEEP removal.
3. If a patient presented with hypoxemia at any time during the protocol (saturation $\leq$ 88% measured through pulse oximetry), the measurements were aborted and the patient was excluded.

Lung volumes (EELV and FRC) were measured twice using the nitrogen washout/washin technique available in Engström Carestation ICU ventilator as previously described [24, 26]. Washout/washin technique is a multiple breath maneuver that with a modification of 0.1 in FiO_2 calculates the residual nitrogen in the lung (assuming there is not exchange of nitrogen) by continuous measurements of oxygen and carbon dioxide. The ventilator was carefully calibrated before the measurements according to the manufacturer's specifications. We obtained four values for each lung volume. The mean of the four values was used. As previously suggested [27], patients were excluded if the differences between the four values were more than 20% (cutoff determined by the manufacturer).

After the procedures in SP, the patients were turned to PP and 1 h later the same procedures (from 1 to 4 above) were made in PP. This time span was based in previous data showing that after 1 h in PP gas exchange is stable in the majority of patients [28, 29]. If a patient presented with hypoxemia (oxygen saturation $\leq$ 88%) at any time during the protocol, the measurements were aborted and the patient was excluded.

The normal reference values for FRC (liters) in the SP were calculated according to the equation described by Ibáñez and Raurich [30], as follows: 5.48 × height—7.05 for men and 1.39 × height—0.424 for women; height units are in meters. Compliance (ml/cm H_2O) was calculated as Vt/(Pplat minus total PEEP), being total PEEP the sum of PEEP plus intrinsic PEEP. Predicted body weight was calculated as follows: 50 + 0.91(height—152.4) for men and 45.5 + 0.91(height—152.4) for women; height units are in centimeters. Driving airway pressure was calculated as the difference between Pplat and total PEEP [31].

Calculation of lung volumes and strain

(a) The PEEP-induced increase in lung volume was calculated as EELV minus FRC (see Fig. 1).
(b) PEEP-induced lung volume recruitment (Vrec) was calculated as PEEP-induced increase in lung volume minus the Vt, delivered from ZEEP, that generated a Pplat equal to the basal PEEP (see Fig. 1).
(c) Strain was calculated as previously described [24, 32, 33]:

1. Dynamic strain at ZEEP = Vt/FRC.
2. Dynamic strain at PEEP = Vt/(FRC + Vrec).
3. Static strain at PEEP = (EELV − FRC)/(FRC + Vrec).
4. Global strain at PEEP = (static strain at PEEP + dynamic strain at PEEP) = (EELV − FRC + Vt)/(FRC + Vrec).

Statistical analysis

Data are expressed as mean ± SD. We used Wilcoxon test to compare variables between supine and prone positions and *U* the Mann–Whiney test to compare early and non-early ARDS patients. A p value < 0.05 was considered statistically significant. The SPSS® Statistics (version 20.0, Chicago, IL, USA) statistical software was used for statistical analysis.

Results

The study was conducted from July 2010 to December 2013. Twenty-three patients were included in the study, and twenty were analyzed. One patient was excluded because of hypoxemia during the FRC measurement, and two were excluded because of a technical problem. (The differences between FRC measurements were > 20%.)

Table 1 summarizes the patients' main characteristics at baseline. The mean age of patients was 58 ± 18 years. The main causes of ARDS were pneumonia ($n = 11$) and septic shock ($n = 4$). The study was performed 4 ± 3 days

Table 1 Patients' characteristics at study entry (with FiO_2 0.8)

Patient	Age (years)	Days on MV before study	SAPS III	Vt (ml/kg PBW)	RR (rpm)	PEEP (cm H_2O)	Pplat (cm H_2O)	Δ Paw (cm H_2O)	PaO_2/FiO_2 (mm Hg)	$PaCO_2$ (mm Hg)	Cause of ARDS	Outcome
1	43	6	65	7.4	24	8	28	20	255	40	Pneumonia	S
2	66	1	52	6.1	22	10	20	10	254	60	Pneumonia	S
3	77	5	91	6.7	20	10	22	12	165	44	Pneumonia	S
4	68	4	69	8.4	24	12	21	9	255	44	Pneumonia	S
5	75	4	65	7.8	22	10	18	8	115	38	Pneumonia	S
6	65	7	94	9.2	30	10	21	11	240	53	Pneumonia	S
7	55	2	67	6.8	20	10	22	12	229	35	Peritonitis	S
8	43	2	77	8.1	20	8	26	18	151	48	Peritonitis	D
9	78	3	100	6.3	27	10	29	19	188	41	Peritonitis	D
10	74	2	82	11.0	25	10	28	18	198	43	Pneumonia	D
11	81	4	89	6.7	24	10	20	10	230	34	Septic shock	S
12	30	4	83	6.8	21	10	23	13	265	41	Septic shock	D
13	58	5	71	5.0	30	10	20	10	173	43	Pneumonia	S
14	69	1	101	5.9	28	10	28	18	300	44	Septic shock	D
15	50	14	95	6.0	30	10	25	15	206	42	Septic shock	D
16	55	3	68	7.0	20	8	19	11	129	37	Thoracic Trauma	S
17	30	4	64	6.2	24	12	22	10	104	41	Pneumonia	S
18	37	3	76	5.0	30	12	22	10	299	29	Pneumonia	D
19	80	2	82	6.1	17	12	19	7	230	35	Pneumonia	S
20	31	5	65	6.7	26	12	27	15	218	24	Pancreatitis	D
Mean ± SD	58 ± 18	4 ± 3	78 ± 14	6.9 ± 1.4	24 ± 4	10 ± 1	23 ± 4	13 ± 4	41 ± 8	41 ± 8		

ARDS acute respiratory distress syndrome, *D* died, *PBW* predicted body weight, *MV* mechanical ventilation, *PEEP* positive end-expiratory pressure, *Pplat* end-inspiratory plateau airway pressure, *RR* respiratory rate, *S* survived, *SAPS III* simplified acu e physiology score III, *Vt* tidal volume, *Δ Paw* driving airway pressure

after starting mechanical ventilation. At baseline, mean Vt was 6.9 ± 1.4 ml/kg of predicted body weight and mean PEEP was 10 ± 1 cm H_2O.

After assuming the PP, the PaO_2/FiO_2 ratio increased significantly, from 210 ± 57 mm Hg in supine to 281 ± 109 mm Hg in prone ($p = 0.008$) (Table 2).

The mean FRC in SP was significantly lower than its reference value in healthy normal subjects (965 ± 397 vs. 2424 ± 459 ml, $p \leq 0.001$). The change from SP to PP significantly increased both FRC (from 965 ± 397 to 1140 ± 490 ml, $p = 0.008$) and EELV (from 1566 ± 476 to 1832 ± 719 ml, $p = 0.008$) (Figs. 2, 3).

We did not calculate Vrec and derived parameters in four patients because the tidal volume delivered from ZEEP, that generated a Pplat equal to the basal PEEP, was not measured in accordance to the protocol. Vrec (n = 16) did not significantly vary with the change of position (269 ± 186 ml in SP to 324 ± 188 ml in PP, $p = 0.263$) (Fig. 2).

We found a significant decrease in the dynamic strain at PEEP with the change from SP to PP from 0.38 ± 0.14 to 0.33 ± 0.13 ($p = 0.040$) (Fig. 4). The dynamic strain at ZEEP also decreased, from 0.52 ± 0.23 in SP to 0.44 ± 0.18 in PP ($p = 0.047$). The remaining variables did not change significantly between supine and prone positions (Table 2) (Additional file 2: Table S1).

In the whole population, the driving pressure in the non-survivor group ($n = 8$) was significantly higher than in the survivor group ($n = 12$) in both SP (16 ± 3 cm H_2O vs. 11 ± 3 cm H_2O, respectively, $p = 0.003$) and in PP (15 ± 3 cm H_2O vs. 11 ± 3 cm H_2O, respectively, $p = 0.005$). Additional data are also shown (Additional file 2: Table S2).

Discussion

The main findings in this study were that: (1) Prone position significantly increased lung volumes; (2) dynamic strain decreased significantly in prone position compared to supine position; and (3) the change of position from supine to prone did not modify the calculated PEEP-induced lung volume recruitment.

Prone position, oxygenation and lung volumes

In ARDS patients, lung volumes at ZEEP (FRC) and at PEEP (EELV) are typically decreased [18]. Two previous studies have shown that PP significantly increases FRC in ARDS patients [15, 16]. Nevertheless, data about the changes in EELV with the change from SP to PP in ARDS patients are not consistent. Four previous studies have shown that PP increases EELV in ARDS patients as compared to SP [14–17], but another study [4] found that the change of EELV from SP to PP was not significant. These contradictory findings might be explained by differences in lung recruitability, distribution and extension of lung volume alterations, differences in chest wall compliance, the influence of abdominal weight and heart compression, the inclination from the horizontal plane and the use or not of ventral supports [3, 9, 34, 35].

In the present study, we found a 40% decrease in FRC as compared to its reference value in SP, confirming

Table 2 Main characteristics of all patients in each position

Variable	Supine $n = 20$	Prone $n = 20$	*p*
PaO_2/FiO_2 (mm Hg)	210 ± 57	281 ± 109	0.021
$PaCO_2$ (mm Hg)	41 ± 8	42 ± 9	0.400
Peak airway pressure (cm H_2O)	41 ± 7	41 ± 6	0.284
Pplat (cm H_2O)	23 ± 4	23 ± 4	0.446
Compliance (ml/cm H_2O)	36 ± 11	37 ± 10	0.594
Δ Paw (cm H_2O)	13 ± 4	12 ± 4	0.446
FRC (ml)	965 ± 397	1140 ± 490	0.021
EELV (ml)	1566 ± 476	1832 ± 719	0.009
Vt delivered from ZEEP, that generated a Pplat equal to basal PEEP [ml ($n = 16$)]	333 ± 105	360 ± 127	0.073
Vrec [ml ($n = 16$)]	269 ± 186	324 ± 188	0.501
Dynamic strain at ZEEP	0.52 ± 0.23	0.44 ± 0.18	0.040
Dynamic strain at PEEP ($n = 16$)	0.38 ± 0.14	0.33 ± 0.13	0.020
Static strain at PEEP ($n = 16$)	0.51 ± 0.16	0.48 ± 0.13	0.438
Global strain at PEEP ($n = 16$)	0.89 ± 0.24	0.81 ± 0.18	0.121

Data are presented as mean ± SD. Dynamic strain at ZEEP = Vt/FRC; dynamic strain at PEEP = Vt/(FRC + Vrec); static strain at PEEP = (EELV − FRC)/(FRC + Vrec); global strain at PEEP = (EELV − FRC + Vt)/(FRC + Vrec)

EELV end-expiratory lung volume, *FRC* functional residual capacity, *PEEP* positive end-expiratory pressure, *Pplat* end-inspiratory plateau airway pressure, *Vrec* PEEP-induced lung volume recruitment, *Vt* tidal volume, *Δ Paw* driving airway pressure

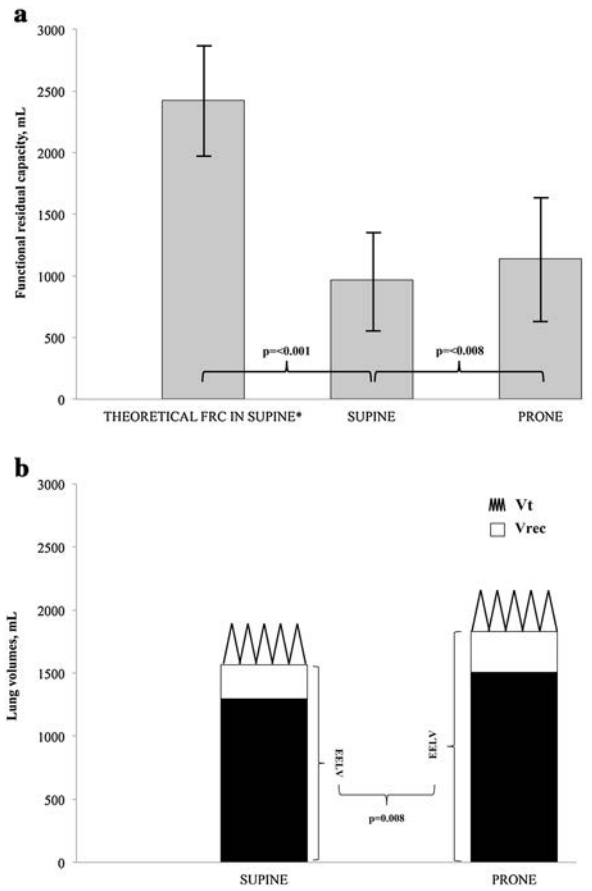

Fig. 2 Variation of lung volumes with the change of position. **a** Comparison of different values of functional residual capacity. **b** Comparison of EELV and Vrec in supine position and prone position. EELV, end-expiratory lung volume; Vrec, PEEP-induced lung volume recruitment; Vt, tidal volume. Data are presented in mean (ml) and SD. *According to the equation described by Ibañez and Raurich [30]

previous results [18]. We also observed that the FRC and EELV increased significantly with the change of position (18% in FRC and 17% in EELV). Santini et al. [7] performed a study in animals with normal lungs, and they found a significant increase in FRC with the change from SP to PP. The increase in resting lung volume was mainly related to a redistribution of aeration: a minor decrease in non-aerated lung tissue (3%), a major decrease in poorly aerated tissue (17%) and a major increase (20%) in well-aerated tissue. Since recruitment, as precisely measured by thoracic CT scan, refers to tissue recruitment (i.e., amount of non-inflated tissue that reinflates at a higher pressure), the decrease in poorly aerated tissue and the increase in well-aerated tissue (which contribute to the end-expiratory lung volume increase induced by PEEP) are thus considered as better gas distribution within the lung and not recruitment per se [36].

Prone position and strain

During passive mechanical ventilation, the force applied by the ventilator generates an internal tension in the fibers of the lung skeleton, called "stress," and the elongation of these fibers from their resting position is called "strain" [2]. High values of dynamic lung strain (lung deformation caused by Vt) and static lung strain (lung deformation caused by PEEP) are associated with ventilator-induced lung injury [32, 37].

In an animal model, Protti et al. [33] showed that for the same global strain, a large static strain is less harmful than a large dynamic strain. On the same vein, González-López et al. [38] found that increased strain was associated with a proinflammatory lung response in patients with acute lung injury. Moreover, Bellani et al. [39] found in patients with acute lung injury that the intensity of metabolic activity (a surrogate of inflammation) detected by positron emission tomography was correlated with regional strain. Consequently, the significant decrease in dynamic strain in PP as compared to SP could be another mechanism of protection of PP against ventilator-induced lung injury. Therefore, the measurement of lung volumes at bedside may be an important tool to deliver a more physiologically based ventilation and encourage physicians to increase the use of PP in moderately to severe ARDS patients [40].

Prone position and PEEP-induced lung volume recruitment

It is still unclear whether the PEEP-induced alveolar recruitment varies with the change from SP to PP. In an experimental study in animals with lung injury, Richard et al. [5] analyzed the variation of alveolar recruitment at PEEP 10 cm H_2O in SP and PP by means of the positron emission tomography technique. They found that in PP, PEEP-induced alveolar recruitment was not higher than in SP. Interestingly, in this study, the authors observed a redistribution of densities in PP (recruitment in dorsal regions with derecruitment in ventral regions). Cornejo et al. [6] performed another study in ARDS patients to determine the effects of PEEP and PP on alveolar recruitment. Using the CT scan technique, they found that increasing PEEP from 5 cm H_2O to 15 cm H_2O significantly increased alveolar recruitment. However, the percentage of recruitment was similar in both positions (36% in SP and 33% in PP). Using a different methodology, the data from our study are consistent with these findings, indicating that the effects of PEEP on lung volume recruitment are similar in both positions (around 17% of EELV).

A previous study by Grasso et al. [41] found that alveolar recruitment was higher in the early phase (1 ± 0.3 days of mechanical ventilation) than in the late phase of ARDS, but a subsequent study by Gattinoni

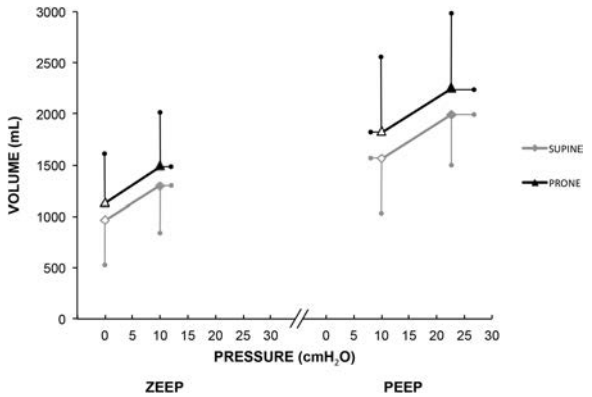

Fig. 3 Variation in lung volumes in supine and prone positions. Clear triangles and clear rhombus are the resting lung volumes at ZEEP and at PEEP. Dark triangles and dark rhombus represent end-inspiratory lung volumes and end-inspiratory lung pressure (Pplat) at ZEEP and at PEEP. PEEP, positive end-expiratory pressure; ZEEP, zero end-expiratory pressure. Data are shown as mean and SD

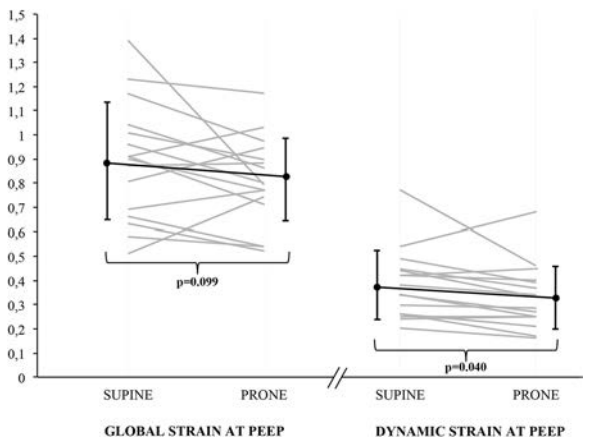

Fig. 4 Variation of individual values of global and dynamic strain at PEEP with the change of position. Dark lines represent mean and SD. PEEP, positive end-expiratory pressure

et al. [42] did not find the same results. In the study of Gattinoni et al. [42], they found that the number of days of mechanical ventilation before the study was similar in patients with a lower percentage of potentially recruitable lung and those with a higher percentage (5 ± 6 vs. 6 ± 6 days, respectively, $p = 0.50$). In our study when we classified ARDS patients in the early phase (< 72 h) and in late phase (> 72 h) (Additional file 2: Table S2), we observed results similar to those of Gattinoni et al. [42]: no statistical differences in lung volume recruitment between the early and late phase group were detected. In our study, however, in the early phase of ARDS, lung volumes increased and strain decreased with the change from SP to PP, whereas in late phase ARDS we did not observe these findings (Additional file 2: Table S2). These differences could be related to the presence of some degree of hydrostatic pulmonary edema in the early phase of ARDS, and to the presence of fibrosis in the non-early phase of ARDS that predisposes to non-responsiveness to PP in terms of increasing in lung volumes and decreasing strain [43]. Our findings thus suggest that the survival benefit may, in part, be related to the early application of PP as it increases resting lung volumes and decreases lung strain compared to SP. It is also tempting to speculate that the lack of differences in Vrec between supine and prone, and the increase in overall lung volume in prone as compared to supine, can be explained by a decrease of poorly ventilated areas and an increase of well ventilated areas, which in turn might help to decrease lung inhomogeneity. It has been shown that the extent of lung inhomogeneities (as quantified by the amount of poorly ventilated tissue) is associated with worse outcomes in ARDS patients, possibly due to a mechanism of "stress raisers" [44].

Limitations

Like many physiological studies [4, 6, 14–17, 34], our study has a relatively low number of patients. Another limitation is that the measurement of FRC could be subject to the tolerance to PEEP removal and the FiO_2 used. However, when the study was performed, all the patients met the criteria for mild–moderate ARDS according to the Berlin definition [22]. We did not perform a multislice spiral lung computed tomography to measure the quantitative changes in alveolar aeration induced by PEEP and PP. Other measurements of lung mechanics (i.e., esophageal pressure and derived variables) and lung biomarkers could help to further explain the effects of PEEP and positioning in ARDS patients, but we did not do these because of lack of adequate equipment at the time of the study. Finally, to confirm the changes, it might have been useful to return the patients from PP to SP and to repeat the same procedures and measurements; this was not done, however, because most patients remained in the PP as per clinical decision after the study had been completed.

Conclusions

As compared to supine, prone position increases resting lung volumes without significantly changing the recruited volume kept by PEEP. Moreover, the change of position from supine to prone decreases dynamic lung strain. These findings help to better understand the beneficial effects of prone position in ARDS patients.

Additional file

Additional file 1. The institutional protocol.

Additional file 2. Additional patient per patient physiological data in supine and prone position (Table S1 and Table S2).

Abbreviations

ARDS: acute respiratory distress syndrome; EELV: end-expiratory lung volume; FRC: functional residual capacity; PEEP: positive end-expiratory pressure; PP: prone position; Pplat: end-inspiratory plateau airway pressure; SP: supine position; Vrec: PEEP-induced lung volume recruitment; Vt: tidal volume; ZEEP: zero end-expiratory pressure.

Authors' contributions

All authors participated in the study design, data collection and analysis, manuscript writing and final approval. All authors read and approved the final manuscript.

Competing interests

General Electric provided the equipment (Engström Carestation ICU ventilator) to conduct this research.

Acknowledgements

Not applicable.

Availability of data and materials

Not applicable.

Consent for publication

The patients' relatives gave written informed consent to participate and publish.

Ethics approval and consent to participate

The ethics committee of Hospital de la Santa Creu i Sant Pau approved the study (Reference 68/2010).

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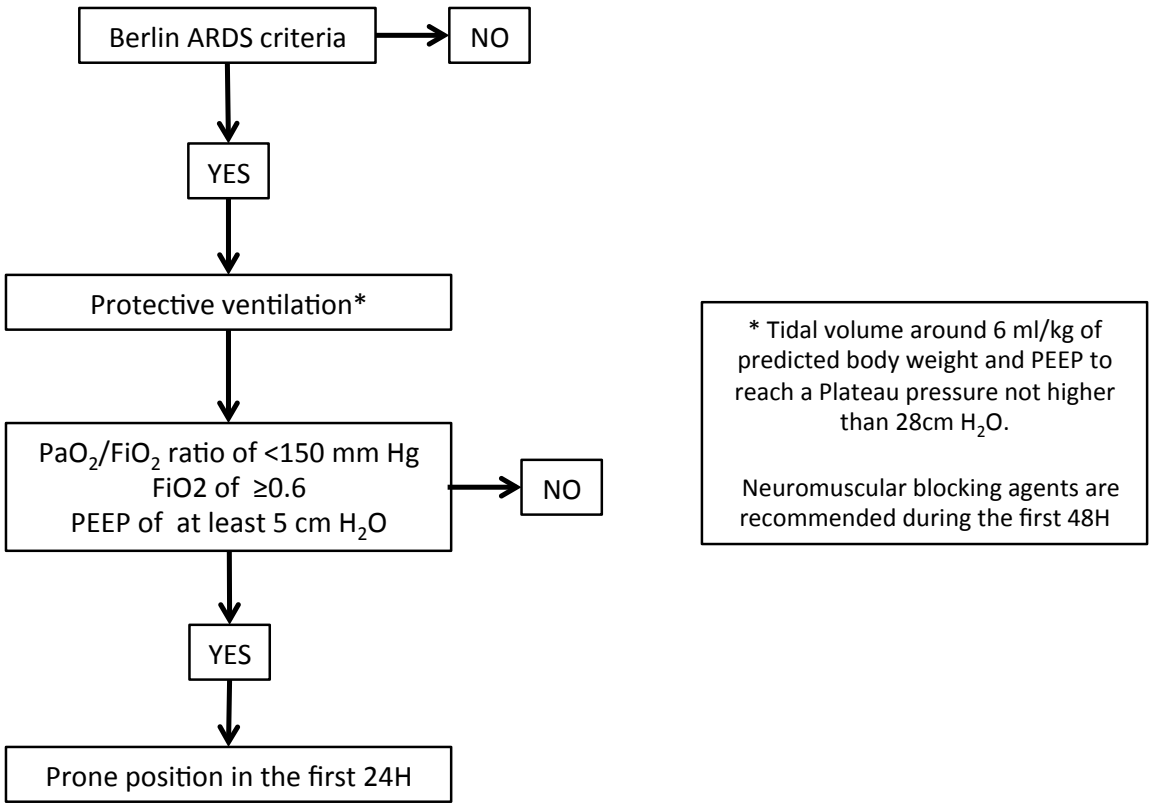
Additional file 1. The institutional protocol.

Institutional Protocol

Our institutional protocol is based on previous data and experience[1-3] and is detailed below.



Mechanical ventilation settings in ARDS patients

The volume assist-control mode with constant inspiratory flow is used. We recommend to use protective ventilation with individualized low tidal volume (Vt) and moderate PEEP levels. Essentially, PEEP is titrated according to the gas exchange (Sat O2, measured by pulse oxymeter, around 95%) with end-inspiratory plateau airway pressure (Pplat) not higher than 28 cm H2O and without hemodynamic instability (mean arterial pressure above 65 mmHg and no need for fluid replacement), and an inspiratory to expiratory ratio ≤ 1:2 have to be set immediately after ARDS diagnosis.

Prone Position

If patient have a PaO_2/FiO_2 ratio of <150 mm Hg and FiO_2 of ≥0.6 with PEEP of at least 5 cm H_2O the physician must to consider prone position. The patients have to be maintained in PP for at least 16 consecutive hours. The prone sessions could be stopped when PaO_2/FIO_2 ratio are ≥ 150 mmHg with PEEP ≤ 10 cm H_2O and FiO_2 ≤0.6 measured in supine position and after one our of the last prone position phase.

Five people were usually involved and the process typically took five to ten minutes. One person has to be dedicated to the management of the head of the patient, the endotracheal tube and the ventilator lines. This person at the head of the bed had to coordinate the steps of the procedure.
After the turn, the patients' arms were placed alongside their bodies. Their heads and necks were moved from lateral to midline to contralateral positions at varying intervals. Special care was taken to protect the eyes. A slight reverse Trendelenburg position is used to minimize facial edema.
Neuromuscular blocking agents are used early and have to be stopped at the discretion of the attending physician from 48 hours of ARDS treatment.
In supine and prone position the inclination was 30° from the horizontal.

Weaning
When the prone sessions were stopped the physician could considered to start weaning phase. First we made a gradually decrease of PEEP (steps of 2 cm H_2O) up to 8 cm H_2O (keeping arterial oxygen saturation between 93 and 98%, estimated by a pulse oximeter). Then FiO_2 was gradually decreased to 0.45 to keep the same arterial oxygen saturation. At this time, the use of pressure support ventilation could be considered. The initial level of pressure support was titrated to achieve a respiratory rate of 25-30 breaths/minute and was decreased twice per day (2-4 cm H_2O each time) as clinically tolerated. Lastly, PEEP was decreased to 5 cm H2O. At this moment, extubation had to be considered if patients are capable of resuming spontaneous breathing. Spontaneous breathing trial was conducted either with pressure support ventilation (7cm H_2O of pressure support at ZEEP) or T-piece trials in 30 – 120 minutes. Spontaneous breathing trials were performed once or twice per day.

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Additional file 2. Additional patient per patient physiological data in supine and prone position (Table S1 and Table S2).

Table S1. Patients' respiratory characteristics at each position.

	Supine Position								Prone Position							
Patient	Vt at ZEEP (ml)	Pplat at ZEEP (cmH_2O)	Crs at ZEEP (ml/cm H_2O)	Δ Paw at ZEEP (cm H_2O)	Vt at PEEP (ml)	Pplat at PEEP (cmH_2O)	Crs at PEEP (ml/cm H_2O)	Δ Paw at PEEP (cm H_2O)	Vt at ZEEP (ml)	Pplat at ZEEP (cmH_2O)	Crs at ZEEP (ml/cm H_2O)	Δ Paw at ZEEP (cm H_2O)	Vt at PEEP (ml)	Pplat at PEEP (cmH_2O)	Crs at PEEP (ml/cm H_2O)	Δ I (cr
1					500	28	25	20					500	26	28	
2					425	20	43	10					425	20	43	
3					350	22	29	12					350	21	32	
4					475	21	53	9					475	24	40	
5	375	10	38	10	425	18	53	8	400	10	40	10	425	18	53	
6	280	10	28	10	450	21	41	11	300	10	30	10	450	22	38	
7	325	10	33	10	450	22	38	12	450	10	45	10	450	20	45	
8	160	8	20	8	475	26	26	18	200	8	25	8	475	21	37	
9	185	10	19	10	350	29	18	19	200	10	20	10	350	30	18	
10	300	10	30	10	425	28	24	18	325	10	33	10	425	25	28	
11	525	10	53	10	475	20	48	10	525	10	53	10	475	20	48	
12	230	10	23	10	375	23	29	13	220	10	22	10	375	23	29	
13	350	10	35	10	375	20	38	10	475	10	48	10	375	20	38	
14	325	10	33	10	375	28	21	18	350	10	35	10	375	29	20	
15	350	10	35	10	475	25	32	15	370	10	37	10	475	22	40	
16	350	8	44	8	450	19	41	11	250	8	31	8	450	20	38	
17	375	12	31	12	400	22	40	10	350	12	29	12	400	20	50	
18	255	12	21	12	350	22	35	10	375	12	31	12	350	23	32	
19	550	12	46	12	400	19	57	7	675	12	56	12	400	19	57	
20	400	12	33	12	500	27	33	15	300	12	25	12	500	30	28	
Mean ± SD	333 ± 105	10 ± 1	33 ± 10	10 ± 1	425 ± 51	23 ± 4	36 ± 11	13 ± 4	360 ± 127	10 ± 1	35 ± 11	10 ± 1	425 ± 51	23 ± 4	37 ± 10	1

Data are presented as mean ± standard deviation.

Abbreviations: Crs, Compliance; PEEP, positive end-expiratory pressure; Pplat, end-inspiratory plateau airway pressure; Vt, Tidal volume; Vt at ZEEP, Vt delivered from ZEEP, that generated a Pplat equal to basal PEEP; ZEEP, Zero end-expi pressure; Δ Paw, Driving airway pressure.

Table S2. Main characteristics of patients in each position according to number of days of mechanical ventilation before the study.

Variable	Early			Late		
	Supine n=9	Prone n=9	P	Supine n=11	Prone n=11	P
Vt, ml/Kg of PBW (n=20)	6.9 ± 1.7	6.9 ± 1.7		7.0 ± 1.2	7.0 ± 1.2	
PEEP, cm H_2O (n=20)	10 ± 1	10 ± 1		10 ± 1	10 ± 1	
PaO_2/FiO_2, mm Hg	220 ± 60	302 ± 128	0.093	202 ± 56	264 ± 94	0.075
$PaCO_2$, mm Hg	41 ± 9	42 ± 10	0.999	40 ± 7	42 ± 9	0.182
Peak airway pressure, cm H_2O	39 ± 5	42 ± 5	0.064	42 ± 9	41 ± 7	0.905
Pplat, cm H_2O	24 ± 4	23 ± 4	0.491	22 ± 3	22 ± 3	0.932
Compliance, ml/cm H_2O	34 ± 12	35 ± 12	0.499	38 ± 10	38 ± 9	0.999
Δ Paw, cm H_2O	14 ± 5	13 ± 4	0.491	12 ± 3	12 ± 3	0.932
FRC, ml	851 ± 332	1085 ± 354	0.011	1058 ± 436	1185 ± 593	0.424
EELV, ml	1388 ± 435	1772 ± 557	0.011	1711 ± 477	1880 ± 853	0.248
Vt delivered from ZEEP, that generated a Pplat equal to basal PEEP, ml (n=16)	306 ± 120 (n=8)	353 ± 157 (n=8)	0.068	361 ± 87 (n=8)	368 ± 99 (n=8)	0.671
Vrec, ml (n=16)	237 ± 132 (n=8)	275 ± 136 (n=8)	0.674	302 ± 233 (n=8)	374 ± 228 (n=8)	0.575
Dynamic strain at ZEEP	0.57 ± 0.28	0.41 ± 0.12	0.011	0.47 ± 0.17	0.46 ± 0.21	0.722
Dynamic strain at PEEP, (n=16)	0.43 ± 0.16 (n=8)	0.33 ± 0.08 (n=8)	0.012	0.33 ± 0.12 (n=8)	0.33 ± 0.17 (n=8)	0.674
Static strain at PEEP, (n=16)	0.53 ± 0.13 (n=8)	0.49 ± 0.16 (n=8)	0.484	0.49 ± 0.19 (n=8)	0.47 ± 0.10 (n=8)	0.673
Global strain at PEEP, (n=16)	0.96 ± 0.23 (n=8)	0.82 ± 0.16 (n=8)	0.093	0.83 ± 0.25 (n=8)	0.80 ± 0.21 (n=8)	0.484

Data are presented as mean ± standard deviation. Abbreviations: EELV, end-expiratory lung volume; FRC, functional residual capacity; PBW, Predicted body weight; PEEP, Positive end-expiratory pressure; Pplat, end-inspiratory plateau airway pressure; Vrec, PEEP-induced lung volume recruitment; Vd/Vt, dead space; Vt, tidal volume; Δ Paw, Driving airway pressure (VT / Crs). Dynamic strain at ZEEP = Vt / FRC; Dynamic strain at PEEP = Vt / (FRC + Vrec); Static strain at PEEP = (EELV - FRC) / (FRC + Vrec); Global strain at PEEP = (EELV - FRC + Vt) / (FRC + Vrec).

8. RESULTADOS

En el estudio del alargamiento de la pausa inspiratoria a todos los pacientes se pudo alargar la pausa inspiratoria a 0.7sg manteniendo una PEEP intrínseca < a 1 cmH_2O y sin invertir la relación inspiración-espiración. El alargamiento de la pausa inspiratoria disminuyó significativamente la fracción de espacio muerto (Vd/Vt) y la $PaCO_2$ con respecto a la situación basal (0.70 ± 0.07 frente a 0.64 ± 0.08, p=<0.01 y 54 ± 9 mmHg frente a 50 ± 8 mmHg, p=<0.01 respectivamente).

La prolongación de la pausa inspiratoria permitió en la tercera fase del estudio una disminución significativa del Vt por Kg de peso predicho (PBW) comparado con los parámetros basales (6.3 ml/Kg/PBW frente a 5.6 ml/Kg/PBW, p=<0.01) manteniendo los mismos niveles de pH y $PaCO_2$ que en la situación basal.

Las medidas de mecánica respiratoria, intercambio de gases y hemodinámia están presentadas en la Tabla 1.

Tabla 1. Mecánica respiratoria, intercambio de gases y hemodinámia durante el estudio.

	Phase 1 (Basal)	Phase 2 (Alargamiento de pausa inspiratoria)	Phase 3 (Reducción de Vt)	*p* =	Diferencias intergrupos
EIP (segundos)	0.12 ± 0.04	0.7 ± 0	0.7 ± 0	<0.001	a, b
Ppico (cmH_2O)	38 ± 6	38 ± 6	35 ± 5	<0.001	b, c
Pmedia (cmH_2O)	15 ± 3	18 ± 2	17 ± 2	<0.001	a, b, c
Pplat (cmH_2O)	24 ± 3	24 ± 3	22 ± 3	<0.001	b, c
PEEPi (cmH_2O)	0.2 ± 0.2	0.5 ± 0.4	0.5 ± 0.4	0.06	
Vt (mL)	378 ± 73	378 ± 73	336 ± 61	<0.001	b, c
Vt (mL/Kg/PBW)	6.3 ± 0.8	6.3 ± 0.8	5.6 ± 0.8	<0.001	b, c
Vd_{fis} (mL)	267 ± 71	244 ± 65	216 ± 58	<0.001	a, b, c
Vd/Vt	0.70 ± 0.07	0.64 ± 0.08	0.64 ± 0.08	<0.001	a, b
Crs (mL/cmH_2O)	29 ± 9	29 ± 9	32 ± 11	0.001	b, c
∆ **Paw** (cmH_2O)	13.6 ± 3.6	13.4 ± 3.6	10.9 ± 3.1	<0.001	a, b, c
R_{aw} ($cmH_2O/L/sg$)	14 ± 5	13 ± 5	13 ± 4	0.28	
pH	7.31 ± 0.07	7.34 ± 0.09	7.31 ± 0.08	<0.001	a, c
PaO_2 (mmHg)	102 ± 23	98 ± 23	105 ± 29	0.35	
$PaCO_2$ (mmHg)	54 ± 9	50 ± 8	54 ± 10	<0.001	a, c
$EtCO_2$ (mmHg)	41 ± 6	39 ± 6	43 ± 7	0.002	a, c
P(a-et)CO_2 (mmHg)	13 ± 6	12 ± 8	12 ± 9	0.27	
PAM (mmHg)	80 ± 12	76 ± 9	77 ± 12	0.08	
FC (latidos/min)	87 ± 19	83 ± 20	86 ± 21	0.14	
Temperature (°C)	36.7 ± 0.9	36.7 ± 0.9	36.6 ± 0.8	0.61	

Los datos están presentados como número (%) o media ± desvío estándar.
Crs, Compliancia estática del sistema respiratorio; EIP, pausa inspiratoria; $EtCO_2$, dióxido de carbono exhalado al final de la espiración; FiO_2, fracción inspirada de oxigeno; FC, frecuencia cardiaca; PAM, presión arterial media; PaO_2, Presión parcial de oxígeno en sangre arterial; $PaCO_2$: Presión parcial de dióxido de carbono en sangre arterial; PBW, Peso Predicho; PEEPi, Presión positiva intrínseca al final de la espiración; Pmedia, presión media; Ppico, presión pico; Pplat, presión plateau; P(a-et)CO_2, gradiente de CO_2 entre valor arterial y valor exhalado; Raw, resistencia de vías aéreas; Vd_{fis}, espacio muerto fisiológico; Vd/Vt, fracción de espacio muerto; Vt, volume corriente; ∆Paw, presión de distensión estática del sistema respiratorio (Pplat – PEEP). .
Diferencias intergrupos (p<0.05): a, fase 1 frente a fase 2; b, fase 1 frente a fase 3; c, fase 2 frente a fase 3.

En el estudio de los volúmenes pulmonares la relación entre la PaO_2 y FiO_2 aumento significativamente con el cambio de supino a prono (210 ± 57 mmHg frente a 281 ± 109 mmHg, p=0.02). Los volúmenes pulmonares aumentaron significativamente con el cambio de posición (EELV en supino 1566 ± 476 ml frente a EELV en prono 1832 ± 719 ml, p=<0.01 y la CRF en supino 965 ± 397ml frente a CRF en prono 1140 ± 490 ml, p=0.02), sin embargo el Vrec no cambió (269 ± 186 ml en supino frente a 324 ± 188 ml en prono, p=0.5). Con el cambio de posición de supino a prono se evidenció una disminución significativa del *strain* dinámico con PEEP (0.52 ± 0.23 frente a 0.44 ± 0.18, p=0.04) y del *strain* dinámico sin PEEP (0.38 ± 0.14 frente a 0.33 ± 0.13, p=0.02).

Se clasificó a los pacientes de acuerdo al tiempo de diagnóstico de SDRA en temprano (< 72 horas) n=9 (45%) y tardío (> 72 horas) n=11 (55%). Con el cambio de posición de supino a prono en los pacientes con SDRA temprano se encontró un aumento significativo de la CRF (851 ± 332 ml en supino frente a 1085 ± 354 ml en prono, p=0.01) y del EELV (1388 ± 435m ml en supino frente a 1772 ± 557 ml en prono, p=0.01) sin cambio significativo del Vrec (237 ± 132 ml en supino frente a 275 ± 136 ml en prono, p=0.67) y una disminución significativa del *strain* dinámico sin PEEP (0.57 ± 0.28 en supino frente a 0.41 ± 0.12 en prono, p=0.01) y del *strain* dinámico con PEEP (0.43 ± 0.16 en supino frente a 0.33 ± 0.08 en prono, p=0.01). Sin embargo, en los pacientes con SDRA tardío, estos cambios no fueron significativos.

Las principales variables del estudio están detalladas en la Tabla 2.

Tabla 2. Características principales de los pacientes en cada posición.

	Supino n=20	**Prono n=20**	**p=**
PaO_2/FiO_2, mmHg	210 ± 57	281 ± 109	0.021
$PaCO_2$, mmHg	41 ± 8	42 ± 9	0.400
Ppico, cmH_2O	41± 7	41 ± 6	0.284
Pplat, cmH_2O	23 ± 4	23 ± 4	0.446
Crs, ml/cmH_2O	36 ± 11	37 ± 10	0.594
∆ Paw, cmH_2O	13 ± 4	12 ± 4	0.446
CRF, ml	965 ± 397	1140 ± 490	0.021
EELV, ml	1566 ± 476	1832 ± 719	0.009
Vt necesario para generar P. Plateau igual a la PEEP basal, ml (n=16)	333 ± 105	360 ± 127	0.073
Vrec, ml (n=16)	269 ± 186	324 ± 188	0.501
***Strain* dinámico con ZEEP**	0.52 ± 0.23	0.44 ± 0.18	0.040
***Strain* dinámico con PEEP, (n=16)**	0.38 ± 0.14	0.33 ± 0.13	0.020
***Strain* estático con PEEP, (n=16)**	0.51 ± 0.16	0.48 ± 0.13	0.438
***Strain* global con PEEP, (n=16)**	0.89 ± 0.24	0.81 ± 0.18	0.121

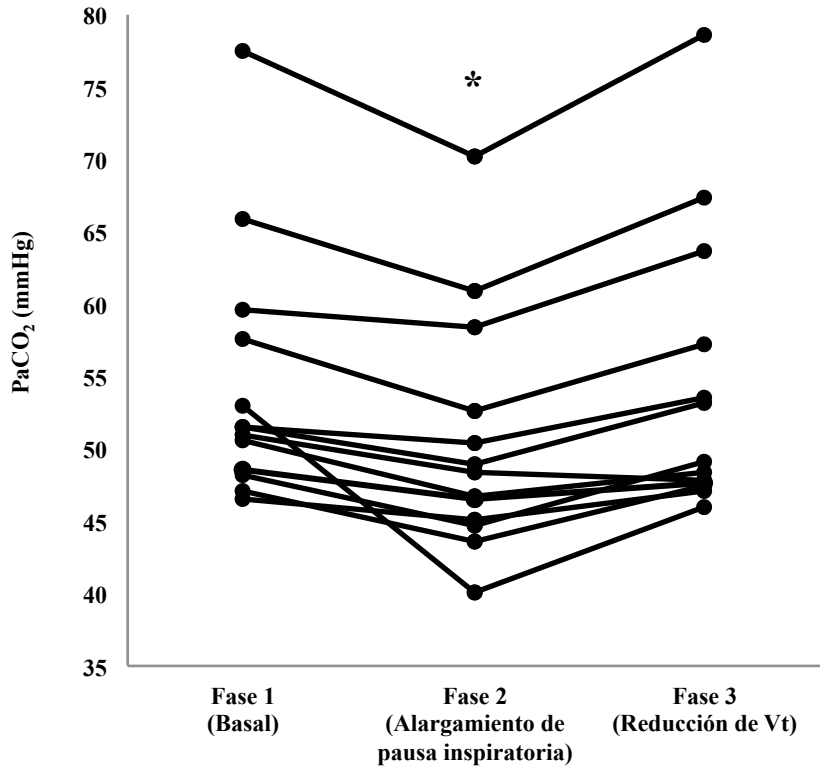
Los datos están presentados en media ± desvio estandar.

Crs, Compliancia estática del sistema respiratorio, EELV, volumen pulmonar al final de la espiración; CRF, capacidad residual funcional; PaO_2, Presión parcial de oxigeno en sangre arterial; $PaCO_2$: Presión parcial de dióxido de carbono en sangre arterial; PEEP, presión positiva al final de la espiración; Ppico, presión pico; Pplat, Presion plateau; Vrec, volumen pulmonar reclutado inducido por la PEEP; Vt, volumen corriente; ∆ Paw, presión de distensión estática del sistema respiratorio. *Strain* dinámico con ZEEP = Vt / CRF; *Strain* dinámico con PEEP = Vt / (CRF + Vrec); *Strain* estático con PEEP = (EELV - CRF) / (CRF + Vrec); *Strain* global con PEEP = (EELV - CRF + Vt) / (CRF + Vrec).

9. DISCUSIÓN

La hipótesis del estudio sobre el alargamiento de la pausa inspiratoria planteaba que esta prolongación podría permitir disminuir el volumen corriente administrado y de esta manera proporcionar una herramienta mas para ayudar en la ventilación protectiva. Efectivamente el principal hallazgo de este estudio fue que el alargamiento de la pausa inspiratoria permite disminuir significativamente el Vt administrado manteniendo los mismos niveles de $PaCO_2$ (ver Figura 2). Como consecuencia de esto, la presión plateau (Pplat) y la presión de distensión estática del sistema respiratorio (∆ Paw) disminuyeron significativamente mejorando la mecánica respiratoria.

Figura 2. Valores individuales de $PaCO_2$ en cada fase del estudio. El asterisco marca la reducción significativa de los valores de $PaCO_2$ durante el alargamiento de la pausa inspiratoria.



Como se ha descrito previamente, una de las principales consecuencias de utilizar Vt bajos en la ventilación protectiva es la hipercapnia. Algunas maniobras han sido descritas para disminuir la hipercapnia, una de ellas es el uso de humidificadores activos que disminuyen el espacio muerto sin aumentar las resistencias de las vías aéreas (13, 48). Otra opción para disminuir la hipercapnia puede ser aumentar la frecuencia respiratoria. Sin embargo, el uso de frecuencias respiratorias elevadas puede producir un aumento de la presión positiva intrínseca al final de la espiración (PEEPi) (14, 49) y puede producir daño pulmonar inducido por la ventilación (50, 51). Mas aún, un estudio de Vieillard-Baron et al. (52) demostró que el aumento de la frecuencia respiratoria no reduce la $PaCO_2$, produce una hiperinflación dinámica y reduce el gasto cardíaco.

Diversos estudios han demostrado que el alargamiento de la pausa inspiratoria aumenta significativamente la eliminación de la $PaCO_2$ disminuyendo la hipercapnia y el espacio muerto fisiológico (15-20). Esto se explica porque la difusión del CO_2 a través de la membrana alveolo-capilar es tiempo dependiente y el alargamiento de la pausa inspiratoria aumenta el tiempo disponible para el intercambio (53-55). Se debe considerar que el alargamiento de la pausa inspiratoria puede producir hiperinflación y alteraciones en el gasto cardiaco al producir un aumento de la presión media de las vías aéreas, de la PEEPi y una inversión en la relación inspiración-espiración (52, 56). Sin embargo, en el estudio de Devaquet et al. (18) y en el presente estudio, se consiguió un aumento significativo del alargamiento de la pausa inspiratoria acompañado de una disminución significativa de la $PaCO_2$ sin producir estos

efectos adversos. De esta manera, si al alargar la pausa inspiratoria se realiza una monitorización de la PEEPi y de la relación inspiración-espiración, el alargamiento de la pausa inspiratoria es una herramienta útil para disminuir significativamente la $PaCO_2$. Estos resultados constituyen el aporte clínico del presente estudio ya que el alargamiento de la pausa inspiratoria permite disminuir significativamente el Vt administrado, ayudando en la ventilación protectiva. Además esta estrategia mejora la mecánica respiratoria con una disminución significativa del espacio muerto fisiológico (Vd_{fis}), Pplat y de la Δ Paw. Con el presente trabajo se propone una estrategia de ventilación que puede ser utilizada por los médicos responsables de los pacientes con SDRA en etapas tempranas.

La hipótesis del estudio sobre los volúmenes pulmonares planteaba que la posición prono podría aumentar los volúmenes pulmonares y disminuir el *strain* en el tejido pulmonar. Efectivamente, el principal hallazgo de este estudio fue que la posición prono en comparación con la posición supino, aumenta los volúmenes pulmonares disminuyendo el *strain* dinámico en el tejido pulmonar y que el volumen pulmonar reclutado inducido por la PEEP no se modifica con el cambio de posición.

En la actualidad la información sobre la variación de los volúmenes pulmonares debido al cambio de posición de supino a prono en pacientes con SDRA es contradictoria. Dos estudios demostraron que la PP aumenta el EELV (36, 37). Sin embargo el estudio realizado por Pelosi et al. (38) no encontró un aumento significativo del EELV en la PP. El estudio realizado por Mentzelopoulos et al. (40) encontró un aumento significativo del EELV y de la CRF y en otro estudio

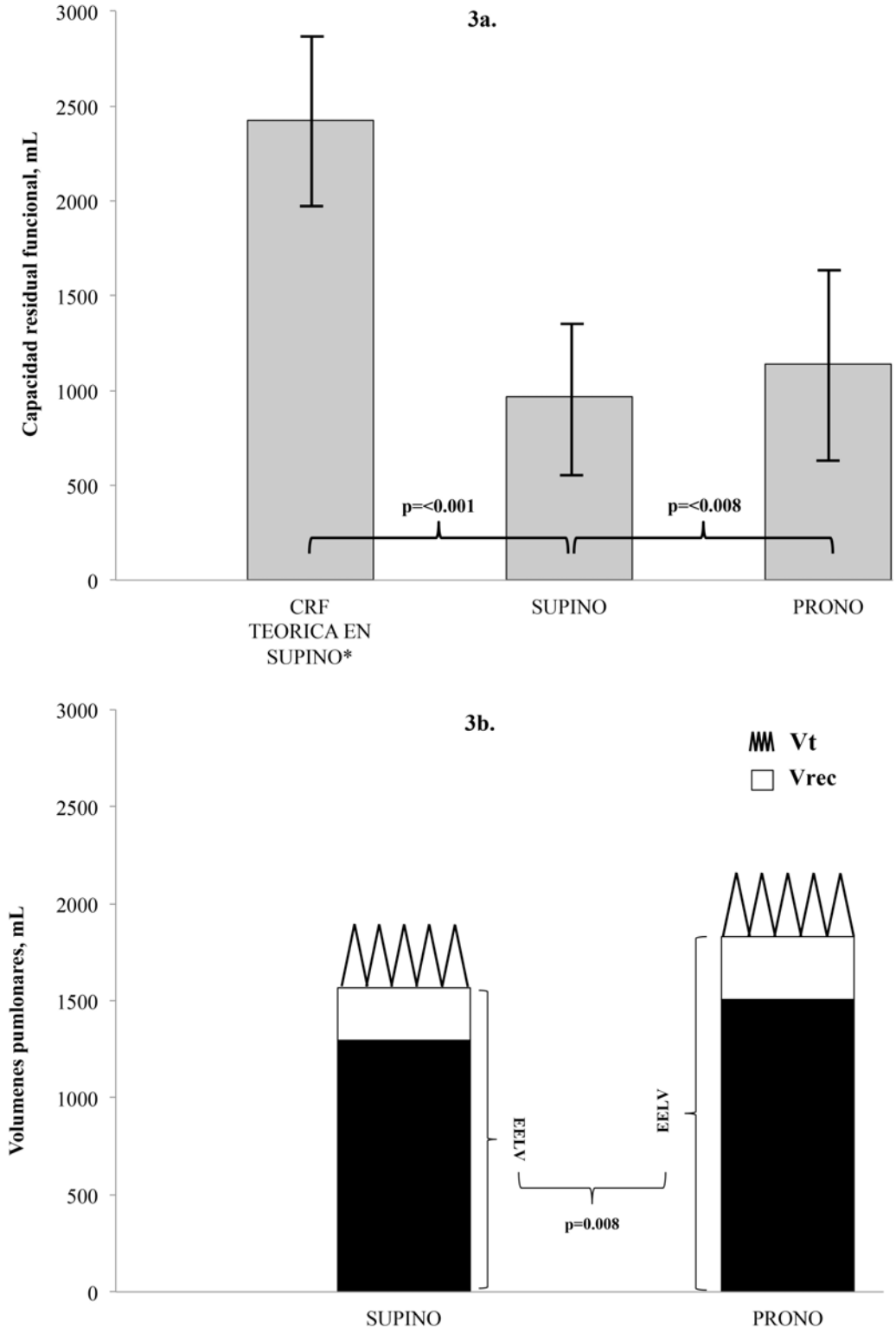
realizado por este mismo grupo de investigadores (39) se encontró que la PP en pacientes con SDRA aumenta el EELV y disminuye el *strain*. La razón por la cual existen datos contradictorios de la variación de los volúmenes pulmonares con el cambio de posición de supino a prono en los estudios previos puede ser explicada por diferencias entre los pacientes con respecto a su mecánica respiratoria, extensión y distribución de lesión pulmonar y presencia de mayor o menor presión abdominal (25, 57).

En este estudio se confirma que los volúmenes pulmonares aumentan en la posición prono, con un aumento del 18% de CRF y un 17% en el EELV. El aumento de los volúmenes pulmonares en posición prono se debe a que con el cambio de posición aumenta el porcentaje de volumen pulmonar bien aireado a expensas de una disminución del porcentaje de volumen pulmonar poco aireado. Esta modificación de los porcentajes de tejidos pulmonares se debe considerar como una mejor distribución del gas administrado más no un aumento del reclutamiento del tejido pulmonar (28, 58) (ver Figura 3). Esta llamada “redistribución del aire administrado” puede explicar también porque el Vrec no varia con el cambio de posición de supino a prono.

Un estudio previo realizado en animales con daño pulmonar (26) y otro estudio realizado en pacientes con SDRA (27) evidenciaron mediante tomografía computarizada que el porcentaje de Vrec fue similar en posición supino y prono. Con diferente metodología, los datos de nuestro estudio corroboran estos resultados (ver Figura 3), lo cual sugiere que en la posición prono el aumento de los aumento de los volúmenes pulmonares se debe probablemente a la redistribución del gas intrapulmonar (aumento de porcentaje de tejido bien aireado a expensas de una disminución del tejido poco aireado) y no a un

aumento del reclutamiento (entendido como disminuición del tejido no aireado) inducido por la PEEP.

Figura 3. Variación de los volúmenes pulmonares con el cambio de posición.



3a. Comparación de diferentes valores de la CRF. 3b. Comparación del EELV y Vrec con el cambio de posición. Los datos estan presentados en media y desvio estándar. * De acuerdo a la ecuación descrita por Ibañez y Raurich. (Ibañez J, Normal values of FRC in the sitting and supine positions. Intensive Care Med. 1982;8:173-7).

Niveles altos de *strain* estático (deformación del tejido pulmonar causado por la PEEP) y de *strain* dinámico (deformación del tejido pulmonar causado por el Vt) se han asociado con daño pulmonar inducido por la ventilación (45, 59). En un modelo animal, Protti et al. encontraron que el *strain* más perjudicial es el *strain* dinámico (46). Los hallazgos de nuestro estudio demuestran una disminución significativa del *strain* mas perjudicial (*strain* dinámico) en la posición prono. Estos datos podrían constituir otro mecanismo de protección de la PP contra el daño pulmonar inducido por la ventilación y explicar el beneficio encontrado en la supervivencia de los pacientes con SDRA grave.

Se realizó una división de los pacientes en SDRA temprano y tardío: en los pacientes con SDRA temprano los volúmenes pulmonares aumentan y el *strain* dinámico disminuye pero en los pacientes con SDRA tardío estos hallazgos no fueron observados. Esto puede ser explicado por la presencia de mayor afectación intersticial en la fase tardía del SDRA (60). Estos hallazgos pueden explicar el beneficio del uso temprano de la PP en la supervivencia de los pacientes con SDRA.

10. CONCLUSIONES

1. El estudio de los efectos fisiológicos de las dos estrategias estudiadas en pacientes con insuficiencia respiratoria grave (alargamiento de la pausa inspiratoria y posición prono) proporcionan nueva información para ayudar en la ventilación mecánica de estos pacientes.
2. El alargamiento de la pausa inspiratoria constituye una herramienta relativamente inocua y fácil para disminuir el volumen corriente administrado y el espacio muerto y ayudar en la ventilación protectiva.
3. La posición prono aumenta los volúmenes pulmonares y disminuye el *strain* dinámico en el tejido pulmonar lo cual ayuda a comprender el efecto beneficioso del prono en la supervivencia.
4. En la posición prono existe una mejor distribución del gas administrado lo que explica un aumento de los volúmenes pulmonares y que el volumen pulmonar reclutado por la PEEP no varíe.

11. IMPLICACIONES FUTURAS

La relativa sencillez e inocuidad de las maniobras estudiadas en la presente tesis facilita su aplicación en el manejo clínico diario de los pacientes con insuficiencia respiratoria aguda severa.

El estudio del alargamiento de la pausa inspiratoria demuestra que la prolongación de la pausa inspiratoria permite disminuir significativamente el volumen corriente administrado. Sus implicaciones futuras son importantes porque proporciona una nueva herramienta a pie de cama para ayudar en la ventilación mecánica protectiva. De la misma manera, los hallazgos del estudio servirán de base para futuros estudios clínicos que valoren el uso de esta maniobra en otras patologías.

El aumento de los volúmenes pulmonares y la disminución del strain dinámico en la posición prono, proporciona una explicación para uno de los posibles mecanismos por los cuales la posición prono mejora los desenlaces clínicos y justifica continuar con su uso en pacientes con SDRA severo. En este estudio, también se evidenció que el volumen pulmonar reclutado inducido por la PEEP no se modifica con el cambio de posición de supino a prono. Esto genera varias hipótesis sobre el sinergismo de la posición prono y la PEEP. Los datos encontrados sirven de base para futuros estudios clínicos individualizados en un primer momento y aleatorizados después que valoren el ajuste de la PEEP en la posición prono y su influencia en los desenlaces clínicos.

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