TESIS DOCTORAL

OPTIMIZACIÓN DE LA MECÁNICA RESPIRATORIA EN EL TRATAMIENTO DE SOPORTE VENTILATORIO DE PACIENTES CON INSUFICIENCIA RESPIRATORIA AGUDA GRAVE

Doctorando

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Departamento de Medicina. Barcelona, 2013

HOSPITAL DE LA SANTA CREU I SANT PAU
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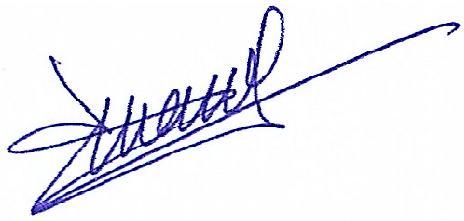

Dr. Jordi Mancebo Cortés

PRESENTACIÓN

Esta Tesis Doctoral se articula como compendio de publicaciones de conformidad con lo que dispone la Normativa académica de la Universitad Autónoma de Barcelona (UAB) aplicable a los estudios universitarios regulados por el RD 1393/2007, de 29 de octubre, modificado por el RD 861/2010, de 2 de julio (texto refundido aprobado por el Acuerdo del Consejo de Gobierno de 2 de marzo de 2011).

Las publicaciones que constituyen esta Tesis se engloban en una misma línea de investigación clínica y fisiopatológica enfocada a analizar, principalmente, los efectos sobre la mecánica respiratoria y el intercambio de gases de diferentes estrategias aplicadas en el transcurso de la ventilación mecánica invasiva. Los resultados obtenidos han aportado información relevante que ha sido utilizada para la elaboración de cuatro artículos publicados en revistas médicas de prestigio internacional y con impacto científico contrastado. Los artículos se presentan en su versión original en lengua inglesa.

La Comisión de Doctorado de la UAB, en la sesión que tuvo lugar el día 18 de julio de 2012, considerando que este formato cumple los requisitos que dispone la normativa, autorizó la presentación de la Tesis Doctoral como compendio de publicaciones.

AGRADECIMIENTOS

Esta tesis doctoral es el resultado del trabajo y el esfuerzo continuado de un gran equipo de profesionales, así como, de la generosa participación de los pacientes y sus familias. Todos ellos han contribuido de forma imprescindible para obtener los resultados aquí recogidos. Muchas gracias a todos.

Quiero expresar mi agradecimiento al Doctor Jordi Mancebo por su competente dirección, su inestimable dedicación y su incansable e implacable empeño en reenseñarme a leer y a escribir.

Gracias a mis maestros y compañeros los Doctores Net, Sánchez, Marruecos, Roglán, Quintana, Betbesé, Santos, Vera, Zapata y Roche por sus innumerables enseñanzas y su apoyo. Su brillo como profesionales y excelencia como personas me hace sentir orgulloso de pertenecer a su familia de intensivistas.

A los Doctores Blanch, Fernández, Fernández-Mondéjar, Zavala, Bellapart, Cabello, Vari y Manero, coautores de las publicaciones que conforman esta tesis, gracias por sus aportaciones. Sin ellas este trabajo no hubiera sido posible.

Gracias a todo el equipo profesional y humano del Servicio de Medicina Intensiva del Hospital de la Santa Creu i Sant Pau que me ha visto y ayudado a crecer como intensivista y como persona.

También quiero dar las gracias a todos los educadores que por acción u omisión han contribuido a mi formación. Gracias a la exactitud de la matemática de Cristina y al pensamiento metódico y reflexivo de Amelia.

Gracias a mi familia que ha moldeado mis valores y conocimientos. Gracias a Eugenio por mostrarme que la pasión por el buen hacer y el detalle marcan diferencia sustancial. Gracias a Felicisimo por enseñarme la importancia de la prudencia y el silencio.

Mis más sinceras gracias a mis padres. Gracias por todo lo que me han dado y por todo lo que me han negado a su debido tiempo. A mi padre, Indalecio, gracias por ejemplarizarme el valor de la humildad, el respeto y el trabajo. A mi madre, Angela, gracias por duplicar su cariño, sus cuidados y su guía.

Quiero agradecerle a mi paciente compañera Mª Eugenia su entrega, sacrificio y sus lecciones acerca de modos, formas, medios y fines. Muchas gracias por completarme y mejorarme.

Finalmente, a mi inagotable pequeño maestro, mi hijo Ignacio, mil gracias por iluminarnos la vida con la inteligencia de tu mirada y un deseo: poder retornarte multiplicadas las enseñanzas que me muestras a diario con la misma sencillez y naturalidad con las que tú lo haces.

A mis padres, esposa e hijo;

por todo y con todo.

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1. LISTADO DE ABREVIATURAS

Crs: Compliancia del sistema respiratorio

DE: Desviación estándar

EPOC: Enfermedad pulmonar obstructiva crónica

FC: Frecuencia cardiaca

FiO_2: Fracción inspirada de oxígeno

FR: Frecuencia respiratoria

GC: Gasto cardiaco

HH: *Heated humidifiers* / Humidificación activa

HME: *Heat and moisture exchangers* / Humidificación pasiva

LPA: Lesión pulmonar aguda

M: Media

n: Número de pacientes evaluados

NAV: Neumonía asociada a la ventilación

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

PaO_2: Presión parcial de oxígeno en sangre arterial

PAM: Presión arterial sistémica media

PAPM: Presión arterial pulmonar media

PCP: Presión capilar pulmonar

PEEP: Presión positiva total al final de la espiración

pH: pH arterial

Ppico: Presión pico de la vía aérea

Pplat: Presión plateau o meseta de la vía aérea

RM: *Recruitment Maneuver /* Maniobra de reclutamiento

SAPS II: Simplified acute physiology score II

SDRA: Síndrome de distrés respiratorio agudo

SMI: Servicio de medicina intensiva

TET: Tubo endotraqueal

Vc: Volumen compresible

Vd: Espacio muerto

Vd_{alv} : Espacio muerto alveolar

Vd_{aw}: Espacio muerto de la vía aérea

Vd_{phys}: Espacio muerto fisiológico

Vd/Vt: Espacio muerto / Volumen circulante

Vt: Volumen circulante o tidal

VM: Ventilación mecánica

VMNI: Ventilación mecánica no invasiva

WOB: *Work of breathing* / Trabajo respiratorio

2. INTRODUCCIÓN

La ventilación mecánica (VM) es un procedimiento ampliamente empleado en la atención de los pacientes con insuficiencia respiratoria aguda grave desde 1952 (1). Sin embargo, existen diferencias significativas en su empleo si atendemos a los modos ventilatorios, los parámetros empleados y la mortalidad de los pacientes sometidos a VM entre diferentes países e incluso entre diferentes centros de un mismo país. Estudios descriptivos realizados en la década de los setenta cifran la mortalidad de los pacientes sometidos a VM en porcentajes entre el 47% y el 63% (2, 3). Esta variabilidad es conocida puesto que la enfermedad desencadenante, su gravedad y las comorbilidades individuales tienen un papel decisivo en el pronóstico de los pacientes ventilados (4).

Desde un punto de vista general, la potencialidad de los beneficios de las intervenciones clínicas para mejorar la atención de los pacientes con insuficiencia respiratoria aguda grave sometidos a VM puede ser amplia. Los estudios multicéntricos internacionales, prospectivos y observacionales llevados a cabo por Esteban y colaboradores en 1998 y 2004 son los descriptivos más extensos hasta la actualidad acerca del empleo de la VM (5, 6). En el primero de ellos, los autores describen una mortalidad global en los pacientes sometidos a VM del 31%, siendo de hasta el 52% en los pacientes con síndrome de distres respiratorio agudo (SDRA). En este primer estudio (5), los principales factores asociados de forma independiente al aumento de mortalidad fueron la presencia de coma en el momento de instaurar la VM, las presiones plateau (Pplat) elevadas durante el manejo de la VM y la presencia de una relación entre la presión arterial de

oxígeno y la fracción inspirada de oxígeno bajas (PaO_2/FiO_2<100). En el segundo estudio (6) y a pesar de haberse implementado diferentes prácticas para mejorar el pronóstico en la rutina asistencial de los pacientes bajo VM respecto al estudio de 1998 con aspectos como: el aumento del uso de la ventilación mecánica no invasiva (VMNI), el descenso en los volúmenes circulantes (Vt) y el aumento de los niveles de presión positiva al final de la espiración (PEEP), se demuestra que la mortalidad en el SDRA no ha disminuido.

Dentro del espectro de la indicación y el empleo de la VM hay dos fases que son primordiales para la evolución de estos pacientes. La primera es la fase inicial de la insuficiencia respiratoria aguda que precisa de la instauración de la VM y la indicación de los parámetros ventilatorios más adecuados para un paciente determinado en la fase más crítica. Una vez resuelta esta fase y en un continuo inmediato pasamos al periodo de liberación de la VM, que en condiciones ideales debería ser lo más corto posible y concluir exitosamente con la extubación del paciente, es decir, sin necesidad de reintubación. Ambas fases son cruciales en el pronóstico de los pacientes sometidos a VM y de ahí que los estudios que conforman esta tesis abarquen ambos periodos.

Como hemos comentado, la expresión más catastrófica de la insuficiencia respiratoria aguda grave es el SDRA (7), cuya definición se ha modificado recientemente (8). El SDRA presenta mortalidades que oscilan según los estudios entre 34 y 65% (5, 6, 9-11), sin que haya disminuido sustancialmente en los últimos años (6, 12). Resultados dispares y controvertidos se extraen de los estudios que han evaluado el empleo de diferentes estrategias ventilatorias y agentes farmacológicos en estos pacientes como: el decúbito prono (13-16), la

ventilación de alta frecuencia (17, 18), las técnicas de oxigenación extracorpórea (19, 20), el óxido nítrico inhalado (21), los corticoides (22, 23) u otros como la prostaciclina inhalada (24) o los β-bloqueantes (25). Sin embargo, las únicas terapias que han demostrado modificar la mortalidad de los pacientes adultos con SDRA es la forma en la que se seleccionan los parámetros ventilatorios en las fases precoces de la enfermedad (26) y el decúbito prono (16% de mortalidad en los pacientes pronados respecto un 32% en los que no) (27). Cinco estudios randomizados y controlados han evaluado los efectos del uso de bajos Vt en la supervivencia de los pacientes con SDRA obteniendo resultados dispares entre ellos (28-32). Además, diferentes análisis sobre el empleo del Vt durante la VM sugieren que la relación entre la Pplat y la mortalidad puede ser un gráfico con curva en forma de "J" en la que la mortalidad aumenta en los extremos de la curva (33-35). De toda esta discusión, lo que ha quedado aclarado es que el uso de Vt elevados que generen elevadas Pplat se asocia a aumento de la mortalidad (36-38), siendo el empleo de Vt elevado determinante en el aumento de la permeabilidad alveolar (39). La controversia continúa en la actualidad en lo que respecta al empleo de Vt bajos o al uso de PEEP elevadas en los pacientes con SDRA (40-43). No obstante, parece que la indicación de niveles de PEEP elevados en los pacientes más graves puede ser beneficioso (44) y que el uso de PEEP alta pudiera disminuir el uso de otras maniobras ventilatorias de rescate (45). En este contexto, hay múltiples estudios que evalúan el empleo de diferentes maniobras de reclutamiento alveolar (RM) como terapia coadyuvante durante la VM para mejorar el intercambio de gases, la mecánica respiratoria e incluso optimizar los niveles de PEEP (46, 47). Sin embargo, su empleo, tanto en

términos del tipo de maniobra como de la propia necesidad de su uso, sigue siendo controvertido a día de hoy (48, 49). Hasta la fecha de publicación de nuestro estudio, únicamente dos estudios habían evaluado el efecto de las RM a altas presiones en este tipo de pacientes obteniendo resultados divergentes (46, 47). Por esto último; diseñamos un estudio dirigido a responder la siguiente cuestión; ***¿Se puede mejorar el intercambio de gases, la mecánica respiratoria y optimizar la PEEP en los pacientes con SDRA mediante una maniobra de reclutamiento alveolar alcanzando altas presiones de vía aérea? (50).***

Durante el tiempo de uso de la VM, el empleo de un dispositivo de humidificación que proporcione una adecuada humidificación y calentamiento de los gases es vital para preservar esta función del sistema respiratorio (51). Estos dispositivos necesariamente añaden espacio muerto instrumental, modificando la mecánica ventilatoria y el intercambio de gases (52). Además, cualquier tipo de estrategia terapéutica que facilite la disminución del Vt, disminuyendo la Pplat generada puede ser de utilidad en el manejo de los pacientes con lesión pulmonar aguda (LPA) o SDRA puesto que tanto la acidosis respiratoria como las Pplat elevadas son datos importantes a tener en cuenta en la selección de los parámetros ventilatorios. Solo dos estudios clínicos han evaluado el papel que sobre el intercambio de gases tiene el tipo de humidificación empleado en la fase aguda de los pacientes con SDRA (53, 54). Por ello, nos preguntamos; ***¿Podemos disminuir la carga ventilatoria y mejorar la mecánica respiratoria de nuestros pacientes con LPA/SDRA en función del tipo de humidificador que empleemos en la fase aguda de la enfermedad? (55).***

Como hemos comentado, una vez resuelta la causa desencadenante de la insuficiencia respiratoria y superada la fase crítica que generó su indicación se inicia el proceso de la liberación del ventilador (también denominado *weaning* o destete de la VM) (56, 57). Este proceso puede fracasar por diferentes motivos en aproximadamente un 30% de los pacientes (58-61). En estos casos, el tiempo de desconexión de la VM puede representar el 40% del tiempo total de VM (56, 57). El conocer esta circunstancia es importante, puesto que, la prolongación innecesaria del tiempo de intubación del paciente conlleva un aumento de la morbilidad, principalmente por la aparición de neumonía asociada a la ventilación (NAV) (62). Una vez que finaliza el periodo de desconexión de la VM y que se identifica al paciente como desconectable del respirador se procede, habitualmente, a la realización de un test de respiración espontánea para valorar la extubación (63, 64). Se ha demostrado que los métodos más apropiados para realizar este test son el Pieza en T o un bajo nivel de presión de soporte, siendo similar el índice de fracaso y reintubación entre ambos test (56, 57). Sin embargo, el trabajo respiratorio necesario para superar un test de respiración espontánea con Pieza en T es mayor que para superar un test con bajos niveles de presión de soporte (65, 66) y el porcentaje de fracasos en la tolerancia al test con Pieza en T es significativamente mayor que con presión de soporte (57, 66). Esto es especialmente evidente en pacientes que ya han fracasado en un primer test de respiración espontánea. En este momento, la progresiva obstrucción del tubo endotraqueal (TET) secundario a la adhesión de secreciones respiratorias y al consecuente aumento de las resistencias durante el transcurso de la VM (67-70) se ha asociado a la disminución del diámetro del TET con el consecuente

aumento del trabajo respiratorio (WOB) (71). Este hecho. modifica el patrón respiratorio de los pacientes y prolonga el destete ventilatorio (72-74). La obstrucción del TET ha sido propuesta como una medida indirecta de la idoneidad de la humidificación y calentamiento de los gases inspirados durante la VM (69). En esta situación, una correcta indicación del tipo de humidificación a emplear puede evitar un aumento innecesario de la resistencia del TET. Este aumento de la resistencia podría ser causa de intolerancia a las pruebas de respiración espontánea y, eventualmente, prolongar los días de VM. Por lo que, también, creemos que sería interesante responder la siguiente pregunta; ***¿Cómo se afecta la resistencia al flujo aéreo debida a la adherencia de secreciones al tubo endotraqueal en función del tipo de humidificación empleada durante la VM y que implicación fisiológica puede tener desde el punto de vista del trabajo respiratorio? (75).***

El conocimiento de todos estos aspectos de la fisiopatología respiratoria, puede evitar decisiones poco acertadas que podrían sumarse y, eventualmente, ser limitantes de una idónea evolución de nuestros pacientes sometidos a VM. Nosotros creemos que la optimización individualizada paciente a paciente de todos los parámetros y las terapias ventilatorias coadyudantes puede mejorar la mecánica respiratoria y el intercambio de gases. Además, el conocimiento de los posibles mecanismos limitantes para la desconexión de la VM nos puede ayudar a no prolongarla de forma innecesaria y evitar así morbilidad añadida. Se trataría de minimizar los efectos deletéreos inherentes a la VM que, paradójicamente, pueden ser indistinguibles de la enfermedad que desencadenó su necesidad (76).

3. OBJETIVOS Y JUSTIFICACIÓN

Los objetivos a estudiar y las justificaciones científicas en que se basan las cuestiones que hemos formulado en la introducción se resumen seguidamente:

Primero. EFECTOS FISIOLÓGICOS AGUDOS DE UNA MANIOBRA DE RECLUTAMIENTO ALCANZANDO ALTAS PRESIONES DE LA VÍA AÉREA EN PACIENTES CON SÍNDROME DE DISTRES RESPIRATORIO AGUDO.

Durante la VM de la fase aguda de la LPA o del SDRA la estrategia ventilatoria habitual para proteger el pulmón consiste en el empleo de Vt y presión de vía aérea moderados (6). Además, hay autores que han sugerido que el empleo de maniobras de apertura pulmonar que combinen RM y niveles de PEEP suficientes pueden ser de utilidad para abrir y mantener abierto el pulmón (77, 78). En este contexto, no debemos olvidar que los efectos clínicos y fisiológicos de las RM pueden variar sustancialmente en función del Vt y de la PEEP empleados antes y tras la RM (35, 79-83), el tipo de maniobra aplicada (48, 49) , la estrategia ventilatoria (84-87) y el tipo de lesión pulmonar (85). Además, la aplicación de las RMs se puede acompañar de efectos indeseados, principalmente hemodinámicos (85, 88). Por todos estos factores, la utilidad de las RM sigue siendo controvertida desde hace años (48) (Anexo I).

El uso de presiones de vía aérea por encima de 40 cmH_2O se han propuesto para alcanzar el máximo reclutamiento pulmonar. Dos estudios clínicos realizados en pacientes con LPA/SDRA han evaluado diferentes RMs realizadas a estas presiones (46, 47) . En uno de ellos (46) se empleó basalmente un Vt de 6 ml/Kg

del peso predicho del paciente y un nivel de PEEP de 5 cmH_2O y aplicaron una RM escalonada hasta alcanzar una combinación de Pplat y PEEP de 60/45 cmH_2O. Estos autores observaron un aumento de la oxigenación homogéneo entre pacientes y detectaron, mediante tomografía, un reclutamiento alveolar significativo. En el otro estudio (47), los autores usaron basalmente un Vt de 8,8 ml/Kg y unos niveles de PEEP media de 11 cmH_2O, a los que superpusieron una RM que combinaba durante 2 minutos una Pplat de 45 cmH_2O con una PEEP de 5 cmH_2O, observando una respuesta muy variable tanto en términos de reclutamiento como de oxigenación. Dados los diferentes diseños entre ambos estudios es imposible determinar la influencia de la estrategia ventilatoria basal y la RM. Nosotros proponemos el estudio clínico fisiológico de la aplicación de una RM escalonada a elevadas presiones seguida de una estrategia decreciente de PEEP para tratar de optimizar su ajuste (46). Añadimos esta estrategia a la VM rutinaria de los pacientes con LPA/SDRA (47) con la intención de analizar los efectos a corto plazo sobre el intercambio de gases, la mecánica respiratoria y la hemodinámica en la fase precoz de la VM de los pacientes con LPA/SDRA.

Segundo. COMPARACIÓN DE LOS EFECTOS SOBRE LA MECÁNICA RESPIRATORIA Y EL INTERCAMBIO DE GASES DE LA HUMIDIFICACIÓN PASIVA Y LA HUMIDIFICACIÓN ACTIVA EN LOS PACIENTES CON LPA/SDRA.

La humidificación y el calentamiento de los gases empleados durante la VM es de vital importancia puesto que la función de la vía aérea superior está anulada por el TET (51). En la rutina asistencial se emplean dos tipos de dispositivos para

humidificar; los pasivos ("*heat and moisture exchangers*" o HME) y los activos ("*heated humidifiers*" o HH). Tanto la humidificación insuficiente como la excesiva puede producir disfunción de la mucosa respiratoria y el consecuente riesgo de obstrucción del tubo endotraqueal (89, 90).

Durante el empleo de la VM, el equipo instrumental respiratorio añade espacio muerto (Vd) (TET, humidificador, conectores). En el paciente sometido a VM, este Vd se considera parte del espacio muerto de la vía aérea (Vd_{aw}) (espacio muerto anatómico e instrumental). El espacio muerto fisiológico (Vd_{phys}) incluye el Vd_{aw} y el alveolar (Vd_{alv}) y es el porcentaje del total del Vt que no participa en el intercambio de gases (Vd/Vt) (52). En consecuencia, el tipo de humidificación empleado puede jugar un papel importante, tanto en la mecánica respiratoria como en el intercambio de gases. Este aspecto, puede ser importante en los pacientes con LPA/SDRA puesto que la acidosis respiratoria y las Pplat elevadas pueden ser limitantes en los ajustes de la VM.

Hasta la fecha, dos estudios se han centrado en los efectos de la disminución del espacio muerto instrumental sobre la presión parcial arterial de dióxido de carbono ($PaCO_2$) en pacientes adultos con LPA/SDRA, (53, 54). Nosotros planteamos un estudio clínico fisiológico que además de estudiar el intercambio de gases producido por la minimización del Vd instrumental mediante la substitución de los dispositivos tipo HME por HH, ha evaluado los efectos de esta estrategia sobre la distensión alveolar en términos de Pplat y compliancia del sistema respiratorio (Crs) cuando se mantiene invariada la $PaCO_2$.

Tercero. COMPARACIÓN DE LOS EFECTOS DE DOS SISTEMAS DE HUMIDIFICACIÓN EN LA RESISTENCIA AL FLUJO AÉREO DEL TUBO ENDOTRAQUEAL DURANTE LA VENTILACIÓN MECÁNICA.

Durante la VM las secreciones respiratorias de los pacientes se adhieren a la superficie interna del TET, con lo que el diámetro efectivo de TET disminuye y la resistencia al flujo aéreo aumenta (67, 68). Este efecto puede ser mayor con el uso prolongado de los HME que con los HH (69, 70). En este contexto, la correcta elección del tipo de humidificador a emplear es importante puesto que el rendimiento de los diferentes dispositivos puede ser muy dispar (91, 92). En lo que se refiere a incidencia de NAV, morbilidad o mortalidad, el análisis de los datos de que disponemos hasta la actualidad no ha demostrado diferencias entre los dispositivos activos y los pasivos (93, 94). Por todo ello, la elección del tipo de humidificación se debe basar en la patología del paciente (54, 55), la mecánica respiratoria (72), la calidad de las secreciones respiratorias (95), la estrategia ventilatoria (96) y la temperatura ambiente y del paciente (97).

La progresiva obstrucción del TET secundario a la adhesión de secreciones se ha asociado a aumento del trabajo respiratorio, que puede prolongar el destete ventilatorio y modificar el patrón respiratorio de los pacientes (72-74).

Dos estudios monocéntricos han estudiado la caída de presión a través del TET generado por la adherencia de las secreciones respiratorias. Ambos asignaron el tipo de humidificación de forma aleatoria y observaron que la resistencia del TET era significativamente mayor cuando los gases inspiratorios se acondicionaron con un HME pasivo en lugar de un HH activo (69, 70). Nosotros proponemos

valorar la resistencia al flujo aéreo del TET tras la extubación en un grupo de pacientes con necesidad de ventilación mecánica prolongada. En este estudio comparamos los cambios en la resistencia del TET cuando ambos tipos de dispositivos de humidificación son asignados en función de las necesidades clínicas y ventilatorias individuales de los pacientes, siguiendo las recomendaciones actuales de indicación del tipo de humidificación (98, 99).

Seguidamente se resumen los métodos empleados en los estudios y se muestran los principales resultados obtenidos, seguidos de las correspondientes publicaciones científicas.

4. MÉTODOS

Primero; el estudio de los efectos fisiológicos agudos de una RM a altas presiones, se realizó mediante un estudio clínico multicéntrico, prospectivo y abierto que incluyó 13 pacientes adultos en la fase aguda precoz de la LPA / SDRA bajo VM.

El estudio, resumidamente, constó de cuatro fases:

- Se realizó una RM en ventilación controlada por presión a FiO_2 de 1, partiendo de la ventilación pautada por su facultativo responsable. La RM se inició con una combinación Pplat/PEEP de 40/25 cmH_2O. Cada 2 minutos aumentamos la presión de la vía aérea 5 cmH_2O hasta una PaO_2/FiO_2 de 350 mmHg o una Pplat/PEEP de 60/40 cmH_2O.
- Se disminuyó la PEEP escalonadamente 2 cmH_2O cada 4 minutos hasta que se observó una caída en la PaO_2 mayor al 10% de la máxima obtenida durante la insuflación. Este nivel de presión se consideró el mínimo necesario para evitar la reaparición del colapso alveolar.
- Se repitió durante 1 minuto la máxima Pplat/PEEP empleada para reclutar cada paciente, se ajustó la PEEP 2 cmH_2O por encima de la presión de colapso alveolar hallada en la segunda fase del estudio y se mantuvo hasta el final del periodo de seguimiento.
- Se realizó un seguimiento estricto de todas las variables de mecánica respiratoria, intercambio de gases y hemodinámicas durante las dos horas siguientes a la RM.

Los criterios para abortar la RM fueron, una variación ± 20% en la frecuencia cardiaca (FC), o un descenso > 20% en la presión arterial sistémica media (PAM), la PaO_2 o el gasto cardiaco (GC) si estaba monitorizado. Se realizó una radiografía de tórax justo tras la maniobra y a las 24 horas de la misma.

Segundo; la comparación de los efectos a corto plazo del tipo de humidificación empleada (HH versus HME) en la mecánica respiratoria y en la gasometría, se realizó mediante un estudio clínico monocentro, prospectivo y abierto que incluyó 17 pacientes en la fase aguda precoz de la LPA / SDRA invasivamente ventilados. El estudio, resumidamente, se diseñó en tres fases:

- Se realizaron determinaciones basales con los pacientes humidificados con HME y ventilados con los parámetros pautados por su facultativo responsable.
- Se mantuvieron todos los parámetros ventilatorios, se procedió al cambio del tipo de humidificación por HH y se realizaron nuevas determinaciones.
- Usando el mismo HH, se procedió a disminuir el Vt hasta que las cifras de $PaCO_2$ retornaron a los niveles basales.

Durante todo el estudio se mantuvieron invariables los niveles de FiO_2, frecuencia respiratoria (FR) y PEEP. En cada una de las fases, una vez alcanzada la estabilidad ventilatoria tras las modificaciones, se recogieron datos de mecánica respiratoria, Vd_{phys}, intercambio de gases, parámetros hemodinámicos y temperatura de los pacientes.

Tercero; para la comparación de los efectos del tipo de humidificación en la resistencia al flujo aéreo del TET durante la VM, se asignó el tipo de humidificación (HH versus HME) en función de las recomendaciones clínicas actuales.

Se diseñó un estudio clínico prospectivo de cohortes llevado a cabo en nuestro Servicio de Medicina Intensiva (SMI). El acondicionamiento de los gases durante la VM se realizó usando dispositivos tipo HH en 22 pacientes y tipo HME en otros 22. Para poder realizar la comparación entre grupos, los pacientes se emparejaron por el diámetro del TET, los días de ventilación mecánica, el *Simplified acute physiology score II* (SAPS II) y el balance hídrico (por este orden).

La medida de la resistencia al flujo aéreo de los TET se realizó justo tras la extubación de los pacientes y con TET limpios de idéntico diámetro para poder calcular el aumento de resistencias.

Realizamos una estimación del incremento de WOB relacionado con el aumento de la caída de presión a través de los TET tras la extubación respecto a los TET limpios; para este cálculo se asumió un Vt de 500 ml, un flujo inspiratorio constante de 60 L/min y una FR de 20/min (tiempo inspiratorio de 0,5 segundos y tiempo espiratorio de 2,5 segundos).

5. ANÁLISIS ESTADÍSTICO

El análisis estadístico fue realizado mediante el software SPSS® (versión 17.0, Chicago, IL, USA). Para la comparación de medidas repetidas en el tiempo aplicamos el análisis de varianza (ANOVA). Si se observaron diferencias significativamente estadísticas aplicamos el análisis de Student-Newman-Keuls para comparar diferentes fases de los estudios. Para confirmar la distribución normal y la igualdad de las varianzas se emplearon respectivamente los test de Kolmogorov-Smirnov y de Levene. En los casos en que los datos obtenidos mostraron una distribución normal y el análisis de las varianzas no obtuvo diferencias usamos el test de Student para la comparación. Para las variables que no siguieron una distribución normal empleamos el test de Mann-Whitney. Las variables dicotómicas se compararon mediante el método de Chi cuadrado junto con el test exacto de Fisher para dos colas. Un valor de p menor de 0,05 se consideró estadísticamente significativo. Los datos están expresados en medias más/menos desviación estándar (M±DE). El cálculo de la muestra para el estudio de las resistencias de los TET en función del humidificador empleado se realizó asumiendo lo siguiente: Primero, calculamos la resistencia basal de los TET limpios (6,8 ± 1,1 $cmH_2O/l/seg$). Segundo, y de acuerdo con los datos previos (69, 70), consideramos clínicamente relevante una diferencia absoluta en la resistencia del TET de 1,0 $cmH_2O/l/seg$ entre los grupos. Tercero, basados en las dos premisas anteriores, para detectar una diferencia significativa entre los grupos mediante un test de dos colas (error Tipo I de 5%; $\alpha = 0,05$) con al menos una potencia estadística del 80% ($\beta = 0,20$), precisándose 22 pacientes por grupo.

6. RESULTADOS

EFECTOS FISIOLÓGICOS AGUDOS DE LA APLICACIÓN DE UNA MANIOBRA DE RECLUTAMIENTO ALVEOLAR ESCALONADA ALCANZANDO ALTAS PRESIONES DE VÍA AÉREA EN PACIENTES CON SDRA.

Los principales resultados obtenidos en este estudio se recogen en la Tabla 1.

Tras la RM, la Crs aumento respecto a la basal en seis pacientes (Grupo 1) pero no aumentó en los otros siete (Grupo 2). Entre ambos grupos, la Crs basal fue significativamente diferente (34±9 versus 24±7 ml/cmH_2O; p=0,045, Grupo 1 y 2 respectivamente). Tras la RM, la Crs también fue diferente entre estos grupos (42±8 versus 22±6 ml/cmH_2O; p<0,001, Grupo 1 y 2 respectivamente). La Pplat basal no presentó diferencias entre grupos (27±5 versus 33±5 cmH_2O; Grupo 1 y 2 respectivamente, p=0,067). Al final del estudio, la Pplat fue 28±4 cmH_2O en el Grupo 1 comparada con 35±6 cmH_2O en el 2 (p=0,021) a pesar de la tendencia al empleo de un Vt más elevado en el Grupo 1 (8,4 versus 7,0 ml/kg; p=0,125). El aumento de Crs correlacionó con el de PaO_2 (r=0,719; p=0,006).

Globalmente, la PEEP empleada al final del estudio fue más alta que la basal (15±4 versus 12±3 cmH_2O; p<0,001). En 8 pacientes la PEEP se aumento ≥2 cmH_2O (de 12±3 a 17±4 cmH_2O); en los otros 5 la PEEP se mantuvo ±1 cmH_2O respecto a la inicial (12±4 cmH_2O); entre ambos subgrupos las diferencias fueron significativas en términos de PEEP (p<0,05). Los cambios en la PEEP al final del estudio respecto a la basal correlacionaron con los aumentos individuales de PaO_2 (r=0,673; p=0,012).

Tabla 1. Variables respiratorias, mecánica pulmonar, intercambio de gases y parámetros hemodinámicos antes de la RM, durante la máxima RM y durante el periodo de seguimiento tras la RM escalonada (FiO_2 1) (n= 13 pacientes, excepto si se especifica otra).

	Pre-RM	Max-RM	15 min RM	120 min RM	*P*
FR; respiraciones/min	26±7	26±7	26±7	26±7	1
PEEP; cmH_2O	12±3 [a]	38±3 [b]	15±4	15±4	< 0,001
Vt; ml	470±68	256±118 [b]	464±80	458±85	< 0,001
Vt; ml/kg	7,8±1,2	4,3±2 [b]	7,8±1,6	7,7±1,6	< 0,001
Pplat; cmH_2O	30±6	55±4 [b]	32±6 [c]	32±6 [c]	< 0,001
Crs; ml/cmH_2O	28±9	16±7 [b]	31±11	31±12	< 0,001
pH	7,35±0,06	7,20±0,11 [b]	7,31±0,07 [d]	7,34±0,05	< 0,001
PaO_2; mmHg	187±102 [a]	303±148	361±165	339±136	< 0,001
$PaCO_2$; mmHg	46±10	70±17 [b]	51±12 [d]	48±11	< 0,001
FC; latidos/min	96±21	105±31	105±26	102±27	0,143
PAM; mmHg	83±15	79±25	81±12	84±15	0,615
PAPM; mmHg (n=10)	31±5	44±6 [b]	31±4	30±4	< 0,001
GC; l/min (n=10)	6,7±2,3	5,4±2,4 [c]	6,2±2,4	6,3±2,6	0,031
PCP; mmHg (n=9)	15±3	27±4 [b]	15±3	16±3	< 0,001

Pre-RM= antes de la maniobra de reclutamiento; Max-RM= máxima presión de vía aérea; 15 min-RM=tras 15 minutos del final de la RM; 120 min-RM=tras 120 minutos del final de la RM; Valores expresados como media ± desviación estándar.

Diferencias entre fases (p<0,05): a = pre-RM vs otras fases; b = max-RM vs otras fases; c = respecto pre-RM; d = 15' post-RM vs 120' post-RM

Siete pacientes no alcanzaron la meta de PaO_2>350 mmHg durante la máxima combinación de Pplat/PEEP empleada. A pesar de no haber diferencias basales en términos de PaO_2 o $PaCO_2$; en el momento de máxima presión en la vía aérea, la PaO_2 fue significativamente mayor en el Grupo 1 (en los que aumento la Crs al final del estudio) que en el Grupo 2 (400±54 versus 221±156 mmHg; p=0,023); y la $PaCO_2$ menor en el Grupo 1 (59±9 versus 80±17 mmHg; p=0,17).

Los cambios hemodinámicos durante la RM revirtieron en los primeros 15 minutos tras la RM. El GC (n= 10) fue menor al final del estudio respecto a los basales

comparando los pacientes en los que no se aumentó la PEEP respecto a los que si se les pudo aumentar (4,5 versus 8 l/min; p=0,047; cinco pacientes por grupo).
La RM se abortó en cuatro pacientes por efectos deletéreos. En tres de los pacientes por caída del GC mayor al 20% respecto a la basal, en uno de ellos la disminución del GC se asoció a hipotensión arterial severa y caída en la PaO_2. Otro paciente presentó una taquicardia paroxística supraventricular. Todos estos efectos adversos revirtieron al disminuir las presiones de la vía aérea.

USO DE HUMIDIFICACIÓN ACTIVA EN LA FASE AGUDA DE LA LPA/SDRA.

Los principales resultados obtenidos en este estudio se recogen en la Tabla 2.
El cambio de humidificación pasiva (HME) a activa (HH) fue responsable de un descenso en la $PaCO_2$ (46±9 mmHg a 40±8 mmHg, p<0,001) y un aumento en el pH (7,34±0,10 a 7,39±0,11, p<0,001). El descenso en la $PaCO_2$ se correlacionó con la $PaCO_2$ inicial (r=0,59; p=0,016). El descenso en la $PaCO_2$ secundario al cambio de humidificación no presentó diferencias significativas (p=0,48) comparando los pacientes hipercápmicos (n=6) con los no hipercápmicos (n=11).
Respecto a la situación basal, el uso de HH redujo el Vd/Vt (0,69±0,11 a 0,60±0,13, p<0,001) y en el Vd_{phys} (352±63 a 310±74 ml, p<0,001). El Vd/Vt fue diferente entre los pacientes hipercápmicos y no hipercápmicos en la primera fase del estudio (0,76±0,09 versus 0,65±0,11 respectivamente; p = 0,036).
En la tercera fase del estudio, la combinación de HH y Vt bajo (sin cambios gasométricos respecto a la situación inicial con HME y Vt basal) consiguió un descenso en el Vt empleado de 521±106 a 440±118 ml, p<0,001 (7,3±1,1 a

6,1±1,3 ml/kg del peso medido al ingreso y de 8,3±1,6 a 6,9±1,8 en términos de peso predicho (PBW), p<0,001 en ambos). La Pplat disminuyó de 25±6 a 21±6 cmH_2O; p<0,001) y la Crs aumento de 35±12 a 42±15 ml/cmH_2O, p=0,003. El descenso del Vt realizado entre la 2ª y 3ª fase se correlacionó con la mejora en la Crs (r= 0,52, p=0,031). Los cambios en el Vt y el Vd_{phys} entre las mismas fases también se correlacionó significativamente (r= 0,78; p<0,001).

Tabla 2. Datos de la mecánica respiratoria e intercambio de gases (n= 17).

	HME (1ª fase)	**HH (2ª fase)**	**HH- lowVt (3ª fase)**	***p***	***Diferencias entre grupos***
Ppico; cmH_2O	36±8	34±7	29±8	< 0,001	a, b, c
Pplat; cmH_2O	25±6	25±6	21±6	< 0,001	a, b
PEEPtot; cmH_2O	9±2,5	9±2,5	9±2,5	1	
Vt; ml	521±106	521±106	440±118	< 0,001	a, b
Vt; ml/kg[1]	7,3±1,1	7,3±1,1	6,1±1,3	< 0,001	a, b
Vt; ml/kg[2] (n=12)	8,3±1,6	8,3±1,6	6,9±1,8	< 0,001	a, b
Vd_{phys}; ml	352±63	310±74	269±80	< 0,001	a, b, c
Vd/Vt	0,69±0,11	0,60±0,13	0,62±0,12	< 0,001	a, b, c
FR; respiraciones/min	20±6	20±6	20±6	1	
Crs; ml/cmH_2O	35±12	35±12	42±15	= 0,001	a, b
pH	7,34±0,10	7,39±0,11	7,33±0,10	< 0,001	b, c
PaO_2; mmHg	96±22	99±29	91±19	=0,28	
$PaCO_2$; mmHg	46±9	40±8	45±9	< 0,001	b, c
FiO_2	0,5±0,2	0,5±0,2	0,5±0,2	1	
Vc; ml	53±29	52±28	43±25	< 0,001	a, b
Vt_{Vc}; ml	468±110	469±109	397±117	< 0,001	a, b
$Vd_{phys\text{-}Vc}$; ml	316±66	279±74	243±79	< 0,001	a, b, c
Crs_{Vc}; ml/cmH_2O	32±12	32±12	38±15	=0,002	a, b

[1]Peso medido al ingreso; [2]Peso predicho calculado. Vc = Volumen compresible Vt_{Vc}, $Vd_{phys\text{-}Vc}$, Crs_{Vc} = volumen circulante, espacio muerto fisiológico y compliancia respiratoria teniendo en cuenta el volumen compresible. Valores expresados como media ± desviación estándar.
Diferencias entre fases (p<0,05): a = 1ª fase vs 3ª fase; b = 2ª fase vs 3ª fase; c = 1ª fase vs 2ª fase.

El descenso tanto en la Pplat como en el Vd_{phys} no se correlacionó sus niveles basales. En cambio, las cifras de Vt y Vd_{phys} basales se correlacionaron entre si (r=0,60; p=0,011) y el descenso en la Pplat entre la 1ª y la 3ª fase se correlacionó con el descenso en el Vd_{phys} entre las mismas fases (r=0,59; p=0,013).
Todos los parámetros hemodinámicos se mantuvieron estables durante el estudio. Ningún paciente tuvo que excluirse por cambios en la temperatura corporal.

EFECTOS DEL TIPO DE HUMIDIFICADOR EN LA RESISTENCIA AL FLUJO AÉREO DEL TUBO ENDOTRAQUEAL.

Los principales resultados obtenidos en este estudio se recogen en la Tabla 3.
Se estudiaron 44 TETs prospectiva y consecutivamente, 22 de pacientes humidificados activamente (grupo HH) y 22 de pacientes humidificados pasivamente (grupo HME); todos intubados orotraquealmente con TET de diámetros entre 7,0 y 8,5 mm. La resistencia medida de los TET fue significativamente mayor tras la extubación que antes de su uso (10,4±4,0 versus 6,8±1,1 $cmH_2O/L/seg$; p<0,001). La resistencia de los TET aumentó en ambos grupos; de 6,8±1,1 a 10,6±4,3 $cmH_2O/L/seg$ (p<0,001) en los pacientes del grupo HH y de 6,8±1,1 a 10,2±3,8 $cmH_2O/L/seg$ (p<0,001) en los pacientes del grupo HME. El aumento de las resistencias de los TET no se correlacionó con la duración de la VM en ninguno de los grupos. El porcentaje de aumento de las resistencias de los TET fue similar entre grupos (57 versus 51 %, p=0,771; HH y HME, respectivamente). Respecto a los TET limpios, el WOB teórico causado por el aumento de la resistencia de los TET tras su uso fue mayor (6,8±1,1 versus 10,4±4,0 J/min, p<0,001; respectivamente).

Catorce pacientes (32% del total, 7 por grupo) desarrollaron NAV. La duración de la ventilación en estos pacientes fue mayor (14,6±6,7 versus 8,4±5,1 días; p=0,002); sin que se hallaran diferencias en las resistencias de los TET de los pacientes con NAV y los que no la presentaron (9,6±3,3 vs 10,1±4,3 cmH_2O/L/seg respectivamente; p=0,33).

Cinco pacientes del grupo HH (23%) y tres del grupo HME (14%) requirieron ser reintubados por fracaso respiratorio (p=0,69). No se hallaron diferencias en la mortalidad entre ambos grupos: 4/22 pacientes (18%) fallecieron en cada grupo.

Tabla 3. Comparación entre los grupos humidificados con HH y HME.

	HH (n=22)	**HME (n=22)**	***p***
Edad; años	63,8 ± 12,4	62,8 ± 11,8	0,777
Sexo; Hombre / Mujer (n)	16 / 6	16 / 6	1
SAPS II score	41,0 ± 13,6	42,0 ± 11,4	0,795
PaO_2; mmHg	86 ± 18	99 ± 33	0,135
FiO_2	0,6 ± 0,2	0,4 ± 0,1	0,004
PEEP; cmH_2O	7,2 ± 2,3	6,0 ± 1,2	0,056
Diagnóstico principal al ingreso			
Neumonía	8 (18,2%)	4 (9,1%)	0,310
EPOC descompensado	4 (9,1%)	0 (0%)	0,108
Insuficiencia cardiaca congestiva	1 (2,3%)	3 (6,8%)	0,607
Cirugía abdominal	5 (10,9%)	4 (9,1%)	1
Sepsis	1 (2,3%)	1 (2,3%)	1
Patología neurológica	3 (6,8%)	10 (22,7%)	0,045
TET diámetro; mm	7,9 ± 0,4	7,9 ± 0,3	0,989
Ventilación mecánica; días [(1)]	11,3 ± 7,7	9,5 ± 4,5	0,347
Uso broncodilatadores; días	3,2 ± 4,1	1,9 ± 3,7	0,084
Balance hídrico; ml	-2552 ± 6268	-2579 ± 5422	0,988
Resistencia flujo (TET limpio) ; cmH_2O/L/seg	6,8 ± 1,1	6,8 ± 1,1	0,989
Resistencia flujo (TET usado) ; cmH_2O/L/seg	10,6 ± 4,3	10,2 ± 3,8	0,767

Valores expresados como media ± desviación estándar.

Los porcentajes son respecto a la totalidad de pacientes incluidos.

7. PUBLICACIONES FUNDAMENTALES DE LA TESIS

PRIMERA PUBLICACIÓN

Título: Acute physiologic effects of a stepwise recruitment maneuver in acute respiratory distress syndrome.

Autores: Indalecio Morán, Lluis Blanch, Rafael Fernández, Enrique Fernández-Mondéjar, Elisabeth Zavala, Jordi Mancebo.

Revista: Minerva Anestesiologica (2011); 77: 1167-1175.

Factor de Impacto: 2,656 según la ISI Web of Knowledge^{SM} de 2011.

ORIGINAL ARTICLE

Acute physiologic effects of a stepwise recruitment maneuver in acute respiratory distress syndrome

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ABSTRACT

Background. Stepwise recruitment maneuvers (RM) applied with high airway pressures may optimize lung recruitment, but this kind of intervention may lead to widely heterogeneous responses with possible side effects. To assess the clinical impact of these maneuvers, we performed a stepwise maximal-recruitment strategy superimposed on routine mechanical ventilation.

Methods. We studied 13 adults with early-phase acute lung injury/acute respiratory distress syndrome (ALI/ARDS). We used pressure-control ventilation at an FiO_2 of 1. Starting from a Pplat/positive end-expiratory pressure (PEEP) of 40/25, we sequentially increased airway pressure in 5 cmH_2O steps until a PaO_2/FiO_2 of 350 mmHg or a Pplat/PEEP of 60/40 cmH_2O was reached. The PEEP was then progressively reduced until the PaO_2 decreased by more than 10% of the maximum PaO_2; the PEEP was subsequently set to 2 cmH_2O above this level. An intra-arterial catheter continuously displayed blood gas measures. The respiratory mechanics and hemodynamics were monitored at each phase and during the two-hour follow-up.

Results. Two hours after the RM, the PaO_2/FiO_2 was higher than at baseline (187±102 *versus* 339±136 mmHg, P<0.001). In 8 patients, the PEEP increased from 12±3 cmH_2O to 15±4 cmH_2O after the RM (P<0.001). In the other five, it closely mirrored the basal PEEP. Seven patients did not reach the 350-mmHg PaO_2 target. The respiratory system compliance decreased in seven patients. The RM was discontinued due to severe complications in four patients.

Conclusion. Although stepwise-RM improves oxygenation, it has a heterogeneous impact on respiratory mechanics and may cause adverse hemodynamic effects and transient hypoxemia. If the use of this kind of RM is considered, it should be adapted to individual patient needs, applied carefully and closely monitored.

(Minerva Anestesiol 2011;77:1167-75)

Key words: Acute lung injury - Respiratory distress syndrome, adult - Positive-pressure respiration.

During the mechanical ventilation of patients in the early phases of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS), the usual ventilatory strategy to protect the lungs applies moderate tidal volumes and airway pressures.[1] Some authors, however, have suggested that adding open lung maneuvers that combine recruitment maneuvers (RM) and sufficient positive end expiratory pressure (PEEP) may be useful for opening the lungs and keeping them open.[2, 3] It should be kept in mind, however, that the physiological effects of RM in humans may vary widely depending on the ventilatory settings (tidal volume [Vt] and PEEP levels) applied before and after the opening maneuver,[4-9] the type of maneuver applied,[10, 11] the ventilatory strategy implemented [12-15] and the type of lung injury.[15] Furthermore, the use

of RM can be accompanied by adverse effects, especially hemodynamic instability.[15, 16] In view of these factors, the usefulness of superimposing RM on routine ventilatory protective treatment remains controversial.

The use of airway pressures above 40 cmH_2O has been proposed to achieve maximum lung recruitment.[9, 17] Two clinical studies performed in ALI/ARDS patients have evaluated different RMs at these pressure levels.[17, 18] Borges *et al.*[17] used a baseline setting of 6 ml/kg of predicted body weight (PBW) for Vt and 5 cmH_2O for PEEP together with a stepwise maximum-RM strategy of 60/45 cmH_2O plateau pressure/PEEP. They obtained major and homogeneous increases in oxygenation and significant alveolar recruitment, as assessed by computed tomography (CT) scanning. Gattinoni *et al.*[18] used a Vt of 8.8 mL/kg and a PEEP of 11 cmH_2O combined with an RM strategy consisting of 45 cmH_2O of plateau pressure and 5 cmH_2O of PEEP for 2 minutes. They found, however, an extremely variable response in terms of recruitment and gas exchange. In view of the different designs of these studies, it is not possible to determine the respective roles of the baseline ventilator settings and the RM *per se*.

To evaluate the short-term effects of high-pressure RM on gas exchange, respiratory system mechanics and hemodynamics during mechanical ventilation in early ALI/ARDS patients, we investigated a stepwise maximal-recruitment followed by decremental-PEEP strategy [17] that was superimposed on routine mechanical ventilation.[18]

Materials and methods

The intensive care units of four hospitals participated in the study. Each center's ethics committee approved the study, and the patients' next of kin provided written informed consent.

Patients

We studied 13 patients with early phase ALI/ARDS (as defined by the American-European

Table I.—*Patients' clinical characteristics prior to inclusion.*

	Sex/Age (years)	Main diagnosis	ARDS/ALI origin	AP II	PaO_2 (mmHg)	FiO_2	PEEPtot (cmH_2O)	Vt (mL)	Vt (mL/Kg)	Pplat (cmH_2O)	Crs (mL/cmH_2O)
1	F / 51	Abdominal sepsis	NP	13	144	0.8	14	500	9.3	30	31
2	F / 73	Abdominal sepsis	NP	17	125	0.7	10	420	8.4	40	14
3	F / 74	Peritonitis	NP	31	73	0.5	8	430	8.1	28	24
4	M / 66	Pancreatitis	NP	36	106	0.5	8	570	8.6	25	34*
5	M / 80	Urinary sepsis	NP	15	98	0.5	8	570	8.0	26	32
6	F / 64	Sepsis	NP	21	78	1	12	420	7.4	30	27*
7	M / 40	Pneumonia	P	26	76	0.9	14	490	6.5	35	23
8	M / 33	Severe trauma	P	28	166	0.6	14	509	7.7	29	34*
9	M / 57	Severe trauma	P	24	125	1	10	540	9.5	22	45*
10	F / 67	Abdominal sepsis	NP	18	82	0.8	14	400	9.3	28	29*
11	M / 35	Pneumonia	P	14	85	1	18	435	5.8	37	23
12	F / 65	Pneumonia	P	14	111	1	15	350	5.9	35	18
13	M / 49	Sepsis	NP	NA	84	0.5	10	480	7.5	22	40*
	58±15			21.4±7.5	104±29	0.75±0.2	12±3	470±68	7.8±1.2	30±6	28±9

M: male; F: female; Age: years; NP: non-pulmonary ARDS/ALI; P: pulmonary ARDS/ALI; AP II: acute physiologic and chronic health evaluation on admission; PaO_2: partial pressure of oxygen in arterial blood; FiO_2: fraction of inspired oxygen; PEEPtot: total positive end-expiratory pressure; Vt: tidal volume; Pplat: plateau airway pressure; Crs: respiratory system compliance.
Values are expressed as mean±SD.
*Group 1: patients in whom Crs increased after recruitment maneuver.

Consensus Conference criteria[19]) who had been on mechanical ventilation for less than 72 hours. All had fulfilled the ALI/ARDS criteria for more than 24 hours despite clinical optimization of their ventilation parameters. Table I lists the patients' baseline demographic and clinical characteristics. The patients were sedated by an intravenous infusion of propofol, midazolam, and opiates, both alone and in combination.

The exclusion criteria were age less than 18 years, previous barotrauma, head injury and persistent hemodynamic instability despite fluid administration or vasopressors.

Study protocol

In all of the patients, the baseline mechanical ventilation was volume assist-control ventilation (VCV) with constant flow. The Vt and PEEP were established by the attending physician. Thirty minutes before the stepwise RM, the inspired oxygen fraction (FiO_2) was switched to 1, and it was kept constant at this level during the study, as has been described previously.[17] We used an FiO_2 of 1 to eliminate the possible effects of a ventilation-perfusion mismatch caused by the complex relationship between changes in FiO_2, physiological shunting and ventilation-perfusion mismatching.[20] We collected data at baseline, just before the RM with the basal ventilatory settings and an FiO_2 of 1 (pre-RM), during the highest pressure application (maximum-RM), fifteen minutes after the RM (15-min-RM), and two hours after the RM (120-min-RM). During the follow-up, ten patients received VCV and three received pressure-control ventilation (PCV). After the RM, the $PEEP_{tot}$ level (the sum of the external PEEP and the intrinsic PEEP, if present) was adjusted using a decremental PEEP trial similar to one that has been described elsewhere.[17]

The ventilators were equipped with compressible volume compensation systems. The plateau pressure (Pplat) and PEEPtot were measured by performing end-inspiratory and end-expiratory occlusions, respectively, using the appropriate ventilator buttons. The respiratory system compliance (Crs) was calculated as Vt/(Pplat-PEEPtot). After the RM, we classified the patients according to their Crs evolution as follows: Group 1 (Crs increased from baseline), and Group 2 (Crs diminished or remained unchanged).

Respiratory-system mechanics, gas-exchange and hemodynamic data were collected at each phase of the protocol. The pressure and volume variables were recorded directly from the ventilator monitoring system. The gas exchange was monitored using an intra-arterial catheter (Paratrend 7FL, Diametrics Medical Ltd, Buckinghamshire, England) that provided continuous recordings of PaO_2, $PaCO_2$, and pH measurements. When a Swan-Ganz catheter was in place, the cardiac output (CO) (N.=10), mean pulmonary artery pressure (MPAP) (N=10), and pulmonary capillary wedge pressure (PCWP) (N.=9), were obtained. The patients' predicted body weight (PBW) was calculated as has been described elsewhere.[21]

Phases of the study

After 30 minutes of baseline ventilation at an FiO_2 of 1, the RM with PCV was performed. The RM consisted of four phases (Figure 1).

In the first phase, the PCV was adjusted to initially deliver a Pplat/PEEP of 40/25 cmH_2O. This period was followed by consecutive, simultaneous stepwise increases in Pplat and PEEP of 5 cmH_2O every two minutes, either until the PaO_2/FiO_2 reached 350 mmHg or until a maximum Pplat/PEEP of 60/40 cmH_2O was achieved, as has been described previously [17]. A Pplat/PEEP of 40/25 cmH_2O was applied for one minute between each increase in the Pplat/PEEP.

In the second phase, the PEEP was decreased by 2 cmH_2O every four minutes until the PaO_2 had decreased by more than 10% of the maximum PaO_2 obtained during the inflation phase of the RM. This PEEP value was considered to be the level at which alveolar collapse reappeared.

To regain recruitment in the third phase, the RM was repeated in PCV mode with the maximum Pplat and PEEP used in the first phase.

In the fourth phase, the ventilatory settings were switched to VCV or PCV mode, but the PEEP was set to 2 cmH_2O higher than the level at which we observed a drop in the PaO_2 >10% during the decremental PEEP trial; it was maintained at this level for two hours.

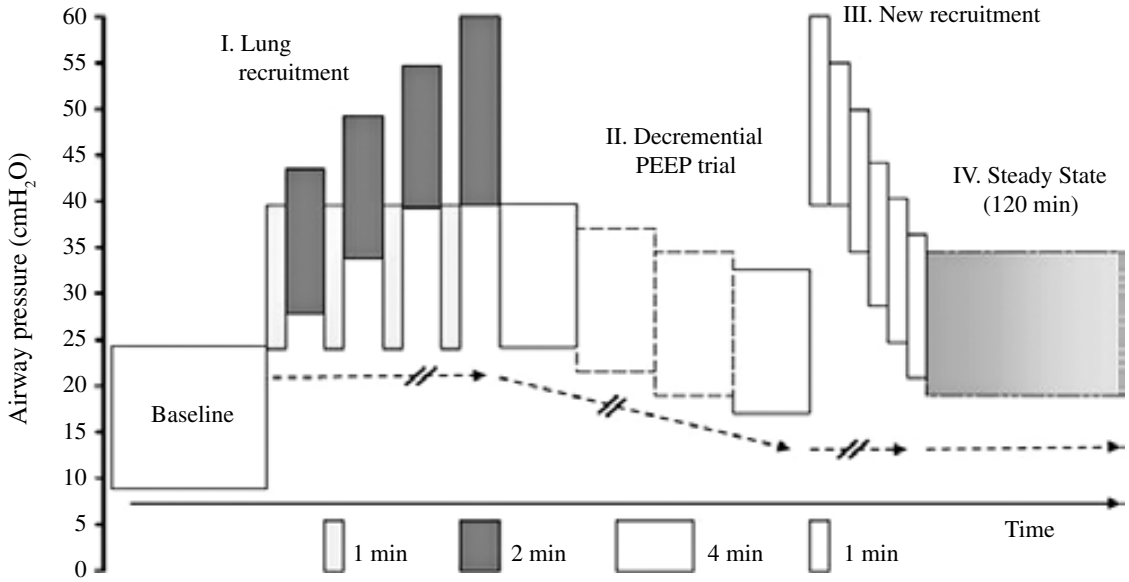

Figure 1.—Diagram of progressive, stepwise-RM applied in the study.

The criteria for aborting the RM were a ±20% variation in heart rate (HR) or a 20% decrease in mean arterial pressure (MAP), PaO_2, or CO, if recorded. Chest X-rays were obtained immediately after the fourth phase and again within 24 hours.

Statistical analysis

The results were analyzed using a one-way analysis of variance for repeated measures (ANOVA) model. If significance was achieved, a Student-Newman-Keuls analysis was used to compare the study phases. Statistical significance was set at $P<0.05$. The data are expressed as means ± standard deviation. We used SPSS (v 17.0) for the statistical analyses.

Results

Table II shows the respiratory variables, lung mechanics and arterial blood gas responses and summarizes the hemodynamic parameters before (Pre-RM), during (Max-RM) and after (15 min-RM and 120 min-RM) RM. Pplat increased significantly at the maximum airway pressure used in the study and remained significantly higher during the follow-up period, as compared to the baseline. This effect was due to significant increases in the external PEEP.

After the RM, the Crs increased relative to the baseline in six patients (Group 1) but did not increase in seven patients (Group 2). The baseline Crs differed significantly between the groups (34±9 *versus* 24±7 mL/cmH_2O for Group 1 *vs.* Group 2, P=0.045). After the RM, the Crs also differed between Groups 1 and 2 (42±8 *versus* 22±6 mL/cmH_2O, $P<0.001$). The baseline Pplat was not significantly different between Groups 1 and 2 (27±5 vs. 33±5 cmH_2O, P=0.067). At the end of the study, however, the Pplat was 28±4 cmH_2O in Group 1, compared with 35±6 cmH_2O in Group 2 (P=0.021), despite a trend towards a higher Vt in Group 1 (8.4 *versus* 7mL/kg, P=0.125). At the end of the study, the Group 1 patients showed a trend towards a higher PaO_2 than those in Group 2 (407±83 *vs.* 280±150 mmHg), but this was not statistically significant (P=0.085). The increase in Crs correlated with the improvement in PaO_2 at the end of the study (r=0.719, P=0.006) (Figure 2).

The PEEP level after the RM was higher than that at baseline (15±4 *vs.* 12±3 cmH_2O, $P<0.001$). In 8 patients, the PEEP was increased ≥2 cmH_2O (from 12±3 to 17±4 cmH_2O); in the other five, the PEEP after the RM was within ±1 cmH_2O of the initial PEEP (12±3 cmH_2O).

TABLE II.—*Respiratory variables, lung mechanics, gas exchange and hemodynamic parameters before RM, at maximum RM and after the stepwise-RM (FiO_2 1) (n= 13 patients unless otherwise specified).*

	Pre-RM	Max-RM	15 min-RM	120 min-RM	Overall P
RR; breath/min	26±7	26±7	26±7	26±7	1
PEEP; cmH_2O	12±3 [a]	38±3 [b]	15±4	15±4	< 0.001
Vt; mL	470±68	256±118 [b]	464±80	458±85	< 0.001
Vt; mL/kg	7.8±1.2	4.3±2 [b]	7.8±1.6	7.7±1.6	< 0.001
Pplat; cmH_2O	30±6	55±4 [b]	32±6 [c]	32±6 [c]	< 0.001
Crs; mL/cmH_2O	28±9	16±7 [b]	31±11	31±12	< 0.001
pH	7.35±0.06	7.20±0.11 [b]	7.31±0.07 [d]	7.34±0.05	< 0.001
PaO_2; mmHg	187±102 [a]	303±148	361±165	339±136	< 0.001
$PaCO_2$; mmHg	46±10	70±17 [b]	51±12 [d]	48±11	< 0.001
HR; beats/min	96±21	105±31	105±26	102±27	0.143
MAP; mmHg	83±15	79±25	81±12	84±15	0.615
MPAP; mmHg (N.=10)	31±5	44±6 b	31±4	30±4	< 0.001
CO; l/min (N.=10)	6.7±2.3	5.4±2.4 c	6.2±2.4	6.3±2.6	0.031
PCWP; mmHg (N.=9)	15±3	27±4 b	15±3	16±3	< 0.001

N.: number of patients evaluated; Pre-RM: just before recruitment maneuver; Max-RM: at maximum airway pressures used; 15 min-RM: after 15 minutes of the end of RM; 120 min-RM: after 120 minutes of the end of RM; RR: respiratory rate; PEEP: positive end-expiratory pressure; Vt: tidal volume; Pplat: airway plateau pressure; Crs: respiratory system compliance; PaO_2: partial pressure of oxygen in arterial blood; PaO_2: partial pressure of carbon dioxide in arterial blood; HR: heart rate; MAP: mean arterial pressure; MPAP: mean pulmonary artery pressure; CO: cardiac output; PCWP: pulmonary capillary wedge pressure.
Values are expressed as mean ± SD.
Intergroup differences (P<0.05): a: preRM vs other phases; b: maxRM vs other phases; c: respect to preRM; d: 15' post RM vs 120' postRM

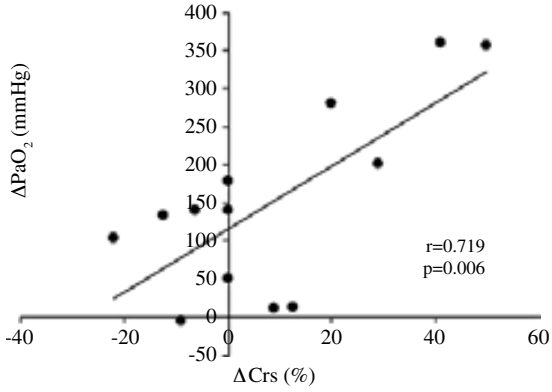

Figure 2.—The relationship between the increase in PaO_2 (ΔPaO_2) and the percentage increase in Crs (ΔCrs) from baseline to the end of the study. The linear correlation was highly significant.

The total PEEP at the end of the study was significantly lower in these five patients than in the other 8 patients (12±4 cmH_2O versus 17±3 cmH_2O, P<0.05). The changes in PEEP from baseline to 120-min-RM were correlated with the individual PaO_2 gains (r=0.673, P=0.012).

The overall PaO_2 increased significantly during the RM and remained higher than baseline. Figure 3 shows the individual changes in PaO_2. At the maximum Pplat/PEEP used, seven patients did not reach the target of PaO_2>350 mmHg, but two of these surpassed the target during the follow-up period. The $PaCO_2$ increased and the

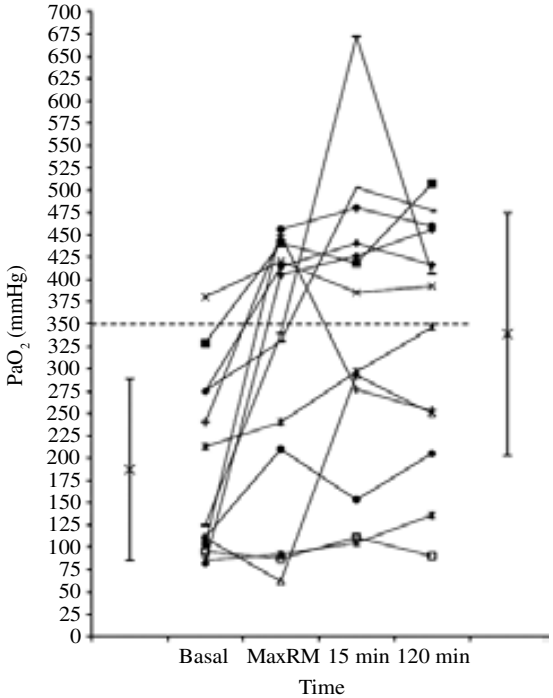

Figure 3.—The PaO_2 values for the individual patients during the four phases of the study. The dashed line marks the level of PaO_2 above which was considered to indicate lung recruitment.

pH decreased significantly during the RM, but they returned to baseline 15 minutes after the RM. At the maximum Pplat/PEEP, the PaO_2

was higher in Group 1 (in which the Crs increased relative to the baseline) than in Group 2 (in which the Crs did not increase) (400±54 *vs.* 221±156 mmHg, P=0.023), and the $PaCO_2$ was lower in Group 1 (59±9 *vs.* 80±17 mmHg, P=0.017). No differences in PaO_2 or $PaCO_2$ were found between the groups at baseline.

We observed two main differences between the five patients with pulmonary ARDS and the eight with non-pulmonary ARDS. First, the basal PEEP level was higher in the pulmonary patients (14±3 *vs.* 11±3 cmH_2O, P=0.034). Second, the $PaCO_2$ at the end of the study was higher in the pulmonary than in the non-pulmonary ARDS patients (58±7 *vs.* 42±7 mmHg, P=0.004).

The hemodynamic changes observed during the RM returned to baseline 15 minutes after the RM and remained constant thereafter. However, the CO (N.=10) was lower at the end of the RM than at baseline in the patients (five per group) for whom the PEEP did not increase (4.5 *versus* 8 l/min, P=0.047).

The stepwise-RM was discontinued in four patients due to adverse effects. During the recruitment phase, the maneuver was terminated in three patients because their CO decreased by more than 20% relative to the baseline; in one of them, the decrease in CO was associated with arterial hypotension and an acute drop in PaO_2. Another patient experienced supraventricular tachycardia. All of these adverse effects disappeared (within 15 minutes of stopping the maneuver) when the airway pressure was decreased.

Discussion

The main findings of this study were as follows: 1) stepwise-RM superimposed on common ventilatory settings increased arterial oxygenation; 2) in 5/13 patients, the PEEP levels after the RM did not differ from the baseline values; 3) despite the high airway pressures used, the Crs did not increase in 7/13 patients after the RM; and 4) the RM sequence had to be stopped in 4/13 patients due to hemodynamic side effects.

The results from RM studies in ALI/ARDS patients differ, and the optimal maneuver remains controversial.[2, 11] Many studies have demonstrated that RM improves oxygenation and lung mechanics.[12, 22] These beneficial effects will likely remain if the PEEP is increased after the RM,[23] but they may be lost if the PEEP is returned to the baseline level.[24] Other studies have found a minor, variable response to RM when ARDS patients are ventilated with high PEEP superimposed on a lung-protective strategy.[13-15, 25]

Some authors have claimed that the Vt at high, sustained PEEP induces alveolar recruitment in a time-dependent manner and obviates the need for additional RM superimposed on the high PEEP levels.[13, 15, 25, 26] Borges *et al.*[17] tested an incremental stepwise-RM in ARDS and obtained nearly full lung recruitment (defined as PaO_2+$PaCO_2$≥400 mmHg) in 24/26 patients (92%). The type and duration of RM, clinical conditions and respiratory mechanics (Crs≈28 mL/cmH_2O and mean Pplat ≈30 cmH_2O) at inclusion were similar to those in our study. However, the dissimilar physiological response seen after the RM in our patients could be due to their higher baseline PEEP (12 cmH_2O *vs.* 5 cmH_2O) and to the Vt selected (7.8 mL/kg of PBW in our study and 6 mL/kg in Borges *et al.*). In the Borges *et al.* patients, the reduced Vt and low PEEP may have caused the alveolar derecruitment, which was reversed and prevented after the RM by increasing the PEEP.[14]

After the RM, we found that the PEEP levels did not differ from the baseline levels in 5/13 of the patients, while it increased by 5±2.5 cmH_2O in the other 8 patients. Our patients' heterogeneous responses to the RM may be explained by their wide range of baseline PEEP values (8-18 cmH_2O),[15, 27] by their alveolar capillaries collapsing due to alveolar overdistension in the more compliant lung areas, and/or by increased venous admixture due to blood flow redistribution to regions where the lung was collapsed.[15, 28]

The increase in Crs with lung inflation may be a marker for the expansion of collapsed alveolar units after RM.[28, 29] We observed a consistent correlation between Crs increases and overall PaO_2 increases (Figure 2). Unlike similar clinical studies [17], however, we observed no increase in Crs in 7/13 of our patients (Group 2). The patients in Group 2 had higher baseline Pplat and lower Crs values than those in Group 1. Group 2 also had

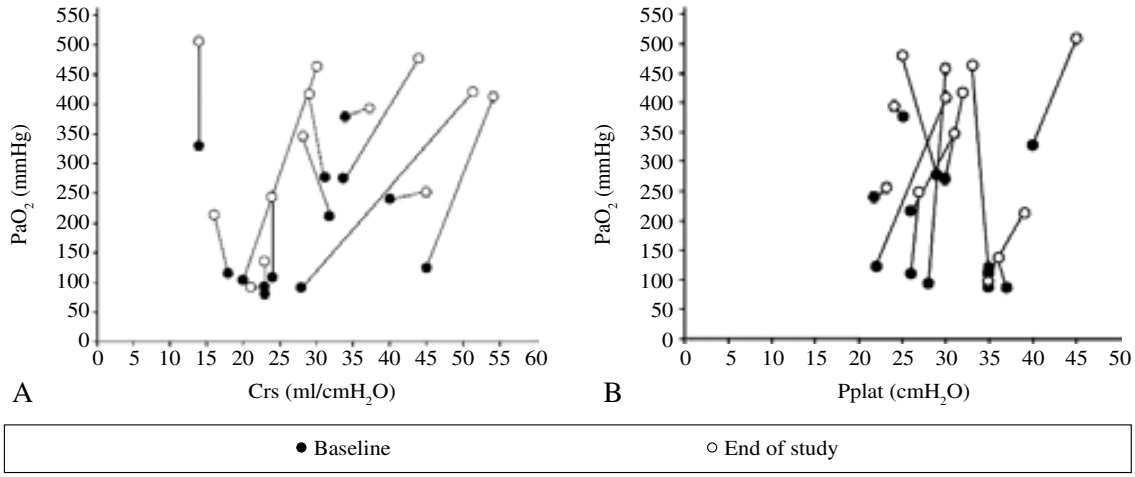

Figure 4.—The changes in individual PaO_2 values from baseline to the end of the study in relation to respiratory system compliance (Crs) (A) and plateau airway pressure (Pplat) (B). Note that despite a general increase in PaO_2, the individual responses were heterogeneous, both in terms of Crs (which decreased in 7/13 patients) and in terms of Pplat (which increased in 8/13 patients).

higher Pplat values at the end of the study despite a relatively low Vt compared to Group 1. In addition, the PaO_2 increase in Group 2 was markedly lower than that in Group 1 (Figure 4). Gattinoni *et al.* have found that the patients who had a lower baseline Crs (40±18 mL/cmH_2O) had a higher potential for recruitment than those who had a higher baseline Crs (49±16 mL/cmH_2O).[18] This higher-baseline Crs group was formed by a relatively high percentage (41%) of patients who had ALI (14/34). The Group 2 patients in our study, in whom Crs did not increase, met all of the criteria for ARDS and had low baseline Crs values (24±7 mL/cmH_2O). Hence, one can speculate that Gattinoni's patients who had lower recruitment did so because they were already well "recruited" at baseline (Crs = 49±16 mL/cmH_2O, PaO_2/FiO_2 = 200±77 mmHg and Pplat = 23±3 cmH_2O). We believe that our Group 2 patients were mainly "non-recruitable" at inclusion (Crs = 24±7 mL/cmH_2O, PaO_2/FiO_2 = 146±45 mmHg and Pplat = 33±5 cmH_2O).These data, taken together, reinforce the notion that the greater the lung impairment (as assessed by Crs), the lower the likelihood of recruitability. Indeed, in a meta-analysis, Fan *et al.*[11] have shown that patients with low Crs at baseline (<30 mL/cmH_2O) exhibit a poor response to RM. In addition, Villagra *et al.*[15] have shown that decreased Crs and no increase in oxygenation after RM were associated with increased venous admixture, suggesting further lung hyperinflation.

In recent years, diverse clinical and experimental studies have analyzed the cardiovascular effects of RM.[16, 30-34] The main hemodynamic effect is decreased CO during the RM. This phenomenon is generally reversible within a few minutes. The CO can drop by up to 60%, however, and the patients may require vasoactive drugs to return to hemodynamic stability.[34] In general, the changes observed in MAP are less pronounced than those in CO,[33, 34] so monitoring arterial pressure underestimates the cardiovascular effects of RM. The clinical impact of the hemodynamic deterioration depends largely on the blood volume at the time of the RM [32] and on the transmission of pressure from the airway to the pleural space.[35] Because the deleterious hemodynamic effects of RM are short-lasting, it can be argued that RM is acceptably safe. However, the degree of hemodynamic deterioration, which may combine pulmonary hypertension, arterial hypotension and decreased CO, can be life-threatening in hypovolemic septic patients and in those with right-ventricle dysfunction. Consistent with the above, we found that the CO was significantly lower in the patients whose PEEP values remained unchanged than in those whose PEEP values increased relative to baseline. In addition, hemodynamic complications required us to stop the

maneuver in 4/13 patients (31%); three patients suffered a CO drop of >20% relative to baseline, and another experienced paroxysmal supraventricular tachycardia. Using a less aggressive RM, Meade *et al.* have reported a 22% complication rate from an open-lung ventilation strategy.[36]

Our study has several limitations. Because it is a physiological study using a small sample that consisted of patients with different underlying disorders, the findings cannot be generalized. Furthermore, we did not use a direct method, such as CT scaning,[18] transpulmonary pressure [37, 38] or electrical impedance tomography,[39, 40] to guide and assess lung recruitment. These methods have been proposed for ventilator management based on the individual patient physiology, but we do not use these tools in our routine care. We performed our study guided by continuous online intra-arterial measurements because this method of monitoring responds quickly to changes in oxygenation and because it is easier to use in routine practice than the above techniques.[3] Another limitation is that we conducted our protocol with an FiO_2 of 1 to minimize the effects of ventilation-perfusion mismatch.[20] The increase in the FiO_2 to 1 during the pre-RM stabilization phase may have partly explained the improvement in the PaO_2 observed in our study.[20] Another mechanism that may have accounted for the increase in the PaO_2 was the drop in the CO and pulmonary blood flow redistribution during the RM due to airway pressure increases.[41] In mechanically ventilated ALI/ARDS patients, however, breathing pure oxygen may promote resorption atelectasis due to the collapse of unstable alveolar units with low ventilation-perfusion ratios and may aggravate intrapulmonary shunting.[42, 43] In this setting, RM may be more effective at improving PaO_2.[15]

Conclusions

In early ALI/ARDS patients, stepwise-RM performed with high airway pressures and a decremental PEEP trial improves oxygenation but may worsen respiratory-system compliance and provoke severe hemodynamic impairment during the procedure. Therefore, we do not recommend this technique for routine clinical use when a ventilatory strategy combining a moderate tidal volume and PEEP is used. If this type of RM is considered, we suggest it should be adapted to the individual patient needs, applied with extreme care and closely monitored.

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Conflicts of interest.—E. Fernández-Mondéjar is a Member of the Medical Advisory Board of Pulsion.

Acknowledgments.—The authors thank Miguel de Foronda from Phillips for technical support and John Giba for editorial assistance. CIBER de Preliminary data from this study were presented previously at the 15th Annual Congress of the European Society of Intensive Care Medicine (Barcelona, Spain) [I. Morán et al. Intensive Care Med 2002; 28: Suppl 1 (A541)] and at the International Conference of the American Thoracic Society (Atlanta, USA) [I. Morán et al. Am J Respir Crit Care Med 2002; 165 (8) (B31)].
Enfermedades Respiratorias is an initiative of Instituto de Salud Carlos III (Spain).

Received on November 17, 2009 - Accepted for publication on April 19, 2011.

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SEGUNDA PUBLICACIÓN

Título: Heat and moisture exchangers and heated humidifiers in acute lung injury / acute respiratory distress síndrome patients. Effects on respiratory mechanics and gas exchange.

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Revista: Intensive Care Medicine (2006); 32: 524-531.

Factor de Impacto: 4,406 según la ISI Web of Knowledge^{SM} de 2006.

Erratum to: Heat and moisture exchangers and heated humidifiers in acute lung injury / acute respiratory distress síndrome patients. Effects on respiratory mechanics and gas exchange. Intensive Care Medicine (2012); 38: 1242.

Intensive Care Med (2006) 32:524–531
DOI 10.1007/s00134-006-0073-1

ORIGINAL

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Heat and moisture exchangers and heated humidifiers in acute lung injury/acute respiratory distress syndrome patients. Effects on respiratory mechanics and gas exchange

Received: 17 January 2006
Accepted: 17 January 2006
Published online: 24 February 2006

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Abstract *Objective:* To compare, in acute lung injury/acute respiratory distress syndrome (ALI/ARDS) patients, the short-term effects of heat and moisture exchangers (HME) and heated humidifiers (HH) on gas exchange, and also on respiratory system mechanics when isocapnic conditions are met. *Design:* Prospective open clinical study. *Setting:* Intensive Care Service. *Patients:* Seventeen invasively ventilated ALI/ARDS patients. *Intervention:* The study was performed in three phases: (1) determinations were made during basal ventilatory settings with HME; (2) basal ventilatory settings were maintained and HME was replaced by an HH; (3) using the same HH, tidal volume (Vt) was decreased until basal $PaCO_2$ levels were reached. FiO_2, respiratory rate and PEEP were kept unchanged. *Measurements and results:* Respiratory mechanics, Vd_{phys}, gas exchange and hemodynamic parameters were obtained at each phase. By using HH instead of HME and without changing Vt, $PaCO_2$ decreased from 46 ± 9 to 40 ± 8 mmHg ($p < 0.001$) and Vd_{phys} decreased from 352 ± 63 to 310 ± 74 ml ($p < 0.001$). Comparing the first phase with the third, Vt decreased from 521 ± 106 to 440 ± 118 ml ($p < 0.001$) without significant changes in $PaCO_2$, Vd/Vt decreased from 0.69 ± 0.11 to 0.62 ± 0.12 ($p < 0.001$), plateau airway pressure decreased from 25 ± 6 to 21 ± 6 cmH_2O ($p < 0.001$) and respiratory system compliance improved from 35 ± 12 to 42 ± 15 ml/cmH_2O ($p < 0.001$). PaO_2 remained unchanged in the three phases. *Conclusions:* Reducing dead space with the use of HH decreases $PaCO_2$ and more importantly, if isocapnic conditions are maintained by reducing Vt, this strategy improves respiratory system compliance and reduces plateau airway pressure

Keywords ARDS · ALI · Dead space · Heat and moisture exchanger · Heated humidifier

Introduction

Humidification and warming of inspired gases during mechanical ventilation is a crucial issue. Two types of humidifiers are commonly used in clinical practice: heat and moisture exchangers (HME) and heated humidifiers (HH) [1]. Inadequate gas humidification can provoke airway mucosa dysfunction and endotracheal tube occlusion [2]. Management decisions and reduced costs may account for the recent more generalized use of HME [3]. When mechanical ventilation is used, ventilator equipment adds additional dead space (Vd) due to the endotracheal tube, humidification devices and connectors. This instrumental dead space is considered part of the airway Vd (Vd_{aw}) (instrumental and anatomic dead space). Physiologic dead space (Vd_{phys}) is comprised of Vd_{aw} and alveolar Vd (Vd_{alv}) and is the portion of tidal volume (Vt) that does not participate in gas exchange [4]. Therefore, humidification devices might play an important role in pulmonary gas exchange and lung

Table 1 Patients' clinical characteristics at inclusion

	Sex	Age (years)	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	FiO_2	PEEPtot (cmH_2O)	Main diagnosis on admission	APACHE II
1	M	65	80	37	0.6	7	Viral pneumonia	31
2	F	39	129	43	0.5	12	Bacterial pneumonia	22
3	F	69	116	42	0.4	12	Aspiration pneumonia	36
4	F	62	94	59	0.75	11	Bacterial pneumonia	20
5	M	25	83	43	0.55	9	Thoracic trauma	11
6	F	54	95	36	0.35	8	Upper airway obstruction (po)	16
7	M	81	114	38	0.4	10	Aspiration pneumonia	24
8	M	76	82	72	0.7	14	Lung hemorrhage	23
9	F	74	66	52	0.6	10	Peritonitis (po)	18
10	M	49	155	39	0.6	8	Dissecting aortic aneurysm (po)	17
11	M	52	93	41	0.4	6	Benzodiazepine overdose	9
12	M	77	84	45	0.5	10	Dissecting aortic aneurysm (po)	20
13	M	67	88	43	0.4	6	Bacterial pneumonia	23
14	F	75	103	42	0.4	6	Multiple trauma	15
15	F	62	99	56	0.9	9	Bacterial pneumonia	28
16	M	70	69	50	0.3	6	Bacterial pneumonia	22
17	M	63	85	49	0.4	10	Cerebral hemorrhage	8
Mean ± SD		62 ± 15	96 ± 22	46 ± 9	0.5 ± 0.2	9 ± 2.5		20.2 ± 7.4

Abbreviations: PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; FiO_2, fraction of inspired oxygen; PEEPtot, total positive end-expiratory pressure; APACHE II, Acute Physiology and Chronic Health Evaluation on admission; po, postoperative status

mechanics. In acute lung injury/acute respiratory distress syndrome (ALI/ARDS) patients, respiratory acidosis and high airway plateau pressures are a serious limitation to mechanical ventilation adjustment.

Richecoeur et al. [5] have demonstrated that optimization of mechanical ventilation associated with a reduction in instrumental dead space is a useful combination method to reduce $PaCO_2$ in severe ARDS patients with hypercapnia. Other investigators have confirmed these data [6]. Recently, Wald and coworkers [7], using a preterm infant's test lung, showed that mean CO_2 elimination time was decreased when instrumental dead space was reduced and suggested that such an approach might decrease volutrauma.

Two previous studies performed in ALI/ARDS patients have focused on the effects of instrumental dead space removal in $PaCO_2$ [8, 9]. Our investigation aimed at accruing new knowledge into this issue not only on gas exchange parameters, but mainly to analyze the impact of such strategy on respiratory system mechanics in ALI/ARDS patients. Indeed, the novelty of our study is to analyze the effects of minimizing instrumental dead space on alveolar distension, respiratory system compliance and end-inspiratory plateau pressure while keeping $PaCO_2$ unchanged. Preliminary data of this study have been presented [10].

Materials and methods

The study was performed in the Intensive Care Service of the Hospital de la Santa Creu i Sant Pau, Barcelona (Spain). Given the nature of measurements to be performed and the routine use of humidification in mechanical ventilation, the requirement for informed consent was waived by the institutional ethics committee after approval of the protocol.

Patients

The study involved 17 patients (10 men and 7 women) with a mean age of 62 ± 15 years (range 25–81 years) from the Intensive Care Service. The patients' demographic and clinical characteristics are listed in Table 1. ALI/ARDS was diagnosed based on the American-European Consensus Conference criteria [11]. All patients were intubated and mechanically ventilated. Sedation was achieved with titrated intravenous infusion of propofol, midazolam and opiates, alone or in combination regimens, to ensure that the patient did not trigger the ventilator. Neuromuscular blockade was used in seven patients. Exclusion criteria were age under 18 years, severe hemodynamic instability, previous barotrauma, intracranial hypertension and uncontrolled fever. Patients were excluded from the protocol if body temperature varied by 0.5°C or more during the study [12].

Protocol

Basal mechanical ventilation used was volume assist-controlled ventilation with a constant flow, low tidal volume (Vt) and moderate positive end-expiratory pres-

Table 2 Lung mechanics and gas exchange (mean ± SD) during the study period ($n = 17$ patients unless otherwise specified)

	HME (phase 1)	HH (phase 2)	HH-lowVt (phase 3)	Overall p Value	Intergroup differences
Ppeak (cmH_2O)	36 ± 8	34 ± 7	29 ± 8	< 0.001	a, b, c
Pplat (cmH_2O)	25 ± 6	25 ± 6	21 ± 6	< 0.001	a, b
PEEPtot (cmH_2O)	9 ± 2.5	9 ± 2.5	9 ± 2.5	1	
Vt (ml)	521 ± 106	521 ± 106	440 ± 118	< 0.001	a, b
Vt (ml/kg[1])	7.3 ± 1.1	7.3 ± 1.1	6.1 ± 1.3	< 0.001	a, b
Vt (ml/kg[2]) ($n = 12$)	8.3 ± 1.6	8.3 ± 1.6	6.9 ± 1.8	< 0.001	a, b
Vd_{phys} (ml)	352 ± 63	310 ± 74	269 ± 80	< 0.001	a, b, c
Vd/Vt	0.69 ± 0.11	0.60 ± 0.13	0.62 ± 0.12	< 0.001	a, b, c
RR (breaths/min)	20 ± 6	20 ± 6	20 ± 6	1	
Crs (ml/cmH_2O)	35 ± 12	35 ± 12	42 ± 15	= 0.001	a, b
pH	7.34 ± 0.10	7.39 ± 0.11	7.33 ± 0.10	< 0.001	b, c
PaO_2 (mmHg)	96 ± 22	99 ± 29	91 ± 19	= 0.28	
$PaCO_2$ (mmHg)	46 ± 9	40 ± 8	45 ± 9	< 0.001	b, c
FiO_2	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2	1	
Vc (ml)	53 ± 29	52 ± 28	43 ± 25	< 0.001	a, b
Vt_{Vc} (ml)	468 ± 110	469 ± 109	397 ± 117	< 0.001	a, b
$Vd_{phys-Vc}$ (ml)	316 ± 66	279 ± 74	243 ± 79	< 0.001	a, b, c
Crs_{Vc} (ml/cmH_2O)	32 ± 12	32 ± 12	38 ± 15	= 0.002	a, b

Abbreviations: Ppeak, peak airway pressure; Pplat, airway plateau pressure; PEEPtot, total positive end-expiratory pressure; Vt, tidal volume; [1] Weight measured at admission; [2] Predicted body weight; Vd_{phys}, physiologic dead space; RR, respiratory rate; Crs, respiratory system compliance; pH, arterial pH; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; FiO_2, fraction of inspired oxygen; Vc, compressible volume; Vt_{Vc}, $Vd_{phys-Vc}$, Crs_{Vc} , tidal volume, physiologic dead space and respiratory system compliance taking into account compressible volume, respectively.
Intergroup differences: a, phase 1 vs phase 3; b, phase 2 vs phase 3; c, phase 1 vs phase 2

sure (PEEP) to keep plateau airway pressure (Pplat) ≤ 35 cmH_2O, as established by the responsible physician. The inspired oxygen fraction (FiO_2) and PEEP were kept constant during the study. Vd_{phys} was calculated using the Enghoff modification of the Bohr equation [13]; $Vd/Vt = (PaCO_2 – PeCO_2)/PaCO_2$, where Vd is the physiologic dead space, Vt is tidal volume, $PaCO_2$ is the partial pressure of carbon dioxide in arterial blood and $PeCO_2$ is the partial pressure of carbon dioxide in mixed expired gas. Expired gases were collected over 3 min using a Douglas bag (P-341–60; Warren E. Collins Inc., Boston, MA, USA) attached to the expiratory port of the ventilator. Arterial blood gases were obtained during the 3rd min of expired gas collection. Expired and arterial gases were measured using an automated analyzer (ABL 520; Radiometer A/S, Copenhagen, Denmark). Fourteen patients were ventilated with 900 C Servo ventilators (Siemens-Elema, Solna, Sweden) and three patients were ventilated with Evita 4 ventilators (Dräger, Lübeck, Germany). Only the Evita 4 ventilators have a compressible volume compensation system. One ventilator per patient was used and maintained throughout the protocol sequence to avoid intra-patient variability.

Ventilatory parameters were recorded directly from the ventilator monitoring system. PEEPtot was measured by performing end-expiratory occlusions with the appropriate buttons built into the ventilators. Respiratory system compliance (Crs) was calculated as Vt/(Pplat – PEEPtot); where Pplat is the plateau airway pressure and PEEPtot is the sum of external PEEP and intrinsic PEEP, if any.

Respiratory system mechanics, gas exchange, physiologic dead space and hemodynamics were measured at each phase of the protocol. Cardiac output (CO), mean pulmonary artery pressure (MPAP) and pulmonary capillary wedge pressure (PCWP) were obtained if a Swan–Ganz catheter was in place.

Patients' body weight was measured at admission in 15 patients with a calibrated balance (Maximove™, Arjo Ltd., Gloucester, UK). In the other two patients (patients 10 and 12 in Table 1) we did not measure their actual body weight because severe hemodynamic instability at ICU admission. In these two patients, the weight was estimated from the previous operating room records. The predicted body weight (PBW) was calculated as described [14]: for male patients as equal to 50+0.91(centimeters of height–152.4), and for female patients as equal to 45.5+0.91(centimeters of height–152.4).

The study was divided into three phases. In phase 1 (basal conditions), an HME (Edit Flex; Datex Engstrom®, Helsinki, Finland; Vd of 90 ml, including integrated flexible tube and a filter, and "in vitro" resistive pressure drop of 0.5 and 1.4 cmH_2O at constant flows of 30 and 60 l/min respectively) was placed distally to the Y piece of the circuit if not already in use. Mechanical ventilation at clinically established parameters was maintained for 45 min and all study data were then collected. The stabilization

period during the different phases of the study was based on a previous study on the dynamics of CO_2 elimination after ventilator resetting [15]. In phase 2, a HH (Fisher & Paykel; MR 290 chamber, MR 850 ALU electric heater; Panmure, New Zealand; internal volume 280 ml and a resistive pressure drop of 2 cmH_2O at 40/l/min airflow) was placed in the inspiratory limb of the circuit in accordance with the manufacturer's recommendations. Data were collected after 45 min of stable mechanical ventilation with the same ventilatory settings as in the first phase. In phase 3, tidal volume was decreased by 20–30 ml each 30 min. The same data were collected at each step until a $PaCO_2$ value equal to that of phase 1 was reached. We did not use a recruitment maneuver after ventilator disconnection to change humidification devices.

Statistical analysis

The results were analyzed using one-way analysis of variance for repeated measures (ANOVA). If significance was achieved, then Student–Newman–Keuls analysis was used for comparison between the study phases. A p value less than 0.05 was considered statistically significant. Data are expressed as means ± standard deviation. The SPSS (v 11.5) statistical software was used for statistical analysis.

Results

Respiratory data obtained in the three phases of the study are shown in Table 2. The change in the humidification system (from phase 1 using HME to phase 2 using HH) was responsible for a significant decrease in $PaCO_2$ (from 46 ± 9 mmHg to 40 ± 8 mmHg, $p < 0.001$), and a significant increase in pH (from 7.34 ± 0.10 to 7.39 ± 0.11, $p < 0.001$). Individual changes in $PaCO_2$ are shown in Fig. 1. The $PaCO_2$ decrease was correlated ($r = 0.59$; $p = 0.016$) with the initial $PaCO_2$ level. The effect of removing HME was not more pronounced in patients with higher Vt. Correlation between the Vt (expressed as ml/kg of body weight measured at admission) in our 17 patients and the decrease of $PaCO_2$ comparing phase 1 (HME, basal Vt) and phase 2 (HH, basal Vt) did not achieve statistically significant differences ($r = -0.07$; $p = 0.78$). Furthermore, if the same correlation was performed using ml/kg of PBW ($n = 12$) the statistical analysis was not significant ($r = -0.2$; $p = 0.52$). The decrease in $PaCO_2$ levels due to the humidification device switch did not differ significantly ($p = 0.48$) between hypercapnic ($n = 6$) and non-hypercapnic ($n = 11$) patients.

With respect to basal conditions, the use of HH induced a significant reduction in Vd/Vt (from 0.69 ± 0.11 to 0.60 ± 0.13, $p < 0.001$) and a significant decrease in Vd_{phys} (from 352 ± 63 to 310 ± 74 ml, $p < 0.001$). Vd/Vt was statistically different between hypercapnic and non-hypercapnic groups in the phase 1 (0.76 ± 0.09 vs 0.65 ± 0.11 respectively; $p = 0.036$).

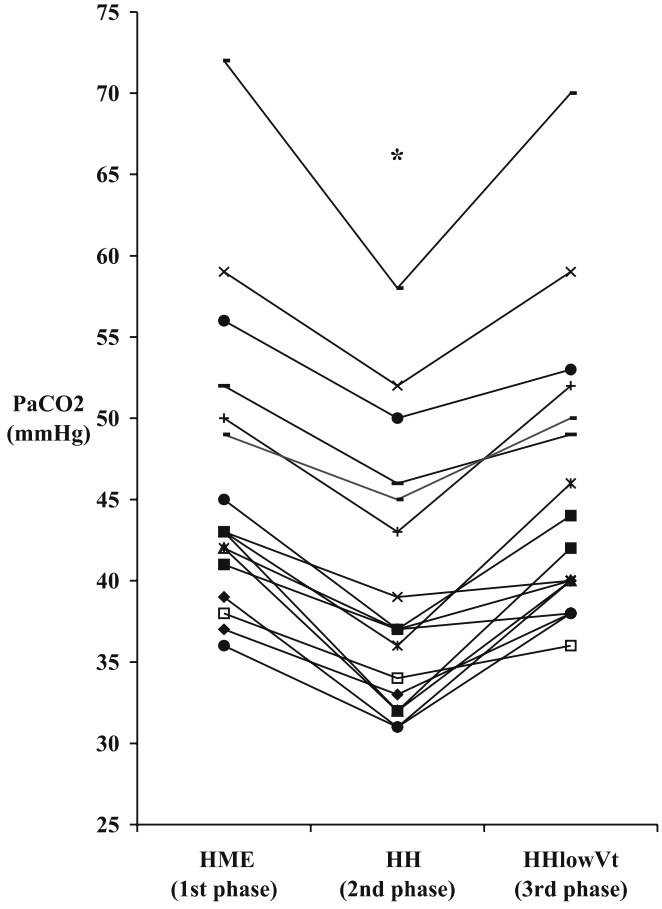

Fig. 1 Individual values for $PaCO_2$ in the three phases of the study. The *asterisk* denotes statistically significant differences ($p < 0.001$) between phase 2 and the other phases

No significant difference was noted in total PEEP, Pplat or Crs between phase 1 (HME, basal Vt) and phase 2 (HH, basal Vt). Peak airway pressure (Ppeak) showed a significant decrease (from 36 ± 8 to 34 ± 7 cmH_2O, $p < 0.01$) and total airway resistance decreased significantly between the same phases (from 12.8 ± 5.4 cmH_2O/l/seg to 11.7 ± 4.2 cmH_2O/l/seg, $p = 0.049$).

In phase 3 (HH, low Vt) arterial blood gases showed no significant difference with phase 1 (HME, basal Vt) and Vt was decreased from 521 ± 106 to 440 ± 118 ml, $p < 0.001$ (7.3 ± 1.1 to 6.1 ± 1.3 ml/kg of weight measured at admission and 8.3 ± 1.6 to 6.9 ± 1.8 of PBW, $p < 0.001$ in both). Ppeak and Pplat decreased from 34 ± 7 to 29 ± 8 and from 25 ± 6 to 21 ± 6 cmH_2O, respectively (both $p < 0.001$). Crs increased from 35 ± 12 to 42 ± 15 ml/cmH_2O, ($p = 0.003$; see Table 2). Vd_{phys} decreased significantly during the different phases of the study, as shown in Table 2. Individual changes in Vd_{phys} are shown in Fig. 2. Vd/Vt ratio differed significantly

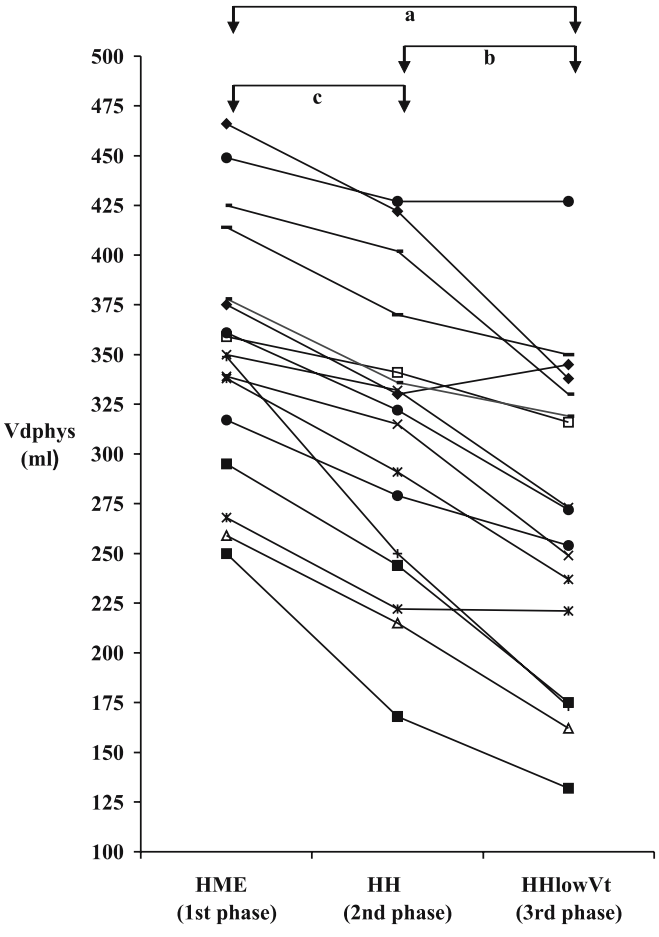

Fig. 2 Individual values for Vd_{phys} during the three phases of the study. There were statistically significant differences among the groups: a, b, c, all $p < 0.001$

among the three phases (Table 2). The decrease in Vt between phase 2 (HH, basal Vt) and the phase 3 (HH, low Vt) was also correlated with an improvement in Crs ($r = 0.52$, $p = 0.031$). Changes in Vt and Vd_{phys} between the same phases of the study strongly correlated ($r = 0.78$; $p < 0.001$), as shown in Fig. 3. The decrease in Pplat between phase 1 (HME, basal Vt) and phase 3 (HH, low

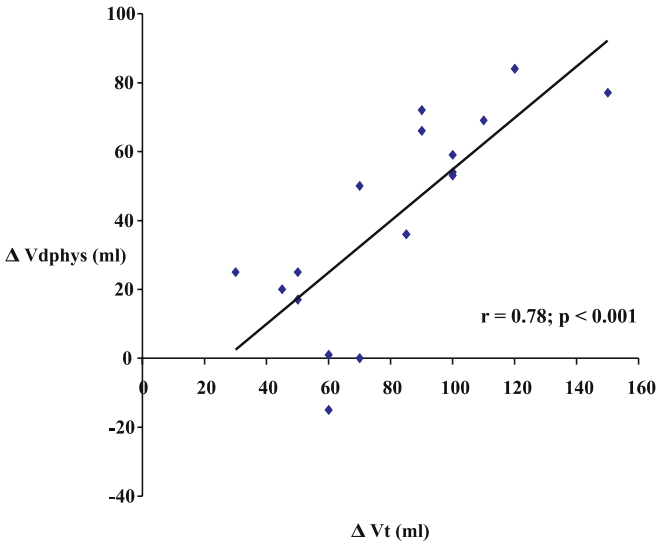

Fig. 3 Relationship between the decrease in Vt (ΔVt) between phase 2 and phase 3, and the decrease in Vd_{phys} (ΔVd_{phys}) between the same phases. The linear correlation was highly significant

Vt) did not correlate with the Pplat level in the phase 1 of the study ($r = 0.34$; $p = 0.12$). Additionally, the drop in Vd_{phys} at the end of the study did not correlate with the initial Vd_{phys} level ($r = 0.18$; $p = 0.5$). However, Vt and Vd_{phys} levels in basal conditions strongly correlated ($r = 0.60$; $p = 0.011$), and the decrease in Pplat between phase 1 and phase 3 had a good correlation with the decrease in Vd_{phys} between the same phases ($r = 0.59$; $p = 0.013$).

All hemodynamic parameters remained unchanged during the study (see Table 3). No patient needed to be excluded from the protocol because of temperature variations.

Discussion

The main findings in this study were: (1) The reduction in instrumental dead space in ALI/ARDS patients by means of HH significantly decreased $PaCO_2$ levels. (2) At iso-

Table 3 Hemodynamic parameters (mean ± SD) during the study period ($n = 17$ patients unless otherwise specified)

	HME (phase 1)	HH (phase 2)	HH-lowVt (phase 3)	Overall *p* Value
HR (beats/min)	91 ± 18	92 ± 18	95 ± 18	0.11
MAP (mmHg)	76 ± 11	77 ± 14	79 ± 12	0.45
CVP (mmHg)	12 ± 4	12 ± 4	12 ± 4	0.56
MPAP (mmHg) ($n = 7$)	26 ± 2	26 ± 3	28 ± 2	0.14
CO (l/min) ($n = 6$)	6.2 ± 2.7	6.0 ± 2.4	6.5 ± 2.2	0.24
PCWP (mmHg) ($n = 7$)	14 ± 2	14 ± 3	14 ± 2	0.68

Abbreviations: *n*, number of patients evaluated; HR, heart rate; MAP, mean arterial pressure; CVP, central venous pressure; MPAP, mean pulmonary artery pressure; CO, cardiac output; PCWP, pulmonary capillary wedge pressure

capnic conditions, HH permitted the use of lower tidal volumes, which led to a significant decrease in Vd_{phys} and Pplat. (3) Tidal volume reduction significantly improved respiratory system compliance in our patients.

Several studies carried out in ALI/ARDS patients have demonstrated significant changes in $PaCO_2$ and/or Vd/Vt values using different humidification devices. Campbell and colleagues [6] showed significant Vd/Vt and $PaCO_2$ increments when exchanging a HH for a HME. In a similar study that evaluated gas humidification devices, Prin and co-workers [9] observed a significant decrease in $PaCO_2$ using HH instead of HME. In a more recent study performed in ten hypercapnic ARDS patients, Prat et al. [8] demonstrated that a progressive reduction in the artificial airway dead space led to a proportional $PaCO_2$ decrease at each device switch. Our data are consistent with this observation. The decrease in Vt in phase 3 of our study was correlated with an improvement in Crs. Our strategy of HH and low Vt further decreased Vd_{phys}. Such change in Vd_{phys} correlated with an improvement in Crs. This suggests that a certain degree of overdistension occurred when ventilating our patients with baseline Vt, since compliance increased when Vt was reduced in phase 3 of the study, and this Vt reduction was also accompanied by a decrease in Vd_{phys}. Our results suggest that, all else unchanged, the effects of exchanging HME for HH would help to minimize potentially injurious ventilation. Interestingly, we found that the amount of decrease in Vd_{phys} at the end of the protocol (HH, low Vt) was not confined to only those patients who had the highest Vd_{phys} at baseline (HME, basal Vt).

A recent study performed in early ARDS patients has demonstrated that an increased dead space fraction was an independent risk factor for death [16]. The authors did not mention which kind of humidifier was used. However, it seems clinically reasonable to assume that in those individuals in whom a high Vd_{phys} was measured, this reflected a worse lung status rather than the effects of different humidifying devices. Our data showing that a reduction in Vt is correlated with a Vd_{phys} decrease, together with the finding of an increased Crs when isocapnic conditions were met when using a HH with low Vt, suggest that this intervention can help minimize potentially harmful ventilation.

The "in vitro" HME volume of the new and unused devices (90 ml) decreased "in vivo", especially due to the condensate accumulation in the filter and in the flexible tube. We occasionally measured the "in vivo" HME internal volume immediately after HME replacement and it averaged 50–60 ml. In our study the decrease in Vd_{phys} observed between phase 1 and phase 2 was approximately 40 ml (from 352 ± 63 to 310 ± 74 ml); this drop is attributed directly to a humidification device switch. Similar data were found by Richecoeur et al. [5], who removed the 15-cm-long tubing connecting the Y piece to the endotracheal tube and obtained a reduction in the total dead space of 40 ml during optimized mechanical ventilation.

Ventilation with low tidal volumes may induce hypercapnia and increases in both cardiac output and pulmonary artery pressure, which could be deleterious and/or contraindicated in some patients [17]. Hypercapnic acidosis may also impair right ventricular function by inducing pulmonary hypertension [18, 19]. In addition, respiratory acidosis has been reported to be significantly and independently involved in acute cor pulmonale development in ARDS patients [20]. We found, however, that the hemodynamic differences were not statistically significant, probably because the magnitude of $PaCO_2$ changes was moderate (from 46 to 40 mmHg between phase 1 and phase 2) in our study. Nevertheless, the small number of patients in whom these determinations were performed precludes drawing definitive conclusions. In this scenario, increasing respiratory rate can be used to counterbalance minute ventilation decrease and prevent respiratory hypercapnia. An increase in respiratory rate, however, may enhance ventilator-induced lung injury, as demonstrated in experimental models [21, 22]. The clinical relevance of these findings is unknown. Investigators have also demonstrated that increasing respiratory rate to avoid Vt reduction-induced hypercapnia may, in turn, induce substantial gas trapping and generate auto-PEEP in ALI/ARDS patients [23, 24, 25]. Vieillard-Baron et al. showed that the increasing respiratory rate might not only produce dynamic hyperinflation but also impair right ventricular function without any decrease in $PaCO_2$ [24]. The strategy implemented in our study facilitated tidal volume reduction in ALI/ARDS patients without changing respiratory rate. In our study, the decrease in $PaCO_2$ due to the humidification device switch was similar in hypercapnic and non-hypercapnic patients. Nevertheless, Vd/Vt was statistically different between the two groups, suggesting greater lung damage in hypercapnic patients. These data were supported by a larger improvement in Crs in hypercapnic than in non-hypercapnic patients; this did not reach statistical significance, probably because of the small number of patients studied (Crs increased by $11 \pm 8 ml/cmH_2O$ in hypercapnic and by 5 ± 7 ml/cmH_2O in non-hypercapnic patients; $p = 0.17$).

Other factors which might change Vd_{phys}, such as PEEP levels and inspiratory pause, were kept constant in our study [26, 27, 28, 29]. High PEEP levels increase ventilation to high ventilation/perfusion areas and may worsen the Vd/Vt ratio [30]. In the current study, a progressive decrease in Vd_{phys} values was observed during reduced Vt ventilation phase after HH implementation, without changes in arterial oxygenation. This finding may be attributed to alveolar overdistension before Vt reduction, and could also explain the improvement observed in respiratory system compliance after Vt was decreased. We did not observe any total PEEP change in our patients, in accordance with previous results [8, 9]. The differences in Ppeak between phase 1 and phase 2 may be explained by a decrease in a total airway resistance

due to changes in humidification devices between these study periods.

Other mechanical ventilation adjuncts to reduce dead space and hypercapnia have been proposed, such as aspiration of dead space during expiration or tracheal gas insufflation [31, 32, 33, 34]. These methods, however, are not of common use and further devices must be applied to the mechanical ventilation apparatus. This may complicate their clinical feasibility. Reducing instrumental airway dead space with the use of HH instead of HME seems to be a simple maneuver to limit undesired hypercapnia when low tidal volume ventilation is used in ALI/ARDS patients. Alternatively, if $PaCO_2$ is of no concern, our results show new physiological and eventual clinical implications of this intervention (i.e. reducing instrumental dead space) since can help to reduce a potentially harmful Vt.

We did not observe any episodes of endotracheal tube occlusion during our study, but our protocol was performed only to evaluate the short-term effects of humidification devices on gas exchange and lung mechanics. In a recent multicenter randomized study evaluating the incidence of ventilator-associated pneumonia and comparing HH and HME in 369 patients, the endotracheal tube became occluded and required emergency reintubation on six occasions, five times with HH and once with HME [35]. These findings did not reach statistical significance and may be explained by poor humidification of inspired gas with some HH, especially when ambient air temperature, minute ventilation and ventilator output gas temperature were high [36]. This situation did not occur in our intensive care service since the ambient temperature is kept at a constant 21°C and we did not use turbine-based ventilators. Nevertheless, Jaber and colleagues demonstrated that the accumulation of mucous secretions in an endotracheal tube caused by prolonged use of humidification devices is higher with HME than with HH [37]. The risk of endotracheal tube occlusion may be diminished using automatic compensation systems for HH or using an HME that provides at least 30 mgH_2O/l of absolute humidity [36]. Besides, Ricard and coworkers demonstrated the absence of statistical significance on clinical parameters and hygrometric measurements and did not observed any episode of endotracheal tube occlusion changing the HME only once a week [38].

In conclusion, reducing artificial airway dead space due to a change in humidification devices appears to be a useful and simple maneuver to control $PaCO_2$ levels. In addition, if moderate hypercapnia is not an issue, using HH instead of HME allows further reduction in Vt, which is accompanied by a diminished mechanical load. In our patients, this intervention entailed an improvement in respiratory system compliance (Crs), a decrease in plateau airway pressure (Pplat) and a decrease in physiologic dead space (Vd_{phys}), suggesting less overdistension.

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Intensive Care Med (2012) 38:1242
DOI 10.1007/s00134-012-2603-3

ERRATUM

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Erratum to: Heat and moisture exchangers and heated humidifiers in acute lung injury/ acute respiratory distress syndrome patients. Effects on respiratory mechanics and gas exchange

Published online: 24 May 2012

The online version of the original article can be found under doi:10.1007/s00134-006-0073-1.

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Erratum to: Intensive Care Med (2006) 32:524–531 DOI 10.1007/s00134-006-0073-1

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TERCERA PUBLICACIÓN

Título: Comparison of the effects of two humidifier systems on endotracheal tube resistance.

Autores: Indalecio Morán, Belen Cabello, Elisabet Manero, Jordi Mancebo.

Revista: Intensive Care Medicine (2011); 37: 1773-1779.

Factor de Impacto: 5,399 según la ISI Web of Knowledge^{SM} de 2011.

Intensive Care Med (2011) 37:1773–1779
DOI 10.1007/s00134-011-2351-9

ORIGINAL

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Comparison of the effects of two humidifier systems on endotracheal tube resistance

Received: 15 April 2011
Accepted: 1 September 2011
Published online: 27 September 2011

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-011-2351-9) contains supplementary material, which is available to authorized users.

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Abstract *Purpose:* To compare the effects of two humidifier systems on endotracheal tube (ETT) resistance during mechanical ventilation, either an active heated humidifier (HH) or a passive heat and moisture exchanger (HME) was selected using current clinical recommendations. *Methods:* This was a prospective clinical cohort study performed in an intensive care unit. Gas conditioning was performed using the HH in 22 patients and the HME in another 22. Patients were matched for endotracheal tube diameter, days of mechanical ventilation, simplified acute physiology score II (SAPS II), and fluid balance. *Results:* Used-ETT resistance was measured immediately after extubation. Unused-ETT resistance was calculated with an identical, clean ETT. No differences were found between the HH and HME groups in ETT diameter (7.9 ± 0.4 vs. 7.9 ± 0.3 mm; $p = 0.98$), days of mechanical ventilation (11.3 ± 7.7 vs. 9.5 ± 4.5; $p = 0.34$), SAPS II (41.0 ± 13.6 vs. 42.0 ± 11.7; $p = 0.79$), or fluid balance ($-2{,}552 \pm 6{,}268$ vs. $-2{,}579 \pm 5{,}422$ mL; $p = 0.98$). ETT resistance increased from intubation to extubation: from 6.8 ± 1.1 to 10.6 ± 4.3 $cmH_2O\ L^{-1}\ s^{-1}$ in the HH group, ($p < 0.001$) and from 6.8 ± 1.1 to 10.2 ± 3.8 $cmH_2O\ L^{-1}\ s^{-1}$ in the HME group ($p < 0.001$), which is a 53% average increase in resistive load. *Conclusions:* We did not find differences between the two types of humidifiers in terms of airflow resistance during prolonged mechanical ventilation when the devices were selected on the basis of individual clinical needs. The increase in resistive load is physiologically relevant.

Keywords Mechanical ventilation · Endotracheal tube resistance · Heated humidifier · Heat and moisture exchanger

Introduction

Humidification and warming of inspired gases are of major importance during mechanical ventilation because the upper respiratory airway is bypassed by the endotracheal tube [1]. Two types of humidifiers are commonly used in clinical practice: heat and moisture exchangers (HME) and heated humidifiers (HH). Insufficient or excessive humidification can provoke airway mucosa dysfunction and abnormal humidification of respiratory secretions, eventually leading to endotracheal tube occlusion [2, 3]. The type of humidification, selected for use in this setting, is relevant because devices can exhibit disparate humidification efficiency [4, 5].

While patients are intubated and mechanically ventilated, respiratory secretions adhere to the inner surface of

the endotracheal tube (ETT). As the diameter of the tube decreases, airflow resistance increases. This effect is common in acute respiratory failure patients under mechanical ventilation [6, 7] and it may be greater with prolonged use of passive humidification devices than with active devices [8, 9]. ETT patency has been proposed to indirectly reflect the quality of inspired gas humidification during mechanical ventilation [8]. Current data show no preferential performance of either HME or HH devices in mechanically ventilated patients concerning the incidence of ventilator-associated pneumonia, mortality, or morbidity [10, 11]. The type of humidification used during routine mechanical ventilation should be chosen on the basis of a patient's underlying disease [12, 13], respiratory mechanics [14], quality of respiratory secretions [3, 15], the mechanical ventilation settings [16], and ambient and patient temperature [17, 18].

ETT narrowing is associated with increased work of breathing. It can prolong weaning from mechanical ventilation and artifactually alter the breathing pattern [14, 19, 20]. Two single-center studies observed that ETT resistance was significantly higher when inspiratory gases were conditioned via an HME as compared to an HH [8, 9]. These data, however, have not been replicated. The aim of our study was to assess the impact of two humidification devices (passive HME vs. active HH) on in vivo ETT resistance to airflow during long-term invasive mechanical ventilation in unselected acute respiratory failure patients. Preliminary data from this study have been previously presented [21].

Materials and methods

The study was performed in the Intensive Care Unit at Hospital de la Santa Creu i Sant Pau, Barcelona (Spain). Given the nature of measurements and the fact that HH and HME are used in routine practice during mechanical ventilation in our institution, the requirement for signed informed consent was waived by the institutional ethics committee after approval of the protocol. All patients included in the study were intubated and mechanically ventilated for more than 48 h. Exclusion criteria were age below 18, tracheotomy, or enrolment in another clinical trial.

The mechanical ventilation parameters used in the study were those used in routine clinical management. ETTs used were high-volume, low-pressure cuffed tubes (Rüschelit® Rüsch; Karmunting, Malaysia). They were all the same brand and model, but internal diameters differed according to patients' clinical and anthropometric characteristic. Ventilator circuits remained unchanged throughout the course of mechanical ventilation. Secretion removal from ETTs or upper airways was conducted following open suction technique based on clinical detection or suspicion of secretions due to increased airway pressures in the ventilator display. Only the first episode of extubation was included in the study in patients who presented multiple episodes of extubation. Our routine clinical practice considers using an HH based on current recommendations [18, 22] in the following scenarios: previous presence of profuse bloody or copious mucous secretions, tenacious sputum, episode of ETT or tracheotomy occlusion, acute respiratory distress syndrome, asthma, exacerbation of chronic obstructive disease, and hypothermia.

Each ETT from a patient humidified with an HH was matched with an ETT from a patient in whom an HME was used. Four variables were assessed, in the following order: ETT diameter, days of mechanical ventilation, simplified acute physiology score II (SAPS II), and fluid balance.

The HH devices (Fisher & Paykel; MR 290 and MR 850 ALU; Panmure, New Zealand) were placed in the inspiratory limb of the circuit in accordance with the manufacturer's recommendations. The HME devices (Edit Flex, Datex Engstrom®, Helsinki, Finland) had a dead space of 90 mL that included an integrated flexible tube and a filter. The "in vitro" HME resistive pressure drop described by the manufacturer was 1.4 cmH_2O at a constant flow of 60 L/min. HMEs were placed between the Y piece and the ETT. Mechanical ventilation was maintained at routine parameters established by the responsible physician.

ETT resistance was measured directly from the respiratory monitoring system of the Puritan-Bennett 7200 ventilator (Puritan-Bennett Corporation, Carlsbad, CA, USA) after proper calibration of the ventilator following the manufacturer's recommendation and using a standard disposable breathing circuit connected to the proximal end of the ETT in an identical manner as done with patients. The distal end of the ETT was open to the atmosphere. ETT resistance (R measured in $cmH_2O\ L^{-1}\ s^{-1}$) was calculated as the pressure drop between the proximal and distal end of the ETT (measured in cmH_2O) divided by flow (measured in L/s). During ETT resistance measurements, flow was passed constantly at 60 L/min (1 L/s). For clean ETT resistance ("unused-ETT") and immediately after extubation ETT resistance measurements ("used-ETT"), we used the same setup. Experimental setting and measurements are shown in the Electronic Supplementary Material (ESM Figs. 1, 2).

We calculated the theoretical increase in work of breathing (WOB), expressed in joules (J/min), provoked by the increased resistance of the ETT after use (i.e., the difference between after extubation ETT resistance and unused-ETT resistance). This theoretical calculation was performed assuming a respiratory rate of 20/min, inspiratory time of 0.5 s, and constant inspiratory flow of 60 L/min (i.e., a breathing pattern with a respiratory rate of 20/min, a tidal volume of 500 mL, inspiratory time of 0.5 s, and an expiratory time of 2.5 s).

All patients in the study were subjected to our usual weaning process. This was accomplished by reducing the

pressure support ventilation (PSV) and positive end-expiratory pressure (PEEP) levels as described [23, 24]. Planned extubation was performed when a patient tolerated low levels of PSV ($\approx$7 cmH_2O) without PEEP or T-piece trial with FiO_2 less than 0.5, between 30 and 120 min. We performed endotracheal suctioning during the extubation procedure. This suctioning consisted of disconnecting the patient from the ventilator and inserting a suction catheter of 12–14 Fr through the ETT into the airways until resistance was met. The catheter was then pulled back 1–2 cm. Negative suctioning pressure at 150–200 mmHg was continuously applied for 10–15 s while the catheter was rotated and removed simultaneously with the ETT [25, 26]. Patients not subjected to weaning but eventually extubated (i.e., those who died) were also included.

Statistical analysis

Sample size calculation was performed assuming the following: (1) we calculated the baseline resistance of unused-ETT, which was of 6.8 ± 1.1 $cmH_2O\ L^{-1}\ s^{-1}$; (2) a difference in ETT resistance of 1.0 $cmH_2O\ L^{-1}\ s^{-1}$ between the two humidification systems would be considered as clinically relevant according to previously published data [8, 9]; (3) taking into consideration (1) and (2), to detect a two-tailed significant difference (type I error of 5%; $\alpha = 0.05$) with at least an 80% statistical power ($\beta = 0.20$), 22 patients per group are required; (4) to confirm normal data distribution and equal variances between groups we performed the Kolmogorov–Smirnov test and the Levene test, respectively. Therefore, since the data regarding used-ETT resistances were normally distributed and variances did not show differences, we used the Student's *t* test for the comparison. For non-normally distributed variables we used the Mann–Whitney *U* test. Dichotomous variables were compared using the chi-square method with a two-tailed Fisher's exact test. A *p* value less than 0.05 was considered statistically significant. Data are expressed as means $\pm$ standard deviation (SD). The SPSS® (version 17.0, Chicago, IL, USA) statistical software was used for statistical analysis.

Results

The study involved a total of 44 ETT that were recovered from prospective consecutive matched patients. Twenty-two ETTs were from patients humidified with an HH (HH group) and 22 were from patients humidified with an HME (HME group). Table 1 lists patients' demographic data, the main indication for mechanical ventilation, and clinical characteristics at admission. In addition, Table 1 shows number of days intubated, days of bronchodilator therapy, fluid balance, ETT diameter, and unused-ETT and used-ETT flow resistance.

All patients were orotracheally intubated and ETT diameters ranged from 7.0 to 8.5 mm. The measured ETT resistances were statistically higher among the endotracheal tubes after extubation than in the ETT before use (10.4 ± 4.0 vs. 6.8 ± 1.1 $cmH_2O\ L^{-1}\ s^{-1}$; $p < 0.001$). Figure 1 shows patient per patient ETT resistance changes in the HH and HME groups. ETT resistances increased significantly in both groups: from 6.8 ± 1.1 to 10.6 ± 4.3 $cmH_2O\ L^{-1}\ s^{-1}$ ($p < 0.001$) in HH patients and from 6.8 ± 1.1 to 10.2 ± 3.8 $cmH_2O\ L^{-1}\ s^{-1}$ ($p < 0.001$) in HME patients. Increases in ETT resistance for endotracheal tubes did not correlate with mechanical ventilation duration in the HH group ($r = 0.067$; $p = 0.766$) or in the HME group ($r = 0.117$; $p = 0.603$). The average increase of ETT resistances between groups was similar (57 vs. 51%, $p = 0.771$; HH and HME, respectively). Besides, Fig. 1 shows the distribution of the diameter of ETTs at baseline and the theoretical effective inner diameter of ETTs related to changes in the resistance measured after extubation.

As expected, the estimated WOB related to the resistive pressure drop across the ETT was significantly higher in the used-ETT compared with the unused-ETT: 10.4 ± 4.0 vs. 6.8 ± 1.1 J/min, ($p < 0.001$). This estimate assumes a tidal volume of 500 mL, a constant inspiratory flow of 1 L/s, and a respiratory rate of 20/min.

Fourteen (32%) patients developed ventilator-associated pneumonia (VAP) (7 in the HH group and 7 in the HME group; $p = 1$). The duration of mechanical ventilation was significantly longer for the 14 patients that presented VAP than in patients who did not suffer VAP (14.6 ± 6.7 vs. 8.4 ± 5.1 days; $p = 0.002$). Nevertheless, ETT resistance in endotracheal tubes removed from patients who developed VAP showed no statistical differences compared with ETTs removed from patients without VAP (9.6 ± 3.3 vs. 10.1 ± 4.3 $cmH_2O\ L^{-1}\ s^{-1}$ respectively; $p = 0.33$).

Five patients in the HH group (23%) and three in the HME group (14%) required reintubation for respiratory failure after extubation ($p = 0.69$). No differences in intensive care unit (ICU) mortality were seen between the two groups: 4/22 (18%) patients died in each group.

Discussion

The main finding in this study was that we did not observe any differences between HH and HME in endotracheal tube resistance as used in routine clinical practice. ETT resistance increased significantly from intubation to extubation day, representing a non-negligible increase in mechanical workload with both devices.

Table 1 Comparison between the HH and HME groups

	HH ($n = 22$ patients)	HME ($n = 22$ patients)	p value
Age (years)	63.8 ± 12.4	62.8 ± 11.8	0.777
Gender			
Male (*n*)	16	16	1
Female (*n*)	6	6	1
SAPS II score	41.0 ± 13.6	42.0 ± 11.7	0.795
PaO_2 (mmHg)	86 ± 18	99 ± 33	0.135
FiO_2	0.6 ± 0.2	0.4 ± 0.1	0.004
PEEP (cmH_2O)	7.2 ± 2.3	6.0 ± 1.2	0.056
Main diagnosis at admission			
Pneumonia	8 (18.2%)	4 (9.1%)	0.310
COPD exacerbation	4 (9.1%)	0 (0%)	0.108
Congestive heart failure	1 (2.3%)	3 (6.8%)	0.607
Abdominal surgery	5 (10.9%)	4 (9.1%)	1
Sepsis	1 (2.3%)	1 (2.3%)	1
Neurological disorder	3 (6.8%)	10 (22.7%)	0.045
ETT diameter (mm)	7.9 ± 0.4	7.9 ± 0.3	0.989
Mechanical ventilation (days)[a]	11.3 ± 7.7	9.5 ± 4.5	0.347
Bronchodilators use (days)	3.2 ± 4.1	1.9 ± 3.7	0.084
Fluid balance (mL)	−2,552 ± 6,268	−2,579 ± 5,422	0.988
Unused-ETT flow resistance ($cmH_2O\ L^{-1}\ s^{-1}$)[b]	6.8 ± 1.1	6.8 ± 1.1	0.989
Used-ETT flow resistance ($cmH_2O\ L^{-1}\ s^{-1}$)[c]	10.6 ± 4.3	10.2 ± 3.8	0.767

Percentages are with respect to *all* patients included. Other values are mean ± SD unless indicated otherwise

HH heated humidifiers, *HME* heat and moisture exchangers, *n* number of patients evaluated, *SAPS II* simplified acute physiology score II, PaO_2 partial pressure of oxygen in arterial blood, FiO_2 fraction of inspired oxygen at inclusion, *PEEP* positive end-expiratory pressure, *ETT* endotracheal tube, *COPD* chronic obstructive pulmonary disease

[a] Mechanical ventilation expressed in days from intubation to extubation for each ETT evaluated

[b] Airflow resistance measured in clean unused ETTs

[c] Airflow resistance measured in ETTs after extubation

Humidification devices decrease the adherence of respiratory secretion onto the ETT surface by conditioning the inspired gases [22]. Nevertheless, their efficiency regarding humidification levels [27, 28] and incidence of ETT occlusion [8] is highly variable. Our results confirm that deposits of respiratory secretions on the inner wall of ETTs reduce their lumen and thus increase airflow resistance.

In contrast with findings by Villafane et al. [8] and Jaber et al. [9], we did not observe differences in resistance between patients using HHs and patients using HMEs. These authors [8, 9] studied patients who were randomly assigned to different types of airway humidifiers, whereas we performed a matched-pair study controlled for ETT diameter, days of mechanical ventilation, SAPS II, and fluid balance. Our patients were assigned to HH or HME according to clinical needs and common recommendations [3, 12–15]. This clinical selection of the type of humidifier carried out in our study, according to the main respiratory diagnosis and secretion management needs, instead of randomization performed in those studies, may explain the differences found in the ETT resistance over time when comparing our study with those previously published. The fact that the HH and HME populations were not strictly identical may suggest a clinical bias favoring the use of one system over the other. This is, however, difficult to ascertain since in our study we did not analyze either quantity or quality of respiratory secretions.

An increase in mechanical workload due to a reduction in ETT inner diameter may generate a spurious weaning trial failure and prolong mechanical ventilation [14, 19, 20, 29, 30]. This deleterious situation can be avoided by applying adequate inspiratory pressure support [19, 31], but titration of pressure support is almost impossible to predict individually in these circumstances. Furthermore, it must be taken into account that HMEs may increase inspiratory resistance, dead space ventilation, inspiratory work of breathing, and dynamic hyperinflation. These variables may pose an extra burden on the respiratory muscles during the weaning process, leading to clinical intolerance to spontaneous breathing trials [14, 16, 32].

In a study involving healthy volunteers, Shapiro et al. [29] described that increases in WOB were magnified when ETT diameter decreased below 7 mm. The increase in WOB caused by the increase in resistance of ETTs may be clinically relevant in certain patients. In our study no patients were intubated with an ETT smaller than 7 mm. Nevertheless, we showed that in 34% of our patients (7 in the HH group and 8 in the HME group) the ETT airflow resistance at extubation time corresponded to the

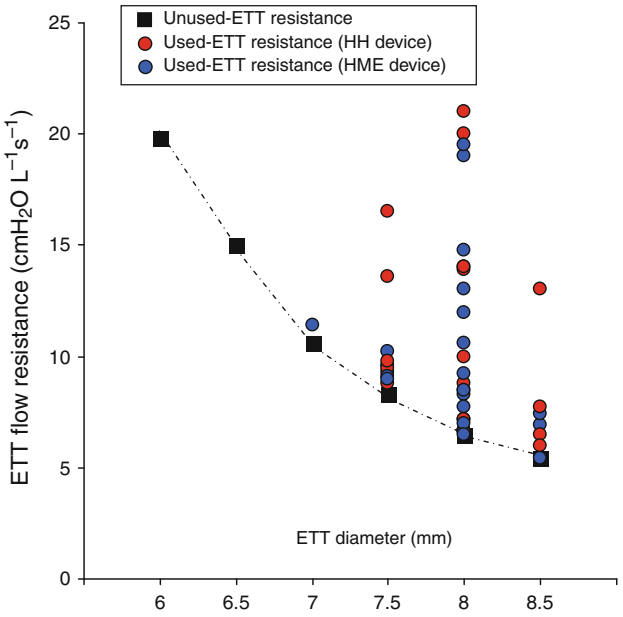

Fig. 1 *Black squares* show flow resistance of unused-ETTs in relation to their diameter. *Circles* show individual values in ETT resistance measured after extubation, from patients humidified with HH (*red circles*) and from patients humidified with HME (*blue circles*). All resistance values were calculated at a constant flow of 1 L/s. All ETTs used were from the same brand and model varying only in the internal diameter among them. The *dotted line* represents the exponential increase in flow resistance in relation to the diameter of the unused-ETTs. As can be seen, 15 (34%) of used-ETTs had real resistances at extubation corresponding to unused-ETT with inner diameter below 7 mm

resistance of a clean ETT with an inner diameter between 5.5 and 7 mm (Fig. 1).

Many studies have proposed ETT patency as an indirect parameter to reflect gas conditioning during mechanical ventilation [7–9, 33–35]. Several of these studies [7–9] did not find differences between HMEs and HHs in the overall reduction in ETT mean diameter in the short term (5–6 days). Nevertheless, Shah et al. [7] and Jaber et al. [9] described significantly higher ETT airflow resistance with HMEs than with HHs in prolonged mechanical ventilation (10 ± 6 days). However, over a virtually identical duration of mechanical ventilation, we did not find statistical differences between the two devices in ETT airflow resistance. This could be explained as a result of differences between studies in clinical strategies, concerning, for example, the efficiency of humidifiers, patient selection, mechanical ventilation strategy, diagnosis and management of VAP, and strategies for suctioning airway secretions. ETT resistance may also be influenced by general patient hydration [6, 36] but we did not find statistically significant differences in fluid balance in our two groups. Besides, as reported by Boqué and co-workers [6], we did not find a correlation between the increase in ETT resistance and the days of ETT use.

To avoid the influence of patients' spontaneous activity and flow pattern on the measurements of airflow resistance we studied isolated ETT resistance [36, 37]. We measured the resistance for each ETT immediately post-extubation maintaining identical ETT deformation and secretion accumulation and trying to minimize any change of the mucous material adhered within the ETT [8, 38]. Theoretically, our routine ETT suctioning procedure may cause artifacts in the results of the study because of mucus secretion removal from the ETT during extubation and measurement of resistance of the used-ETT after it. However, this practice was always identical in the HH and HME groups and we thus believe that the impact on results is minimal since our practice was equally distributed between the two groups.

With respect to patients who develop VAP, the reduction in the internal diameter of an ETT due to increases of respiratory secretions has been proposed as a factor that increases mechanical ventilation days [7]. Our data did not show higher ETT resistance in patients with VAP compared to that in patients without VAP.

The present study has several limitations. First, this was a case–control study with a sample size of 22 patients per group in which we did not randomly select the humidification device type. Second, as diagnoses at inclusion differed between groups and we did not measure heating or humidification levels we can not guarantee that the degree of humidification was identical. Furthermore, although we indirectly assessed gas conditioning (ETT airflow resistance) with both humidification devices, we did not examine secretion characteristics or eventual epithelial respiratory damage. Third, our theoretical increases in WOB probably overestimate the real workload attributable to increased resistance of the ETT, because we did the calculation assuming a gas flow of 1 L/s. Actually, Vassilakopoulos et al. [39] measured a mean inspiratory flow of 0.71 ± 0.19 L/s with an average tidal volume of 460 mL and average respiratory rate of 27/min during a successful T-piece trial.

In conclusion we did not find differences between the two types of humidifiers in terms of airflow resistance. However, ETT resistance increased significantly during mechanical ventilation with both the HH and HME devices. Such increases in resistance may be relevant from a clinical point of view, in particular, during the weaning phase from mechanical ventilation and the performance of spontaneous breathing trials.

Acknowledgment B.C. was supported by grants from the Instituto de Salud Carlos III (Expedient CM04/00096, Ministerio de Sanidad) and the Instituto de Recerca Hospital de la Santa Creu i Sant Pau.

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8. DISCUSIÓN

A la luz de los resultados obtenidos, las respuestas a las cuestiones que nos planteábamos en la introducción de esta tesis son las siguientes:

¿SE PUEDE MEJORAR EL INTERCAMBIO DE GASES, LA MECÁNICA RESPIRATORIA Y OPTIMIZAR LA PEEP EN LOS PACIENTES CON SDRA MEDIANTE UNA MANIOBRA DE RECLUTAMIENTO ALVEOLAR ALCANZANDO ALTAS PRESIONES DE VÍA AÉREA?

La RM estudiada añadida a nuestra VM rutinaria mejoró la oxigenación de los pacientes. Sin embargo, a pesar de las elevadas presiones aplicadas, la Crs no aumento en 7 pacientes y la PEEP se mantuvo invariada respecto a la basal en 5 de los 13 pacientes estudiados. Además, la RM se tuvo que detener en 4 pacientes por inestabilidad hemodinámica.

A pesar de que la RM aplicada en nuestro estudio fue similar a la estudiada por Borges *et al*. (46) y la mecánica respiratoria en el momento de la inclusión de los pacientes fue superponible (Crs ≈28 ml/cmH_2O y Pplat ≈30 cmH_2O), la respuesta fisiológica observada tras la RM en nuestro estudio fue diferente. Estos hallazgos se pueden explicar por lo siguiente: nuestros pacientes estaban ventilados basalmente con una PEEP (12 cmH_2O vs. 5 cmH_2O) y un Vt (7,8 ml/kg vs. 6 ml/kg) relativamente más altos. En el estudio de Borges *et al*. tanto los bajos niveles de PEEP como el Vt reducido pudo causar colapso alveolar basal que fue revertido y prevenido tras la RM con el aumento de PEEP (87). La heterogeneidad

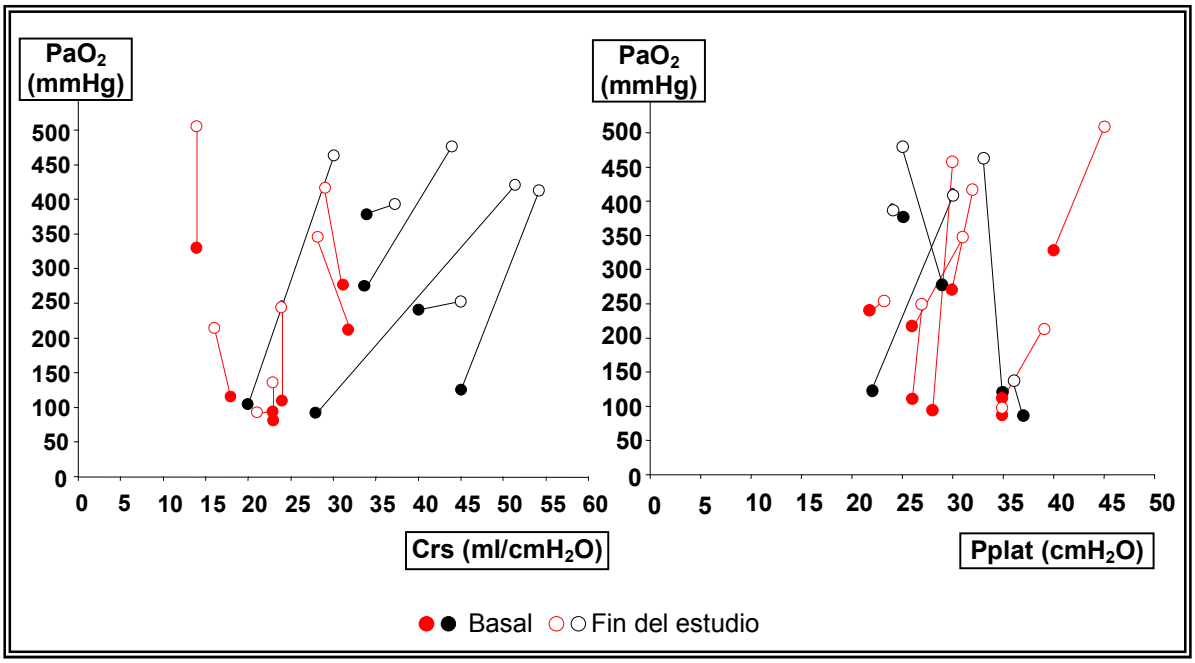
en la respuesta a la RM observada en nuestros pacientes se podría explicar por el amplio rango de los niveles de PEEP empleados en el inicio (de 8 cmH_2O a 18 cmH_2O), al colapso capilar debido a la sobredistensión alveolar en las áreas más compliantes y quizá por el aumento del shunt intrapulmonar por la redistribución del flujo sanguíneo hacia zonas no ventiladas durante la maniobra (85, 100, 101).

Está descrito que el aumento de la Crs tras la RM puede ser un marcador de expansión pulmonar (101, 102). Pero a diferencia de estudios previos similares al nuestro (46), nosotros no observamos mejora en la Crs en 7 de los 13 pacientes estudiados (Grupo 2). Estos pacientes tenían basalmente una Pplat más alta y una Crs más baja que los del Grupo 1 (en los que sí observamos una mejora de la Crs). Además el aumento de la PaO_2 en el Grupo 2 fue notablemente menor que en el Grupo 1. Todos nuestros pacientes del Grupo 2 cumplían criterios de SDRA (7), presentaban valores muy bajos de Crs (24 ml/cmH_2O) y de FiO_2/PaO_2 (146±45 mmHg) y niveles de Pplat elevados (33±5 cmH_2O). Todos estos hallazgos refuerzan la idea de que a mayor lesión pulmonar, definida en términos de Crs, menor es la capacidad de reclutamiento (49) (Ver figura 1). En el trabajo de Gattinoni *et al.* los pacientes menos reclutables eran aquellos con mayor Crs, pero a diferencia de los nuestros, el 41% (14/34) tenían criterios de LPA en lugar de SDRA y probablemente estaban "bien reclutados" basalmente (Crs = 49±16 ml/cmH_2O; FiO_2/PaO_2 = 200±77 mmHg; Pplat = 23±3 cmH_2O).

En lo que respecta a las alteraciones hemodinámicas durante las RMs, hay que tener en cuenta que el incremento agudo de la $PaCO_2$ durante la maniobra puede generar disfunción de la contractilidad cardiaca por acidosis intracelular (103) y que la acidosis respiratoria en los pacientes con SDRA se ha relacionado de

forma independiente con *cor pulmonale* agudo por aumento de la presión arterial pulmonar (104) y con deterioro del intercambio de gases por aumento del shunt intrapulmonar (105). A estas alteraciones hemodinámicas, hay que añadir que el impacto del deterioro hemodinámico depende también en parte, de la volemia durante la RM (106) y de la transmisión de la presión de la vía aérea al espacio pleural (107).

Figura 1.



Variación individual de la PaO_2 desde el momento basal hasta el final de la monitorización tras la RM, en relación con la Crs (izquierda) y la Pplat (derecha). A pesar del aumento generalizado de la PaO_2 la respuesta individual de la mecánica respiratoria fue muy heterogénea. Esto fue así tanto en la evolución de la oxigenación en relación a la respuesta de la de Crs (que disminuyó en 7 de los 13 pacientes; círculos rojos) como en relación a los cambios observados en la Pplat (aumentó en 8 de los 13 pacientes; círculos rojos).

En general, durante las RMs, los cambios observados en la PAM son menores que los observados en el GC (108, 109), por lo que monitorizar este tipo de maniobra únicamente mediante la presión arterial puede infraestimar sus efectos sobre el sistema cardiovascular e infravalorar posibles efectos deletéreos. En cuatro de nuestros pacientes (31%) tuvimos que parar la RM. En tres por caída del GC >20% y en otro tras presentar una taquicardia paroxística supraventricular durante la insuflación. Esta cifra de complicaciones es similar a la descrita previamente (22%) con el uso de una RM menos agresiva que la nuestra y enmarcada en una estrategia de apertura pulmonar (45).

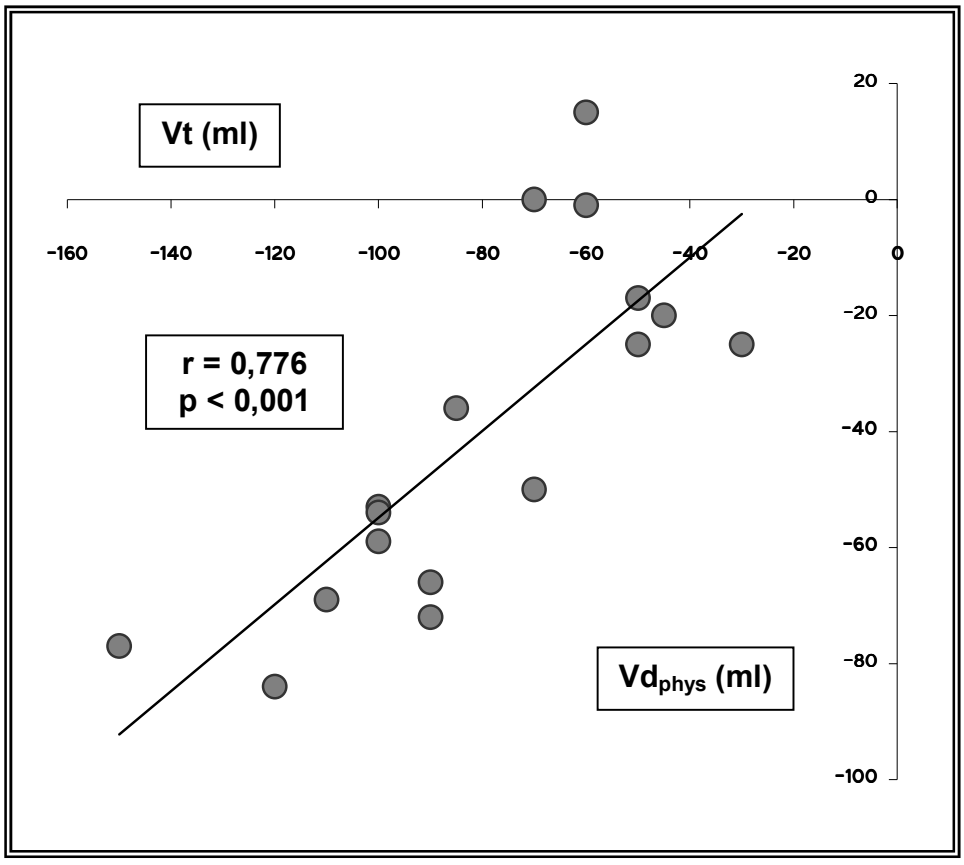
¿PODEMOS DISMINUIR LA CARGA VENTILATORIA Y MEJORAR LA MECÁNICA RESPIRATORIA DE NUESTROS PACIENTES CON LPA/SDRA EN FUNCIÓN DEL TIPO DE HUMIDIFICADOR QUE EMPLEEMOS EN LA FASE AGUDA DE LA ENFERMEDAD?

La disminución del espacio muerto generada por el uso de humidificadores tipo HH en lugar de HME disminuyó los niveles de $PaCO_2$. Además, en condiciones isocápnicas respecto a los valores basales, los HH permitieron el uso de volúmenes circulantes más bajos, con el consiguiente descenso del Vd_{phys} y de la Pplat y la consecuente mejora de la Crs en nuestros pacientes.

Nuestros datos son consistentes con los de estudios previos que demuestran cambios paralelos de los niveles de $PaCO_2$ en relación al aumento o la disminución del Vd instrumental (53, 54, 110). Pero además, el descenso del Vt combinado con el uso de HH se correlacionó con una mejora de la Crs y una

caída más marcada del Vd_{phys}. La disminución del Vd_{phys} durante la combinación de HH y Vt bajos fue generalizada, no limitándose a los pacientes con mayor Vd_{phys} basal. Estos datos, interpretados en conjunto, sugieren cierto grado de sobredistensión alveolar causado por el Vt empleado en la ventilación basal de nuestros pacientes y que, en el caso de mantener el resto de parámetros ventilatorios invariados, el cambio de la humidificación (HME por HH) nos puede ayudar a disminuir el Vt empleado y la sobredistensión alveolar (Figura 2).

Figura 2.



Correlación entre el descenso del Vt y el descenso en el Vd_{phys} observados entre la segunda (HH) y la tercera fase (HH y Vt bajo) del estudio.

El uso de Vt bajo durante la VM puede producir hipercapnia. Estos cambios en la $PaCO_2$ pueden variar el GC y alterar la función del ventrículo derecho por aumento de la presión arterial pulmonar (PAP) (111-113), condiciones que pueden ser deletéreas y estar contraindicadas en ciertos pacientes. Además, la acidosis respiratoria se ha relacionado de forma independiente con el *cor pulmonale* agudo que desarrollan algunos pacientes con SDRA (104). Para contrarrestar estos efectos del aumento de la $PaCO_2$ se ha sugerido el aumento de la frecuencia respiratoria, sin embargo, esta maniobra se ha asociado a lesión inducida por la VM en estudios experimentales (114, 115) y a presencia de auto-PEEP en pacientes con LPA/SDRA por atrapamiento aéreo secundario a la disminución del tiempo espiratorio (116-118). En nuestro estudio, el cambio del dispositivo HME por HH fue suficiente para disminuir la $PaCO_2$ sin realizar ninguna variación en la frecuencia respiratoria. Además, no encontramos diferencias significativas en la magnitud de la respuesta comparando los pacientes hipercápnicos con los que no lo estaban basalmente. Otros factores que pueden modificar el Vd_{phys} como la PEEP total (119-121) y la prolongación de la pausa inspiratoria (122), se mantuvieron invariados durante todo el estudio. El hecho de no observar cambios en la oxigenación arterial tras la implementación del dispositivo HH y el descenso del Vt en la tercera fase del estudio, y que sí detectáramos un progresivo descenso del Vd_{phys} y mejora en la Crs es altamente sugestivo de presencia de sobredistensión alveolar basal. Además, la aplicabilidad de nuestra estrategia para disminuir el Vd_{phys} es más simple que la de otros métodos propuestos con la misma finalidad como son la aspiración del espacio muerto durante la espiración (123) o la insuflación de gas traqueal (124).

¿CÓMO SE AFECTA LA RESISTENCIA AL FLUJO AÉREO DEBIDA A LA ADHERENCIA DE SECRECIONES AL TUBO ENDOTRAQUEAL EN FUNCIÓN DEL TIPO DE HUMIDIFICACIÓN EMPLEADA DURANTE LA VM Y QUE IMPLICACIÓN FISIOLÓGICA PUEDE TENER DESDE EL PUNTO DE VISTA DEL TRABAJO RESPIRATORIO?

La resistencia al flujo aéreo del TET aumentó de forma idéntica en el transcurso de la VM, comparando los pacientes humidificados con dispositivos tipo HH o HME. El aumento de la resistencia al flujo aéreo puede generar un incremento no despreciable del WOB de los pacientes durante la fase de desconexión de la VM.

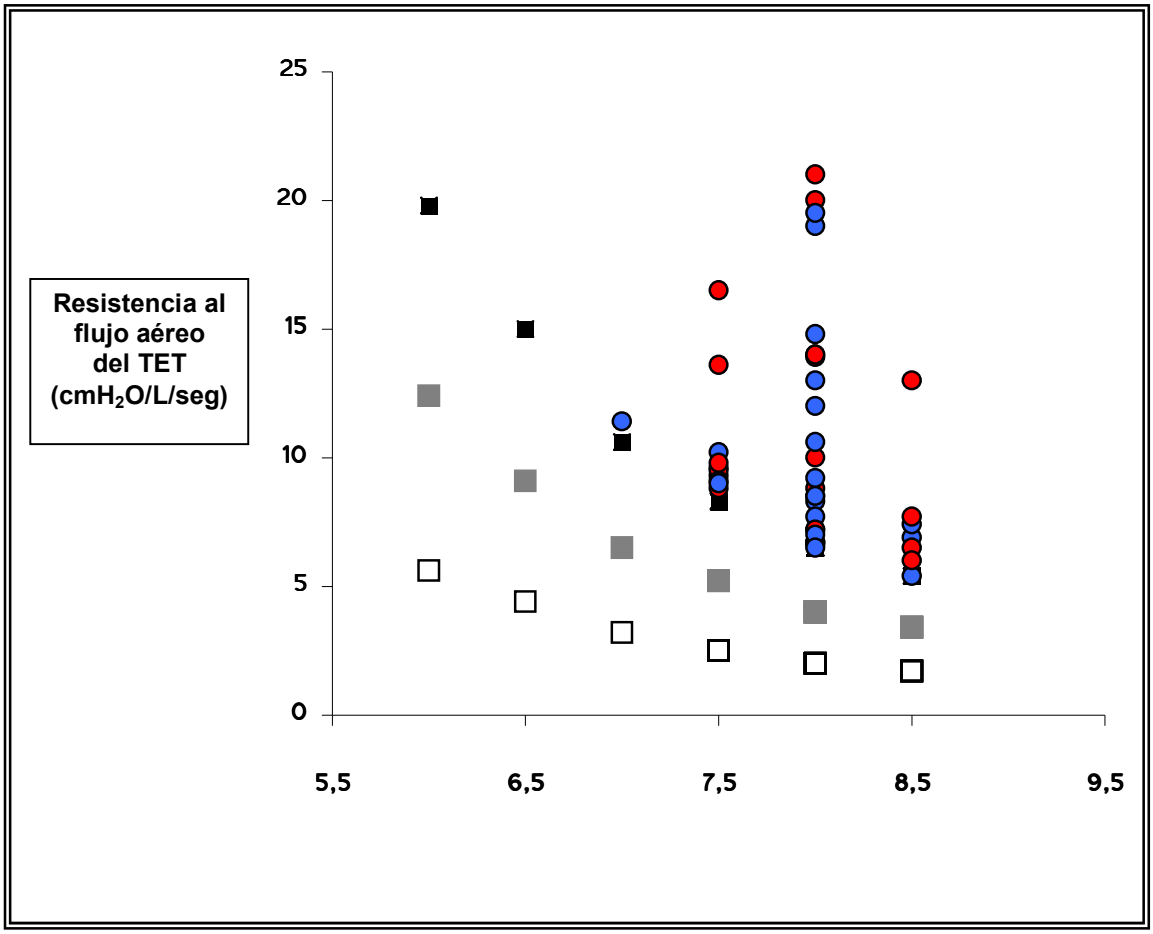
En términos generales, una correcta humidificación disminuye la adherencia de las secreciones respiratorias a la pared interna del TET (99). Si bien, la eficiencia de los diferentes dispositivos en términos de niveles de humidificación es muy variable (125, 126). Nuestros resultados ratifican que los depósitos de secreciones en el TET aumentan las resistencias al flujo aéreo. Sin embargo, a diferencia de estudios previamente publicados (69, 70), nosotros no encontramos diferencias en la resistencia entre los TET de los pacientes humidificados con HH o con HME. En estos estudios la asignación de la humidificación de los pacientes se hizo de forma aleatorizada. En nuestro estudio, sin embargo, el tipo de humidificación se asignó en función de las necesidades clínicas de los pacientes (55, 72, 95). Además, para hacer comparables ambos grupos se hizo un apareamiento de datos de las siguientes variables: diámetros del TET, días de VM, SAPS II y balance hídrico. La selección de la humidificación en función del diagnóstico principal de los pacientes y las diferentes necesidades del manejo de

las secreciones respiratorias puede explicar las diferencias encontradas respecto a los estudios previamente publicados. El hecho de que las poblaciones incluidas en cada grupo no sean completamente idénticas puede hacer suponer una desviación clínica que favorecería el empleo de un dispositivo respecto del otro, pero en nuestro estudio no se cuantificó ni la cantidad ni la calidad de las secreciones de los pacientes.

El aumento del WOB secundario al aumento de la carga mecánica por el aumento de las resistencias puede generar fracaso en la retirada de la ventilación mecánica y prolongación de la misma (71, 72, 74). Hay estudios que describen que este tipo de eventualidad se puede corregir adecuando los niveles de presión de soporte (73, 127). Sin embargo, la elección de los niveles correctos de presión de soporte es imposible de predecir en estas circunstancias. Además, en el caso particular de los HMEs está descrito el aumento de las resistencias y del Vd por el propio dispositivo, con el consecuente aumento del WOB e hiperinsuflación dinámica. Todo ello podría generar intolerancia durante las pruebas de respiración espontánea (72, 96, 128).

En un estudio en voluntarios sanos se describió que el WOB se magnificaba cuando el diámetro del TET era menor de 7mm (71). En nuestro estudio ningún paciente estaba intubado con TETs de diámetro menor a 7mm, sin embargo, encontramos que en el 34% de nuestros pacientes (7 con HH y 8 con HME) la resistencia al flujo aéreo en el momento de la extubación se correspondía con una resistencia de TETs limpios de diámetros entre 5,5 y 7mm (Ver la figura 3).

Figura 3.



Los cuadrados negros muestran la resistencia al flujo aéreo de los TETs limpios en relación con su diámetro. Los círculos muestran los valores individuales de la resistencia medida inmediatamente tras la extubación, tanto de los TETs de los pacientes humidificados con HH (círculos rojos) como con HME (círculos azules). Todas las resistencias se calcularon con un flujo constante de 1 litro por segundo. Los cuadrados grises y los blancos muestran, respectivamente, la resistencia teórica al flujo aéreo de TETs limpios calculada a 0,75 y 0,5 litros por segundo. Todos los TETs empleados fueron del mismo fabricante y modelo, variando entre ellos únicamente su diámetro. En 15 (34%) de los TETs usados se obtuvo una resistencia en el momento de la extubación correspondiente a un diámetro de TET limpio menor a 7 mm.

Diferentes estudios han propuesto el descenso del diámetro de los TET como un indicador indirecto de la calidad de la humidificación (68-70, 129-131). Algunos de ellos (68-70) no describen diferencias en la media de descenso del diámetro de los TET entre los humidificados con HH o HME durante la VM de corta duración (5-6 días). Sin embargo, hay estudios (68, 70) que describen un aumento de las resistencias significativamente mayor en los TET de los pacientes humidificados con HME en lugar de HH durante la VM prolongada (10±6 días). Nosotros mostramos que en pacientes ventilados durante idénticos periodos de tiempo no hay diferencias en las resistencias generadas en el TET comparando ambos tipos de humidificadores. Este aspecto se puede explicar, entre otras posibles causas, por diferencias en las estrategias clínicas de ventilación, manejo de las secreciones respiratorias y por los modelos de los humidificadores empleados.

La resistencia del TET puede estar influenciada por la hidratación general del paciente (67, 132). Nosotros no encontramos diferencias en el balance hídrico de los pacientes entre ambos grupos. Tampoco encontramos correlación entre el grado de obstrucción y la duración de la VM, como se había descrito previamente (67). Para evitar la influencia del patrón respiratorio sobre la resistencia al flujo (132, 133), las mediciones se realizaron justo tras la extubación y tratando de no generar cambios en el contenido del TET ni en su deformación (69, 134).

Por último, se ha argumentado que en los pacientes que desarrollan NAV, la disminución del diámetro interno del TET por el aumento de las secreciones adheridas podría explicar, en parte, el aumento de los días de ventilación mecánica (68), En cambio, nuestros datos de resistencias de los TETs no mostraron diferencias comparando los pacientes que sufrieron NAV y los que no.

9. LIMITACIONES

La presente tesis tiene algunas limitaciones generales que seguidamente explicitamos. Las limitaciones particulares de cada estudio se detallan y discuten de forma puntual en los correspondientes artículos (50, 55, 75).

Los estudios que componen esta tesis son estudios que incluyen un relativo bajo número de pacientes y el motivo principal por el que requirieron soporte con VM es heterogéneo. Del total de los 74 pacientes incluidos en los 3 estudios, 66 han sido estudiados en nuestro propio SMI, por lo que los resultados obtenidos pueden estar, al menos parcialmente, influenciados por múltiples aspectos concretos del manejo rutinario de la VM de nuestro servicio (p.e; selección de parámetros ventilatorios, manejo postural, la aspiración de secreciones de la vía aérea…) que pueden hacer que los datos presentados no sean totalmente extrapolables a otros centros con otras estrategias de manejo de la VM.

Al tratarse de tres estudios clínicos y fisiológicos dirigidos a evaluar aspectos muy particulares durante la VM, los resultados se deben evaluar e interpretar de forma independiente. La valoración de la mortalidad no ha sido la finalidad de ninguno de ellos, por lo que no podemos hipotetizar sobre lo que sería el efecto individual o el sumatorio de las diferentes maniobras que hemos estudiado para la optimización de la VM en términos de evolución ni de mortalidad en estos pacientes.

10. CONCLUSIONES

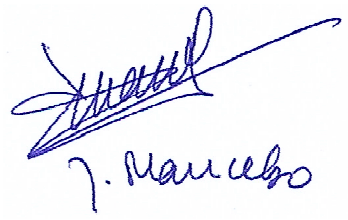
Las conclusiones que se desprenden de los resultados de los estudios que hemos presentado son;

Primero; el empleo de una RM alcanzando elevadas presiones en la vía aérea y con estrategia de PEEP decreciente mejora la oxigenación en la fase precoz de la VM de los pacientes con LPA/SDRA. Sin embargo, puede empeorar la mecánica respiratoria tanto en términos de Pplat como de Crs. Además, este tipo de maniobra puede provocar inestabilidad hemodinámica importante durante el procedimiento. En los casos que la terapia ventilatoria combine niveles moderados de Vt y PEEP, no creemos que esté indicado el empleo rutinario este tipo de maniobra. En el caso de considerar necesario su uso como maniobra de rescate, sugerimos que se adapte individualmente, que se realice con extrema precaución y con el paciente estrechamente monitorizado.

Segundo; el hecho de disminuir el espacio muerto instrumental mediante la substitución de la humidificación pasiva por activa es una maniobra sencilla y útil para controlar los niveles de $PaCO_2$. Además, esta estrategia de humidificación nos ayuda a disminuir el Vt empleado, con la consecuente disminución de la carga ventilatoria. En nuestros pacientes, este tipo de intervención ha generado disminución del Vd_{phys}, de la Pplat y mejora de la Crs, resultados que tomados en conjunto sugieren disminución de la sobredistensión alveolar.

Y tercero; cuando la selección del tipo de humidificador empleado durante la VM se realiza teniendo en cuenta las necesidades clínicas y mecánicas individuales de cada paciente, el aumento de resistencias del TET es significativo en el transcurso de la VM a largo plazo, pero idéntico comparando el empleo de humidificación pasiva con la activa. Este aumento en las resistencias puede ser relevante desde un punto de vista clínico, en particular, durante la fase de destete de la ventilación mecánica y los test de respiración espontánea.

En resumen, los resultados obtenidos han aportado datos clínicos relevantes para la comprensión de la fisiopatología de la insuficiencia respiratoria aguda grave en pacientes sometidos a ventilación mecánica. Del entendimiento de los aspectos estudiados y a la luz de los resultados obtenidos se extraen estrategias ventilatorias que son útiles en la optimización individual de la ventilación mecánica, tanto de la fase más aguda y crítica de la enfermedad, como en la fase de desconexión del respirador. Todos los resultados tienen una aplicabilidad clínica rutinaria, habida cuenta de que se trata de estrategias que se pueden llevar a cabo en cualquier servicio de medicina intensiva de forma sencilla, segura y a la cabecera de la cama del paciente.



Doctorando Director de Tesis

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12. ANEXO I. PUBLICACIÓN NO FUNDAMENTAL DE LA TESIS

Título: Recruitment manoeuvres in acute lung injury / acute respiratory distress syndrome.

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Revista: European Respiratory Journal (2003); 42:37s-42s.

Factor de Impacto: 2,999 según la ISI Web of Knowledge^{SM} de 2003.

Eur Respir J 2003; 22: Suppl. 42, 37s–42s
DOI: 10.1183/09031936.03.00420603
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European Respiratory Journal
ISSN 0904-1850

Recruitment manoeuvres in acute lung injury/acute respiratory distress syndrome

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Recruitment manoeuvres in acute lung injury/acute respiratory distress syndrome. I. Morán, E. Zavala, R. Fernández, L. Blanch, J. Mancebo. ©ERS Journals Ltd 2003.
ABSTRACT: Acute respiratory distress syndrome/acute lung injury is characterised by profound hypoxaemia due to a permeability pulmonary oedema.

In this setting, recruitment manoeuvres (RMs) can be a useful tool as adjuncts to lung protective ventilatory strategies to prevent cyclic alveolar stress and avoid alveolar collapse.

Many experimental and physiological studies have discussed the use of RMs but only a few heterogeneous clinical experiences have demonstrated the beneficial and deleterious effects that can occur using these manoeuvres. Besides, a lot of questions remain to be answered to find the best way to perform optimal RMs.

Further experimental and clinical trials are needed to understand the potential beneficial effects of recruitment manoeuvres when using a protective mechanical ventilation strategy. This paper is a general review of experimental works that support application of recruitment manoeuvres emphasising the clinical studies that have been published to date in acute respiratory distress syndrome patients.
Eur Respir J 2003; 22: Suppl. 42, 37s–42s.

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Keywords: Acute lung injury, acute respiratory distress syndrome, lung protective strategy, mechanical ventilation, positive end-expiratory pressure

Abnormalities that occur in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) are mainly alveolar flooding, alveolar collapse and loss of aerated lung volume. These alterations cause ventilation-perfusion heterogeneity and an increase in intrapulmonary shunt, which worsens arterial and tissue oxygenation.

Mechanical ventilation can produce lung damage that is indistinguishable from the pulmonary alterations caused by ARDS itself and may contribute to mortality in ARDS patients. Alveolar overdistention, cyclic collapse and re-inflation of alveolar units with tidal breathing are major factors contributing to further lung damage. DREYFUSS and SAUMON [1] emphasised the idea that the main determinant of "volutrauma" seems to be the end-inspiratory volume that causes excessive tissue stretching. These investigators suggested that the risk of volutrauma in the lungs of ARDS patients lie in the most compliant ventilated regions as they could be overdistended, whereas the collapsed areas are relatively protected.

Lung-protective strategies during mechanical ventilation have been proposed for ARDS patients. Such strategies try to avoid high alveolar pressures by using small tidal volumes (VT) and attempt to keep alveoli open at end expiration with sufficient positive end-expiratory pressure (PEEP) [2–5]. Recent clinical trials in patients with ALI or ARDS have demonstrated that lung-protective strategies led to improvements in clinical outcomes [3, 5]. Vascular pressures and flow can also play a role in oedema formation, and it has been shown that lung injury can be significantly decreased in a fixed mechanical ventilation model, if pulmonary vascular pressures are strictly limited [6, 7].

It is essential to know the internal mechanism of the heterogeneous distribution of regional atelectasis, lung tissue damage, oedema formation and inflammatory response in ARDS patients undergoing mechanical ventilation. Indeed, many studies have attempted to explain the effects of the ventilator on regional lung structure and mechanical function in ARDS patients. Since the pioneering studies [8–11] it is known that the entire lung volume is considerably reduced, and the distribution of regional atelectasis is irregular in the early phase of ARDS. These studies reinforced the idea that many areas of an injured lung are derecruited [11, 12] and such findings are the basis of the "baby lung" concept.

If mechanical ventilation perpetuates cyclic opening and closing of alveoli and if high pressure is applied repeatedly in previous expanding units, these induce lung injury. Mechanisms explaining lung damage include: tangential shearing forces that produce stress on the alveoli wall, sustain epithelial and endothelial damage in such a way that capillary stress fractures and eventually haemorrhagic oedema may occur [6, 13].

In a *post mortem* analysis, ROUBY *et al.* [14] found alveolar overdistention and/or intraparenchymal pseudocysts in a group of ARDS patients who were ventilated with high VT (12 mL·kg^{-1}) and high airway pressures. MUSCEDERE *et al.* [15] explain barotrauma as the result of mechanical factors. They observed epithelial lesions in alveolar ducts and small airways in an *ex vivo* lung rat model, after ventilating lungs with a PEEP level below the lower inflation point (LIP) of the pressure/volume (P/V) curve. This PEEP below LIP did not avoid cyclic opening and closing in determined alveolar units. On the contrary, when a PEEP level above LIP was applied, a marked decrease in lung damage was observed.

Similar data were found by GATTINONI *et al.* [16] using chest computed tomography (CT) scans in patients at different ARDS stages. These authors also observed histological signs of airspace enlargement. There was a significant increase in the number of bullae at the hilium and in the basal

parts of the lungs in patients with intermediate or late phase ARDS. Furthermore, lung lesions were less evident at the apex. Cyclic opening and closing at the dependent parts of the ARDS lung may explain these data. The same group attributed the atelectasis observed in the dependent parts of the lung to the increased lung weight and oedema formation, and suggested that PEEP should be adjusted to the level needed to reopen collapsed airways and alveoli [8, 9].

Several groups of investigators have demonstrated the role of inflammatory mediators in the pathophysiology of multisystem organ failure and shock [1]. There is considerable evidence suggesting that mechanical ventilation may contribute to the initiation and propagation of a systemic inflammatory response. TREMBLAY *et al.* [17] observed an increase in the level of cytokines and c-fos messenger ribonucleic acid expression in an *ex vivo* nonperfused lung rat model ventilating at high transpulmonary pressure with zero PEEP.

The same experimental model was used by RANIERI *et al.* [18] to study the effect of PEEP on inflammatory mediator release using *P*/*V* curves to adjust a noninjurious ventilatory strategy. In a previous randomised controlled trial, the same investigators described the effect of protective mechanical ventilation on reducing inflammatory mediators in patients with ARDS [4].

Additionally, in experimental models of lung infection, overdistention and cyclic collapse ventilatory strategies have demonstrated the effect of mechanical ventilation on bacterial and endotoxin translocation from the alveoli to the bloodstream. Applying a moderate PEEP level can significantly reduce these effects even at the same transpulmonary pressure at end inspiration [19–21].

SLUTSKY and TREMBLAY [22] and SLUTSKY [23] emphasised the relationships between mechanical ventilation and multiple organ failure [22] and coined the term "biotrauma", a complex concept that combines the relationship between pulmonary mechanics, histopathology, oedema formation, mechanotransduction and inflammation in ARDS [23].

In a recent review, HUBMAYR [24] discussed two hypotheses that emphasised the distinction between oedema and collapse. In the first of these, oedema fluid and foam fill dependent regions in the wet lung, and the pressure in the airways is required to drive foam out and inflate alveoli with high surface tension. In the second hypothesis the mechanisms of collapse and atelectasis in dependent parts of the wet lung are an increased weight in these regions, and the pressure that is applied is used to open collapsed airways. HUBMAYR [24] pointed out the intimate relationship between alveolar damage and cell response to the mechanical stress induced by mechanical ventilation.

In short, all of these studies indicate the importance of preventing lung collapse or oedema formation and suggest the implementation of ventilatory strategies with small *V*T and PEEP [3, 5, 25].

Experimental studies that support recruitment manoeuvres

Many experimental studies support the use of alveolar recruitment manoeuvres (RM) in surfactant depletion and in saline lavage models [26–30]. In an animal model of saline lavage induced ALI, BOND *et al.* [26], found an improvement in the respiratory system compliance and arterial oxygenation during high frequency oscillatory ventilation after performing RMs. This only happened when the animals were ventilated with low *V*T and zero end expiratory pressure.

In a similar model, RIMENSBERGER and co-workers [31, 32] compared the effects of a single RM when PEEP was below the LIP of the *P*/*V* curve, and the effects of PEEP above the LIP but without RM. Their results showed a better oxygenation and no increase on histological lung damage when applying the first strategy. The same group described the beneficial effects on oxygenation, on static lung compliance and lung volume during ventilation that were reached by means of single sustained RM (PEEP 30 cmH_2O).

Some data suggest that RMs have different effects determined by the type of lung insult. VAN DER KLOOT *et al.* [33] studied the effects of RMs on gas exchange and lung volumes in three experimental models of ALI; saline lavage, oleic acid and pneumonia. Only in the surfactant depletion model did oxygenation improve when RM was performed. This occurred when PEEP below LIP and low *V*T was used. No benefit from RMs was observed in any model when *V*T or PEEP level was set above LIP.

LU *et al.* [34] demonstrated that the application of an RM after endotracheal suctioning completely reversed the atelectasis, the bronchoconstriction and the decrease in arterial oxygen saturation which were observed after endotracheal suctioning in an anaesthetised sheep model.

Other studies underscore the importance of body posture (supine or prone) on regional distribution of intrapulmonary ventilation and perfusion [35]. CAKAR *et al.* [36] showed similar data and a better oxygenation response to RMs during prone position in comparison to supine, in an oleic acid-induced lung injury model. The beneficial effects on arterial blood gases were sustained over time in prone position and with a lower PEEP level than in supine position.

The optimal airway pressure to be applied during RMs has been evaluated in mathematical and experimental studies [37–39]. These models have demonstrated that alveolar recruitment is completed during tidal inflation and reaches the maximum volume at airway pressures >40 cmH_2O. Similar data have been reported by CROTTI *et al.* [40], who performed thoracic CT scans at different PEEP levels and plateau pressures (maximal PEEP: 20 cmH_2O, maximal plateau pressure 45 cmH_2O). They found that alveolar recruitment occurred along the entire *P*/*V* curve, independently of the lower and upper inflection point, and was progressive from nondependent to dependent lung parts.

Recruitment manoeuvres in patients: what has been learnt to date?

Very few works on clinical practice have studied the effects of RMs in ALI/ARDS patients. ROTHEN and coworkers [41–43] made important contributions in different studies focusing on atelectasis induced by anaesthesia in surgical patients. By means of chest CT scans, they described lung re-expansion by applying a vital capacity manoeuvre or by an inflation pressure of 40 cmH_2O and showed that greater reduction in collapsed lung can be observed during the first seconds of the vital capacity manoeuvre [41–43].

Various groups have described the important role of composition of inspiratory gas on alveolar collapse. Several factors, including the use of high inspiratory oxygen fraction (F_{I,O_2}) in alveolar units with a low ventilation-perfusion ratio, may promote denitrogenation atelectasis in ARDS patients [42, 44]. This finding indicates the possible role of reabsorption phenomena in the recurrence of collapse in previously re-expanded atelectatic lung that is ventilated with high F_{I,O_2}.

PELOSI *et al.* [45] applied three consecutive sighs per minute at 45 cmH_2O of plateau pressure for 1 h (PEEP 14±2.2 cmH_2O) in patients ventilated with a protective strategy. They found a marked decrease in intrapulmonary shunt and a significant

increase in end-expiratory lung volume. The latter was correlated with the improvement in arterial oxygenation.

FOTI *et al.* [46] applied continuous positive pressure ventilation RM over low PEEP level ventilation strategy in 15 PEEP-responder ARDS patients. These authors observed significantly improved oxygenation and alveolar recruitment compared to patients with low PEEP without RMs (continuous positive pressure ventilation at low positive end-expiratory pressure level (CPPVlo): mean PEEP 9±3 cmH_2O). Most important, they found a better oxygenation after applying a continuous high PEEP level (mean PEEP 16±2) than after performing RMs above CPPVlo. These data suggest that continuous high PEEP level keeps alveoli opened and prevents lung derecruitment between intermittent RMs. However, periodic tidal recruitment and derecruitment may produce ventilator-associated lung injury.

An alternative method for RM performance are sustained lung inflations with continuous positive airway pressure (CPAP). LAPINSKY *et al.* [47] applied sustained high pressure RMs (30–45 cmH_2O for 20 s) and found a significant improvement in arterial oxygenation. Hypotension occurred in some patients during the inflation manoeuvre, but blood pressure rapidly normalised after inflation. The beneficial effects of the RM were lost during the 4 h follow-up in 4 of 14 patients. This response was attributed to basal PEEP levels that were insufficient to maintain the lung opened. LIM *et al.* [48] used an "extended sigh" in ARDS patients. From the baseline (V_T 8 $mL \cdot kg^{-1}$ and PEEP 10 cmH_2O) in volume control ventilation mode, they changed the V_T-PEEP values to 6 $mL \cdot kg^{-1}$-15 cmH_2O, 4 $mL \cdot kg^{-1}$-20 cmH_2O, and 2 $mL \cdot kg^{-1}$-25 cmH_2O, consecutively, each 30 s. After V_T-PEEP 2 $mL \cdot kg^{-1}$-25 cmH_2O, the ventilation model was switched to CPAP of 30 cmH_2O for 30 s. This study showed an improvement in arterial oxygenation which was persistent 1 h after the application of the extended sigh. No major haemodynamic or respiratory complications were encountered.

RICHARD *et al.* [49] analysed the role of V_T and PEEP on alveolar recruitment. The authors demonstrated a decrease in oxygenation in 10 of 15 patients when V_T was switched from 10 to 6 $mL \cdot kg^{-1}$ with PEEP at or above the LIP. This alveolar derecruitment was prevented by increasing PEEP over LIP or transiently reversed by RMs (fig. 1).

RMs performed after endotracheal suctioning may represent one of the most interesting examples of the potential beneficial effects on a previous derecruited lung. Two groups have described advantages of a closed system of endotracheal suctioning performed without disconnection from the ventilator [50, 51]. A closed system allows a lower lung volume drop and a faster volume recuperation and prevents hypoxaemia in patients with an increased tendency to alveolar collapse. RMs have been proposed after patients are disconnected from the ventilator and after suctioning lung secretions [34].

However, recent studies [52] suggest that the effects of RMs in ALI/ARDS patients who are ventilated with low V_T and high PEEP levels are not effective for sustained recruitment. Besides, haemodynamic alterations may limit their use. Similar data were reported by VILLAGRA *et al.* [53]. These authors found a variable response to RMs and suggested that RMs applied to patients with ARDS ventilated with a lung protective strategy were not effective in improving arterial oxygenation in the majority of cases. These authors also reported that intrapulmonary shunt increased during RMs and attributed this finding to a redistribution of blood flow to nonventilated areas due to the alveolar overdistention of ventilated areas induced by the RMs.

Preliminary data from the current author's group [54] showed significant beneficial effects of a RM on arterial blood gases in 11 ARDS patients mechanically ventilated with an Acute Respiratory Distress Syndrome clinical Network (ARDSnet) strategy. RMs were performed by stepwise increases of PEEP and plateau pressure up to PEEP 40 cmH_2O and plateau pressure 60 cmH_2O (fig. 2). Arterial blood gas improvement was sustained over time (2 h).

Conversely, other studies found marked decreases in intrapulmonary shunt [45, 55]. In eight patients with early ARDS, MANCINI *et al.* [55] showed an improvement in arterial oxygen tension (P_{a,O_2}) and a significant decrease in intrapulmonary shunt. They suggested that a protective ventilatory strategy combining low V_T and high PEEP level above the LIP was the pivotal mechanism to account for improvement in arterial oxygenation by means of recruitment of previously collapsed alveoli and redistribution of pulmonary blood flow from nonventilated alveoli to newly aerated units [55].

More recently, GRASSO *et al.* [56] applied 40 cmH_2O of CPAP for 40 s and defined the patients as RM-responders when arterial oxygenation increased $\geqslant$50% over baseline. Their data suggested that RMs significantly improved arterial oxygenation only in patients with early ARDS and without impairment of chest wall mechanics. These authors suggested that a low static lung elastance could be a marker of the

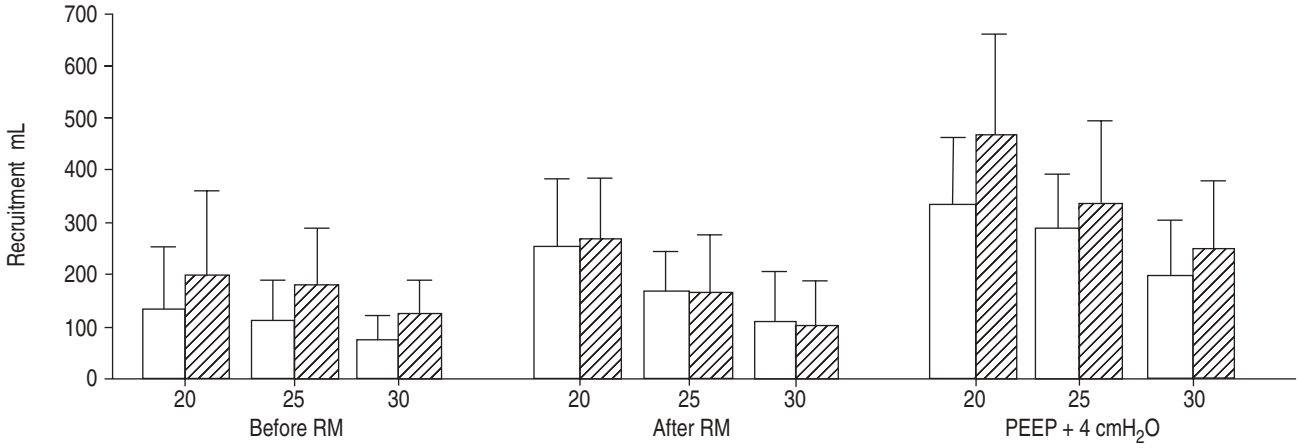

Fig. 1. – Effects of tidal volume (V_T) and positive end-expiratory pressure (PEEP) on recruited volume. When V_T is low and PEEP is set at lower inflation point (LIP) there is a derecruitment in comparison with high V_T (before RM). A recruitment manoeuvre (RM) is useful in this scenario (after RM). When a PEEP level 4 cmH_2O above LIP is used (PEEP+4 cmH_2O), the recruited volume is maximised and no V_T effects are seen. □: low V_T; ▨: conventional V_T. Reproduced with permission from [49].

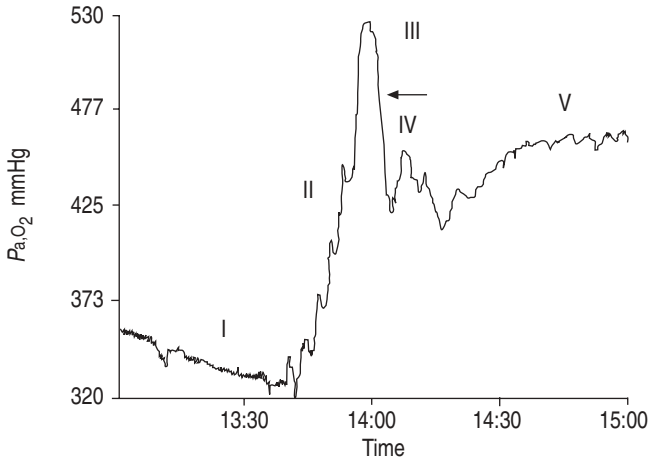

Fig. 2. – Original recording of continuous arterial oxygen tension (P_{a,O_2}) monitoring with an intra-arterial catheter in an early acute respiratory distress syndrome (ARDS) patient with abdominal sepsis. I) Basal: mechanical ventilation with the Acute Respiratory Distress Syndrome Network (ARDSnet) National Institutes of Health (NIH) strategy (inspiratory oxygen fraction (F_{I,O_2}) 0.7; positive end-expiratory pressure (PEEP) 10 cmH_2O). F_{I,O_2} 1 was used to perform the manoeuvre. II) Progressive increase in P_{a,O_2} during a 15 min duration. A PEEP 40 cmH_2O and plateau pressure 60 cmH_2O were reached. P_{a,O_2} increased up to 520 mmHg. III) Gradual decreases of PEEP (2 cmH_2O every 4 min) to find alveolar collapsing pressure (PEEP 13 in this patient, marked with an arrow). Collapsing pressure was defined as decrease in P_{a,O_2}>10% with respect to maximal P_{a,O_2}. IV) The collapsed units were reopened with a new 1-min duration RM (plateau pressure (PP)/PEEP 60/40 mmHg respectively), then a PEEP level 2 cmH_2O higher than collapsing pressure was applied (15 cmH_2O). V) Same ventilatory parameters as I, except for a PEEP set at 15 cmH_2O. Effects on P_{a,O_2} were sustained over time.

potential for recruitment. Cardiac output and mean arterial pressure markedly decreased in nonresponders, although it returned to baseline within 20–30 s after RMs.

PATRONITI *et al.* [57] applied one sigh per minute to baseline pressure support ventilation (PSV) in patients with early ARDS. Sigh was performed by means of a CPAP level 20% higher than the plateau pressure of the PSV breaths or, at least 35 cmH_2O. They observed a significant improvement in arterial oxygenation associated to an increase in end-expiratory lung volume and respiratory system compliance during the sigh period, thus suggesting that sighs promote alveolar recruitment. These changes returned to baseline after sighs were discontinued.

Looking for side-effects of RMs, BEIN *et al.* [58] analysed the impact of RMs on intracranial pressure (ICP) and cerebral metabolism in patients with acute cerebral injury and respiratory failure. They performed a progressive increase in peak pressure up to 60 cmH_2O. The pressure was then maintained for 30 s. An increase of ICP was found at the end of RMs and mean arterial pressure was reduced, with the resulting decrease of cerebral perfusion pressure (72±8 *versus* 60±10 mmHg). Jugular venous oxygen saturation deteriorated at the end of the procedure (69±6 *versus* 59±7%) but arterial minus jugular venous lactate content difference remained unchanged. Ten minutes after RMs, all the haemodynamic and cerebral parameters were normalised and improvement on arterial oxygenation disappeared.

Conclusions

Experimental models and physiological studies have just established the principles to understand the potential beneficial effects of RMs in ARDS patients who are ventilated with a protective strategy. Nevertheless many questions still need to be answered. The clinicians need more information about many aspects of these manoeuvres; namely, the optimal time to perform RMs (first hours after endotracheal intubation, early phase of ARDS, after endotracheal suctioning, *etc.*), how often they should be used, their duration and the recommended ventilatory mode (CPAP, sighs, pressure controlled ventilation, short duration high PEEP level). Moreover, the long-lasting effects of RMs on arterial blood gases are contradictory.

Furthermore, clinicians cannot ignore possible deleterious effects such as barotrauma and increases in intrapulmonary shunt when RMs result only in overdistension of already ventilated lung regions. Major haemodynamic side-effects (decrease on cardiac output, increase on pulmonary arterial pressure and end-diastolic right ventricular pressure, severe hypotension, bradycardia) may occur during or just after RMs are applied. In addition, direct effects of RMs on alveolar cells, *via* mechanotransduction pathways, might also induce further lung damage.

Further studies are needed to clinically evaluate the potential beneficial effects of the different types of recruitment manoeuvres that could be included into protective mechanical ventilation strategies.

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“No hay ningún camino que no se acabe,

como no se le oponga la pereza y la ociosidad.”

Los trabajos de Persiles y Sigismunda (1617)

Miguel de Cervantes Saavedra