Universitat Autònoma de Barcelona

ASINCRONÍAS PACIENTE-VENTILADOR EN LA VENTILACIÓN MECÁNICA INVASIVA: CARACTERIZACIÓN, IMPLICACIONES FISIOLÓGICAS Y TRATAMIENTO

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TESIS DOCTORAL

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Recordarás algo de lo que leas, bastante de lo que oigas,
mucho de lo que veas, y todo lo que hagas

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LISTADO DE ABREVIATURAS

AI índice de asincronías

DC doble ciclado

DC-PT doble ciclado con *trigger* paciente

DC-RT doble ciclado secundario a *trigger* reverso

IC intervalo de confianza

IE esfuerzos inefectivos

IEE esfuerzos inefectivos durante la espiración

IRA insuficiencia respiratoria aguda

Kg quilogramos

mL mililitros

PCV ventilación controlada por presión

PEEP presión positiva al final de la espiración

PSV ventilación con presión soporte

RT *trigger* reverso

SAS *Riker sedation-agitation scale*

SDRA síndrome de distrés respiratorio agudo

SOFA *sequential organ failure assessment*

UCI unidad de cuidados intensivos

VCV ventilación controlada por volumen

VCVDF ventilación controlada por volumen con flujo decelerado

VILI *ventilator-induced lung injury/* lesión inducida por el ventilador

VM ventilación mecánica

ÍNDICE

RESUMEN

Introducción. La ventilación mecánica es un tratamiento de soporte común en los pacientes críticos que salva vidas, aunque no está exenta de complicaciones a corto, medio y largo plazo. La mala interacción paciente-ventilador, comúnmente conocida como asincronías, es una de las complicaciones frecuentes y, muchas veces, infradiagnosticada, y se ha visto que puede empeorar los desenlaces de los pacientes críticos. Entre los diferentes tipos de asincronías, el doble ciclado es una de las más frecuentes, conjuntamente con los esfuerzos inefectivos, y una de las potencialmente más lesivas. La caracterización de las asincronías, la evaluación de los factores relacionados con su aparición y sus consecuencias fisiológicas son necesarias para entender los mecanismos subyacentes y mejorar su manejo, así como para evaluar los efectos deletéreos. Asimismo, es importante analizar la respuesta al manejo actual, basado la mayor parte de las veces en estrategias que no han demostrado un claro beneficio.

Objetivos. *Principal.* Caracterizar el doble ciclado y una de sus presentaciones, el *trigger* reverso, durante todo el período de ventilación mecánica, para evaluar su incidencia así como su patrón de presentación. *Secundarios.* Caracterizar las implicaciones fisiológicas del doble ciclado y el *trigger* reverso. Identificar factores de riesgo asociados al desarrollo de doble ciclado. Analizar el efecto del tratamiento con opioides y sedantes sobre la incidencia de asincronías.

Material y métodos. Se ha diseñado un estudio prospectivo multicéntrico observacional. Se han incluido pacientes con ventilación mecánica durante más de 24 horas. La detección de asincronías y parámetros de mecánica pulmonar, así como parámetros ventilatorios, se ha realizado mediante un registro continuo a través de la plataforma BetterCare™. Esta plataforma captura las señales del monitor y respirador, y detecta las asincronías mediante algoritmos validados, así como la modalidad ventilatoria. Los datos demográficos y clínicos se han obtenido de los registros médicos diarios (nivel de conciencia, gravedad, tratamiento recibido). Los datos se han analizado mediante modelos lineares de efectos mixtos.

Resultados globales. Para la caracterización de las asincronías se han analizado 9.694.573 respiraciones. El doble ciclado ha presentado una incidencia del 0,6%, estando presente en todos los pacientes, en todas las modalidades de ventilación mecánica y con una presentación

variable a lo largo de todo el período de ventilación mecánica. Se ha identificado su presentación en forma de *clusters*, períodos recortados en el tiempo con una elevada incidencia de eventos de doble ciclado. Su incidencia es más frecuente en la modalidad de ventilación controlada por presión. En referencia a las implicaciones fisiológicas, el volumen corriente en las respiraciones con doble ciclado es significativamente superior en las modalidades controladas por volumen que en las controladas por presión. De todas las respiraciones con doble ciclado, el 34,6% se corresponden con *trigger* reverso. La presión pico en la segunda respiración es significativamente superior en volumen control con flujo constante. Los factores fisiológicos asociados de forma positiva a la presencia de doble ciclado son la frecuencia respiratoria, la presión pico y el volumen corriente. El tiempo inspiratorio, el pico de flujo y la presión positiva al final de la espiración se asocian de forma negativa con la presencia de doble ciclado. Para evaluar el efecto del tratamiento sobre el manejo de las asincronías se han analizado 14.166.469 respiraciones. La incidencia de asincronías no difiere entre los grupos que han recibido solo-sedantes, solo-opioides y sedantes+opioides, independientemente de la modalidad de ventilación mecánica. Las dosis de opioides se asocian de forma inversa a la incidencia de asincronías, sin disminuir el nivel de conciencia, contrariamente a los sedantes.

Conclusiones. La incidencia de doble ciclado es baja, pero ocurre en todos los pacientes, a lo largo de todo el período de ventilación mecánica y en forma de *clusters*, siendo, además, un tercio de las respiraciones con doble ciclado secundarias a *trigger* reverso. El volumen total acumulado por las dos respiraciones que conforman un doble ciclado puede llegar a doblar el volumen corriente programado en el respirador, generando un incremento de la fuerza aplicada al pulmón y una mayor deformación pulmonar, lo que puede conducir al desarrollo de lesión pulmonar inducida por el ventilador. La aparición de doble ciclado es multifactorial. El tratamiento con sedantes no garantiza una mejor interacción paciente-ventilador que la que se consigue con el tratamiento con opioides, con independencia de la modalidad ventilatoria, empeorando por el contrario el nivel de conciencia.

ABSTRACT

Introduction. Mechanical ventilation is a common life-support treatment in critically ill patients, although it is not exempt of complications. Poor patient-ventilator interaction, commonly known as asynchronies, is one of the frequent and, often under-diagnosed, complications that have been associated with worse outcomes. Among the different types of asynchronies, double cycling is one of the most frequent, along with ineffective efforts, and one of the most potentially harmful. The characterization of asynchronies, the evaluation of factors related to the development and the analysis of the physiological consequences are necessary to understand the underlying mechanisms of asynchronies and to improve its management, as well as to evaluate its deleterious effects. Likewise, it is important to analyze the response to current management, based, most of the time, on strategies that have not demonstrated a clear benefit.

Objectives. *Primary*. To characterize double cycling and reverse triggering, during the whole period of mechanical ventilation, in order to evaluate its incidence as well as its presentation pattern. *Secondary*. To characterize the physiological implications of double cycling and reverse triggering. To identify risk factors associated with the development of double cycling. To analyze the effect of opioid and sedative treatment on the incidence of asynchronies.

Material and methods. We designed a prospective multicenter observational study. We included patients under mechanical ventilation for more than 24 hours. Asynchronies and pulmonary mechanics, as well as ventilatory parameters, were obtained through BetterCare™ platform. This platform continuously register monitor and ventilator signals and detects asynchronies using validated algorithms, as well as ventilator mode. Demographic and clinical data have been obtained from daily medical records (level of consciousness, severity, treatment administrated). Data have been analyzed using linear mixed-effects models.

Results. We analyzed 9,694,573 breaths to characterize asynchronies. The incidence of double cycling is 0.6%. It is present in all patients and in all modes of mechanical ventilation, and its presentation varies widely throughout the whole period of mechanical ventilation. Clusters of DC have been also identified. Its incidence is more frequent in the pressure

control modes. Regarding physiological implications, tidal volume in double-cycled breaths is significantly higher in volume-controlled modes than in pressure control modes. 34.6% of double-cycled breaths are secondary to reverse triggering. Peak pressure in the second breath is significantly higher in volume control with constant flow mode. The physiological factors positively associated with the presence of double cycling are respiratory rate, peak pressure and tidal volume. Inspiratory time, peak flow and positive pressure at the end of expiration are negatively associated with the presence of double cycling. In order to evaluate the effect of treatment on the management of asynchronies, 14,166,469 breaths were analyzed. The incidence of asynchronies does not differ between groups that have received sedatives alone, opioids alone and sedatives+opioids, regardless of the mechanical ventilation mode. Doses of opioids are inversely associated with the incidence of asynchronies, without decreasing the level of consciousness, contrary to sedatives.

Conclusions. The incidence of double cycling is low, but it occurs in all patients throughout the whole period of mechanical ventilation and in the form of clusters, being, in addition, a third of the respirations with double cycling secondary to reverse triggering. The total volume accumulated during the double cycled breaths can double the current volume programmed in the ventilator, with an increase in the force applied to the lung and a greater lung deformation, leading the development of lung injury induced by the ventilator. The appearance of double cycling is multifactorial. Treatment with sedatives does not guarantee a better patient-ventilator interaction than that achieved with opioid treatment, regardless of the ventilatory modality, worsening the level of consciousness.

1. PRESENTACIÓN

La presente tesis doctoral está estructurada de acuerdo a las directrices del Marco Regulador del Doctorado de la Escuela de Posgrado y del Departamento de Medicina de la Universitat Autònoma de Barcelona (RD 1393/2007), modificada por el RD 861/2010 y se presenta como compendio de publicaciones, tal y como ha aceptado la Comisión Académica del programa de Doctorado de Medicina a fecha 11 de Julio de 2019.

Los estudios que conforman esta tesis doctoral pertenecen a una misma línea de investigación dirigida a caracterizar las asincronías derivadas de una mala interacción paciente-ventilador, evaluar sus consecuencias fisiológicas y establecer cuáles son las medidas más adecuadas para su manejo. En los diferentes apartados de esta tesis se exponen los aspectos generales más destacados de los trabajos, detallando los aspectos más específicos como anexos. La doctoranda ha publicado estos trabajos como primera autora en revistas internacionales de medicina crítica, de primer cuartil y con elevado factor de impacto.

1) Double Cycling During Mechanical Ventilation: Frequency, Mechanisms, an Physiologic Implications. de Haro C, López-Aguilar J, Magrans R, Montanyà J, Fernández-Gonzalo S, Turon M, Gomà G, Chacón E, Albaiceta GM, Fernández R, Subirà C, Lucangelo U, Murias G, Rué M, Kacmarek RM, Blanch L; Asynchronies in the Intensive Care Unit (ASYNICU) Group. Crit Care Med. 2018 Sep;46(9):1385-1392.

   Factor de impacto de la revista: 6,971 según *ISI Journal Citation Reports* 2018.

2) Effects of sedatives and opioids on trigger and cycling asynchronies throughout mechanical ventilation: an observational study in a large dataset from critically ill patients. de Haro C, Magrans R, López-Aguilar J, Montanyà J, Lena E, Subirà C, Fernandez-Gonzalo S, Gomà G, Fernández R, Albaiceta GM, Skrobik Y, Lucangelo U, Murias G, Ochagavia A, Kacmarek RM, Rue M, Blanch L; Asynchronies in the Intensive Care Unit (ASYNICU) Group. Crit Care. 2019 Jul5;23(1):245.

   Factor de impacto de la revista: 6,959 según *ISI Journal Citation Reports* 2018.

Todos los coautores han aprobado el uso de los estudios presentados, por parte de la doctoranda, como trabajo de tesis doctoral.

Durante la realización de los estudios que conforman esta tesis, la doctoranda ha participado en otros trabajos vinculados a la investigación de la presente tesis doctoral que se adjuntan en el anexo 3.

2. INTRODUCCIÓN

Ventilación Mecánica

La ventilación mecánica (VM) puede definirse como la técnica por la cual se realiza el movimiento de gas hacia y desde los pulmones por medio de un equipo externo conectado directamente al paciente, que reemplaza el mecanismo normal de respiración espontánea (1). La VM es un tratamiento de soporte vital común en las Unidades de Cuidados Intensivos (UCI) tanto en pacientes con insuficiencia respiratoria aguda (IRA) como en otras patologías (2). En función de la gravedad y el curso de la enfermedad del paciente, la VM puede controlar y suprimir completamente el trabajo respiratorio del paciente o hacerlo de modo parcial preservando el esfuerzo espontáneo. Los principales objetivos de la VM son mantener un adecuado intercambio gaseoso, disminuir el trabajo respiratorio y mejorar el confort del paciente.

En términos generales se pueden concretar en tres los métodos básicos de aplicación de la VM: la ventilación con presión negativa, la ventilación con presión positiva y la ventilación de alta frecuencia.

La ventilación con presión negativa aparece en 1832 y representa el origen de la VM. Los respiradores de presión negativa producen una ventilación similar a la respiración espontánea sin necesidad de vía aérea artificial. Estos respiradores crean un espacio cerrado alrededor del cuerpo del paciente que se conecta a una bomba de presión. Durante la inspiración, dicha bomba genera una presión negativa en el espacio hermético e impulsa la pared del tórax hacia fuera simulando el trabajo de los músculos respiratorios. Esta presión negativa se transmite al espacio intrapleural y al espacio alveolar, disminuyendo su presión por debajo de la presión atmosférica (presión de apertura de vía aérea). La espiración ocurre de forma pasiva mediante el retroceso elástico del pulmón tras eliminar la presión negativa generada alrededor de la pared torácica. Este tipo de VM ofrece algunas ventajas, como el hecho de no ser necesario un acceso artificial a la vía aérea del paciente o el trabajar en unas condiciones muy similares a las fisiológicas. Sin embargo, el uso de este tipo de VM ha desaparecido, debido, principalmente, a la dificultad de acceso al paciente y el gran aparataje necesario (1).

En la ventilación con presión positiva es el respirador el encargado de introducir el aire dentro de los pulmones, mediante una interface (tubo orotraqueal o máscara a presión), generando un gradiente de presión positiva durante la inspiración que hace que la presión alveolar aumente de forma progresiva y se transmita al espacio pleural. Al final de la inspiración, el respirador dejará de administrar esta presión positiva, lo que generará un gradiente entre los alveolos y la presión de apertura de la vía aérea, que provoca la salida del aire de forma pasiva. La ventilación con presión positiva es la más común en el paciente adulto con necesidad de VM (1).

En último lugar cabe mencionar la ventilación de alta frecuencia que se basa en el uso de frecuencias ventilatorias superiores a las consideradas normales, con volúmenes ligeramente inferiores a la normalidad que favorecen el intercambio gaseoso. Este tipo de ventilación se aplica mayoritariamente en pediatría y su uso en adultos es menos habitual (1).

Modalidades de VM

La VM con presión positiva es la más ampliamente utilizada durante el manejo del paciente crítico en la UCI y es objeto de estudio en este trabajo de tesis doctoral. Por ello, a partir de este punto y a lo largo del texto la abreviatura VM se utilizará para hacer referencia específicamente a la ventilación con presión positiva.

Como se ha mencionado anteriormente, existen diferentes tipos de VM en función de si se suprime o no por completo la función respiratoria del paciente, y dentro de estos tipos existen diferentes modalidades en función de la variable límite (el objetivo que se desea alcanzar en cada respiración). Además, hay que tener en cuenta que, en función del tipo de respirador utilizado o de la marca comercial del mismo, las modalidades pueden variar e incluso adoptar nombres distintos.

Atendiendo a ello, a continuación se describen las principales modalidades de VM que se han considerado de interés para este trabajo de tesis doctoral:

- Ventilación controlada por volumen (VCV): En esta modalidad el equipo asistencial programa el volumen corriente que el respirador debe administrar en cada respiración, así como la frecuencia respiratoria (FR), el flujo inspiratorio, la presión positiva al final de la espiración (PEEP) y la fracción inspirada de oxígeno (FiO_2). En VCV el tiempo inspiratorio está predeterminado por las relaciones entre el

volumen, el pico inspiratorio y la onda de flujo, siendo por lo tanto el tiempo inspiratorio fijo, una de las principales diferencias con respecto a las modalidades espontáneas. La VCV puede ser controlada o asistida-controlada, en función de si se anula por completo la función del paciente o si se permite que el paciente pueda iniciar cada respiración mediante la detección por parte del respirador del esfuerzo inspiratorio del paciente.

- Ventilación controlada por presión (PCV): esta modalidad también puede ser controlada o asistida-controlada, bajos los mismos criterios que la modalidad VCV. En este caso el objetivo que se fija en cada respiración es la presión inspiratoria máxima. En esta modalidad también se programarán la FR, la PEEP y la FiO_2. El flujo, en cambio, dependerá del respirador y será variable y adaptable a las necesidades del paciente. En PCV la distribución del flujo se produce de forma decelerada, a diferencia de VCV donde el flujo se mantiene constante durante toda la inspiración. El tiempo inspiratorio también será constante, y el respirador tratará de mantenerlo hasta un tiempo determinado prefijado o hasta llegar a un porcentaje del pico de flujo.
- Ventilación controlada por volumen con flujo decelerado (VCVDF): en esta modalidad, que también puede ser controlada o asistida-controlada, se pauta un objetivo de volumen para cada respiración pero el respirador ajusta la presión en cada ciclo para conseguir ese volumen en función de la mecánica pulmonar, lo que hace que la distribución del flujo no sea constante y varíe de respiración en respiración. En algunos pacientes esta modalidad es mejor tolerada, aunque no se ha demostrado de forma clara que sea más beneficiosa que las otras.
- Ventilación con Presión soporte (PSV): esta modalidad se considera espontánea. El esfuerzo inspiratorio del paciente es el que inicia la respiración y es asistido por el respirador hasta un límite de presión previamente fijada. Si el paciente no realiza este esfuerzo inspiratorio el respirador no administrará la respiración, por lo que el paciente debe tener un centro respiratorio intacto y un patrón respiratorio fiable. El volumen corriente será variable y vendrá determinado por el nivel de presión soporte, el tiempo inspiratorio, la mecánica pulmonar y el esfuerzo inspiratorio del paciente. Asimismo, el tiempo inspiratorio dependerá del paciente, por lo que también puede ser variable.

- Ventilación proporcional asistida: se trata de una modalidad asistida en la que todas las respiraciones son espontáneas. Se programa el porcentaje de asistencia que el respirador ha de proporcionar al esfuerzo inspiratorio del paciente. Cuando cesa el esfuerzo del paciente, cesa la asistencia del respirador. Esta modalidad requiere la integridad funcional del sistema respiratorio así como un nivel de alerta adecuado del paciente, por lo que la sedación podría afectar su funcionamiento. En esta modalidad no se programa un volumen, ni una presión ni un flujo, sino que únicamente se programa la proporcionalidad de la asistencia. Al igual que en PSV, el tiempo inspiratorio será controlado por el paciente, por lo que puede ser variable.

Consecuencias/Efectos de la ventilación mecánica

La VM se utiliza como técnica de soporte vital ante un amplio espectro de eventos agudos que afectan al enfermo crítico. La VM demostró ser indispensable durante la epidemia de poliomielitis en el 1952, al disminuir la mortalidad de los pacientes desde más del 80% hasta aproximadamente el 40%. A pesar de los claros beneficios de la aplicación de esta terapia, se ha observado que los pacientes que requieren VM presentan una mortalidad elevada que se cifra alrededor del 35% (3). Diversos estudios preclínicos y clínicos han asociado la mortalidad a múltiples factores, entre los que se encuentran complicaciones como el barotrauma/volutrauma (lesión por presiones/volúmenes elevados), toxicidad secundaria a la alta concentración de oxígeno administrado o alteraciones hemodinámicas, todas ellas relacionadas con la VM. Además se ha visto que la VM puede causar lesión estructural sobre el pulmón. Esta lesión se caracteriza histopatológicamente por la aparición de infiltrados de células inflamatorias, membranas hialinas, aumento de la permeabilidad vascular y edema pulmonar. El conjunto de consecuencias pulmonares de la VM se denomina Lesión Pulmonar Inducida por el Respirador (comúnmente conocida por las siglas *VILI,* del inglés *"ventilator-induced lung injury"*) (4). Los cuatro mecanismos fundamentales que pueden implicar el desarrollo de VILI son:

- Barotrauma: la presión necesaria para insuflar los pulmones en cada respiración es la suma de la presión necesaria para vencer las resistencias de la vía aérea y la presión necesaria para vencer las propiedades elásticas del pulmón. Cuando el flujo de aire es cero, la principal fuerza que mantiene el pulmón abierto es la presión transpulmonar (la diferencia entre la presión alcanzada en los alveolos y la presión

pleural). La sobredistensión regional causada por un aumento excesivo de estas presiones se considera que es una de las principales causas de la lesión pulmonar. El término barotrauma puede resultar engañoso, ya que se refiere a la sobredistensión regional como causante de la lesión pulmonar y no al aumento de las presiones *per se* (4).

- Volutrauma: la ventilación con volúmenes corrientes elevados puede provocar ruptura alveolar y fugas aéreas debido al incremento en la sobrecarga pulmonar (*strain*), siendo otra de las causas de lesión pulmonar. La información derivada de modelos experimentales ha demostrado la ruptura de la barrera alveolo-capilar ante la aplicación de volúmenes elevados y el consecuente incremento de edema pulmonar respecto al uso de volúmenes adecuados (5).
- Atelectrauma: este tipo de lesión pulmonar es secundaria a la ventilación con volúmenes corrientes bajos que provocan la apertura y cierre repetitivos de la vía aérea y de los alveolos en cada ciclo respiratorio. Este tipo de lesión afecta al surfactante pulmonar y produce hipoxia regional y se caracteriza por el desprendimiento del epitelio, la aparición de membranas hialinas y edema pulmonar. Además, en aquellos pacientes que presentan heterogeneidad pulmonar, la lesión pulmonar se magnifica (6).
- Biotrauma: en respuesta a los tres fenómenos descritos anteriormente, el pulmón se expone a la liberación de mediadores a nivel local, bien mediante un mecanismo que afecta directamente a las células pulmonares o de forma indirecta a través de la activación de diferentes vías de señalización celular en células epiteliales, endoteliales e inflamatorias. Algunos mediadores actúan lesionando de forma directa el pulmón mientras que otros lo dañan como consecuencia del reclutamiento de otras células, como los neutrófilos, que pueden liberar sustancias más dañinas (7).

La lesión pulmonar inducida por la VM puede producir alteraciones hemodinámicas y daño de órganos a distancia e incluso condicionar el fallo multiorgánico (7,8). Estas alteraciones incrementan la morbi-mortalidad de los supervivientes a corto o largo plazo y pueden comprometer su estado funcional y dificultar el desarrollo de las actividades de la vida diaria (9), generando un importante problema socio-económico. En un estudio epidemiológico realizado en Estados Unidos, la VM representaba 2,7 episodios por 1000 habitantes y suponía un coste estimado de 27 mil millones de dólares, lo que se cifra en el 12% del gasto

hospitalario total (10). Los pacientes que reciben VM, por lo tanto, se consideran una población de alto riesgo y elevados costes.

Interacción paciente-ventilador

Teniendo en cuenta que la VM puede suprimir de forma parcial o total la función respiratoria del paciente, en base a la modalidad ventilatoria elegida, la adecuación de la VM a las necesidades del paciente en cada situación puede mejorar la interacción paciente-ventilador. Recientemente se ha descrito que una interacción paciente-ventilador inadecuada puede contribuir también a incrementar la morbi-mortalidad observada en los pacientes con VM.

Las asincronías son el producto de una mala interacción entre el paciente y el respirador, y pueden producir molestias en el paciente, incrementar la ansiedad y la sensación de disnea, y además, puede conllevar el uso excesivo de sedantes, influyendo en la disfunción diafragmática, en la aparición de delirium, incrementando los días de VM así como la estancia en la UCI y en el hospital junto con otros desenlaces no deseados (11,12).

Las asincronías son un problema frecuente en los pacientes con VM y constituyen uno de los mayores retos a abordar en el momento actual. Las asincronías ocurren cuando las fases de la respiración generada por el respirador no concuerdan con el patrón respiratorio neural del paciente, o esta respiración es inadecuada para satisfacer las necesidades o demanda de flujo del paciente (13). Las asincronías son un fenómeno complejo que implica la interacción del respirador con diferentes órganos, entre los que se encuentran los pulmones, los músculos respiratorios, el diafragma y sistema nervioso central, y de manera específica el centro respiratorio (14). Los estudios demuestran que los pacientes que reciben VM durante más de 24 horas presentan una elevada incidencia de asincronías incluso si son capaces de iniciar la respiración por sí mismos (11). Las asincronías ocurren durante todo el período de VM, aparecen en todos los modos de VM, aunque son discretamente más frecuentes en la VM en presión soporte que en que en los modos controlados por volumen o por presión (11) y pueden asociarse a diversos desenlaces, sobretodo si se agrupan en forma de *clusters* (15). Además, no se han encontrado diferencias en la incidencia de asincronías entre el período diurno y nocturno (11).

Clasificación de las asincronías

Las asincronías suelen clasificarse en función de la fase del ciclo en la que suceden: período inspiratorio o fase de presurización, fase de ciclado a espiración y fase espiratoria (16). Esta clasificación ha sido ampliamente utilizada, ya que facilita su diagnóstico a pie de cama mediante la inspección visual de las curvas disponibles en el respirador. Sin embargo, esta clasificación no se corresponde adecuadamente con los mecanismos tanto fisiopatológicos como clínicos implicados en su desarrollo.

Es importante destacar que cada tipo de asincronía puede ser el reflejo de distintas condiciones clínicas y, por otro lado, un determinado mecanismo fisiopatológico puede desencadenar distintos tipos de asincronías. Es por ello que recientemente se ha empezado a utilizar una clasificación basada en las condiciones que generan la mala interacción entre el paciente y el respirador, que hace referencia a la adecuación del nivel de asistencia ofrecido por el respirador y las demandas del paciente (17). El control de la respiración durante la VM es complejo e incluye una retroalimentación de diversas señales provenientes de los quimiorreceptores centrales y periféricos así como de los mecanoreceptores pulmonares, de la pared torácica y de los músculos respiratorios (18). Otros estímulos adicionales como el dolor, la ansiedad o la endotoxemia pueden tener también una influencia directa sobre el centro respiratorio y por lo tanto condicionar la aparición de asincronías. Un aumento de la demanda metabólica, una alteración del intercambio gaseoso y/o un estímulo mecánico intenso de los receptores pulmonares puede dar lugar a un incremento del esfuerzo respiratorio (19). Por el contrario, una depresión del sistema nervioso central, habitualmente por sobresedación y/o excesivo soporte ventilatorio, puede disminuir el esfuerzo respiratorio. De todos modos, las asincronías pueden ocurrir tanto en el contexto de un esfuerzo respiratorio elevado (asociado normalmente a una asistencia insuficiente por el respirador) o debido a un esfuerzo respiratorio disminuido (derivado de una asistencia excesiva). Esta aproximación se centra en la causa o condición que ha conducido a la aparición de la asincronía, y facilita la comprensión del mecanismo subyacente lo que permite diseñar una mejor estrategia para su manejo. En la tabla 1 se muestran dos tipos de clasificación de las asincronías, la forma más clásica que se relaciona con la fase del ciclo respiratorio en la que ocurren las asincronías y la que clasifica las asincronías en función del centro respiratorio.

Tabla 1. Clasificación de las asincronías

EN FUNCIÓN DE LA FASE DEL CICLO		
Período inspiratorio	Transición de inspiración a espiración (ciclado)	Período espiratorio
• Trigger retardado • Disincronía de flujo • Ciclado corto (o prematuro) • Ciclado prolongado (o retrasado) • *Trigger* reverso	• Doble ciclado debido a ciclado corto o *trigger* reverso • Contracción muscular espiratoria debido a ciclado prolongado	• Esfuerzos inefectivos durante la espiración • Auto-*triggering* • Contracción muscular espiratoria
EN FUNCIÓN DEL IMPULSO DEL CENTRO RESPIRATORIO		
Impulso respiratorio elevado (Asistencia insuficiente)		Impulso respiratorio bajo (Sobreasistencia)
• Disincronía de flujo • Ciclado corto (o prematuro) • Doble ciclado		• *Trigger* reverso • Ciclado prolongado (o retrasado) • Esfuerzos inefectivos

Tipos de asincronías

Doble ciclado

El doble ciclado (DC) puede ser considerada una de las asincronías más importantes por su potencial lesivo y la dificultad que comporta la evaluación de sus consecuencias. El DC aparece cuando el esfuerzo inspiratorio se mantiene y persiste más allá del tiempo inspiratorio del respirador, del cese del flujo inspiratorio o del inicio de la espiración mecánica. La musculatura inspiratoria se encuentra aún activa al inicio de la espiración impulsada por el respirador, lo que impide el retroceso elástico del sistema respiratorio y genera un aumento de la presión alveolar. De esta forma el flujo inspiratorio máximo se interrumpe y, si la magnitud y la duración del esfuerzo inspiratorio del paciente alcanza el umbral de activación inspiratoria, el respirador administra una segunda respiración. Por ello la aparición del DC depende, en parte, de los ajustes del respirador. Por ejemplo, en la

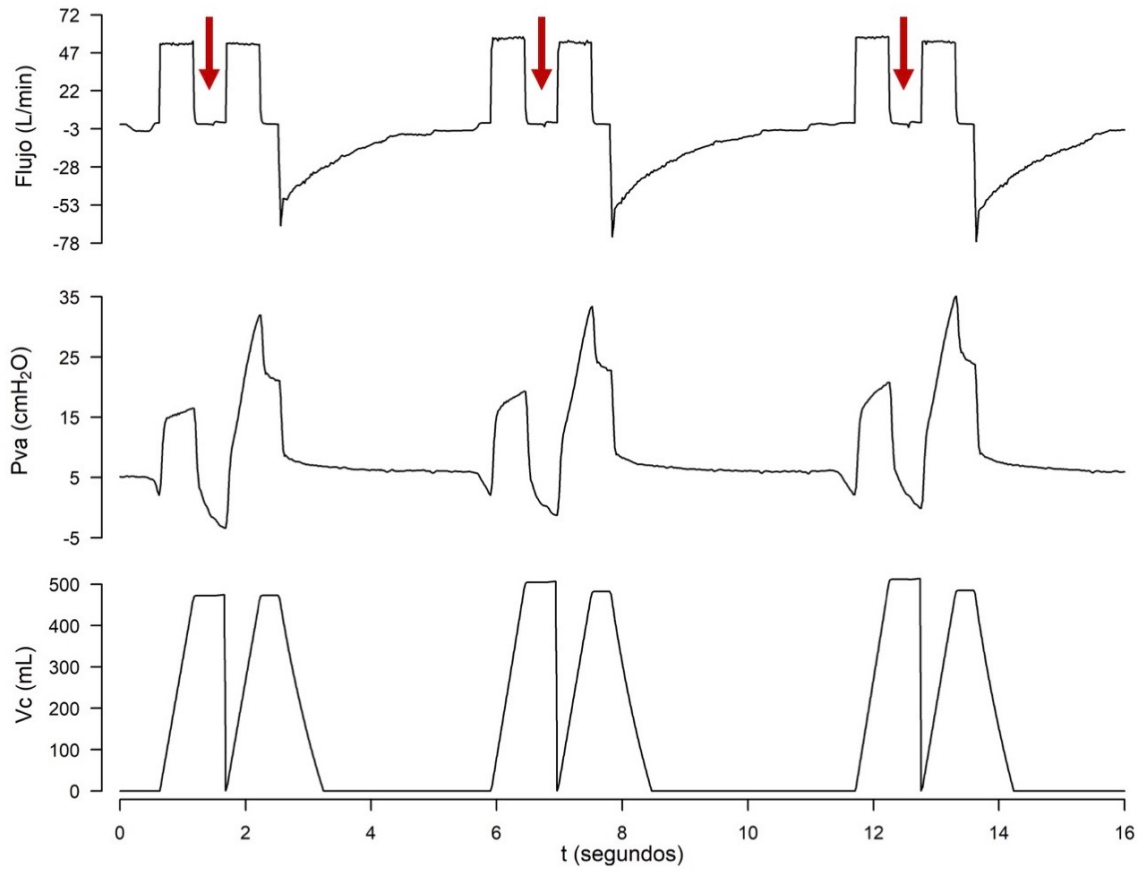
modalidad ventilatoria PSV, cuando el esfuerzo inspiratorio sostenido persiste y/o es lo suficientemente elevado como para superar el umbral de activación inspiratoria, se puede desarrollar lo que se denomina ciclo corto (*short cycling*), debido a que el descenso del flujo inspiratorio desde su máximo hasta el umbral preestablecido puede activar la fase espiratoria del respirador. Por el contrario, en VCV o PCV, una vez que se alcanza el umbral de activación, el respirador administrará una segunda respiración consecutiva completa, sin que exista una exhalación completa entre ambas, a menos que una alarma de presión o volumen preestablecida evite la segunda respiración mecánica.

La principal consecuencia del DC es que parte o todo el volumen corriente de la segunda respiración se suma al de la primera (13), por ello esta asincronía se denomina en inglés *breath stacking*. El elevado volumen corriente resultante de la acumulación de dos respiraciones consecutivas, puede generar altos gradientes de presión transpulmonar y transvascular, incrementando el estrés y la sobrecarga (*strain*) de los tejidos, y puede producir una distribución desigual de la presión en las zonas dependientes del pulmón (20), lo que puede favorecer la lesión pulmonar inducida por el respirador (21,22). Además, el DC provoca una contracción diafragmática prolongada que puede dar lugar a una disfunción muscular derivada de la activación de músculos inspiratorios durante la fase de deflación mecánica (23).

La definición clásica de DC tiene en cuenta solo la duración del tiempo espiratorio (inferior a la mitad del tiempo inspiratorio medio) sin definir un umbral de volumen corriente. Por esta razón, recientemente, algunos autores insisten en que el DC no puede usarse como sinónimo de *breath stacking*, y que el término *breath stacking* debe usarse solo para referirse a la consecuencia clínica del DC cuando la exhalación incompleta entre respiraciones resulta en un incremento del volumen corriente superior al previsto (22).

El DC también puede aparecer como respuesta a un impulso respiratorio elevado del paciente secundario a una asistencia insuficiente por parte del respirador. Además, Thille et al. (24) han descrito una incidencia superior de DC cuando se da alguna de las siguientes circunstancias: baja relación PaO_2/FiO_2, VCV como modalidad ventilatoria, un tiempo inspiratorio más corto, una presión inspiratoria máxima alta y un elevado nivel de PEEP. Recientemente también se ha demostrado que la ventilación con volúmenes corrientes bajos puede tener relación con el desarrollo de DC (21).

Figura 1. Asincronía de doble ciclado. En la figura se muestran trazados de las curvas de flujo, presión y volumen corriente en un paciente en VM en modalidad VCV. Las flechas rojas señalan las respiraciones con DC. Se observa cómo se suceden dos respiraciones sin espiración entre ellas, con el consecuente aumento de presión y acúmulo de volumen corriente.



Trigger reverso

Otro tipo de asincronía, menos reconocida, es el *trigger* reverso (RT). El RT es una forma de asincronía que refleja una relación anormal entre el respirador y el paciente, donde las insuflaciones mecánicas generadas por el respirador provocan una respuesta neuronal del paciente (activan su centro respiratorio) y desencadenan un esfuerzo muscular.

El centro respiratorio es un oscilador biológico, por lo que es susceptible de "arrastre" por la imposición periódica de los estímulos procedentes del respirador, que es conocido bajo el

término inglés "*entrainment"* (25); en otras palabras, la insuflación pulmonar periódica puede establecer una relación temporal fija y repetitiva entre los ciclos respiratorios neurales y mecánicos. Este fenómeno se ha observado en modelos animales en conejos (26,27), gatos (25,28), perros y también en pacientes (29,30). El fenómeno de "*entrainment*" se desarrolla de forma más frecuente cuando el volumen corriente del respirador, la frecuencia respiratoria y el flujo inspiratorio son muy similares al patrón de respiración neural de los pacientes. La fisiopatología del "*entrainment"* implica probablemente la adaptación lenta y rápida de los receptores elásticos en los pulmones, así como de las fibras C vagales. Sin embargo, este fenómeno de "*entrainment*" también se ha observado en pacientes receptores de trasplante pulmonar vagotomizados (30) así como en pacientes en muerte cerebral en los que hay ausencia de impulso respiratorio del tronco cerebral (31). Esto sugiere que la activación de los músculos respiratorios tras la insuflación del respirador esté mediada por diversos factores aferentes.

El término RT se ha adoptado para describir esta asincronía, que es resultado del fenómeno de "*entrainment*" respiratorio (32). Es importante matizar que el fenómeno de "*entrainment*" no es una asincronía, sino el mecanismo subyacente que desarrolla el RT. Una vez aparece el "*entrainment*", el RT puede desarrollar otras asincronías, como por ejemplo IE o DC, por lo que desde un punto de vista clínico puede ser útil distinguir entre RT-IE y RT-DC.

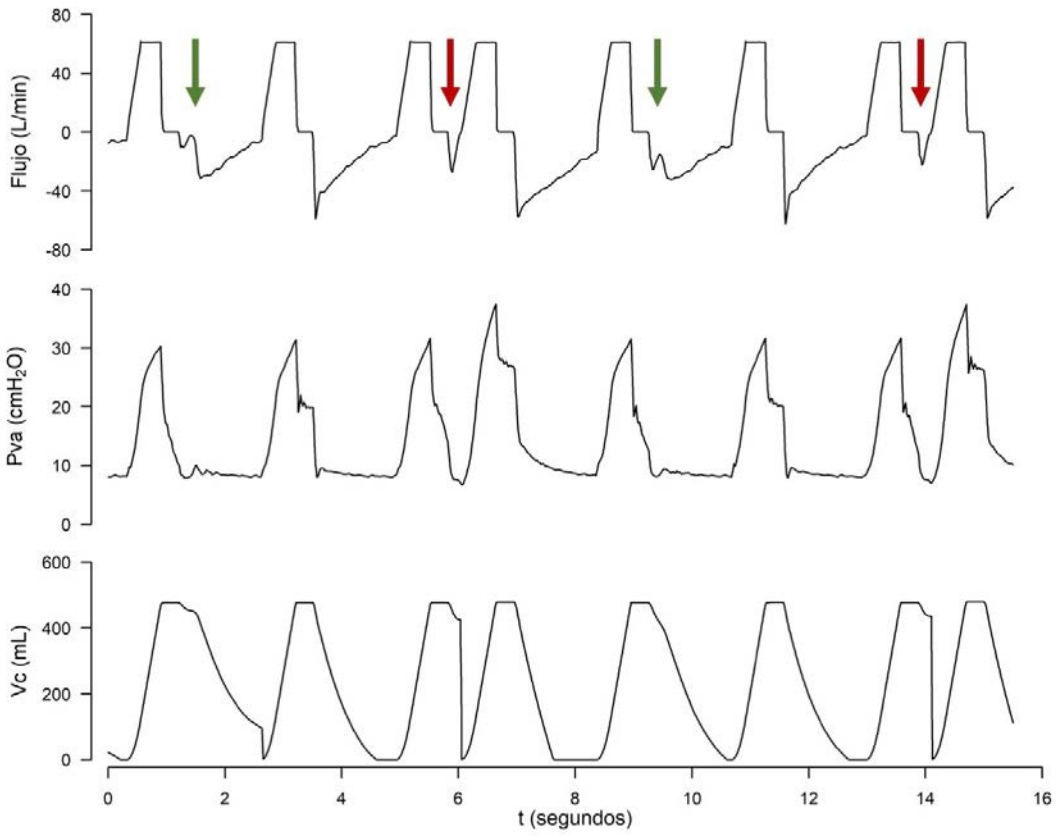
El RT puede clasificarse en función de la relación entre respiraciones mecánicas y las contracciones diafragmáticas del paciente. El patrón más comúnmente observado en modelos animales y en humanos es 1:1, pero se han reportado 2:1 y 3:1 (26,28,32). Hasta el momento, la única forma fiable de reconocer el RT es detectando la contracción muscular por presión esofágica después de la insuflación mecánica (32,33), aunque un análisis cuidadoso de las curvas del respirador también podría ser útil para su detección (34). Los algoritmos automatizados prometen detectar el RT de forma fiable y rápida sin necesidad de monitorización de la presión esofágica.

El RT puede provocar lesiones pulmonares y musculares. Tanto los IE como los DC secundarios a RT presentan los mismos mecanismos fisiopatológicos de lesión que cuando estas asincronías se desarrollan por otras causas. Su et al. (35) han objetivado como el 30% de los pacientes con síndrome de distrés respiratorio agudo (SDRA) presentan RT, que se desarrolla en la fase inspiratoria tardía (41%) y en la fase espiratoria temprana (59%), y que

se asocia con un incremento del volumen corriente y fluctuaciones superiores en la presión transpulmonar, lo que sugiere que la lesión pulmonar consecuente puede ser secundaria tanto a volutrauma como a barotrauma.

En la actualidad, el conocimiento sobre la prevalencia y la traducción clínica del RT es limitado debido a que se trata de un fenómeno que se ha empezado a reconocer de forma reciente (32,36). Diferentes estudios observacionales muestran como el RT es frecuente en pacientes con SDRA con sedación profunda, pero no hay información sobre su prevalencia en otros escenarios clínicos (32,35,37).

Figura 2. *Trigger* reverso. En la figura se muestran trazados de las curvas de flujo, presión y volumen corriente en un paciente en VM en modalidad VCV. Las flechas rojas señalan las respiraciones con RT que desencadenan DC (RT-DC). Las flechas verdes señalan las respiraciones con RT que desencadenan IE (RT-IE). La respiración que precede al RT es mandatoria (administrada por el respirador sin esfuerzo del paciente). En este ejemplo se observa el fenómeno de *entrainment* 1:2.



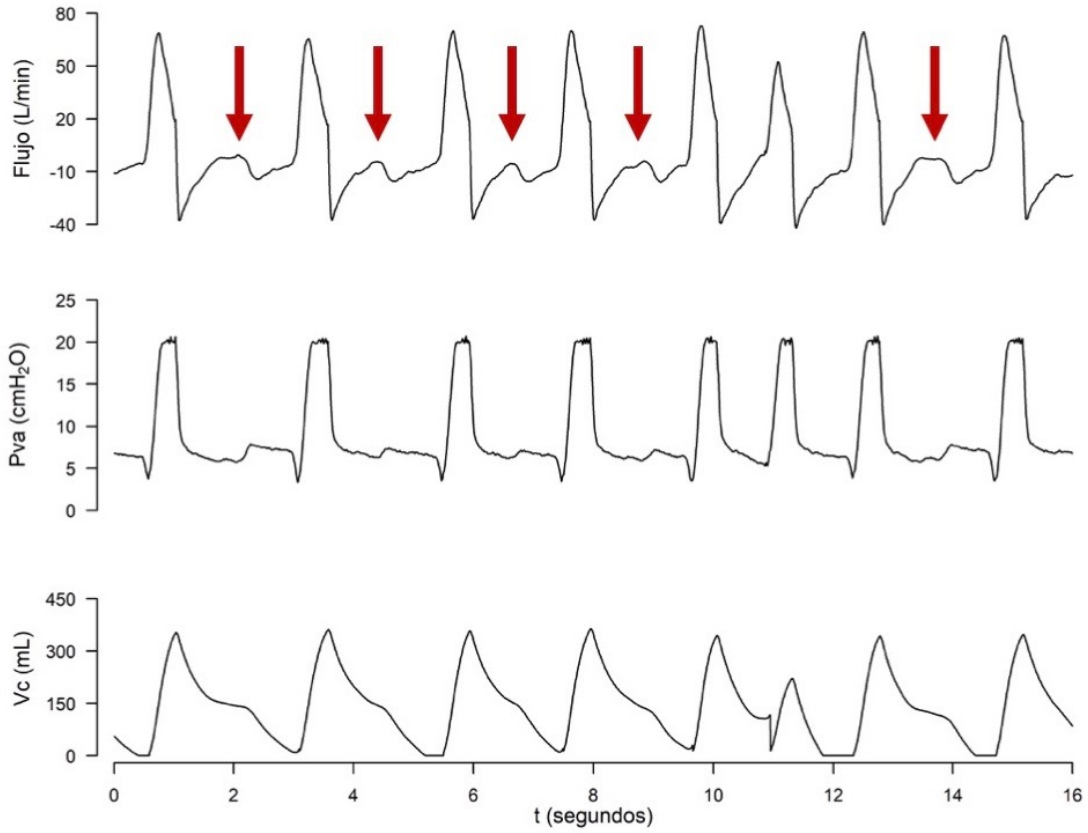
Esfuerzos inefectivos

Los esfuerzo inefectivos (IE), constituyen una las asincronías más frecuentes, afectando alrededor del 50% de los pacientes que reciben VM (24). Los IE se definen como un esfuerzo muscular inspiratorio que no es seguido por la administración de una respiración por parte del respirador. Esta asincronía ocurre frecuentemente cuando el intento del paciente por iniciar una respiración no alcanza el umbral de activación del respirador. El respirador no puede detectar los esfuerzos inspiratorios del paciente, lo que se caracteriza fisiológicamente por un incremento de la presión transdiafragmática (por ejemplo un descenso en la presión esofágica y un incremento en la presión gástrica) y/o un incremento en la actividad eléctrica del diafragma (38,39). El resultado es una frecuencia respiratoria del paciente superior a la del respirador. Los IE se diagnostican al objetivar un descenso en la curva de presión con un ascenso simultaneo en la curva de flujo. Muchos de los IE se detectan durante la fase espiratoria; sin embargo, pueden ocurrir también durante la inspiración, donde se caracterizan por un incremento abrupto en el flujo inspiratorio (en la modalidad de presión soporte) o un descenso transitorio en la curva de presión (en la modalidad de volumen control) que no es capaz de disparar una segunda respiración (39).

Los IE pueden estar presentes en todas las modalidades de VM y se derivan de diferentes condiciones clínicas. Entre las principales causas de IE destacan los ciclados retardados, la sobreasistencia y la hiperinsuflación, y todos ellos derivan en un incremento de la presión intrínseca al final de la espiración (40–42). La disminución del impulso respiratorio por otros mecanismos, como la sedación, aumenta también la incidencia de IE. La administración de propofol para obtener una sedación más profunda durante PSV se asocia con una mayor frecuencia de IE (43,44).

La principal consecuencia clínica de los IE es el daño muscular. En el contexto de la sobreasistencia, los IE pueden provocar en poco tiempo atrofia miofibrilar y disfunciones contráctiles (miotraumatismo por sobreasistencia) (45,46). La carga contráctil excesiva mientras el músculo se alarga (contracciones excéntricas) es particularmente perjudicial; este miotrauma excéntrico ocurre cuando el músculo se contrae activamente durante la fase de espiración del respirador (46).

Figura 3. Esfuerzos inefectivos. En la figura se muestran trazados de las curvas de flujo, presión y volumen corriente en un paciente en VM en modalidad PSV. Los esfuerzos inefectivos (flechas rojas) están presentes durante la fase espiratoria. Se observa un descenso en la presión junto con un incremento en el flujo, que no va seguido de una respiración. En este caso, la frecuencia respiratoria del paciente es bastante superior a las respiraciones administradas por el respirador.



Consecuencias de las asincronías

En los últimos años han aparecido diversos trabajos dirigidos al estudio de las consecuencias de las asincronías, aunque la principal limitación es que muchos de estos estudios no están diseñados específicamente para evaluar los *outcomes*. Los esfuerzos inefectivos se asocian con un incremento en los días de VM y con una menor tasa de éxito en el destete de la VM (47). Estudios más recientes han confirmado también estos resultados. De Wit *et al.* (48) describieron como un índice de esfuerzos inefectivos superior al 10% se asociaba con una

prolongación en los días de VM. En otro estudio, Thille et al. (24) observaron que un índice de asincronías superior al 10% se asociaba también con más días de VM y a su vez con mayor necesidad de traqueostomía. En un estudio más reciente, en el que se evaluaba más del 80% del tiempo de VM, se encontró una asociación con la mortalidad en aquellos pacientes con un índice de asincronías superior al 10% (11). Al usar modelos Bayesianos para el análisis de las asincronías y su impacto en los *outcomes*, no se ha encontrado suficiente evidencia que demuestre que las asincronías tienen un impacto en la mortalidad, contrariamente a lo que sucede al evaluar el SOFA (49).

Recientemente se ha observado que las asincronías, no solo aparecen de forma aislada, sino que en muchos casos tienden a ocurrir de manera agrupada formando lo que se denomina *clusters* de asincronías. Vaporidi et al. (15) definieron los *clusters* de IE como períodos de 3 minutos con más de 30 eventos de IE, y encontraron una asociación entre la aparición de *clusters* y la prolongación de la VM y mayor mortalidad hospitalaria.

La principal limitación de muchos de estos estudios es que se limitan al análisis de cortos períodos de tiempo de VM, por lo que para confirmar estas asociaciones son necesarios estudios que evalúen períodos de tiempo más amplios, o incluso de forma ideal todo el período de tiempo en el que el paciente recibe VM. Además, seguramente el impacto de las asincronías que ocurren en los primeros días de VM, cuando los pacientes son ventilados en modalidades controladas, no tienen el mismo significado ni el mismo impacto que las asincronías que ocurren en modalidades de soporte parcial o durante las fases finales o de destete de la VM. Sin embargo, aunque asociación no siempre es sinónimo de causalidad, existen fuertes razonamientos fisiológicos que pueden explicar estas asociaciones, por lo que el diagnóstico y manejo de las asincronías merece ser un punto de especial atención.

Identificación de las asincronías

En la actualidad para la identificación de las asincronías durante la VM se emplean diversos métodos que abarcan desde el análisis visual de las curvas del respirador a pie de cama, el uso de un *software* específico que analiza las curvas, la evaluación de la actividad eléctrica del diafragma (EAdi) y la medición de la presión esofágica o transdiafragmática.

La detección de las asincronías mediante la visualización de las curvas de presión y flujo que muestra la pantalla del respirador a pie de cama requiere de un examen minucioso y

amplios conocimientos de fisiología respiratoria, además de un examen del patrón respiratorio del paciente. Este método puede llevar a errores de clasificación o infradiagnóstico de las asincronías ya que requiere la continuada visualización de la pantalla del respirador por parte del experto. Incluso en el caso del DC, que *a priori* es una de las asincronías más fáciles de reconocer, puede haber errores en distinguir si una asincronía es DC o RT, por la dificultad que comporta distinguir si se trata de un disparo automático o bien si existe esfuerzo inspiratorio del paciente. Los IE, que habitualmente pueden identificarse por el descenso en la curva de presión o aumento en la curva de flujo, pueden pasar también inadvertidos. Algunos autores han evaluado la capacidad del equipo asistencial en la detección de las asincronías mediante este método de inspección visual (50). Los resultados indican una sensibilidad del 22% y una especificidad del 91%, siendo la sensibilidad significativamente mayor cuando se trataba de personal experto. Además, hay que tener en cuenta que a mayor prevalencia de asincronías la capacidad de detección adecuada disminuía. Esta capacidad de detección se ve altamente influenciada por la experiencia y el tipo de asincronía (51). Los resultados de estos estudios reflejan la necesidad de otros métodos que faciliten no solo la identificación sino también la cuantificación de las asincronías.

Fruto de esta necesidad, han surgido los sistemas de monitorización continua, que integran en tiempo real las señales del monitor y del respirador a los que está conectado el paciente, y mediante la aplicación de algoritmos validados pueden resultar de ayuda en la identificación de las asincronías de forma automática y continua (38,39,52,53) a lo largo de todo el período ventilatorio. Chen *et al.* desarrollaron un algoritmo computarizado para reconocer y cuantificar los IE durante la fase espiratoria mediante el análisis de las desviaciones del flujo y de la presión (38). Observaron que estas desviaciones era diferentes entre pacientes, y buscaron unos valores óptimos fijados en 5,45 L/min y 0,45 cmH2O para poder generalizarlo. Blanch *et al.* validaron un algoritmo capaz de detectar los IE durante la espiración, también a través del análisis de las formas de las curvas (39). Este algoritmo se encuentra integrado en un *software* que calcula la curva teórica de flujo espiratorio del paciente y posteriormente calcula el porcentaje de desviación a partir de la curva de flujo real. Estos autores consideraban IE una desviación superior al 42%, obteniendo un área bajo la curva del 0,964. Mulqueeny *et al.* desarrollaron un algoritmo para detectar los IE y el DC (52). Los IE se identificaban mediante la presencia de perturbaciones en la señal de la curva

de flujo espiratorio sin que se acompañasen de una respiración mecánica. El DC se detectaba mediante el análisis de la curva de presión, identificándolo cuando se sucedían dos respiraciones seguidas separadas menos de 500 ms. El algoritmo mostró una sensibilidad del 87,3% y una especificidad del 99,1% al compararlo con la inspección visual de la presión transdiafragmática. Gutiérrez *et al.* (53) utilizaron el análisis espectral del flujo para la detección de asincronías, considerando la presencia de asincronía cuando se obtenía un patrón espectral menos organizado. La sensibilidad y la especificidad superaron el 80% al compararlo con observadores entrenados.

Otras técnicas, como la monitorización de la presión esofágica o el EAdi, pueden aumentar de forma significativa las posibilidades de monitorización e identificación de las asincronías. La presión esofágica garantiza una adecuada estimación del esfuerzo inspiratorio del paciente; en su contra, cabe mencionar que es un procedimiento semi-invasivo y bastante complejo de realizar. Esto hace que no se utilice de forma rutinaria en la práctica clínica (54). Por otro lado, la monitorización mediante EAdi también requiere la colocación de una sonda de alimentación específica y del uso de un respirador también específico. Las ondas de EAdi se pueden visualizar de forma continua en la pantalla del respirador junto a las demás curvas convencionales (55). Sinderby *et al.* propusieron el uso del índice combinado NeuroSync (56) para evaluar las asincronías en base al análisis simultáneo del EAdi y las señales neumáticas del respirador. Este índice evalúa de forma automática el desfase entre los esfuerzos neuronales y la asistencia por el respirador y presenta mejor sensibilidad en la detección de las asincronías que otros índices utilizados anteriormente. Otros autores compararon, en un subanálisis, la detección de asincronías mediante la inspección visual con un método computarizado que combinaba el EAdi y las curvas de flujo y presión. Observaron como el método visual infradiagnosticaba las asincronías (0,3/min) respecto el método automático (4,7/min) (57).

Por todo ello la búsqueda de métodos de identificación que a su vez permitan la cuantificación de las asincronías a lo largo de todo el período de VM, continúan siendo un reto en la práctica clínica diaria. Son necesarios sistemas de identificación de forma continua y en tiempo real que faciliten la identificación de los distintos tipos de asincronías, su caracterización y que también contribuyan a mejorar el manejo de las mismas.

Manejo de las asincronías

Las asincronías son resultado de diferentes mecanismos subyacentes, lo que hace que su impacto clínico sea diferente en función de la causa que lo produce, y por ello también su manejo. El impulso respiratorio de los pacientes críticos puede verse afectado por diversos factores como la existencia de dolor, la temperatura, el nivel de citoquinas inflamatorias, las alteraciones en el intercambio gaseoso, las demandas metabólicas, la afectación neurológica e incluso otros factores asociados con el sueño (18,58,59).

Los dos enfoques más comunes que se realizan para abordar el manejo de las asincronías son por un lado el ajuste de los parámetros del respirador y/o el uso de sedación y/o analgesia en función de las características del paciente.

El tratamiento de la causa subyacente de las asincronías mediante el ajuste de los parámetros del respirador debería ser el enfoque principal. En un estudio unicéntrico en pacientes con VCV, la mayoría con *breath stacking*, se encontró que los ajustes de los parámetros del respirador fue más efectivo que el incremento de la sedación a la hora de reducir las asincronías (60). Para realizar estos ajustes, es importante tener en cuenta los conceptos fisiológicos implicados, ya que existe una interacción entre el respirador y el centro respiratorio del paciente, por lo que cualquier cambio en los ajustes del respirador (volumen corriente, flujo, tiempo inspiratorio, etc.) alterará la actividad de los mecanoreceptores y la retroalimentación neuromecánica. Quizás, uno de los retos más complicados es el manejo de las asincronías de flujo, ya que el incremento del flujo para satisfacer las necesidades del paciente puede asociarse con un descenso del tiempo inspiratorio neural y consecuentemente un incremento de la frecuencia respiratoria (61). Por lo que cualquier ajuste en el respirador para intentar mejorar las asincronías precisa de una observación detallada del patrón respiratorio posterior y de la evaluación de sus consecuencias. Si los pacientes pueden respirar de forma espontánea, los modos proporcionales asistidos podrían ayudar al control de las asincronías en pacientes seleccionados. En este sentido, algunos estudios han descrito una mayor proporción del tiempo de VM sin asincronías en pacientes ventilados con la modalidad de VM proporcional asistida, que comporta beneficios frente al uso de PSV (62). Se han hallado resultados similares al comparar NAVA con PSV (63).

A pesar de ello, los sedantes siguen manteniendo un papel principal en el manejo de las asincronías en los pacientes con VM, aun no estando exentos de efectos adversos. Los

sedantes pueden provocar depresión respiratoria afectando el tiempo y el impulso respiratorio y pueden empeorar la interacción paciente-ventilador de forma proporcional a la diminución del nivel de conciencia (44,64). En este contexto se ha objetivado como el mantenimiento de niveles de sedación profunda disminuyen el impulso respiratorio y desencadenan la aparición de IE (43,44). De Wit el al. (44) observaron un incremento del índice de IE correspondiente al 2,7% por cada punto de descenso en la escala de sedación y agitación de Richmond. Del mismo modo, otro estudio evidenció como los niveles profundos de sedación con propofol aumentaban la incidencia de IE en PSV (43), como se ha mencionado anteriormente. Además, la sedación en el paciente crítico se ha asociado con un empeoramiento de los *outcomes* a corto y largo plazo (65,66). Por todo ello, las recomendaciones recientes se centran en evitar o minimizar el uso de sedantes en los pacientes con VM (67–69).

Hay pocos estudios que hayan analizado los efectos del uso de sedantes sobre el control de las asincronías. Algunos de ellos muestran como el uso de sedantes fracasa en el control del DC y además prolonga los días de VM y la estancia en UCI (60). Sin embargo, muchos de los estudios que analizan los efectos del nivel de sedación sobre las asincronías presentan resultados dispares. En algunos estudios se ha descrito que los niveles de sedación profunda incrementan las asincronías mientras que en otros, como el estudio de Sottile et al., las asincronías se ven reducidas aunque no del todo eliminadas (43,70).

Los opioides se usan de forma habitual en la UCI para el control del dolor y el confort del paciente crítico y se desconoce qué papel pueden jugar en el desarrollo de asincronías, ya que pocos estudios han abordado esta cuestión. Solo existe evidencia de que la combinación de sedantes con opioides disminuía la presencia de asincronías por encima de lo observado en aquellos pacientes que solo recibían sedación (71).

Debido a los conocidos efectos deletéreos de los sedantes, las últimas recomendaciones apuntan a minimizar su uso, y sumado a la falta de evidencia sobre su efecto en el control de las asincronías, se hace necesario investigar su papel en la interacción paciente-ventilador. Además, teniendo en cuenta el conocido efecto de los opioides sobre el control del dolor y el confort, es importante establecer si éstos pueden favorecer una mejor interacción paciente-ventilador evitando los efectos deletéreos de los sedantes.

Retos actuales

La identificación de las asincronías durante todo el período de VM es el primer paso para poder cuantificar su incidencia real. Esta identificación, además, nos permitirá una mejor caracterización e identificación de los factores asociados y mecanismos subyacentes, establecer las implicaciones fisiológicas que tienen las asincronías, y su relación con los diferentes *outcomes*. Asimismo, la identificación de las asincronías en tiempo real permitirá personalizar su manejo y, a su vez, evaluar de inmediato el efecto de las diferentes intervenciones clínicas destinadas a optimizar la gestión clínica de las mismas.

Por todo ello, el presente trabajo de tesis doctoral se dirige a resolver algunas de las cuestiones que se presentan como grandes retos en el campo de la interacción paciente-ventilador. Utilizando el registro continuo de las señales biomédicas y la identificación automática con algoritmos validados, se pretender poder caracterizar el DC y el RT. El presente trabajo se focaliza en estos dos tipos de asincronías ya que se considera que son frecuentes y, potencialmente, de las más lesivas. Utilizando una plataforma de monitorización continua se pretenden analizar la incidencia, factores relacionados e implicaciones fisiológicas. Asimismo, teniendo en cuenta la falta de unificación acerca del manejo de las asincronías, en parte debida a la falta de datos acerca de las mismas, se pretende analizar el papel de diferentes fármacos utilizados de forma común durante el manejo de los pacientes críticos con VM (sedantes y opioides), para contribuir a mejorar la interacción paciente-ventilador.

3. HIPÓTESIS

El uso de herramientas que permitan analizar de manera automatizada y continua las variables respiratorias durante la ventilación mecánica, mediante el uso de algoritmos, junto con otras variables que concurren en el paciente crítico sometido a ventilación mecánica invasiva, posibilitará la correcta caracterización de las asincronías, su patrón de presentación, las implicaciones fisiológicas y el análisis de los factores relacionados con su desarrollo, así como las estrategias más adecuadas para su manejo.

4. OBJETIVOS

Objetivo principal

- Identificar de manera automática y continua las asincronías doble ciclado y *trigger* reverso durante todo el período de ventilación mecánica para evaluar su incidencia y su patrón de presentación.

Objetivos secundarios

- Caracterizar las implicaciones fisiológicas del desarrollo de las asincronías doble ciclado y *trigger* reverso durante todo el período de ventilación mecánica.
- Identificar factores de riesgo asociados al desarrollo de doble ciclado.
- Analizar el efecto del tratamiento con opioides y sedantes sobre la incidencia de distintos tipos de asincronías.

5. METODOLOGÍA GENERAL

Diseño del estudio

La presente tesis se fundamenta en un estudio prospectivo observacional, en el que han participado cuatro UCIs de ámbito nacional (registrado en ClinicalTrial.gov NCT03451461). Todos los centros participantes están equipados con la plataforma BetterCare™ (BetterCare S.L., Barcelona, España) que facilita la monitorización continua basada en la conectividad y la interoperabilidad de diferentes dispositivos (respiradores y sistemas de monitorización) e incorpora algoritmos específicos para el diagnóstico de las asincronías paciente-ventilador. Los datos derivados de la monitorización continua, junto con el resto de datos clínicos y demográficos, se incorporaron a una base de datos. En la presente tesis se han analizado datos de pacientes incluidos en el período comprendido entre octubre de 2011 hasta enero de 2013.

Los sujetos incluidos en los estudios que conforman la tesis doctoral son pacientes críticos adultos, intubados y ventilados mecánicamente en los que se preveía que la VM se mantuviera al menos durante 24 horas, y que fueran admitidos en habitaciones que estuvieran equipadas con la plataforma BetterCare™ (BetterCare S.L., Barcelona, España). Se excluyeron los menores de 18 años, pacientes embarazadas, pacientes con órdenes de adecuación del esfuerzo terapéutico, portadores de tubos torácicos con sospecha de fístula bronchopleural, y pacientes admitidos para donación de órganos. Aquellos pacientes en los que se obtuvo un registro de datos inferior a 48 horas de seguimiento fueron excluidos del estudio a posteriori.

El equipo asistencial fue informado del desarrollo del estudio, y la inclusión de los pacientes en el estudio no modificó la práctica clínica habitual, más allá de la conexión a la plataforma de monitorización. Todos los pacientes recibieron los mismos cuidados, y se empleó una estrategia de ventilación mecánica protectora siguiendo los indicadores de calidad de la Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias. La modalidad ventilatoria, al igual que el ajuste del resto de parámetros ventilatorios, fue seleccionada por el equipo asistencial en función del estado clínico del paciente. Si el equipo asistencial detectaba mala interacción paciente-ventilador, se realizaban los ajustes de ventilación y tratamiento habituales a criterio clínico, pero estos ajustes no estuvieron protocolizados. Los

sedantes y la analgesia se han administrado siguiendo los protocolos de cada UCI basados en las recomendaciones de la Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias.

Recogida de datos

Tras la inclusión en el estudio, todos los pacientes fueron conectados a la plataforma BetterCare™ (BetterCare S.L., Barcelona, España) que permite registrar, de forma continua, las ondas de los dispositivos médicos (respiradores y monitores multiparamétricos) conectados al paciente. El sistema BetterCare™ captura y almacena las ondas de flujo, presión y el volumen corriente del respirador utilizando *drivers* diseñados específicamente para interactuar con la señal de salida de los diferentes dispositivos a pie de cama. La plataforma captura los datos a una frecuencia de 200 puntos/segundo, los sincroniza, los procesa y analiza por medio de algoritmos propios, y almacena tanto los datos capturados como el resultado del análisis de los algoritmos en una base de datos relacional PostgreSQL (Berkeley, CA; https://www.postgresql.org/).

Para la detección de asincronías, BetterCare™ identifica el inicio de la inspiración y de la espiración en cada ciclo respiratorio, y realiza el análisis respiración a respiración, por medio de un conjunto de algoritmos que combinan métodos de procesamiento digital de la señal y de *machine learning* validados previamente. La plataforma identifica cuatro tipos de asincronías paciente-ventilador: doble ciclado, esfuerzos inefectivos durante la espiración, ciclado corto y ciclado prolongado. Además, computa un índice global de asincronías (AI) que indica el porcentaje de ciclos asincrónicos respecto al número total de ciclos.

En los estudios que conforman la tesis, se computaron los índices de asincronías por hora y, para algunos análisis, se promediaron por día. Además, en el caso del DC se evaluó si esta asincronía se presentaba de manera aislada o bien de forma agrupada en el tiempo formando *clusters*, y se analizó la intensidad y la duración de los mismos. Se definió *cluster* como la presencia de eventos de DC igual o superior a un 10% en un período de tiempo de 3 minutos.

La plataforma BetterCare™ se utilizó también para registrar y analizar otras variables fisiológicas, como los valores de presión pico y presión positiva al final de la espiración, el pico de flujo inspiratorio, la frecuencia respiratoria, el tiempo inspiratorio, así como la identificación del modo ventilatorio (72) y del tipo de *trigger* en cada ciclo. Los períodos en

los que el registro fue interrumpido debido a intervenciones clínicas, traslados fuera de la UCI, incidentes técnicos u otros problemas fueron excluidos del análisis.

Además de los datos propiamente relacionados con las variables respiratorias, a partir de los registros médicos se obtuvieron los datos demográficos y clínicos de los pacientes a estudio. En todos los pacientes se evaluó cada cuatro horas el nivel de conciencia mediante la *Riker Sedation-Agitation Scale* (SAS) y se obtuvo el valor medio por día. A su vez se registró diariamente la severidad de la enfermedad mediante el *Sequential Organ Failure Assessment* (SOFA) y la dosis total de opioides (morfina y fentanilo) y de sedantes (midazolam, propofol y lorazepam) administrados. Con el fin de estandarizar las dosis entre pacientes que reciben fármacos distintos, todos los valores se transformaron en equivalentes de midazolam (sedantes) y morfina (opioides) siguiendo estudios previos. Todos los días en los que el paciente recibió VM fueron clasificados en un grupo de tratamiento según los fármacos recibidos como: 1) no-fármacos, 2) solo-sedantes, 3) solo-opioides y 4) sedantes+opioides.

Análisis estadístico

Las características de los pacientes se presentan como mediana (percentil 25-75) para las variables continuas, o en porcentajes para el resto de variables. Se han utilizado *boxplots* para describir gráficamente el comportamiento de algunas de las variables fisiológicas a estudio, en función del modo ventilatorio aplicado.

Para la evaluación de los resultados de esta tesis se han utilizado modelos lineales de efectos mixtos. En estos modelos la respuesta media es la suma de efectos fijos y efectos aleatorios. Los efectos fijos representan el comportamiento medio de toda la muestra, mientras que los efectos aleatorios se refieren a las variaciones de cada sujeto (concretamente, variaciones de intercepto y pendiente determinados de manera independiente para cada sujeto de la muestra). Así, en el caso que compete al estudio realizado en esta tesis, el modelo tiene en consideración la variabilidad intra e inter-sujeto ya que cada paciente difiere de la respuesta media global por una constante específica individual que aplica a lo largo del tiempo. Este tipo de análisis se considera apropiado cuando no existe independencia estadística en los datos y las observaciones están agrupadas por algún factor y comparten una o más características similares, o bien si los valores están afectados por valores previos en el tiempo (p.e. datos procedentes de una estructura jerárquica, estudios de medidas repetidas y/o datos longitudinales).

Teniendo en cuenta que en la literatura no existe una metodología general y bien establecida para el cálculo del tamaño muestral cuando se aplican modelos mixtos en estudios de medidas repetidas con correlaciones específicas entre las observaciones de un mismo sujeto, en este estudio no se estimó el tamaño de muestra necesario para alcanzar un valor de potencia estadística. Además, al tratarse de un estudio exploratorio, se consideró que no era imprescindible el cálculo de tamaño muestral.

Para el análisis de las variables continuas, como son el SAS y el SOFA, se han utilizado modelos lineales de efectos mixtos con intercepto aleatorio. Para modelar variables respuesta resultantes de un conteo de eventos, como es el caso de las asincronías, se aplicaron los modelos generalizados según distribución binomial negativa. Esta distribución binomial negativa se usa en modelos de regresión para describir variables discretas, no negativas, y sesgadas positivamente donde la mayoría de las observaciones tienen valores cercanos a cero. Además, en los modelos generalizados se ha incorporado una variable de exposición (o término *offset*) que representa el número de veces que un evento de asincronía pudo haber ocurrido en un determinado lapso de tiempo, pues el interés ha sido modelar la tasa de ocurrencia (o *rate*) de los eventos y no únicamente su mero conteo.

Para estudiar como influyen las variables fisiológicas en la aparición del doble ciclado, en cada uno de los modos ventilatorios, se han usado modelos lineales generalizados de efectos mixtos multivariados. Este análisis fue considerado la mejor aproximación por su robustez al evaluar simultáneamente la interacción entre las variables y sus efectos sobre el doble ciclado.

Como control de calidad de los análisis de inferencia aplicados y para asegurar su validez y una correcta interpretación de los resultados, se han verificado los supuestos de los modelos realizados. En los modelos lineales de efectos mixtos, aplicados para variables respuesta continuas, se ha verificado el supuesto de normalidad para los efectos aleatorios estimados y para los residuos intra-sujeto utilizando gráficos Q-Q normal. En los modelos lineales generalizados de efectos mixtos, utilizados para variables respuesta discretas, se ha evaluado la sobredispersión a través de la comparación gráfica de los residuos estandarizados y los valores estimados.

Todo el análisis se ha realizado mediante el software R 3.3.1 (R Core Team, Vienna, Austria, URL http://www.R-project.org). Los modelos de efectos mixtos se han construido y

analizado con el paquete lme4 y el paquete lsmeans. La significación estadística se ha establecido en $p < 0,05$ en el análisis del DC, y en una $p < 0,01$ para la evaluación de los efectos del tratamiento con sedantes y/o opioides.

Consideraciones éticas

El protocolo del estudio ha sido aprobado por el Comité de Ética de cada centro. Este estudio se ha desarrollado de acuerdo a los Principios de la Declaración de Helsinki (1964) y la Ley 14/2007 de Investigación Biomédica.

El tratamiento, la comunicación y la cesión de los datos de carácter personal de todos los sujetos participantes se ha ajustado a lo dispuesto en la Ley Orgánica 15/1999 de 13 de diciembre de protección de datos de carácter personal, sustituida posteriormente por el Reglamento 2016/679 del Parlamento Europeo y del Consejo de 27 de abril de 2016 de Protección de Datos (RGPD).

A continuación se presentan los trabajos que conforman esta tesis doctoral:

PUBLICACIÓN 1

Double Cycling During Mechanical Ventilation: Frequency, Mechanisms, an Physiologic Implications.

de Haro C, López-Aguilar J, Magrans R, Montanya J, Fernández-Gonzalo S, Turon M, Gomà G, Chacón E, Albaiceta GM, Fernández R, Subirà C, Lucangelo U, Murias G, Rué M, Kacmarek RM, Blanch L; Asynchronies in the Intensive Care Unit (ASYNICU) Group. Crit Care Med. 2018 Sep;46(9):1385-1392.

Factor de impacto de la revista: 6,971 según *ISI Journal Citation Reports* 2018. 1er Cuartil

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https://journals.lww.com/ccmjournal/Abstract/2018/09000/Double_Cycling_During_Mechanical_Ventilation_.1.aspx

PUBLICACIÓN 2

Effects of sedatives and opioids on trigger and cycling asynchronies throughout mechanical ventilation: an observational study in a large dataset from critically ill patients.

de Haro C, Magrans R, López-Aguilar J, Montanyà J, Lena E, Subirà C, Fernandez-Gonzalo S, Gomà G, Fernández R, Albaiceta GM, Skrobik Y, Lucangelo U, Murias G, Ochagavia A, Kacmarek RM, Rue M, Blanch L; Asynchronies in the Intensive Care Unit (ASYNICU) Group. Crit Care. 2019 Jul 5;23(1):245.

Factor de impacto de la revista: 6,959 según *ISI Journal Citation Reports* 2018. 1er Cuartil

Double cycling during mechanical ventilation: incidence, mechanisms and physiologic implications

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Keywords: asynchronies, tidal volume, reverse triggering, breath stacking, lung injury

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Abstract

Objective: Double cycling (DC) generates larger than expected tidal volumes (VT) that contribute to lung injury. We analyzed the incidence, mechanisms, and physiologic implications of DC during volume- and pressure-targeted mechanical ventilation (MV) in critically ill patients.

Design: Prospective, observational study.

Setting: Three general intensive care units in Spain.

Patients: Sixty-seven continuously monitored adult patients undergoing volume-controlled (VCV), volume-controlled-decelerated flow (VCVDF), or pressure-targeted (PCV) MV>24h.

Interventions: None

Measurements and Main Results: We analyzed 9251 hours of MV corresponding to 9,694,573 breaths. DC occurred in 0.6%. All patients had DC, however, the distribution of DC varied over time. The mean percentage (95%CI) of DC was higher in PCV 0.54(0.34,0.87) than in VCV 0.27(0.19,0.38) or VCVDF 0.11(0.06,0.20). VT in double-cycled breaths was higher in VCV and VCVDF than in PCV. Double-cycled breaths were patient-triggered in 65.4% and reverse-triggered (diaphragmatic contraction stimulated by a previous passive ventilator breath) in 34.6% of cases; the difference was largest in VCVDF (80.7% patient-triggered and 19.3% reverse-triggered).. Peak pressure of the second stacked breath was highest in VCV, regardless of trigger type. Various physiologic factors, none mutually exclusive, were associated with DC.

Conclusions: DC is uncommon, but occurs in all patients. Periods without DC alternate with periods with clusters of DC. The volume of the stacked breaths can double the set VT in VCV. Gas delivery must be tailored to neuroventilatory demand because interdependent ventilator-setting-related physiologic factors can contribute to DC. One-third of double-cycled breaths were reverse-triggered, suggesting that repeated respiratory muscle activation after time-initiated ventilator breaths occurs more often than expected.

Introduction

Coordinating patient-ventilator interaction is a major clinical challenge during invasive mechanical ventilation (MV). Asynchronies occur when the ventilator's breath delivery does not match the patient's neural ventilatory pattern or is inadequate to meet the patient's flow demand (1-3).

Recent studies highlight the importance of the asynchrony double cycling (DC), also named double triggering or breath stacking. DC consists of a sustained inspiratory effort that persists beyond the ventilator's inspiratory time, triggering a second ventilator breath, which may or may not be followed by a short expiration, where all or part of the volume of the first breath is added to the second breath. The resulting larger-than-expected tidal volume (VT) could cause ventilator-induced lung injury (4-10). Whether the incidence and effects of DC differ between pressure-targeted and volume-targeted modes is unknown.

Another recently described phenomenon, reverse triggering, occurs when a periodic diaphragmatic contraction stimulated by a previous passive ventilator breath is strong enough to originate a DC (11-12).

To assess the relevance of DC in MV patients, we aimed to determine: 1) the incidence of DC in volume-targeted and pressure-targeted modes; 2) the effects of DC on delivered VT and airway pressure in each mode; 3) the distribution of DC over time; 4) the proportion of DC due to reverse triggering, and 5) physiological factors associated with DC in each mode.

Materials and Methods

Patients and software

The study was conducted between October 2011 and January 2013 in three general ICUs equipped with the Better Care® platform (Better Care SL; Barcelona, Spain) in patients ventilated with Evita 4 (Dräger, Lübeck, Germany), Puritan Bennet 840 (Covidien, Plymouth, MN, USA), or Servo I (Maquet, Fairfield, NJ, Sweden) ventilators. The institutional review board approved the protocol and waived informed consent because the study was non-interventional, posed no added risk to patients, and did not interfere with usual care. The study prospectively included intubated adult patients expected to undergo invasive MV>24 hours with volume control-continuous mandatory ventilation with constant flow (VCV), volume control-continuous mandatory ventilation with decelerated flow (VCVDF), or pressure control-continuous mandatory ventilation (PCV) (13). Patients who were pregnant, had do-not-resuscitate orders or chest tubes with suspected bronchopleural fistula, or were admitted for organ donation were excluded.

The attending ICU team was aware of the study, and all patients were managed under lung-protective MV strategies. Ventilator mode and alarm settings were set by attending physicians, as part of usual care. Recordings were initiated in the first 24 hours after intubation and were continued until extubation. Better Care™ platform was used to capture digital outputs from the ventilators (9, 14), detects the ventilator mode (13), determines whether the breath is patient-triggered or ventilator-delivered, and classifies double-cycled breaths as patient-triggered or reverse-triggered (Supplemental digital content 1, Supplemental Table 1 and Supplemental Fig.1).

Detection of DC was based on mathematical calculations previously published (8-10, 15-16). The system identifies DC when: 1) expiratory time is 50% shorter than the averaged inspiratory time or 2) when two consecutive inspiratory cycles (positive flow–

zero flow–positive flow) are detected with no expiration (negative flow) before the second inspiratory time. We included cycles in which the first cycle was triggered by the patient or time cycled by the ventilator. Once inspiratory time is validated, expiratory time is automatically calculated. Supplemental Fig. 2 shows representative waveforms (flow, airway pressure and volume) of double-cycled breaths (reverse- or patient-triggered).

The system measures VT in conventional breaths and calculates the accumulated volume due to absent or incomplete exhalation between consecutive inspiratory cycles. Variables evaluated were: ventilatory mode, type of trigger, peak airway pressure (Ppeak), peak inspiratory flow, VT, respiratory rate, inspiratory time (Ti), total PEEP, and number of double-cycled breaths. To perform all the analyses variables were structured and stored (PostgreSQL) in two different databases containing: 1) breath-by-breath measures and 2) averaged values per hour. Hours with missing data due to interruptions in the recording related to clinical interventions, out-of-ICU transfers, technical incidents, or other issues were excluded from the analysis. The frequency of DC was computed as a percentage of the total number of breaths each hour. The identification of clusters of DC is described in supplemental digital content 2.

Statistical analysis

Patient's characteristics are reported as median (25^{th}, 75^{th} percentiles) for continuous variables, unless otherwise specified. Our study was exploratory in nature and no sample size calculation was performed. Comparisons of VT and peak airway pressure recorded breath by breath among ventilatory modes, and in DC (reverse-triggered or patient-triggered breaths) are depicted graphically with boxplots.

To assess the association between DC and ventilatory mode, we used a generalized linear mixed-effects model with random effects at the intercept for each patient to account for the intra-subject variability of longitudinal data (17). This model assumed a negative binomial distribution for the rate of DC. To investigate physiological variables thought to affect DC, we used a multivariate approach, allowing variations of slope (degree of change) for ventilatory modes (Supplemental Digital Content 3, Supplemental Fig.3).

We used R 3.3.1 (R Core Team, Vienna, Austria, URL http://www.R-project.org/) with the RPostgreSQL package for interfacing the database; p-value <0.05 was considered significant for all analyses.

Results

Table 1 reports demographic and clinical data of the 67 patients studied. We analyzed 9251 hours of MV data comprising 9,694,573 breaths; 59265 (0.6%) breaths were double-cycled breaths (Fig.1). A single mode of ventilation was used in 43.3% of patients; the single mode was VCV in 89.7% and PCV in 10.3%.

DC rates varied widely among patients and modes (Supplemental Fig.4a). All patients had DC but the distribution of DC differed within patients. Some patients had very few DC during the ventilatory period (Supplemental Fig. 4b), others had DC at the beginning or end of ventilation (Supplemental Fig. 4c and 4d), and others had a high incidence of DC throughout the ventilatory period (Supplemental Fig. 4e).

The distribution of DC among ventilatory modes was evaluated in the 8732 hours corresponding to PCV (2480 h), VCV (5119 h) and VCVDF (1133 h) (Fig. 1). The mean percentage of DC per hour (95% CI) estimated with the statistical model was 0.54(0.34,

0.87) for PCV, significantly higher than 0.27(0.19, 0.38) for VCV and 0.11(0.06, 0.20) for VCVDF ($p<0.05$ and $p<0.001$, respectively) (Fig.2).

DC due to patient triggering was more common than DC due to reverse triggering (65.4% vs. 34.6%) (Fig. 1) overall and in every mode (PCV: 68.1% vs. 31.9% , VCV: 62.2% vs. 37.8%, VCVDF: 80.7% vs. 19.3%, respectively).

Figure 3 (left top panel) shows VT in double-cycled and normal breaths. In normal breaths, VT was similar in all three ventilatory modes. In double-cycled breaths, the increase in VT was higher in VCV and VCVDF than in PCV. In patient-triggered breaths, VT was lower in PCV than in both volume-controlled modes. In reverse-triggered breaths, VT was higher in VCV than in PCV or VCVDF (Fig. 3, right top panel).

Peak pressure in normal breaths (Fig. 3 bottom) was slightly lower in PCV than in VCV and VCVDF. In patient-triggered breaths, Ppeak was higher in VCV than in PCV or VCVDF. In reverse-triggered breaths, Ppeak in volume-targeted modes was higher than in PCV. To describe whether the Ppeak pattern differed between first and second breaths, we evaluated the two breaths composing DC separately (Supplemental Table 2). Ppeak values for the second breath were generally greater than for the first. This difference was greatest in VCV, mainly for patient-triggered breaths (84.7% vs. 15.1%), and more balanced in VCVDF (56.0% vs. 43.0%).

Table 2 shows estimated coefficients for factors associated with DC in each mode. The statistical model was fitted to the 7580 hours (86.8%) free of missing data. Respiratory rate was positively associated with DC in all modes. Ventilator inspiratory time was negatively associated with DC in all modes. Peak flow was negatively related to DC in PCV and VCV. PEEP was negatively related to DC in PCV and VCVDF and positively related in VCV. Ppeak was positively associated with DC in PCV, but

negatively associated in VCV. VT was positively associated with DC in PCV and VCVDF, but negatively associated in VCV. Levels of significance are reported in Table 2. Supplemental Fig. 5 shows boxplots for each physiological variable and ventilatory mode included in the model.

Clusters of DC were identified and characterized (supplemental digital content 2). When clusters were defined as ≥10% DC breaths within a 3-min period, a 59.7% of the total number of patients exhibited clusters, with a median of 6 cluster events per patient, a power of 41 DC breaths per cluster, median duration 15.5 min and an area under the curve of 20.3. See supplemental digital content 2 for DC clusters characteristics with other definition.

Discussion

To our knowledge, this is the first study presenting a rigorous quantification of DC as result of continuous monitoring of patients during volume- and pressure-targeted time-cycled modes throughout the complete MV period. DC was infrequent, but occurred in all patients. Its distribution and clustering over time varied widely among patients (Supplemental Fig. 4 and supplemental digital content 2), underlining the importance of continuous real-time analysis of asynchrony events, which normally go undetected.

Tthe delivered volume accumulated during DCwas very high, sometimes even doubling the VT of normal breaths in volume-targeted modes (Fig. 3 and Supplemental Fig. 2) as reported by others (4, 8). This might result in overinflation, which can lead to ventilator-induced lung injury. Low VT, recommended for lung-protective ventilation (18), results in more frequent DC (8) and flow asynchrony (2, 6). In our study, DC was more frequent in PCV than in VCV and VCVDF, although the overall volume delivered

during DC in PCV was lower than in VCV or VCVDF. However, this does not mean PCV is more lung protective. In pressure-preset or pressure-targeted modes, the negative pleural pressure during vigorous spontaneous diaphragmatic contractions is added to the peak alveolar pressure, potentially establishing harmful transpulmonary pressure swings (19-21). This phenomenon also occurs in double-cycled breaths in VCV, where Ppeak of the second breath is markedly elevated (Supplemental Table 2). Yoshida et al. (22-23) recently showed that vigorous spontaneous inspiratory efforts promote tidal recruitment associated with pendelluft (lung volume redistribution) and consequent regional lung overdistension.

In low VT ventilation, especially in healthy lungs, DC could be due to natural sighs; whether this situation is harmful will depend on the generated transpulmonary pressure and frequency of DC. Recent evidence suggest that VT should also be limited in patients without ARDS (24); therefore, clinicians might believe they are delivering 6-8 ml/kg VT, but the patient is actually receiving >10 ml/kg VT, a setting that might affect outcome even in non-ARDS patients. We also found that clusters of DC were often present. Vaporidi et al. (25) found that clusters of ineffective efforts were often present in patients receiving MV, and unlike overall incidence, clusters were associated with prolonged MV and increased mortality. Therefore, Vaporidi et al (25) and study of ours show the variability of asynchrony events during MV and suggest that clusters of DC could increase the mechanical power (a measure that integrates different ventilator-related causes of lung injury) transferred from the ventilator to lungs (7).

The statistical model determined that numerous physiologic factors, selected for clinical suspicion, were associated with DC. This model is robust since it took into account inter-patient variability, and that there were different ventilatory modes and covariates, allowing us to investigate their simultaneous effects on DC. In this context,

each variable is influenced by the other variables, making interpretation more complex, and each coefficient represents the additive effect on the response of its corresponding variable while holding all other variables fixed (26). Patient's inspiratory demands may vary throughout MV without the critical care team being aware of it. This may explain DC occurring throughout the MV period and underlines the need to tailor ventilator settings to the patient's needs at all times.

Longer inspiratory time and higher inspiratory peak flow were associated with less DC in all modes, probably suggesting better matching between neural inspiratory time, ventilator inspiratory time, and inspiratory demand. Likewise, we found more asynchronies at higher ventilator respiratory rates, attributable to shorter ventilator inspiratory times. Setting a shorter inspiratory time to improve patient comfort can produce mismatch between neural time and ventilator time and thus increase the probability of DC. However, Pohlman et al. (8) found respiratory rate did not affect DC. Duty-cycles are crucial in generating double-cycled breaths. Thus, increasing respiratory rates at similar duty cycles decreases inspiratory time, which may favor DC, whereas promoting longer inspiratory times at higher rates may decrease DC. In fact, clinical strategies against DC are switching from VCV to pressure-support ventilation or increasing inspiratory time or peak airflow (5, 27) to prolong ventilator assist during diaphragm activation (28) and decrease flow asynchrony (29). However, this approach might result in undesirably high volumes. Furthermore, when assistance is relatively high and mechanical inflation extends well into neural expiration, other asynchronies (e.g., ineffective efforts) may develop (5, 30-31).

Unlike Thille et al. (10), who observed more DC at higher PEEP or Robinson et al. (32), who found PEEP had no effect on DC, we found higher PEEP was associated with less DC in PCV and VCVDF. At higher PEEP levels, a decrease in the inspiratory effort

can occur at higher lung volumes, explaining the decrease in the incidence of DC. Consistent with Pohlman et al. (8), we found low VT favors DC in VCV. In PCV, the positive association between VT and DC may be related to ventilator settings other than VT. Finally, the fact that low peak airway pressure in VCV favored DC may reflect the presence of unmet ventilatory demand and flow asynchrony. The opposite occurs in PCV, where more DC occurred at high levels of peak airway pressure. Since patients in all modes were ventilated at low VT, the fast decay in airflow during PCV may reflect unmet inspiratory demand and flow asynchrony.

Therefore, several physiologic factors, none of which are mutually exclusive, may account for DC. At the bedside careful adjustment of ventilator settings specific for each patient's diagnosis and neurorespiratory physiology; specific measures that can be useful for managing DC, include increasing ventilator inspiratory time, use of pressure-support ventilation or proportional assist modes, and considering paralyzing/sedating agents if VT is markedly elevated (1-2, 4, 8).

Patient-ventilator interaction induces continuous crosstalk between respiratory muscles, lung, and brain (33-34). Our work is the first examining separately reverse-triggered and patient-triggered DC breaths during the whole period of MV. We found that one-third of DC breaths originated from respiratory muscles contractions triggered by the ventilator or reverse-triggered breaths. Such a high proportion of DC originated by reverse triggering has never been reported. Reverse-triggered efforts may generate higher plateau pressure in VCV and large VT in VCV and PCV; although DC is reduced by deep sedation, potentially deleterious tidal volumes may still be delivered (35). This phenomenon was reported several years ago (36-37) and was recently described as entrainment; it usually occurs in heavily sedated patients, mostly with ARDS, and often goes unnoticed (11, 38-40). However, the incidence of reverse triggering in the general

population of ICU patients was unknown. In our series, the proportions of DC and type of breath initiation (patient- or reverse-triggered) were not different in the 5 ARDS patients compared with the other patients studied (Supplemental Table 3). In addition, the number of hours patients in each mode were under pharmacologic-controlled ventilation was not available, and the differences in the frequency of DC between PCV and VCV may be a result of when and the amount of time each approach was used in given patients. Just considering the percentage of the breaths that were reversed-triggered in VCV (37.8%) vs. those in PCV (21.9%) and VCVDF (19.3%) one would assume patients spent a greater percentage of the time were under controlled ventilation during VCV.

Our study focused on the incidence and physiologic mechanisms associated with DC. However, some reverse-triggered breaths may have resulted in ineffective triggering of the ventilator, so DC did not occur (12), thus underestimating the real incidence of reverse triggering. Prospective studies are needed to investigate respiratory entrainment in different forms of respiratory failure, at different levels of consciousness, and under different sedation and pain control regimens.

Our study has some limitations. The algorithm-based approach might underestimate the frequency of DC compared to gold-standard approaches based on monitoring esophageal pressure or electrical activity of the diaphragm. The study analyzed the incidence, physiologic implications and factors favoring DC; however, the design was based on breath analysis, regardless of the heterogeneity of the patients' clinical characteristics (e.g. severity of illness, reason for intubation, and others). We did not measure plateau airway pressures (unreliable in the context of active patient inspiration); thus, our assumptions on the effects of high transpulmonary swings inducing lung injury might not be accurate. We used only three types of ventilators for this study, and we cannot assume that other ventilators would produce similar patient-ventilator interactions

using the same modes. Similarly, we analyzed breaths only in VCV, PCV, and VCVDF modes, so we cannot infer the incidence of DC in other modes such as adaptive pressure control modes or in the frequently used pressure support mode. Reverse triggering was assessed only in DC breaths, precluding conclusions about the overall incidence of reverse triggering during MV. Finally, the design of our study does not allow us to assess the effect of different sedation levels on DC or the effects of DC on long-term cognitive dysfunction in critical care survivors (41).

In conclusion, DC is much less frequent than physicians might think, even when VT is set low and DC might appear in clusters. The total volume of the two stacked breaths can double the set VT in VCV and VCVDF. Since various interdependent physiologic factors related to patients' clinical conditions and ventilator settings can cause DC, it is crucial to tailor gas delivery to patients' neuroventilatory demand. When DC is present, reverse triggering occurs more frequently than previously thought. One-third of double-cycled breaths were ventilator-triggered diaphragmatic contractions and this phenomenon seems common in all ICU patients receiving MV.

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APPENDIX 1. Asynchronies in the Intensive Care Unit (ASYNICU) Group

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Figure Legends

Figure 1. Flow chart representing the distribution of ventilatory modes and incidence of double cycling.

DC=double cycling; PCV=pressure control-continuous mandatory ventilation; VCV=volume control-continuous mandatory ventilation with constant flow; VCVDF=volume control-continuous mandatory ventilation with decelerated flow; RT= reverse-triggered; PT=patient-triggered

Figure 2. Mean percentages of double-cycle breaths estimated with the generalized linear mixed-effects model by ventilatory modes. A higher percentage of double-cycled breaths per hour were found in PCV than in VCV or VCVDF. Data are represented as mean (95% CI). Statistical significance among means in each mode is indicated in the figure.

DC=double cycling; PCV=pressure control-continuous mandatory ventilation; VCV=volume control-continuous mandatory ventilation with constant flow; VCVDF=volume control-continuous mandatory ventilation with decelerated flow

Figure 3. Descriptive notched boxplots for tidal volume (top) and peak pressure (bottom) in each ventilatory mode. Left panels: Breaths without double cycling (white) *vs*. double-cycled breaths (gray). Right panels: Reverse-triggered (light-gray) *vs*. patient-triggered (dark-gray) double-cycled breaths. Red dots represent means and box plots indicate medians and 25^{th}-75^{th} percentiles. Note that outliers have been omitted for visualization purposes.

DC=double-cycled breaths; RT=reverse-triggered breaths; PT=patient-triggered breaths; VT=tidal volume; Ppeak=Peak pressure; PCV=pressure control-continuous mandatory ventilation; VCV=volume control-continuous mandatory ventilation with constant flow; VCVDF=volume control-continuous mandatory ventilation with decelerated flow

Figure 1

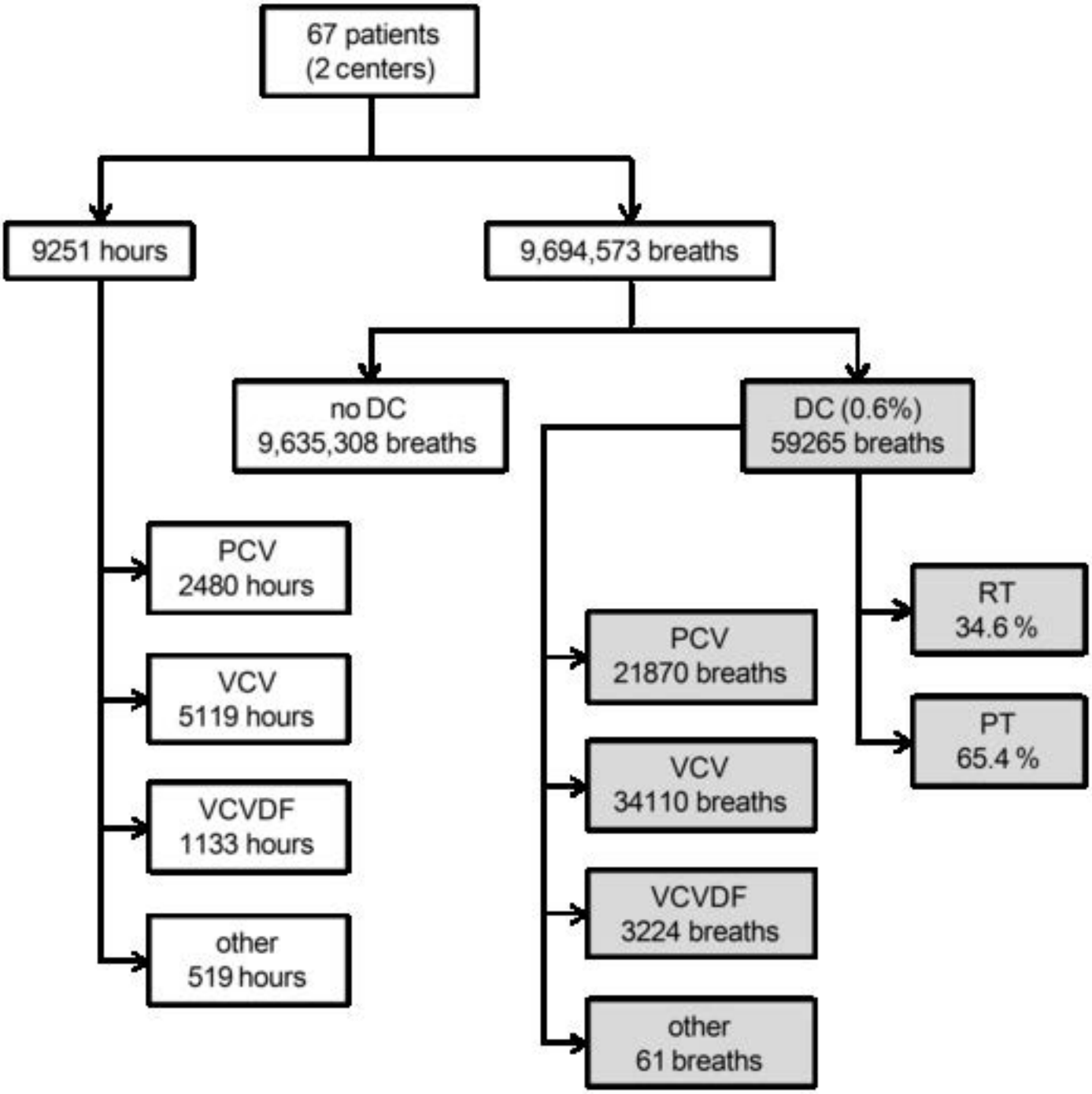
67 patients
(2 centers)
9251 hours
9,694,573 breaths
no DC
9,635,308 breaths
DC (0.6%)
59265 breaths
PCV
2480 hours
VCV
5119 hours
VCVDF
1133 hours
other
519 hours
PCV
21870 breaths
VCV
34110 breaths
VCVDF
3224 breaths
other
61 breaths
RT
34.6 %
PT
65.4 %

Figure 2

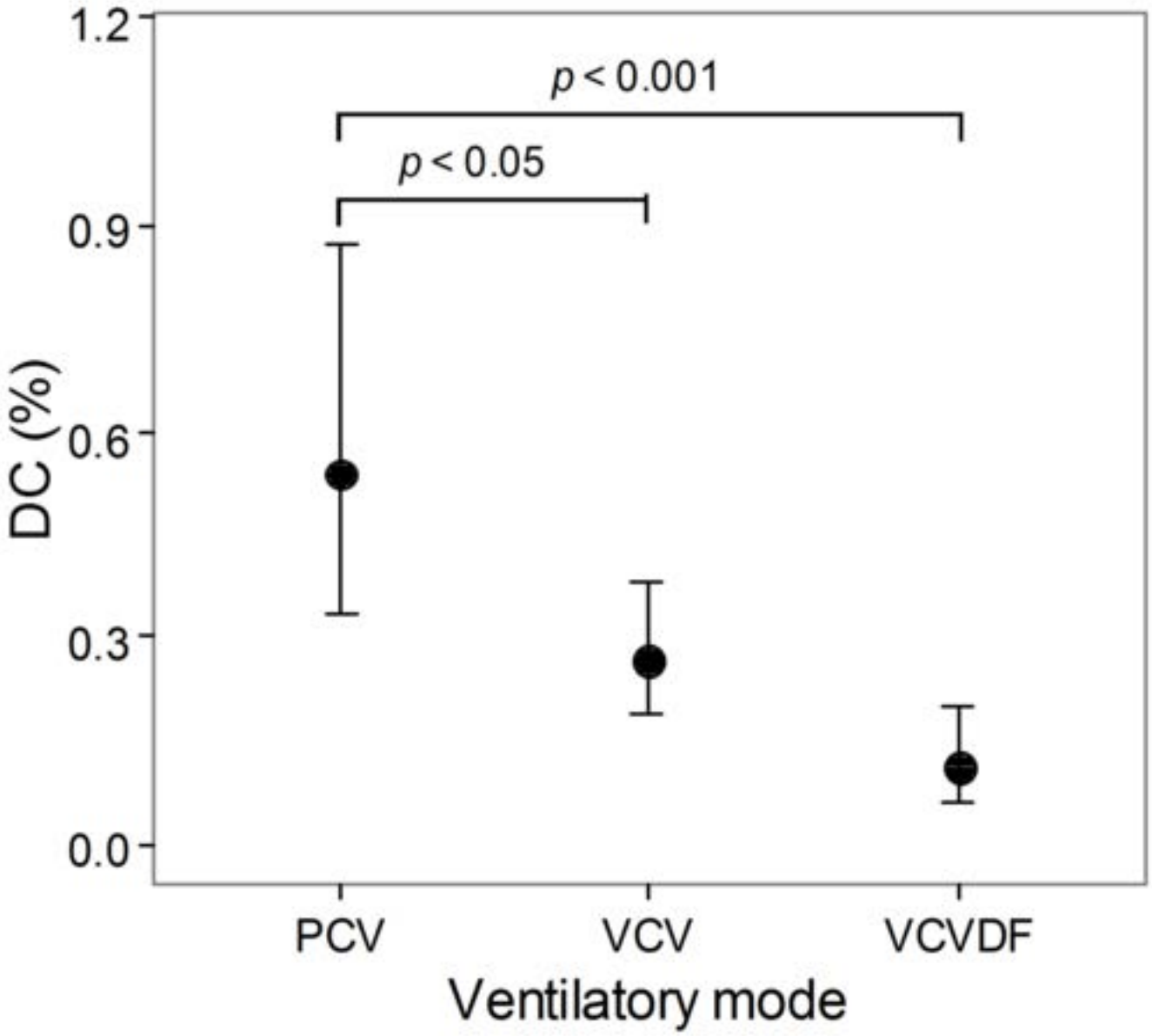

Figure 3

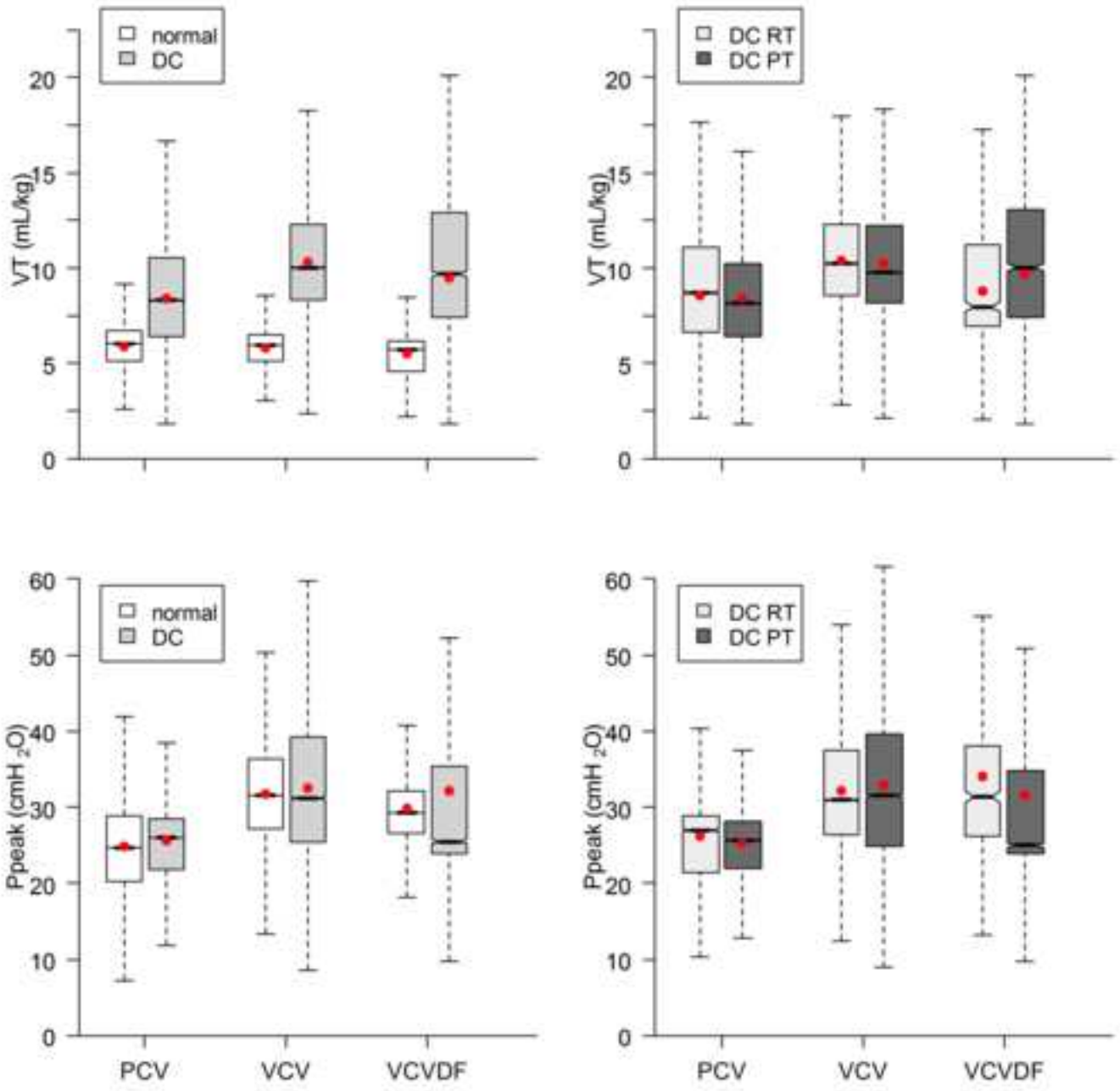
normal
DC
VT (mL/kg)
0
5
10
15
20
DC RT
DC PT
Ppeak (cmH 2O)
0
10
20
30
40
50
60
PCV
VCV
VCVDF

Table 1

TABLE 1. Patients' demographic and clinical data.

Variables and clinical outcomes	n	%	median (25th, 75 th percentiles)
Patients	67		
Age (years)			65 (55, 77)
Sex (male)		62.7	
Reason for mechanical ventilation			
Acute respiratory failure:	***51***	***76.12***	
cardiorespiratory arrest	7	10.45	
trauma	2	2.99	
bronchoaspiration	1	1.49	
pneumonia	6	8.96	
sepsis/septic shock	12	17.91	
congestive heart failure	2	2.99	
ARDS	5	7.46	
postsurgical	8	11.94	
other	8	11.94	
Coma:	***11***	***16.42***	
stroke	4	6	
intoxication	1	1.19	
traumatic brain injury	3	4.48	
metabolic	3	4.48	
COPD:	***4***	***5.97***	
asthma	1	1.49	
COPD exacerbation	3	4.48	
Neuromuscular disease:	***1***	***1.49***	
Apache II			16 (10, 23.5)
SOFA at admission			7 (5, 10.75)
Length of MV (days)			6 (3, 11.5)
ICU stay (days)			10 (6, 18)
Hospital stay (days)			26.5 (15.5, 68.0)
ICU mortality		23.88%	

Abbreviations: MV=mechanical ventilation; ARDS=Acute respiratory distress syndrome; COPD=Chronic obstructive pulmonary disease; SOFA=Sequential Organ Failure Assessment score; ICU =Intensive Care Unit

Table 2

TABLE 2. Mean effects[a] for the factors influencing double cycling: Multivariate analysis for variables clinically suspected to impact the development of double cycling.

Factors	Ventilatory modes		
	PCV	VCV	VCVDF
Ti	-2.32(-2.94, -1.69)***	-0.58(-1.11, -0.05)*	-2.71(-4.29, -1.13)***
Peak Flow	-0.10(-0.11, -0.08)***	-0.01(-0.03, -0.00)*	-0.01(-0.04, 0.03)
Ppeak	0.08(0.06, 0.10)***	-0.06(-0.08, -0.05)***	-0.01(-0.05, 0.03)
PEEP	-0.05(-0.10, -0.00)*	0.03(-0.01, 0.07)	-0.25(-0.34, -0.16)***
RR	0.08(0.04, 0.11)***	0.03(0.02, 0.05)***	0.07(0.01, 0.12)*
VT	0.01(0.01, 0.01)***	-0.00(-0.01, -0.00)***	0.01(0.01, 0.02)***

[a]Mean effects are in the logarithmic scale and expressed as mean (95% CI). The negative sign indicates an inverse association between the factor and double cycling (dependent variable).

Statistically significant associations between the explanatory variable and the response are indicated as: ***$p < 0.001$; **$p<0.01$; *$p<0.05$.

Abbreviations: PCV=pressure control-continuous mandatory ventilation; VCV=volume control-continuous mandatory ventilation with constant flow; VCVDF=volume control-continuous mandatory ventilation with decelerated flow. Ti=inspiratory time; Ppeak=peak airway pressure; PEEP=positive end-expiratory pressure; RR=respiratory rate; VT=tidal volume

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Critical Care

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Effects of sedatives and opioids on trigger and cycling asynchronies throughout mechanical ventilation: an observational study in a large dataset from critically ill patients

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Abstract

Background: In critically ill patients, poor patient-ventilator interaction may worsen outcomes. Although sedatives are often administered to improve comfort and facilitate ventilation, they can be deleterious. Whether opioids improve asynchronies with fewer negative effects is unknown. We hypothesized that opioids alone would improve asynchronies and result in more wakeful patients than sedatives alone or sedatives-plus-opioids.

Methods: This prospective multicenter observational trial enrolled critically ill adults mechanically ventilated (MV) > 24 h. We compared asynchronies and sedation depth in patients receiving sedatives, opioids, or both. We recorded sedation level and doses of sedatives and opioids. BetterCare™ software continuously registered ineffective inspiratory efforts during expiration (IEE), double cycling (DC), and asynchrony index (AI) as well as MV modes. All variables were averaged per day. We used linear mixed-effects models to analyze the relationships between asynchronies, sedation level, and sedative and opioid doses.

Results: In 79 patients, 14,166,469 breaths were recorded during 579 days of MV. Overall asynchronies were not significantly different in days classified as sedatives-only, opioids-only, and sedatives-plus-opioids and were more prevalent in days classified as no-drugs than in those classified as sedatives-plus-opioids, irrespective of the ventilatory mode. Sedative doses were associated with sedation level and with reduced DC ($p < 0.0001$) in sedatives-only days. However, on days classified as sedatives-plus-opioids, higher sedative doses and deeper sedation had more IEE ($p < 0.0001$) and higher AI ($p = 0.0004$). Opioid dosing was inversely associated with overall asynchronies ($p < 0.001$) without worsening sedation levels into morbid ranges.

(Continued on next page)

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(Continued from previous page)
Conclusions: Sedatives, whether alone or combined with opioids, do not result in better patient-ventilator interaction than opioids alone, in any ventilatory mode. Higher opioid dose (alone or with sedatives) was associated with lower AI without depressing consciousness. Higher sedative doses administered alone were associated only with less DC.

Trial registration: ClinicalTrial.gov, NCT03451461

Keywords: Asynchronies, Mechanical ventilation, Sedatives, Opioids, Double cycling, Ineffective inspiratory efforts during expiration

Background

Patient-ventilator asynchronies are frequent during invasive mechanical ventilation (MV) [1, 2]. Poor patient-ventilator interaction could be associated with prolongation of MV, longer intensive care unit (ICU) and hospital stays [2], and increased mortality [1, 3]. Thus, optimizing patient-ventilator interaction may improve outcomes [4].

Many aspects of clinical management affect patient-ventilator interaction. Adjusting ventilator settings can decrease asynchronies and associated anxiety and dyspnea [5, 6]. Sedatives can cause ventilatory depression affecting respiratory drive and timing, worsening patient-ventilator interaction in proportion to decreasing level of consciousness [7, 8]; these effects appear to differ with different drugs [9, 10]. Sedation is associated with deleterious side effects. Deep sedation is associated with worse short- and long-term outcomes [11–14]. Forgoing or minimizing sedatives during MV is increasingly recommended [15–17].

The relationship between asynchronies, level of consciousness (sedation level), and sedatives and opioids is poorly understood. Increasing sedatives in ICU patients with double cycling (DC) not only failed to correct this asynchrony [6], but also prolonged MV and ICU and hospital stays. The rate of ineffective inspiratory efforts increases proportionately with the depth of sedation [8]. Different studies have reported disparate effects of sedative dosage on the overall rate of asynchronies. Whereas one study found that light sedation with propofol did not affect the rate of asynchronies but deep sedation with propofol increased it [10], another found that deep sedation reduced but did not eliminate asynchronies [18]. A recent study showed that deep sedation, benzodiazepines, and cumulative doses of benzodiazepines were associated with higher mortality [19]. In another trial, patients on dexmedetomidine had slightly fewer asynchronies than those on propofol [20]. However, these studies did not take opioid administration into account.

Opioids are commonly used in ICU patients. In a study comparing midazolam vs. fentanyl plus midazolam, patients receiving fentanyl had fewer asynchronies than those receiving only midazolam [21]. Thus, the effects of opioids alone or together with sedatives on asynchronies warrant investigation. Adequate opioid treatment with minimal doses of sedatives might enable more spontaneous breathing and improve patient-ventilator interaction; however, the relationships between opioids, level of consciousness, and asynchronies remain to be elucidated. We hypothesized that opioids alone would improve trigger and cycling asynchronies and result in more wakeful patients than sedatives alone or sedatives-plus-opioids.

Methods

Study population and design

We obtained data from an ongoing database started in 2011 in four centers in Spain. The database was constructed prospectively with funding for a project to develop a connectivity platform to interoperate signals from different ventilators and monitors and subsequently compute algorithms to diagnose patient-ventilator asynchronies (ClinicalTrial.gov, NCT03451461); each institution's review board approved the database.

This prospective observational study included adult patients admitted to four ICUs between October 2011 and January 2013. The institutional review boards approved the protocol, waiving informed consent because the study was non-interventional, posed no added risk to patients, and did not interfere with usual care.

Patients were prospectively included when the following criteria were met: admission to a bed equipped with BetterCare™ software and intubated for MV expected to last > 24 h. To avoid selection bias, members of the research team were not involved in assigning patients to a bed equipped with BetterCare™ software. Exclusion criteria were < 48 h of data, age < 18 years, pregnancy, do-not-resuscitate orders, admission for organ donation, and chest tubes with suspected bronchopleural fistula.

Patient management and data collection

Demographic and clinical data were obtained from medical records. Level of consciousness was assessed every 4 h with the Riker Sedation-Agitation Scale (SAS), and the mean value of these assessments was computed to

obtain a daily average. Illness severity was assessed daily with the Sequential Organ Failure Assessment (SOFA). ICU teams were aware of the recording system, but not of the study hypothesis. All patients were managed with similar processes of care and lung-protective ventilation strategies (tidal volume 6 mL/kg ideal body weight and plateau pressure under 30 cmH_2O) following the quality indicators of the Spanish Society of Intensive Care Medicine (https://semicyuc.org/wp-content/uploads/2018/10/quality_indicators_update_2011.pdf) throughout the study. Patients were ventilated with Evita 4 (Dräger, Lübeck, Germany), Puritan Bennet 840 (Covidien, Plymouth, MN, USA), or Servo I (Maquet, Fairfield, NJ, Sweden) ventilators, receiving volume assist/control, pressure assist control, or pressure support based on clinicians' assessment of clinical status. Ventilatory modes were analyzed as previously described [22]. The predominant mode for each day analyzed was classified as assist-control or pressure-support if the patient remained in that mode for ≥ 70% of the time. Other ventilator parameters were also adjusted at the discretion of the attending physician following national recommendations. Clinicians adjusted ventilator settings when asynchronies were observed at the bedside, but adjustments were not protocolized.

Total doses of opioids (morphine and fentanyl) and sedatives (midazolam, propofol, and lorazepam) administered each day were recorded and converted to morphine and midazolam equivalents [6]. We classified each day of MV for a given patient as (1) no-drugs, (2) sedatives-only, (3) opioids-only, or (4) sedatives-plus-opioids. To avoid misleading classifications due to residual treatment effects, days were classified according to all medications administered during the day; thus, a day in which a patient received sedatives-plus-opioids for > 2 h and opioids-only thereafter would be classified as "sedatives-plus-opioids." Days in which patients were treated with neuromuscular blockers were excluded from the analysis. Sedatives and analgesia were managed following each ICU's protocols based on the Spanish Society of Intensive Care Medicine recommendations [23], SAS level, and pain and discomfort assessments.

For the analyses, data was structured as averaged measures per day. Therefore, every treatment group could include a different number of patients depending on the day.

Analysis of asynchronies

Asynchronies were detected by BetterCare™ software (Barcelona, Spain), which continuously records airflow, airway pressure, and tidal volume from admission to extubation or death. BetterCare™ identifies the beginnings of inspiration and expiration to analyze and store data breath by breath. It analyzes each breath to detect four types of asynchronies (ineffective inspiratory efforts during expiration (IEE), DC, short cycling/aborted inspiration, and prolonged cycling [1, 2]) and computes the asynchrony index (AI) (Additional file 1) [24]. Periods in which recording was interrupted due to clinical interventions, out-of-ICU transfers, technical problems, or other issues were excluded from the analysis, which was done on the remaining valid periods.

All asynchronies were averaged per day. The rates of IEE, DC, and the overall AI were computed considering the total number of breaths (ventilator-delivered cycles plus IEE), enabling us to compare days, despite varying respiratory rates.

Statistical analysis

Patients' characteristics are summarized as medians (25th–75th percentiles) or percentages. Sample size calculation was considered unnecessary for this exploratory study.

To analyze the level of consciousness and illness severity by treatment groups, we used linear mixed-effects (LME) models with random intercepts for the patients. This approach takes inter- and intra-subject variability in longitudinal data into account; each patient differs from the overall mean response by an individual-specific constant that applies equally over time [25]. To analyze asynchronies by treatment groups, we used generalized LME (GLME) models assuming a negative binomial distribution for the response variable (number of asynchrony events) because the variable response was discrete, limited to non-negative values, and positively skewed with most observations having values near zero. Negative binomial distributions are often used in regression models with count data. Furthermore, to analyze the number of asynchrony events as a rate, we incorporated an exposure term (total number of respiratory cycles per day) that indicates the number of times a particular event occurred.

To assess the effects of level of consciousness and severity of illness on each type of asynchrony, we also used GLME models with random intercepts for the patients and allowing variation in SAS and SOFA slopes by treatment groups for the population mean.

To explore the effects of dosage on level of consciousness and asynchronies, we used a LME model and GLME models, respectively. This analysis included the opioids-only, sedatives-only, and sedatives-plus-opioids groups. These models used random intercepts only for the patients and allowed variations in slopes for dose equivalents by treatment groups for the population mean. Additionally, we investigated the effect of severity (SOFA) as a potential confounding variable that could influence both the asynchronies and the treatment group.

We used R 3.3.1 (R Core Team, Vienna, Austria, URL http://www.R-project.org) for all analyses, building the

mixed-effects models with the lme4 package [25] and summarizing the mean (95% CI) effects by treatment groups with the lsmeans package. When using LME models for the continuous response variables, we checked the normality assumptions for the estimated random effects and for the within-subject residuals by graphical methods (normal Q-Q plots). When the response variable was discrete, we assessed overdispersion by graphical comparison of the standardized residuals versus the fitted values. Significance was set at $p < 0.01$. Pairwise comparisons among treatment groups were two-sided and adjusted by the Bonferroni method to maintain the significance level.

Results

Table 1 reports on the demographic, clinical, and outcome data for the 79 patients. We analyzed 579 days on invasive MV, comprising 14,166,469 breaths.

Relationship between asynchronies and treatment group

Figure 1 shows the relationship between each asynchrony and treatment group. No statistically significant differences in AI, IEE, or DC were found between sedatives-only, opioids-only, and sedatives-plus-opioids days. The AI and rates of IEE and DC were higher for no-drugs days than for sedatives-plus-opioids days; AI was also higher for no-drugs than for opioids-only days.

Table 1 Patients' demographic and clinical characteristics

Total population ($n = 79$)	Median [25th, 75th percentiles]	Percentage
Age (years)	63 [52, 75]	
Sex (% men)		64.5%
Reason for admission *n*		
Acute respiratory failure		39 (49.4%)
- Sepsis		12 (15.2%)
- Pneumonia		7 (8.7%)
- ARDS		5 (6.3%)
- COPD		3 (3.8%)
- Congestive heart failure		2 (2.5%)
- Other		10 (12.7%)
Neurologic		15 (19%)
Cardiac arrest		10 (12.7%)
Postsurgical		8 (10.1%)
Multiple trauma		6 (7.6%)
Neuromuscular disease		1 (1.3%)
APACHE II	17 [10, 26]	
SOFA at admission	7 [5.25, 10.75]	
Length of mechanical ventilation (days)	6 [3, 10.5]	
ICU stay (days)	10 [6, 18]	
Hospital stay (days)	23 [11, 50]	
Mortality ICU		27.9%

ARDS acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disease, *APACHE* Acute Physiology and Chronic Health Evaluation, *SOFA* Sequential Organ Failure Assessment score, *ICU* intensive care unit

Relationships between treatment group, level of consciousness, and severity of illness

Mean daily SAS in sedatives-plus-opioids days [2.4 (95%CI 2.2–2.6)] was lower than in opioids-only [3.1 (95%CI 2.8–3.4); $p < 0.0001$], sedatives-only [2.9 (95%CI 2.6–3.2); $p = 0.002$], and no-drugs days [3.3 (95%CI 3.1–3.6); $p < 0.0001$]. Mean daily SAS in no-drugs days was higher than in sedatives-only days ($p = 0.006$) (Fig. 2). SOFA scores in sedatives-plus-opioids days were higher than in no-drugs ($p < 0.0001$), sedatives-only ($p = 0.004$), and opioids-only days ($p = 0.008$); SOFA scores were similar in the no-drugs, sedatives-only, and opioids-only groups (Fig. 2).

Table 2 summarizes the relationships of the level of consciousness and severity with asynchronies in the treatment groups. Higher level of consciousness was associated with higher DC rates ($p < 0.0001$) in sedatives-plus-opioids and sedatives-only days ($p < 0.0001$). However, the level of consciousness was not associated with AI or IEE regardless of exposure to opioids or sedatives. SOFA was not associated with AI or IEE, but was associated with a higher DC rate in no-drugs days ($p = 0.008$).

Relationship between asynchronies and drug doses

Figure 3 illustrates the relationship between each asynchrony and doses of sedatives (left) and opioids (right). In opioids-only days (red, right panel, Fig. 3), the opioid dose was inversely associated with AI ($p < 0.001$), IEE ($p = 0.0002$), and DC ($p < 0.0001$). In sedatives-plus-opioids days (blue, right panel, Fig. 3), opioid dose was also inversely associated with AI, IEE, and DC ($p < 0.0001$), whereas sedative dose was directly associated with AI ($p = 0.0004$) and IEE ($p < 0.0001$), but not with DC (in blue, left panel Fig. 3). However, in sedatives-only days (red trace, left panel Fig. 3), sedative doses were inversely associated only with DC ($p < 0.0001$). Additional file 2: Table S1 reports on the regression coefficients and performance of the model examining the relationship between medication dose and asynchronies.

When SOFA score was included as a potential confounding factor (Additional file 2: Table S2), the direction of the above statistically significant associations remained unchanged, except in the opioids-only for the DC model, where the association was no longer significant. In addition, the SOFA was not associated with any of the asynchrony variables.

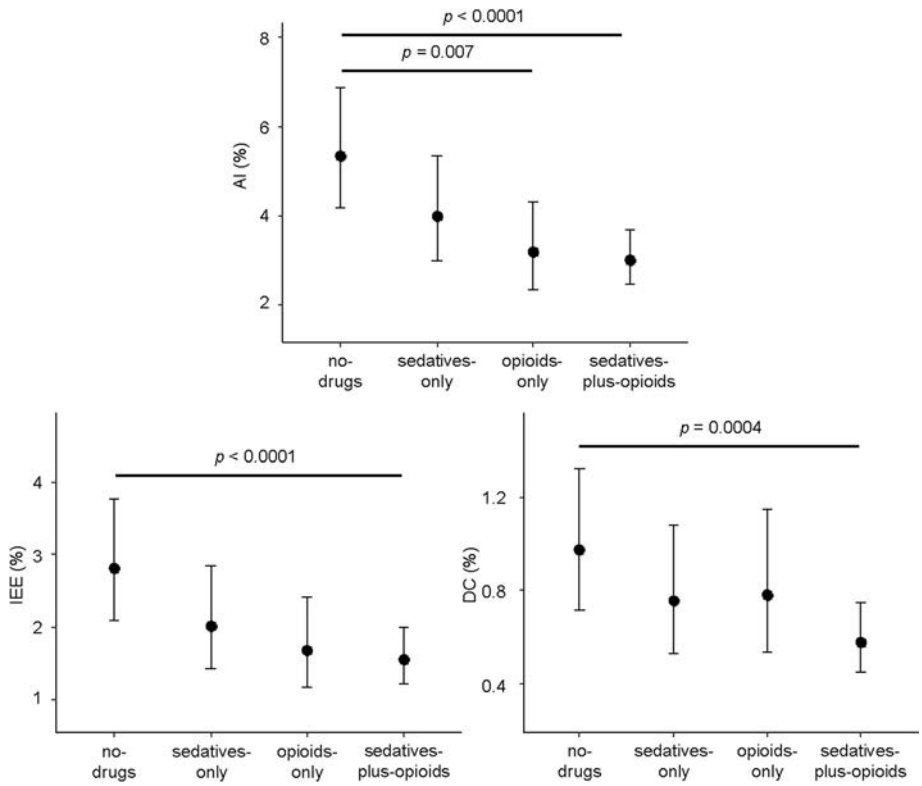

Fig. 1 Mean percentages of asynchronous breaths estimated with the generalized linear mixed-effects model by treatment groups. Data are represented as mean (95% CI). Statistical significance (two-sided) among groups is indicated; *p* values are adjusted by the Bonferroni method

Relationship between drug dose and level of consciousness

Additional file 3: Figure S2 shows the relationship between the level of consciousness and doses of sedatives (left panel) and of opioids (right panel). Higher sedative doses were associated with a lower level of consciousness, in both sedatives-only ($p < 0.0001$; red, left panel) and sedatives-plus-opioids days ($p = 0.004$; blue, left panel). Opioid doses were not associated with the level of consciousness.

Relationship between asynchronies, treatment group, and mechanical ventilation modes

We analyzed the effect of MV modes in the incidence of asynchronies in each treatment group. There were no statistically significant differences in the AI, IEE, or DC

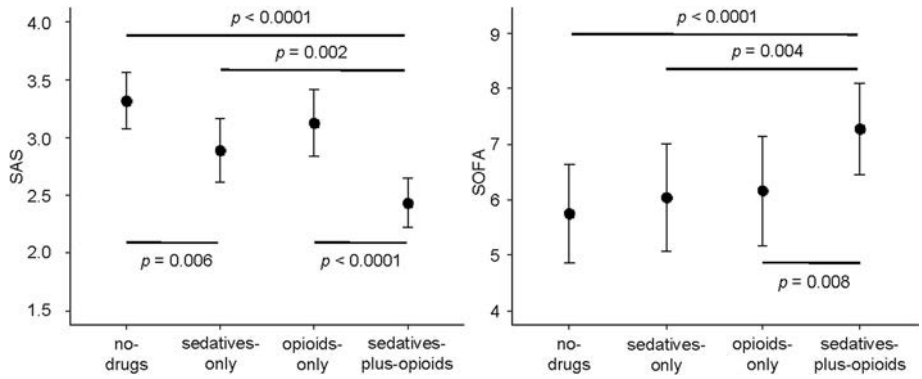

Fig. 2 Mean levels of SAS and SOFA estimated with the linear mixed-effects model by treatment groups. Data are represented as mean (95% CI). Statistical significance (two-sided) among groups is indicated; *p* values are adjusted by the Bonferroni method. The within-subject residuals of the SOFA model departure from the theoretical normal distribution (see Additional file 5: Figure S4 left)

Table 2 Mean estimated effect from the regression coefficient of SAS and SOFA on asynchronies, by treatment group

Treatment group	Asynchrony Index	Ineffective inspiratory efforts during expiration	Double cycling
SAS			
No drugs	− 0.10 (− 0.29, 0.10) $p = 0.34$	− 0.14 (− 0.36, 0.09) $p = 0.24$	− 0.02 (− 0.25, 0.21) $p = 0.87$
Sedatives	0.11 (− 0.09, 0.31) $p = 0.29$	− 0.04 (− 0.27, 0.20) $p = 0.76$	0.46 (0.23, 0.69) $p < 0.0001$
Opioids	− 0.17 (− 0.37, 0.04) $p = 0.12$	− 0.20 (− 0.44, 0.04) $p = 0.10$	0.08 (− 0.18, 0.33) $p = 0.55$
Sedatives + opioids	0.14 (0.03, 0.26) $p = 0.17$	0.12 (− 0.02, 0.26) $p = 0.09$	0.30 (0.17, 0.44) $p < 0.0001$
SOFA			
No drugs	0.02 (− 0.03, 0.07) $p = 0.38$	0.02 (− 0.04, 0.08) $p = 0.52$	0.08 (0.02, 0.13) $p = 0.008$
Sedatives	0.02 (− 0.05, 0.09) $p = 0.55$	0.06 (− 0.02, 0.14) $p = 0.17$	− 0.03 (− 0.12, 0.05) $p = 0.45$
Opioids	− 0.06 (− 0.13, 0.02) $p = 0.13$	− 0.05 (− 0.13, 0.03) $p = 0.25$	− 0.09 (− 0.17, − 0.01) $p = 0.03$
Sedatives + opioids	− 0.01 (− 0.05, 0.03) $p = 0.66$	− 0.00 (− 0.05, 0.05) $p = 0.98$	− 0.00 (− 0.05, 0.04) $p = 0.91$

Results are expressed as mean estimated effect and 95% CI. A negative sign indicates an inverse association. Statistically significant associations are indicated
SAS Sedation Assessment Scale, *SOFA* Sequential Organ Failure Assessment

between assist-control and pressure support modes in any treatment group ($p > 0.01$). In assist-control mode, the opioids-only and sedatives-plus-opioids groups had a lower AI than the no-drugs group ($p = 0.0065$ and $p = 0.0028$, respectively) (Fig. 4) (Additional file 4: Table S3).

Discussion

This is the first study to present data relating asynchronies and treatment with sedatives and opioids throughout the complete MV period. The overall rate of asynchronies did not differ between days classified as opioids-only, sedatives-only, and sedatives-plus-opioids. Patients receiving sedatives had a lower level of consciousness than those receiving opioids-only; sedatives-plus-opioids decreased the level of consciousness, but did not result in fewer asynchronies than the other treatments. Interestingly, in sedatives-plus-opioids days, the sedative dose was directly associated with the rate of asynchronies and with a lower level of consciousness, whereas higher opioid doses were associated with a lower AI without worsening level of consciousness. Thus, opioid administration seems a clinically sound approach to improve patient-ventilator synchrony while preserving consciousness.

Patients with shock or severe respiratory failure often require sedatives. Moreover, sedatives are sometimes administered in attempts to improve patient-ventilator interaction. However, deep sedation has been associated with worse outcomes [13]. Lighter or no-sedation is favored in partial ventilatory support modes, where patient-ventilator synchrony is crucial. Physiological studies show that sedatives have varying effects on asynchronies. Increasing sedatives/analgesia is relatively ineffective in abolishing severe breath-stacking [6]. Deep sedation with propofol increases asynchronies during pressure support ventilation, whereas light sedation does not [10]; deeper sedation is associated with increased ineffective triggering events [8] and with increased mortality [26]. Thus, sedative management in MV is a modifiable variable that could improve outcomes [26].

Associations between sedatives and asynchronies are probably confounded by many factors, especially by clinicians' ventilator adjustments. In our study, the incidence of asynchronies was associated with the drugs used (sedatives and opioids), irrespective of the ventilatory mode. However, sedatives lowered patients' level of consciousness without decreasing asynchronies beyond opioids alone. Inadequate pain control worsens patient-ventilator synchrony [21] and is associated with agitation, which negatively affects outcomes [27]. Richman et al. [21] found that patients receiving midazolam-plus-opioids had fewer asynchronies/day over a 3-day period than those receiving midazolam alone. Our results support these findings, showing that opioids could help improve asynchronies beyond sedatives, although prospective trials are necessary to determine whether appropriate opioids favor better synchrony by ensuring adequate analgesia without depressing consciousness and without affecting respiratory drive or minute ventilation [28–30].

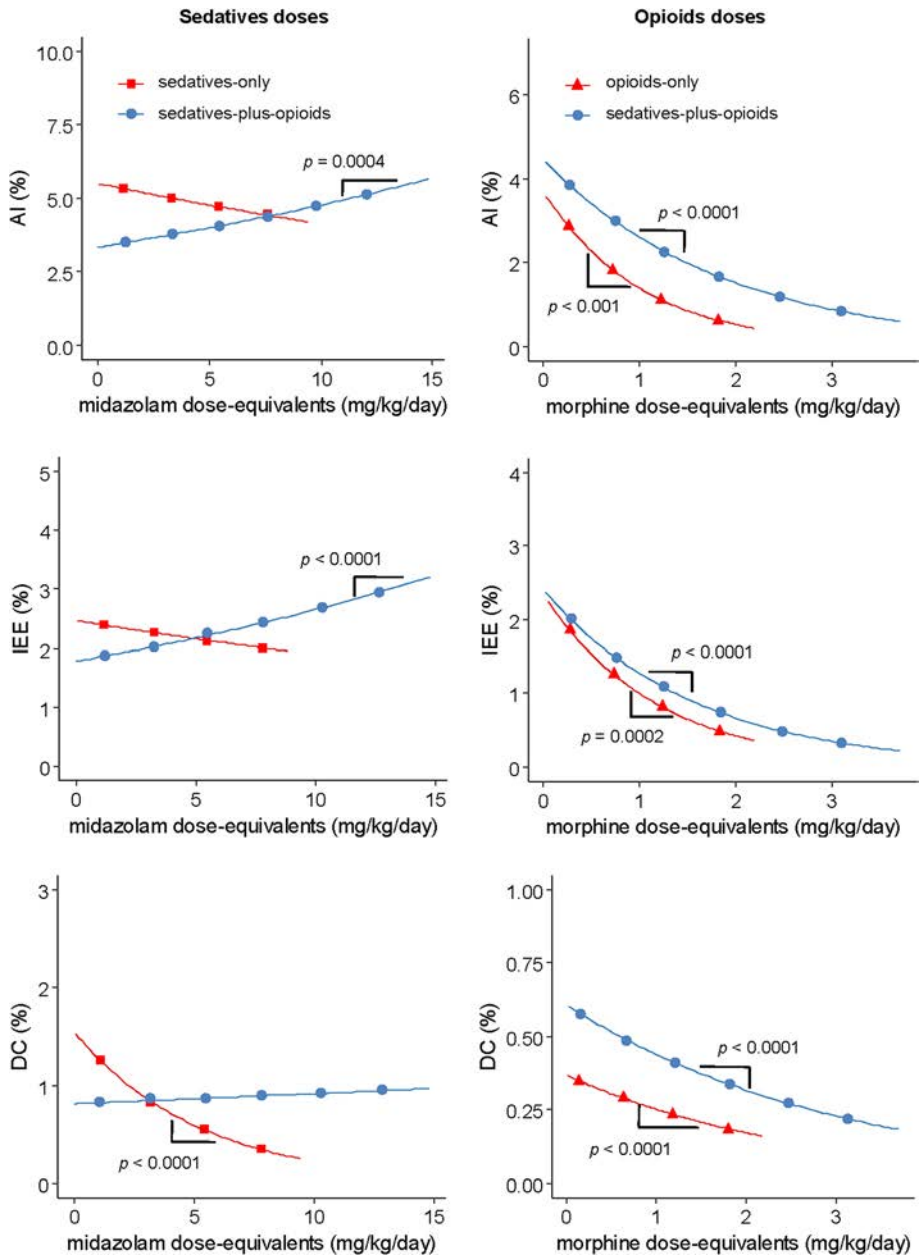

Fig. 3 Effect of the dose of sedatives and opioids administered on asynchronies. Average change in asynchronies per one unit change in dose equivalent

Increasing sedative doses prolongs MV and ICU and hospital stays [12, 14]. Paired with pain management protocols [17], sedation protocols including light sedation or daily interruptions of sedation [13, 15, 16] improve ICU patients' outcomes. Our results suggest that, compared with treatments including sedatives, treatment with opioids-only enables patients to be more awake without increasing asynchronies. Opioids-only treatment resulted in a higher level of consciousness than treatment with sedatives-plus-opioids. Our findings on the effects of sedatives and opioids throughout MV are in line with those of a randomized clinical trial where MV patients receiving morphine had more ventilator-free days and shorter ICU stays than those receiving sedatives-plus-morphine, without increases in accidental extubation or ventilator-associated pneumonia [16]. Moreover, we found that in assist-control modes, compared with no-drugs, treatment with sedatives-plus-opioids and opioids-only favored better patient-ventilation interaction (lower AI), suggesting that opioids might improve patient comfort. Thus, it might be beneficial to maintain opioid treatment until liberation from MV.

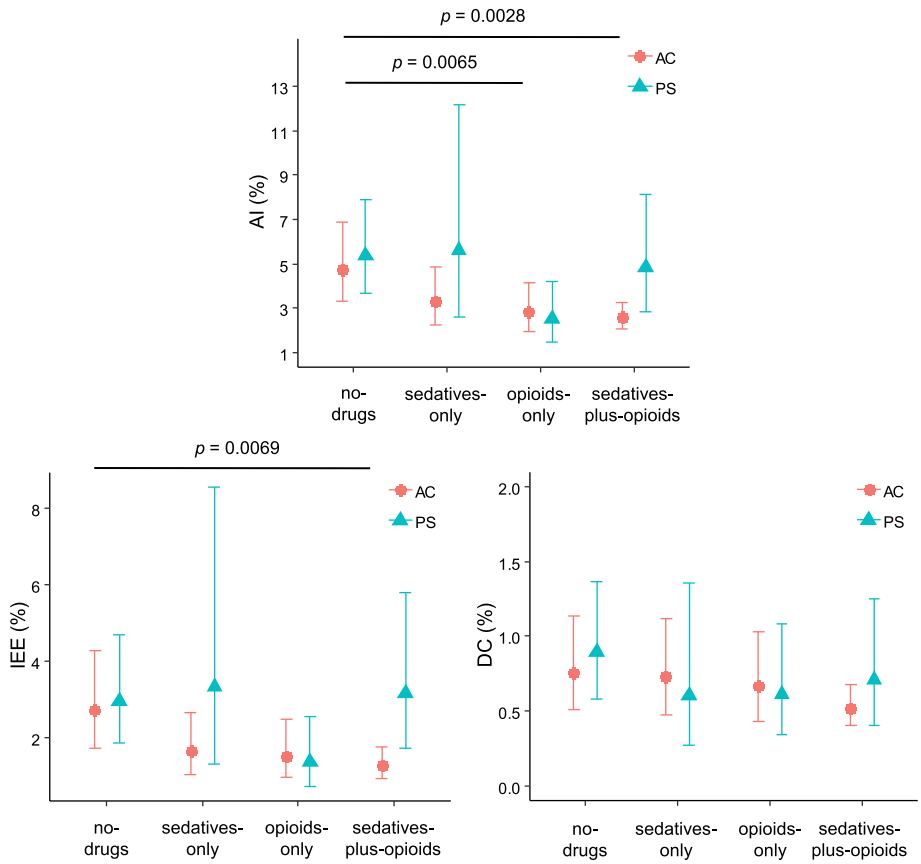

Fig. 4 Mean percentages of asynchronous breaths estimated with the generalized linear mixed-effects model according to mechanical ventilator mode, by treatment groups. Data are represented as mean (95% CI)

We also found significantly lower AI, IEE, and DC in sedatives-plus-opioids than in no-drugs days. However, asynchronies in MV patients who do not require sedatives or opioids probably are intrinsically different from those that occur in patients who require these treatments, and therefore, they probably require a different clinical approach. Rue et al. [31, 32] recently used a Bayesian joint model incorporating longitudinal ICU stay markers to evaluate outcome determinants. Finding that overall AI was not associated with severity of illness or vital status, they postulated that some asynchronies could be a marker of life. In our study, we considered the effect of severity of illness to better understand this possible confounding factor. We found no associations between severity and AI or IEE (Table 2), so patients with more asynchronies were not necessarily more severely ill. The lower severity and higher rates of asynchronies in no-drugs days compared with sedatives-only, opioids-only, and sedatives-plus-opioids days are likely due to differences in the origin and behavior of the asynchronies that occur in the different groups. Therefore, from a clinical perspective, it makes no sense to compare asynchronies and their management in no-drugs versus in treatment days [3, 33].

Finally, our analysis of the relationship between asynchronies and drug dosage found that, unlike sedatives, increasing doses of opioids were associated with decreasing rates of asynchronies, without significantly affecting the level of consciousness, independently of the level of severity. This finding highlights the importance of titrating opioids for comfort, and possibly asynchronies, in addition to pain control.

Unlike some physiological studies, we found that sedatives, alone or together with opioids, did not decrease asynchronies more than opioids-only. On the other hand, our findings of increased rates of asynchronies, especially IEE, with an increased daily dose of sedatives are in line with physiological studies [8, 10]. Whereas physiological studies analyze only short time periods, our study considered the entire period of MV, making it closer to clinical practice. One strength of our study is that it is based on prospectively accrued physiological data with enough breadth and depth to characterize a patient's condition throughout MV. Observational trials like this are increasingly being used because conclusions drawn from data collected in real-world situations can be more generalizable than the more restricted, if more

vigorous, conclusions of randomized clinical trials [34–36]. Our findings add to the growing body of evidence pointing to the inability of sedatives to prevent and/or correct asynchronies in daily practice and the association of opioids with improved asynchrony rates, thus supporting the strategy of managing pain while maintaining the lightest sedation possible [17, 37].

Our study has several limitations. First, patients were not randomized to each drug regimen. Furthermore, patients received opioids, sedatives, or no-drugs in any sequence or combination as deemed clinically necessary. Granular data for sedative or opioid doses over smaller time intervals were unavailable, thus precluding analyses of temporal associations between sedatives/opioids and asynchronies that might have enabled causal inferences and greater insight. Moreover, we did not consider factors that influenced clinicians to modify sedative or opioid dosing. Patients often receive more drugs early in MV and less when approaching weaning; however, to counterbalance this bias, we explored the relationship between severity and drugs and asynchronies, but found no relevant associations. Additionally, we did not analyze other painkillers such as acetaminophen and nonsteroidal anti-inflammatory drugs, which may influence patient-ventilator interaction differently, so our findings cannot be extrapolated to other non-opioid drugs. We used no objective measures of pain levels, precluding the analysis of associations between pain and asynchronies. Likewise, we did not measure surrogates of respiratory center activity, so we cannot evaluate associations between respiratory drive and different asynchronies. As individual patients could be considered in more than one group because management strategies evolved from day-to-day, our analysis of drug doses could not take into account the prolonged half-life and accumulation of some sedatives [38]. Nevertheless, we found a good relationship between SAS score and the sedative treatment group. We analyzed only IEE and DC because they are the most relevant asynchronies; we did not analyze flow asynchronies because they cannot be established from ventilator airway pressure and flow scalars alone. Thus, our findings cannot be extrapolated to these asynchronies. Additionally, because the measure unit was days rather than patients, it was difficult to analyze the effect of the underlying disease on the results. In an attempt to overcome this difficulty, we adjusted the results by including SOFA score as a marker of severity, but we found no effect of severity in the incidence of asynchronies per group. Finally, clinically detected asynchronies were treated according to each ICU's protocols; thus, differences between centers might have affected the results. We performed an analysis to evaluate the influence of each center and we did not find significant differences between centers.

Conclusions

Our findings suggest that sedatives, alone or together with opioids, do not decrease asynchronies beyond what can be achieved with opioids alone, independently of MV mode. Optimal titration of opioids might improve patient-ventilator interaction while avoiding the deleterious effects of sedatives.

Additional files

Additional file 1: Patient-ventilator asynchronies. (DOCX 278 kb)

Additional file 2: Asynchronies and medication dose and asynchronies and medication dose plus SOFA as a potential confounding variable. (DOCX 86 kb)

Additional file 3: Sedatives and opioids dose and level of consciousness. (DOCX 68 kb)

Additional file 4: Asynchronies and treatment group plus mechanical ventilation mode. (DOCX 78 kb)

Additional file 5: Checking assumptions of the (generalized) linear mixed-effects models. (DOCX 369 kb)

Abbreviations

AI: Asynchrony index; DC: Double cycling; ICU: Intensive care unit; IEE: Inspiratory efforts during expiration; MV: Mechanical ventilation; SAS: Riker Sedation-Agitation Scale; SOFA: Sequential Organ Failure Assessment

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Authors' contributions

Contributors CdH, RM, JM, JLA, SFG, and LB conceived and designed the study. GG, CdH, CS, GMA, AO, and SFG contributed to the recruitment of trial participants. CdH, GG, CS, EL, JM, and RM were responsible for the acquisition of data and their integrity. RM, MR, and JLA did the statistical analysis and prepared the figures and tables. All authors participated in the interpretation of the results. CdH, JLA, RM, and LB wrote the first draft of the manuscript, which was reviewed by all authors. UL, RMK, RF, YS, GM, GMA, and AO critically reviewed and revised the manuscript for important intellectual content. All authors approved the final version for publication.

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Availability of data and materials
The datasets used and analyzed during this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The institutional review boards of each participating ICU approved the protocol, waiving informed consent because the study was non-interventional, posed no added risk to patients, and did not interfere with usual care.

Consent for publication
Not applicable.

Competing interests
Drs. Blanch and Murias are inventors of the Corporació Sanitaria Parc Taulí owned US patent: "Method and system for managing related patient parameters provided by a monitoring device," US Patent No. *12/538,940*. Blanch, Montanya, Murias, and Lucangelo own stock options of BetterCare S.L., which is a research and development spinoff of Corporació Sanitària Parc Taulí (Spain). Kacmarek is a consultant for Medtronic and Orange Medical and has received research grants from Medtronic and VennerMedical. The other authors declare that they have no competing interests.

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Publisher's Note

6. RESULTADOS GLOBALES

Evaluación de las asincronías doble ciclado y *trigger* reverso

Para caracterizar las asincronías de DC y RT se ha analizado una muestra de 67 pacientes, que corresponden a un total de 9.251 horas de VM y 9.694.573 respiraciones. Las características demográficas se muestran en la tabla 2. La incidencia global de DC ha sido del 0,6% (59.265 respiraciones). Como se ha mencionado anteriormente, también se ha analizado la distribución en el tiempo de la asincronía DC y la presencia de *clusters*. El 59,7% de los pacientes han presentado algún episodio de *cluster* de DC, con una mediana de 6 *clusters* por paciente, una potencia de 41 DC por *cluster*, una duración mediana de 15,5 minutos y un área bajo la curva de 20,3. En la figura 4 se muestra un ejemplo representativo de cómo se presentan los *clusters* de DC.

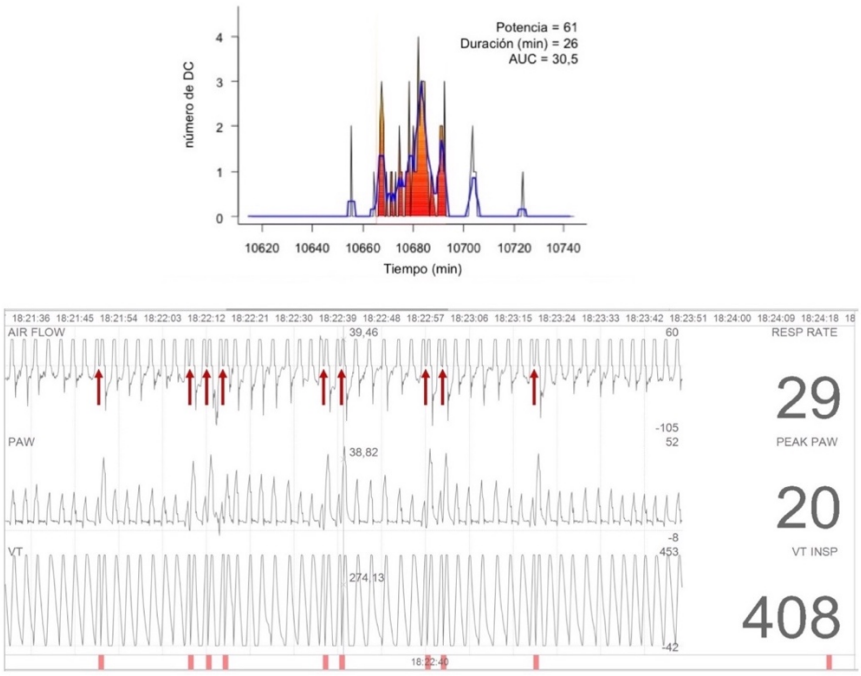
Tabla 2. Características demográficas de los pacientes y variables clínicas

Variables	n	%	Mediana (percentil 25-75)
Pacientes	67	-	-
Edad (años)	-	-	65 (55-77)
Sexo (hombres)	-	62,7	-
Motivo para ventilación mecánica			
Insuficiencia respiratoria aguda	51	76,12	-
• Paro cardiorrespiratorio	7	10,45	-
• Traumatismo	2	2,99	-
• Broncoaspiración	1	1,49	-
• Neumonía	6	8,96	-
• Sepsis/Shock Séptico	12	17,91	-
• Insuficiencia Cardíaca Congestiva	2	2,99	-
• SDRA	5	7,46	-
• Postquirúrgico	8	11,94	-
• Otros	8	11,94	-
Coma	11	16,42	-
• Ictus	4	6	-
• Intoxicación	1	1,19	-
• Traumatismo craneoencefálico	3	4,48	-
• Metabólico	3	4,48	-
EPOC	4	5,97	-

• Asma	1	1,49	-
• Exacerbación EPOC	3	4,48	-
Enfermedad neuromuscular	1	1,49	-
APACHE II	-	-	16 (10-23,5)
SOFA al ingreso	-	-	7 (5-10,75)
Duración de la ventilación mecánica (días)	-	-	6 (3-11,5)
Estancia UCI (días)	-	-	10 (6-18)
Estancia Hospital (días)	-	-	26,5 (15,5-68)
Mortalidad UCI	-	23,88	-

SDRA: Síndrome de Distrés Respiratorio Agudo; EPOC: Enfermedad Pulmonar Obstructiva Crónica; APACHE: *Acute Physiologic and Chronic Health Evaluation*; SOFA: *Sequential Organ Failure Assessment*

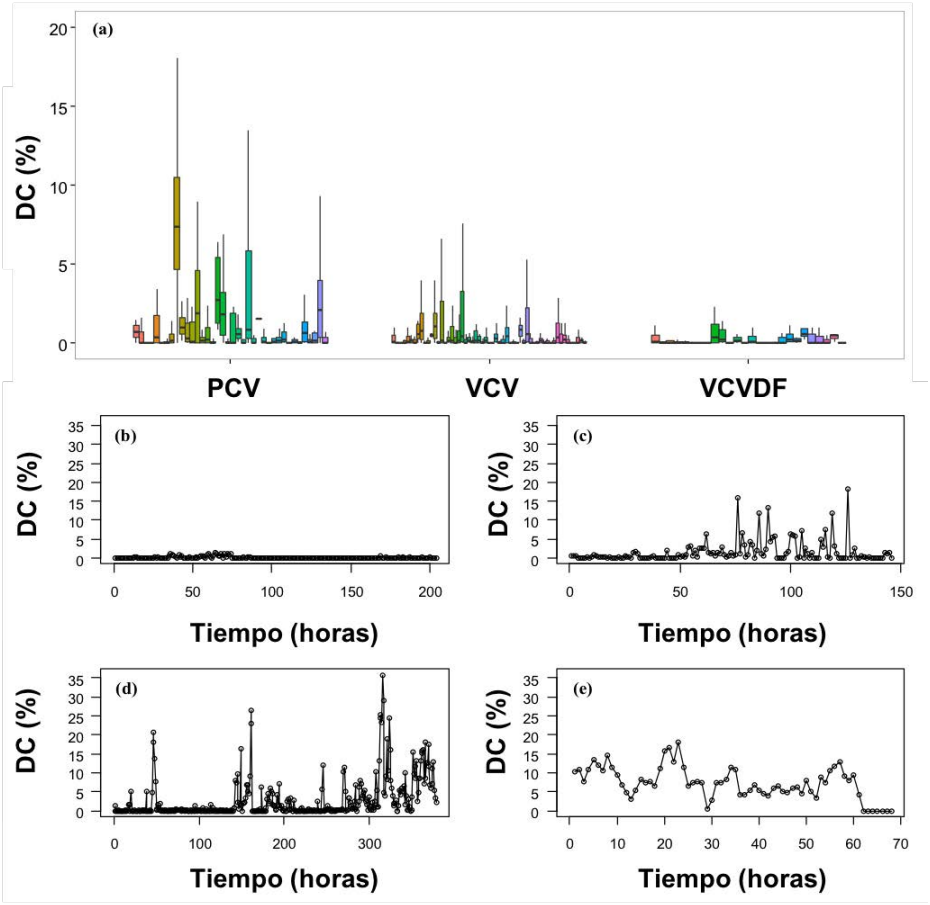
Figura 4. Distribución del DC en forma de *clusters*. En la parte superior, se muestra la imagen de un *cluster* de 26 minutos de duración. En la parte inferior, se muestran las curvas de flujo, presión y volumen obtenidas del respirador correspondientes a un episodio de *cluster* de DC.



La incidencia de DC varía ampliamente entre los diferentes pacientes y también según el modo de VM. Todos los pacientes presentan DC en algún momento del período completo de VM, pero su distribución en el tiempo difiere entre ellos. Algunos pacientes presentan pocos eventos de DC a lo largo de todo el período de VM, otros pacientes presentan más

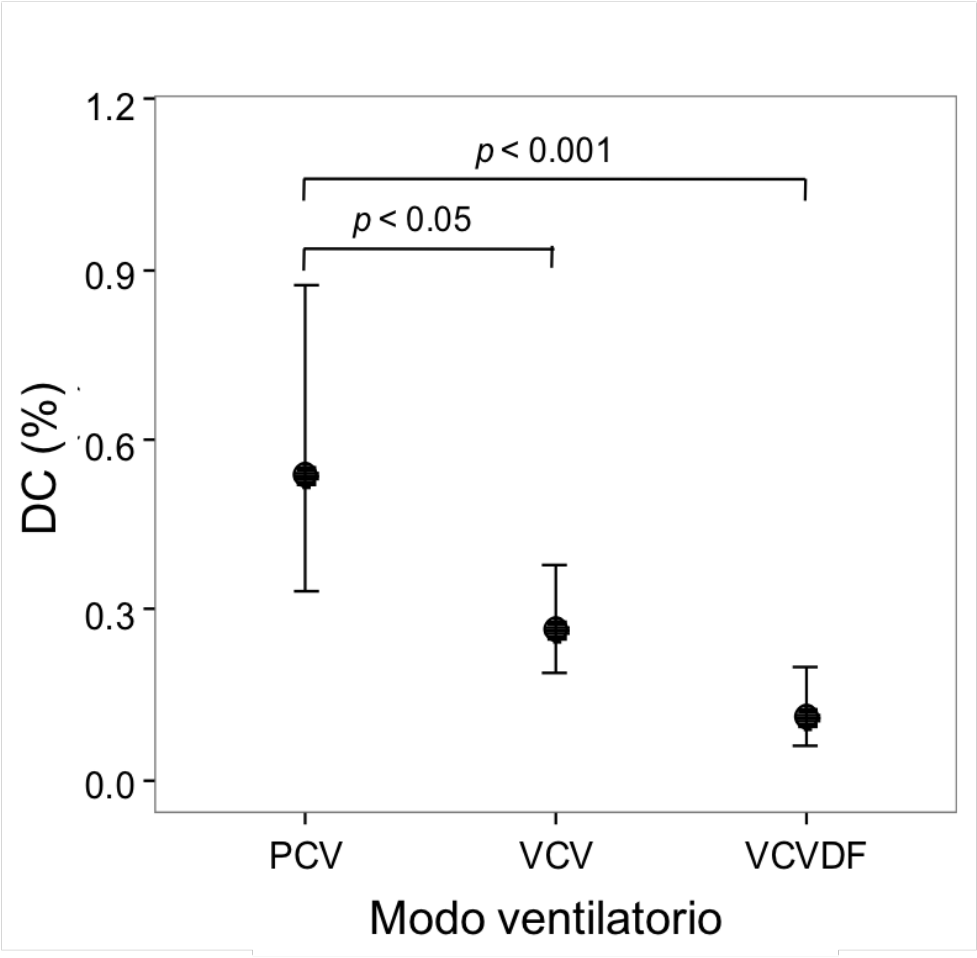
episodios de DC al inicio o final de la VM y otros pacientes presentan una elevada incidencia a lo largo de todo el período de VM. En la figura 5 se muestra una representación de la incidencia de DC a lo largo de todo el período de VM.

Figura 5. Incidencia de DC en el período de VM. En la parte superior (a) se muestra la variabilidad del DC inter e intrapacientes según el modo ventilatorio. Cada *boxplot* representa la variabilidad individual en cada modo y cabe tener en cuenta que un paciente puede ser ventilado en diferentes modos durante la estancia en UCI. En la parte inferior de la figura (b, c, d, e), se muestran cuatro patrones representativos de la distribución del DC durante el período de VM: (b) paciente que presenta un porcentaje bajo de DC a lo largo de todo el período de VM, (c)-(d) paciente que presenta algunos episodios de DC con duración y distribución en el tiempo variable, y (e) paciente que presenta un elevado porcentaje de DC que se mantiene durante todo el período de VM.



Al analizar la distribución del DC en los diferentes modos de VM, se ha observado una media de DC correspondiente al 0,54% en la modalidad PCV, que ha resultado ser significativamente mayor que el 0,27% de DC observado en VCV ($p<0,05$) y el 0,11% de DC en VCVDF ($p<0,001$). En la figura 6 se muestra la representación gráfica de la incidencia de DC en cada una de las modalidades ventilatorias analizadas.

Figura 6. Incidencia de DC en función de la modalidad ventilatoria. Los valores se expresan como medias (IC 95%). La significación estadística se indica en la figura.



Además, se ha analizado la incidencia de una nueva asincronía en la que el DC es secundario a la aparición de RT (DC-RT). Los resultados indicaron que la incidencia de DC-RT se sitúa en el 34,6%, siendo inferior a la observada en el DC secundario a *trigger* del paciente (DC-PT) que es del 65,4%.

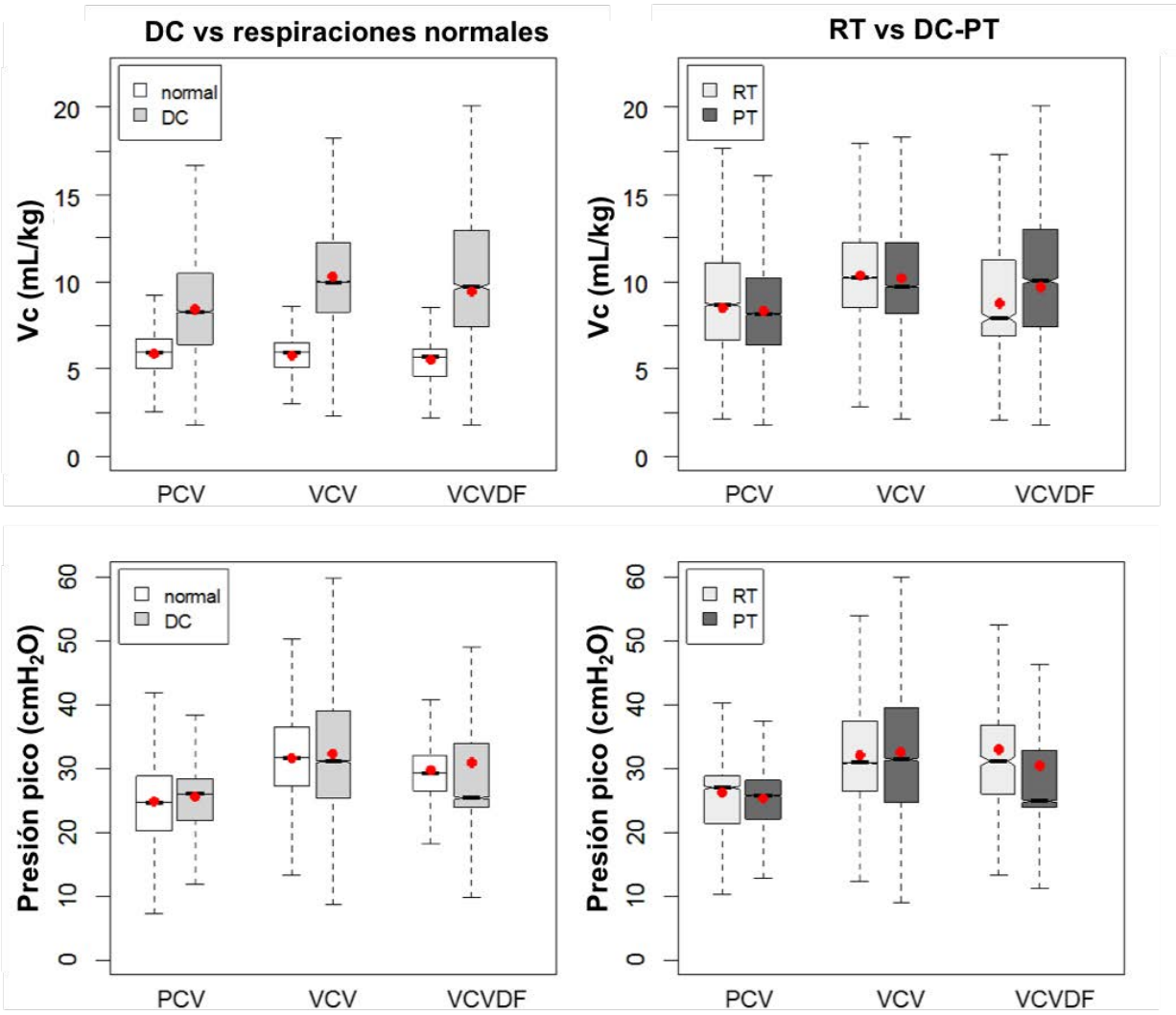
Implicaciones fisiológicas del DC

Para evaluar las posibles consecuencias del DC, en primer lugar se ha analizado su efecto sobre el volumen corriente en todas las modalidades ventilatorias estudiadas. Mientras que el volumen corriente en las respiraciones normales (sin DC) fue similar en las 3 modalidades ventilatorias analizadas, al analizar las respiraciones con DC de forma global (sin distinguir entre DC-PT y el DC-RT), se observó que el volumen corriente en los modos VCV y VCVDF era superior al administrado en PCV. Al analizar de forma separada el DC-PT, se observó que el volumen corriente era menor en PCV que en los modos controlados por volumen (VCV y VCVDF). Por el contrario, en el DC-RT el volumen corriente fue superior en VCV que en VCVDF y PCV.

También se evaluó el efecto del DC sobre la presión máxima (presión pico). En las respiraciones sin DC, la presión máxima fue discretamente inferior en PCV que en VCV y VCVDF. En las respiraciones con DC-PT, la presión pico era superior en VCV que en PCV y VCVDF. Sin embargo, en los DC-RT la presión pico en todos los modos controlados por volumen fue más alta que en PCV. También se analizó si existían diferencias en los valores de presión máxima entre los dos ciclos que componen un DC. En general, las presiones pico alcanzan valores más altos en la segunda respiración que en la primera, siendo esta diferencia más importante en VCV en las respiraciones DC-PT (84,7% vs 15,1%) y más balanceada en VCVDF (56% vs 15,1%).

En la figura 7 se representan las diferencias de volumen corriente y presión pico en cada modalidad ventilatoria comparando por un lado el DC global con respiraciones normales (izquierda) y por otro lado el DC-PT con DC-RT (derecha).

Figura 7. Volumen corriente y presión máxima en las diferentes modalidades ventilatorias. En la izquierda se representan las respiraciones normales (blanco) y las respiraciones correspondientes a DC (gris). En la columna de la derecha se representan las respiraciones DC y se compara DC-RT (gris claro) con DC-PT (gris oscuro). Los puntos rojos representan las medias y los *boxplots* indican las medianas y los percentiles 25-75.



Factores relacionados con la presencia de DC

Para evaluar cuáles son los factores que pueden estar relacionados con el desarrollo de DC, se han analizado 7.580 horas de VM, que corresponden a un 86,8% del tiempo global de ventilación. La frecuencia respiratoria se ha asociado de forma positiva con la presencia de DC mientras que el tiempo inspiratorio del respirador se asocia negativamente con el DC en todos los modos ventilatorios. El pico de flujo también presentó una asociación negativa con la presencia de DC en los modos PCV y VCV, igual que la PEEP en PCV y VCVDF. Por el contrario, la PEEP se asoció de forma positiva con el DC en el modo VCV. Por otro lado, la presión pico se asoció positivamente con el DC en PCV y de forma negativa en VCV, igual que el volumen corriente, que además también se asoció de forma positiva con DC en VCVDF. En la figura 8 se muestra la descripción de cada variable en función de la modalidad ventilatoria, y en la tabla 3 la asociación independiente de cada una de ellas con la presencia de DC.

Figura 8. Descripción de las diferentes covariables incluidas en el modelo para el estudio de factores relacionados con la presencia de DC. Los puntos rojos representan las medias y los *boxplots* indican las medianas y percentiles 25-75.

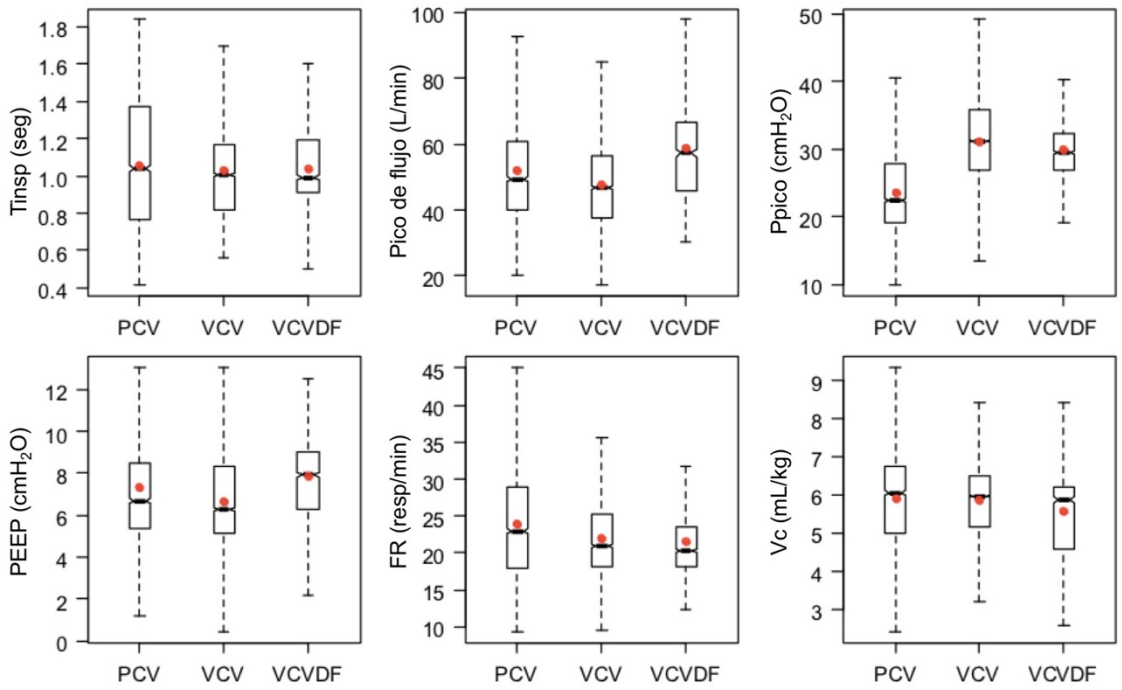


Tabla 3. Análisis multivariado para evaluar los efectos de las variables evaluados por sospecha clínica de impacto sobre el desarrollo de DC.

	Modos Ventilatorios		
Factores	**PCV**	**VCV**	**VCVDF**
Ti	-2,32(-2,94 – -1,69)**	-0,58(-1,11 – -0,05)*	-2,71(-4,29 – -1,13)**
Pico flujo	-0,10(-0,11– -0,08)**	-0,01(-0,03 – -0,00)*	-0,01(-0,04–0,03)
Presión pico	0,08(0,06–0,10)**	-0,06(-0,08 – -0,05)**	-0,01(-0,05–0,03)
PEEP	-0,05(-0,10 – -0,00)*	0,03(-0,01–0,07)	-0,25(-0,34 – -0,16)**
FR	0,08(0,04–0,11)**	0,03(0,02–0,05)**	0,07(0,01–0,12)*
Vc	0,01(0,01–0,01)**	-0,00(-0,01 – -0,00)**	0,01(0,01–0,02)**

*p < 0,05; **p < 0,001

Los efectos medios están en escala logarítmica y se expresan como media (95% IC). El signo negativo indica una asociación inversa entre el factor y el DC (variable dependiente).

Relación entre el desarrollo de asincronías y el uso de opioides y/o sedantes

Para explorar si existe una relación entre la aparición de asincronías y el uso de sedantes y/o opioides, se han analizado un total de 579 días de VM y 14.166.469 de respiraciones, que corresponden a 79 pacientes. Las características demográficas se muestran en la tabla 4. Los días se etiquetaron en cuatro categorías según los fármacos utilizados: solo sedantes, solo opioides, sedantes+opioides, o ninguno de ambos.

Tras el análisis no se observaron diferencias significativas en el AI, DC y IEE entre los días de tratamiento de solo-sedantes, solo-opioides y sedantes+opioides. Sin embargo, en los días en los que los pacientes no recibían ni sedantes ni opioides, las tasas de AI, DC y IEE fueron más altas respecto a las observadas en los días en los que se combinaba el uso de sedantes

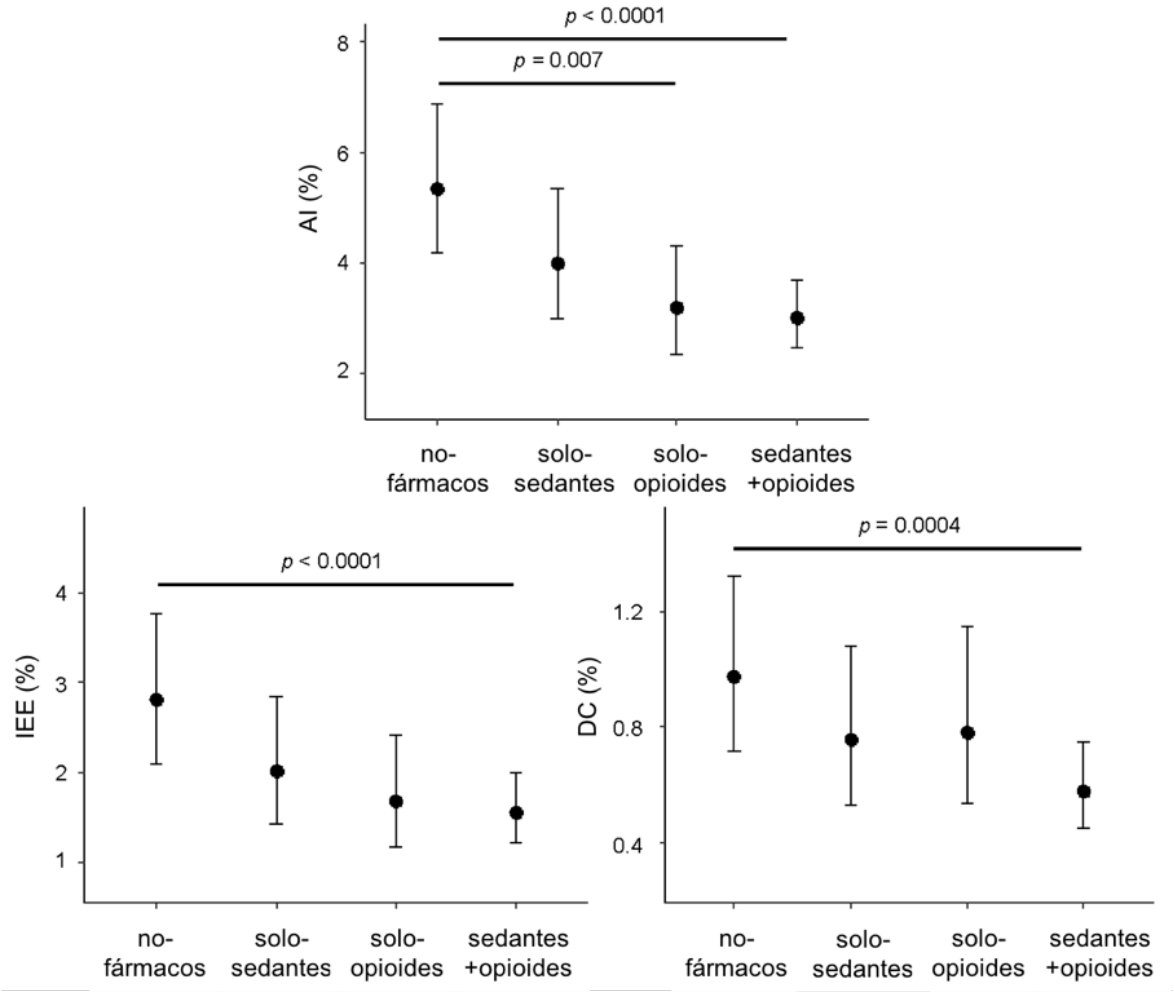
con opioides. El AI también fue significativamente superior en los días libres de fármacos respecto al conjunto de días en los que solo se administraron opioides. En la figura 9 se representa la incidencia de asincronías en función de cada tipo de tratamiento.

Tabla 4. Características demográficas y variables clínicas

Variables	n	%	Mediana (percentil 25-75)
Pacientes	79	-	-
Edad (años)	-	-	63 (52-75)
Sexo (hombres)	-	64,5	-
Motivo para ventilación mecánica			
Insuficiencia respiratoria aguda	39	49,4	-
• Neumonía	7	8,7	-
• Sepsis	12	15,2	-
• Insuficiencia Cardíaca Congestiva	2	2,5	-
• SDRA	5	6,3	-
• Otros	10	12,7	-
Neurológico	15	19	-
Paro Cardiorrespiratorio	10	12,7	-
Postquirúrgico	8	10,1	-
Politraumatismo	6	7,6	-
Enfermedad neuromuscular	1	1,3	-
APACHE II	-	-	17 (10-26)
SOFA al ingreso	-	-	7 (5,25-10,75)
Duración de la ventilación mecánica (días)	-	-	6 (3-10,5)
Estancia UCI (días)	-	-	10 (6-18)
Estancia Hospital (días)	-	-	23 (11-50)
Mortalidad UCI	-	27,9	-

SDRA: Síndrome de Distrés Respiratorio Agudo; EPOC: Enfermedad Pulmonar Obstructiva Crónica; APACHE: *Acute Physiologic and Chronic Health Evaluation*; SOFA: *Sequential Organ Failure Assessment*

Figura 9. Porcentajes medios de asincronías en función de los grupos de tratamiento con opioides y/o sedantes. Los datos se presentan como medias (95% IC). La significación estadística se muestra en la figura. Los valores p se han ajustado según el método de Bonferroni.



Relación entre grupo de tratamiento y el nivel de conciencia y la gravedad

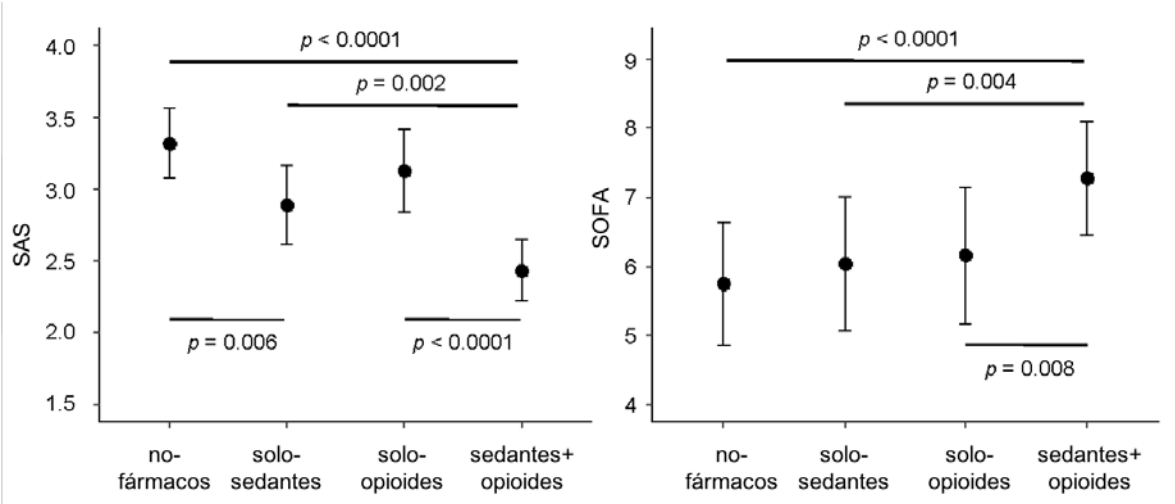
Se ha analizado la relación entre cada uno de los cuatro grupos de tratamiento y el nivel de conciencia (evaluado mediante la escala SAS) así como en relación a la gravedad de la enfermedad (evaluada con el *score* de SOFA).

El SAS medio diario en los días en los que los pacientes recibieron la combinación sedantes+opioides fue inferior [2,4 (IC95% 2,2-2,6)] que en los días en los que solo se

administraron opioides [3,1 (IC 95% 2,8-3,4);p<0,0001], o solo-sedantes [2,9 (IC95% 2,6-3,2);p=0,002], y también en aquellos días libres de fármacos [3,3 (IC95% 3,1-3,6;p<0,0001]. El valor medio del SAS en los días sin tratamiento fue superior al observado en los días en los que solo se administraron sedantes (p = 0,006).

Los pacientes tratados con una combinación de sedantes+opioides presentaban más gravedad que los pacientes que no recibían tratamiento (p<0,0001), que los que recibían solo sedantes (p = 0,004) y que los que solo recibían opioides (p = 0,008). No se encontraron diferencias significativas en el SOFA entre los días que se etiquetaron como no-fármacos, solo-sedantes y solo-opioides. En la figura 10 se muestran los valores de SAS y SOFA en cada grupo de tratamiento.

Figura 10. Niveles medios de SAS (nivel de conciencia) y SOFA (gravedad) según el grupo de tratamiento. Los datos se representan como media (IC 95%). La significación estadística se muestra en la figura. Los valores p se han ajustado según el método de Bonferroni.



Para determinar qué variable tiene mayor influencia, de forma independiente, sobre el desarrollo de asincronías se evaluaron de forma conjunta en un mismo modelo el nivel de conciencia, el grupo de tratamiento farmacológico y el tipo de asincronía. Como resultado del análisis, se observó que en aquellos pacientes que presentaban un mayor nivel de conciencia, es decir que estaban más despiertos, la incidencia de DC era más alta si recibían como tratamiento sedantes+opioides o solo-sedantes (p<0,0001). Sin embargo, no se

encontró asociación entre el nivel de conciencia y AI ni el IEE, independientemente de la exposición a sedantes u opioides.

Por otro lado, no se encontró asociación entre la gravedad y el AI o IEE, pero sí con una tasa superior de DC en los días en los que los pacientes no recibían tratamiento (p = 0,008). En la tabla 5 se muestra el efecto de cada variable en relación a la incidencia de asincronías tras evaluarlas en el modelo conjunto.

Tabla 5. Efecto medio estimado del coeficiente de regresión del SAS y SOFA en las asincronías por grupo de tratamiento.

Grupo Tratamiento	**Índice de Asincronías**	**Esfuerzos inefectivos durante la espiración**	**Doble ciclado**
		SAS	
No-fármacos	-0,10 (-0,29–0,10)	-0,14 (-0,36–0,09)	-0,02 (-0,25–0,21)
	p = 0,34	p = 0,24	p = 0,87
Sedantes	0,11 (-0,09–0,31)	-0,04 (-0,27–0,20)	0,46 (0,23–0,69)
	p = 0,29	p = 0,76	p < 0,0001
Opioides	-0,17 (-0,37–0,04)	-0,20 (-0,44–0,04)	0,08 (-0,18–0,33)
	p = 0,12	p = 0,10	p = 0,55
Sedantes+Opioides	0,14 (0,03–0,26)	0,12 (-0,02–0,26)	0,30 (0,17–0,44)
	p = 0,17	p = 0,09	p < 0,0001
		SOFA	
No-fármacos	0,02 (-0,03–0,07)	0,02 (-0,04–0,08)	0,08 (0,02–0,13)
	p = 0,38	p = 0,52	p = 0,008
Sedantes	0,02 (-0,05–0,09)	0,06 (-0,02–0,14)	-0,03 (-0,12–0,05)
	p = 0,55	p = 0,17	p = 0,45
Opioides	-0,06 (-0,13–0,02)	-0,05 (-0,13–0,03)	-0,09 (-0,17–-0,01)
	p = 0,13	p = 0,25	p = 0,03
Sedantes+Opioides	-0,01 (-0,05–0,03)	-0,00 (-0,05–0,05)	-0,00 (-0,05–0,04)
	p = 0,66	p = 0,98	p = 0,91

Resultados expresados como efecto estimado media y IC95%
Un signo negativo indica una asociación inversa.
Las asociaciones estadísticamente significativas están indicadas.

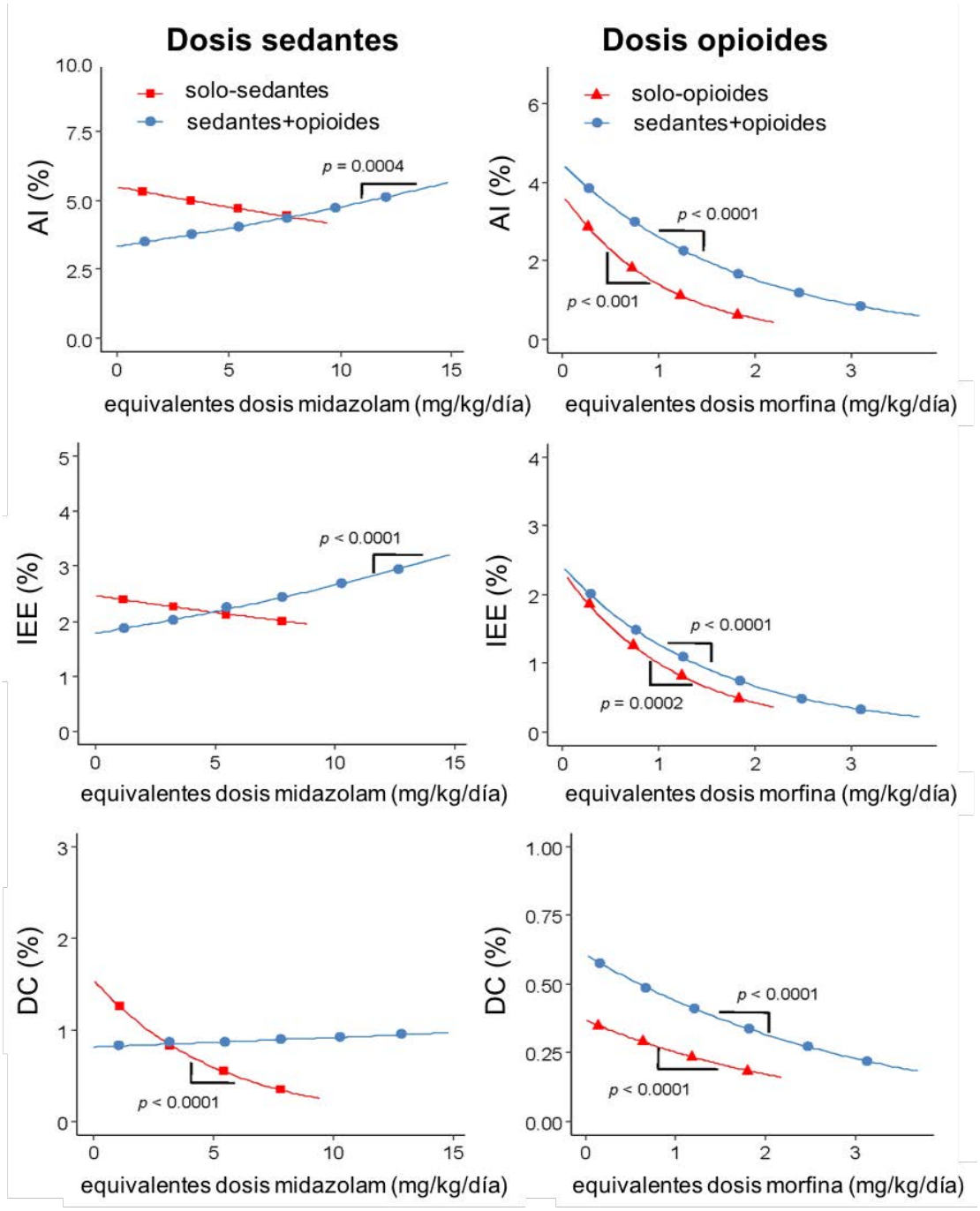
Relación entre las asincronías y las dosis de fármacos

Más allá del análisis del papel de los fármacos (sedantes y opioides) a nivel cualitativo, también se analizó el efecto de las dosis de fármacos administrados sobre la incidencia de asincronías. Para ello, como se ha mencionado anteriormente, se realizó una conversión de las dosis totales a equivalentes de midazolam (sedantes) o equivalentes de morfina (opioides).

En los días en los que solamente se administraron opioides, la dosis de opioides se asoció de forma inversa con el AI ($p<0,001$), IEE ($p = 0,0002$) y DC ($p<0,0001$). En los días en los que se combinaron sedantes+opioides, la dosis de opioides también se ha asoció inversamente con el AI, IEE y DC ($p<0,0001$), mientras que la dosis de sedantes se asoció de forma directa con una mayor tasa de AI ($p = 0,0004$) e IEE ($p<0,0001$), aunque no con el DC. Sin embargo, en los días en los que solo se administraron sedantes, las dosis de sedantes se asociaron de forma inversa con la presencia de DC ($p<0,0001$). En la figura 11 se muestra la relación entre las dosis de cada fármaco y el efecto sobre las asincronías.

También se avaluó si el SOFA podría ser un factor de confusión. Pero al incluir el SOFA en el modelo, las asociaciones observadas no variaron, con una única excepción de la pérdida de significación estadística en la relación entre la tasa de DC en los días en los que solo se administraron opioides. Estos resultados apuntan a que el nivel de gravedad no afecta a la asociación entre las dosis de sedantes y/o opioides y la incidencia de asincronías.

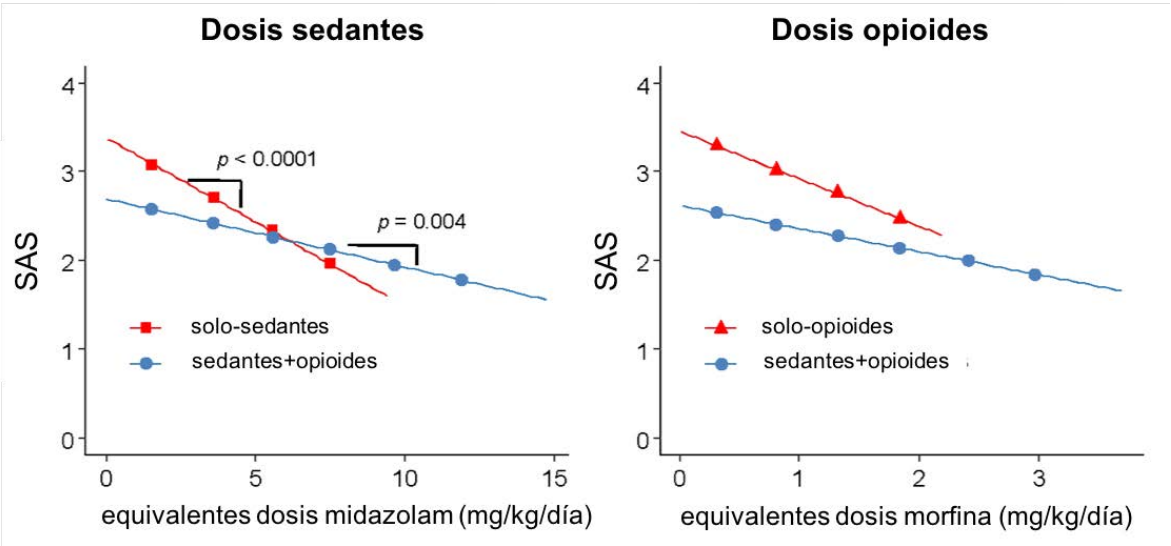
Figura 11. Efecto de la dosis de sedantes y opioides administrados en el desarrollo de asincronías.



Relación entre las dosis de fármacos y el nivel de conciencia

Se evaluó el efecto de las dosis de los diferentes fármacos administrados sobre el nivel de conciencia constatando que cuando se administraban dosis elevadas de sedantes el nivel de conciencia disminuía de forma significativa tanto si se usaban solos ($p<0,0001$) como en combinación con opioides ($p = 0,004$). Sin embargo, las dosis de opioides no mostraron ningún efecto sobre el nivel de conciencia. En la figura 12 se muestra la representación de las dosis de fármacos sobre el nivel de conciencia.

Figura 12. Efecto de las dosis de sedantes y opioides sobre el nivel de conciencia

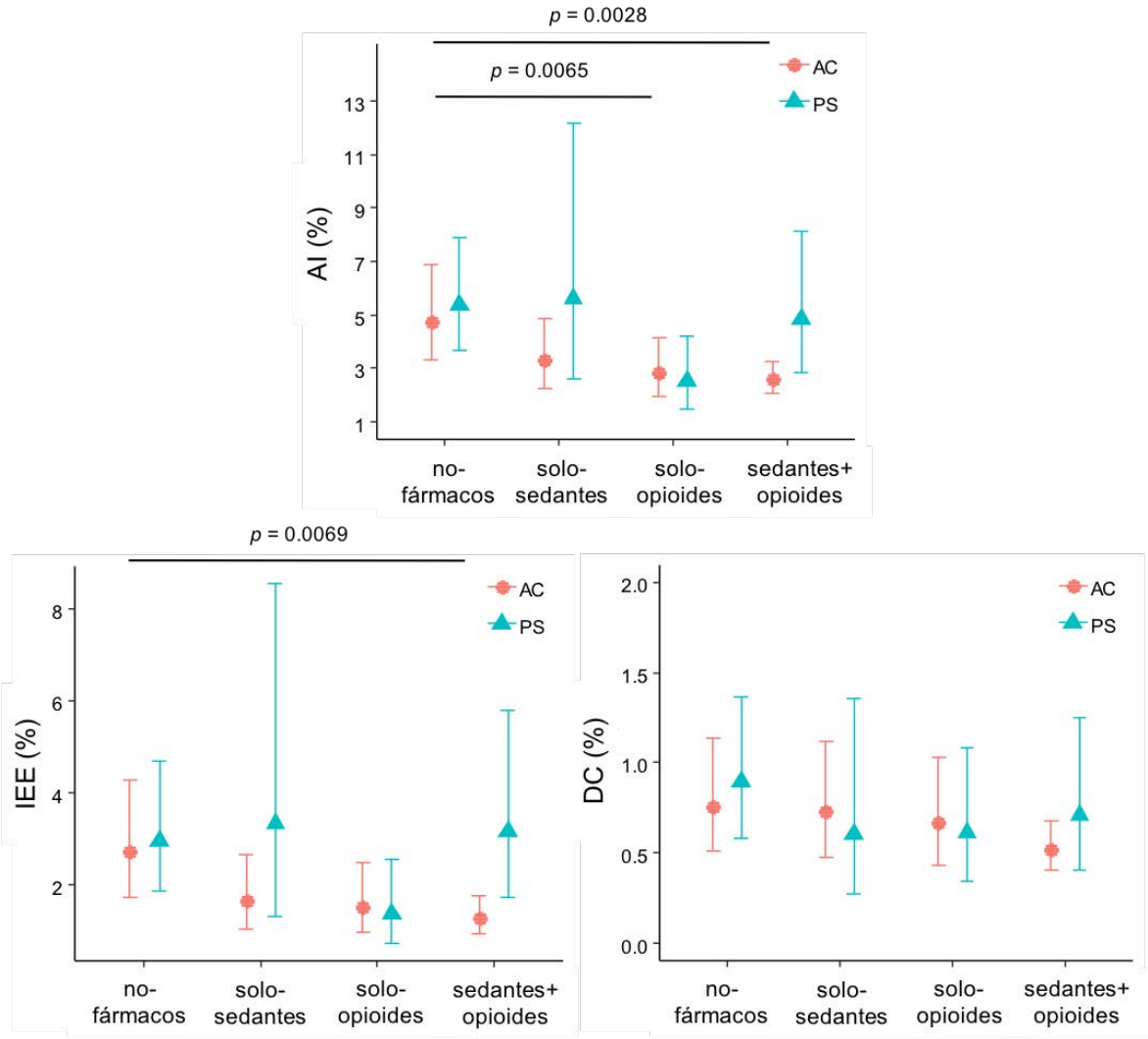


Influencia del modo ventilatorio en la relación entre las asincronías y uso de sedantes u opioides

Para evaluar si el efecto del tratamiento sobre la incidencia de asincronías depende de la modalidad ventilatoria, se realizó un análisis secundario. Las modalidades respiratorias se dividieron en dos grupos: asistidas-controladas o espontáneas. No se encontraron diferencias en el AI, IEE o DC entre los modos asistidos-controlados y presión soporte en ninguno de los grupos de tratamiento ($p>0,01$). En los modos asistidos-controlados, los días en los que se administraron solo-opioides o sedantes+opioides presentaron un AI menor que los días en los que no se administraron fármacos ($p = 0,0065$ y $p = 0,0028$, respectivamente). En la

figura 13 se muestran las incidencias de los distintos tipos de asincronías en función de cada grupo de tratamiento y modalidad respiratoria.

Figura 13. Porcentajes medios de asincronías en relación a la modalidad de VM y en función del grupo de tratamiento. Los datos se presentan como media (IC 95%). La significación estadística se muestra en la figura.



7. DISCUSIÓN GLOBAL

Este trabajo de tesis presenta los resultados de dos estudios realizados en pacientes críticos que fueron monitorizados durante todo el proceso de VM durante su ingreso en UCI. El análisis realizado ha permitido caracterizar la incidencia de asincronías, sus implicaciones fisiológicas y los factores relacionados con su desarrollo, incluyendo el papel de los sedantes y opioides junto con otros parámetros. Ambos estudios aportan datos relevantes relativos a la evaluación de las asincronías durante todo el período de VM, lo que representa una gran novedad respecto a los estudios publicados anteriormente.

Caracterización del DC y RT

El objetivo principal de la presente tesis fue la caracterización de las asincronías DC y RT a lo largo de todo el tiempo de VM. Hasta el momento, la incidencia real de DC y RT era desconocida ya que en la literatura los estudios se limitaban al análisis de cortos períodos de tiempo de observación que no permitían cuantificarlas en su conjunto. Además, la monitorización continua de la VM ha permitido aportar información acerca del patrón de distribución de las asincronías a lo largo del tiempo y de cuáles son los mecanismos subyacentes, factores precipitantes o posibles consecuencias fisiológicas del desarrollo de las mismas.

En la muestra de pacientes analizada en esta tesis doctoral, la incidencia de la asincronía DC es del 0,6% del total de ciclos respiratorios, aunque está presente en todos los pacientes, en todas las modalidades y a lo largo de todo el período de VM. Además, la aparición del DC responde a un patrón de distribución en forma de *clusters* a lo largo de todo el período de VM, que puede variar ampliamente entre los pacientes. Todos estos datos refuerzan la necesidad de implementación de sistemas de monitorización continua de las asincronías, y justifican la oportunidad de realizar su análisis en tiempo real, para garantizar que los eventos no pasen desapercibidos para el equipo asistencial.

A pesar de que la baja incidencia de DC podría considerarse un evento menor si solo nos limitáramos a evaluar el porcentaje total de eventos correspondientes a DC, al evaluar su distribución en el tiempo se ha puesto de relevancia que su patrón de presentación responde a la agrupación en forma de *clusters* de DC, que por el contrario sí son frecuentes. Otros

autores han demostrado en estudios recientes que los *clusters* de IE son también frecuentes en los pacientes ventilados y que se relacionan con una prolongación de los días de VM y con tasas de mortalidad más altas (15). También se observa una gran variabilidad en el patrón de presentación de las asincronías a lo largo del período de VM, que justifica la necesidad de evaluarlas de manera continua más allá de centrar el análisis en períodos cortos de observación o presentarlas como un índice global. La aparición de *clusters* de asincronías de poca duración pero de elevada potencia pueden incrementar la potencia mecánica que se transfiere del respirador a los pulmones (73) y derivar en consecuencias adversas para los pacientes.

Durante todo el período de VM es de gran importancia distinguir entre el DC-PT, debidos a *trigger* generado por el paciente, del DC-RT. El análisis de todo el período de VM nos ha permitido cuantificar, por primera vez en la literatura, que una tercera parte de los DC correspondían a DC-RT. Hasta el momento los estudios publicados no aportaban datos acerca de la incidencia real de DC-RT en la población general de pacientes críticos sometidos a VM. En los pacientes con SDRA no se han observado diferencias en la incidencia de RT respecto al resto de pacientes, lo que podría ser atribuible al bajo número de pacientes con SDRA en la muestra objeto del estudio. Hay que tener en cuenta que la incidencia de RT global podría estar infraestimada, ya que solo se han considerado aquellas respiraciones que desencadenaban DC y no los RT que generan únicamente IE. Estos datos son relevantes, ya que aunque las implicaciones fisiológicas sean las mismas, el mecanismo subyacente del RT que desencadena el DC es completamente diferente al del DC sin RT, lo que implica un manejo clínico específico de esta asincronía.

Implicaciones fisiológicas del DC

Las características de la asincronía DC hacen que pueda considerarse como una asincronía potencialmente lesiva a nivel pulmonar. Por ello, uno de los objetivos de este trabajo de tesis ha sido evaluar las implicaciones fisiológicas del DC.

Los datos han demostrado que el volumen corriente acumulado durante las respiraciones con DC es elevado, pudiendo llegar a doblar el volumen corriente de las respiraciones normales en los modos controlados por volumen, lo que concuerda con resultados previos en la literatura (21,22). Este incremento de volumen, por encima del volumen programado, puede producir sobredistensión y derivar en lesión pulmonar inducida por el ventilador. En la

literatura existen evidencias de que la aplicación de ventilación con volúmenes corrientes bajos, recomendada como ventilación protectora (74), puede resultar en un incremento de DC (21) y de asincronía de flujo (75,76). De modo que, en los pacientes en los que el manejo con ventilación protectora es mandatorio para disminuir los efectos nocivos de la VM, la presencia de DC puede implicar la entrega de un volumen corriente superior al deseado con el consiguiente efecto lesivo. En la muestra de pacientes evaluados en este estudio, el DC apareció con más frecuencia en el modo PCV que en VCV y VCVDF, aunque el volumen global entregado en las respiraciones con DC en PCV fue inferior. Esto no significa que PCV pueda considerarse una modalidad más protectora puesto que, en los modos controlados por presión, la presión pleural negativa que se genera en las contracciones diafragmáticas espontáneas se suma a la presión alveolar, y puede generar niveles de presión transpulmonar potencialmente dañinos (77–79). Este mismo fenómeno también se observa en la modalidad VCV, donde la presión pico de la segunda respiración, correspondiente al DC, es más elevada. Recientemente, otros estudios, han demostrado como el desarrollo de esfuerzos inspiratorios espontáneos vigorosos pueden provocar el reclutamiento de más volumen corriente, lo que se ha asociado al efecto *pendelluft* y a la consiguiente sobredistensión pulmonar regional (20,80). En la ventilación con volúmenes corrientes bajos, especialmente cuando se aplican en el pulmón sano, el DC puede ser secundario a la existencia de suspiros naturales y, si esta situación es deletérea o no dependerá de la presión transpulmonar que genere y de la frecuencia del DC. La evidencia reciente sugiere que el volumen corriente debería también limitarse en pacientes sin SDRA (81), aunque otros estudios aportan datos contradictorios (82). Sin embargo, lo que se debería tener en cuenta es el volumen real que recibe el paciente, ya que aunque se haya programado un volumen corriente bajo o moderado del orden de 6-8 mL/kg, si ocurre DC, el volumen entregado puede ser superior a 10mL/kg, y comportar efectos adversos en los pacientes con y sin SDRA.

Factores relacionados con el desarrollo de DC

En este trabajo de tesis se han evaluado todos aquellos factores que a priori se consideró que podrían tener relevancia clínica en relación al desarrollo de DC. Todos estos factores se introdujeron en el modelo descrito anteriormente, cuyo análisis ha determinado que son múltiples los factores asociados con el desarrollo de DC, sin ser, ninguno de ellos, mutuamente excluyentes. Tanto el tiempo inspiratorio largo como el valor de pico de flujo

inspiratorio elevado se han asociado con una menor incidencia de DC en todos los modos ventilatorios. Esto sugiere que existe un mejor acople entre el tiempo neural del paciente, el tiempo inspiratorio del respirador y la demanda inspiratoria del paciente. De igual modo, se observó mayor incidencia de DC coincidiendo con frecuencias respiratorias altas, lo que se ha atribuido a la presencia de tiempos inspiratorios más cortos. El hecho de programar un tiempo inspiratorio más corto para intentar mejorar el confort del paciente (principalmente para aumentar el flujo), a veces, puede producir un desajuste entre el tiempo neural y el tiempo inspiratorio del respirador, e incrementar la probabilidad de DC. Aunque otros autores han descrito que la frecuencia respiratoria no afecta a la incidencia de DC (21), los tiempos de ciclado son cruciales en este aspecto, y el hecho de aumentar la frecuencia respiratoria puede conllevar un descenso del tiempo inspiratorio y puede favorecer la aparición de DC.

Aunque otros estudios no habían mostrado un papel claro de la PEEP en el desarrollo de asincronías (13,83), tras el análisis continuo de la muestra de pacientes incluidos en este estudio, se evidenció una menor incidencia de DC cuando se aplicaron niveles de PEEP más elevados. En respuesta al uso de una PEEP más alta se produce un descenso en el esfuerzo respiratorio y por ello en la capacidad de activar el *trigger*, debido a volúmenes elevados, lo que explicaría este descenso en el DC. Esto es consistente con otro de los resultados observados, en los que se ha asociado la ventilación con volúmenes corrientes bajos con una mayor incidencia de DC en VCV, igual que en estudios previos (21). Sin embargo, la asociación positiva que se ha encontrado entre DC y magnitud del volumen corriente en PCV podría deberse al ajuste de otros parámetros del respirador independientes del volumen corriente.

Finalmente se ha observado que, en la modalidad VCV, los niveles de presión pico bajos favorecían la aparición de DC, lo que podría reflejar una satisfacción de la demanda de flujo del paciente inadecuada. Lo contrario ocurre en PCV, donde niveles altos de presión se asocian con más DC. Esto podría explicarse como consecuencia del rápido descenso del flujo que ocurre en los modos regulados por presión, y que también puede derivar en una falta de satisfacción de las demandas de flujo inspiratorio del paciente.

Papel de los sedantes y opioides en el desarrollo de asincronías

Los sedantes son fármacos ampliamente utilizados en los pacientes críticos en el intento de mejorar la interacción paciente-ventilador. Sin embargo, los niveles profundos de sedación se han asociado con peores desenlaces (65) y por ello las recomendaciones más recientes sugieren minimizar el tratamiento con sedantes en los pacientes críticos debido a sus efectos deletéreos. Algunos estudios fisiológicos difieren respecto el papel de los sedantes sobre las asincronías, pero alguno de ellos han objetivado como el incrementar la sedación es inefectivo para controlar el DC (60) o como la sedación profunda con propofol puede incluso incrementar las asincronías en modalidades espontáneas (43). Además algunos autores señalan que la optimización de los parámetros ventilatorios es la opción más adecuada para reducir las asincronías en los pacientes ventilados (60).

En base a todo ello, en este trabajo de tesis doctoral se consideró relevante evaluar cómo responden las asincronías al tratamiento con sedantes y/o opioides utilizando un sistema de monitorización continua que permitiera evaluar todo el período ventilatorio. Los resultados muestran que la incidencia de asincronías era similar en los días en que los pacientes recibían solo opioides, solo sedantes y la combinación de sedantes+opioides como tratamiento. De hecho, el añadir sedantes al tratamiento del paciente no mejoró el control de las asincronías con independencia del modo ventilatorio utilizado. Estos hallazgos son importantes, ya que la asociación entre sedantes y asincronías puede verse confundida por diversos factores, entre ellos el modo ventilatorio y los ajustes del respirador, pero nuestros resultados demuestran que el efecto del tratamiento es independiente. Por otra parte, la administración de sedantes se asoció a un menor nivel de conciencia al observado en los días en que los pacientes recibieron solo opioides. Además, la dosis de sedantes administrada se relacionaba de forma directa con un menor nivel de conciencia en los días en que los pacientes recibían una combinación de sedantes+opioides.

Por otra parte, el uso de opioides tiene un efecto positivo sobre el confort y el control del dolor de los pacientes, factores que pueden influir en la interacción paciente-ventilador. En estudios previos, otros autores han demostrado que al combinar opioides con sedantes los pacientes presentan un menor índice de asincronías respecto a los que reciben únicamente sedantes (71). Estos resultados concuerdan con los resultados de esta tesis que muestran que una dosificación adecuada de opioides puede facilitar la interacción con el respirador a la

vez que se asegura un nivel de analgesia óptimo sin disminuir el nivel de conciencia y sin afectar el impulso respiratorio del paciente, como se ha demostrado previamente (84,85). Por otro lado, según los resultados obtenidos en este estudio, el tratamiento únicamente con opioides, al no disminuir el nivel de conciencia, facilita que el paciente esté más alerta y colaborador. Además, el incremento de la dosis de opioides no solo no empeora el nivel de conciencia sino que también se asocia con una disminución de la incidencia de asincronías. El hecho de añadir un opioide al tratamiento, a diferencia de no hacerlo, favorece también una mejor interacción en los modos asistidos-controlados, favoreciendo el confort del paciente. Los protocolos más recientes, en cuanto al manejo de la analgesia y la sedación en el paciente crítico, abogan por la sedación ligera y la interrupción diaria de la sedación (65,67,68), ya que el aumento de los sedantes prolonga los días de VM y la estancia en la UCI y en el hospital (66). Por todo ello, el mantener el tratamiento con opioides hasta la retirada de la VM podría ser una estrategia beneficiosa para el paciente y la interacción paciente-ventilador.

Un hallazgo destacable es la observación de una menor incidencia de AI, IEE y DC en los días en los que los pacientes recibieron el tratamiento combinado de sedantes+opioides al compararlos con los días en que los pacientes no recibieron tratamiento. Esto podría explicarse porque las asincronías que acontecen en el grupo de pacientes que no requieren de ningún tratamiento analgésico o sedante, son intrínsecamente diferentes de las que ocurren en el resto de pacientes. Probablemente las asincronías traducen un mecanismo causal subyacente diferente, y por ello precisan también un abordaje diferente según el estado evolutivo del paciente, la fase de la enfermedad, o el período de VM. Aunque múltiples estudios han demostrado la relación entre las asincronías y los desenlaces no deseados, un estudio reciente, mediante el uso de modelos bayesianos, muestra como las asincronías no están claramente asociadas con una mayor mortalidad, e incluso podrían ser un marcador de vida (49). Además, al igual que en este estudio, las asincronías tampoco presentan una asociación significativa con la gravedad de la enfermedad. Esto da lugar a la introducción del concepto de asincronías “permisivas”, es decir, podríamos considerar que no todas las asincronías tienen la misma traducción clínica y es posible que esto dependa, en parte, de la fase evolutiva de la VM en la que se producen y de su forma de presentación (aisladas o en forma de *clusters*). De hecho, la baja gravedad junto con el elevado índice de asincronías observado en el grupo de pacientes que no recibían fármacos comparado con el

resto de pacientes, refuerza el concepto de un origen y comportamiento distinto de las asincronías en los diferentes grupos. Esto nos conduce a considerar la posibilidad de que quizás no todas las asincronías requieran el mismo manejo. Por ello, las asincronías que se asocian con desenlaces no deseados precisan de un manejo activo para llegar a reducirlas, mientras que otras asincronías, con efectos no deletéreos, pueden ser toleradas o incluso en un futuro podrían ser utilizadas como marcadores de evolución del estado de los pacientes. Es necesario explorar este nuevo enfoque de las asincronías en estudios futuros.

En resumen, el hecho de administrar sedantes no aporta beneficios en la reducción de las asincronías respecto al uso de opioides y, por el contrario, sí impacta disminuyendo el nivel de conciencia. Estos resultados sugieren que la administración de opioides podría constituir una aproximación adecuada para el control de asincronías sin conllevar los efectos deletéreos de los sedantes.

Limitaciones

La primera de las limitaciones del estudio se deriva de que, para el análisis del DC y RT, hemos utilizado un algoritmo que puede infraestimar la incidencia en comparación con otros métodos de análisis como la monitorización de la presión esofágica o la actividad eléctrica del diafragma, lo que podría explicar la baja incidencia global observada en la muestra estudiada. Sin embargo, en los estudios de esta tesis doctoral no ha existido una sobreestimación de las asincronías, evitando de esta manera el efecto "*garbage data*" que es una de las limitaciones de los estudios con *big data*. Por otro lado, la monitorización continua ha demostrado que el DC se presenta en forma de *clusters* a lo largo de todo el período de VM, lo que representa una nueva forma de evaluar las asincronías que aporta información de gran valor y que se relaciona de forma robusta con los desenlaces.

Por otro lado, en esta tesis se ha analizado la frecuencia, las implicaciones fisiológicas y los factores relacionados con el desarrollo de DC, y por ello el diseño del estudio se ha centrado en el análisis de los ciclos respiratorios, sin tener en cuenta la propia heterogeneidad de las características clínicas de los pacientes, como por ejemplo las causas de VM, entre otras. En consecuencia, fruto de este análisis no podemos objetivar si un mismo patrón de DC, en pacientes con características distintas, puede tener implicaciones fisiológicas también distintas. Además, teniendo en cuenta que la caracterización del DC se ha limitado a las

modalidades ventilatorias PCV, VCV y VCVDF, no podemos extrapolar los resultados obtenidos a otros modos o a otros modelos de respirador.

En relación a la evaluación del efecto de los sedantes y los opioides sobre la incidencia de asincronías, la principal limitación se deriva de que se trata de un estudio observacional, no intervencionista, por lo que los pacientes no se han aleatorizado y han sido tratados según criterio del equipo clínico. Cabe tener en cuenta que recientemente está creciendo la aceptación de estudios observacionales, como el realizado en esta tesis, debido a que las conclusiones que se pueden obtener de los datos recogidos en situaciones cotidianas y reales se considera que pueden ser mucho más generalizables que las conclusiones obtenidas de los estudios randomizados, que son más restrictivas. También es necesario comentar que no se han analizado otros fármacos para el control del dolor (como paracetamol o antiinflamatorios no esteroideos), que podrían haber tenido un efecto también sobre la interacción paciente-ventilador. Asimismo, tampoco se han recogido medidas objetivas del nivel de dolor.

Al analizar el efecto sobre el desarrollo de asincronías según la pauta de tratamiento de sedantes y/o opioides diaria, y dado que un mismo paciente puede estar en diferentes grupos de tratamiento, no se han podido tener en cuenta las características particulares de cada paciente en el análisis. Sin embargo, sí que se ha podido evaluar el nivel de gravedad, que se recogía diariamente. Como en el caso anterior, el estudio se limita al análisis de unos determinados modos de VM, y se centra en el desarrollo de dos tipos de asincronías, el DC y IEE, por lo que los resultados no son extrapolables a otros modos ni tipos de asincronías. Asimismo, las asincronías se han manejado a criterio clínico, sin un protocolo específico, por lo que la variabilidad asistencial y de las diferentes unidades podría afectar los resultados. A pesar de ello, se ha analizado la influencia de cada centro y no se han encontrado diferencias significativas.

8. CONCLUSIONES GENERALES

La incidencia global de la asincronía doble ciclado es baja aunque está presente en todos los pacientes. Un tercio de los dobles ciclados se corresponden con *trigger* reverso. El doble ciclado aparece en forma de *clusters* que suceden a lo largo de todo el período de ventilación mecánica.

El volumen total acumulado por las dos respiraciones que conforman un doble ciclado puede llegar a doblar el volumen corriente programado en el respirador por el equipo asistencial, y puede conducir al desarrollo de lesión pulmonar inducida por el respirador.

La aparición de doble ciclado es multifactorial, y entre los factores identificados ninguno es mutuamente excluyente. Un tiempo inspiratorio corto, picos de flujo inspiratorio bajos, volúmenes corrientes bajos, frecuencias respiratorias altas y PEEP bajas se asocian con mayor incidencia de doble ciclado en algunas modalidades ventilatorias.

El tratamiento con sedantes no garantiza una mejor interacción paciente-ventilador que la que se consigue con el tratamiento con opioides, con independencia de la modalidad ventilatoria. Además, la ventaja aportada por los opioides es que no disminuyen el nivel de conciencia, a diferencia de lo que pasa con los sedantes.

9. LÍNEAS DE FUTURO

Los resultados obtenidos en esta tesis doctoral abren varias líneas de investigación en el ámbito del estudio de las asincronías paciente-ventilador.

En esta tesis se ha puesto de relevancia que el análisis continuo de las asincronías es un factor determinante para profundizar en su correcta caracterización, en el estudio de su impacto en los desenlaces y para evaluar los factores que las determinan para poder personalizar los posibles abordajes terapéuticos. Uno de los principales factores limitantes en el estudio y manejo de las asincronías es la dificultad en su identificación con los medios de que se dispone actualmente. Por ello, estamos diseñando líneas de futuro centradas en la elaboración de sistemas de detección automática de las asincronías en tiempo real, junto con el diseño de algoritmos que faciliten al clínico tanto su identificación como su manejo. Será necesario evaluar el impacto de la introducción de estos sistemas de monitorización en la reducción de la incidencia de asincronías.

La introducción de nuevos algoritmos y su incorporación a sistemas de detección permitirá adecuar los tratamientos de forma personalizada y orientada a la prevención de las asincronías y de desenlaces no deseados. En esta línea se quiere investigar el papel que pueden tener las asincronías como predictoras del fracaso del destete de la ventilación mecánica o de los episodios de autoextubaciones. La gran variabilidad de las asincronías detectadas en determinados períodos de ventilación mecánica puede ser analizada mediante la entropía, lo que puede ser una gran herramienta predictiva y de ayuda a la ventilación mecánica personalizada. Es por ello que, a raíz de algunos resultados de los análisis de esta tesis doctoral, se ha solicitado la patente de un dispositivo creado capaz de analizar la variabilidad de las interacciones paciente-ventilador mediante el cálculo de entropía.

Además, la aplicación de estos novedosos sistemas de análisis continuo, durante todo el período de VM, permitirá generar grandes bases de datos longitudinales y transversales de pacientes en las que se podrá explorar mediante la aplicación de inteligencia artificial y de *machine learning* la optimización del manejo de los pacientes ventilados y el desarrollo de modelos predictivos.

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11. ANEXO 1: MATERIAL SUPLEMENTARIO

Material Suplementario en relación a la publicación #1 del trabajo de tesis doctoral (Double Cycling During Mechanical Ventilation: Frequency, Mechanisms, an Physiologic Implications. de Haro C, López-Aguilar J, Magrans R, Montanya J, Fernández-Gonzalo S, Turon M, Gomà G, Chacón E, Albaiceta GM, Fernández R, Subirà C, Lucangelo U, Murias G, Rué M, Kacmarek RM, Blanch L; Asynchronies in the Intensive Care Unit (ASYNICU) Group. Crit Care Med. 2018 Sep;46(9):1385-1392.)

Platform

Commercial software (Better Care™, Barcelona, Spain) was used to capture digital output from a number of different ventilators (S1-S3). The software continuously recorded airflow, airway pressure, and tidal volume from admission until liberation from the ventilator or death. Interruptions in the recordings due to clinical interventions, out-of-ICU transfers, technical problems, or other issues were excluded from the analysis. The software analyzes data on a breath-by-breath basis, determining the beginning and end of inspiration and expiration, and stores patient data for later analysis.

Identification of the mechanisms to initiate a ventilator breath

To label the breaths as "ventilator-triggered" or "patient-triggered", we measured the drop in airway pressure, from the lowest to the highest sensitivity levels, in patients ventilated with flow triggering systems. Airway pressure waveforms were filtered by a low pass filter (cutoff frequency 2.5 Hz) to reduce ECG interference. At the beginning of inspiration, the corresponding drop in airway pressure ranged from 0.98 to 0.44 cmH2O. See Supplemental Table 1 (Supplemental Digital Content 2,) for airway pressure values with the different ventilators used. We defined a ventilator-triggered breath as a decrease in airway pressure less than 90% of the minimum pressure drop achieved in the validation (0.9 * 0.44 = 0.4 cmH2O). We studied 5 selected patients admitted to the Department of Perioperative Medicine, Intensive Care and Emergency, Cattinara Hospital (Trieste, Italy) ventilated with Servo i (Maquet, Sweden) ventilators with a NAVA EAdi catheter (S4) recording electrical activity of the diaphragm (EAdi). Institutional IRB approval was obtained and patients or approved relatives provided informed consent prior to their inclusion in the study. One of the patients was excluded due to technical problems with the EAdi signal. Consequently, the

algorithm was validated in 4 patients for a total number of 7728 random ventilator- or patient-triggered breaths, defined by EAdi values of <1μV and ≥1μV, respectively. The global accuracy reached 92%, with sensitivity 71% for ventilator-triggered breaths and 98% for patient-triggered breaths (Cohen's Kappa index of 0.76 attests to good concordance between the algorithm and EAdi). Supplemental Figure 1 shows specific examples of patient-triggered and ventilator-triggered breaths.

Supplemental References

S1. Blanch L, Sales B, Montanya J, et al. Validation of the Better Care(R) system to detect ineffective efforts during expiration in mechanically ventilated patients: a pilot study. Intensive Care Med 2012;38(5):772-780.

S2. Blanch L, Villagra A, Sales B, et al. Asynchronies during mechanical ventilation are associated with mortality. Intensive Care Med 2015;41(4):633-641.

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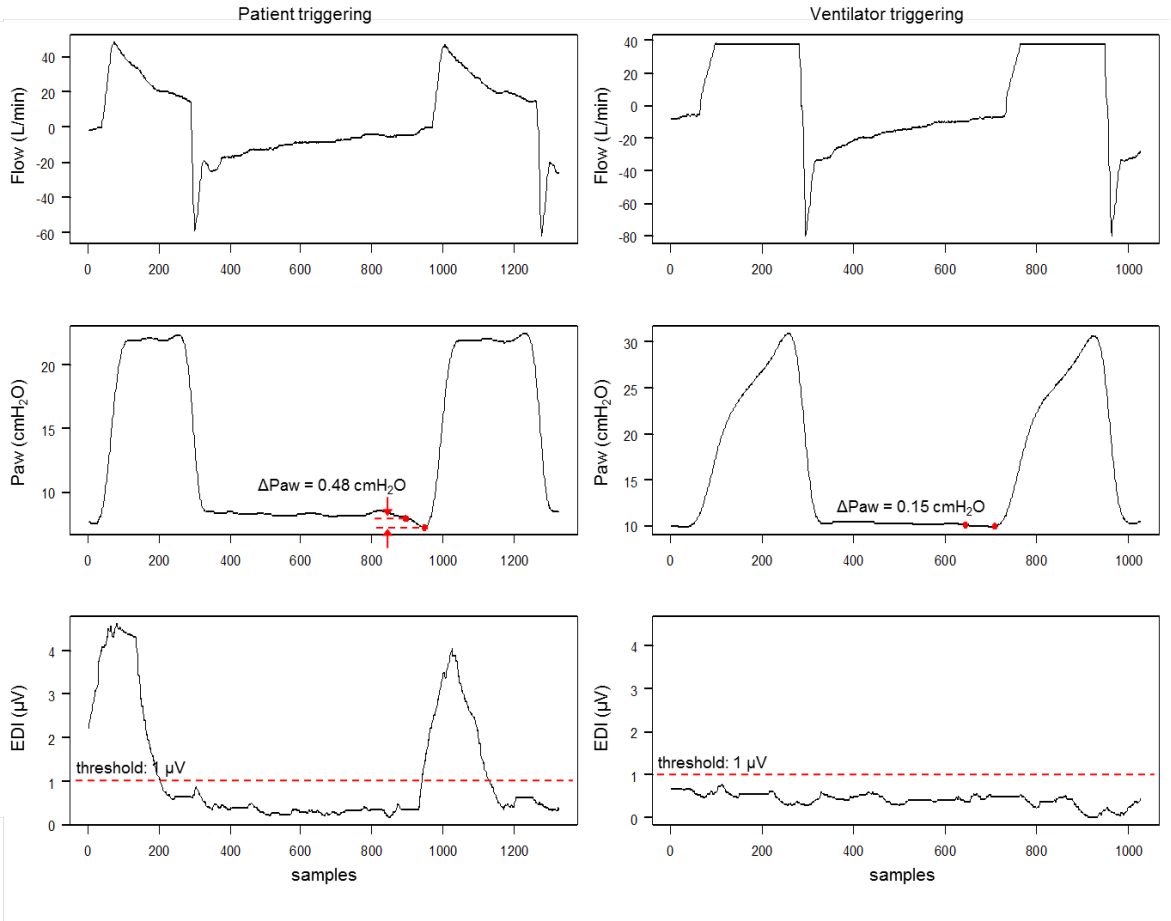
Supplemental Table 1.

Airway pressure drop in patient-triggered breaths at different flow trigger sensitivities. Data from the three ventilators used in the study

Ventilator	Flow-trigger sensitivity	Airway pressure drop (cmH_2O)
Evita XL/Evita 4	Lowest	0.51
	Highest	0.98
PB 840	Lowest	0.61
	Highest	0.93
Servo-i	Lowest	0.44
	Highest	0.66

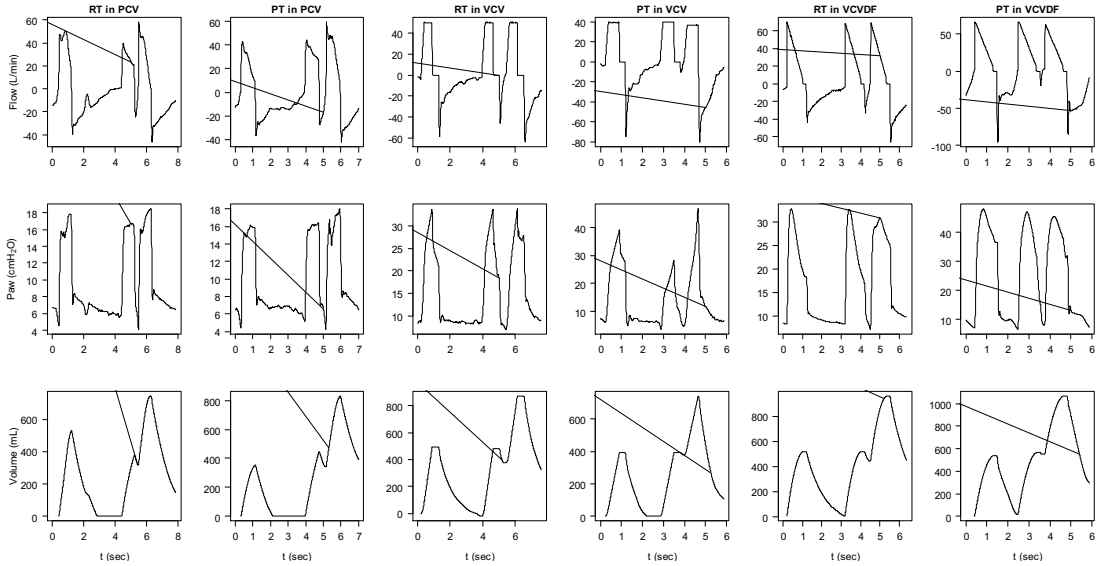
Supplemental Figure 1.

Mechanisms to initiate a ventilator breath determined on the filtered airway pressure signal and validated with the EAdi signal: patient triggering (left) and ventilator triggering (right). Note that for the patient-triggered case, the variation in the air pressure at the beginning of inspiration is greater than 0.4 cmH_20, which is the maximum fall defined to be labeled as a ventilator-triggered breath



Supplemental Figure 2.

Representative waveforms of airflow, airway pressure, and volume during patient-triggered double cycling and reverse-triggered double cycling events in each ventilatory mode. Double cycling consists of a prolonged inspiratory effort that persists beyond the ventilator inspiratory time and consequently triggers a second ventilator breath with no or very short expiratory time. Consequently, all or part of the volume of the first breath is added to the second breath. Paw=airway pressure; RPT=reverse patient-triggered; PT=patient-triggered; PCV=pressure control-continuous mandatory ventilation; VCV=volume control-continuous mandatory ventilation with constant flow; VCVDF=volume control-continuous mandatory ventilation with decelerated flow



Double cycling (DC) cluster computation

The computation of DC clusters was based on the definition of clusters of ineffective efforts (IEs) published by Vaporidi *et al.* (S1), where a cluster was defined as 30 wasted efforts occurring in a period of 3 minutes (a frequency of approximately 50%), assuming a respiratory rate of 20 breaths per minute. Taking into account that the incidence of DC is lower than the incidence of IEs, and that DC may be potentially more harmful than IEs, we decided to use a lower threshold to define the presence of a DC cluster. Thus, we explored clusters in 3-min periods with 3 different thresholds selected at 10%, 20%, and 30% (i.e., at least 6, 12, or 18 DC breaths in a 3-minute period, respectively). Once clusters were identified, they were characterized in terms of their power (i.e. number of DC events contained in the cluster), duration and area under the curve (AUC) determined by integrating the portion of the DC event time-series conforming the cluster. Next table summarizes the mean characteristics of DC clusters. Adjunct figure shows a portion of waveforms (airflow, airway pressure and volume) from a representative patient where an episode of DC cluster was identified.

In the table: Characteristics of double cycling clusters in terms of their power, duration and area under the curve, for the three different thresholds used to define a DC cluster. Values are indicated as median (25th, 75th percentiles) unless otherwise specified.

AUC=area under the curve; bpm=breaths per minute

	Threshold (minimum number of DC events in 3-min. period assuming a respiratory rate of 20 bpm)		
	10% (6)	20% (12)	30% (18)
Patients with DC cluster, n(% of total patients)	40(59.7%)	17(40.3%)	15(22.4%)
Cluster per patient, n	5.5(2, 12.5)	2(1, 5.5)	2(1, 3)
Power	41(19.7, 55.8)	76.7(43, 135.3)	144(76.8, 556)
Duration (min)	15.5(9.1, 29.3)	24.2(17, 43.7)	25(18, 86.4)
AUC	20.3(9.8, 27.7)	36.9(20.4, 65.1)	71.6(38.2, 278)

Supplemental References

S1. Vaporidi K, Babalis D, Chytas A, Lilitsis E, Kondili E, Amargianitakis V, Chouvarda I, Maglaveras N, Georgopoulos D. Clusters of ineffective efforts during mechanical ventilation: impact on outcome. Intensive Care Med 2017; 43:184-191.

Generalized linear mixed-effects model with random intercept

For a proper analysis of the repeated measures data (i.e., several measurements along time during MV for each subject), we built a generalized linear mixed-effects model (GLMM) with random intercept.

Briefly, the idea is to explain variations in the desired response, Y (i.e. DC), by a set of variables $X = \{X_j\}$ that represent the fixed effects of the model, taking into account the degree to which responses vary across subjects (the random effects). Explanatory variables were derived from the breathing pattern and respiratory mechanisms on a breath-by-breath basis during PCV, VCV and VCVDF modes.

The GLMM model assumed a negative binomial distribution (NB) for the dependent variable. The reason for this probability distribution was that our response variable is discrete (number of occurrences of DC), limited to non-negative values, and positively skewed with most of the observations having a value close to zero (**Supplemental Fig. 3**, Supplemental Digital Content 7, http://links.lww.com/CCM/D714). NB distribution has often been used in regression models with count data, as here (S5). Considering we are interested in modeling the number of events as a rate, we incorporated an exposure variable (the total number of respiratory cycles per hour) in the model, which indicates the number of times the DC events could have happened.

We did not estimate the sample size needed to achieve a specific power. No general and well-established sample size methodology exists for mixed models in longitudinal studies with specific correlations among observations from the same individual. Simulation methods are recommended, but this is out of the scope of our study. We have analyzed an observational study with all the available data (9,694,573 breaths and 9251 hours of mechanical ventilation).

Mathematical formulation of the model

The following is an explanation of the model from which we derived the statistics reported in Supplemental Figure 4.

If Y is a response variable consisting of counts with values restricted to $Y \in [0, +\infty]$, then the expected value of Y can be modeled as a negative binomial distribution:

$$Y|X \sim NB(\lambda, \alpha),$$

where λ is the expected value for the counts, $\lambda = E(Y|X)$, and α is the overdispersion parameter of the distribution.

To model the expected rate of the occurrence of events rather than the counts, the log-linear regression model with negative binomial distribution is:

$$log(\lambda/N) = \beta_0 + \beta_1 X_1 + \cdots + \beta_p X_p$$

$$log(\lambda) - log(N) = \beta_0 + \beta_1 X_1 + \cdots + \beta_p X_p$$

$$log(\lambda) = \beta_0 + \beta_1 X_1 + \cdots + \beta_p X_p + log(N),$$

where λ/N is the expected value of the rate Y/N

N is the number of respiratory cycles per hour, the unit of analysis in our study

$log(N)$ is an "offset", a term with fixed coefficient equal to 1 that is included to account for the number of respiratory cycles.

β are the coefficients of the p explanatory variables Xs, plus the intercept (β_0).

Merging the above within a generalized linear mixed-effects model and rewriting to fit our case,

$$log(\lambda_{ji}) = \beta_0 + \beta_1 I(VCV) + \beta_2 I(VCVDF) + (b_{0ki} * vmode_{ki}) + log(N_{ji}) + \varepsilon_{ji},$$

where: λ_{ji} is the expected j^{th} value for level i of the grouping variable "Patient"; here, the expected value of DC events.

β_m (m = 1, ..., p) are the fixed-effects coefficients plus the intercept (β_0).

$I(VCV)$ and $I(VCVDF)$ are dummy variables to indicate the ventilatory mode; its value is 1 for the present mode and 0 otherwise. The level with no dummy variable (PCV) is the reference category.

b_{0ki} are the intercept random effects for each level i of the grouping variable "Patient". Here, the intercept was allowed to vary by modes within patient to account for the possible

heterogeneity the ventilatory mode impacts on the response; vmode represents the categorical variable for the ventilatory modes (with k levels). This interaction random term (b_{0ki}*$vmode_{ki}$) significantly improved model fits versus the more simplistic random intercept model (i.e. that where the influence of patient i is explained by a single intercept value), as it was suggested by a likelihood ratio test.

$log(N_{ji})$ is the offset term, i.e., the logarithm of the total number of breaths per hour for each patient.

ε_{ji} is the vector of random errors.

We also investigated the effect of the time (i.e. hours) on DC by using a random intercept and slope model to account for trends over time within patients, but the variable time was not significant, thus the model described above was chosen for simplicity. Statistics derived from that model is reported in Supplemental Figure 4 (Supplemental Digital Content 8, http://links.lww.com/CCM/D715) and in the Results section in the main text.

Additionally, to investigate factors affecting the development of DC, we accommodated physiological variables thought to affect DC (i.e., insp. time, peak flow, respiratory rate, etc.) in the above regression equation accordingly. We used a multivariate approach allowing separate fits per modes for the population (*vmode:InspTime* + *vmode:PeakFlow* and so on, where *vmode* is the categorical variable for the ventilatory modes). Statistics are reported in Table 2 (main text).

We used the lme4 package (S6) and the lsmeans package (S7) to fit and analyze the GLMM.

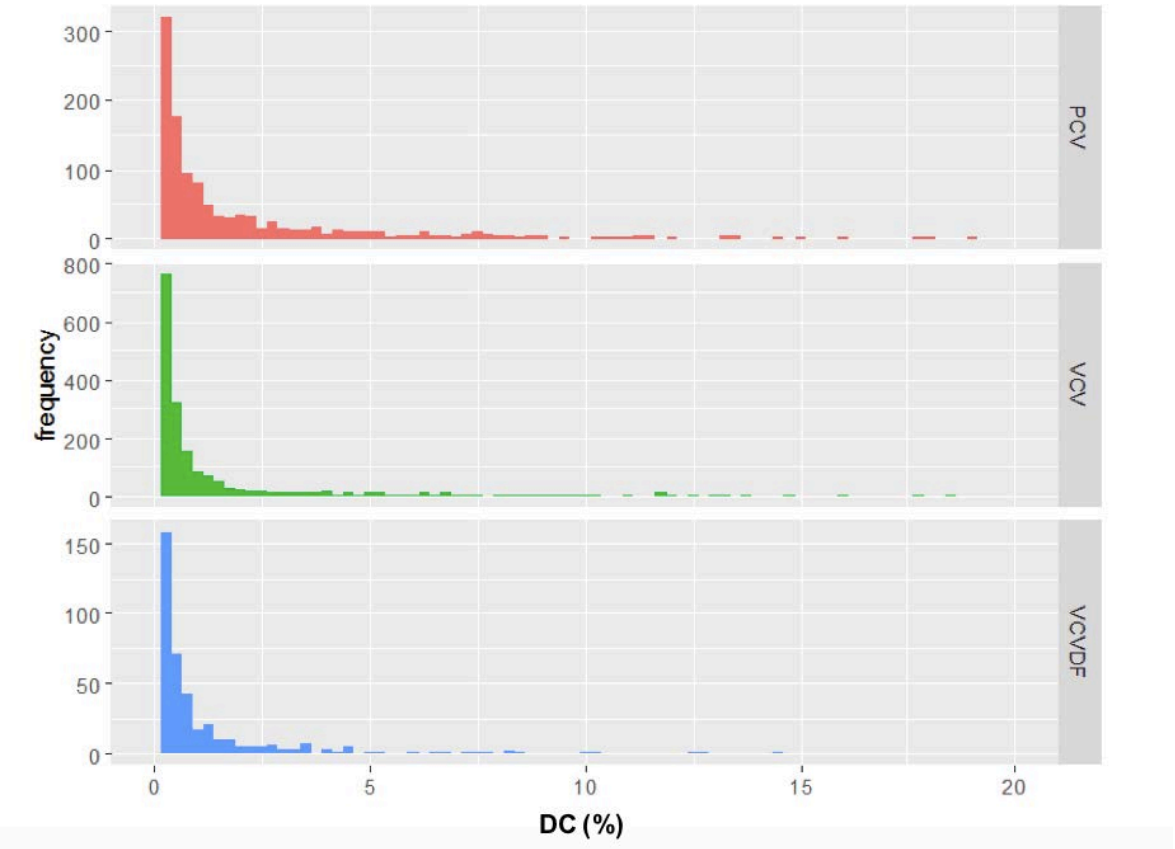
Supplemental References

S5. Cameron AC, Trivedi PK. Regression Analysis of Count Data: Cambridge University Press; 2013.

S6. Bates D, Maechler M, Bolker B, et al. Fitting Linear Mixed-Effects Models Using lme4. Journal of Statistical Software, 2015;67(1):1-48.

S7. Lenth RV. Least-Squares Means: The R Package lsmeans. Journal of Statistical Software 2016;69(1):1-33

Supplemental Figure 3.
Histogram of double-cycled breaths.



Supplemental Table 2.

Descriptive values for the peak airway pressure (Ppeak, in cmH_2O) for the first and second breaths composing double cycling when $Ppeak_{br2} > Ppeak_{br1}$ and when $Ppeak_{br2} < Ppeak_{br1}$. In general, the Ppeak value was greater for the second breath. Values are indicated as median (25th, 75th percentiles). The proportion of DC events where Ppeak in br2 >br1 or Ppeak in br2 < br1 is also shown

Ppeak= Airway Peak Pressure; br1=breath 1; br2 = breath 2; PCV=pressure control-continuous mandatory ventilation; VCV=volume control-continuous mandatory ventilation with constant flow; VCVDF=volume control-continuous mandatory ventilation with decelerated flow

	Reverse-triggered		Patient-triggered	
Mode	br2 > br1	br2 < br1	br2 > br1	br2 < br1
PCV br1 br2	74.2% 24.5 (19.3, 28.0) 25.7 (22.4, 29.0)	24.2% 28.1 (26.4, 32.2) 26.9 (25.0, 30.1)	61.3% 24.8 (19.7, 27.5) 26.3 (22.8, 28.6)	36.5% 26.4 (24.7, 28.5) 25.2 (23.7, 27.1)
VCV br1 br2	80.0% 30.2 (26.4, 35.0) 39.3 (32.4, 43.3)	19.8% 29.3 (21.5, 37.9) 26.0 (17.0, 32.8)	84.7% 28.2 (22.0, 35.2) 37.6 (29.2, 43.9)	15.1% 34.9 (27.3, 43.5) 28.7 (22.4, 37.4)
VCVDF br1 br2	56.0% 26.8 (24.1, 32.3) 33.2 (29.0, 38.1)	43.0% 33.1 (30.6, 44.4) 30.1 (28.2, 32.6)	59.0% 24.3 (23.9, 28.5) 24.7 (24.0, 32.2)	36.0% 27.7 (24.3, 42.9) 25.5 (24.1, 33.9)

Supplemental Table 3.

Individual data for double-cycled breaths in patients with ARDS. DC: Double cycling; RT: Reverse triggering; PT: Patient triggering

Patient	Total breaths n	DC breaths n (%)	DC due to RT n	DC due to PT n
#1	37367	3 (0.008%)	1	2
#2	46489	110 (0.24%)	21	89
#3	72230	99 (0.14%)	19	80
#4	25291	14 (0.06%)	2	12
#5	135172	1389 (1.03%)	1234	155

Material Suplementario en relación a la publicación #2 del trabajo de tesis doctoral

(Effects of sedatives and opioids on trigger and cycling asynchronies throughout mechanical ventilation: an observational study in a large dataset from critically ill patients. de Haro C, Magrans R, López-Aguilar J, Montanyà J, Lena E, Subirà C, Fernandez-Gonzalo S, Gomà G, Fernández R, Albaiceta GM, Skrobik Y, Lucangelo U, Murias G, Ochagavia A, Kacmarek RM, Rue M, Blanch L; Asynchronies in the Intensive Care Unit (ASYNICU) Group. Crit Care. 2019 Jul5;23(1):245)

Additional file 1. Patient-ventilator asynchronies

Briefly, patient-ventilator asynchrony occurs when the phases of breath delivered by the ventilator do not match those of the patient. To meet the patient's demands, the ventilator's inspiratory time and gas delivery must match the patient's neural inspiratory time [E1]. There are different types of patient-ventilator asynchronies. Among the most prevalent are ineffective inspiratory efforts, double cycling (DC), short cycle, and prolonged cycle. Figure E1 shows some common forms of patient-ventilator asynchronies.

Asynchronies were detected by BetterCare™ software (Barcelona, Spain), which continuously records airflow, airway pressure, and tidal volume from admission to extubation or death. The software computed the asynchrony index (AI), defined as the number of asynchronous events described above divided by the total number of ventilator cycles (machine- or patient-triggered) plus the total number of IEE multiplied by 100 [E2].

Double cycling

Double cycling, also named double triggering or breath stacking, consists of a sustained inspiratory effort that persists beyond the ventilator's inspiratory time, triggering a second ventilator breath, which may or may not be followed by a short expiration, where all or part of the volume of the first breath is added to the second breath [E3]. The resulting larger-than-expected tidal volume could cause ventilator-induced lung injury [E4-E6].

Detection of DC was based on previously used mathematical calculations [E3, E6-E7]. The system Better Care™ identifies DC when 1) expiratory time is ≥ 50% shorter than the

averaged inspiratory time or 2) when two consecutive inspiratory cycles (positive flow –zero flow–positive flow) are detected with no expiration (negative flow) before the second inspiratory time. Additional information on factors influencing DC and its physiological implications are given in de Haro et al. [E8].

Ineffective inspiratory efforts

Ineffective inspiratory efforts are contractions of the inspiratory muscles, primarily the diaphragm, not followed by a ventilator breath. This asynchrony occurs when the patient's attempt to initiate a breath does not reach the ventilator's trigger threshold; physiologically, it is characterized by an increase in transdiaphragmatic pressure (decrease in esophageal pressure, increase in gastric pressure) and/or electrical activity of the diaphragm [E2-E9]. Ineffective inspiratory efforts result in the patient's respiratory rate being higher than the ventilator's rate; ineffective efforts usually occur during expiration (IEE), but can also occur during the inspiratory phase.

To detect IEE, Better Care™ computes a theoretical mono-exponential expiratory flow curve and compares it with the actual ones by evaluating its percentage deviation (0%=no deviation; 100%=maximum deviation). The theoretical curve results from the averaging of the 20 previous normal expirations in which there are no deviations that could represent an IEE. See Blanch et al. for additional information [E2].

Short and prolonged cycle

Short cycle is defined as an inspiratory time less than one-half the mean inspiratory time, whereas prolonged cycle occurs when an inspiratory time is greater than twice the mean inspiratory time [E3] The inspiratory time is defined as the time during which gas flow is positive, and mean inspiratory time is calculated over the previous 20 cycles.

Supplementary References

E1. Subira C, de Haro C, Magrans R, et al. Minimizing Asynchronies in Mechanical Ventilation: Current and Future Trends. *Respir Care* 2018;63(4):464-478.

E2. Blanch L, Sales B, Montanya J, et al. Validation of the Better Care(R) system to detect ineffective efforts during expiration in mechanically ventilated patients: a pilot study. *Intensive Care Med* 2012;38(5):772-780.

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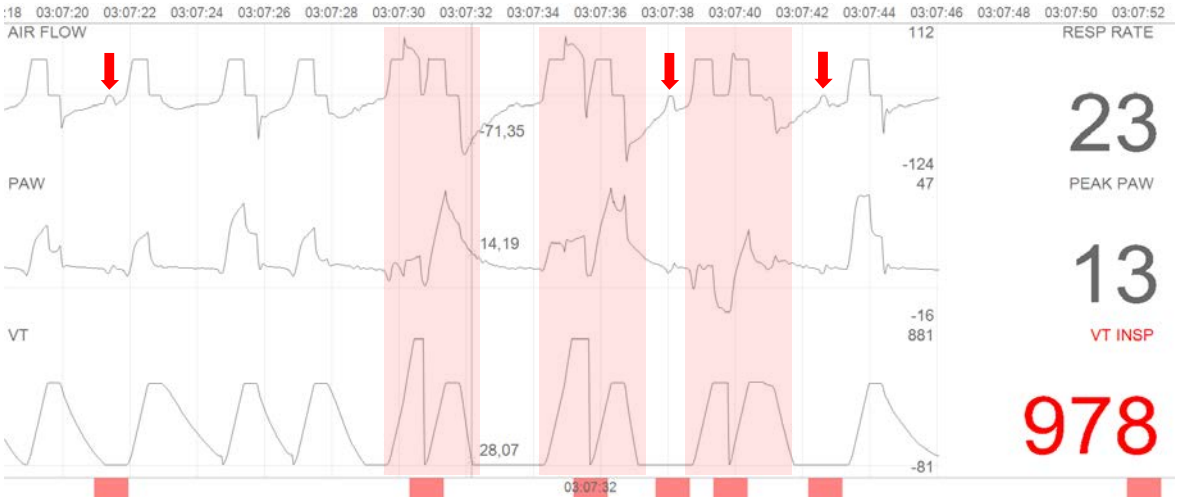
E7. Blanch L, Villagra A, Sales B, et al. Asynchronies during mechanical ventilation are associated with mortality. *Intensive Care Med* 2015;41(4):633-641.

E8. de Haro C, Lopez-Aguilar J, Magrans R, et al. Double Cycling During Mechanical Ventilation: Frequency, Mechanisms, and Physiologic Implications. *Crit Care Med* 2018;46(9):1385-1392.

E9. Georgopoulos D, Prinianakis G, Kondili E. Bedside waveforms interpretation as a tool to identify patient-ventilator asynchronies. *Intensive Care Med* 2006;32(1):34-47.

Figure E1. Example of some common forms of patient-ventilator asynchronies. Capture of Better Care^{TM} software showing tracing of airflow, airway pressure and volume. Episodes of double cycling (red shaded areas) and ineffective efforts during expiration (red arrows) were identified by Better Care™ (red marks bottom).



Additional file 2. Asynchronies and medication dose and asynchronies and medication dose plus SOFA as a potential confounding variable

Table S1. Mean estimated effect from the regression coefficients of medication dose on asynchronies, by treatment group.

TG:DE	Asynchrony Index	Ineffective inspiratory efforts during expiration	Double cycling
Regression coefficients			
TG1:DE1	-0.081 (-0.164, 0.003) p = 0.058	-0.015 (-0.112, 0.082) p = 0.762	-0.200 (-0.289, -0.111) p < 0.0001
TG3:DE1	0.090 (0.040, 0.139) p = 0.0004	0.137 (0.080, 0.195) p < 0.0001	0.037 (-0.005, 0.078) p = 0.082
TG2:DE2	-1.130 (-1.682, -0.577) p < 0.001	-1.166 (-1.782, -0.550) p = 0.0002	-0.662 (-0.735, -0.590) p < 0.0001
TG3:DE2	-0.565 (-0.801, -0.328) p < 0.0001	-0.685 (-0.960, -0.411) p < 0.0001	-0.485 (-0.554, -0.417) p < 0.0001
Model's structure and performance			
Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod']			
Family: Negative Binomial (log)			
Formula: AsinCount ~ TG + TG:DE1 + TG:DE2 + (1 | Id)			
Offset: log (Totalbreath + IEE)			
AIC	6733.0	6273.6	5289.8
BIC	6769.6	6310.2	5326.5
Loglik	-3357.5	-3127.8	-2635.9

Results are expressed as mean estimated effect and 95% CI

A negative sign indicates an inverse association.

TG Treatment group (TG1 sedatives-only, TG2 opioids-only, TG3 sedatives-plus-opioids)

DE Dose-equivalents (DE1 midazolam dose-equivalents, DE2 morphine dose-equivalents)

AsinCount count of asynchronies for AI, IEE, or DC each day

Id Subject factor

Totalbreath number of ventilator-delivered cycles each day

AIC Akaike information criterion

BIC Bayesian information criterion

Loglik Log likelihood

Table S2. Mean estimated effect from the regression coefficients of medication dose and SOFA on asynchronies, by treatment group.

TG:DE and TG:SOFA	**Asynchrony Index**	**Ineffective inspiratory efforts during expiration**	**Double cycling**
Regression coefficients			
TG1:DE1	-0.074 (-0.160, 0.012) p = 0.090	-0.009 (-0.109, 0.090) p = 0.854	-0.189 (-0.280, -0.098) p < 0.0001
TG3:DE1	0.089 (0.039, 0.138) p = 0.0005	0.137 (0.079, 0.195) p < 0.0001	0.037 (-0.021, 0.095) p = 0.208
TG2:DE2	-1.032 (-1.627, -0.437) p = 0.0007	-1.048 (-1.709, -0.387) p = 0.0019	-0.370 (-1.110, 0.370) p = 0.327
TG3:DE2	-0.549 (-0.793, -0.305) p < 0.0001	-0.675 (-0.960, -0.390) p < 0.0001	-0.481 (-0.765, -0.198) p = 0.0009
TG1:SOFA	0.007 (-0.067, 0.080) p = 0.861	0.050 (-0.034, 0.135) p = 0.244	-0.069 (-0.156, 0.017) p = 0.117
TG2:SOFA	-0.029 (-0.108, 0.049) p = 0.466	-0.033 (-0.124, 0.057) p = 0.472	-0.087 (-0.181, 0.007) p = 0.069
TG3:SOFA	-0.010 (-0.055, 0.035) p = 0.654	0.004 (-0.050, 0.057) p = 0.896	-0.028 (-0.077, 0.022) p = 0.270
Model's structure and performance			
Generalized linear mixed model fit by maximum likelihood (Laplace Approximation) ['glmerMod'] Family: Negative Binomial (log) Formula: AsinCount ~ TG + TG:DE1 + TG:DE2 + TG:SOFA + (1 | Id) Offset: log(Totalbreath + IEE)			
AIC	6615.0	6170.9	5191.3
BIC	6663.6	6219.5	5239.9
Loglik	-3295.5	-3073.4	-2583.6

Results are expressed as mean estimated effect and 95% CI

A negative sign indicates an inverse association.

TG Treatment group (TG1 sedatives-only, TG2 opioids-only, TG3 sedatives-plus-opioids)

DE Dose-equivalents (DE1 midazolam dose-equivalents, DE2 morphine dose-equivalents)

SOFA Sequential Organ Failure Assessment

AsinCount count of asynchronies for AI, IEE, or DC each day

Id Subject factor

Totalbreath number of ventilator-delivered cycles each day

AIC Akaike information criterion

BIC Bayesian information criterion

Loglik Log likelihood

Additional file 3. Asynchronies and treatment group plus mechanical ventilation mode

Table S3. Statistical significances for the comparisons between mechanical ventilation modes (AC vs. PS) in each treatment group, and among treatment groups, in each mode.

TG and MV mode	Asynchrony Index	Ineffective inspiratory efforts during expiration	Double cycling
TG0:AC vs TG0:PS	p = 0.2537	p = 0.1812	p = 0.4005
TG1:AC vs TG1:PS	p = 0.0348	p = 0.0246	p = 0. 8634
TG2:AC vs TG2:PS	p = 0.2080	p = 0.1263	p = 0.7744
TG3:AC vs TG3:PS	p = 0.0527	p = 0.0156	p = 0.6006
Assist-control modes			
TG0:AC vs TG1:AC	p = 0.1293	p = 0.1505	p = 0.9417
TG0:AC vs TG2:AC	**p = 0.0065**	p = 0.0135	p = 0.5795
TG0:AC vs TG3:AC	**p = 0.0028**	**p = 0.0069**	p = 0.0797
TG1:AC vs TG2:AC	p = 0.3452	p = 0.4367	p = 0.6601
TG1:AC vs TG3:AC	p = 0.3485	p = 0.4509	p = 0.1310
TG2:AC vs TG3:AC	p = 0.7545	p = 0.7772	p = 0.3861
Pressure-support modes			

TG0:PS vs TG1:PS	p = 0.4792	p = 0.4036	p = 0.5009
TG0:PS vs TG2:PS	p = 0.1277	p = 0.2380	p = 0.1690
TG0:PS vs TG3:PS	p = 0.4099	p = 0.6880	p = 0.2566
TG1:PS vs TG2:PS	p = 0.1212	p = 0.1515	p = 0.7819
TG1:PS vs TG3:PS	p = 0.2638	p = 0.3315	p = 0.8932
TG2:PS vs TG3:PS	p = 0.5684	p = 0.5023	p = 0.8566

TG Treatment group (TG0 no drugs, TG1 sedatives-only, TG2 opioids-only, TG3 sedatives + opioids)

Mechanical ventilation modes (AC assist-control, PS pressure support)

Statistically significant $p < 0.01$

Additional file 4. Checking assumptions of the (generalized) linear mixed-effect models

When using LME models for the continuous response variables (SAS and SOFA), we checked the normality assumptions for the estimated random effects and for the within-subject residuals by graphical methods (normal Q-Q plots). When the response variable was discrete, as for the number of asynchronies, we assessed overdispersion by graphical comparison of the standardized residuals versus the fitted values.

To summarize, the assumptions of the LME and GLME models were met for the set of models developed, as is shown in the diagnostic plots, except for the LME model for the SOFA according to treatment group, where the within-subject residuals depart from the theoretical normal distribution (Figure S2 left). Results of the diagnostics for each model are shown in the following subsections.

Normality of the LME model for the SAS level according to treatment group

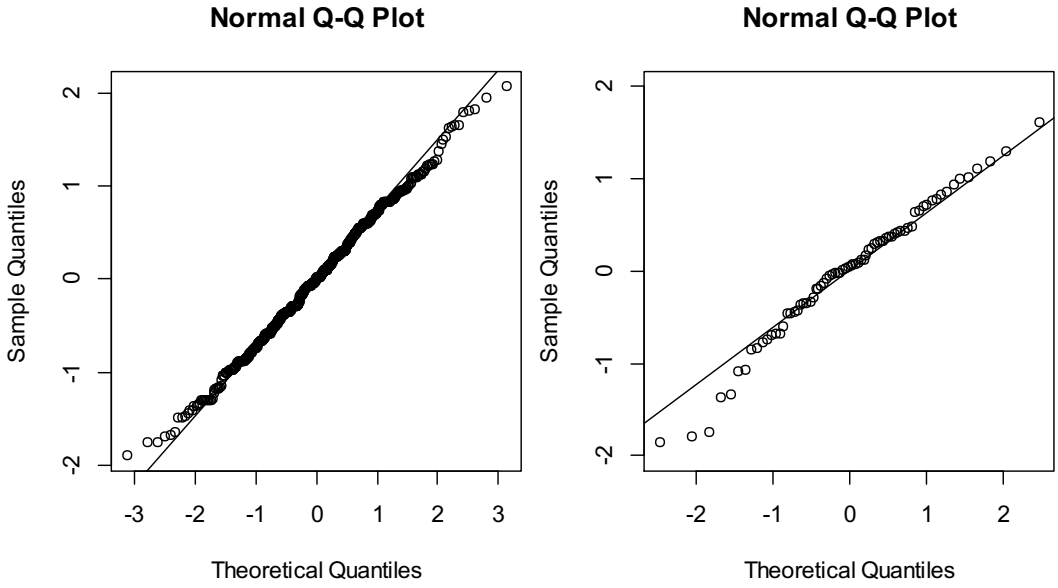


Figure E2. Q-Q plots of the within-subject residuals (left) and for the estimated random effects (right) of the LME model for SAS level according to treatment group.

Normality of the LME model for the SOFA according to treatment group

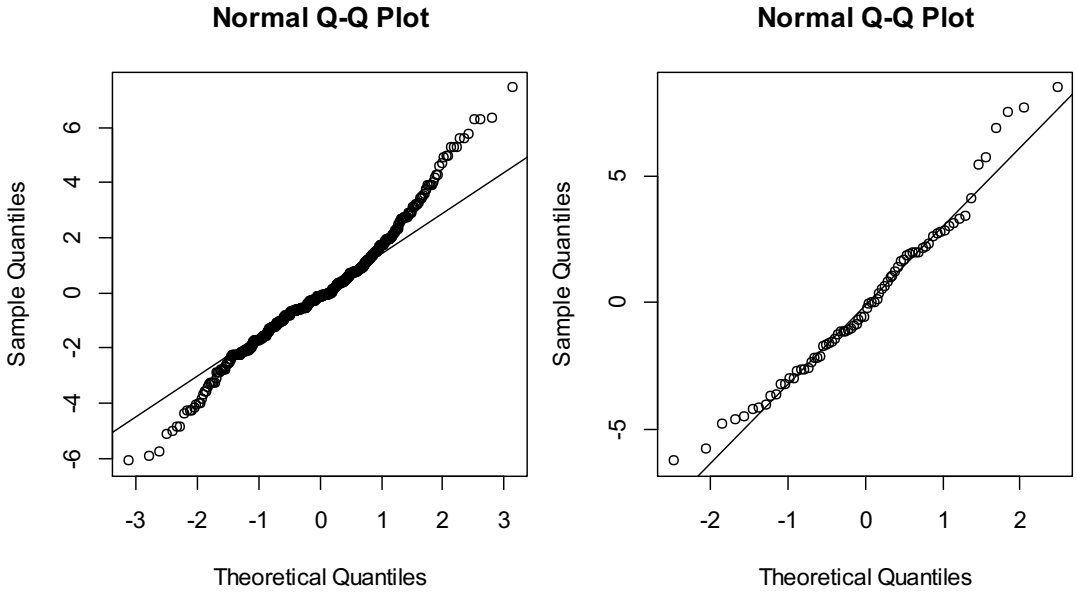


Figure E3. Q-Q plots of the within-subject residuals (left) and for the estimated random effects (right) of the LME model for the SOFA according to treatment group.

Assessing overdispersion of the GLME models for the asynchrony rates according to treatment group

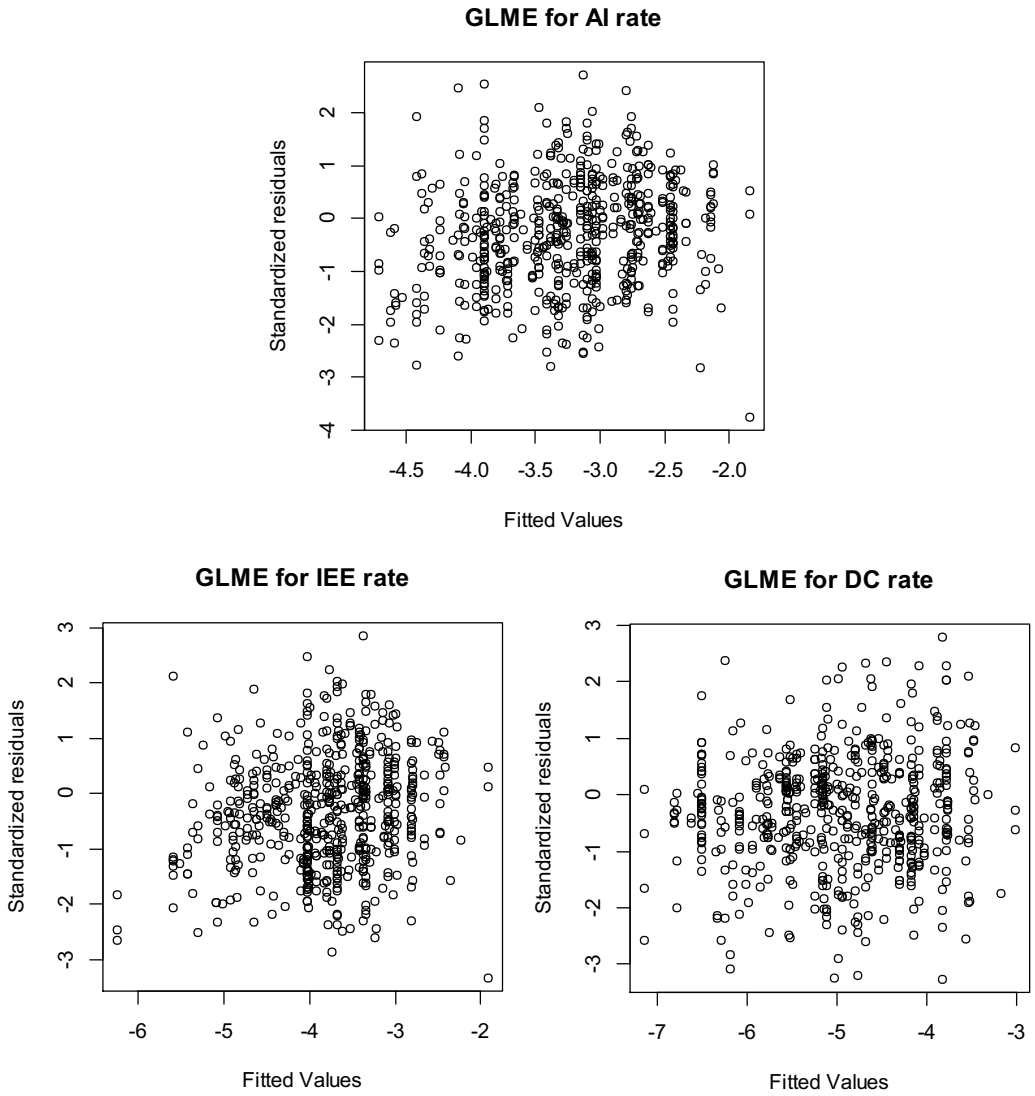


Figure E4. Standardized residuals versus fitted values of the GLME models for the AI (top), IEE (bottom-left) and DC (bottom-right) rates according to treatment group.

Assessing overdispersion of the GLME models for the asynchrony rates according to SAS level and treatment group, and according to SOFA and treatment group.

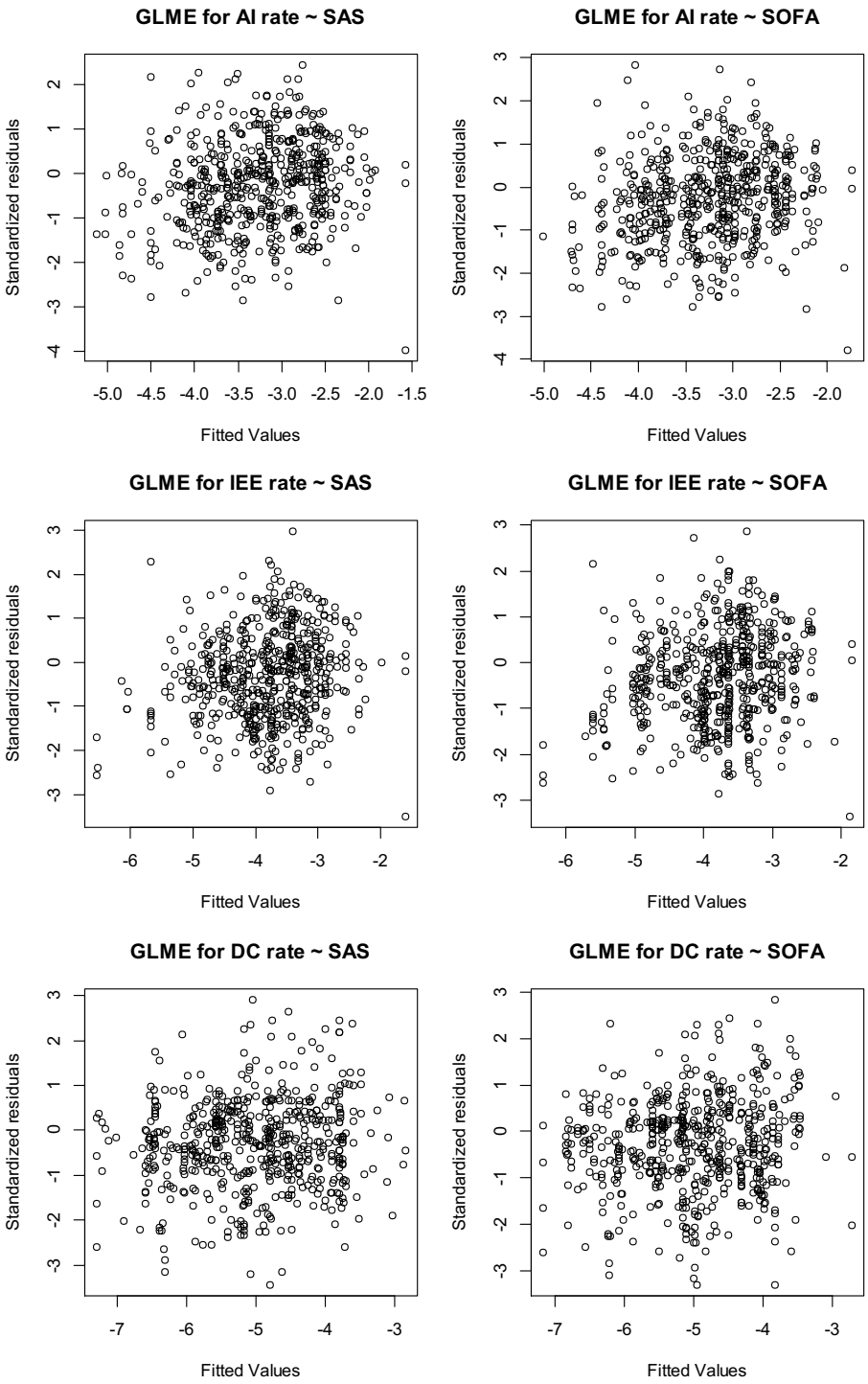


Figure E5. Standardized residuals versus fitted values of the GLME models for the AI (top), IEE (middle), and DC (bottom) rates according to SAS level and treatment group (left), and according to SOFA and treatment group (right).

Assessing overdispersion of the GLME models for the asynchrony rates according to medication doses and treatment group

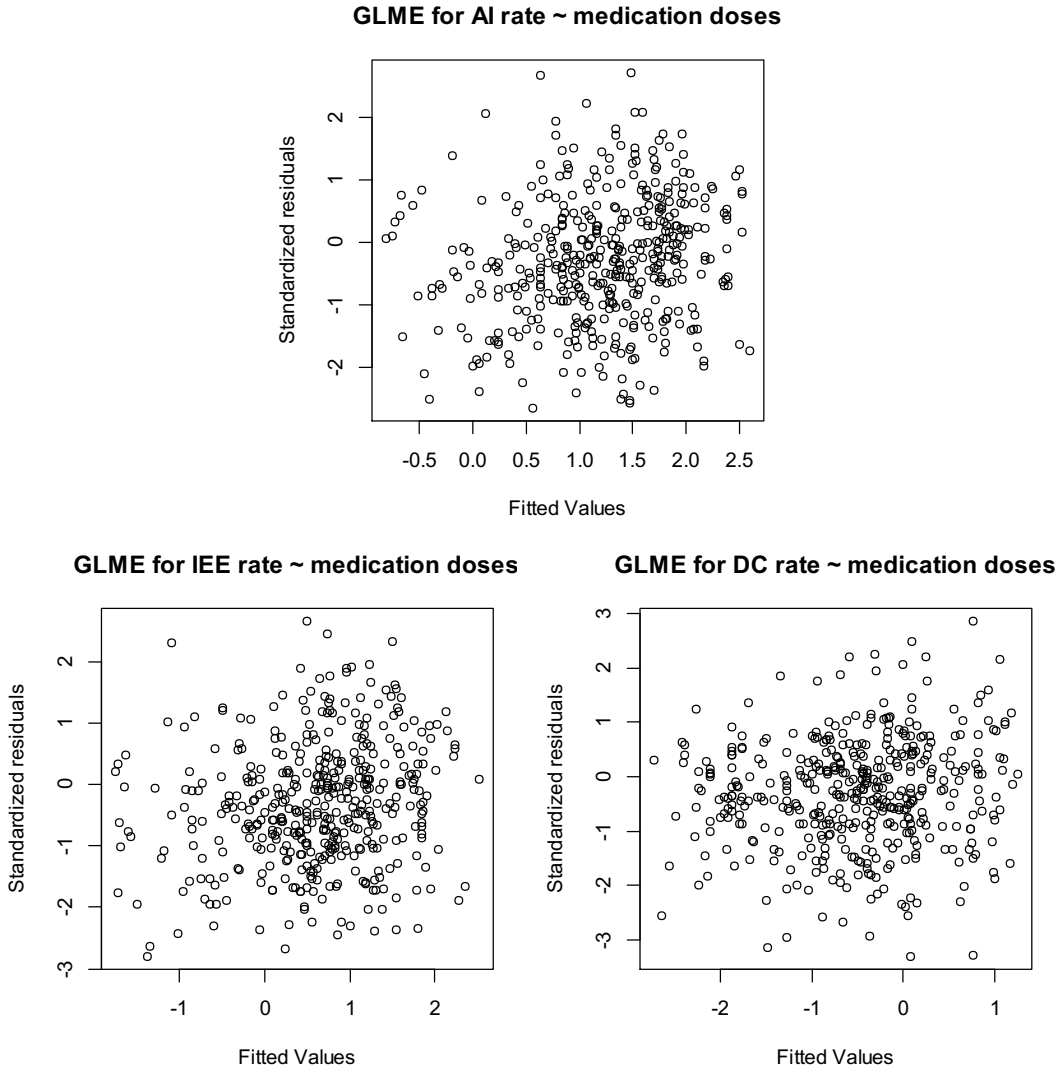


Figure E6. Standardized residuals versus fitted values of the GLME models for the AI (top), IEE (bottom-left), and DC (bottom-right) rates according to medication doses and treatment group.

Normality of the LME model for the SAS level according to medication doses and treatment group

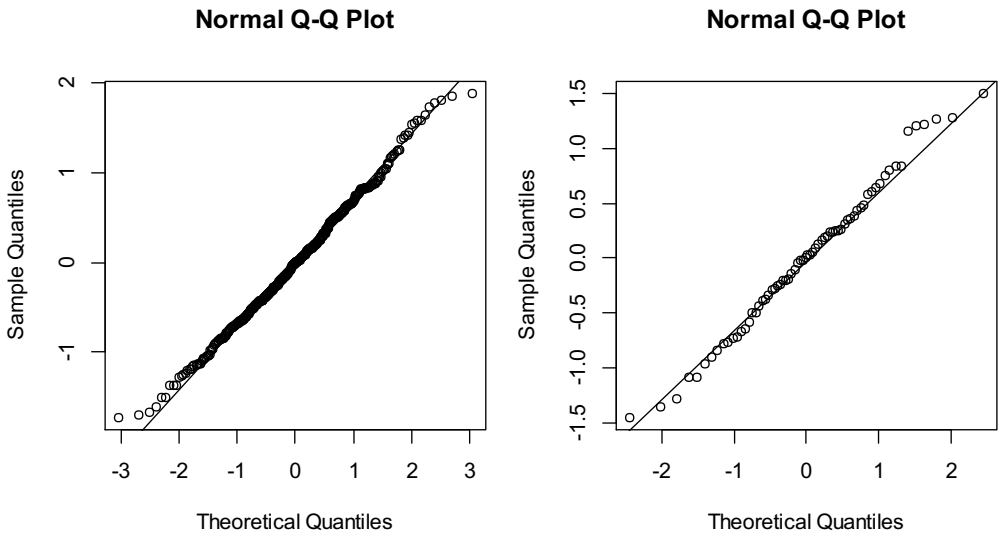


Figure E7. Q-Q plots of the within-subject residuals (left) and for the estimated random effects (right) of the LME model for the SAS level according to medication doses and treatment group.

Assessing overdispersion of the GLME models for the asynchrony rates according to medication doses and treatment group and SOFA

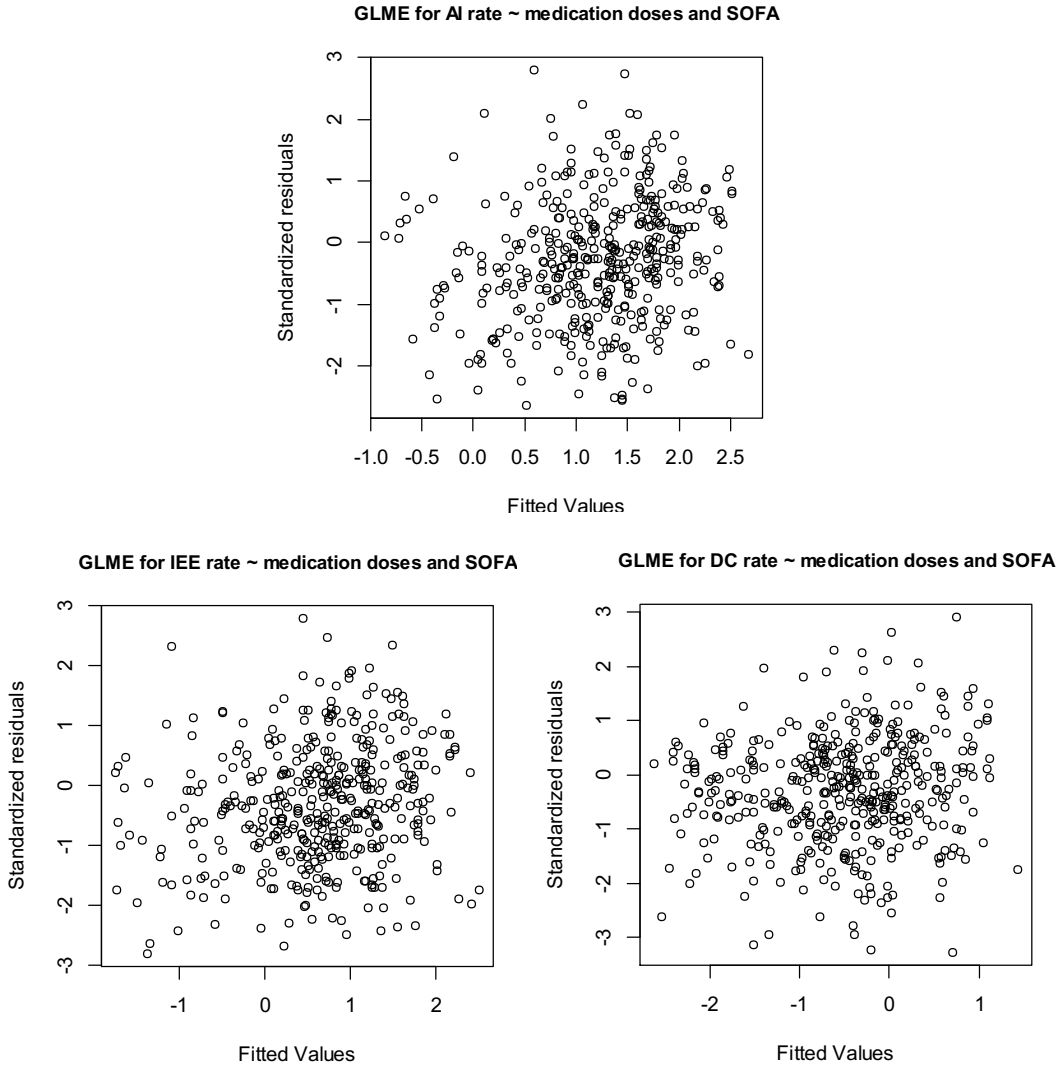


Figure E8. Standardized residuals versus fitted values of the GLME models for the AI (top), IEE (bottom-left), and DC (bottom-right) rates according to medication doses and treatment group with SOFA as a potential confounding factor.

Assessing overdispersion of the GLME models for the asynchrony rates according to ventilatory mode and treatment group.

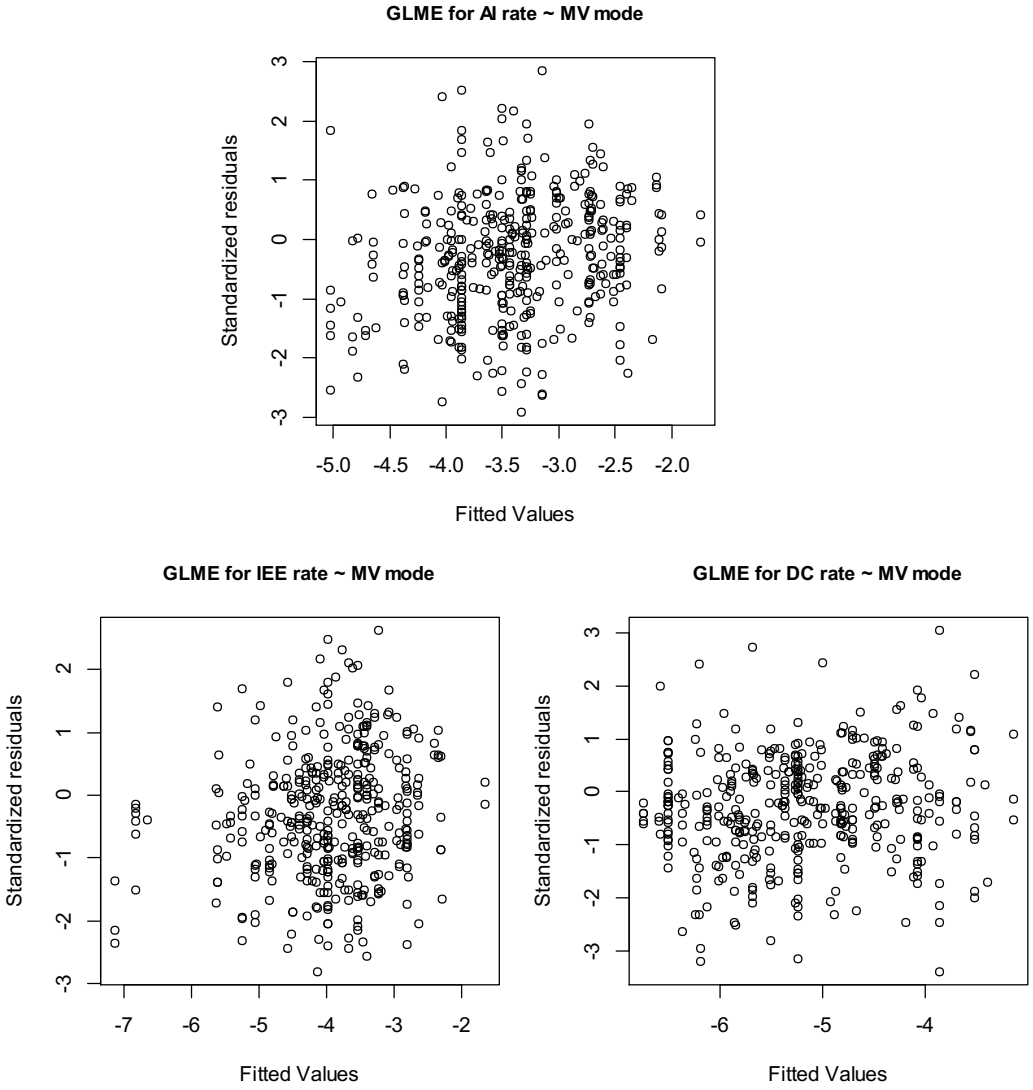


Figure E9 Standardized residuals versus fitted values of the GLME models for the AI (top), IEE (bottom-left), and DC (bottom-right) rates according to ventilatory mode and treatment group.

12. ANEXO 2: OTRAS PUBLICACIONES EN RELACIÓN A LA TESIS DOCTORAL

- de Haro C, Ochagavia A, López-Aguilar J, Fernandez-Gonzalo S, Navarra-Ventura G, Magrans R, Montanyà J, Blanch L; Asynchronies in the Intensive Care Unit (ASYNICU) Group. Patient-ventilator asynchronies during mechanical ventilation: current knowledge and research priorities. Intensive Care Med Exp. 2019 Jul 25;7(Suppl 1):43.

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de Haro et al. Intensive Care Medicine Experimental 2019, 7(Suppl 1):43
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Intensive Care Medicine Experimental

REVIEW Open Access

Patient-ventilator asynchronies during mechanical ventilation: current knowledge and research priorities

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Abstract

Background: Mechanical ventilation is common in critically ill patients. This life-saving treatment can cause complications and is also associated with long-term sequelae. Patient-ventilator asynchronies are frequent but underdiagnosed, and they have been associated with worse outcomes.

Main body: Asynchronies occur when ventilator assistance does not match the patient's demand. Ventilatory overassistance or underassistance translates to different types of asynchronies with different effects on patients. Underassistance can result in an excessive load on respiratory muscles, air hunger, or lung injury due to excessive tidal volumes. Overassistance can result in lower patient inspiratory drive and can lead to reverse triggering, which can also worsen lung injury. Identifying the type of asynchrony and its causes is crucial for effective treatment.
Mechanical ventilation and asynchronies can affect hemodynamics. An increase in intrathoracic pressure during ventilation modifies ventricular preload and afterload of ventricles, thereby affecting cardiac output and hemodynamic status. Ineffective efforts can decrease intrathoracic pressure, but double cycling can increase it. Thus, asynchronies can lower the predictive accuracy of some hemodynamic parameters of fluid responsiveness.
New research is also exploring the psychological effects of asynchronies. Anxiety and depression are common in survivors of critical illness long after discharge. Patients on mechanical ventilation feel anxiety, fear, agony, and insecurity, which can worsen in the presence of asynchronies. Asynchronies have been associated with worse overall prognosis, but the direct causal relation between poor patient-ventilator interaction and worse outcomes has yet to be clearly demonstrated.
Critical care patients generate huge volumes of data that are vastly underexploited. New monitoring systems can analyze waveforms together with other inputs, helping us to detect, analyze, and even predict asynchronies. Big data approaches promise to help us understand asynchronies better and improve their diagnosis and management.

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Conclusions: Although our understanding of asynchronies has increased in recent years, many questions remain to be answered. Evolving concepts in asynchronies, lung crosstalk with other organs, and the difficulties of data management make more efforts necessary in this field.

Keywords: Patient-ventilator interaction, Asynchronies, Mechanical ventilation, Outcome, Heart lung interaction, Psychological disorders, Cognitive, ICU, Critically ill, Big data

Background

Invasive mechanical ventilation is the most common means of life support applied in critical care medicine. Although mechanical ventilation often helps save lives, the mortality associated with this technique is very high. In addition, survivors of mechanical ventilation may experience significant long-term morbidity resulting in substantially reduced functional status and ability to complete activities of daily living [1–3]. Optimal patient-ventilator interaction is crucial to assure comfort with mechanical ventilation and to avoid poor outcomes [4]. Patient-ventilator asynchronies (PVA) are the consequence of a mismatch between patients' needs and the assistance delivered by the ventilator. PVA can be classified depending on the phase of the respiratory cycle in which they occur. The most frequent PVA are ineffective efforts, followed by double cycling. Its causes, consequences, and management vary depending on the type (Figs. 1 and 2) [5, 6]. This review article aims to summarize what is known about patient-ventilator interaction and asynchronies in mechanical ventilation, to show its effects on outcomes, and to describe new directions in research about these questions.

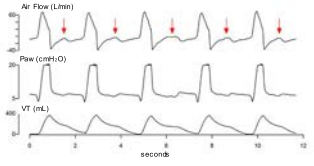
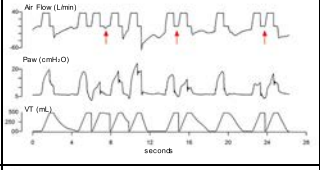
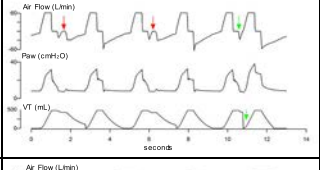
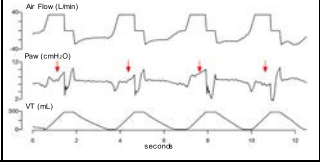
Asynchrony	Graphic representation	Description	Causes
Ineffective Efforts		Inspiratory muscle efforts not followed by a ventilator breath (red arrows)	Inadequate trigger sensitivity Excessive assistance Overdistension/Air trapping Low respiratory drive Low level of pCO2 Oversedation
Double Cycling		Inspiratory effort that continues beyond the ventilator inspiratory time producing a second or a third ventilator breath (red arrows) without expiration. Consequently, the volume of the first breath is added to the second or third breath.	Inadequate setting of ventilator inspiratory time Inadequate trigger sensitivity (too sensible) Inadequate circuit pressurization Patient effort too strong Reverse triggering
Reverse Triggering		Ventilator insufflations that trigger diaphragmatic muscle contractions (red arrows) in response to passive insufflation of the lungs. When the diaphragmatic muscle contraction occurs at the end of inspiration a double cycled breath can occur (green arrow) .	Oversedation Overdistension/Air trapping
Inspiratory Airflow Dyssynchrony		Strong patient inspiratory effort (concavity in pressure tracing) due to insufficient inspiratory airflow in a patient ventilated in assist-volume controlled mode.	Inadequate gas flow Dyspnea Delirium/Pain

Fig. 1 Representation and description of the most common asynchronies. Ineffective efforts, double cycling, reverse triggering, and inspiratory airflow dyssynchrony are graphically represented and described together with their causes. Red arrows indicate where the asynchrony described is present

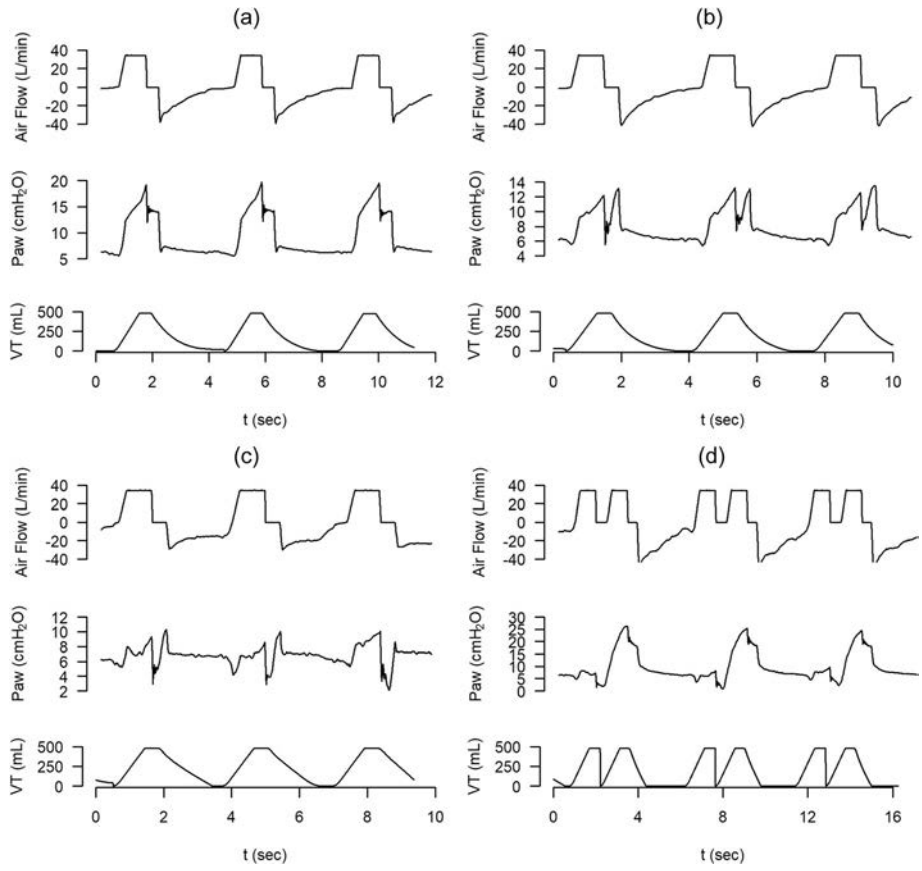


Fig. 2 Inspiratory airflow dyssynchrony. Sequence of airflow and airway pressure waveforms corresponding to a same patient in the same day ventilated in assist volume control mode. Set airflow is insufficient for the patient's needs and originated different degrees of airflow dyssynchrony or starvation. **a** Mild airflow dyssynchrony. **b**, **c** The progression of airflow dyssynchrony through a more severe stage. **d** The appearance of double cycling secondary to a huge and large inspiratory effort

Main text

Evolving concepts on patient-ventilator interaction and asynchronies

Patient-ventilator interaction has been investigated for years [5, 7, 8]. Authors have examined various factors related to ventilator mode, ventilator settings, and patient characteristics that can affect patient-ventilator interaction [4, 5, 9], and have identified many types of asynchronies. Some factors associated with different types of asynchronies have been analyzed, and different mechanisms to reduce their incidence have been studied [10]. Nevertheless, detecting PVA remains a challenge, requiring the application of advanced knowledge about respiratory physiology to interpret ventilator waveforms by analyzing their shape during different periods of the breath cycle (inspiration, transition from inspiration to expiration, and expiration) [5, 6, 8, 11, 12]. Until recently, such analyses required the physical presence of an expert physician at the bedside and were thus only possible during brief, intermittent periods.

PVA occurs when there is a mismatch between the ventilator and the patient in terms of demand or breath delivery timing. Recently, Pham et al. [6] proposed a classification of PVA based on the appropriateness of the level of assistance provided by the

ventilator. Assistance is deemed insufficient when the ventilator fails to meet the patient's flow demand. Inspiratory airflow dyssynchrony due to insufficient ventilator airflow (also named flow starvation) results in the patient's inspiratory effort continuing beyond the ventilator's inspiratory time. When the patient's effort is strong enough, a second breath can be triggered with no or minimal expiration (called double cycling or breath stacking), resulting in a potentially dangerous increase in tidal volume. Inspiratory airflow dyssynchrony develops mainly when ventilators are set to deliver fixed flow and/or lower tidal volumes in patients with high inspiratory flow demands that vary from breath to breath [13, 14]. Potential consequences of low assistance are excessive load on the respiratory muscles, air hunger promoting limbic, paralimbic, and cerebellar activation in the brain [15], and ventilator-induced lung injury due to excessive tidal volume. Moreover, strong inspiratory efforts can increase transvascular pressure gradients and tidal recruitment associated with pendelluft flow and regional lung overdistension [16, 17]. Vigorous spontaneous efforts impact non-dependent and dependent lung regions differently, increasing inspiratory distension but also apparently worsening injury in the dependent lung because diaphragm contraction is poorly transmitted to the remainder of the pleural surface and is thus "confined" to the dependent lung [18]. It can be difficult to detect asynchronies due to insufficient assistance.

By contrast, assistance is deemed excessive when the ventilator provides flow in excess of the patient's demand. Patients with low inspiratory drive due to sedation or excessive ventilator assistance can develop ineffective efforts occurring during either inspiration or expiration, delayed or prolonged cycling, and reverse triggering [6]. The concept of reverse triggering is evolving. Reverse triggering is a frequently under-recognized form of PVA in which the patient's respiratory center is activated in response to a passive insufflation of the lungs. This PVA originates in respiratory muscle contractions triggered by the ventilator [19]. The physiologic mechanism responsible for reverse triggering seems to be related with mechanoreceptors in the muscles and/or chest wall or in complex spinal reflexes [6]. Passive insufflation of the lungs activates the patient's neurological respiratory center [20]. Recent research has found that reverse triggering could occur not only in patients with acute respiratory distress syndrome or diagnosed of brain death but in all patients receiving mechanical ventilation. Since reverse triggering might be more frequent than expected and could be associated with lung or diaphragm injury, the incidence and causes of reverse triggering warrant urgent investigation [6, 21, 22]. Esophageal pressure monitoring can help to identify this PVA in deeply sedated patients: a drop in esophageal pressure can be related to diaphragmatic contractions triggered by ventilator insufflations [19]. Reverse triggering can result in stretching in the dependent lung. Proportional to negative intrathoracic pressure, stretching due to reverse triggering can be equivalent to that caused by applying 15 ml/kg tidal volume. Yoshida et al. [18] recently demonstrated how reverse triggering can worsen pre-existing lung injury through a pendelluft effect from non-dependent lung areas toward dependent areas due to poor transmission of the diaphragm contraction across the pleural surface in an injured lung. Moreover, reverse triggering can result in increased strain and stretch due to breath stacking during double cycling caused by insufficient assistance [19, 23].

In a recent publication, we used the term double cycling to refer to both reverse-triggered or patient-triggered mechanical breaths occurring at any point in

mechanical ventilation [21]. Other authors [24] use double cycling only when the first breath in a reverse-triggering event is a ventilator-programmed breath not triggered by the patient. Only the breaths originated by a patient's high inspiratory drive were considered as double triggering. Moreover, reverse triggering that does not cause double cycling can be considered an ineffective effort during the different phases of inspiration. Several authors have speculated that reverse triggering without double cycling can cause lengthening contractions of the diaphragm and with double cycling breath-stacking with increased tidal volume in assist pressure control mode, and both tidal volume and airway pressure in assist volume control mode. Recent investigations suggest that reverse triggering is common in critical patients. Interestingly, de Haro et al. [21] found that one third of double-cycling breaths were reverse-triggered. Clinicians must differentiate between double cycling due to insufficient assistance and double cycling due to reverse triggering because these phenomena call for different treatments. Double cycling due to insufficient assistance is associated with rapid respiratory rates, low ventilator airflow, and short ventilator inspiratory time [21, 25]; by contrast, double cycling due to reverse triggering is associated with deep sedation in patients not triggering the ventilator. However, the mechanisms involved in reverse triggering are poorly understood, so the best treatment approach remains to be determined [6]. At present, detecting these types of PVA requires trained observers analyzing waveforms on ventilator screens at the bedside.

Heart-lung interaction in patients with asynchronies

The heart and lungs are anatomically and functionally linked. The interactions between cardiovascular and respiratory physiology are very complex and include effects related to changes in intrathoracic pressure and lung volumes [26, 27]. Moreover, the hemodynamic effects of ventilation and asynchronies depend on the hemodynamics' stability and the previous status of the cardiopulmonary system.

In mechanically ventilated patients, the inspiratory increase in intrathoracic pressure reduces venous return by increasing right atrial pressure and reduces left ventricular afterload by decreasing transmural left ventricular systolic pressure. Conversely, it can also increase the afterload of the right ventricle considerably. Increased right ventricular afterload results from progressive increases in transpulmonary pressure (difference between alveolar pressure and pleural pressure) associated with increasing lung volume; this effect can be especially important in patients with acute respiratory distress syndrome. Moreover, left ventricular preload can be affected by changes in right ventricular preload and by ventricular interdependence [26–28]. Interestingly, heart-lung interactions may be useful to assess fluid responsiveness in critical care [28, 29].

urthermore, changes in heart load conditions can in turn lead to lung injury. In a recent experimental study, Katira et al. [30] showed that abrupt deflation after sustained inflation can cause acute lung injury; in critical patients, deflation could occur when positive end-expiratory pressure is removed or the patient is disconnected from the ventilator. Apparently, lung injury results from acute left ventricular decompensation (increased left ventricular preload and afterload), which raises the pressure in the pulmonary microvasculature, injuring the endothelium and causing edema, which is in turn potentiated by the surge in pulmonary perfusion. Whether this phenomenon

observed in experimental animals could occur in patients under mechanical ventilation warrants further investigation.

Unfortunately, the hemodynamic effects caused by different PVA have not been extensively studied. In theory, ineffective efforts decrease intrathoracic pressure and could consequently increase venous return and right ventricular filling. However, there are no physiological data to confirm this hypothesis. On the other hand, our group recently showed that the tidal volume accumulated during double cycling is very high, sometimes even doubling that of normal breaths in volume-targeted modes [21]. In addition, the peak pressure of the second breath is generally greater than that of the first. Both increased volume and pressure could significantly affect preload and afterload, but the hemodynamic consequences of these effects have not been evaluated.

Although dynamic parameters based on heart-lung interactions such as pulse pressure variation (PPV) and stroke volume variation (SVV) accurately predict fluid responsiveness in patients passively adapted to the ventilator, these parameters are not good predictors of fluid responsiveness in patients with spontaneous respiratory activity probably due to multiple causes such as increased preload induced by negative intrathoracic pressure during patient inspiration and the variability of the breathing pattern [31]. In the presence of asynchronies, this effect could be magnified.

In a recent study examining whether PVA affected PPV's ability to predict fluid responsiveness in patients receiving pressure support ventilation, Messina et al. [32] compared 27 patients without PVA versus 27 with PVA as determined by visual inspection of ventilator waveforms. The area under the receiver operating characteristic curve was 0.86 (CI 0.68–0.96) in patients without PVA but only 0.53 (CI 0.33–0.73) in those with PVA ($p = 0.018$); PPV ≥ 13% predicted fluid responsiveness with 78% sensitivity and 89% specificity in patients without PVA but only 36% sensitivity and 46% specificity in those with asynchronies. PVA significantly affected PPV prediction of fluid responsiveness (OR 8.8 [2.0–38.0]; $p = 0.003$). They hypothesize that PVA affect the cyclical changes in intrathoracic pressure, resulting in unpredictable and persistent variations of right ventricular preload and left ventricular stroke volume, thereby altering the reliability of PPV in assessing fluid responsiveness. Nevertheless, more physiological and clinical data are needed to determine the implications of these findings in clinical practice.

Can asynchronies impact major outcomes?

PVA are frequent but underdiagnosed, and they have been associated with worse prognosis: discomfort; sleep disorders [33], which increase the need for sedatives [34]; prolongation of mechanical ventilation [7, 35]; increased intensive care unit (ICU) and hospital stays [33]; and increased mortality [4]. Thus, it seems crucial to take action to reduce their incidence [5]. Nevertheless, a direct causal relation between poor patient-ventilator interaction and worse outcomes has yet to be clearly demonstrated, and there is no direct evidence to demonstrate that reducing PVA guarantees better outcomes.

To clarify whether PVA are a direct causative factor of worse outcomes, it is necessary to identify and quantify the occurrence of PVA throughout the entire period of mechanical ventilation. To this end, monitoring systems have recently been developed

to enable such analyses, and these systems are helping elucidate the potential harmful physiological effects of different types of PVA [36, 37].

Monitoring systems have made possible to analyze the magnitude of PVA and how they are distributed over time, which are crucial factors in the evaluation of the impact of PVA on clinical outcomes. In a secondary analysis, Blanch et al. [4] found that although patients with an asynchrony index > 10% had similar rates of reintubation and tracheostomy compared to those with lower rates, an asynchrony index > 10% was associated with higher ICU and hospital mortality and with a trend toward longer duration of mechanical ventilation. Beyond the frequency of PVA, Vaporidi et al. [38] focused on the presence of clusters of ineffective efforts as well as their power and duration, finding that all these aspects were associated with prolonged mechanical ventilation and higher hospital mortality and highlighting the need to examine different dimensions of patient-ventilator interaction. Finally, Rue et al. [39] used Bayesian joint modeling of bivariate and competing risks data to investigate the added value of adding information about the rate of PVA to Sequential Organ Failure Assessment (SOFA) scores to predict outcomes. They found an association between the asynchrony index and live discharge, but including this information did not improve the accuracy of the prognosis of the SOFA score alone. They concluded that a more detailed analysis of PVA, together with other multidimensional data, would be necessary to confirm a causal role on ventilated patients' outcomes and comorbidities. It also remains to be demonstrated whether strategies to optimize patient-ventilator interactions improve outcomes.

De Haro et al. [21] analyzed the incidence, mechanisms, and physiologic implications of double cycling in 67 adults continuously monitored while undergoing various modes of volume- and/or pressure-targeted mechanical ventilation for more than 24 h. They found that, as previously observed by others, the volume of stacked breaths resulting from inspiratory airflow dyssynchrony can double the set tidal volume in volume-controlled ventilation [21]. This higher-than-expected tidal volume exceeds the optimal value set for protective ventilation and could harm lung tissue and respiratory muscles [21, 25], thus contributing to ventilation-associated lung injury [21, 24, 25, 40, 41].

Regarding neuropsychological outcomes, new research is exploring how mechanical ventilation is linked to psychological disorders observed in critically ill patients [42, 43]. Anxiety is one of the most common psychological symptoms reported by critically ill patients [44], affecting between 30 and 80% of all patients [45]. Patients on mechanical ventilation report worries about breathlessness, choking, or being left alone [46], and up to 47% of ICU survivors report having felt anxiety and/or fear during mechanical ventilation [47]. It seems that, even after tracheotomy, levels of anxiety do not decrease [44]. However, the direct link between anxiety and asynchronies in mechanically ventilated patients has not been explored yet. Nevertheless, respiratory difficulties, including synchronizing with the respirator, cough, and dyspnea [45, 46], are considered potent drivers of anxiety, agony, and insecurity. Anxiety has been independently associated with dyspnea in critically ill patients undergoing mechanical ventilation, and when ventilator settings are adjusted, dyspnea is reduced in at least a third of patients [48]. Therefore, asynchronies and anxiety in ICU patients could be, somehow, potentially related.

Anxiety is a state of psychological distress and physiological discomfort that, if prolonged, delays healing and predisposes to difficulties in weaning from mechanical ventilation [44]. Jubran et al. [49] also found that mechanically ventilated patients with depressive symptoms were three times more likely to experience weaning failure and death. Furthermore, high levels of anxiety often prompt professionals to apply higher sedation doses or restraints, leading to immobility, decreased level of consciousness, and loss of protective reflexes [46].

Despite the importance of the early detection of adverse psychological outcomes during ICU stay, neither anxiety nor depressive symptoms are routinely assessed in mechanically ventilated critically ill patients. In fact, most of the little information available about psychological disorders derives from the studies in ICU survivors [46]. After ICU discharge, 23 to 50% of survivors have generalized, nonspecific anxiety [2, 50, 51], and although it improves over time, anxiety levels in ICU survivors are higher than those observed in medical inpatients (5 to 20%) [2]. Nevertheless, 15 to 43% of survivors continue to have symptoms of anxiety 6 months [51] and 1 year [52] after discharge, and 60% also have other mental health problems such as post-traumatic stress disorder (PTSD) [53–55] and depression [50, 56]. These long-term mental health problems in ICU survivors are often associated with worse quality of life [2, 3].

Big data techniques applied to large observational databases to improve the management of ventilated patients

In medical research, pragmatic research attempts to approach problems from a broad and, in a sense, a realistic perspective. For example, observational studies of medical interventions may more closely reflect daily clinical practice [57]. However, the main drawback of observational studies is the potential bias and confounding factors, being difficult to establish an independent association between methods/strategies/treatments and outcome variables. The access to large databases of heterogeneous populations with high levels of complexity is key for observational studies to the extent researchers are aware of confounding and able to measure them.

Mechanically ventilated critically ill patients continuously generate huge volumes of data of varying complexity and temporal resolution [36, 58]. Some data (e.g., physiologic waveforms) are generated at very high temporal resolutions, while others are generated at much lower temporal resolutions. Whereas data about laboratory test results might be generated on a daily basis, two medical devices (e.g., multiparameter monitor and ventilator) connected to a mechanically ventilated patient record about 10 different waveforms (electrocardiographic, plethysmographic, capnographic, respiratory, arterial blood pressure, airway pressure, gas flow, volume) at 200 points per second or more, thus producing a total of 172.8 million data points each day or 1.04 billion over the average duration of mechanical ventilation. Traditionally, most of these data are underexploited, becoming unavailable immediately or within 24 to 48 h [58, 59]. Thus, the potential to discover new patterns and extract valuable information to support diagnosis or to predict the time course of a patient's condition is lost.

During mechanical ventilation, patient-ventilator interaction alternates between periods of complete synchrony and periods with clusters of frequent asynchronies [38]. Yet, physicians optimize mechanical ventilation by assessing waveforms on bedside

monitors based on their understanding of the physiological principles involved and evidence from previous studies; however, today's guidelines for ICUs derive from a scant evidence base, considering the potential evidence base given the massive data generated in the ICU [59]. It should come as no surprise that most physicians perform poorly at managing patient-ventilator interactions and do not recognize common forms of patient-ventilator asynchronies [11], but an equally important problem is that even the most highly skilled professionals can observe only a small proportion of these waveforms, thus increasing the probability of misinterpretation due to sampling errors.

For this reason, there is an urgent need for technological and analytic tools to deal with these pragmatic observational data. Big data promises to help refine our approach to PVA, improving our understanding of the various phenomena, their detection, and their treatment. At present, the continuous and automatic detection of asynchronies is an emerging technological area. Table 1 shows a comparison of some automated methods for patient-ventilator asynchrony detection [60]. However, it can be challenging to implement big data solutions in ICUs. These solutions involve new ethical issues; require investments in technical deployment to resolve problems related to interoperability, network connections, digital storage, etc.; depend on active

Table 1 Comparison of some automated methods for patient-ventilator asynchrony detection

	Type of PVA	Algorithm	Performance
Gholami et al. (2018) [69]	Cycling asynchrony (premature and delayed cycling)	ML: Random forest and *k*-fold cross validation Pressure and airflow signals *N* = 11 patients (1377 breaths)	Se 89–97%, Sp 93–99%, Kappa index 0.9
ventMAP platform Adams et al. (2017) [70]	Double-trigger and breath stacking	Rule-based algorithm Pressure and airflow signals Derivation cohort, *N* = 16 patients (5075 breaths); validation cohort, *N* = 17 patients (4644 breaths)	Se 94–96.7%, Sp 92–98%, Acc 92.2–97.7% (on the validation cohort)
NeuroSync index Sinderby et al. (2013) [71]	Patient-ventilator interaction classification (asynchronous, dyssynchronous or synchronous)	Rule-based timings algorithm EAdi and pressure signals *N* = 24 patients	ICC 0.95 vs. Colombo et al. (2011) [5]
Better Care® system Blanch et al. (2012) [37]	Ineffective efforts during expiration	Rule-based combining digital signal processing techniques and ROC curves Airflow signal Cohort 1: *N* = 8 patients (1024 breaths) Cohort 2: *N* = 8 patients (9600 breaths) with EAdi signal as reference	Se 91.5%, Sp 91.7%, PPV 80.3%, NPV 96.7%, Kappa index 0.797 (vs. the expert's classification) Se 65.2%, Sp 99.3%, PPV 90.8%, NPV 96.5%, Kappa index 0.739 (vs. EAdi signal)
Gutierrez et al. (2011) [72]	Index for asynchronous/no asynchronous breaths	Time-frequency analysis Airflow signals *N* = 110 patients	Se 83%, Sp 83% when index < 43% for AI > 10%
Mulqueeny et al. (2007) [73]	Ineffective triggering and double triggering	Rule-based and digital signal processing methods Airflow and pressure signals *N* = 20 patients (3343 breaths)	Se 91%, Sp 97%
PVI monitor Younes et al. (2007) [74]	Ineffective efforts	Rule-based Equation of motion from pressure, airflow, and Peso signals *N* = 21 patients	Se 79.7%

Abbreviations: *ML* machine learning, *Se* sensitivity, *Sp* specificity, *ICC* intraclass correlation coefficient, *Acc* overall accuracy, *Peso* esophageal pressure, *PPV* positive predictive value, *NPV* negative predictive value, *ROC* receiver operating characteristics, *AI* asynchrony index according to the definition from Thille et al. [7]

collaboration among experts from a wide range of areas (physicians, biologists, statisticians, and engineers); and must meet quality standards [61]. Big data solutions to support daily clinical decision making and improve patient care are based on storing and exploring extremely large observational datasets [58, 61–63].

Fortunately, some steps are being taken in this direction. The Multiparameter and Intelligent Monitoring in Intensive Care (MIMIC) database contains thousands of ICU records reflecting daily clinical routines from a wide variety of sources, making it extremely useful for assessing clinical decision, monitoring algorithms, and testing new research hypothesis [64]. Another interesting initiative is the AEGLE project [65, 66], aimed at identifying ineffective efforts with big data analytics. AEGLE also addresses lung overstretching during assisted ventilation, identifying injurious high levels of pressure, and predicting the risk of this phenomenon developing within the next few minutes. A recent proof-of-concept study showed that it is feasible to use Hidden Markov Models to predict PVA in critically ill patients and to infer the probability that the number of asynchrony events will be above a given threshold [67]. All these approaches have potential health and economic benefits. Given the growing interest in devising better evidence-based care in the ICU, physicians should become familiar with the opportunities and challenges of big data [68] (Fig. 3).

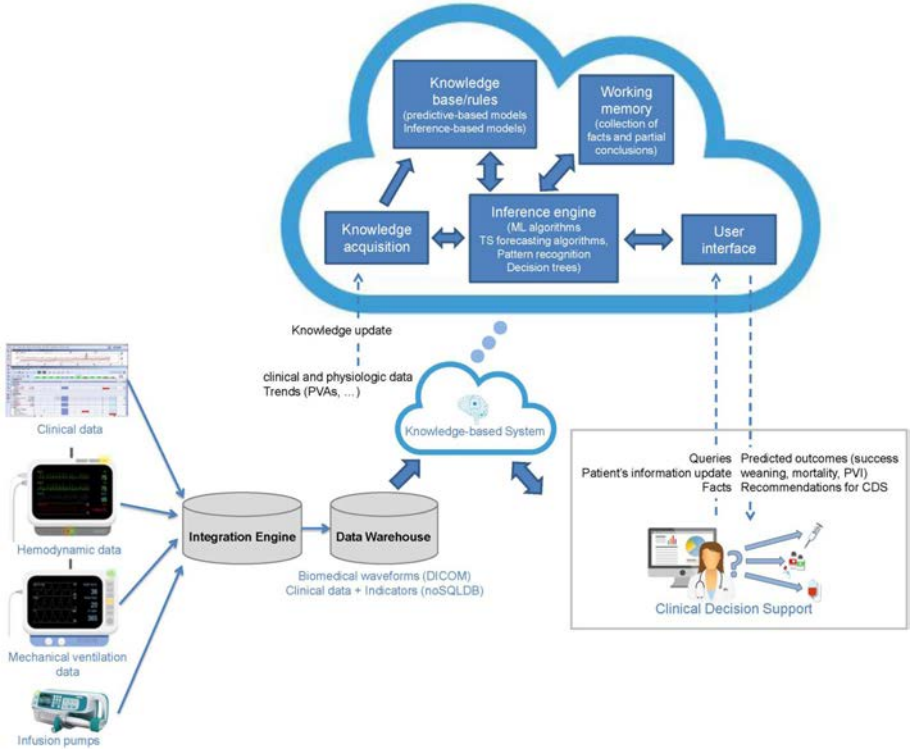


Fig. 3 Future medical trends in real-time clinical decision making for mechanically ventilated critically patients in ICU. With adequate interoperability and data storage, clinical decision support systems based on big data analytics can automatically recognize patterns in data; moreover, these systems have the ability to improve continuously by "learning" from past and new inputs. Using the cloud for big data analytics makes it easier to make predictions and better understand trends

Conclusion

The results of observational studies evidence that poor patient-ventilator interaction might cause lung and vascular injury and thereby increase mortality. The effects of asynchronies on clinical outcomes remain to be clarified, but the type and presentation of asynchronies over time seems important. Together with damage resulting from the patient's original disease, the short- and long-term consequences of poor patient-ventilator interaction can have devastating effects that hinder discharged patients' complete return to normal activities. Therefore, critical care professionals must strive to improve patient-ventilator interaction. Observational studies could have some limitations on establishing association between patient-ventilator asynchronies and outcomes, and future multicenter studies with bigger population are needed. Finally, software solutions that can identify and analyze asynchronies online and offline may lead to better care and improve outcomes.

Abbreviations

Acc: Overall accuracy; AI: Asynchrony index; CI: Confidence interval; EAdi: Electric activity diaphragm; ICC: Intraclass correlation coefficient; ICU: Intensive care unit; ML: Machine learning; NPV: Negative predictive value; OR: Odds ratio; PAW: Pressure airway; PPV: Positive predictive value; PuPV: Pulse pressure variation; PTSD: Post-traumatic stress disorder; PVA: Patient-ventilator asynchronies; ROC: Receiver operating characteristics; Se: Sensibility; SOFA: Sequential Organ Failure Assessment; Sp: Specificity; SVV: Stroke volume variation; V_t: Tidal volume

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Authors' contributions

CdH and LB have contributed to the section "Evolving concepts on patient-ventilator interaction and asynchronies". AO has contributed to the section "Heart Lung Interaction in patients with asynchronies". JLA, SFG, and GNV have contributed to the section "Can asynchronies impact major outcomes?" RM and JM have contributed to the section "Big data techniques applied to large observational databases to improve the management of ventilated patients". All authors read and approved the final manuscript.

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Competing interests
Mr. Montanya and Dr. Blanch own stock options of Better Care SL, which is a research and development spinoff of Corporació Sanitària Parc Taulí (Spain). Drs. Blanch discloses that he is inventor of one Corporació Sanitaria Parc Taulí owned US patent: "Method and system for managed related patient parameters provided by a monitoring device," U.S. Patent No. 12/538,940. The remaining authors declare that they have no competing interests.

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SCIENTIFIC LETTER

Double and multiple cycling in mechanical ventilation: Complex events with varying clinical effects

Doble y múltiples ciclados en ventilación mecánica: eventos complejos con diferentes significado clínico

Dear Editor,

In order to effectively unload inspiratory muscles and provide a safe ventilation (enhancing gas exchange and protect the lungs), the ventilator should be in synchrony with patient's respiratory rhythm. The complexity of such interplay leads to several concerning issues that clinicians should be aware and able to recognize.[1] Double-cycling, probably the second most common patient-ventilator dyssynchrony, consists of a sustained inspiratory effort that persists beyond the ventilator's inspiratory time increasing tidal volume in pressure assist-control mode and both tidal volume and airway pressure in volume assist-control mode. Double-cycling can cause prolonged diaphragm contraction with potential muscle dysfunction; breath-stacking, because of all or part of the tidal volume from the first breath is added to the second; and eventually ventilator-induced lung injury.[2,3]

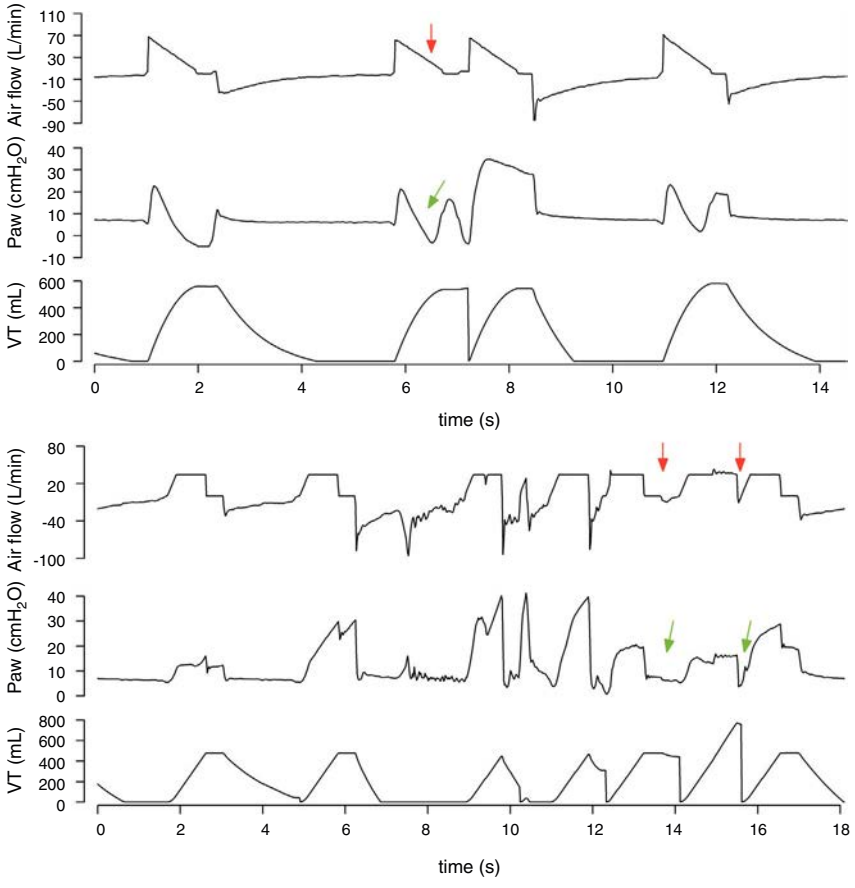

Figure 1 Flow dyssynchrony in volume-assist control ventilation with decelerating (a) and constant flow (b). Delivered flow is insufficient to meet the patient's demand, resulting in a strong inspiratory effort, reflected as a drop in airway pressure (Paw) (green arrows), lasting longer than ventilator inspiratory time, that triggers second and third mechanical inspirations (red arrows).

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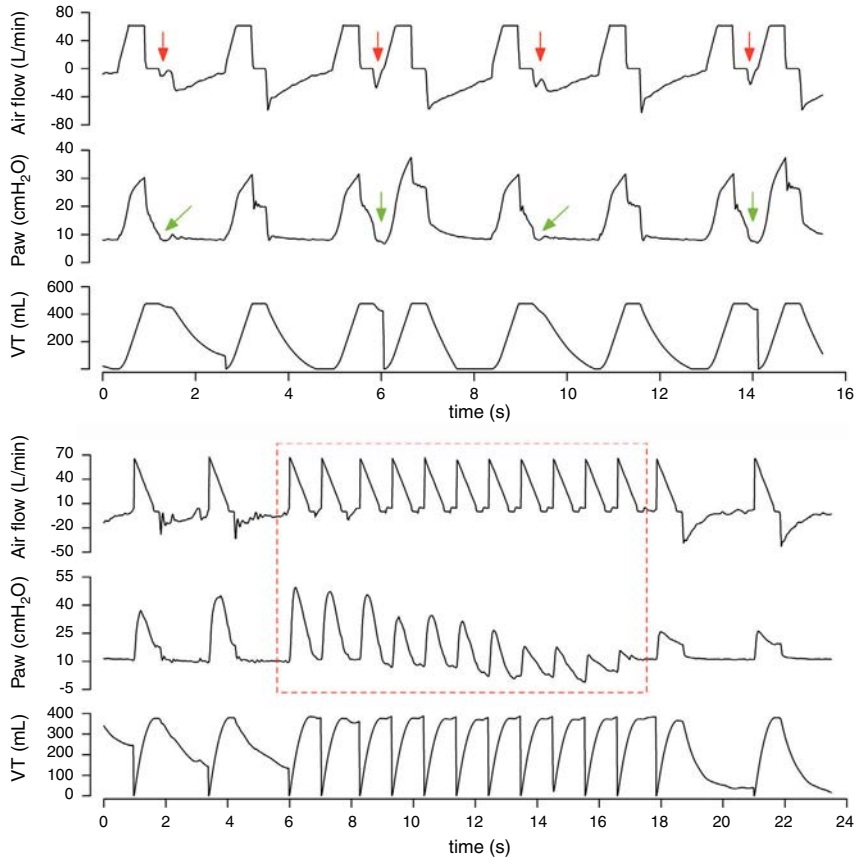

Figure 2 (a) Reverse-triggering in volume-assist control ventilation. In the first breath, mechanical insufflation is time-triggered; at the end of mechanical inspiration, reverse-triggering is seen as a negative deflection in airway pressure (Paw) (green arrows) and an increase in expiratory flow (red arrows). The third time-triggered breath is followed by a fourth, induced by reverse-triggering before complete exhalation, resulting in breath-stacking; this pattern repeats in following cycles. (b) Multiple cycling in volume-assist control ventilation with decelerating flow: the sudden cluster of mechanical insufflations without associated expiratory flow and automatic change from time-triggering to flow-triggering with progressive decrease in airway pressure (Paw) (dotted-line square) are due to massive air leakage caused by endotracheal tube displacement from the main airway; after spontaneous tube repositioning, Paw and expiratory flow recover, resulting in a change back from flow-triggering to time-triggering. This situation carries a high risk of unplanned extubation, which here occurred shortly afterward.

Nevertheless, under the same phenomenon witnessed in the ventilator screen, different pathophysiological mechanism hides which should be differentiated by clinicians. Here we report different scenarios in where double-cycling occurs with meaningful differences.

High respiratory drive generates strong inspiratory efforts resulting in flow dyssynchrony, in where the flow delivered is insufficient to meet patient's demand, consequently, two or three mechanical inflations are delivered within a single neural inspiration (Fig. 1a and b). Vigorous inspiratory efforts could cause load-induced injury when the diaphragm muscle is sensitized to mechanical stress by systemic inflammation.[4] Moreover, eccentric (lengthening) contractions during expiration or during patient-ventilator dyssynchrony may be particularly injurious.[5,6] The resulting breath-stacking generates high transpulmonary and transvascular pressure gradients, as well as elevated local stress and uneven distribution of pressure in dependent zones of the lung.[7]

Breath-stacking also occurs in reverse-triggering, an entrainment phenomenon recently described referring to an abnormal relationship between the ventilator and the patient where the external stimulus, in this case, mechanical insufflation by the ventilator, elicits a reflexive neural response that initiates a diaphragmatic exertion. Ratios of 1:1, 2:1, 3:1 and also 1:2 of mechanical to reverse-triggered breath have been described. Breath-stacking could develop when the diaphragmatic contraction (neural time) exceed the mechanical insufflation time and drives an ineffective effort that, if strong and long enough, generates a second mechanical breath (Fig. 2a), thus delivering large tidal volumes with consequent high stress and strain upon the lungs.[2,8,9]

By contrast, in flow-triggered modes, repeated double or multiple cycling without expiration or breath-stacking in very short periods accompanied by a progressive decrease in airway pressure (Fig. 2b) strongly suggests partial dislocation of the endotracheal tube and high risk of unplanned extubation.

Waveforms presented were acquired with Better Care™ and plotted with R3.3.1.

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SCIENTIFIC REPORTS

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Predicting Patient-ventilator Asynchronies with Hidden Markov Models

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In mechanical ventilation, it is paramount to ensure the patient's ventilatory demand is met while minimizing asynchronies. We aimed to develop a model to predict the likelihood of asynchronies occurring. We analyzed 10,409,357 breaths from 51 critically ill patients who underwent mechanical ventilation >24 h. Patients were continuously monitored and common asynchronies were identified and regularly indexed. Based on discrete time-series data representing the total count of asynchronies, we defined four states or levels of risk of asynchronies, z1 (very-low-risk) – z4 (very-high-risk). A Poisson hidden Markov model was used to predict the probability of each level of risk occurring in the next period. Long periods with very few asynchronous events, and consequently very-low-risk, were more likely than periods with many events (state z4). States were persistent; large shifts of states were uncommon and most switches were to neighbouring states. Thus, patients entering states with a high number of asynchronies were very likely to continue in that state, which may have serious implications. This novel approach to dealing with patient-ventilator asynchrony is a first step in developing smart alarms to alert professionals to patients entering high-risk states so they can consider actions to improve patient-ventilator interaction.

Patients in intensive care units (ICU) sometimes need mechanical ventilation to improve alveolar ventilation and oxygenation while decreasing the load on the respiratory muscles. Patients may undergo mechanical ventilation for several days until their condition improves. Although mechanical ventilation is a life-saving intervention, numerous complications can develop. Ventilator cycles must match the patient's own rhythm of breathing; however, mismatching is common, resulting in poor patient-ventilator interaction with deleterious consequences[1–5]. When patient-ventilator asynchronies occur, breathing becomes more difficult and the patient's condition can worsen. Asynchronies are more dangerous when their frequency is relatively high[4]. Asynchronies can prolong mechanical ventilation and ICU stays[4,6], increase the probability of respiratory muscle and lung injury[7,8], increase mortality[3,9], and lead to other complications[10,11].

Personalized or precision medicine is an emerging concept that will change clinical practice in ICUs in the short-to-mid term, helping physicians choose the right therapy at the right time[12,13]. ICU patients are intensely and continuously monitored, generating extremely large datasets. All this data is readily available and can be exploited with big data tools and automated learning systems, providing a unique opportunity to improve decision-making in this demanding environment.

Based on their understanding of the physiological principles involved and evidence from clinical studies, physicians manage mechanical ventilation by assessing waveforms on bedside monitors. However, most perform poorly at managing patient-ventilator interactions, often failing to identify common forms of asynchronies[14,15]. Moreover, patients take several thousands of breaths each day, and busy professionals can observe only a small proportion of these. Early detection of an increased frequency of asynchronies could alert physicians to

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immediately diagnose and manage the problem. Although new technologies enable continuous bedside monitoring to detect asynchronies automatically[3,16–19], monitoring systems are as yet unable to predict asynchronies in real time.

Time series forecasting aims to predict future events based on past observations. A hidden Markov model (HMM)[20,21] is a kind of statistical approach applied in data mining for recognizing patterns over time. Sequential data can be represented as a Markov chain of latent (or hidden) states with observable, state-dependent output (in the form of data points). HMM have proven useful in a variety of fields, such as computational biology[22], physiological time series analysis[23,24], speech recognition[25], financial problems[26], and others[27]. Currently, the incidence of asynchronies is classified as low or high with an arbitrary cut-off of 10%[4,28]. In the setting of this study, the hidden states can be interpreted as proxies for patients' level of synchrony with the ventilator; each state can be associated with a different frequency of events and therefore results in a different level of risk.

We aimed to obtain proof of concept that regularly indexing the most common types of patient-ventilator asynchronies along time can generate a discrete time series that can be used to predict the probability of asynchronies occurring in future periods. To this end, we employed an HMM. To take into account the wide heterogeneity among ICU patients and high complexity of critical illness, we considered time series covering the entire period of mechanical ventilation in patients with different conditions. Although not a specific aim of this study, we also conducted a subanalysis of the probable effects of asynchronies on some cardiovascular parameters.

Methods

Patients and data. Patients admitted to rooms equipped with the Better Care® system (Better Care SL, Spain) in one of two ICUs in the period comprising September 2011 through May 2016 were potentially eligible. Exclusion criteria were age <18 years, mechanical ventilation for <24 hours, pregnancy, do-not-resuscitate orders, chest tubes with suspected bronchopleural fistula, and admission for organ donation. Finally, 51 patients who met the above criteria were selected.

The Comitè d'Ètica d'Investigació amb medicaments at the Corporació Sanitària Parc Taulí and the Clinical Research Ethics Committee of Fundació Unió Catalana d'Hospitals approved the study and waived informed consent because the study was observational, posed no added risk to the patient, and did not interfere with usual care.

ICU rooms were equipped with one of the following ventilators: Evita 4 (Dräger, Germany), Puritan Bennet 840 (Covidien, US), or Servo I (Maquet, Sweden). Better Care® uses drivers specifically designed to continuously capture output signals from different bedside medical devices (ventilators, multiparameter monitors, etc.)[3,16,19]. These signals are resampled at 200 Hz and processed with dedicated algorithms to obtain a set of physiological variables and time events. From the airway pressure and airflow signals, the system detects the most common types of asynchronies (ineffective inspiratory efforts, double cycling, short cycling, and prolonged cycling). See the Supplementary Methods and the Supplementary Fig. S1 for definitions of each asynchrony. For each breath, the system determines whether one or more asynchrony events are present and stores this information in a PostgreSQL (Berkeley, CA; https://www.postgresql.org/) database for further analyses.

Sampling at regular periods of time (T), we generated time series representing the number of events (i.e., the asynchronies listed above) that occurred in each period. In this study, respiratory cycles were grouped in periods of 5, 10, 15, 20 and 25 minutes, and asynchrony events occurring in each of these time intervals were counted throughout recording.

Figure 1 shows representative examples of the evolution of the number of events and their distributions in three patients.

Algorithm. Because HMMs can detect states with different frequencies of events, they may be able to predict the number of asynchrony events that will occur. HMMs automatically detect whether a patient is in a 'low-risk state' (i.e., low frequency of asynchrony events) or in a 'high-risk state' (i.e., high frequency of asynchrony events). The number of states is a parameter that needs to be set by the user before training the model. Given any number of possible predefined states, the model finds the most probable distribution for each state, a posteriori, and also makes it possible to detect when the patient changes from one state to another. Then, the uncertainty of being in each state, represented by this posterior probability distribution, can be summarized in terms of credible intervals.

According to previous investigations[3,29], the model was estimated with four states, z1–z4, that would match usual clinical judgement at the bedside. The state with the lowest number of events is z1 (very-low-risk state), representing good interaction with the ventilator with almost no asynchronies; states z2 and z3 are intermediate states (low-risk and high-risk states, respectively) with increasing mismatch between the patient and the ventilator; and z4 is the state with the highest number of events (very-high-risk state), where asynchrony is severe because the incidence of events is high and might lead to considerable patient distress and might increase the risk of ventilator-associated lung injury.

We used a Poisson distribution for the emission probabilities associated with each state (also known as output probabilities). Therefore, the HMM consisted of a Poisson regression with intercept only and the patient's state as a categorical variable. The model and the predictions were built using time intervals of 5, 10, 15, 20, and 25 minutes. The predictions are one-step ahead forecasts of the number of events. The expectation maximization (EM) algorithm iteratively computes the transition and emission probabilities[21]; the EM algorithm initializes with random values for the transition and emission probabilities. Next, the Viterbi algorithm[30] uses the emission and transition probabilities estimated earlier to find the most likely sequence of latent states (i.e., the posterior probability distribution) that generated the data. See the Supplementary Methods for more specific details about HMM.

In addition to the predictions of the expected counts, we also made predictions of the expected rate of asynchrony events (i.e., number of event counts divided by the total number of respiratory cycles per period of observation T) to obtain values that would be easier to interpret clinically. This step used a generalized linear model with the parameter obtained from the fitted HMM. See the Supplementary Methods for additional information.

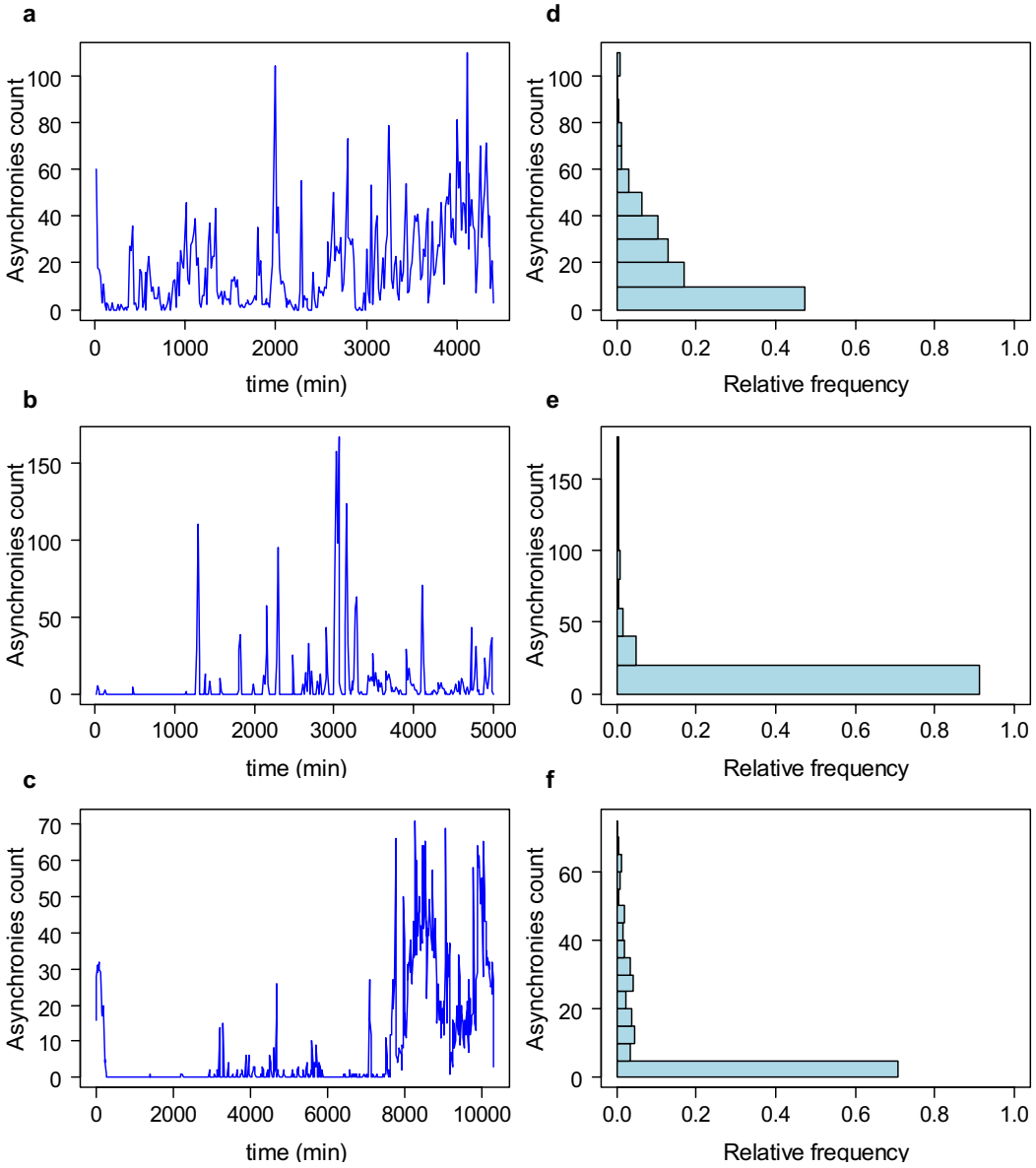

Figure 1. Time series of asynchronies count indexed each 15 min (**a**–**c**) and their corresponding histograms (**d**–**f**) from three representative patients. Note these are discrete time series of non-negative values, and positively skewed (histogram characterized by a long tail in the positive direction) with several observations having a value close to zero, which justifies the use of a Poisson distribution to model this kind of data.

We used R 3.3.1 (R Core Team, Vienna, Austria, URL http://www.R-project.org/) with the RPostgreSQL package (Berkeley, CA; https://CRAN.R-project.org/package=PostgreSQL) to interface with the database and the depmixS4 package[31] to fit and analyze the HMM models.

Analysis of cardiovascular parameters. From the posterior probability distributions, summarized in terms of credible intervals, we identified periods of asynchronies belonging to each state and matched them with the corresponding periods in the cardiovascular time series (heart rate and oxygen saturation time series) sampled every 15 minutes. Then, we used descriptive statistics to analyze the mean heart rate in beats per minute (bpm), the mean level of oxygen saturation (%), and episodes of bradycardia, tachycardia, and hypoxemia.

Results

Patients' baseline characteristics (Supplementary Table S1) are reported as medians (25^{th}, 75^{th} percentiles) for continuous variables, unless otherwise specified. We analyzed a total of 10,409,357 breaths from the 51 patients. To test the model's ability to predict new data and to estimate the model's generalizability, we used a k-fold cross validation (k = 5) procedure. This validation procedure was also used to test the fit of the HMM with only intercept versus a base model whose prediction is always zero events, as this is the most likely outcome. The final model was constructed on the total sample of patients.

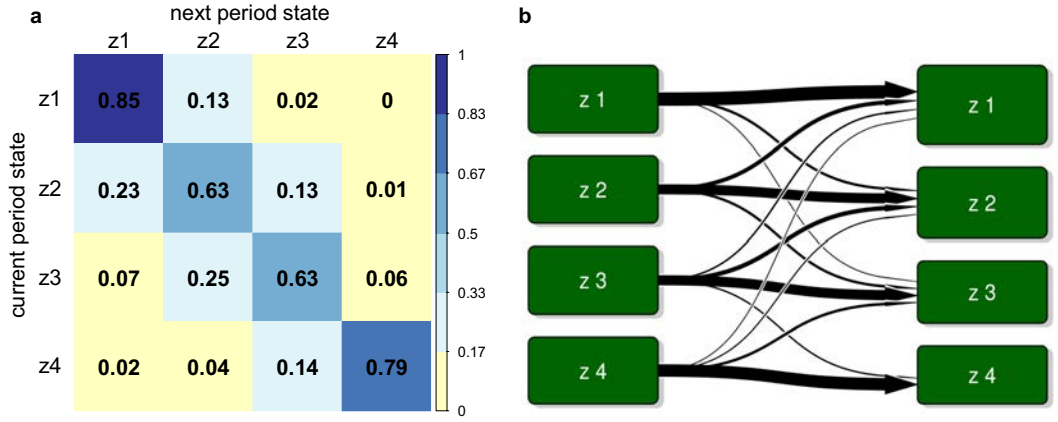

Figure 2. State transition for the Poisson hidden Markov models from the time series indexed each 15 min. (**a**) Transition probability matrix. Values in each cell represent average probability computed on the total sample of patients. Diagonal of the matrix represents the probabilities of not changing in the next period. Cells with zero probability represent a value < 0.005. (**b**) State transition diagram. Arrows indicate the probability of transition from each state to other ones: thicker arrows indicate higher probability; no arrow indicates the probability is zero (or near zero).

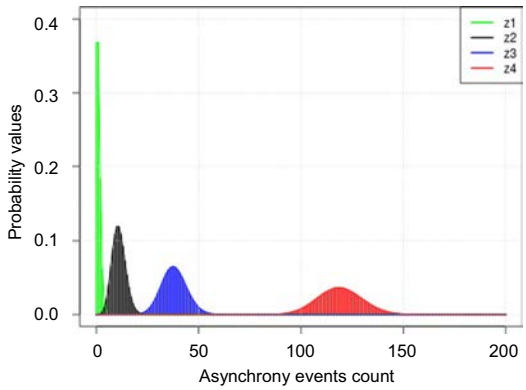

Figure 3. Emission probabilities for each state (z1–z4) in a 15-minute interval. Note state z1 (i.e., that with the lowest number of events and consequently lowest level of risk) is the most likely, whereas state z4 (i.e., that with the highest level of risk) is the less likely.

Variable	Values for each state			
	z1	z2	z3	z4
λ	1 (0, 3)	11 (5, 18)	38 (26, 51)	119 (98, 141)
rate (%)	0.2 (0.19, 0.2)	3.38(3.36, 3.39)	11.6(11.6, 11.7)	35.1(35.0, 35.3)
tspent	0.52	0.28	0.14	0.06

Table 1. Mean (95% CI) expected number (λ) of asynchrony events for time series defined each T = 15 minutes, approximate expected rate determined by a generalized linear model, and time spent in each state (tspent) represented as a proportion of the total time.

Figure 2 shows the transition probabilities of the model for time intervals of 15 minutes. The probability of switching from one state to another decreased with the distance between states, being 0.13 for the switch from z1 to z2, 0.02 for the switch from z1 to z3, and <0.005 for the switch from z1 to z4. The probability values of the diagonal were large, signifying that all four states were highly persistent. Thus, the state at period $t+1$ is very likely to be the same as the state at period t. Analyzing time series defined for the other time intervals yielded similar results (see Supplementary Fig. S2).

The probability distributions of the observations for the four states were computed with only intercept. This means that there is a unique probability distribution for each state. Figure 3 shows the probability distribution for each of the four states for a time interval of 15 minutes. Table 1 shows the average number of events expected to occur in each state and the proportion of time that patients spent in each state. Patients spent 52% of the time

Episodes	Values for each state			
	z1	z2	z3	z4
Bradycardia				
%episode	8.36	7.74	4.55	9.07
tepisode	4.42 (18.8)	2.43 (12.9)	1.11 (8.58)	1.86 (11.7)
Tachycardia				
%episode	39.3	42.4	46.3	36
tepisode	25.5 (40.9)	22.9 (38.3)	28.2 (40.9)	26.9 (42.6)
Hypoxemia				
%episode	5.94	11.5	16.1	15.1
tepisode	1.95 (12.2)	2.51 (12.6)	3.66 (14.9)	5.13 (19.4)

Table 2. Characterization of some cardiovascular episodes during asynchronies, by state. Percentage of 15-minute periods (%episode) with at least one episode of bradycardia, tachycardia, and/or hypoxemia, with respect to the total number of T = 15-minute periods; and mean (SD) percentage of time within each T = 15-minute periods (tepisode) with episodes of tachycardia, bradycardia, and/or hypoxemia. Bradycardia episode = heart rate <60 bpm; Tachycardia episode = heart rate >100 bpm; Hypoxemia episode = oxygen saturation <90%.

in the lowest state, z1, where a mean (95% CI) of asynchrony event expected to occur was 1 (0, 3). By contrast, patients spent 14% of the time in z3 (where a mean of 38 (26, 51) asynchrony events occurred) and 6% of the time in z4 (where a mean number of 119 (98, 141) asynchrony events occurred). The approximate percentage of asynchrony events (Table 1) is 11.6 (11.6, 11.7) in z3 and 35.1 (35, 35.3) in z4. See Supplementary Table S2 for the analyses with the other time intervals.

To assess the accuracy of the models, we computed the root mean square error (RMSE) for the HMM with only intercept and the base model. This step was conducted by means of k-fold cross validation on five different training and validation subsets. The HMM's predictions with only intercept were better, RMSE(mean and (standard error)) = 19.5 (3.12), than the base model's predictions, RMSE = 35.4 (6.58).

Descriptive information about the behaviour of some cardiovascular parameters in each state is reported in Table 2 and Supplementary Fig. S3. Oxygen saturation (Supplementary Fig. S3) seemed to decrease during state z4, and consequently, both the frequency and duration of hypoxemia episodes (Table 2) seemed to increase. By contrast, the heart rate and bradycardia and tachycardia episodes were similar in the different states.

Discussion

This proof-of-concept study shows that it is feasible to use HMMs to predict patient-ventilator asynchronies in critically ill patients and to infer the probability that the number of asynchrony events will be above a given threshold. Previous studies[3,14,16,32,33] aimed to detect asynchronies once they occurred; to our knowledge, this is the first study focused on predicting asynchrony events before they happen. Unlike other studies based on very limited observation periods in narrowly defined subpopulations of patients with specific conditions[7,28], we analyzed the entire period of mechanical ventilation in a heterogeneous population of ICU patients with a wide variety of critical illnesses, increasing the generalizability of the results and the model's ability to take trends into account.

The HMM was able to detect states with different levels of risk depending on the expected count of asynchrony events. Patients spent long periods of time with very few events and short periods of time with many events. Large shifts between states were unlikely, as the most probable switches were to "neighbouring" states. Patients tended to remain in the same state even when large intervals of time were considered. This implies that once patients entered a state with a high number of asynchronies, they would very likely continue in that state in the following periods, increasing the likelihood of serious complications.

The intensity of the asynchronies probably has more prognostic importance than the overall average occurrence[34]. Vaporidi *et al.*[9] recently found that although the overall rate of ineffective inspiratory efforts as a percentage of total breaths was not associated with outcome even when it was greater than 10%, clusters of ineffective efforts were associated with prolonged MV and increased mortality, suggesting a dose effect. Similarly, double cycling can also occur in clusters, although the clinical importance of clusters of double-cycling events remains to be characterized[29]. Therefore, although the states with higher numbers of asynchronies do not last long, they are likely to have more clusters of asynchronies.

How long patients tolerate poor interaction with the ventilator is unknown. Vaporidi *et al.*[9] considered periods of ineffective efforts lasting more than 3 min to be clusters, although the median duration of the clusters ranged from 23 min to 17 min during their 6-day follow-up period. Similarly, de Haro *et al.*[29], defining clusters of double cycling as periods in which at least 10% all breaths in a 3-min period were double cycled, found that the median duration of clusters was 15.5 min. Thus, we decided that a 15-min interval would be a reasonable period for physicians to deal with asynchronies. However, we also analysed other intervals (results in supplementary material).

Patient-ventilator asynchrony can lead to considerable patient distress, and it also impedes the effectiveness of the ventilator in decreasing work of breathing or providing adequate alveolar ventilation, which may lead to an episode of acute hypoxemia[35]. Interestingly, our subanalysis found that more and longer-lasting episodes of low

oxygen saturation levels occurred in z4 states, suggesting that periods of severe dyssynchrony between the patient and the ventilator might constitute a medical emergency.

HMMs could be used to create a system that could predict the likelihood of asynchrony events and alert professionals to the danger of clusters of asynchronies developing. Alarms could be set to go off when the predicted number of events exceeded a certain threshold or when the patient has entered in a state where a large number of events are expected and the possibility of clusters is greater. Such a tool would aid medical decision making, allowing staff to take actions (if necessary) to improve patient-ventilator interaction and to avoid complications from poor interaction. The implementation of such a system in routine daily care is beyond the scope of this proof-of-concept study; to guarantee reasonable performance, this approach must be validated with data from multiple ICUs to ensure that our results can be generalized.

Our computations of the HMM could not model the expected rate of the occurrence of events; rather they merely modelled the counts. To a certain extent, this technical shortcoming was overcome when making the predictions taking into account the total number of respiratory cycles per period of observation. This allowed us to express the average number of events in terms of a rate, providing an approximate value to illustrate the magnitude of the problem from a clinical standpoint.

Although HMMs seem feasible in this setting, other statistical models or machine-learning algorithms could also be used to predict asynchronies. Furthermore, additional physiologic variables (e.g., respiratory rate, inspiratory time, positive end-expiratory pressure, etc.) and ventilatory parameters (ventilation mode, tidal volume/peak pressure, etc.) could improve the accuracy of the predictions.

In summary, HMMs can predict periods with high frequencies of asynchrony events and could be used in an early-warning system. This study represents another step towards precision medicine in the ICU, which could lead to a more individualized ventilatory strategies and, consequently, better clinical outcomes and patient experiences.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author Contributions

Study concept and design: Y.M., R.M., B.S., J.M. and L.B. Data acquisition: G.M., C.d.H., C.S. and R.M. Analysis and interpretation: Y.M., R.M., J.L.A. and L.B. Statistical analysis: Y.M. and R.M. Drafting of the manuscript: Y.M., R.M. and J.L.A. Revision of manuscript for important intellectual content: R.M., J.L.A., C.d.H., R.F., R.M.K. and L.B. Study supervision: R.M., B.S., J.M., J.L.A. and L.B. Data access and responsibility: L.B. had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of the data analysis. Y.M. and R.M. contributed equally to the study. All authors reviewed the manuscript.

Additional Information

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Minimizing Asynchronies in Mechanical Ventilation: Current and Future Trends

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Patient-ventilator asynchrony exists when the phases of breath delivered by the ventilator do not match those of the patient. Asynchronies occur throughout mechanical ventilation and negatively affect patient comfort, duration of mechanical ventilation, length of ICU stays, and mortality. Identifying asynchronies requires careful attention to patients and their ventilator waveforms. This review discusses the different types of asynchronies, how they are generated, and their impact on patient comfort and outcome. Moreover, it discusses practical approaches for detecting, correcting, and preventing asynchronies. Current evidence suggests that the best approach to managing asynchronies is by adjusting ventilator settings. Proportional modes improve patient-ventilator coupling, resulting in greater comfort and less dyspnea, but not in improved outcomes with respect to the duration of mechanical ventilation, delirium, or cognitive impairment. Advanced computational technologies will allow smart alerts, and models based on time series of asynchronies will be able to predict and prevent asynchronies, making it possible to tailor mechanical ventilation to meet each patient's needs throughout the course of mechanical ventilation. *Key words: patient-ventilator asynchrony; mechanical ventilation; monitoring; ineffective inspiratory efforts; reverse-triggered breath; double triggering; flow asynchrony; proportional modes.* [Respir Care 2018;63(4):464–478.

Introduction

In critically ill patients, mechanical ventilation aims to improve oxygenation and decrease the work of breathing and load on the respiratory muscles to support patients until their condition improves. Optimal patient-ventilator interaction can help avoid excessive sedation, anxiety, dis-

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Drs Subirà and de Haro contributed equally to this work.

Table 1. Types of Asynchronies

Inspiratory Period	During the Transition From Inspiration to Expiration	Expiratory Period
· Trigger delay	· Double triggering due to short cycling or reverse triggering	· Ineffective inspiratory effort
· Inspiratory flow mismatching	· Expiratory muscle contraction due to prolonged cycling	· Auto-triggering
· Short cycling		· Expiratory muscle contraction
· Prolonged cycling		
· Reverse triggering		

comfort, episodes of fighting with the ventilator, diaphragmatic dysfunction and atrophy due to disuse, potential cognitive alterations, prolonged mechanical ventilation, and additional lung or respiratory muscle injury.[1,2] Research has shown that patients ventilated for > 24 h who are able to trigger the ventilator have a high incidence of asynchrony during assisted mechanical ventilation.[3] Asynchronies are common throughout mechanical ventilation, occur in all mechanical ventilation modes, and might be associated with outcome,[4] especially when they occur in clusters.[5] This review discusses the different types of asynchronies and how they are generated, their impact on patient comfort and outcome, and practical approaches for detecting, correcting, and preventing them.

Briefly, patient-ventilator asynchrony exists when the phases of breath delivered by the ventilator do not match those of the patient. To meet the patient's demands, the ventilator's inspiratory time and gas delivery must match the patient's neural inspiratory time. Many authors have classified asynchronies and their causes.[6-10] Asynchronies occur with minimal differences between day and night, and the most prevalent asynchrony overall and in every mechanical ventilation mode is ineffective inspiratory efforts, followed by double triggering.[3,4,11,12] When the entire period of mechanical ventilation is taken into account, asynchronies are slightly more frequent in pressure support ventilation (PSV) than in volume control-continuous mandatory ventilation or pressure control-continuous mandatory ventilation.[4] Nevertheless, within each mode the settings for peak air flow, airway pressure, minute ventilation, and rise time, as well as the criteria to terminate inspiration, can have strong effects on asynchrony generation.

Types of Asynchronies

Table 1 summarizes the different types of asynchronies and specifies the phase of the respiratory cycle in which they occur. Ineffective triggering is defined as inspiratory muscle effort not followed by a ventilator breath. This asynchrony occurs when the patient's attempt to initiate a breath does not reach the ventilator's trigger threshold. In other words, the ventilator fails to detect the patient's inspiratory efforts, which are characterized physiologically by an increase in transdiaphragmatic pressure (ie, a decrease in esophageal pressure and an increase in gastric pressure) and/or electrical activity of the diaphragm (EA_{di}).[10,13,14] Ineffective triggering results in the patient's breathing frequency being higher than the ventilator's rate. Waveforms show ineffective inspiratory efforts as a decrease in airway pressure associated with a simultaneous increase in air flow (Fig. 1). Most ineffective efforts are detected during mechanical expiration; however, they can also occur during inspiration, where they are characterized by an abrupt increase in inspiratory flow (during PSV) or a transient abrupt decrease in airway pressure (during volume control-continuous mandatory ventilation) that fails to trigger a full additional breath.[3,14,15]

Double triggering consists of a sustained inspiratory effort that persists beyond the ventilator inspiratory time, cessation of inspiratory flow, or the beginning of mechanical expiration, and it consequently triggers a second ventilator breath, which may or may not be followed by a short expiration, where all or part of the volume of the first breath is added to the second breath.[4,6,16-20] The delivered volume accumulated during the 2 breaths without normal exhalation is very high and can even double the tidal volume (V_T) of normal breaths in volume-targeted modes (Fig. 2). Therefore, high V_T from double triggering might

Dr Blanch is the inventor of a system registered as U.S. Patent No. 12/538,940, owned by Corporació Sanitaria Parc Taulí. Dr Blanch owns stock options of Better Care S.L., which is a research and development spinoff of Corporació Sanitària Parc Taulí, Sabadell, Spain. The other authors have disclosed no conflicts of interest. This work was funded by projects PI09/91074 and PI13/02204, integrated in the Plan Nacional de R+D+I and co-funded by the ISCIII-Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional. CIBER Enfermedades Respiratorias, Fundación Mapfre, Fundació Parc Taulí, Plan Avanza TSI-020302-2008-38, MCYIN, and MITYC in Spain.

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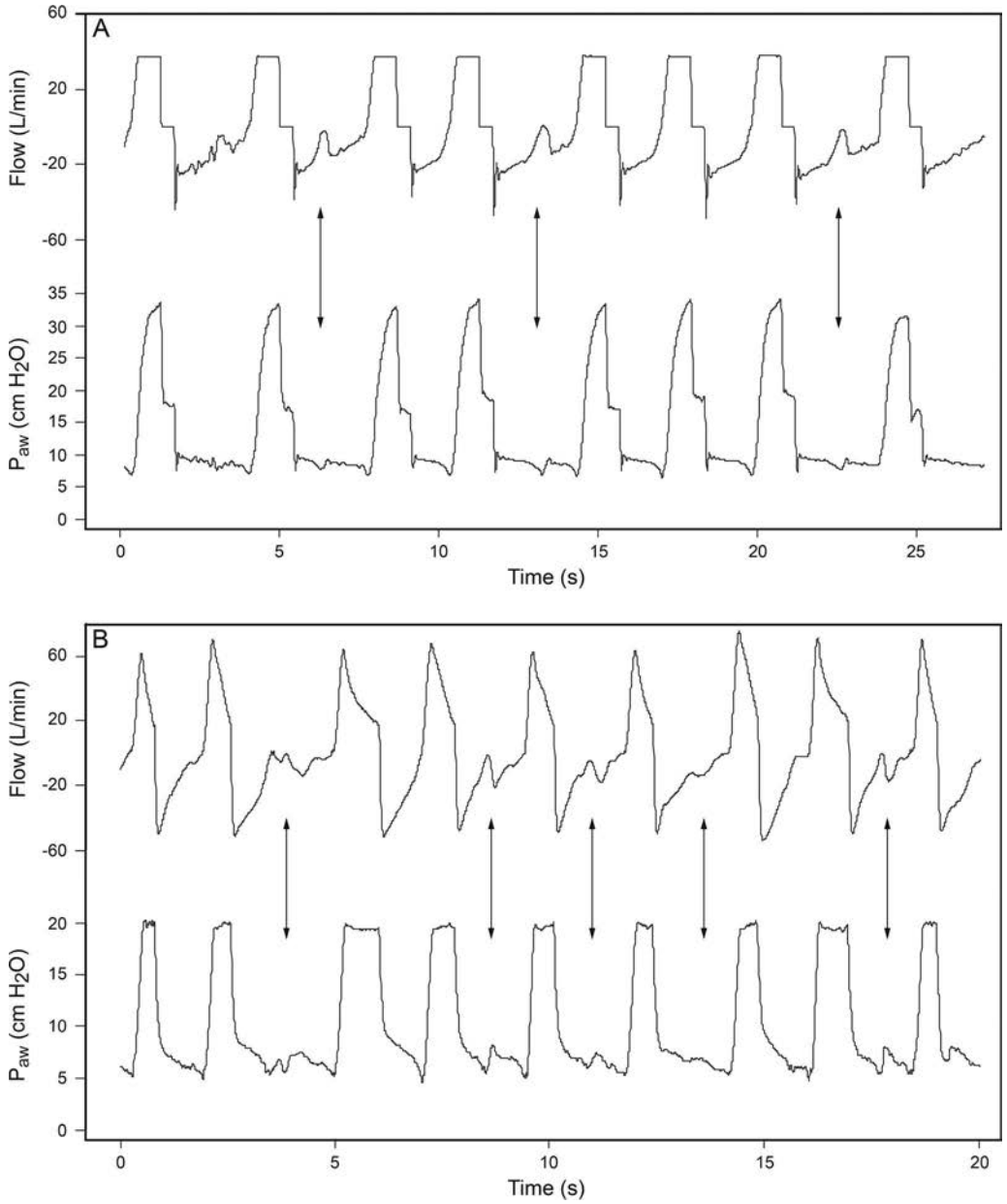

Fig. 1. Gas flow and airway pressure tracings in a representative patient receiving mechanical ventilation in A: volume control-continuous mandatory ventilation and B: pressure support ventilation. Ineffective inspiratory efforts are present during expiratory periods (arrows). The patient's breathing frequency does not match the ventilator's frequency. P_{aw} = airway pressure.

result in overinflation and high transpulmonary pressures leading to pulmonary barotrauma, excessive stress and strain, and increased inflammatory response.[21-23] Double triggering can occur at any time during the course of mechanical ventilation,[4] so its overall incidence and potential effects on outcome are unknown.

Another under-recognized form of asynchrony is reverse triggering, in which ventilator insufflations trigger diaphragmatic muscle contractions through activation of the patient's respiratory center in response to passive insufflation of the lungs. Flick et al[24] showed that controlled mechanical ventilation breaths were associated with phasic electromyographic activity late in breath during inspiration at the point where delivered V_T was close to spontaneous V_T. Similarly, Kallet et al[25] reported a common observation during lung-protective ventilation, whereby chest-wall stiffening at the onset of a mechanical breath results in an initially low ventilator flow delivery that begins to taper off. When the patient's inspiratory effort begins later in the inspiratory phase, the resulting ventilator flow paradoxically becomes ascending, and inspiratory effort continues into the expi-

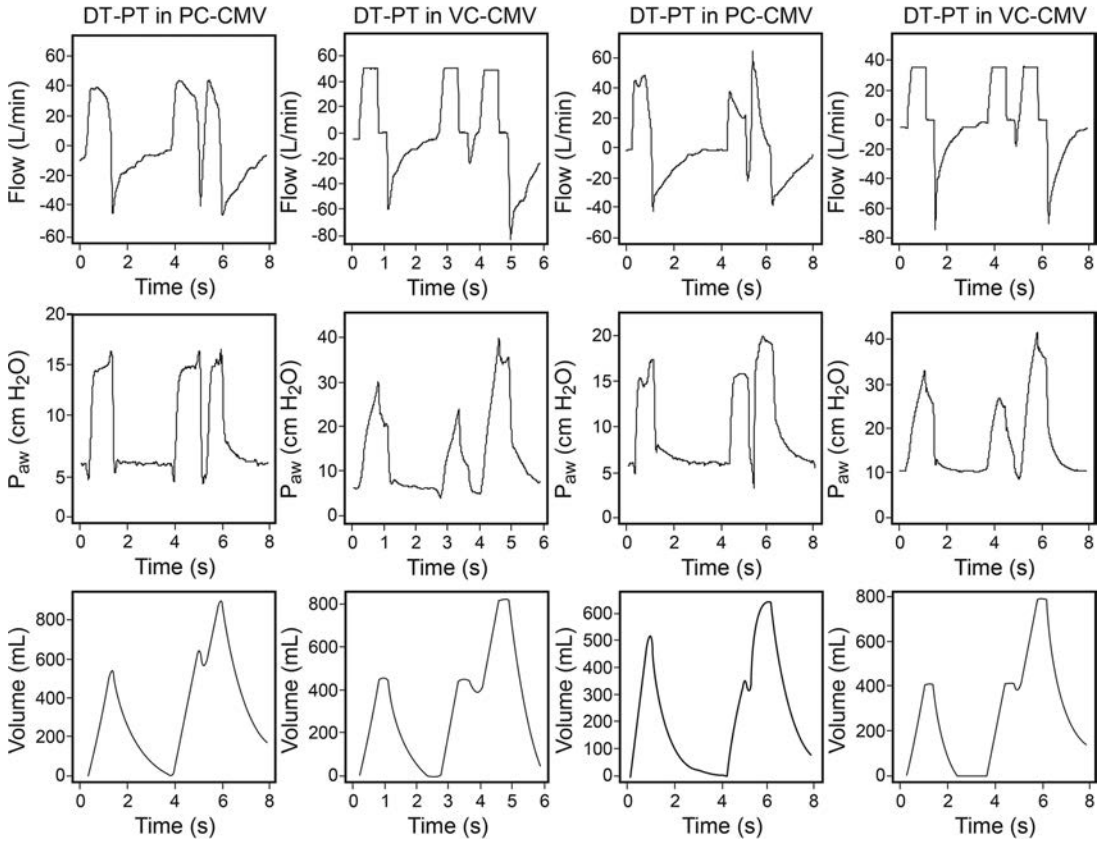

Fig. 2. Representative waveforms of gas flow, airway pressure, and volume during patient-triggered double triggering and reverse-triggered double triggering events in pressure control-continuous mandatory ventilation (PC-CMV) and VC-CMV modes. DT = double trigger; PT = patient triggering; RT = reverse triggering; VC-CMV = volume control-continuous mandatory ventilation with constant flow; P_{aw} airway pressure.

ratory phase and, if strong enough, could result in a double-triggered breath.

Akoumianaki et al[26] analyzed recordings of flow, airway pressure, and esophageal pressure or EA_{di} obtained in 8 consecutive subjects, documenting that reverse triggering occurred during 12–100% of the total recording period. During reverse triggering, the patient's inspiratory effort starts after and usually persists beyond the machine breath. Because the patient's inspiratory muscles are still active at the beginning of expiration, impeding the elastic recoil of the respiratory system from increasing alveolar pressure, the peak expiratory flow is markedly reduced.[27] When the patient's effort is sufficiently deep and long, the decrease in airway pressure can trigger a second ventilator breath with a nil or very short expiratory time[26-28] (Fig. 2). The low V_T and short inspiratory times recommended for protective ventilation can increase the risk of double triggering. In the ARDS Network trial, subjects receiving 8 mL/kg V_T had fewer asynchronies than those receiving 6 mL/kg,[29,30] so patients with double triggering while ventilated with 6 mL/kg V_T and plateau pressure < 30 cm H_2O might benefit from increasing V_T to 7–8 mL/kg, provided there is no added risk of superimposed lung injury.

Inspiratory flow mismatching occurs when the ventilator fails to meet the patient's flow demand. Inadequate flow delivery is most common when ventilator flow delivery is set inappropriately low, or the combination of V_T and inspiratory time does not result in adequate flow during acute respiratory failure, or when inspiratory flow demands are high and vary from breath to breath.[24,31,32] Inspiratory flow mismatching is more frequent in modalities where it is impossible to modify the flow, such as volume control-continuous mandatory ventilation [6,31] (Fig. 3). MacIntyre et al[33] demonstrated that inspiratory flow mismatching could be improved by increasing ventilator flow delivery or, when subjects were ventilated with a flow-limited strategy, by using the variable flow pressure-limited breath. It is particularly important to track inspiratory flow mismatching during lung-protective ventilation because vigorous inspiratory efforts could promote pulmonary edema by increasing the transvascular pressure gradient[34] and tidal recruitment associated with pendelluft flow (lung volume redistribution) and consequent regional

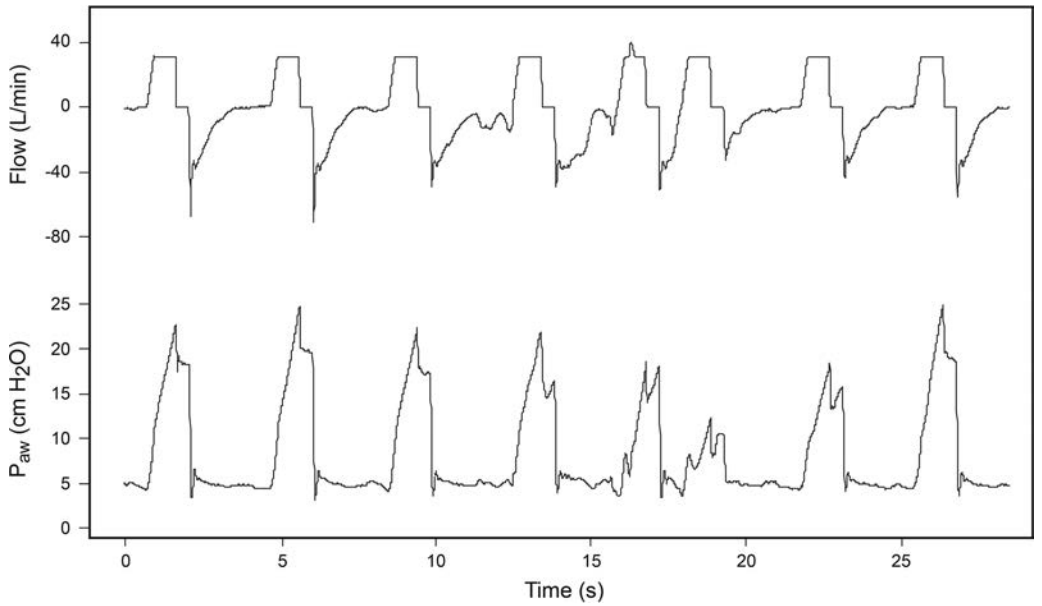

Fig. 3. Gas flow and airway pressure tracings in a patient with acute brain injury receiving mechanical ventilation in VC-CMV. Almost passive fully assisted ventilator breaths, where respiratory muscle activity is required only for breath triggering, coexist with breaths where airway pressure appears pulled down because respiratory effort persists during the inspiration period. In this case, inspiratory-flow mismatching occurs in breaths with high ventilator demands where set ventilator gas flow is insufficient to meet the patient's demands. VC-CMV = volume control-continuous mandatory ventilation with constant flow; P_{aw} = airway pressure.

lung overdistention, which can occur in flow- and pressure-limited breaths in volume control-continuous mandatory ventilation and volume control decelerated flow, as well as in pressure control-continuous mandatory ventilation.[21-23] Interestingly, during lung-protective ventilation in patients with ARDS, work of breathing is inversely related to the difference between the ventilator-delivered V_T and patient-generated V_T during a brief trial of spontaneous breathing, and this effect of V_T on work of breathing is independent of changes in peak inspiratory flow.[20]

Cycle asynchrony or termination asynchrony usually occurs when there is a mismatch between the patient's inspiratory time (ie, neural time) and the ventilator's inspiratory time. Premature or short cycling occurs when the neural time is greater than the ventilator's inspiratory time. The ventilator ends flow delivery, but the patient's inspiratory effort continues. If the patient's effort exceeds the trigger threshold, it can activate another breath, generating a double trigger. Prolonged or delayed cycling occurs when the patient initiates the exhalation while the ventilator is still delivering flow. On waveform graphics, this is readily observable as a sharp pressure spike originated by recruitment of the expiratory muscles as an instinctive response to excessive muscle loading, which can be confirmed by palpating the abdominal muscles for activity. Modern ventilators incorporate active exhalation valves that allow gas to be released from the exhalation valve during the inspiratory phase if the patient makes an expiratory effort, thereby reducing expiratory resistance.[35] The most frequent causes are inappropriate cycling settings or a leak, which is infrequent in invasive mechanical ventilation. A gas leak can prevent airway flow from reaching the cycling-off threshold, and in this scenario an added time criterion ends inspiration. Accurate interpretation of cycle asynchronies would require monitoring not only usual ventilator waveforms but also esophageal pressure or EA_{di}.[3,6,11]

Management of Asynchronies at Bedside: A Practical Approach

Identifying asynchronies requires careful attention to patients and their ventilator waveforms. Table 2 summarizes the different approaches that can be used to correct each type of asynchrony. Although sedation and analgesia are often used to treat asynchronies, this approach raises various concerns. Deep sedation is actually an independent risk factor for ineffective inspiratory efforts.[36] de Wit et al[11] observed that subjects with a Richmond Agitation-Sedation Scale score of 0 had no asynchronies, but the proportion of ineffective efforts increased linearly for every decrease of 1 point on the scale. The Ineffective Triggering Index was 2% in conscious subjects and 11% in unconscious subjects; on the other hand, they found no differences between subjects who were delirious and those who were not. Furthermore, deep sedation is associated with longer mechanical ventilation duration and ICU stays.[37]

Table 2. Strategies for Managing Asynchronies

Asynchrony	Action
Inspiratory flow mismatching	Increase gas flow; decrease respiratory drive and assess adequacy of analgesia and sedation; check for dyspnea.
Short or prolonged cycling	Increase or decrease inspiratory period; check cycling off in pressure support; use proportional modes.
Double triggering	Increase ventilator inspiratory time; try pressure support, titrating flow termination criteria to improve synchrony, or proportional modes; consider paralyzing agents if tidal volume is too elevated (> 8 mL/kg) in ARDS or in patients with risk factors for developing lung injury.
Double triggering due to reverse triggering	Decrease sedation; check breathing frequency; consider paralyzing agents if tidal volume is too elevated (> 8 mL/kg) in ARDS or in patients with risk factors for developing lung injury.
Expiratory muscle contraction due to prolonged cycling	Reduce inspiratory period by checking cycling off and tidal volume; check for comfort.
Ineffective inspiratory efforts	Check trigger sensitivity and excessive air trapping; check for excessive assistance (excessive set frequency and or inspiratory time during controlled modes or excessive pressure support ventilation level); counterbalance auto-PEEP by using external PEEP; check for dyspnea; consider proportional modes.
Auto-triggering	Check trigger sensitivity; check for leaks and water in the ventilator circuit.
Expiratory muscle contraction during expiration	Check for excessive assistance; check for air trapping and auto-PEEP.

Adjusting ventilator settings seems to be a better approach. When Chanques et al[36] analyzed subjects with asynchronies treated with no intervention, increased sedation-analgesia, or changes in ventilator settings, they found asynchronies only significantly decreased after changes in ventilator setting. Sedation is used in combination with opioids to provide comfort, pain control, and treatment of dyspnea in patients receiving mechanical ventilation. Opioids can help bring about better patient-ventilator interaction because they can reduce active expiration and affect the respiratory center, reducing the central perception of dyspnea and anxiety. Once asynchronies are resolved, however, the interaction between the patient and ventilator must be carefully reevaluated by the entire attending clinical team. It is essential to detect dyspnea caused by low assistance and to adjust the breathing frequency to ensure that each inspiratory effort is followed by a ventilator breath, while evaluating the potential for lung injury and mortality from the newly elevated V_T.

Asynchronies and Respiratory Sensations

The classic picture of severe patient-ventilator asynchrony includes diaphoresis, nasal flaring, tachycardia, tachypnea, sternomastoid activity, abdominal paradox, and recession of the suprasternal, supraclavicular, and intercostal spaces. This common clinical situation alerts nurses, respiratory therapists, and physicians to possible pain, dyspnea, delirium, anxiety, inappropriate ventilator settings, or severe unresolved acute disease, prompting them to proceed with the most appropriate treatment.[38] Often described as fighting with the ventilator, this situation results from a mismatch between the patient's respiratory efforts and the ventilator-delivered breaths. Ventilator support must be adapted to be synchronous to the neural drive to breathe; when the imposed load increases respiratory demand, the result is dyspnea.

Dyspnea is a subjective state of breathing discomfort that consists of qualitatively different sensations that vary in intensity. Dyspnea starts with a physiologic impairment that alters the function of the respiratory pump via stimulation of afferent receptors like chemoreceptors and chest wall and pulmonary receptors.[39-42] Additional mechanisms include corollary discharges, which involve neural messages sent from the motor to the sensory cortex; the intensity of these discharges correlates with increased neural output to the ventilatory muscles. This phenomenon, called neuroventilatory dissociation, which alters the ventilatory pump and has a direct effect on dyspnea, reflects a mismatch between outgoing signals from the respiratory controller and the response of the respiratory system components. The altered sense of effort or work of breathing may increase the intensity of dyspnea.[40,43,44] In ICU patients undergoing mechanical ventilation, multiple factors contribute to dyspnea; the most important of these are air hunger and increased respiratory work/effort.[45,46]

Dyspnea and discomfort can result from flow delivery that is insufficient to meet the patient's air flow demands; this usually occurs in acute respiratory failure. When inspiratory flow demands are high and differ from breath to breath, discomfort and dyspnea develop when ventilator flow delivery are set inappropriately low. Inspiratory flow mismatch appears to be more common with ventilatory settings that deliver fixed flow (flow-targeted breaths) than with those in which flow can vary with effort (pressure-targeted breaths).[6,7] When dyspnea is associated with vigorous spontaneous diaphragmatic contractions in pressure-pre-set or pressure-targeted modes, pressure delivery is

synchronized with vigorous patient inspiratory efforts, establishing harmful transpulmonary pressure swing.[21,22] Recently, Yoshida et al[23] showed that spontaneous inspiratory efforts could promote tidal recruitment associated with pendelluft flow (lung volume redistribution) and consequent regional lung overdistention. Moreover, limiting V_T and transpulmonary pressure on the basis of esophageal pressure calculations does not eliminate harm from spontaneous breathing in experimental and human ARDS, unless the level of spontaneous effort is lowered and local lung stress is reduced.

Functional imaging studies of dyspnea and air hunger have shown that the perception of dyspnea involves the limbic system, and its activation can alter the affective dimension of pain, memory, or emotions, which can lead to severe psychological trauma.[47,48] Cognitive impairment in ICU patients deserves increased recognition and action from both clinicians and researchers.[48-50]

In a 6-month observational study, Schmidt et al[51] assessed the prevalence of dyspnea in mechanically ventilated subjects in which 96 subjects were enrolled as soon as they could answer symptom-related questions assessing dyspnea caused by air hunger or respiratory effort, pain, and anxiety on visual analog scales. Interestingly, half of the subjects reported dyspnea, and dyspnea was associated with anxiety, assist/control ventilation, and increased heart rate. Adjusting ventilator settings improved dyspnea in one third of subjects, and successful extubation within 3 d was significantly less frequent in subjects whose dyspnea failed to recede after ventilator settings were adjusted. Therefore, patient perception of breathing is essential for symptom management, and ventilator setup seems related to extubation success. However, health care workers' ability to assess a patient's experiences of breathing is debatable. To assess the degree of agreement between nurses, physicians, and subjects, Haugdahl et al[52] used an 11-point numerical scale considering dyspnea, perception of security, and improvement of respiratory function in 100 ICU subjects at the end of a spontaneous breathing trial performed for the most part with some level of support. Two thirds of the subjects reported moderate or severe dyspnea; the intensity of dyspnea reported by the subjects was more than twice that reported by nurses and physicians, and the underestimation of breathlessness was not associated with professional competencies. In a recent editorial, Banzett and Schwartzstein[53] stressed the importance of asking patients about breathing discomfort, urging ICU professionals to routinely assess and document dyspnea in the same manner as pain.

Controversy exists on the potential of ineffective efforts to generate dyspnea. Ineffective or wasted inspiratory effort can be present in all modes of mechanical ventilation except neurally adjusted ventilatory assist (NAVA).[54-57] Ineffective efforts can occur as a result of an insensitive or poorly responsive triggering system and auto-PEEP. In this situation, the patient's respiratory muscles must first overcome auto-PEEP in the alveoli before any circuit pressure or flow change can trigger a ventilator breath.[58] Ineffective efforts may develop when inspiratory assistance is too high. Vitacca et al[59] reported that comfort followed a U-shaped trend under different levels of PSV (irrespective of COPD diagnosis) and that high assistance caused not only less comfort, but also an increase in ineffective efforts.

Patient comfort can be improved more by adjusting ventilatory settings to improve patient-ventilator synchrony than by increasing sedation.[36,55,60]. In PSV and other modes, ventilator adjustments can reduce ineffective triggering events without decreasing tolerance.[6,61] Some studies have shown that reducing pressure support or inspiratory duration eliminated ineffective triggering in most subjects with weaning difficulties and a high percentage of ineffective efforts, and this approach did not cause excessive work of breathing or modifying their breathing frequency.[16,62] Schmidt et al[63] measured the electrical activity of extradiaphragmatic respiratory muscles, a surrogate measure of dyspnea, during variations in pressure support and expiratory triggers in 12 subjects ventilated with PSV. They found that, independent of the expiratory trigger, high levels of PSV increased ineffective efforts without inducing dyspnea. However, dyspnea was significantly higher at low pressure support levels where ineffective efforts were not found.

Taken all together, these data suggest a close relationship between respiratory sensations and respiratory mechanics. Underassistance results in less dynamic hyperinflation and fewer ineffective efforts, but more dyspnea and more respiratory muscle activity; by contrast, overassistance increases both ineffective efforts and overinflation, but reduces respiratory muscle activity and dyspnea. In fact, in dynamically hyperinflated, spontaneously breathing patients, dyspnea appears when a breath is initiated at higher end-expiratory lung volume, and inspiratory capacity and V_T are limited.[39,40] However, we can speculate that in mechanical ventilation where V_T is not restricted, overassisted patients could have frequent ineffective efforts with less sensation of dyspnea, possibly placing them at risk of acute respiratory muscle fatigue and muscle injury. More studies are warranted to determine the impact of dyspnea and anxiety in mechanical ventilation patients and the suitability of low V_T ventilation strategies beyond ARDS patients.

Asynchronies in PAV and NAVA

The criteria used to choose the best ventilatory mode for a given patient vary along the course of critical illness. In

the initial phase of mechanical ventilation, the most important feature is safety, so full ventilatory support is normally applied, commonly in the volume control-continuous mandatory ventilation mode. This approach enables tight control of V_T and PEEP, aiming for optimal oxygenation and ventilation while avoiding lung damage from overdistention or atelectrauma. Once these goals are achieved, other issues become important, such as reducing sedatives while avoiding discomfort, dyspnea, and asynchronies.

At this point, physicians commonly switch to partial ventilatory support, with PSV being the most common mode. The apparent simplicity of PSV has led to universal acceptance, but PSV is also associated with a significant number of asynchronies.[3-5] Two other methods of partial ventilatory support have been available for > 20 years: proportional assist ventilation (PAV) and NAVA. Both methods are designed for better coupling between the patient's ventilatory pattern and ventilator delivery. PAV is a pneumatic mode that applies pressure to the airways directly proportional to the flow generated by the patient, with the aim of counterbalancing deteriorated compliance and resistance. Thus, ventilator flow starts when the patient's inspiratory flow starts and stops when the patient's flow stops. NAVA is a neurally activated mode that uses a dedicated nasogastric tube with electrical sensors near the diaphragm to detect EA_{di} signals; ventilator flow starts with an increase in the EA_{di} signal and stops with a decrease in the EA_{di} signal. The next section reviews studies dealing with asynchronies in PAV and NAVA in chronological order.

Studies on PAV

Xirouchaki et al[64] randomized 208 mechanically ventilated subjects to receive either PSV or PAV. Failure rate was lower with PAV than with PSV (11.1% vs 22.0%, $P = .04$). The proportion of subjects exhibiting major patient-ventilator asynchronies after adjusting the initial ventilator settings was lower with PAV than with PSV (5.6% vs 29.0%, $P = .001$).

In a physiologic study involving 11 subjects, Costa et al[65] found that the portion of V_T delivered in phase with patient inspiratory time was significantly higher with PAV. The time when subjects remained in synchrony with the ventilator was longer with PAV than with PSV ($P < .01$). With PSV, 45% of subjects showed an asynchrony index > 10%, whereas during PAV the asynchrony index was nil.

Alexopoulou et al[66] studied 14 subjects, most having COPD, during sleep. Compared to PSV, PAV significantly reduced the number of patient-ventilator asynchrony events per hour of sleep (5 vs 40), but PAV was associated with slightly greater sleep fragmentation (19 vs 18 events/h) and less REM sleep (0% vs 5.8%).

Using a mechanical lung simulator, Vasconcelos et al[67] studied 3 respiratory mechanics profiles (normal, obstructive, and restrictive), with variations in the duration of inspiratory effort (0.5, 1.0, 1.5, and 2.0 s). In comparison with PSV, PAV improved patient-ventilator synchrony, with a shorter triggering delay (28 ms vs 116 ms) and no cycling asynchrony in the restrictive profile. PAV prevented premature cycling but not delayed cycling, especially in obstructive respiratory mechanics profiles, and it was associated with lower V_T.

Comparing patient-ventilator asynchrony between PSV and PAV plus (PAV+) in 20 surgical subjects during weaning, Gautam et al[68] found that asynchrony was less common in PSV. The mean number of total asynchronous recorded breaths was 7.05 ± 0.83 during sleep and 4.35 ± 5.62 when subjects were awake in PSV versus 6.75 ± 112.24 and 10.85 ± 11.33, respectively, in PAV+, leading them to conclude that PAV+ was not superior to PSV with respect to cardiorespiratory function.

Studies on NAVA

Piquilloud et al[57] compared PSV and NAVA in 22 spontaneously breathing subjects intubated for acute respiratory failure. NAVA reduced trigger delay (69 vs 178 ms) and improved expiratory synchrony (inspiratory time in excess, 126 vs 204 ms). Fewer asynchrony events were observed with NAVA (1.2 vs 3.1 events/min). NAVA reduced the number of subjects with asynchrony index > 10% by 50%. No ineffective efforts or late cycling were observed with NAVA. Subjects undergoing NAVA had less premature cycling (0 vs 0.14 events/min), but more double triggering (0.8 vs 0).

Cammarota et al[69] used a helmet to study 10 postextubation hypoxemic subjects during three 20-min trials of noninvasive ventilation (NIV) in PSV and NAVA modes. Compared with PSV, the mechanical expiratory time was significantly shorter with NAVA, while the inspiratory time and duty cycle were greater. Time of synchrony between diaphragm contraction and ventilator assistance was better with NAVA (0.79 vs 0.60 s). The asynchrony index exceeded 10% during PSV, but not in NAVA.

Bertrand et al[70] used a crossover design to study 13 subjects with acute respiratory failure during 30-min trials of NIV in PSV and NAVA modes. With NAVA, there were fewer asynchrony events (10 vs 17 events), fewer subjects with asynchrony index > 10%, fewer ineffective efforts, and less delayed cycling. NAVA was also associated with reduced trigger delay (0 vs 90 ms) and reduced inspiratory time in excess (10 vs 125 ms), but neural inspiratory time was similar with PSV and NAVA. The ratio of the EA_{di} signal to its maximal value was higher with NAVA than with PSV.

Vignaux et al[71] studied 6 pediatric subjects on NIV in PSV and NAVA modes and found lower trigger delay with NAVA (61 vs 149 ms). In PSV, the asynchrony index was significantly lower during the period, with the expiratory trigger setting achieving the lowest number of asynchrony events compared to the period after the initial trigger setting (40% [28–65 events] vs 65.5% [42–76 events], $P < .001$). With NAVA, the asynchrony index was lower, with all types of asynchronies except double triggering.

Schmidt et al[72] studied 17 subjects receiving prophylactic postextubation NIV with PSV and NAVA with and without an NIV algorithm. Inspiratory trigger delay was not affected by the NIV algorithm, but this trigger delay was shorter with NAVA. Inspiratory time in excess was shorter with NAVA and PSV with the NIV algorithm than with PSV without the algorithm. The asynchrony index was not affected by the NIV algorithm, but was significantly lower with NAVA. The asynchrony index influenced by leaks was insignificant with NAVA and significantly lower than with PSV. There was more double triggering with NAVA.

Baudin et al[73] studied 11 pediatric subjects with respiratory syncytial virus bronchiolitis with failure of nasal CPAP, comparing ventilation with NAVA versus pressure control-continuous mandatory ventilation. In NAVA mode, the asynchrony index was lower (3% vs 38%) and the trigger delay was shorter (44 vs 116 ms). Ineffective efforts were significantly less frequent with NAVA (0.5 vs 21.8 events/min). Subject breathing frequencies were similar, but the ventilator rate was higher with NAVA (59 vs 49 breaths/min).

Lee et al[74] compared NIV using PSV and NAVA after weaning from mechanical ventilation in 15 preterm infants. Lower values were observed during NAVA for trigger delay (35 vs 294 ms), ventilator inspiratory time (423 vs 534 ms), inspiratory time in excess (32% vs 294%), maximum EA_{di} (13 vs 17 μV), swing EA_{di} (9 vs 12 μV), and peak inspiratory pressure (12 vs 15 cm H_2O). The main asynchrony events with PSV were ineffective efforts and autotriggering. All types of asynchronies except double triggering were reduced with NAVA, and the asynchrony index was significantly lower with NAVA.

Yonis et al[75] studied 30 intubated subjects ventilated with PSV and NAVA for 24-h periods. In NAVA, the total number of asynchronies per minute was lower (0.5 vs 1), the asynchrony index was lower (1.7 vs 3.4), and the rates of ineffective efforts (0.77 vs 0.94) and auto-triggering were lower (0.2 vs 0.7); however, the rate of double triggering was higher (0.76 vs 0.71).

Di Mussi et al[76] randomized 25 subjects ventilated with controlled ventilation for at least 72 h to receive either PSV or NAVA for 48 h. At the end of the 48-h period, neuro-ventilatory efficiency and neuro-mechanical efficiency had increased with NAVA, but not with PSV. The asynchrony index was lower with NAVA (5.4 vs 9.5 with PSV, $P = .04$).

Only Schmidt et al[77] compared PSV with both PAV and NAVA. In a study of 16 intubated subjects, they found PAV and NAVA prevented the increase in V_T with high levels of assistance. EA_{di} was higher with PAV than with PSV. The coefficient of variation of V_T was higher with NAVA and PAV. Ineffective triggering was lower with PAV and NAVA than with PSV, but double triggering was higher with NAVA than with PAV and PSV.

This review allows us to conclude that, compared with PSV, both PAV and NAVA improve patient-ventilator coupling with associated improvement in comfort and dyspnea. PAV is less able to reduce the inspiratory delay with high levels of auto-PEEP, but NAVA appears to achieve consistently less excessive inspiratory time at the cost of a consistent trend toward a higher incidence of double triggering. Nevertheless, these physiological advantages have not improved outcomes such as the duration of mechanical ventilation, delirium, or cognitive impairment.[77]

Consequences of Asynchronies

Interest in asynchronies has increased during the last 10 years. Some studies[3-5,17,78] have reported that asynchronies are more common than expected and are associated with poor prognosis (Fig. 4). de Wit et al[12] recorded pressure-time and flow-time waveforms in 60 subjects for 10 min and found that subjects with an Ineffective Triggering Index > 10% required longer duration of mechanical ventilation. Moreover, Thille et al[3] observed that mechanical ventilation duration and incidence of tracheostomy were greater in subjects with an asynchrony index > 10%, although there were no differences in mortality. However, a recent exhaustive analysis of ventilator waveforms covering > 80% of total ventilatory time found higher ICU and hospital mortality in subjects with an asynchrony index > 10%.[4]

When the flow delivered by the ventilator does not meet a patient's needs, excessive effort and work results in flow asynchrony, causes discomfort, and may lead to fatigue. Excessive stress on the diaphragm and other respiratory muscles can cause functional and anatomic damage to muscle fibers. In animals and humans, excessive exercise can increase pro-inflammatory cytokines, and excessive muscle effort can be detrimental over time. Moreover, during loaded breathing or acute endotoxemia, the diaphragm initiates an inflammatory response and a much greater upregulation of pro-inflammatory mediators relative to other skeletal muscles.[79,80] Sometimes excessive effort and discomfort are treated with sedatives or even neuromuscular blockers, but both neuromuscular blockers and deep seda-

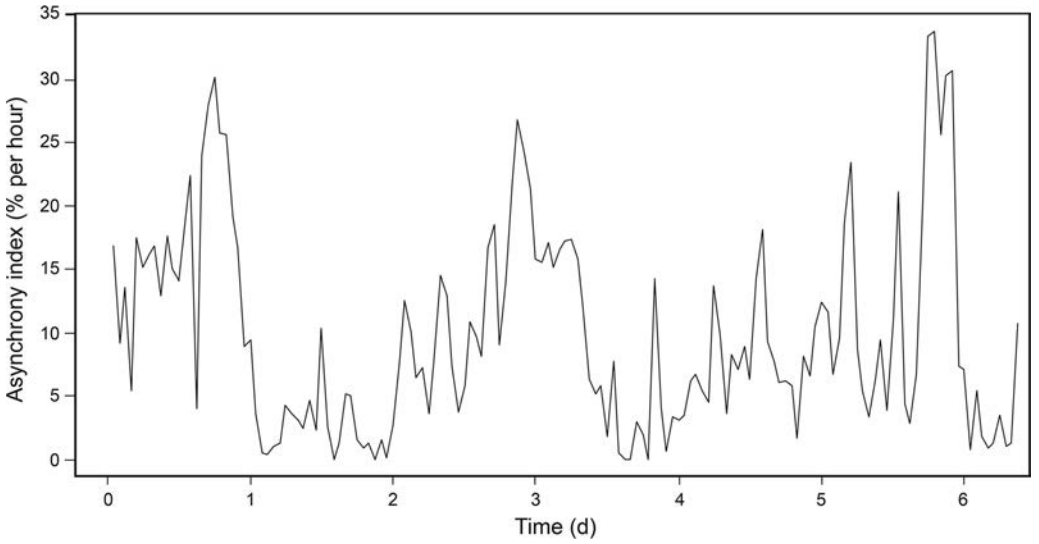

Fig. 4. Asynchrony index percentage per hour, continuously recorded over several days. Recordings show that periods of moderate asynchronies alternated with periods of a high level of asynchronies.

tion increase the risk of respiratory muscle weakness and atrophy; the respiratory muscles can begin to atrophy after as little as 48 h of inactivity.[81,82]

However, keeping the patient passive to mechanical ventilation is not the best approach to treating asynchronies because the consequences of respiratory muscle weakness are prolongation of weaning, increased dependence on the ventilator, and longer ICU stay, all of which increase the risk of death.

The average proportion of asynchronies during mechanical ventilation may be less important for outcomes than the intensity or period in which they occur. Using a Bayesian joint model of bivariate longitudinal and competing risks data, Rué et al[83] found that adding information about the overall incidence of asynchronies to Sequential Organ Failure Assessment scores did not improve mortality prediction. However, in a recent prospective observational study, Vaporidi et al[5] pointed out the relatively greater importance of clusters of ineffective inspiratory efforts compared to global incidence over a long period of time (Fig. 5). Analyzing 24-h recordings obtained in 110 subjects on the first day of PSV or PAV, they found that clusters of ineffective efforts ($>$ 30 in a 3-min period) were often present; unlike overall incidence, duration and power of clusters were associated with prolonged mechanical ventilation and increased mortality. This investigation highlights the importance of variability of ineffective efforts over time within patients and underscores the need for continuous monitoring of airway pressure and air flow. Moreover, investigations are needed to determine the number, type, and duration of asynchronies that spontaneously breathing patients can tolerate.[84,85]

Monitoring Asynchronies in the Era of Precision Medicine

Personalized or precision medicine will change clinical practice in the ICU in the short to medium term, making it possible to choose the right therapy at the right time.[86,87] Continuous monitoring of physiologic signals, ventilator performance, and other point-of-care data comprise the starting point for precision critical care. Monitoring asynchronies during mechanical ventilation will help optimize patient-ventilator interaction, improve comfort, and decrease morbidity and mortality, given that asynchronies, or clusters of asynchronies, have been associated with ICU outcomes.[4,5,84,86,88,89] To date, studies have focused on detecting asynchronies,[90-92] but future studies will also focus on predicting asynchronies and preventing them. Smart alarms and early predictive models based on time series of asynchronies will help improve decision making. Nevertheless, critical illnesses are tremendously complex and patients are heterogeneous,[86] and the analysis of asynchronies is only one piece of the puzzle. ICU data integration is the main challenge in developing effective tools for data analysis.

Together with big data techniques,[93] new approaches such as deep machine learning, artificial neural networks, and nonlinear dynamics are crucial for the development of precision medicine in the ICU.[94] For example, neural networks have been used successfully for breathing-pattern recognition in critical care, weaning from mechanical ventilation, and ICU outcomes prediction.[95-97] Likewise, neural networks may be able to recognize other types of respiratory patterns during periods of poor patient-ventilator interaction. A neural network

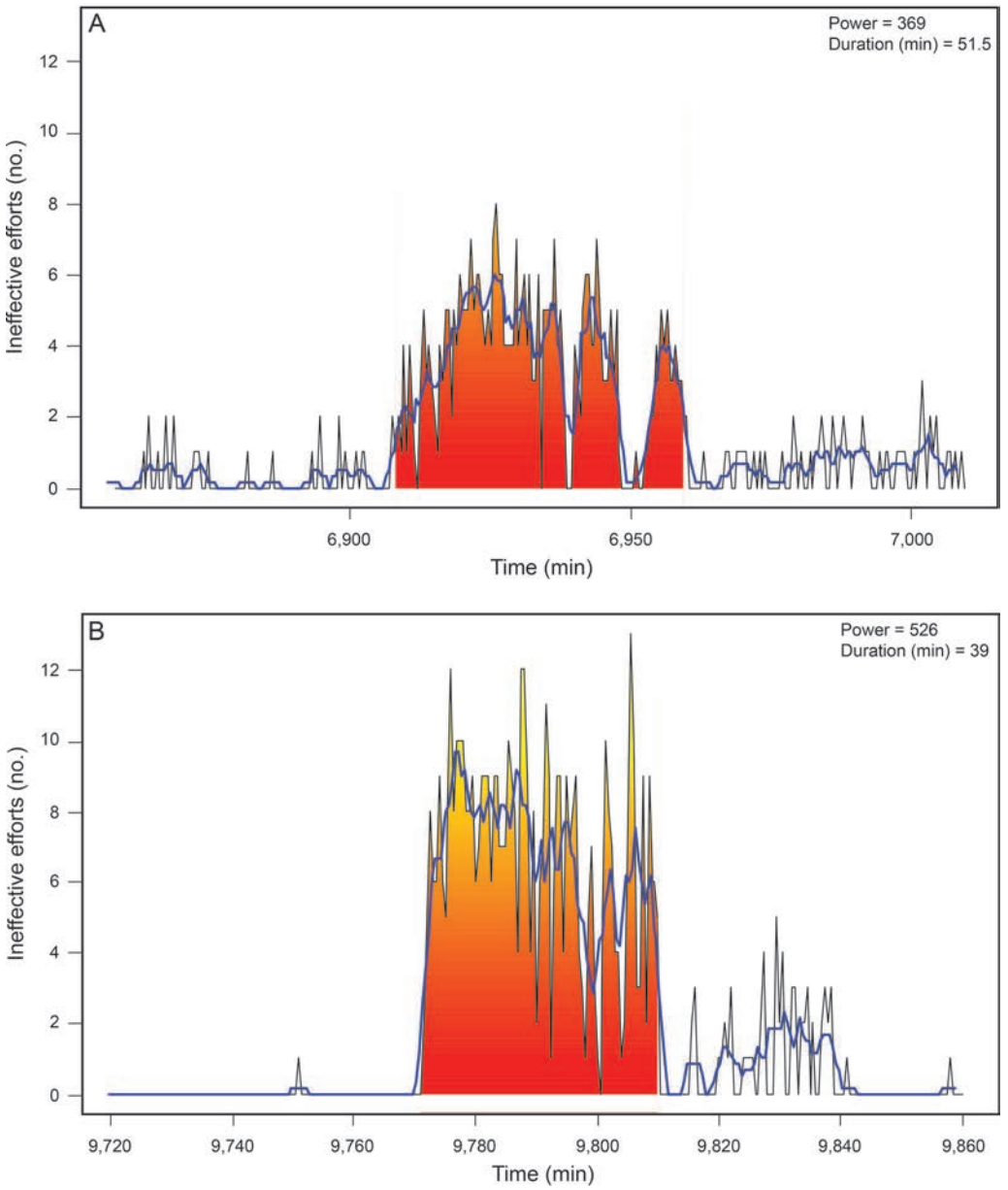

Fig. 5. Clusters of ineffective efforts. Time series of ineffective inspiratory efforts (black lines) computed for non-overlapped 30-s intervals for a selected timeframe, and clusters (shaded area) in a representative patient. The clusters were characterized by power and duration. Clusters were defined as periods of time where ineffective efforts represented > 50% breaths (ie, > 5 events in 30-s intervals, assuming a breathing frequency of 20 breaths/min). Blue lines represent the smoothed time series (running average with 6 points) used by the algorithm to identify clusters. Computations were performed according to the original mathematical description from Reference 5 and using anonymized data from Reference 4.

may be fed with respiratory waveforms (flow, pressure, or both) and trained to recognize normal and asynchronous breaths. Currently, research initiatives (eg, AEGLE project)[98] are focused on systems that can automatically recognize patterns in data and have the ability to improve continuously by learning from new inputs. This approach aims to detect and predict complex events by processing data from heterogeneous signals in real time (Fig. 6). Associating asynchronies with other clinical data could be an important step in the development of smart alerts (eg, via machine-learning methods) that might help reduce alert fatigue in the ICU[99] and help improve clinical decision-making. Rapidly expanding computing capabilities are making it feasible to integrate, process, and analyze very large databases, including information about patient–ventilator interaction, creating opportunities for accelerated machine learning that will help us understand individual variation and develop

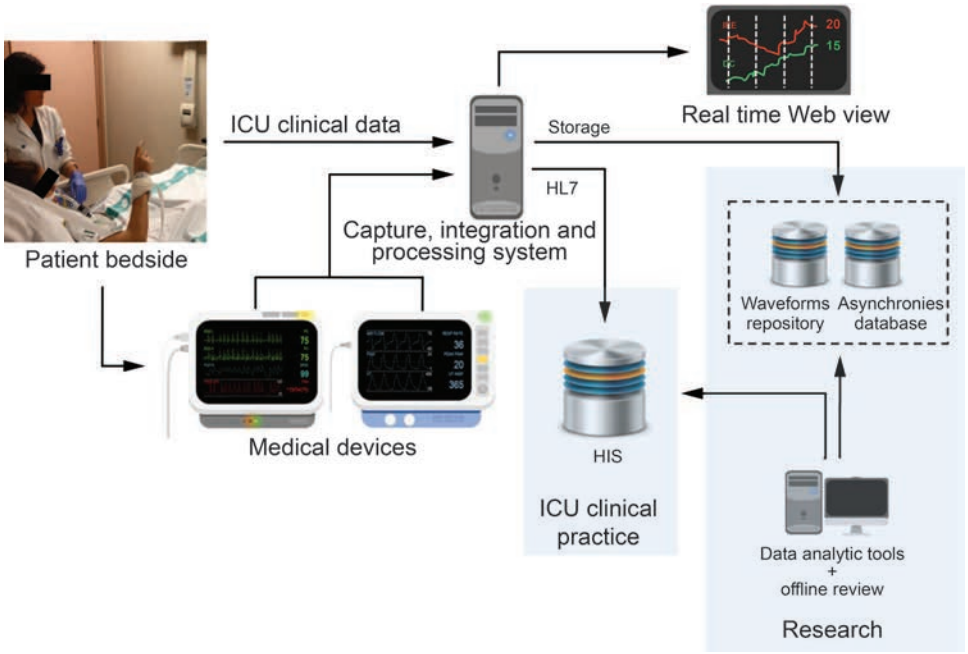

Fig. 6. Example of infrastructure for the continuous detection, storage, and visualization of asynchronies in real time and for their subsequent analysis with offline tools. Given the heterogeneity and high complexity of ICU patients, a repository for raw waveforms and an extensive clinical database are also vital to the development of precision therapy. Linking asynchronies with patients' waveforms and clinical data also promises to help in the development of more sophisticated smart alarms (eg, via machine-learning methods), reducing alert fatigue in the ICU[99] and providing effective support for clinical decision making. HL7 = Health Level 7 international standards; HIS = hospital information system.

predictive models. These achievements promise to reduce the mortality, costs, and long-term impairments associated with critical illness.[100]

Conclusions

Mechanical ventilation is a life-saving supportive treatment in critically ill patients. However, adverse effects associated with mechanical ventilation could also prolong ICU stays and affect outcomes. Patient-ventilator interaction represents a challenge for clinicians. When we fail to ensure that ventilator assistance optimally meets the patient's needs, the patient fights the ventilator and asynchronies are common. Asynchronies can inflict lung injury, cause discomfort, increase dyspnea, prolong ventilator use and ICU stays, and even increase mortality. Evidence suggests that increasing sedation is not the answer, and even using proportional modes cannot provide a definitive solution to fully synchronizing ventilator breaths with the patient's respiratory activity. To improve patient-ventilator interaction, we must deepen our understanding of the principles of respiratory physiology and respiratory system mechanics and improve our ability to apply them in individual patients. Rapidly expanding technological capabilities are making it possible to monitor and analyze ventilated patients' respiratory signals, laying the groundwork for more precise, personalized mechanical ventilation.

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REVIEW

Do sedation and analgesia contribute to long-term cognitive dysfunction in critical care survivors?

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Abstract Deep sedation during stay in the Intensive Care Unit (ICU) may have deleterious effects upon the clinical and cognitive outcomes of critically ill patients undergoing mechanical ventilation. Over the last decade a vast body of literature has been generated regarding different sedation strategies, with the aim of reducing the levels of sedation in critically ill patients. There has also been a growing interest in acute brain dysfunction, or delirium, in the ICU. However, the effect of sedation during ICU stay upon long-term cognitive deficits in ICU survivors remains unclear. Strategies for reducing sedation levels in the ICU do not seem to be associated with worse cognitive and psychological status among ICU survivors. Sedation strategy and management efforts therefore should seek to secure the best possible state in the mechanically ventilated patient and lower the prevalence of delirium, in order to prevent long-term cognitive alterations.

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Supervivientes unidad de cuidados intensivos

¿Contribuye la sedación y la analgesia a la disfunción cognitiva en supervivientes de una enfermedad crítica?

Resumen La sedación profunda durante la estancia en una Unidad de Cuidados Intensivos (UCI) puede afectar negativamente al estado clínico y cognitivo de los pacientes críticos sometidos a ventilación mecánica. En la última década ha aparecido gran cantidad de literatura sobre diferentes estrategias dirigidas a reducir los niveles de sedación en el paciente crítico. Además, ha aumentado el interés sobre la disfunción cerebral aguda o delirium. Sin embargo, el efecto de la sedación sobre los déficits cognitivos a largo plazo continúa siendo poco conocido. Las estrategias centradas en reducir los niveles de sedación en UCI no parecen estar asociadas con un peor estado cognitivo y psicológico de los supervivientes. Por lo tanto, las estrategias de manejo de la sedación en UCI deberían focalizarse en mejorar el estado del paciente ventilado, así como en disminuir el delirium, con el fin de prevenir las alteraciones cognitivas a largo plazo.

Introduction

Sedative and analgesic agents are widely used by physicians to treat pain, stress and discomfort in critically ill patients admitted to Intensive Care Units (ICUs). During the late 1990s, ICUs worldwide developed a culture of very deep and prolonged sedation and paralysis, especially in patients requiring vital support techniques such as mechanical ventilation (MV).

However, sedation may also have deleterious effects. Several negative short- and long-term outcomes have been associated with increased levels of sedation in medical and surgical ICU patients undergoing MV. The administration of sedative agents may produce respiratory depression, hemodynamic instability or metabolic acidosis, and can prolong mechanical ventilation and ICU stay and increase the likelihood of the development of delirium.[1,2]

Over the last decade there has been an increasing interest in the study of acute brain dysfunction, or delirium, in ICU patients.[3–5] This growth can be attributed to the impact of delirium on clinical outcomes in critically ill patients on MV, including increased mortality,[6,7] prolongation of MV and hospital stay,[8] higher costs of care,[9] and long-term cognitive impairment.[10] Various sedative agents have been identified as likely predictors of the development of delirium in mechanically ventilated ICU patients, suggesting a link between sedation and critical illness-associated brain dysfunction.[11–13] However, outside the context of delirium, the contribution of sedation to long-term brain dysfunction in critically ill patients has not been discussed or comprehensively evaluated.[14] Therefore, the aim of this review is to explore the role of sedative dosing strategy in the development of neurocognitive dysfunction after ICU stay.

Clinical outcomes and sedation strategy

The current trend in patients undergoing mechanical ventilation in the ICU is to moderate the depth of sedation. This procedure has been promoted by clinical trials that have indicated the need for lower levels of sedation in critical care and have implemented a variety of strategies including daily sedation interruption, goal-directed sedation, or even no sedation at all.[15]

The daily sedation interruption strategy

Daily sedation interruption is defined as a short-term suspension, holding, discontinuation, or cessation of intravenous sedation or (in some cases) analgesic medication.[16] The first clinical trial using this sedation strategy[16] concluded that daily interruption of the infusion of sedative drugs was a safe and practical strategy to treat ICU patients undergoing MV which also improved clinical outcomes, decreasing the duration of MV and shortening ICU stay. To test whether lower sedation doses in ICU patients might affect the long-term psychological status of ICU survivors, a small sample of the study cohort was monitored for psychological symptoms[17]; at six months, no significant differences between groups were observed for anxiety, depression and functionality. However, patients in the intervention group had a lower Impact of Event Score ($p = 0.02$), suggesting that the daily sedation interruption strategy was beneficial rather than harmful and reduced symptoms of post-traumatic stress disorder.

Since that study, several trials have explored the effect of daily sedation interruption on clinical outcomes in ICU patients.[18] Daily spontaneous awakening trials seem to reduce time in coma, ICU and hospital length of stay, sedation and to increase time off MV, and the 1-year survival rates.[19,20] Although other authors did not find significant improvements in different clinical and psychological outcomes,[21–23] daily sedation interruption has been recommended by the Society of Critical Care Medicine guidelines in order to achieve light levels of sedation in mechanically ventilated ICU patients.[11]

The goal-directed sedation strategy

The impact of deep sedation during the first 48 hurs of ICU admission on the short- and long-term clinical outcomes was

investigated by Shehabi et al. In two different studies, the authors showed that, after adjusting for illness severity and other confounders, early deep sedation was an independent predictor of long-term mortality and time to extubation in mechanically ventilated ICU patients. Although early deep sedation and the cumulative dose of sedative agents were not associated with time to delirium after 48 h, lightly sedated patients had a lower presence of delirium at 48 h,[24] as well as significantly more coma- and delirium-free days at 28 days.[25]

In the light of these findings, the authors proposed a sedation algorithm termed *early goal-directed sedation*. This process is implemented early after initiation of mechanical ventilation, is goal-directed to target light levels of sedation whenever possible, and uses dexmedetomidine as the primary sedative agent, thus minimizing the use of benzodiazepines.[26] Surprisingly, the new process did not show significant benefits in terms of MV duration, ICU/hospital length of stay or mortality when compared with standard care; nor did the duration of ICU delirium improve significantly, although the early goal-directed sedation group had more delirium-free days, received significantly less benzodiazepine or propofol, and required significantly less physical restraint. Therefore, the early goal-directed sedation strategy needs further investigation to clarify its impact on clinical outcomes during ICU stay. Even so, the results obtained so far draw attention to the unnecessary use of benzodiazepines in the ICU and underline the positive effect of avoiding early deep sedation on the mental status and well-being of critically ill patients.

The no sedation strategy

Strom et al.[27] aimed establishing the impact of the application of a no sedation protocol versus daily interruption of sedation on the duration of MV in critically ill patients. Patients under the no sedation protocol had more MV-free days and shorter ICU and hospital stays. However, agitated delirium was more frequent (20% vs. 7%) in the no sedation strategy group, in which the use of haloperidol was significantly increased. The results of this study suggest the striking idea that the no sedation strategy may be beneficial for certain clinical outcomes such as duration of MV or ICU/hospital stay, but not for the occurrence of ICU delirium. Nevertheless, it should be borne in mind that applying a no sedation strategy increases awareness in ICU patients and that delirium cannot be masked under sedation. Therefore, the higher rates of delirium in the no sedation strategy group may reflect better detection and diagnosis of the acute ICU brain dysfunction rather than a relationship between the non-use of sedative agents and ICU delirium.

Choosing the best sedative strategy for the ICU patients may be context-specific and may depend on the clinical population. However, the consistent message from the literature is that, if possible, minimizing sedation in critically ill patients undergoing MV may be beneficial.[28] It seems clear that reducing or even avoiding sedation during the ICU stay does not have a detrimental effect on critically ill patients; in fact, keeping ICU patients lightly sedated allows clinicians to reduce the use of benzodiazepines and sedative agents and thus avoid the associated adverse events. The improvement inpatients' awareness and well-being permits clinical staff to examine their mental state more closely and to achieve a more accurate diagnosis of delirium. We should also bear in mind the potential benefit of a reduction in sedation for the different clinical outcomes during the ICU stay, as well as for survival rates and the psychological status of the ICU survivors.

Impact of sedation in the acute brain dysfunction (delirium) in ICU

Delirium is understood as an acute form of brain dysfunction that affects 14–24% of hospital admissions and 15–53% of postoperative patients.[29] In the critical care context, the prevalence of delirium rises to between 60% and 80% in ICU patients undergoing MV,[6,12,30,31] and delirium duration has emerged as an independent predictor of mortality, ventilation time, ICU length of stay[6,32] and short- and long-term cognitive impairment[10] in critically ill patients and ICU survivors. Furthermore, its presence has been associated with a 39% increase in ICU costs.[9] Thus, delirium can be considered as the first manifestation of cognitive impairment in critically ill.

The list of risk factors for delirium in ICU patients is extensive and heterogeneous.[33–36] In general, the risk factors associated with the presence and duration of delirium in ICU are classified into two types of predisposing factors (patients' characteristics and chronic pathology) and two types of precipitating factors (environment and acute illness status). The precipitating factors are generally considered to be the more modifiable. All the studies and reviews suggest that the management of sedation and analgesia during the critical illness influences the prevalence and duration of delirium in ICU patients. Even in critically ill patients undergoing MV in which clinically-induced coma is required for life-support, avoiding the over-use of the medications should be considered. Although preliminary, current data suggests that the time in burst suppression detected by the bispectral index (BIS) during depth sedation could be an independent predictor of the occurrence and duration of the ICU delirium.[37] Thus, since sedative and analgesic treatment is included among the precipitating factors, the management of pharmacological interventions during the ICU stay should be regarded as a good target for the prevention of delirium in critically ill patients.[38,39]

Sedative agents, sedation strategies and delirium

The influence of benzodiazepine administration on the development of delirium in ICU patients is well documented in the literature.[1,14] Midazolam and lorazepam, the benzodiazepines most commonly used in critical care, have been associated with longer ICU and hospital stays and also increased MV time in comparison with non-benzodiazepine treatment.[1,40–43] Short-acting agents such as propofol, dexmedetomidine or remifentanil can be rapidly adjusted and their use can help to minimize the depth and duration of sedation with a potential reduction of time to extubation and days of delirium in the ICU.[28,42,43] As a result,

non-benzodiazepine treatment, such as dexmedetomidine, may be expected to reduce and even prevent the duration and incidence of delirium in critically ill patients.[44] Due to its sedative and analgesic effects, with a little interaction with other drugs, fewer side effects, and an easy titration, the use of dexmedetomidine could be a better alternative to deliriogenic sedatives and haloperidol or other atypical antipsychotics. Although to date more evidence is needed, preliminary data suggest that the use of dexmedetomedine might be effective preventing and treating agitated delirium during the ICU[25,42,43,45] in both mechanically intubated[46] and nonintubated critically ill patients.[47]

Unlike the effect of individual sedative agents, the impact of each sedative strategy on ICU delirium has not been explored in depth. In one study, the incidence of delirium in ICU patients undergoing protocolized sedation did not decrease when daily sedation interruption was added.[22] Similar results were found in patients managed with a daily spontaneous awakening trial (SAT) followed by a spontaneous breathing trial (SBT) or with sedation per usual care plus a daily SBT.[19] Decreasing sedation in the first two days of the ICU stay improved the incidence of delirium in mechanically ventilated patients, although early deep sedation or the cumulative dose of sedative agents did not predict the time to delirium after 48 h.[24,25] Finally, no sedation strategies may lead to higher rates of agitated delirium,[27] although these results may also reflect the under diagnosis of delirium in sedated ICU patients.

Sedative/analgesic drugs during ICU stay and the long-term cognitive outcomes

The direct relationship between the use of sedative agents and cognitive outcome in ICU survivors has not been widely studied. In fact, only two studies have considered the specific hypothesis that higher doses of sedative and/or analgesic agents may be associated with cognitive impairment after hospital discharge (Table 1).

Jackson et al.[48] followed medical ICU patients from the Awakening and Breathing Controlled Trial[19] at 3 and 12 months after hospital discharge. Only two significant differences were found in the clinical outcomes during the ICU stay between the daily spontaneous awakening trials (SAT)/spontaneous breathing trials (SBT) protocol group and the usual care (patient-targeted sedation and an SBT) protocol group: the SAT/SBT group had higher propofol exposure before enrollment than the usual care group and reduced exposure to benzodiazepines during the trial. At follow-up, both groups showed similar cognitive, psychological and functional outcomes. Cognitive impairment was present in 79% of all patients evaluated at 3 months and in 71% at 12months, but it was significantly less frequent in participants in the SAT/SBT group at the 3-month follow-up. Moreover, fewer patients in this group reported worse overall functional status at 12-month follow-up than before their critical illness. In view of these results, the authors concluded that interrupting or reducing sedation in the ICU improved short-term cognitive outcomes and long-term perception of functional status and did not increase the risk of adverse cognitive, psychological, or other outcomes.

In a multicenter prospective cohort study exploring medical or surgical ICU patients, Pandharipande et al.[49] hypothesized that longer duration of delirium during ICU stay and higher doses of sedative and analgesic agents would be independently associated with more severe cognitive impairment up to 1 year after hospital discharge. In that study, delirium was assessed through the administration of the Confusion Assessment Method for the ICU (CAM-ICU). Daily doses of benzodiazepines, opioids, propofol and dexmedetomidine were recorded. As expected, delirium was an independent factor for a worse cognitive global score and reduced executive function after both 3 and 12 months of follow-up. However, higher benzodiazepine dose emerged as an independent risk factor only for worse executive function performance at 3 months of follow-up. One of the most striking conclusions of the study was that, one year after critical illness, one out of four patients had cognitive impairment similar in severity to that observed in mild Alzheimer's disease, and one out of three had a level of impairment typically associated with moderate traumatic brain injury. The authors concluded that this cognitive impairment is found 'de novo' in the majority of patients and that there is an association between duration of delirium, worse long-term global cognition and decline of executive function. However, the lack of a significant relationship between sedative or analgesic medication and long-term cognitive impairment led the authors to interpret the results with caution, although they did not rule out an association between benzodiazepines and executive function at 3 months of follow-up; they suggested that any intervention (including an appropriate use of sedative agents) directed at reducing delirium may mitigate the brain dysfunction associated with critical illness. A larger randomized trial designed to compare the effect of a no sedation strategy with standard sedation management on the long-term cognitive function of ICU survivors is currently underway (ClinicalTrials identifier: NCT01967680).[50]

From other point of view, three studies have indirectly explored the relation of the sedation received during the ICU stay and the long-term cognitive sequelae of the critically ill survivors (Table 2).

From a different perspective, four other studies have indirectly explored the association between the sedation received during the ICU stay and long-term cognitive sequelae in critically ill survivors (Table 2). Aiming to examine cognitive and depressive status as well as quality of life 6 months after ICU discharge, Jackson et al.[51] carried out a comprehensive assessment of 34 medical and coronary ICU patients. After adjusting for age, educational level and baseline dementia, the authors found that one-third of patients presented impairments on neuropsychological testing at follow-up. The cognitive impairments found in these patients were similar to those observed in mild clinical dementia. Determining the relationship between the clinical variables and the cognitive deficits was beyond the scope of the study; however, and although the differences did not reach statistical significance, more days with ICU delirium and a deeper level of sedation were observed in the cognitively impaired group.

Table 1 Studies whose main objectives include analysis of sedation and cognition.

Authors	Year of publication	Objective/ Hypothesis	Sample and inclusion/exclusion criteria	Sedation strategy	Sedative/ analgesic agents	Assessed Domains	Results
Jackson et al.	2010	To determine the long-term effects (neurocog, psychological and functional) of a wake up and breathe protocol that interrupts and reduces sedative exposure in the ICU	180 Medical ICU > 12 h of MV CP arrest & neurocriticals excluded	Two randomized groups: (1) SATs + SBTs (2) Usual care group: patient-targeted sedation + SBT protocol	Preenrollment sedative exposure • Lorazepam equivalents, mg • Fentanyl equivalents, mg • Propofol Sedative exposure during trial • Lorazepam equivalents, mg • Fentanyl equivalents, ug • Propofol	• Neurocognition • PTSD • Anxiety • Depression • Functionality (comprehensive battery)	SATS + SBTs group vs. *Control group* Exposure to benzodiazepines (lorazepan equivalents, 21 mg – 5–83 vs. 42 mg – 10–296; $p = 0.04$) Exposure to propofol (5.070 μg – 2.290–8.825 vs. 2.600–1.310 – 7.395; $p = 0.04$) **At 3 months:** *SAT + SBT group* vs. *Control group* Cognitive impairment (70% vs. 91%; $p = 0.03$) Depression (64% vs. 58%; $p = 0.59$) Post-traumatic stress (14% vs. 10%; $p = 0.59$) Functional status reported (72% vs. 74%; $p = 0.84$) **At 12 months:** *SAT + SBT group vs. Control group* Cognitive impairment (72% vs. 70%; $p = 0.89$) Depression (59% vs. 62%; $p = 0.82$) Post-traumatic stress (24% vs. 24%; $p = 0.97$) Functional status reported (64% vs. 87%; $p = 0.05$)

Table 1 (*Continued*)

Authors	Year of publication	Objective/ Hypothesis	Sample and inclusion/exclusion criteria	Sedation strategy	Sedative/ analgesic agents	Assessed Domains	Results
Pandharipande, et al.	2013	A longer duration of delirium in the hospital and higher doses of sedative and analgesic agents are independently associated with more severe cognitive impairment up to 1 year after hospital discharge	821 Medical or surgical ICU with respiratory failure, cardiogenic shock or septic shock Short- IQCODE $\geq$3.6 and CDR >2, excluded	No specific sedation strategy reported.	• Benzodiazepine • Propofol • Dexmedeto-midine • Opiate	• Delirium (CAM-ICU) • Neurocognition (RBANS) • Executive functions (TMT B)	Delirium during hospital stay in 74% of the patients (median 4 days) **At 3 months:** Patients with cognitive status below 1.5 standard deviations: 40% Duration of delirium independent risk factor for: • Global cognitive impairment ($p = 0.001$) • Executive dysfunction ($p = 0.004$) Higher benzodiazepine dose independent risk factor for: • Executive dysfunction ($p = 0.04$) **At 12months:** Patients with cognitive status below 1.5 standard deviations: 34% Duration of delirium independent risk factor for: • Global cognitive impairment ($p = 0.04$) • Executive dysfunction ($p = 0.007$)

MV = mechanical ventilation; SAT = spontaneous awakening trials; SBT = spontaneous breathing trials; PTSD = post traumatic stress disorder. Short-IQCODE = Short-Informant Questionnaire on Cognitive Decline in the Elderly. CDR = Clinical Dementia Rating; CAM-ICU = Confusion Assessment Method for the ICU; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; TMT-B = Trail Making Test, part B.

Table 2 Studies whose main objectives do not include analysis of sedation and cognition.

Authors	Year of publication	Objective/ Hypothesis	Sample and inclusion/exclusion criteria	Sedation strategy	Sedative/ analgesic measure	Measures	Results
Jackson, et al.	2003	To examine neuropsychological function, depression, and quality of life 6 months after discharge in ICU patients who underwent MV	275 (34 patients finally analyzed) Medical and coronary ICU patients Neurocritical patients, patients with mental retardation or psychiatric illness excluded	Not specified	• RASS (every 24 h)	• Delirium (CAM-ICU) • Neurocognition • Anxiety • Depression • Quality of life (comprehensive battery)	**At 6 months:** One third of patients were impaired on neuropsychological testing at follow-up. No statistical differences were observed between impaired and non-impaired patients, although duration of delirium was slightly greater for the impaired group(4.5 vs. 4.2 days, $p = 0.24$) and sedation scale scores during the ICU were lower (-2.6 vs. -2.2, $p = 0.44$)

Table 2 (*Continued*)

Authors	Year of publication	Objective/ Hypothesis	Sample and inclu-sion/exclusion criteria	Sedation strategy	Sedative/ analgesic measure	Measures	Results
Hopkins, et al.	2005	To characterize neurocognitive and emotional function and quality of life 1 year after hospital discharge in a prospectively identified cohort of ARDS survivors	120 ARDS patients (74 patients finally analyzed)	Not specified	Days of sedatives Days of narcotics Days of paralytics	Primary outcomes at 1 and 2 years: Neurocognitive Total Score (comprehensive battery) Secondary outcomes at 1 and 2 years: *Neurocognitive measures:* • Verbal IQ • Performance IQ • Verbal Memory • Visual Memory • Attention/Concentration • Delayed recall *Emotional state measures:* • Depression • Anxiety *QoL measure:* • SF-36	**At discharge:** The prevalence of neurocognitive sequelae in ARDS survivors was: 73% at hospital discharge Hypoxemia, but not days of sedation, was modestly correlated with attention, verbal memory and executive function deficits **At 1 year follow-up:** Prevalence of neurocognitive sequelae: 46% Prevalence of severe depression symptoms: 16% Prevalence of anxiety: 24% Improvement of QoL, due to physical amelioration Hypotension, but not days of sedation, was modestly correlated with memory impairment. **At 2 year follow-up:** Prevalence of neurocognitive sequelae: 47% Prevalence of severe depression symptoms: 23% Prevalence of anxiety:23% No changes in QoL

Table 2 (*Continued*)

Authors	Year of publication	Objective/ Hypothesis	Sample and inclusion/exclusion criteria	Sedation strategy	Sedative/ analgesic measure	Measures	Results
Girard et al.	2010	To demonstrate that duration of delirium in ICU is an independent predictor of long-term cognitive impairment after critical illness requiring MV	77 mechanical ventilated ICU patients Neurocriticals, cardiopulmonary arrest, >2week of MV excluded	(1) SAT + SBT (2) Usual care group: patient-targeted sedation + SBT protocol	Total doses of benzodiazepines Total doses of opiates Total doses of propofol	Primary outcomes at 3 and 12 months: • Neurocognition (comprehended battery) Factors and confounders at 3 and 12 months: • Duration of delirium (days with positive CAM-ICU during 28 days) • Age • Years of education • Preexisting cognitive function (IQCODE Short-form) • Severity of illness • Severe sepsis • Total doses of sedatives	**At 3 months:** Cognitive impairment No impairment 21% Mild/moderate 17% Severe 62% Duration of delirium was the only independent predictor of cognitive impairment ($p = 0.02$) after adjusting for age, education, preexisting cognitive function, severity of illness, severe sepsis, treatment group and total exposure to sedatives in the ICU **At 12 months:** Cognitive impairment No impairment 29% Mild/moderate 35% Severe 36% Duration of delirium was the only independent predictor of cognitive impairment ($p = 0.03$) after adjusting for age, education, preexisting cognitive function, severity of illness, severe sepsis, treatment group and total exposure to sedatives in the ICU

Table 2 (*Continued*)

Authors	Year of publication	Objective/ Hypothesis	Sample and inclusion/exclusion criteria	Sedation strategy	Sedative/ analgesic measure	Measures	Results
Treggiari et al.	2009	To investigate whether light sedation favorably affects subsequent patient mental health compared with deep sedation	129 Mixed ICU patients with MV Neurocriticals excluded Follow up 2 (4 weeks) R1-2 = 52/R3-4 = 50	Two randomized groups: (1) Light sedation: Ramsay 1-2 (R1-2) (2) Deep sedation: Ramsay 3-4 (R3-4)	Ramsay scale (every 24 h) RASS (every 24 h) Cumulative doses (every24 h) • Midazolam, mg • Propofol, mg • Etomidat, mg • Morphine equivalents, mg	Primary outcomes at 1 month: • PTSD • Anxiety • Depression	*Light sedation group vs. Deep sedation group* **ICU discharge** Cases of depression: 3 vs. 10; ($p = 0.02$) Cases not evaluable due to cognitive impairment: 0 vs. 4; ($p = 0.04$) Days of MV: 2.9 (5) VS. 5.5 (10.8); ($p = 0.02$) ICU- free days: 4.9 (1−129) vs. 5.5 (2−99); ($p = 0.03$) **1 month follow-up:** PTSD score: 46 (29) vs. 56 (29); ($p = 0.07$)

MV = mechanical ventilation; RASS = Richmond Agitation and Sedation Scale; CAM-ICU = Confusion Assessment Method for the ICU; ARDS = acute respiratory distress syndrome; IQ = intelligence quotient; SAT = spontaneous awakening trials; SBT = spontaneous breathing trials; QoL = quality of life; IQCODE = Informant Questionnaire of Cognitive Decline in the Elderly; PTSD = post traumatic stress disorder.

Hopkins et al.[52] followed a sample of acute respiratory distress syndrome (ARDS) patients for two years in order to determine the prevalence of neurocognitive impairment, emotional symptoms and quality of life. From the 74 patients included in the final analysis, 70% presented cognitive sequelae at hospital discharge, 45% at 1 year and 47% at 2 years. Hypoxemia and hypotension were modestly correlated with various cognitive domains such as attention, memory and executive functions at hospital discharge and at 1 year of follow-up, but not at 2 years. Nevertheless, no other clinical variables during the episode of critical illness, including days receiving sedative, narcotic or paralytic medications, were significantly associated with neurocognitive alterations in critically ill patients.

A subsample of the Awakening and Breathing Controlled Trial was studied by Girard et al.[10] to determine whether duration of delirium was a predictor of long-term cognitive impairment among mechanically ventilated medical ICU patients. Nearly 80% of participants showed cognitive impairment at 3 months follow-up, and 61% at 12 months. After adjusting for age, education, preexisting cognitive function, severity of illness, severe sepsis, treatment group and total exposure to sedatives in the ICU, duration of delirium was the only independent predictor of short- and long-term cognitive impairment; in fact, between one and five days of delirium was associated with a 5-point decline on cognitive performance tasks at 3 months and a 7-point decline at 12 months.

Finally, in a randomized trial of the effect of light versus deep sedation on mental health after critical illness, mechanically ventilated ICU patients were assessed for post-traumatic stress disorder, anxiety and depression at hospital discharge and after four weeks of follow-up.[53] The patients with lower sedative doses showed reductions of one day in the duration of MV and of 1.5 days in ICU stay, without an associated increase in adverse clinical events or adverse mental health effects. Although cognitive status was not considered as a main measure in the study, the authors observed that 6% of the patients in the deep sedation group could not be assessed at ICU discharge due to cognitive impairment, whereas all the patients in the light sedation group were evaluable. No significant differences were found between the groups in age, educational level or illness severity, or in hemodynamic, respiratory, and metabolic variables.

Examining the literature, it remains unclear whether sedation during the ICU stay may impact the long-term cognitive impairment of the ICU survivors. Nevertheless, the probable effect of deeper sedation states and higher doses of benzodiazepines during the ICU stay on the cognitive profile of post-critically ill patients in the short-term follow up should not be underestimated. After ICU and hospital discharge all cognitive domains may be affected, although the executive functions may be especially vulnerable to the aspects of sedation described above. More evident is the non-adverse effect of reducing ICU sedation on ICU survivors' cognition. No harmful effect on the cognitive and psychological status has been found in the literature when strategies aimed at keeping mechanical ventilated patients lightly sedated are applied. The same conclusion can be drawn when benzodiazepine use is reduced during the ICU stay.

How do we explain the relation between sedation and acute/short-term cognitive outcomes? The probable pathophysiological mechanisms

The pathophysiology of ICU delirium remains uncharacterized,[28] although several hypotheses are being studied.[54] The main difficulty lies in the wide range of risk factors that have been related to the development and prevalence of delirium during the ICU stay.[12,33,34,36,38] Nevertheless, and always bearing in mind the multifactorial origin of ICU delirium, iatrogenic medication is considered a contributing and modifiable factor for this acute ICU brain dysfunction.[54]

The central cholinergic deficiency hypothesis is based on the increased risk of ICU delirium associated with the use of $GABA_A$ agonists and anticholinergic drugs.[28] It has been proposed that the action of dexmedetomidine on the central $\alpha 2$ receptors (unlike benzodiazepines or propofol, which act on GABA receptors) is the key to the beneficial effects associated with its use in ICU patients with delirium.[15,41–43] Besides, its anti-inflammatory effect may also contribute to reducing both the risk of delirium and the duration of the brain dysfunction, since inflammation appears to play an important role in the pathophysiology of delirium.[55]

GABAergic agents may induce delirium via a variety of mechanisms: by interrupting cholinergic muscarinic transmission at the level of the basal forebrain and hippocampus,[56] increasing compensatory up-regulation of NMDA and Ca^{2+} channel activity,[57] by disrupting thalamic pathways,[58] causing withdrawal states after cessation, disrupting circadian rhythms of melatonin release[59] and/or interfering with physiologic sleep patterns.[60]

Other medications that are typically administered to critically ill patients may also produce an imbalance in the neurotransmission of acetylcholine, dopamine, and GABA, thus affecting cortical and subcortical pathways involved in behavior, cognitive functioning, emotional regulation, and sleep. Anticholinergic drugs and their metabolites predominantly inhibit striatal cholinergic interneurons by blocking postsynaptic muscarinic receptors (especially M1), leading to hallucinations and attention deficit in post-operative patients.[61] Tricyclic antidepressants, H2 blockers and opioids also have a central anticholinergic effect[62] and possibly narcotics and paralytics as well.[63] If the physiopathological mechanisms underlying the relation between sedative management and ICU delirium are unclear, even less is known about the way sedative and analgesic agents impact long-term cognition in ICU survivors.

Finally, we must bear in mind the complexity and heterogeneity of the ICU patients who undergo MV. Various factors related to the illness itself and to its management can affect the functioning of the brain in these patients, and thus their cognitive states, in both the short and the long term. The etiology of the cognitive impairment in critically ill patients and in survivors must be regarded as multifactorial (Fig. 1). Hypoxemia events, dyspnea and air hunger, and even the MV itself are important components to consider. Experimental studies have shown that systemic PaO2 oscillations cause mild brain injury[64]; specifically, brain structures such as the hippocampus are extremely vulnerable to hypoxemia.[65]

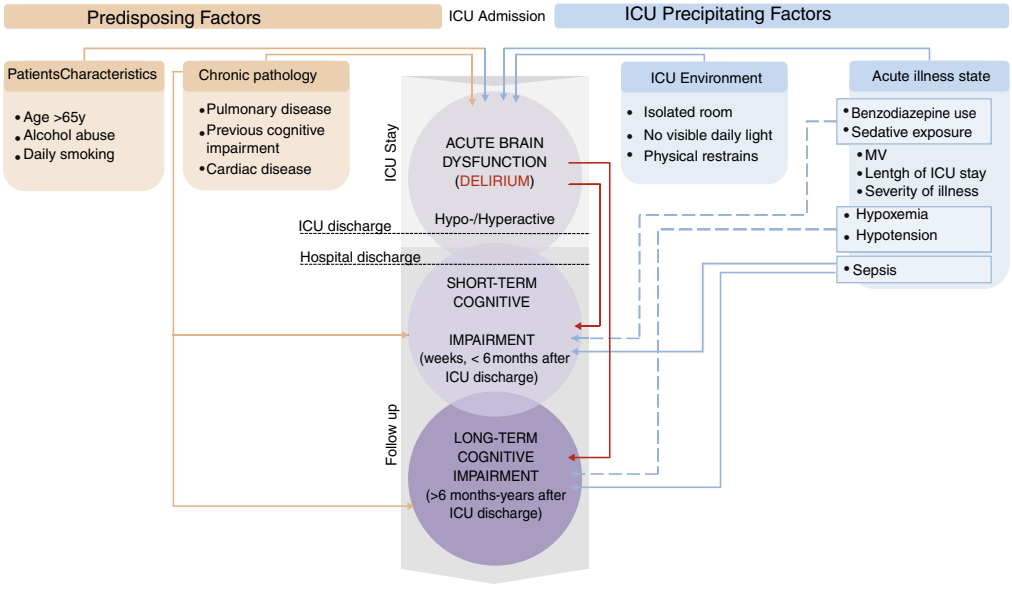

Figure 1 Main predisposing and precipitating factors that critically ill patients may present at ICU admission and their relationship with the cognitive alterations during and after the ICU stay. Predisposing factors are considered as characteristics of patients or their chronic illness. Precipitating factors are related to the ICU environment and illness management, so they are considered more modifiable. Thus, precipitating factors may be potential targets for reducing the risk of cognitive impairment in ICU patients and survivors.
→ Relation to. → → → → Possible relation to.

Furthermore, dyspnea and air hunger cause activation of the afferent pathways through chemo or baroreceptors, reflected by an increase in the signal in magnetic resonance in brain areas such as the limbic system which are related to psychological, emotional and memory disorders.[66] This neurocognitive compromise increases as a result of MV.[67]

The physiological and mechanical mechanisms through which the injured lung and MV may lead to brain dysfunction have been reviewed elsewhere.[68] Mechanoreceptors (baroreceptors/stretch receptors) or chemoreceptors located in the lung can be stimulated during MV, reaching the CNS by several pathways. Several experimental studies have described how MV can lead to brain alterations.[69–71] The brain can respond to this information by altering the permeability of the blood–brain barrier, by modifying cerebral blood flow or even by causing neuronal alterations[72,73] and neuroinflammation, which may generate memory dysfunction.[74] Recent studies by our group have underlined the important role of patient-ventilator decoupling during MV.[75,76] Asynchronies can be presented during the entire MV period[77] and can be influenced by the level of sedation.[78] The presence of asynchrony has been associated with poor outcomes such as longer duration of MV, greater incidence of tracheostomy, longer ICU stay and increased mortality.[79,80] The relation of this patient-ventilator decoupling with sedation strategies and its impact on ICU acute brain dysfunction/delirium, and its neurocognitive sequelae in critically ill survivors, are issues that merit further study.

Conclusion

With the scarcity of the literature available, it would be premature to attempt to draw any firm conclusions on the impact of sedation during critical illness and its role in long-term cognitive deficit. The lack of studies designed for this purpose means that we cannot recommend particular types of sedative strategy during the ICU stay for improving cognitive status in critically ill patients at hospital discharge and during longer follow up. Nonetheless, this review of the current literature suggests that the different sedation strategies applied in ICU patients (daily sedation interruption, goal-directed sedation, or even no sedation) are not associated with a worse cognitive status in ICU survivors than usual treatment. In fact, the trend toward reducing sedation doses during the ICU stay may be related to better cognitive performance. Taking this into account, it seems that the management of sedation and analgesia in ICU patients may in some way be associated with cognitive status, and in particular with executive dysfunction, at hospital discharge and at short-term follow up.

The effect of the sedatives used during the ICU stay on long-term cognition has not yet been demonstrated. A clearer relationship has been described between the impact of ICU delirium and long-term cognitive impairment in ICU survivors. Moreover, sedatives such as benzodiazepines are known to increase the presence of delirium during critical illness. Thus, sedation strategy and management should aim to achieve an optimal condition and to reduce the prevalence of delirium during the ICU stay, in order to prevent long-term cognitive alterations.

Reducing levels of sedation during the ICU stay does not negatively impact the clinical outcomes of critically ill patients, and it improves certain aspects of their management and rehabilitation. Higher levels of awareness in patients allow fuller exploration of their cognitive status, pain, and dyspnea during critical illness and permit the application or improvement of different analgesic or

management strategies. It facilitates patients' communication and collaboration with the clinical staff and favors active participation in their recovery process; it also allows them to interact with their family and friends, ensuring the emotional support needed during critical illness. Finally, other beneficial non-pharmacological interventions such as cognitive stimulation or early mobilization therapy can be applied as part of the rehabilitation process.

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Conflict of interest

The authors have no conflict of interest to disclose.

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Automatic detection of ventilatory modes during invasive mechanical ventilation

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Abstract

Background: Expert systems can help alleviate problems related to the shortage of human resources in critical care, offering expert advice in complex situations. Expert systems use contextual information to provide advice to staff. In mechanical ventilation, it is crucial for an expert system to be able to determine the ventilatory mode in use. Different manufacturers have assigned different names to similar or even identical ventilatory modes so an expert system should be able to detect the ventilatory mode. The aim of this study is to evaluate the accuracy of an algorithm to detect the ventilatory mode in use.

Methods: We compared the results of a two-step algorithm designed to identify seven ventilatory modes. The algorithm was built into a software platform (BetterCare® system, Better Care SL; Barcelona, Spain) that acquires ventilatory signals through the data port of mechanical ventilators. The sample analyzed compared data from consecutive adult patients who underwent >24 h of mechanical ventilation in intensive care units (ICUs) at two hospitals. We used Cohen's kappa statistics to analyze the agreement between the results obtained with the algorithm and those recorded by ICU staff.

Results: We analyzed 486 records from 73 patients. The algorithm correctly labeled the ventilatory mode in 433 (89 %). We found an unweighted Cohen's kappa index of 84.5 % [CI (95 %) = (80.5 %: 88.4 %)].

Conclusions: The computerized algorithm can reliably identify ventilatory mode.

Keywords: Mechanical ventilation, Automatic detection, Ventilatory mode, Information systems in critical care

Background

Monitoring is one of the main reasons for admission to intensive care units (ICUs). Up to 77 % of admissions to medical ICUs take place, at least in part, for monitoring purposes, even though only 10 % of the patients only monitored will subsequently have indications for major interventions [1]. Accordingly, huge investments in monitoring technology have led to the development of a wide array of monitoring devices (bedside monitors, mechanical ventilators, special devices, etc.) that generate large quantities of data. However, these data are underexploited for two main reasons. First, many data are typically presented only fleetingly on screens that clinicians see only when they are at the patient's bedside. So, unless an alarm is triggered, hours of acquired data are lost [2]. Trended data is of little use in identifying asynchronies since asynchronies can occur sporadically and need to be identified as they occur, and displayed as occurring at a frequency over time. Trending data is most useful in identifying physiologic change not short-term events. Second, data that is not interpreted are useless; to become useful, data must become information, by being processed, organized, structured, and contextualized [3]. Valuable information has often remained buried even when the data in which it is based were widely available. For instance, invasive monitoring of arterial blood pressure has been used since the beginnings of ICUs, but in recent years the analysis and processing of

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these data has yielded information far more valuable than arterial blood pressure alone. For example, pulse contour can be used to estimate cardiac output [4, 5], and pulse pressure variation can predict the cardiovascular system's response to a fluid load [6–8]. Tools to transform data from mechanical ventilators into meaningful information should help critical care clinicians anticipate harmful events, and expert systems could help them solve problems quickly and obtain expert advice.

The Better Care® software platform (Better Care S.L., Barcelona, Spain) processes (standardizes, resamples, synchronizes, analyzes, and stores) data from the data ports of mechanical ventilators or other monitoring devices [9]. It has a set of algorithms that evaluate the behavior of airway pressure and flow to automatically detect potentially harmful events (ineffective inspiratory efforts, double triggering, airway secretions, short and long cycles, aborted inspirations). In a previous study assessing the prevalence and time course of asynchronies throughout mechanical ventilation, we found a median of 3.41 % asynchronies in all patients [10]. However, that study probably underestimated the magnitude of the problem because many of the analyses were limited to the expiratory part of the flow tracing, where the shape of the curve does not depend on the ventilatory mode. Most device communication protocols do not provide information about the ventilatory mode in use, and different manufacturers use different, often meaningless, names for identical modes [11, 12]. For a system to detect events during inspiration, it must be able to identify the ventilatory mode. A system that could identify the ventilatory mode would also enable protocols to facilitate communication between medical devices and expert systems by converting data from proprietary device languages to standardized formats guaranteeing interoperability [13]. The aim of the present study is to validate an algorithm to identify the most prevalent ventilatory modes based on the analysis of airflow and airway pressure waveforms.

Methods

Software

The Better Care® system interacts directly with the signal output of medical devices through a device-specific connection driver. Mechanical ventilators and bedside monitors are connected to the system using an ED41000P2-01 remote access server (Lantronix, Irvine, CA, USA). The system standardizes the signals, associating each recorded curve with the parameter it represents, translates proprietary names into standard names, and resamples signals to a frequency of 200Hz. Standardized signals are then analyzed, tagged, converted to Digital Imaging and Communication in Medicine (DICOM) format, and stored in the hospital's picture archiving and communication system (PACS).

Setting

The study took place in two general ICUs (Parc Taulí University Hospital, Sabadell, Spain and Hospital Sant Joan de Deu-Fundació Althaia, Manresa, Spain) with 18 beds (4 beds in one hospital and 14 in the other) equipped with the Better Care® platform and one of the following ventilators: Evita 4 (Dräger, Lübeck, Germany), Puritan Bennet 840 (Covidien, Plymouth, MN, USA), or Servo I (Maquet, Fairfield, NJ, Sweden). The institutional review board of the Parc Tauli University Hospital approved the protocol and waived informed consent because the study was non-interventional, posed no added risk to the patient, and did not interfere with usual care.

Patients

We studied consecutive patients aged >18 years admitted to one of the equipped beds who underwent mechanical ventilation for >24 hours.

Protocol

A team composed of two nurses and one physician who were not involved in any clinical decisions recorded the ventilatory mode at the bedside once a day; the resulting log (including a timestamp for each entry) was used as a gold standard against which the Better Care® system's automatic assignments were compared.

The Better Care® software recorded and analyzed airway pressure and flow waveforms and calculated tidal volumes for every breath during the hour preceding the team's recording of ventilatory mode and applied a two-step algorithm to determine the specific ventilatory mode. The first step analyzes each breath and classifies it in one of seven categories according to the behavior of inspiratory time (TI)s, flow, airway pressure (P_{AW}), and tidal volume (VT) (Table 1). To assess the stability of

Table 1 Breath classification strategy

	Breath characteristics						
	TI	Flow	Flow Slp	P_{AW}	P_{AW} lev	Volume	P_{300}
Type1	V	V	V	V	1	V	No
Type2	C	C	C	V	2	C	No
Type3	C	V	C	V	2	C	No
Type4	C	V	V	C	2	V	No
Type5	V	V	V	C	2	V	No
Type6	V	V	V	V	2	V	Yes
Type7	V	V	V	V	2	V	No

Abbreviations: *TI* inspiratory time, *Flow* inspiratory flow, *Flow Slp* inspiratory flow slope, P_{AW} peek airway pressure, P_{AW} *lev* number of PAW levels, *Volume* tidal volume, P_{300} 300 msec pause between inspiratory an expiratory time, *C* constant, *V* variable

the different parameters, the system calculates a variability index (VI) as follows:

$$VI = \sqrt{\frac{(\text{Actual Value} - \text{Mean Value})^2}{\text{Mean Value}}} \times 100$$

where "Actual Value" is the measured value for a given variable and "Mean Value" is the running mean value for the same variable over the last 20 breaths (even though step 1 of the algorithm is breath-based, the stability of a given parameter is evaluated in the context of the preceding breaths). In other words, VI represents the variation in the parameter as a percentage of the mean value for the last 20 breaths. A variable was considered to be constant if the VI was less than 10 %.

The second step identifies the ventilator mode in proportion of the breaths classified into each category in the hour being analyzed (Table 2): continuous positive airway pressure (CPAP) (at least 90 % of breaths are classified as Type 1); volume control-continuous mandatory ventilation or volume-controlled ventilation with constant flow (VC-CMV) (at least 90 % of breaths are classified as Type 2: volume control-continuous mandatory ventilation with decelerating flow or volume control ventilation with decelerated flow (VC-CMV_{DF}) (at least 90 % of breaths are classified as Type 3); pressure control-continuous mandatory ventilation or pressure-controlled ventilation (PC-CMV) (at least 90 % of breaths are classified as Type 4); pressure control-continuous spontaneous ventilation or pressure support ventilation (PC-CSV) (at least 90 % of breaths are classified as Type 5); spontaneous proportional assist or proportional assist ventilation (PC-CSV_R) (which also includes neurally adjusted ventilatory assist, NAVA) (at least 80 % of breaths are classified as Type 6 and no Type 7 breaths are present); spontaneous proportional assist or proportional assist ventilation + (PC-CSV_R+) (at least 80 % of breaths are classified as Type 6 or Type 7).

If the proportion of breaths classified did not fall into one of the above categories, the system labeled the record as other modes. This label encompassed modes beyond the scope of this algorithm, records that the system was unable to correctly classify, and hours in which the ventilatory mode changed.

Table 2 Mode classification strategy

	Breath type						
	1	2	3	4	5	6	7
CPAP	>80 %						
VC-CMV		>80 %					
VC-CMV_{DF}			>80 %				
PC-CMV				>80 %			
PC-CSV					>80 %		
PC-CSV_R+						>90 %	
PC-CSV_R						0 %	>90 %

Abbreviations: *CPAP* continuous positive airway pressure, *VC-CMV* volume control-continuous mandatory ventilation or volume-controlled ventilation with constant flow, *VC-CMV_{DF}* volume control-continuous mandatory ventilation with decelerated flow; or volume-controlled ventilation with decelerated flow, *PC-CMV* pressure control-continuous mandatory ventilation or pressure-controlled ventilation, *PC-CSV* pressure control-continuous spontaneous ventilation or pressure support ventilation, *PC-CSV_R* spontaneous proportional assist or proportional assist ventilation, *PC-CSV_R+* spontaneous proportional assist or proportional assist ventilation +

Statistical analysis

We used the unweighted Cohen's kappa coefficient to assess the agreement between the team's recordings in the log (gold standard) and the Better Care® mode detection algorithm.

Results

The team recorded the ventilatory mode 486 times (Sabadell: n = 301; Manresa: n = 185) in 73 patients (Sabadell: n = 31; Manresa: n = 42). The algorithm correctly labeled 433 (89 %) hours of ventilation mode (Table 2). The unweighted Cohen's kappa coefficient was 84.5 % [95 % CI: 80.5–88.4 %)].

The system labeled 56 (12 %) records as other modes; this label was correct in 23 cases (5 % of the total) because the mode did not fit any of the studied modes. The system mislabeled a total of 53 (11 %) records; of these 20 (4 % of the total) corresponded to recordings mislabeled as one of the predefined modes and 33 (7 % of the total) corresponded to recordings mislabeled as other modes. Thus, the BetterCare® System was able to correctly label the mode 89 % of the time.

Discussion

Successful clinical decision support systems must provide patient-specific recommendations [14]. To do that, the system requires unequivocal information, at least for some critical variables. For systems advising clinicians about mechanical ventilation, the ventilatory mode being used is critical information that current ventilator communication protocols do not readily provide. The algorithm incorporated in the BetterCare® system correctly identified the ventilatory mode in 433 (89 %) of the 486 hours recorded in 73 patients, with a kappa index of 84.5 % [95 % CI: 80.5–88.4 %]. Landis and Koch [15] proposed the following standards for strength of agreement for the kappa coefficient: ≤0 % = poor, 1–20 % = slight, 21–40 % = fair, 41–60 % = moderate, 61–80 % = substantial and 81–100 % = almost perfect. Although a kappa index of 84.5 % is highly acceptable we still mislabeled 11 % of the cases and continue to improve our recognition algorithms.

Expert systems dealing with mechanical ventilation need to be able to detect ventilatory modes automatically. The

number of ventilatory modes has increased dramatically over the last 30 years. Moreover, within each mode many features can be activated that transform the basic mode into what is effectively another mode. To add further confusion, the lack of standards in ventilatory mode naming [11, 12] has resulted not only in different names for the same ventilatory mode but also in different ventilatory modes with the same name. Although manufacturers' names can be translated into standard names, most communication protocols from mechanical ventilators do not provide information on the ventilatory mode in use. We chose these modes because they accounted for 70 % of the ventilatory time in a recent large international study on the epidemiology of mechanical ventilation [16], and corresponded to 94 % of the modes used in our cohort.

The practical consequences of failing to label a record are different from those of mislabeling a record. If the system cannot determine the ventilatory mode, it cannot provide advice; however, if the system mislabels the mode, it may provide erroneous advice. For example, airway pressure-time profile analysis could provide information about two important determinants of ventilator-induced lung injury: tidal recruitment and overdistention [17]. This analysis derives an index by fitting the central part of the inspiratory airway pressure-time profile to an exponential function. Importantly, however, the index is valid only if the ventilatory mode is VC-CMV and no patient inspiratory efforts are present [17]. Unless both these conditions are met, there is a danger of misinterpretation that could lead to incorrect decisions and place the patient at risk. In the present study, 20 (4 %) records were mislabeled. Of these, eight resulted from problems in differentiating between PC-CMV and VC-CMV_{DF} and four from problems in differentiating between PC-CMV and PC-CSV. Another six records where the actual mode was VC-intermittent mandatory ventilation with pressure support were labeled PC-CSV (two cases) or PC-CMV (four cases).

A critical aspect of our algorithms is to establish if a given parameter is (or is not) stable. If a parameter changed more than 10 %, the algorithm considers it "variable". To reduce the threshold below 10 % would reduce the number of variable parameters considered constant. Unfortunately, it would also increase the number of constant parameters considered variable: even when these thresholds typically are more precise than required by the ISO standard [18], for delivery of pressures, flows, and volumes by ventilators.

For instance, differentiating PC-CMV from PC-CSV is based on the variability of inspiratory time and distinguishing between VC-CMV_{DF} and PC-CMV, which relies on the variability of airway pressure, the slope of the inspiratory flow curve and tidal volume. However, a fixed ventilatory pattern (or the absence of muscular activity) leads to a scenario in which patients ventilated in PC-CMV will have a constant inspiratory volume and slope of inspiratory flow and patients in VC-CMV_{DF} will have consistent airway pressure. Our analysis of mislabeled records showed that most mistakes occurred in records with very regular ventilatory patterns where the variation in parameters expected to vary was below the tolerance limits we had set. Furthermore, the high inspiratory pressure alarm, for instance, can abort inspiration making parameters expected to be constant become very variable (like inspiratory time in PC-CMV and VC-CMV or tidal volume in VC-CMV).

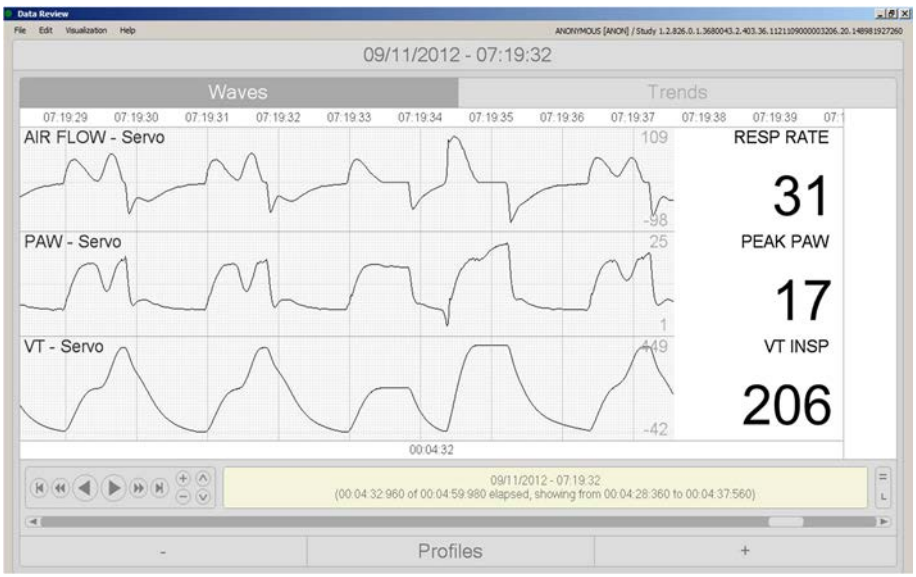

Fig. 1 Irregular traces from a patient in PC-CMV. A second inspiratory peak flow in a machine-triggered breath strongly suggests reverse triggering

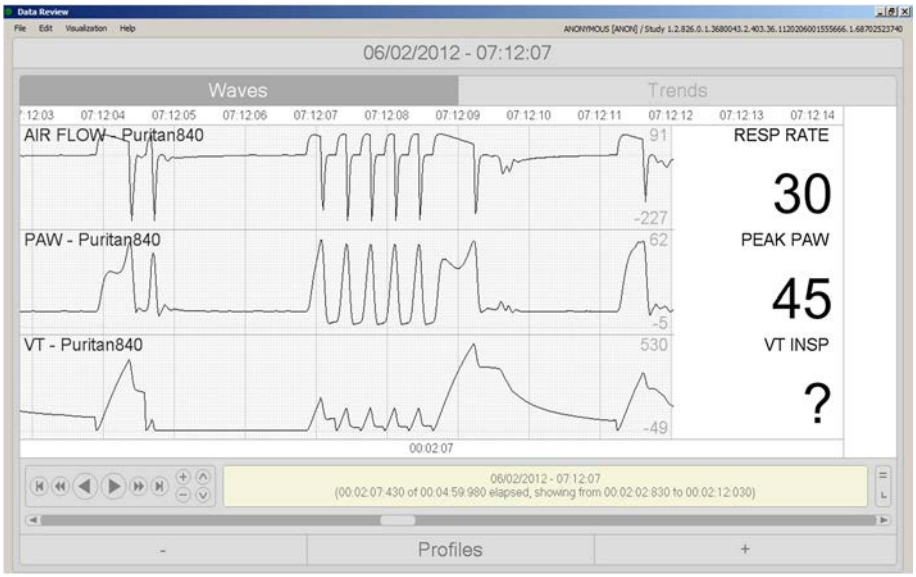

Fig. 2 The airway pressure alarm aborts inspiratory cycles, producing highly variable inspiratory times and volumes and making it difficult for the system to correctly identify the mode as VC-CMV

A total of 56 (12 %) records were not assigned to one of the modes. In 23 cases the decision was correct, because the actual mode was one of the modes that were outside the scope of the algorithm. In 33 cases, however, the system should have assigned the mode. The main reason for these mistakes was severe patient-ventilator asynchrony that resulted in muddled records that were difficult even for expert physicians to classify (Figs. 1 and 2). Another problem, specific to Servo ventilators, is where in VC-CMV the inspiratory valve opens to mitigate flow asynchrony, causing tidal volume to become highly variable and causing the system to fail to recognize the mode as VC-CMV (Fig. 3).

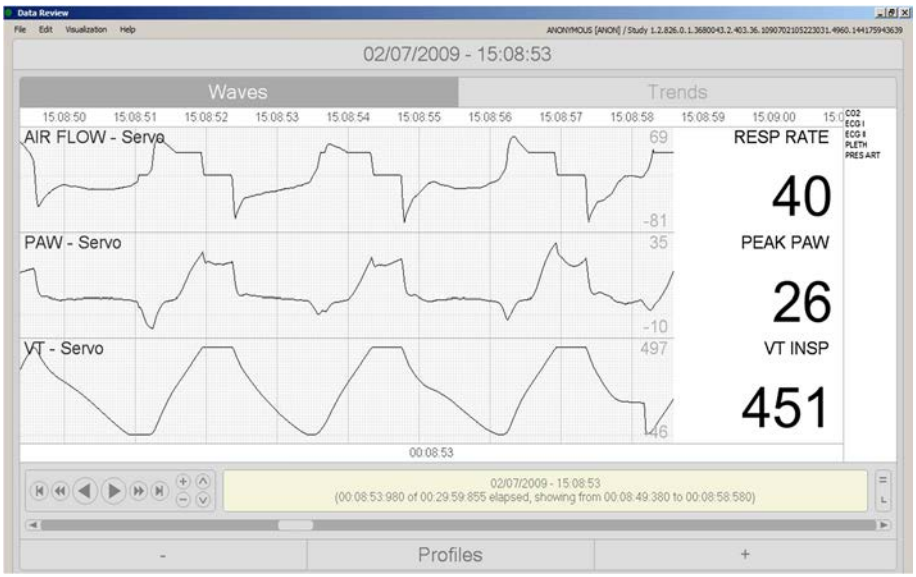

Fig. 3 Manufacturer's non-standard implementation of ventilatory modes. With the goal to increase patient comfort and reduce flow asynchrony, some manufacturers have developed modifications of classic ventilatory modes. For instance, Maquet ventilators in VC-CMV (when airway pressure shows a concavity, inadequate flow to meet patient inspiratory demand), the ventilator opens its demand valve allowing additional gas flow to avoid flow asynchrony leading to an increase in tidal volume potentially violating a lung-protective approach. Beyond its advantages and drawbacks, it causes changes in the inspiratory flow profile and tidal volume that prevent the system from identifying the mode as VC-CMV

Determining the ventilator mode is also very important for detecting the occurrence of inspiratory patient-ventilator asynchrony (flow asynchrony, delayed triggering, and patient-ventilator inspiratory time mismatch). In a recent study of patient-ventilator asynchronies in a general population monitoring the entire period of mechanical ventilation, Blanch et al. [10] found that asynchronies are very frequent and are associated with mortality. However, they probably underestimated the prevalence of ineffective inspiratory efforts because the inability to determine the ventilatory mode limited the system's analyses mostly to the expiratory portion of the ventilatory cycle [9]. Incorporating an algorithm to detect the ventilatory mode in use would enable the entire ventilatory cycle to be analyzed and provide a more complete picture of the problem.

This study's main strength is that it represents real problems occurring in ICUs. The records analyzed came from a wide variety of real ICU patients with asynchronies, cough, airway secretions, etc. Its main limitation is that it considered a limited set of ventilatory modes. We have not developed algorithms to detect dual modes because their use remains marginal [16]. Moreover, the low number of proportional pressure support records in our database precludes the validation of an algorithm to detect those modes. Thus, the reliability of our algorithms to detect ventilatory modes has been only established for VC-CMV, VC-CMV_{DF}, PC-CMV, PC-CSVs PC-CSV_R+, and CPAP.

Conclusions

Automatic systems can accurately identify the most commonly used ventilatory modes, thus providing crucial information that enables the entire ventilatory cycle to be analyzed. More data must be collected to validate the algorithm for identifying less frequently used proportional pressure support modes.

Additional file

Additional file 1: The database on which this study is based. (XLS 77 kb)

Abbreviations

CPAP, continuous positive airway pressure; DICOM, Digital Imaging and Communication in Medicine; ICU, intensive care unit; NAVA, neurally adjusted ventilatory assist; PACS, picture archiving and communication system; P_{AW}, airways pressure; PC-CMV, pressure control-continuous mandatory ventilation or pressure-controlled ventilation; PC-CSV, pressure control-continuous spontaneous ventilation or pressure support ventilation; PC-CSV_R, spontaneous proportional assist or proportional assist ventilation; PC-CSV_R+, spontaneous proportional assist or proportional assist ventilation +; TI, inspiratory time; VC-CMV, volume control-continuous mandatory ventilation or volume-controlled ventilation with constant flow; VC-CMV_{DF}, volume control-continuous mandatory ventilation with decelerated flow; or volume-controlled ventilation with decelerated flow; VI, variability index; VT, tidal volume

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Role of the sponsors: no funding organization or sponsor was involved in the design or conduct of the study, in the collection, management, analysis, or interpretation of the data, or in the preparation, review, or approval of the manuscript.

Availability of data and materials

The database on which this study is based is available as a spreadsheet in Additional file 1.

Authors' contributions

LB had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. LB, JM, UL, GM, RF, JV, and RMK contributed to the study concept and design. BS, JM, EC, and AE carried out acquisition of data. LB, JM, UL, EC, AE, JL-A, CS, RF, JV, GM, and RMK performed analysis and interpretation of data. LB and GM drafted the manuscript. LB, BS, JM, UL, EC, AE, JL-A, RF, JV, GM, and RMK critically revised the manuscript for important intellectual content. JM and GM performed the statistical analysis. LB, BS, and JM provided administrative, technical, or material support. LB, GM, JV, and RMK conducted the study supervision. All authors read and approved the final manuscript.

Competing interests

LB, BS, and GM are inventors of a US patent owned by Corporació Sanitaria Parc Taulí: "Method and system for managing related patient parameters provided by a monitoring device," US Patent No. 12/538,940. LB, BS, GM, and UL own stock options in BetterCare S.L., a research and development spinoff of Corporació Sanitària Parc Taulí (Spain). RMK is a consultant for Covidien and OrangeMed, has received research grants from Covidien and Venner Medical. JV has received research grants from Maquet. JM, EC, AE, CS, CH, JL-A, and RF have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The ethics committees at both institutions approved the study and decided to waive informed consent because the study was observational, signals were encrypted to ensure privacy, no extra effort to on-charge personnel was generated, no changes to usual treatment were required, and no information that could lead to changes in patient care was provided to the attending team.

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Does this ventilated patient have asynchronies? Recognizing reverse triggering and entrainment at the bedside

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Reverse triggering is a frequently under-recognized form of patient–ventilatory asynchrony in which the patient's respiratory center is activated in response to a passive insufflation of the lungs. It can be detected at the bedside by observing airway pressure and airflow waveforms.

Figure 1a and video 1 (in the electronic supplementary material, ESM) show airway pressure and flow waveforms from a patient ventilated in volume-control mode. The breaths are almost certainly machine triggered because no perturbation in airway pressure can be seen at the beginning of the breath. At first sight, the records seem quite normal. However, a closer look shows that breaths marked with arrows are slightly different from other breaths. The airway pressure waveform shows a fall during the inspiratory plateau. Provided there are no air leaks, the amount of gas inside the respiratory system is constant (both the inspiratory and expiratory valves are closed), and a decrease in airway pressure denotes an increase in compliance. In controlled mechanically ventilated patients, the only explanation for this increase in compliance is recruitment of previously closed alveoli or airways. In spontaneously breathing mechanically ventilated patients, this increase in compliance can also be explained by the activation of the patient's inspiratory muscles.

The activation of inspiratory muscles cannot be ruled out even in machine-triggered breaths (Fig. 1 ESM). The respiratory control system (RCS) is a servo-regulated oscillatory system located in the medulla. The RCS's phasic output (motor neural fibers that activate respiratory muscles) is modified by information from several sources (mechanical and chemical signals). Increasing alveolar ventilation (keeping constant tidal volume) can lead to a decrease in $PaCO_2$ and an inhibition of the RCS. However, the machine's breaths can also activate the RCS (entrainment). Thirty 30 years ago, Petrillo et al. [2] and Graves et al. [3] showed that a passive insufflation of the lungs can initiate a ventilatory effort in cats and normal humans, respectively. In other words, the machine triggers the patient. More recently, Akoumianaki et al. [4] found that a mechanically ventilated critically ill patient can behave in the same way, and they call this phenomenon "reverse triggering" (RT).

During entrainment, a phase-locking phenomenon (a constant ratio between machine breaths and patient efforts) can be observed. Usually, the patterns are short lived, as they are interrupted by irregular patterns every 7–15 respiratory cycles [3]. The 1:1 ratio is not only the

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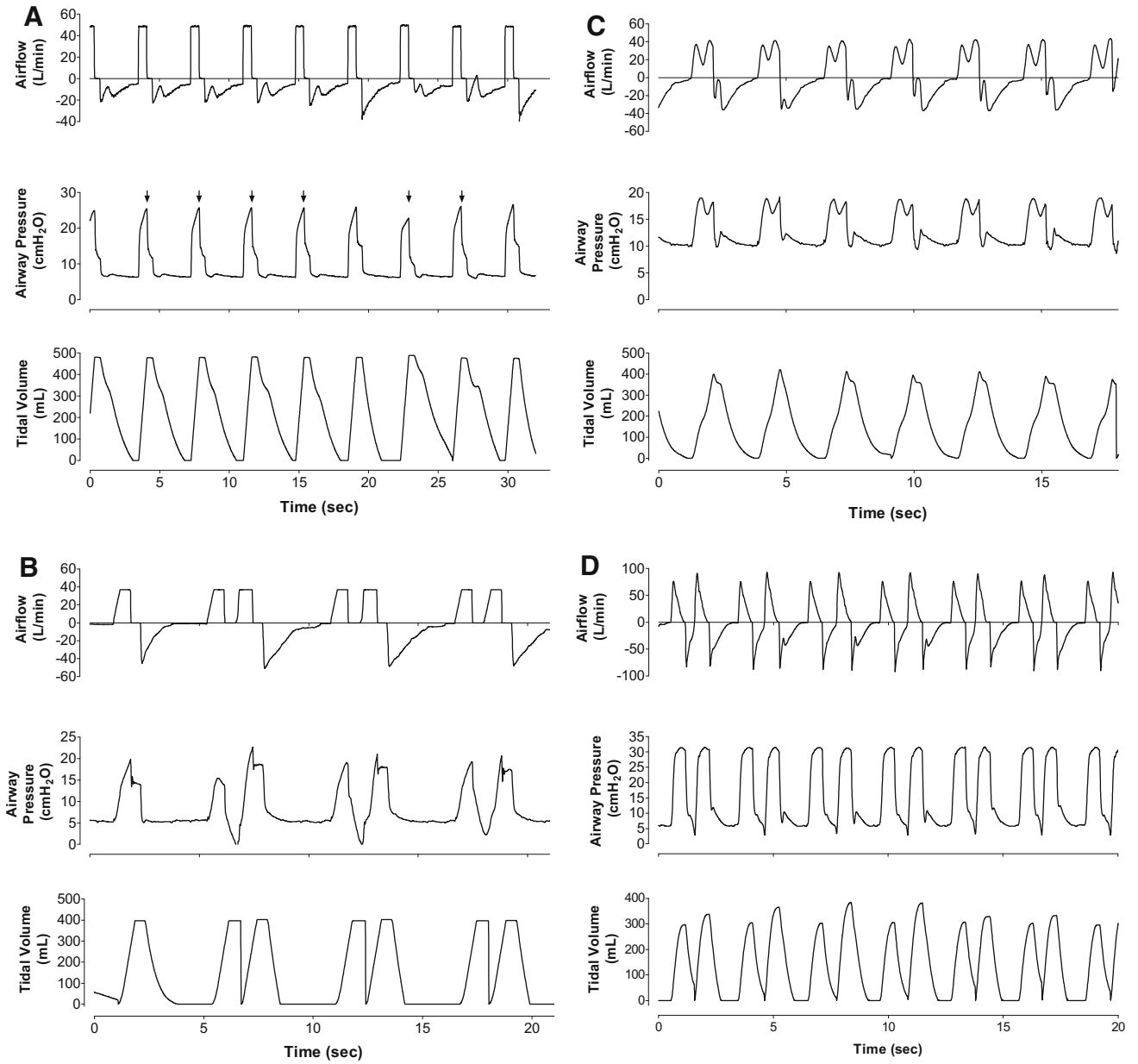

Fig. 1 Traces corresponding to airway pressure, flow, and volume where evidence of reverse triggering can be found. **a** (video 1 ESM) and **b** (video 2 ESM) are records in volume-control ventilation without and with double triggering, respectively. **c** (video 3 ESM) and **d** (video 4 ESM) show the same phenomena in patients in pressure-control ventilation. To avoid drifts, mechanical ventilators usually reset the end-expiratory lung volume to zero at the beginning of a new breath. However, as there is no expiration between double-triggered breaths, tidal volume and end-inspiratory volume substantially increase (**b**, **d**), raising concerns about the risk of lung injury. In airflow tracings in **a** and video 1, expiratory flow is still present at end expiration suggesting some degree of intrinsic PEEP. The presence of intrinsic PEEP should contribute to the inability of the patient to trigger the ventilator. During flow triggering, a relatively small negative deflection in the airway pressure tracing should be observed even in the presence of intrinsic PEEP. In the absence of airway pressure deflections at the beginning of inspiration, the breath is considered triggered by the ventilator [1]. The ESM includes video clips and details of the patients shown in the figures

most frequent, but also the most stable pattern [4]. Graves et al. [3] systematically studied respiratory system entrainment in anesthetized humans. They found that changes in respiratory rate and tidal volume could lead to a variety of regular and irregular patterns of coupling between respiratory system output and passive insufflations of the lungs. The locked condition is less easy to reach when $PaCO_2$ increases or when the level of anesthesia decreases [5]. For this reason, entrainment is far more common in deeply sedated (low conscious) patients.

The delay between the start of the machine-triggered breath and the start of the patient's effort is a fairly constant fraction of the total ventilatory time (phase angle) [4]. Interestingly, apart from passive insufflations of the lungs, several stimuli can entrain the RCS. For instance, entrainment of respiratory and locomotor rhythms is well documented [6–10].

So, the fall in airway pressure shown in this machine-triggered breath could be explained by either recruitment or RT. As during RT the patient's inspiratory effort starts a given amount of time *after* the start of the machine's breath, the patient's inspiratory effort usually persists beyond the end of the machine's breath. Hence, the patient's inspiratory muscles are still active at the beginning of expiration, impeding the elastic recoil of the respiratory system from increasing alveolar pressure and thus aborting the peak expiratory flow. The amputation of the peak expiratory flow seen in this record suggests that RT rather than recruitment explains the event. If deep enough and long enough, the persistent effort could even produce a fall in airway pressure that can lead to double triggering (Fig. 1b and video 2 ESM) [11].

Figure 1c and video 3 ESM show the same phenomenon during pressure-control ventilation. Once again, the breaths remain machine-triggered. Inspiratory flow in machine-triggered pressure-control breaths is expected to present an exponential decay: as the alveolar compartment fills with gas, the pressure gradient between the airway and alveoli falls, reducing flow between compartments and the flow the machine needs to insufflate into the airways to keep airway pressure at the desired level. In this record, however, a second inspiratory peak flow can be seen. This increase in airway flow denotes an increase in airway–alveolus pressure gradient and can only be explained by an increase in compliance (an opening of previously closed units or the activation of the patient's inspiratory muscles). Again, the perturbation in expiratory flow waveform at the beginning of expiration suggests that RT with persistent activation of inspiratory muscles is the most plausible explanation for these findings. Once more, if deep and long enough, the patient's effort can lead to double triggering (Fig. 1d and video 4 ESM).

Entrainment appears to be produced mainly by the stretching of the slowly adapting receptors and a sustained activation of the vagally mediated Hering–Breuer reflex. In fact, in animals, the abolition of the Hering–Breuer reflex by cooling or section of vagal nerves impedes entrainment [2, 5]. In humans, however, the phenomenon can also be seen in transplant patients even when the frequencies of mechanical inflations that can entrain the ventilatory system are clearly narrowed [12].

The prevalence of RT has yet to be addressed. However, subtle effects on flow and pressure waveforms will most likely make it hard to recognize and avoid unless special attention is paid [13, 14]. Moreover, although patient–ventilator asynchronies are in general worrisome [15], the consequences of RT in particular are unknown: while RT producing double-triggering can lead to lung injury, RT could potentially also be used to promote patient–ventilator synchrony [16]. In the meantime, it is worth trying to detect and understand RT.

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Compliance with ethical standards

Conflicts of interest Murias and Blanch are inventors of one Corporació Sanitaria Parc Taulí owned US patent: "Method and system for managed related patient parameters provided by a monitoring device," US Patent No. 12/538,940. Murias and Blanch own stock options of BetterCare S.L., which is a research and development spin-off of Corporació Sanitària Parc Taulí (Spain). Candelaria de Haro has no conflicts of interest.

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