Efectos clínicos y aspectos técnicos de la ventilación no invasiva en la insuficiencia respiratoria aguda

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EFECTOS CLÍNICOS Y ASPECTOS TÉCNICOS DE LA VENTILACIÓN NO INVASIVA EN LA INSUFICIENCIA RESPIRATORIA AGUDA

EFFETS CLINIQUES ET ASPECTS TECHNIQUES DE LA VENTILATION NON INVASIVE DANS L'INSUFFISANCE RESPIRATOIRE AIGUË

Memoria presentada por Ana Córdoba Izquierdo para optar al grado de doctora en medicina con mención internacional

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Barcelona, Enero 2014

AGRADECIMIENTOS

A la *Fundació La Caixa* por concederme la beca que me permitiera llevar a cabo la experiencia personal y profesional más importante de mi vida.

A mis compañeros del Hospital de Bellvitge, que me animaron para emprender la aventura de París y me recibieron con ilusión a mi regreso: Enric Prats, Eva Farrero, Jordi Dorca, Federico Manresa, Jesús Ribas, Pau Romero, Benigno Rodríguez-Sanchón, Mercè Gasa y al resto de médicos y enfermeras del servicio de neumología.

A los compañeros del Hospital Henri Mondor de Créteil. Al profesor Christian Brun-Buisson por acogerme en su servicio. Al profesor Bernard Maitre, por confiar en mí para ocuparme del gabinete de broncoscopias cada miércoles durante tantos meses. A los compañeros del laboratorio de investigación, la *Respiratory Team*, con los que tantas horas de trabajo juntos nos convirtió en amigos: Aysam Lyazidi, Fabrice Galia, Kaouter Saihi, Francesco Sferrazza, Guillaume Carteaux. Al Dr Xavier Drouot, por su entusiasmo y su dedicación al estudio del sueño. A los médicos del servicio de *Réanimation Médicale*: Armand Mekontso, Frédérique Schortgen, Florence Boissier, Elise Cuquemelle, Stephan Ehrmann, Caroline Jannière-Nartrey; a las enfermeras, en especial a Freançoise que tanta paciencia tuvo conmigo, a las secretarias: Sophie, Fiorella y Gina; a todos gracias por permitirme interferir en su trabajo para llevar a cabo el mío y hacerme sentir una más en su servicio. Y sobretodo agradezco al profesor Laurent Brochard y al Dr Arnaud Thille por haberme permitido trabajar a su lado y aprender de ellos, por haberme contagiado la ilusión y el entusiasmo con cada proyecto y por haberme demostrado su confianza en mí. Mi más sincero agradecimiento a ambos.

A mis compañeros de penas y alegrías y que fueron mi familia durante casi dos años en París: Sergio, Gerardo, Marta, Josemi, Idoia, Juanjo, Mourad. Y en especial a mi Irene, a la que tanto echo de menos. Con ellos cerca llenando mi vida la experiencia valió inmensamente la pena.

A mis amigos: Mati, Júlia, Ana, Irene, Rosa, Sara, María, Anna, Albert, Manoli, que permanecen *cerca* pese al tiempo y la distancia.

Y por encima de todos los demás doy las gracias a las personas más importantes de mi vida: mi padre, mi madre y mi hermana. Imprescindibles. Incondicionales.

RESUMEN

Antecedentes: La tasa de fracaso de la ventilación no invasiva (VNI) permanece elevada pese a la experiencia creciente en la técnica. Además, la VNI se realiza con diferentes tipos de ventiladores. El tipo de ventilador utilizado puede tener un impacto sobre la sincronización paciente-ventilador o la calidad del sueño. **Objetivos:** Determinar la tasa de intubación e identificar los factores de riesgo de fracaso de la VNI en pacientes con insuficiencia respiratoria hipercápnica aguda (IRHA). Comparar la sincronización paciente-ventilador entre ventiladores de UCI, transporte (ambos con y sin activación del modo VNI) y ventiladores específicos de VNI. Evaluar el impacto del tipo de ventilador sobre la calidad del sueño de los pacientes hospitalizados en reanimación y que recibe VNI. Además comparar la calidad del sueño entre los periodos de VNI y de respiración espontánea. **Metodología:** Se evaluó la capacidad de sincronización paciente-ventilador de diferentes ventiladores mediante un estudio de laboratorio usando un pulmón artificial y un modelo de fuga calibrada y en dos estudios fisiológicos usando electromiograma de superficie y pletismografía de inductancia. La calidad del sueño se evaluó mediante polisomnografía. **Resultados:** La tasa de fracaso de VNI puede reducirse a menos del 15%. La ausencia de patología respiratoria crónica subyacente o edema agudo de pulmón se estableció como factor predictivo de fracaso de la VNI, pero no la disminución del nivel de conciencia al ingreso. Los ventiladores específicos permiten una mejor sincronización paciente-ventilador que los ventiladores de UCI o los ventiladores de transporte, incluso con la activación del *modo VNI*, aunque existe una gran variabilidad en la eficacia de estos algoritmos entre ventiladores. El tipo de ventilador no tiene influencia sobre la calidad del sueño y los pacientes duermen durante los periodos de VNI. **Conclusiones:** En una unidad con experiencia la tasa de fracaso de la VNI puede reducirse a menos del 15% y la VNI de pacientes con encefalopatía hipercápnica grave puede ser exitosa. Los ventiladores específicos han mostrado una mejor capacidad de sincronización con el paciente, sin haber demostrado diferencias en la calidad del sueño con respecto a los ventiladores convencionales. Mantener la VNI durante las horas de sueño no impide dormir a los pacientes con IRHA.

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JUSTIFICACIÓN

Durante los últimos 20 años la ventilación no invasiva ha incrementando su uso y ha ido desplazando a la ventilación mecánica invasiva (VMI) en el tratamiento de la insuficiencia respiratoria aguda. En este periodo múltiples estudios se han dirigido a identificar los factores que pueden condicionar el fracaso de la técnica y la necesidad de recurrir a la intubación y VMI; y muchas de las preocupaciones relacionadas con la VMI, como la sincronización paciente-ventilador y la calidad del sueño de los pacientes críticos, se han traslado a la VNI.

En VNI la frecuencia de asincronías paciente-ventilador es superior a la VMI debido a la presencia de fuga aérea alrededor de la máscara de ventilación. Los ventiladores existentes en el mercado han sido dotados de algoritmos de funcionamiento que les permiten detectar y compensar esta fuga y mejorar la sincronización con la respiración del paciente. Sin embargo su capacidad de funcionamiento es muy variable. A día de hoy pocos estudios se han interesado por identificar las diferencias entre ventiladores y en especial por determinar si un ventilador con mejor capacidad funcional podría mejorar el confort del paciente.

Por todo ello nos planteamos evaluar la VNI desde dos puntos de vista. Primero desde un punto de vista técnico, comparando el funcionamiento de diferentes ventiladores en presencia de fuga. Segundo desde un punto de vista clínico, analizando el impacto de las diferencias técnicas entre ventiladores sobre variables fisiológicas como la sincronización paciente-ventilador y el sueño. Además analizamos la tasa de fracaso de la VNI y los factores predictivos de fracaso al evaluar una cohorte de pacientes con insuficiencia respiratoria hipercápnica tratados con VNI.

Los resultados de estos estudios conforman la tesis que se expone a continuación.

INTRODUCCIÓN

I. LA VENTILACIÓN MECÁNICA NO INVASIVA Y LA INSUFICIENCIA RESPIRATORIA AGUDA

La insuficiencia respiratoria aguda corresponde a una alteración en el intercambio de gases asociada a un aumento del trabajo de los músculos respiratorios. La ventilación mecánica permite desminuir el trabajo respiratorio al sustituir parcial o totalmente la bomba respiratoria y corregir las alteraciones del intercambio de gases. La ventilación mecánica puede llevarse a cabo de forma invasiva (VMI) a través de un tubo de intubación endotraqueal (IET), o de forma no invasiva (VNI), a través de una máscara. La VNI permite reducir las complicaciones asociadas a la VMI, especialmente las complicaciones infecciosas y en particular la neumonía nosocomial que es frecuente tras la IET[1-3].

Mientras que existe controversia sobre el uso de la VNI en la insuficiencia respiratoria aguda hipoxémica[4], su aplicación es generalizada en la insuficiencia respiratoria aguda hipercápnica (IRAH), fundamentalmente por su efectividad en las agudizaciones graves de enfermedad pulmonar obstructiva crónica (AEPOC)[5-7]. Durante la AEPOC las resistencias de la vía aérea aumentan debido a la inflamación bronquial, la presencia de secreciones muco-purulentas y el broncoespasmo, empeorando la limitación del flujo aéreo y dando lugar a una hiperinsuflación dinámica y a una presión intrínseca positiva al final de la espiración (PEEPi, del inglés *intrinsic positive end expiratory pressure*). En consecuencia se produce un aumento de la carga respiratoria y una debilidad de la musculatura inspiratoria que dan lugar a hipoxemia e hipercapnia[8]. En esta situación la VNI aumenta el volumen corriente y descarga la musculatura inspiratoria, disminuye la disnea y mejora el intercambio de gases[9,10] mientras el tratamiento médico actúa. En comparación con el tratamiento médico aislado, la VNI mejora la supervivencia, disminuye la necesidad de IET y la tasa de complicaciones y acorta la estancia hospitalaria y en las unidades de cuidados intensivos (UCI)[5,6]. Su uso como primera línea de tratamiento en las AEPOC se recomienda en las conferencias de consenso internacionales[4].

La insuficiencia cardíaca constituye la segunda indicación más frecuente de VNI en la practica clínica[11]. La presión positiva en la vía aérea puede abrir los alveolos colapsados y aumentar la capacidad funcional residual, disminuir el *shunt*, mejorar la oxigenación y

mejorar las condiciones hemodinámicas[12]. Si además se añade una presión de soporte se permite una descarga de la musculatura respiratoria[13]. Los estudios aleatorizados que comparan la presión positiva continua (*continuous positive airway pressure,* CPAP) con VNI con dos niveles de presión no muestran diferencias significativas en la tasa de IET o mortalidad, ni siquiera en los pacientes con insuficiencia respiratoria hipercápnica[14-16].

Otras causas frecuentes de IRAH son la hipoventilación asociada a obesidad, las enfermedades restrictivas de la caja torácica y las enfermedades neuromusculares. No existen estudios aleatorizados que evalúen la eficacia de la VNI en las descompensaciones agudas de estas patologías pero los estudios observacionales y de casos-controles apoyan su uso[17-21].

A pesar de la utilización y la experiencia crecientes de la VNI en las UCI[22-24] las tasas de fracaso permanecen altas: entre un 20 y un 30% en las AEPOC[5,25-28], entre el 4 y el 24% en el edema pulmonar cardiogénico[29,30] y superior al 30-40% en los pacientes con IRAH de otra etiología[24,28,31]. La severidad de la hipercapnia y/o la acidosis tras el inicio de la VNI constituyen el mayor factor predictivo de fracaso de la ventilación en los pacientes con AEPOC[25,26,28,31,32]. El bajo nivel de conciencia también se ha asociado con fracaso de la VNI en los pacientes con AEPOC[25,26,28] y constituye una contraindicación clásica para la VNI debido a la falta de cooperación/agitación, la dificultad para el manejo de secreciones por depresión del reflejo de la tos y la imposibilidad de proteger la vía aérea. Sin embargo varias publicaciones recientes reportan buenos resultados cuando la VNI se aplica a pacientes con bajo nivel de conciencia en ausencia de otras contraindicaciones y por equipos con experiencia en un entorno monitorizado donde la intubación pueda llevarse a cabo de forma inmediata[33-35]. Una mala tolerancia a la VNI se ha asociado también con el fracaso de la técnica[24,36].

II. ASPECTOS TÉCNICOS DE LA VENTILACIÓN MECÁNICA

Los dos principales sistemas de presurización utilizados para generar un flujo de gas son el aire comprimido (gas de pared o aire medicinal) y las turbinas. La mayoría de ventiladores de transporte y los ventiladores domiciliarios utilizan turbinas. Éstas funcionan como un compresor: usan el aire ambiente y generan una presión en función de su velocidad de rotación. Los ventiladores convencionales de UCI, en cambio,

funcionan con aire medicinal y utilizan válvulas proporcionales de apertura variable que permite controlar el flujo de aire.

El modo de ventilación más frecuentemente utilizado durante la VNI en cuidados intensivos es el modo presión de soporte. Es un modo espontáneo-asistido en el cual cada insuflación se activa con el esfuerzo inspiratorio del paciente (espontánea) y cada respiración es asistida por una cantidad de presión determinada proporcionada por el ventilador (asistida). En cada insuflación el ventilador aumenta el flujo de aire emitido hasta alcanzar una presión consigna (presión inspiratoria), posteriormente detiene la insuflación y permite la espiración pasiva del paciente. El ciclo de un ventilador en modo presión soporte puede dividirse en tres fases:

- **Primera fase: *trigger* inspiratorio o activación del ventilador.** Cuando el paciente realiza un esfuerzo inspiratorio, el ventilador detecta una disminución en la presión (*trigger* de presión) o en el flujo (*trigger* de flujo) del circuito. En la práctica clínica, el *trigger* de flujo ha demostrado ser el más sensible y permite reducir el esfuerzo del paciente[37,38], aunque el trabajo respiratorio asociado al *trigger* inspiratorio no representa más del 10-15% del esfuerzo inspiratorio[38].

- **Segunda fase: presión de soporte y rampa de presurización.** La capacidad del ventilador de descargar la musculatura respiratoria del paciente depende de la cantidad de asistencia proporcionada durante la inspiración (presión de soporte) y de la velocidad a la que se alcanza la presión consigna (rampa). Cuanto mayor es la presión de soporte[39,40] y más rápida la velocidad de presurización[41] menor es el trabajo inspiratorio del paciente; sin embargo, también se produce mayor fuga aérea y mayor disconfort[41,42].

- **Tercera fase: ciclado inspiración-espiración.** En presión soporte la transición de inspiración a espiración se denomina ciclado y se produce cuando el flujo inspiratorio cae por debajo de valor umbral (también denominado *trigger* espiratorio) que corresponde a un determinado porcentaje del flujo máximo inspiratorio (tradicionalmente 25%).

III. EFECTO DE LA FUGA SOBRE EL FUNCIONAMIENTO DEL VENTILADOR Y SOBRE LA SINCRONIZACIÓN PACIENTE-VENTILADOR

La fuga aérea alrededor de la máscara constituye una característica intrínseca de la VNI que puede comprometer la eficacia de la ventilación y la sincronización con la respiración del paciente. De forma general la fuga provoca un retraso en la detección del esfuerzo inspiratorio del paciente (retrasa el *trigger)*, una disminución en la capacidad de presurización, un retraso del ciclado inspiración-espiración (fundamentalmente durante la fuga inspiratoria) y produce *auto-triggering* (en presencia de fuga espiratoria)[43-47]. Así pues, la capacidad de los ventiladores para compensar el efecto de esta fuga y adaptar la función del *trigger* y el ciclado en cada momento es una de las características más importantes de los ventiladores utilizados para realizar VNI. Los estudios realizados en laboratorio nos muestran que los ventiladores específicos de VNI funcionan mejor que los ventiladores convencionales de UCI en presencia de fuga[44,45,48]. Sin embargo, las nuevas generaciones de ventiladores convencionales de UCI han sido dotadas de algoritmos de funcionamiento (el *modo VNI*) que pretenden minimizar el efecto de la fuga aérea en su funcionamiento y en la sincronización con el paciente. Los resultados obtenidos al evaluar estos algoritmos son muy heterogéneos, probablemente debido a diferencias de funcionamiento entre los ventiladores estudiados, y no permiten obtener conclusiones generales[44,46,49].

En una situación ideal, la ventilación asistida debe funcionar en sincronía con la actividad respiratoria del paciente: debe detectar lo más rápido posible el esfuerzo inspiratorio y proporcionar una asistencia ventilatoria suficiente y ajustada a su tiempo inspiratorio neural. En la realidad la sincronía perfecta entre paciente y ventilador no existe y los problemas que pueden suceder en cualquiera de estos puntos del ciclo respiratorio dan lugar a las asincronías entre paciente y ventilador[50]. Las principales asincronías que pueden identificarse en ventilación asistida son:

- **Esfuerzo ineficaz:** es un esfuerzo inspiratorio generado por el paciente pero no detectado por el ventilador y que por lo tanto no se sigue de una insuflación. Determinadas condiciones del paciente pueden participar en la génesis de esta asincronía. Durante la VNI de pacientes con broncoespasmo pueden tener lugar esfuerzos ineficaces. La mecánica respiratoria obstructiva (resistencia y complianza

elevadas) provoca que el tiempo necesario para la espiración se prolongue y se produzca una hiperinsuflación dinámica, y consecuentemente una presión positiva al final de la espiración (PEEP intrínseca), que necesita ser compensada con el esfuerzo inspiratorio inicial antes de activar el ventilador[51]. Las situaciones que se acompañan de debilidad muscular como las enfermedades neuromusculares[52] o la miopatía de reanimación, o la disminución de *drive* central como sucede en los estados de sedación o en condiciones de hiperventilación[53] también se asocian con esfuerzos ineficaces.

Las características técnicas del ventilador también pueden favorecer la aparición de esfuerzos ineficaces: un *trigger* excesivamente "duro" (umbral muy alto) o un nivel de asistencia ventilatoria elevado podrían favorecerlos. Así, la sobre-asistencia ventilatoria aumenta el volumen corriente, favorece la hiperinsuflación dinámica y la PEEP intrínseca, e inhibe la orden ventilatoria central (que disminuye la intensidad del esfuerzo) dando lugar a esfuerzos ineficaces[51,53]. La fuga aérea alrededor de la máscara también puede contribuir a la génesis de esfuerzos ineficaces. En el estudio de Vignaux[54] los pacientes con esfuerzos ineficaces presentaban un nivel de fuga aérea superior al grupo de pacientes que no presentaban esta asincronía. Es probable que la fuga inspiratoria dé lugar a insuflaciones prolongadas del ventilador durante las cuales el paciente realice esfuerzos inspiratorios que el ventilador es incapaz de detectar (ver más adelante).

- **Auto-*trigger*:** son ciclos del ventilador que se producen en ausencia de esfuerzo inspiratorio por parte del paciente. Suceden cuando el *trigger* del ventilador es muy sensible o en presencia de fuga aérea[47]. La fuga al final de la espiración puede ser reconocida por el ventilador como un esfuerzo inspiratorio del paciente si el flujo de la fuga es superior al *trigger* inspiratorio.
- **Doble *trigger*:** corresponde a dos insuflaciones sucesivas separadas por un tiempo espiratorio muy corto. Suceden cuando la demanda ventilatoria es importante y el tiempo de insuflación del ventilador es demasiado corto o la asistencia insuficiente[53,54]. Si tras el primer ciclo el esfuerzo inspiratorio del paciente no ha terminado se activa un segundo ciclo.
- **Retraso de ciclado o ciclo prolongado:** un ciclo del ventilador se prolonga más allá del fin del tiempo inspiratorio neural. El retraso de ciclado es la asincronía más frecuente en VNI[43,54] debido a la presencia de fuga peri-máscara al final de la

inspiración. Si el flujo de la fuga es superior al umbral de flujo inspiratorio que determina el paso a espiración en modo presión soporte, la insuflación se prolonga hasta el tiempo inspiratorio máximo y se retrasa el ciclado[43]. Limitar el tiempo inspiratorio máximo[43], incrementar el umbral de flujo inspiratorio que determina el *trigger* espiratorio[55] y disminuir la fuga no intencional pueden disminuir la incidencia de ciclos prolongados.

- **Ciclado prematuro:** un ciclo del ventilador que finaliza antes del fin del tiempo inspiratorio neural. Sucede en pacientes con baja complianza del sistema respiratorio[56] en cuyo caso el flujo de insuflación cae rápidamente por debajo del valor umbral de ciclado.

IV. INCIDENCIA Y CONSECUENCIA DE LAS ASINCRONÍAS PACIENTE-VENTILADOR

La asincronía paciente-ventilador es muy frecuente durante la ventilación mecánica. Alrededor de un 25% de los pacientes que reciben VMI[53] y un 43% de los pacientes que reciben VNI por insuficiencia respiratoria aguda[54] presentan una alta incidencia de asincronías (ie, superior al 10% de los ciclos). En el estudio de Vignaux y colaboradores[54] el nivel de fuga aérea y el nivel de presión de soporte se asociaron con una alta incidencia de asincronías paciente-ventilador. Un estudio posterior realizado por el mismo equipo comparó el índice de asincronías en un grupo de 65 pacientes ventilados de forma no invasiva con ventiladores de UCI al activar o no activar el *modo VNI*[49]. El *modo VNI* redujo el índice de asincronías asociadas a fuga, *ie*, la suma de *auto-triggering*, esfuerzos ineficaces y ciclos prolongados, pero el índice global de asincronías no se redujo, probablemente porque varios ventiladores aumentaban la incidencia de ciclos prematuros con el *modo VNI*.

Mientras que en VMI la presencia de una alta incidencia de asincronías se ha asociado a un mayor tiempo de VMI[53], en VNI no se han identificado efectos sobre el pronóstico. En el estudio de Vignaux y colaboradores[54] la tasa de intubación, el tiempo de estancia en UCI o la mortalidad entre los pacientes que presentaban asincronía severa y los que no fue similar, aunque el estudio no se diseñó con esa finalidad. Ese mismo estudio, y uno más reciente realizado con pacientes en situación estable[57], asocian la presencia de asincronías con un peor confort y una peor tolerancia al tratamiento. Teniendo en

cuenta que la tolerancia a la técnica es un factor determinante para su éxito[36] es posible que la reducción en el número de asincronías tenga un efecto positivo en el pronóstico.

V. VENTILACION MECÁNICA Y SUEÑO EN LAS UNIDADES DE CUIDADOS INTENSIVOS

El sueño de los pacientes hospitalizados en UCI se halla severamente alterado, tanto en su distribución a lo largo del día como en su arquitectura[58-60]. Entre los factores que pueden contribuir a esta alteración se halla la ventilación mecánica[52,61-63]. Algunos estudios han puesto de manifiesto que las asincronías paciente-ventilador pueden afectar a la calidad del sueño. Fanfulla y colaboradores[52] demostraron que cuando la ventilación en presión soporte se ajustaba para disminuir el esfuerzo de la musculatura inspiratoria, la incidencia de asincronías (sólo se evaluaban esfuerzos ineficaces) disminuía y la calida de sueño mejoraba. Bosma et al.[61] demostraron una menor incidencia de asincronías paciente-ventilador y una mejor calidad del sueño al utilizar ventilación asistida proporcional en comparación con el modo presión soporte y una correlación entre la incidencia de asincronías y el número microdespertares por hora. Además, la calidad del sueño de los pacientes puede tener relación con el pronóstico. Roche Campo y colaboradores[64] pusieron de manifiesto, en un grupo de pacientes con insuficiencia respiratoria aguda y tratamiento con VNI, una mayor incidencia de fracaso tardío de la VNI y de delirium en aquellos que habían mostrado un sueño de peor calidad caracterizado por más alteración del ritmo circadiano y menor cantidad de sueño REM[64]. Así pues, es posible que al disminuir la incidencia de asincronías paciente-ventilador se produzca un efecto positivo sobre la calidad del sueño y el pronóstico de los pacientes.

HIPÓTESIS PRINCIPAL

1. La tasa de fracaso de la VNI en la insuficiencia respiratoria aguda hipercápnica en una unidad experimentada podría ser inferior al 20-30% reportado en la literatura.

2. El uso de ventiladores específicos de VNI y de ventiladores convencionales de UCI con el *modo VNI* activado permitiría mejorar la sincronización paciente-ventilador con respecto al uso de ventiladores convencionales de UCI sin la activación del *modo VNI*.

3. Las diferencias de funcionamiento entre los ventiladores convencionales y los ventiladores específicos podrían tener, a través de las asincronías paciente-ventilador, un impacto sobre la calidad del sueño de los pacientes con insuficiencia respiratoria aguda hipercápnica.

OBJETIVOS

1. Evaluar las tasas de intubación y los factores predictivos de fracaso de la VNI en pacientes con insuficiencia respiratoria aguda hipercápnica.

2. Comparar el funcionamiento y la sincronización paciente-ventilador entre diferentes tipos de ventiladores utilizados para la VNI: ventiladores convencionales de UCI, ventiladores de transporte (ambos con y sin la activación del *modo VNI*) y ventiladores específicos de VNI. Evaluación primero mediante un estudio en laboratorio utilizando un pulmón artificial y posteriormente mediante un estudio fisiológico con pacientes hospitalizados en una UCI.

3. Evaluar el impacto de dos tipos de ventiladores (un ventilador específico de VNI y un ventilador convencionales de UCI) y de la sincronización paciente-ventilador sobre la calidad del sueño en pacientes con insuficiencia respiratoria aguda hipercápnica que reciben VNI. Además, evaluar el sueño durante los periodos de VNI y compararlo con los periodos de respiración espontánea.

METODOLOGÍA

Los trabajos que se presentan han sido realizados en la unidad de reanimación médica del Hospital Henri Mondor (Créteil, Francia) y dirigidos por el doctor Arnaud W. Thille y el Profesor Laurent Brochard. Cada uno de ellos ha sido aprobado por el comité ético del centro (*Comité de Protection des Personnes Ille-de-France IX*) o de la Sociedad Francesa de Medicina Respiratoria (*Société de Pneumologie de Langue Française*) antes de su realización.

I. PROTOCOLO DE APLICACIÓN DE LA VENTILACION NO INVASIVA

La VNI se aplica por el personal de enfermería y de acuerdo a un protocolo de actuación desde el año 2008. Este protocolo incluye la prescripción facultativa del modo de ventilación y de unos objetivos de volumen corriente, saturación de oxígeno y presión espiratoria (ver material suplementario de la publicación nº 1). Antes de iniciar la VNI el personal de enfermería debe preparar al paciente (explicar el procedimiento y proteger las zonas de presión con apósitos especiales), escoger la mejor máscara y verificar el riesgo de mala evolución clínica (*ie*, fracaso de VNI o paro cardíaco) si existe alguno de los siguientes criterios: un bajo nivel de conciencia, la presencia de abundantes secreciones, la necesidad de fracción inspirada de oxígeno (FiO_2) elevadas y/o el uso de drogas vasoactivas, en cuyo caso la VNI debe realizarse en un entorno de alta monitorización.

Cuando la VNI se aplica en modo presión soporte con un ventilador convencional (la mayoría de las ocasiones), la sesión se inicia con una presión espiratoria de 0 cmH_2O, una presión de soporte de 8 cmH_2O, un *trigger* inspiratorio de 3 L/min, un tiempo inspiratorio máximo de 1 segundo y una FiO_2 determinada según el flujo de oxígeno previo que necesitaba el paciente. De acuerdo con el algoritmo de actuación se ajustan los parámetros del ventilador hasta conseguir los objetivos prescritos. Estas variables se anotan periódicamente, así como el nivel de conciencia, la frecuencia respiratoria, la frecuencia cardíaca, la tensión arterial, la tolerancia y la fuga aérea alrededor de la máscara. La VNI se aplica de forma intermitente en sesiones de al menos 2 horas con una duración total mínima de 6 horas por día, o de forma continua en situación de coma hipercápnico. El protocolo también incluye un algoritmo de actuación en caso de fuga importante.

II. EVALUACIÓN DE VENTILADORES EN BANCO DE PRUEBAS

El montaje que hemos llevado a cabo para la evaluación de los ventiladores en el laboratorio consiste en conectar el ventilador a un pulmón artificial a través de un circuito (figura 1A). El pulmón artificial utilizado en nuestros experimentos es el Active Servo Lung 5000 (ASL 5000, IngMar Medical, Pittsburgh, Pensilvania). Este sistema se basa en un pistón controlado por un computador que se mueve dentro de un cilindro y que permite fijar unas determinadas características mecánicas del sistema respiratorio (resistencia, complianza, presión muscular). Para nuestros experimentos simulamos un patrón obstructivo leve (complianza de 80 cmH_2O/mL y resistencia de 10 cm H_2O/L/s) y fijamos un esfuerzo inspiratorio moderado (flujo inspiratorio de 30 L/minuto), una frecuencia respiratoria de 15/minuto y un tiempo inspiratorio de 0.8 segundos. Para evaluar el efecto de la fuga en la función de los ventiladores, creamos tres condiciones distintas: A. ausencia de fuga; B. fuga continua, con la intención de poner de manifiesto asincronías de la fase espiratoria y C. fuga inspiratoria, para provocar asincronías de ciclado (Figura 1). Todos los ventiladores fueron testados en cada una de las tres condiciones durante 2 minutos. Los datos recogidos en el ASL 5000 (volumen, flujo y presión) fueron almacenados en un ordenador portátil para su análisis posterior con el programa Acqknowledge 3.7.3 (Biopac systems, Goleta, California, EEUU). El funcionamiento de los ventiladores se evaluó utilizando los parámetros que se detallan a continuación.

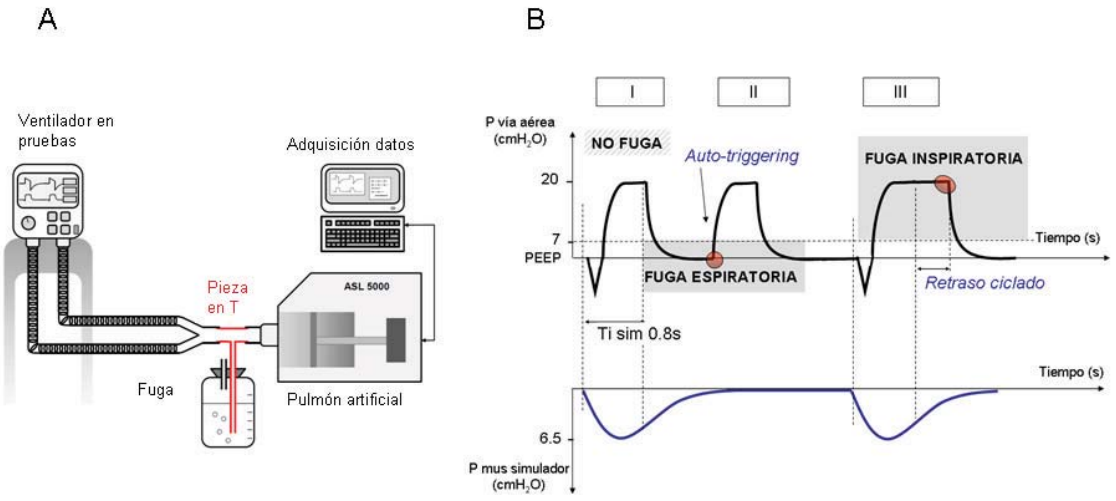

Figura 1. Diseño experimental. **A.** Para reproducir de forma experimental las condiciones de VNI se generó una fuga calibrada colocando una pieza en T entre el ASL 5000 y el circuito del ventilador. Al introducir 7 cm el extremo libre de la pieza en T en un recipiente con agua la fuga se producía cuando la presión del circuito excedía los 7 cmH_2O

(durante la fase inspiratoria). Con este montaje el flujo de la fuga inspiratoria aumentaba de forma no lineal con la presión (pasaba de 0 a 22 L/min cuando la presión aumentaba de 7 a 15 cmH_2O). Cuando el sistema se utilizaba sin introducir la pieza en T en agua se generaba una fuga continua (durante la inspiración y la espiración). En condiciones de fuga continua, para una presión de 5 cm H_2O el flujo de fuga era 16 L/min. **B.** Curvas de presión de la vía aérea y presión inspiratoria del simulador (Pmus simulador). Se representan tres condiciones de fuga: I. no hay fuga (el extremo libre de la pieza en T estaría cerrado); II. Fuga espiratoria (o continua), se representa un *auto-triggering*; III. Fuga inspiratoria, se representa un retraso de ciclado o ciclo prolongado.

El *trigger* inspiratorio se evaluó mediante:

1. El retraso del *trigger* (*triggering delay*) que es el tiempo transcurrido desde el inicio del esfuerzo inspiratorio del simulador hasta el inicio de la presurización del ventilador expresado en milisegundos (figura 2A).
2. El producto presión-tiempo del *trigger* ($PTP_{trigger}$), expresado en cmH_2O.segundo, que es el área bajo la curva presión-tiempo desde el inicio del esfuerzo inspiratorio hasta el punto de retorno a la línea de base (figura 2 A) y que representa esfuerzo gastado para activar el ventilador.
3. La incidencia de auto-*triggering*, expresada en porcentaje y calculada según la fórmula: incidencia de auto-*triggeing* (%) = ciclos *auto-triggered*/ ciclos totales x 100.

La presurización del ventilador se evaluó mediante el producto presión-tiempo durante los primeros 300 ms (PTP_{300}), expresado en cmH_2O.segundo, que corresponde a la superficie bajo la curva presión-tiempo (por debajo y por encima de la presión positiva telespiratoria) desde el inicio del esfuerzo inspiratorio (figura 2 B). El PTP_{300} representa la cantidad de asistencia ventilatoria recibida por el paciente durante la fase inicial del esfuerzo. Puesto que en su cálculo se incluye el $PTP_{trigger}$, el PTP_{300} representa un buen índice de la capacidad de funcionamiento global del ventilador.

La función de ciclado a espiración se evaluó mediante la diferencia entre el tiempo de insuflación del ventilador ($Ti_{ventilador}$) y el tiempo de inspiración del simulador ($Ti_{simulador}$, fijado en 0.8 segundos), expresada como exceso de tiempo de insuflación (Ti_{excess}) y calculado mediante la fórmula: $Ti_{excess} = [(Ti_{ventilador}-Ti_{simulador})/Ti_{simulador}]$ x100. Hemos definido arbitrariamente el retraso de ciclado como $Ti_{ventilador} \geq 2Ti_{simulador}$ y el ciclado prematuro como $Ti_{ventilador} < 2/3\ Ti_{simulador}$.

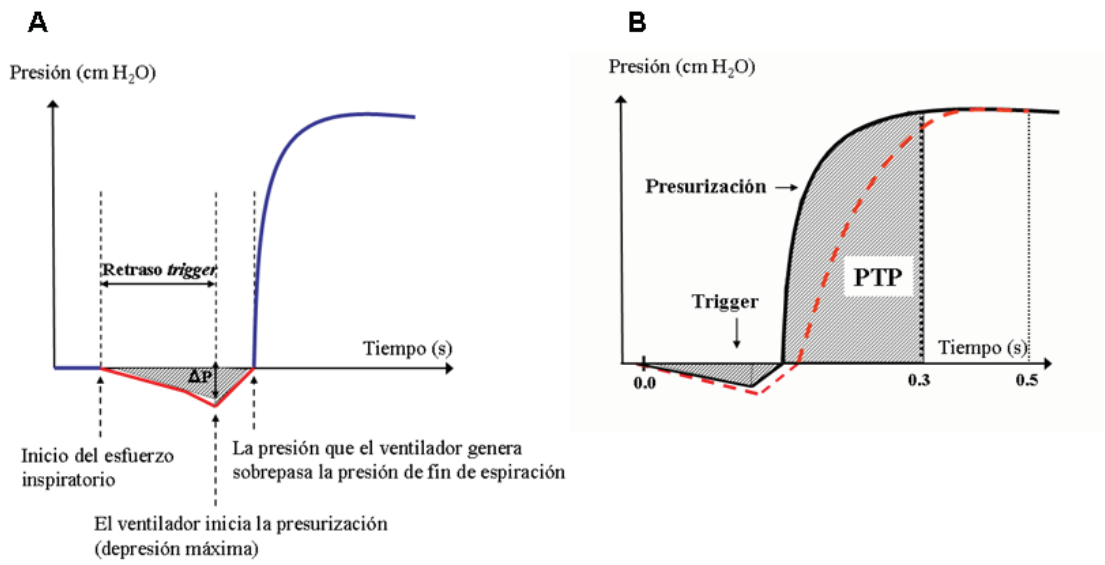

Figura 2. A. Evaluación del funcionamiento del *trigger*. El área rallada representa el PTP *trigger*. **B.** Evaluación de la capacidad de presurización. El área rallada representa el PTP a 0.3 s del inicio del esfuerzo inspiratorio (PTP_{300}). La línea discontinua representa una capacidad de presurización pobre, con un PTP_{300} menor.

III. DETECCIÓN DE ASINCRONÍAS PACIENTE-VENTILADOR

La detección de asincronías paciente-ventilador se ha llevado a cabo mediante la inspección visual de las curvas de flujo y presión de la vía aérea junto con el esfuerzo inspiratorio del paciente detectado a través de la actividad eléctrica de la musculatura inspiratoria por electromiograma (EMG) de superficie[49,54] en el segundo estudio o detectado a través de los movimientos torácicos y abdominales recogidos mediante pletismografía de inductancia[52,61,65] en el tercer estudio.

En el estudio número 2 el flujo se midió mediante un neumotacógrafo (Fleish Nº 2, Lausana, Suiza) colocado entre la máscara y el circuito y conectado a un transductor de presión diferencial (Validyne MP45, ± 2cmH2O, Northridge, California). La presión de la vía aérea se midió con un transductor de presión diferencial (Validyne MP45, ± 70cmH2O, Northridge, California) conectado entre la máscara y el neumotacógrafo. Las señales se recogieron usando un conversor analógico-digital (MP 100; Biopac systems, Goleta, CA, USA) a 200Hz y se guardaron en un ordenador portátil para su análisis posterior con el programa Acqknowledge 3.7.3 (Biopac systems, Goleta, California). El EMG de diafragma se registró mediante electrodos de superficie colocados a cada lado del margen costal con un electrodo de referencia colocado en el esternón[66]. El EMG del cuello se obtuvo con dos electrodos colocados en el triángulo posterior del cuello

(actividad del músculo escaleno) o sobre el esternocleidomastoideo y un electrodo de referencia colocado en el esternón. La señal analógica fue filtrada y digitalizada a una frecuencia de 1000 Hz mediante el módulo Biopac EMG (Biopac systems, Goleta, California) y recogidas en un ordenador portátil para su análisis posterior. El tiempo inspiratorio neural del paciente se consideró como el intervalo entre el incremento inicial y el decremento rápido de la actividad eléctrica de la señal EMG procesada[49,54].

En el estudio número 3 la curva de flujo se obtuvo a partir de un neumotacógrafo no calibrado acoplado entre el circuito y la máscara y conectado a un transductor de presión diferencial (Pneumoflow) cuya señal se integra en el polígrafo (Embla S7000; Embla ResMed, Denver, Colorado) junto con la presión obtenida en la máscara y los movimientos torácicos y abdominales recogidos mediante pletismografía de inductancia. Las señales fueron almacenadas en un ordenador portátil para su análisis posterior con el programa Somnologica para Embletta (Version 3.3; Medcare). La figura 3 muestra un ejemplo de curvas obtenidas en cada uno de los estudios.

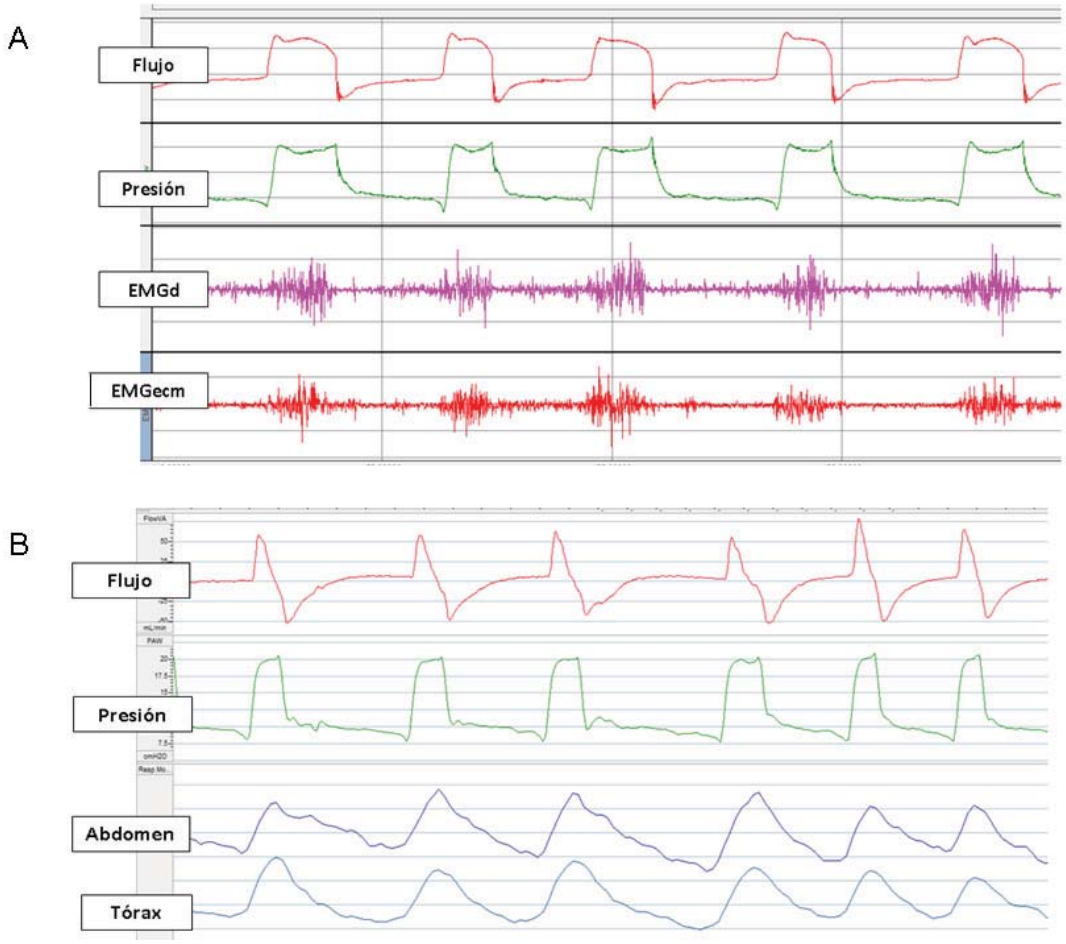

Figura 3. Registros de flujo, presión vía aérea y esfuerzo inspiratorio mediante A. actividad eléctrica de la musculatura inspiratoria recogida mediante electromiograma de diafragma (EMGd) y esternocleidomastoideo (EMGecm) y B. movimientos torácicos (tórax) y abdominales (abdomen) recogidos mediante pletismografía de inductancia.

Para el análisis de las asincronías se han utilizado las siguientes definiciones de acuerdo a publicaciones anteriores[49,53,54]: **Esfuerzo ineficaz:** un esfuerzo inspiratorio que no se acompaña de una insuflación del ventilador. **Doble *triggering***: dos insuflaciones del ventilador en presencia de un único esfuerzo inspiratorio. ***Auto-triggering*:** una o varias insuflaciones consecutivas sin un esfuerzo inspiratorio concomitante. **Ciclo prolongado o retraso de ciclado**: en el segundo estudio se definió como un tiempo de insuflación dos veces superior al tiempo inspiratorio del paciente. En el tercer estudio se definió como un ciclo del ventilador que abarca dos esfuerzos inspiratorios del paciente. **Ciclado prematuro**: se utilizó sólo en el segundo de los estudios y se definió como ciclo en que el tiempo de insuflación es inferior a 2/3 tiempo inspiratorio del paciente. En el tercer estudio se definió **apnea** como una ausencia de insuflaciones del ventilador durante en periodo mayor o igual a 10 s.

En el estudio 2 se calculó el índice de asincronías como número de eventos por minuto; y se consideró que una asincronía era frecuentes sólo si sucedía >1 vez por minuto durante los 20 minutos de registro. Se calculó un índice global de asincronías, expresado en porcentaje, como (número asincronías / [esfuerzos ineficaces + ciclos ventilador]) x 100[42,49,53,54]. En el tercer estudio se calculó la incidencia de asincronías como número de eventos por hora. Se analizaron las asincronías durante todo el tiempo de sueño y durante 20 minutos de ventilación con el paciente despierto.

IV. EVALUACIÓN DEL SUEÑO EN REANIMACIÓN

Para la realización del tercer estudio se llevó a cabo una polisomnografía completa (Embla S7000; Embla ResMed, Denver, Colorado) de 4 pm a 9 am con un equipo portátil colocado en la cabecera del paciente. Se recogieron siete canales de electroencefalograma, electrooculograma izquierdo y derecho y dos EMG de mentón para estadificar las fases del sueño, cuyo análisis se realizó conjuntamente con un neurólogo experto (X. Drout) según los criterios de Rechtschaffen y Kales[67].

Junto con el sueño se recogieron datos de ruido ambiental y eventos respiratorios que podían ser causa de la fragmentación del sueño. El ruido ambiental se recogió cerca de la cabecera del paciente con un audiómetro (Quest Technologies, Oconomowoc, Wisconsin) y los datos obtenidos se integraron con el resto de variables. Los eventos respiratorios estudiados durante la ventilación asistida fueron las asincronías paciente-ventilador y las apneas; y durante los periodos de respiración espontánea las apnea e hipopneas según las recomendaciones de la *American Association of Sleep Medicine*[68]. Se estableció una relación causal entre asincronías paciente-ventilador y despertar o microdespertar cuando estos ocurrían en los 10 segundos siguientes al evento[62,69] y entre pico de ruido (incremento de ≥ 10 dB) y despertar o microdespertar cuando estos sucedían en los 3 segundos siguientes[59,60].

ARTÍCULOS PUBLICADOS

1. Contou D, Fragnoli C, **Córdoba-Izquierdo A**, Boissier F, Brun-Buisson C, Thille AW. ***Noninvasive ventilation for acute hypercapnic respiratory failure: intubation rate in an experienced unit.*** Respiratory Care 2013;58(12):2045-2052. Factor de impacto: 2.03.

2. Carteaux G, Lyazidi A, **Córdoba-Izquierdo A**, Vignaux L, Jolliet P, Thille AW, Richard JC, Brochard L. ***Patient-ventilator asynchrony during noninvasive ventilation: a bench and clinical study.*** Chest 2012;142(2):367-376. Factor de impacto: 5.85.

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Noninvasive Ventilation for Acute Hypercapnic Respiratory Failure: Intubation Rate in an Experienced Unit

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BACKGROUND: Failure of noninvasive ventilation (NIV) is common in patients with COPD admitted to the ICU for acute hypercapnic respiratory failure (AHRF). We aimed to assess the rate of NIV failure and to identify early predictors of intubation under NIV in patients admitted for AHRF of all origins in an experienced unit. METHODS: This was an observational cohort study using data prospectively collected over a 3-year period after the implementation of a nurse-driven NIV protocol in a 24-bed medical ICU of a French university hospital. RESULTS: Among 242 subjects receiving NIV for AHRF (P_{aCO_2} > 45 mm Hg), 67 had cardiogenic pulmonary edema (CPE), 146 had acute-on-chronic respiratory failure (AOCRF) (including 99 subjects with COPD and 47 with other chronic respiratory diseases), and 29 had non-AOCRF (mostly pneumonia). Overall, the rates of intubation and ICU mortality were respectively 15% and 5%. The intubation rates were 4% in CPE, 15% in AOCRF, and 38% in non-AOCRF (*P* < .001). After adjustment, non-AOCRF was independently associated with NIV failure, as well as acidosis (pH < 7.30) and severe hypoxemia (P_{aO_2}/F_{IO_2} ≤ 200 mm Hg) after 1 hour of NIV initiation, whereas altered consciousness on admission and ventilatory settings had no influence on outcome. CONCLUSIONS: With a nurse-driven NIV protocol, the intubation rate was reduced to 15% in patients receiving NIV for AHRF, with a mortality rate of only 5%. Whereas the risk of NIV failure is associated with hypoxemia and acidosis after initiation of NIV, it is also markedly influenced by the presence or absence of an underlying chronic respiratory disease. *Key words: noninvasive ventilation; acute respiratory failure; acute-on-chronic respiratory failure; cardiogenic pulmonary edema; COPD; hypercapnic coma; endotracheal intubation.* [Respir Care 2013;58(12):2045–2052. © 2013 Daedalus Enterprises]

Introduction

Noninvasive ventilation (NIV) reduces the rates of intubation and mortality in patients with severe exacerbation of COPD[1,2] or cardiogenic pulmonary edema (CPE).[3] In our ICU, NIV has been used since the late 1980s, and was shown by Brochard et al[4] to be beneficial in patients admitted with exacerbation of COPD. A subsequent prospective randomized study demonstrated that NIV was associated with reduced rates of endotracheal intubation and mortality in these patients.[5]

Several large surveys show that the use of NIV has become widespread in treatment of severe exacerbation of

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Dr Contou presented a version of this paper at the 2012 meeting of the European Society of Intensive Care Medicine, held October 13–17, 2012, in Lisbon, Portugal.

Supplementary material related to this paper is available at http://www.rcjournal.com.

The authors have disclosed no conflicts of interest.

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DOI: 10.4187/respcare.02456

COPD in Europe and in the United States.[6-8] Despite the increasing experience with this technique, the rate of NIV failure remains high, between 20% and 30% in COPD patients admitted to ICUs.[2,5,9,10] NIV may also be used as first-line management of non-COPD patients having acute hypercapnic respiratory failure (AHRF), but the rate of NIV failure and intubation can exceed 30–40% in this group.[8,11,12] In COPD patients the severity of hypercapnia and/or acidosis after initiation of NIV is a major predictor of NIV failure.[11,13-15] However, no study has evaluated the impact of the NIV ventilatory settings and respiratory parameters under NIV on outcome, and little information is available on hypercapnic non-COPD patients treated with NIV.

The aims of this study were to assess the rate of NIV failure in patients admitted for AHRF, whatever the cause, in an experienced unit, and to identify early predictors of intubation under NIV. Some of the results of this study have been previously reported in the form of an abstract at the 2012 meeting of the European Society of Intensive Care Medicine in Lisbon, Portugal.[16]

QUICK LOOK

Current knowledge

Failure of noninvasive ventilation (NIV) is common in patients with COPD admitted to the ICU for acute hypercapnic respiratory failure. In selected patients the commonly reported failure rate is approximately 30%.

What this paper contributes to our knowledge

With a nurse-driven NIV protocol, the intubation rate was reduced to 15% in patients receiving NIV for acute hypercapnic respiratory failure, with an accompanying mortality rate of only 5%. The risk of NIV failure is associated with hypoxemia and acidosis after initiation of NIV, and is also markedly influenced by the presence or absence of an underlying chronic respiratory disease. Altered consciousness at admission and ventilator settings had no influence on outcome.

Methods

This observational cohort study was conducted in our 24-bed medical ICU at Hôpitaux Universitaires Henri Mondor in Créteil, France. The institutional review board of the French Society for Respiratory Medicine approved this noninterventional study and waived the need for informed consent.

Subjects

We prospectively included all consecutive patients admitted during a 3-year period (June 2008 to June 2011) and who received NIV as initial ventilatory support for AHRF. AHRF was defined as recent dyspnea with sternocleidomastoid muscle activation and a breathing frequency > 25 breaths/min and/or an arterial pH < 7.35, with a P_{aCO_2} above 45 mm Hg. We excluded patients who were intubated before ICU admission or intubated upon ICU admission without prior NIV, and patients for whom NIV was used with a do-not-intubate order.

NIV Protocol and Definitions

The study was conducted after the implementation, in June 2008, of a nurse-driven NIV protocol that included prospective daily collection of clinical data and ventilatory parameters on a specific NIV monitoring form. When the NIV form was unavailable or incomplete, data were retrieved from the subject's records.

All stages of the protocol had been developed within a multidisciplinary working group including ICU physicians, nurses, and respiratory therapists. A daily NIV prescription by the physician indicated the duration of NIV sessions and targeted expiratory tidal volume (around 6–8 mL/kg) and S_{pO_2} (88–92% in subjects with acute-on-chronic respiratory failure [AOCRF], and $\geq$ 94% in other subjects). Given that respiratory therapists are not present every day and all day long in our unit, the protocol aimed at empowering nurses to adjust the ventilatory settings and to improve the subject's tolerance to NIV. Nurses are not as highly skilled in mechanical ventilation as respiratory therapists in the United States can be, and were not involved in the decision to intubate. The first objective was to reach the targeted expiratory tidal volume and S_{pO_2}, and to improve the subject's tolerance to NIV following a simple decision algorithm (see the protocol and algorithm used in the supplementary material at http://www.rcjournal.com).

Pressure-support ventilation was started, using a pressure-support level of 8 cm H_2O, a PEEP level of 0 cm H_2O, an inspiratory trigger of 3 L/min, and a maximal inspiratory time of 1 second. The nurses then adjusted the ventilatory parameters, including pressure-support level and F_{IO_2}, according to the protocol. Pressure-support level was gradually increased by 2 cm H_2O steps to reach the target expiratory tidal volume, and PEEP level was then adjusted as prescribed. F_{IO_2} was gradually adjusted by 5% steps to reach the targeted S_{pO_2}. NIV was applied intermittently for periods of at least 2 hours, with a minimal duration of 6 hours per day, or continuously in case of hypercapnic coma, and was maintained until signs of respiratory distress improved. An algorithm was used by nurses in case of leaks, which involved repositioning of the mask, then reducing the PEEP by 2 cm H_2O, then

reducing the pressure-support level by steps of 2 cm H_2O until the minimal expiratory volume was reached, and then changing the mask interface. Continuous mandatory ventilation could be used transiently in subjects with hypercapnic coma and triggering insufficient tidal volume despite high pressure support levels.

A mobile cart containing all types and sizes of interfaces was available at the bedside during initiation of NIV. NIV was performed via a non-vented oronasal mask (FreeMotion RT041, Fisher & Paykel, Auckland, New Zealand, or Ultra Mirage, ResMed, San Diego, California), with an ICU ventilator using a dedicated NIV mode (Evita XL, Dräger, Lübeck, Germany, or Engström CareStation, GE Healthcare, Little Chalfont, Buckinghamshire, United Kingdom), equipped with a heated humidifier (MR850, Fisher & Paykel, Auckland, New Zealand).

The following criteria were used for endotracheal intubation: hypercapnic coma with inability to deliver tidal volume, loss of consciousness or persistent hypercapnic coma under NIV, psychomotor agitation making nursing care impossible and requiring sedation, pronounced worsening in signs of respiratory distress with a breathing frequency above 40 breaths/min under NIV, S_{pO_2} remaining below 90% despite F_{IO_2} 1.0, and persistent hypotension despite fluid resuscitation requiring vasopressors. Worsening respiratory acidosis or absolute values of pH/P_{CO_2} were not used as criteria for intubation in the absence of other signs cited above.

Data Collection

From the NIV monitoring forms we analyzed the number and duration of NIV sessions, ventilator settings (pressure support level, PEEP, F_{IO_2}), ventilatory parameters (S_{pO_2}, breathing frequency, expiratory tidal volume), level of consciousness (assessed using the Richmond Agitation-Sedation Scale),[17] NIV tolerance (scored from 0 for "poor" to 3 for "excellent"), amount of leaks (scored from 0 for "no leaks" to 3 for "major"), and hemodynamic parameters (heart rate, blood pressure). Poor tolerance was considered as a score of 0 or 1, and major leaks as a score of 2 or 3. Altered consciousness was defined as a Richmond Agitation-Sedation Scale < 0, and coma as a Glasgow coma score ≤ 8. Blood gases were routinely measured 1 hour after initiation of NIV. Clinical data (breathing frequency, S_{pO_2}, blood pressure, heart rate, Glasgow coma score) and blood gases at admission before NIV initiation were retrospectively collected from the medical chart. An independent pulmonologist classified subjects according to the underlying cause of AHRF into one of 3 subgroups: CPE, AOCRF (including subjects having chronic respiratory failure associated with COPD or with other, non-COPD causes), and non-AOCRF, which included subjects without underlying chronic respiratory disease.

Statistical Analysis

Data are expressed as mean ± SD, median and IQR, or number and percent (for dichotomous variables). Qualitative data were compared using the chi-square test, and quantitative data using the unpaired Student *t* test or Kruskal Wallis test.

To evaluate independent factors associated with NIV failure at admission, univariate risk factors with a *P* value $< .10$ were examined using backward stepwise logistic regression analysis. Among related significant univariate factors, only the most clinically relevant were entered into the regression model in order to minimize the effect of collinearity. We therefore included the cause of AHRF, tachypnea, and altered consciousness at admission, and hypoxemia and respiratory acidosis after NIV initiation, whereas Simplified Acute Physiology Score II was not entered into the model. We considered 2-tailed *P* values $< .05$ as significant. The statistical analysis was performed using statistics software (Stata 10.1, StataCorp, College Station, Texas).

Results

Subjects

Over the 3-year period, 242 subjects received NIV for AHRF, including 67 with cardiogenic pulmonary edema (CPE), 146 with AOCRF, and 29 with non-AOCRF (Fig. 1). Prospective data on NIV ventilatory parameters was available for 83% (201/242). Among the 47 subjects with non-COPD AOCRF, 30 had obesity and/or obstructive sleep apnea syndrome (median body mass index 38 kg/m^2), while others had bronchiectasis ($n = 4$), permanent ventilatory impairment due to asthma ($n = 4$), pulmonary cancer ($n = 2$), chest-wall disease ($n = 3$), myopathy ($n = 2$), and myasthenia gravis ($n = 2$). Among the 29 subjects having non-AOCRF and hypercapnia, 24 had pneumonia (including 8 subjects with clinical criteria for ARDS), and 5 had drug intoxication. The subjects' characteristics at admission and their outcomes in ICU are reported in Table 1. Overall, 31 subjects were comatose either at admission ($n = 15$) or during the first 24 hours ($n = 16$).

Rates of NIV Failure and ICU Mortality

The overall rates of intubation and mortality were respectively 15% (36/242) and 5% (13/242). The intubation rates were 4% (3/67) in CPE, 15% (22/146) in AOCRF—with an identical rate in COPD and non-COPD subjects—and 38% (11/29) in non-AOCRF ($P < .001$) (Fig. 2). The corresponding ICU mortality rates were 3% (2/67), 5% (7/146), and 14% (4/29) ($P = .08$) (Fig. 3). The intubation rates were 11% (13/115) in subjects having a pH on ad-

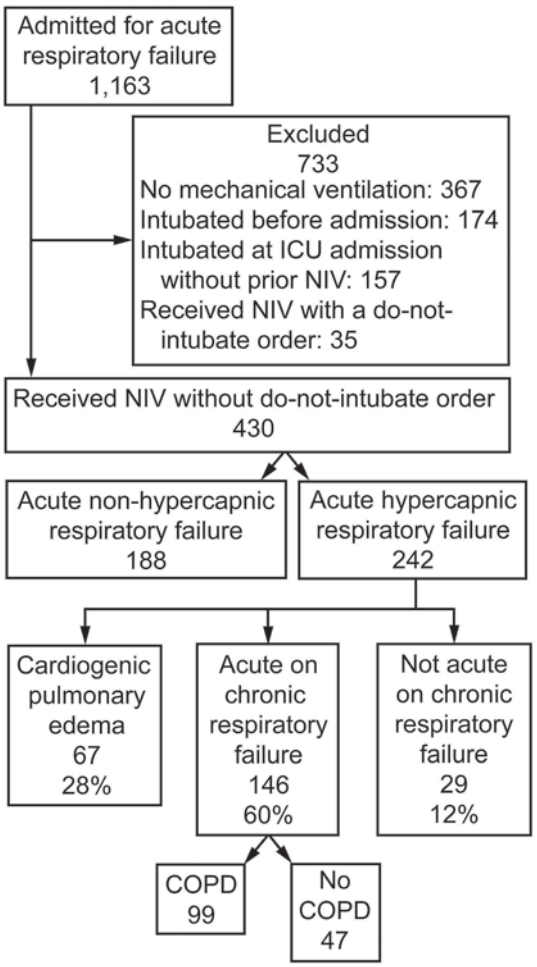

Fig. 1. Flow chart. NIV = noninvasive ventilation.

mission ≥ 7.30 and 18% (23/128) in those having a pH < 7.30 ($P = .15$). The in-ICU mortality rate of intubated subjects was 36% (13/36).

Factors Associated With NIV Failure

Among variables recorded on ICU admission, the etiology of AHRF and tachypnea (> 30 breaths/min) was independently associated with NIV failure (Table 2). Non-AOCRF was an independent predictor of NIV failure, as compared to subjects with AOCRF and CPE.

Pressure-support level adjusted by nurses was significantly greater 1 hour after NIV initiation than at NIV initiation (9.5 ± 3.0 cm H_2O vs 9.2 ± 2.6, $P = .036$), while tidal volume remained similar (468 ± 144 mL vs 465 ± 135, $P = .64$). Although not significantly different, expiratory tidal volume 1 hour after NIV initiation tended to be lower in subjects who failed NIV, compared to those who succeeded in NIV.

Among variables recorded at one hour after NIV initiation, ventilatory settings and subject tolerance to NIV or amount of leaks had no influence on outcome, whereas severe hypoxemia ($P_{aO_2}/F_{IO_2} \leq 200$ mm Hg) and severe acidosis (pH < 7.30) were independently associated with NIV failure.

After adjustment, altered consciousness at admission was not associated with NIV failure and only 23% (14/60) of subjects who had encephalopathy were intubated. Among the 31 comatose subjects, 15 (48%) succeeded in NIV without need for endotracheal intubation.

Discussion

In hypercapnic patients receiving NIV as first-line ventilatory support for acute respiratory failure of various origins, we found that the overall rate of intubation was only 15%. However, this rate differed markedly according to the underlying cause of acute respiratory failure, and reached 38% in patients without chronic respiratory disease (non-AOCRF). Among patients with AOCRF, no difference was found between COPD and non-COPD patients.

Rate of NIV Failure According to the Cause for Acute Hypercapnic Respiratory Failure

The intubation rate of only 4% in subjects receiving NIV for CPE compares favorably with the 14% rate reported in a meta-analysis[3] and the 18% rate reported in a survey from the United States.[12] Some studies have even reported intubation rates exceeding 20% in the subset of hypercapnic patients.[18] Our results are, however, consistent with those of Nava et al,[19] who reported an intubation rate of only 6% in hypercapnic patients with CPE treated in an ICU having extensive experience with NIV.

The 15% intubation rate we recorded in subjects with AOCRF is also lower than the 20–30% rates usually reported in studies evaluating NIV in COPD patients.[5,8-10,12] Plant et al reported an overall intubation rate of only 15% in patients receiving NIV in respiratory wards, but this rate reached 36% in patients with a pH < 7.30,[20] whereas only 18% of our subjects with a pH < 7.30 needed intubation. A recent study reported a rate of NIV failure of only 11% in severe COPD patients admitted to a specialized respiratory ICU,[21] with an ICU mortality rate of 8%, which is close to the 5% recorded in our study. In this large observational study, rates of NIV failure and mortality were significantly lower in patients with obesity-hypoventilation syndrome than in those with COPD.[21] We found a similarly low risk of NIV failure (15%) in subjects having COPD or another underlying chronic respiratory disease. Indeed, NIV has been successfully used in obese patients with severe obstructive sleep apnea syndrome[21-23] or bronchiectasis,[24] and may also be effective, despite mixed

Table 1. Characteristics and Outcomes of 242 Subjects Receiving Noninvasive Ventilation for Acute Hypercapnic Respiratory Failure of All Origins

	All AHRF $n = 242$	CPE $n = 67$	AOCRF $n = 146$	Non-AOCRF $n = 29$	P
Age, y	70 ± 15	76 ± 11*	70 ± 12	56 ± 21*	< .001
Male, no. (%)	144 (60)	36 (54)	88 (60)	20 (69)	.36
SAPS II	35 ± 14	38 ± 14†	33 ± 12*	37 ± 18	< .05
Systolic arterial pressure, mm Hg	143 ± 50	165 ± 81*	136 ± 28*	130 ± 25	< .001
Heart rate, beats/min	99 ± 21	95 ± 20	100 ± 21	105 ± 25	.11
Breathing frequency, cycles/min	29 ± 8	32 ± 7†	28 ± 8*	30 ± 10	.01
Glasgow coma score	14 ± 2	14 ± 2	14 ± 2	14 ± 3	.06
S_{pO_2}, %	91 ± 10	90 ± 12	91 ± 9	94 ± 5	.17
pH	7.28 ± 0.09	7.26 ± 0.10†	7.28 ± 0.07	7.31 ± 0.10†	.02
P_{aCO_2}, mm Hg	68 ± 17	62 ± 15*	72 ± 16*	59 ± 16*	< .001
P_{aO_2}, mm Hg	99 ± 65	118 ± 77*	91 ± 62†	96 ± 38	< .001
Bicarbonate, mmol/L	33 ± 7	29 ± 6*	35 ± 6*	29 ± 7*	< .001
P_{aO_2}/F_{IO_2} at NIV initiation, mm Hg	229 ± 86	235 ± 88	233 ± 79	199 ± 107	.10
Duration of NIV the first day, median (IQR) h	8 (4–11)	7 (4–8)†	9 (4–12)*	6 (4–10)	.01
Total duration of NIV, median (IQR) d	2 (1–4)	2 (1–3)*	3 (1–5)*	1 (1–3)	< .001
Rate of NIV failure, no. (%)	36 (14)	3 (4)*	22 (15)	11 (38)*	< .001
ICU stay, median (IQR) d	6 (4–9)	4 (3–6)*	7 (5–9)	8 (6–14)†	< .001
ICU mortality, no. (%)	13 (5)	2 (3)	7 (5)	4 (14)	.09

± Values are mean ± SD.
* $P < .02$ as compared to all other subjects using the Student t test.
† $P < .05$ as compared to all other subjects using the Student t test.
AHRF = acute hypercapnic respiratory failure
CPE = cardiogenic pulmonary edema
AOCRF = acute-on-chronic respiratory failure
SAPS = Simplified Acute Physiology Score
NIV = noninvasive ventilation

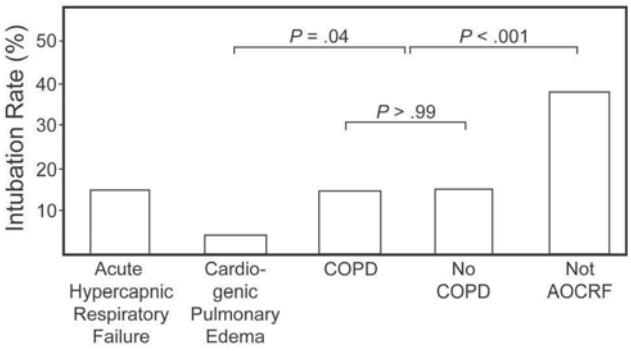

Fig. 2. Intubation rate in subjects receiving noninvasive ventilation for acute hypercapnic respiratory failure, overall and according to the reason for admission. AOCRF = acute-on-chronic respiratory failure.

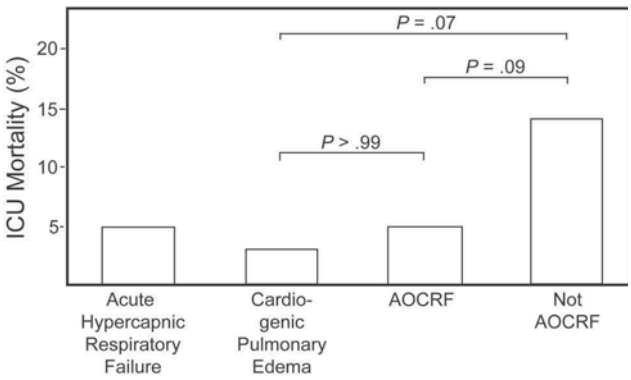

Fig. 3. ICU mortality in subjects receiving noninvasive ventilation for acute hypercapnic respiratory failure, overall and according to the reason for admission. AOCRF = acute-on-chronic respiratory failure.

results, in patients with restrictive pulmonary disease,[25] myasthenia gravis,[26] or neuromuscular disease.[27] Identification of an underlying chronic respiratory disease other than COPD could be of major interest to better assess the risk of NIV failure in hypercapnic patients.

By contrast, we found a markedly higher rate (38%) of NIV failure in hypercapnic subjects with non-AOCRF, mostly associated with pneumonia. High intubation rates of 38%[12] or 47%[11] have already been reported in non-

Table 2. Predictors of Endotracheal Intubation in Subjects Admitted for Acute Hypercapnic Respiratory Failure Receiving Noninvasive Ventilation

	NIV Success $n = 206$	NIV Failure $n = 36$	Bivariate Tests P	Multivariate Logistic Regression		P
				Odds Ratio	95% CI	
Age, y	71 ± 15	65 ± 14	.04	ND	ND	NS
SAPS II	34 ± 14	42 ± 12	< .001	ND	ND	ND
Underlying cause of acute respiratory failure, no. (%)			< .001			
CPE	64 (31)	3 (8)	.03	0.29	0.07–1.07	.06
AOCRF	124 (60)	22 (61)	> .99 (reference)			
Non-AOCRF	18 (9)	11 (31)	.004	3.94	1.44–10.7	.007
At admission, before NIV						
Altered consciousness (RASS < 0), no. (%)	46 (22)	14 (39)	.03	ND	ND	NS
Breathing frequency, breaths/min	29 ± 8	32 ± 7	.08			
Breathing frequency > 30 breaths/min, no. (%)	76 (37)	20 (56)	.03	2.72	1.17–6.31	.02
pH	7.28 ± 0.09	7.27 ± 0.08	.76			
pH < 7.30, no. (%)	105 (51)	23 (64)	.15			
P_{aCO_2}, mm Hg	68 ± 17	69 ± 15	.60			
Bicarbonate, mmol/L	33 ± 7	32 ± 8	.82			
Systolic arterial pressure, mm Hg	143 ± 33	132 ± 24	.06	ND	ND	
Heart rate, beats/min	98 ± 21	104 ± 24	.12			
Ventilatory settings under NIV	$n = 177$	$n = 22$				
F_{IO_2}	0.50 ± 0.24	0.56 ± 0.26	.31			
PEEP, cm H_2O	4.8 ± 1.6	4.2 ± 1.2	.09	ND	ND	NS
Pressure support, cm H_2O	9.2 ± 2.6	9.4 ± 2.8	.74			
Tidal volume, mL	475 ± 140	415 ± 166	.06	ND	ND	NS
Breathing frequency, breaths/min	27 ± 8	29 ± 7	.25			
Important leaks, no. (%)	8 (4.5)	2 (8)	.33			
Poor tolerance, no. (%)	27 (15)	1 (4)	.21			
Blood gases after 1 h of NIV	$n = 188$	$n = 33$				
P_{aO_2}/F_{IO_2}, mm Hg	237 ± 86	192 ± 72	.006			
$P_{aO_2}/F_{IO_2} \leq 200$ mm Hg, no. (%)	60/188 (32)	20/33 (61)	.002	2.85	1.24–6.55	.01
pH	7.33 ± 0.08	7.30 ± 0.12	.03			
pH < 7.30, no. (%)	53/188 (28)	16/33 (48)	.03	2.48	1.06–5.77	.04
Lack of increase in pH, no. (%)	39 (21)	13/33 (39)	.03			
P_{aCO_2}, mm Hg	61 ± 18	68 ± 21	.059			
Decrease in P_{aCO_2}, no. (%)	131 (70)	18 (55)	.10			

± Values are mean ± SD.
Logistic regression was performed using 219 observations: area under the receiver operating characteristic curve 0.79, sensitivity 66%, specificity 76%, positive predictive value 32%, negative predictive value 93%, correctly classified 75%.
NS = not significant
NIV = noninvasive ventilation
ND = no data available or not included
SAPS = Simplified Acute Physiology Score
CPE = cardiogenic pulmonary edema
AOCRF = acute-on-chronic respiratory failure
RASS = Richmond Agitation-Sedation Scale

COPD patients receiving NIV for AHRF when including patients with and without underlying chronic respiratory disease.[11,12] In patients having de novo acute hypoxemic (non-hypercapnic) respiratory failure and no chronic respiratory disease, even higher intubation rates of up to 60% have been reported.[8,12] It is noteworthy that the intubation rate in our subgroup of patients having de novo acute hypercapnic respiratory failure was only 38%, and that, although significantly less hypercapnic, they were not more hypoxemic than the others 2 subgroups.

Predictive Factors for NIV Failure After NIV Initiation

A higher severity score is usually associated with NIV failure in hypercapnic patients.[11,15,28] However, using the Simplified Acute Physiology Score II is clinically impractical since this score is computed only at 24 hours after admission, therefore taking into account any potential complications of intubation in patients who failed NIV within the first 24 hours.

The severity of hypercapnia and/or respiratory acidosis after initiation of NIV is a well known predictor of NIV failure.[11,13-15,29] Probably because we included AHRF of all origins, we also found that severe hypoxemia ($P_{aO_2}/F_{IO_2} \leq 200$ mm Hg) was an independent predictor of intubation in hypercapnic subjects.

By contrast, tolerance to NIV and amount of leaks had no impact on NIV failure. In a survey from 70 ICUs, poor NIV tolerance was a strong predictor of NIV failure.[8] However, this study reported good NIV tolerance in only 27% of patients, and 57% had high levels of leaks. In our series, 86% of subjects had good NIV tolerance, and only 10% had high levels of leaks, probably due to our NIV protocol. Pressure-support level was significantly increased during the first hour of NIV, suggesting that the protocol was correctly applied by nurses. With such good NIV tolerance during the first hour of NIV, the ventilatory parameters or ventilator settings had no influence on outcome. However, the trend toward a lower tidal volume in patients who failed NIV, as compared to patients who avoided intubation, might suggest the need to increase the targeted tidal volume in patients at high risk of failure.

Clinical Implications

In a general ICU using protocolized care and monitoring of NIV by nurses, the overall rate of intubation in hypercapnic patients receiving NIV for acute respiratory failure could be maintained below 15%. This rate can be used as an upper limit, both for COPD patients and for other patients having a chronic underlying respiratory disease. These results are probably due, first, to our NIV protocol optimizing the patient's tolerance to NIV, and, second, to our conservative intubation criteria, enabling continuation of NIV under close monitoring in some patients with altered consciousness. As expected, the rate of intubation was particularly high in patients with persistently or newly occurring severe altered consciousness. Nevertheless, 48% of our comatose patients achieved NIV without the need for intubation. Several studies have already shown that NIV could be successful in patients with hypercapnic coma.[30,31] Moreover, it has been shown that NIV failure was not associated with an increased mortality rate in hypercapnic patients[28]; thus, delayed intubation in some patients likely did not worsen their outcome. In our study the ICU mortality rate for intubated patients was 36%, which is in line with the 30–40% rate reported in large surveys.[12,28] Our results also suggest that, similar to protocols for weaning from mechanical ventilation[32] or sedation,[33] which enabled reduction of the time to extubation, NIV protocols involving nurses and/or respiratory therapists might reduce the intubation rate.

Limitations

Our study was conducted in a single unit with long-standing experience in the practice of NIV, and therefore our results may not be applicable to other centers with less extensive experience. Experience and nurse-driven protocols may improve tolerance to NIV, and we report a poor tolerance rate of only 14% after 1 hour of NIV. Another limitation is the retrospective nature of the study. However, prospective data collection of ventilatory parameters under NIV was available for a vast majority of our subjects, and, because of the availability of computerized medical charts for all subjects, all those receiving NIV for AHRF could be analyzed.

Conclusions

While the rate of NIV failure is usually around 20 to 30% for acute hypercapnic respiratory failure, we found that the intubation rate could be maintained below 15% in a highly experienced unit, with an overall ICU mortality of only 5%. Our study suggests that an NIV trial should be considered in all hypercapnic patients presenting with acute respiratory failure, even when the risk of failure is high because of coma, whether in patients with AOCRF or in patients without underlying respiratory disease. Interestingly, severe hypoxemia was an independent predictor of NIV failure in hypercapnic patients of all origins, whereas altered consciousness at admission and ventilatory settings had no influence on outcome.

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Patient's sticker	**NIV Day___** **DATE**___/___/___	**Physician :** _____ **Nurse day :** _____ **night :** _____

- **Indication(s):** ❒ COPD ❒ CPE ❒ Obstructive Sleep Apnea ❒ Post-Extubation
  ❒ Pneumonia/ARDS ❒ Obesity/hypoventilation ❒ Other_____
- **Humidification :** Heated humidifier (Heat and moisture exchanger with Helmet)
- **NIV initiation** (1st session and/or 1st session after extubation) **:**

  ❒ YES Duration: _____h Arterial Blood Gas (ABG) under NIV H+1 ☒
  ❒ NO
- **Other sessions :**

  Minimal number of sessions/day: ___ (6 max) Minimal number of hours/day:____

  Sessions between 0 and 6h**:** ❒ YES continuously? YES ❒ NO ❒
  ❒ NO
- **Ventilatory mode:** ❒ PSV using NIV mode (Evita 4, XL or Engström)

  Targeted expiratory V_T between : |__| |__| |__| ml and |__| |__| |__| ml

  Minimal PS level: |__| |__| cm H_2O

  ❒ BIPAP: high pressure |__| |__| cm H_2O Ti |__|,|__| s RR |__| |__| /min

  ❒ ACV: V_T |__| |__| |__| ml RR |__| |__| /min Inspiratory Flow : 40L/min
- **Objectives :** **SpO_2 :** ❒ 88-92% ❒ 92-96% ❒ 96%-100%

  PEEP |__| |__| **cm H_2O**
- **Settings at initiation of each session**

All modes	
FiO2	**30% if O_2 < 3l/min** **50% if O_2 3-10 l/min** **100% if O_2 > 10 l/min**

PS mode	
PS level	**8 cmH2O**
PEEP	**0 cmH2O**
Insp. Trigger	**3 L/min**
Max inspiratory. time	**1 sec**
Delay Apnea	**45 sec**

- **ABG:** ◘ At 8 a.m. ❒ under NIV ❒ without NIV (>30 min after the last session)
  ◘ Others : _____
- **Changes during the day:**

Name/hour	Prescription

Before each NIV session:

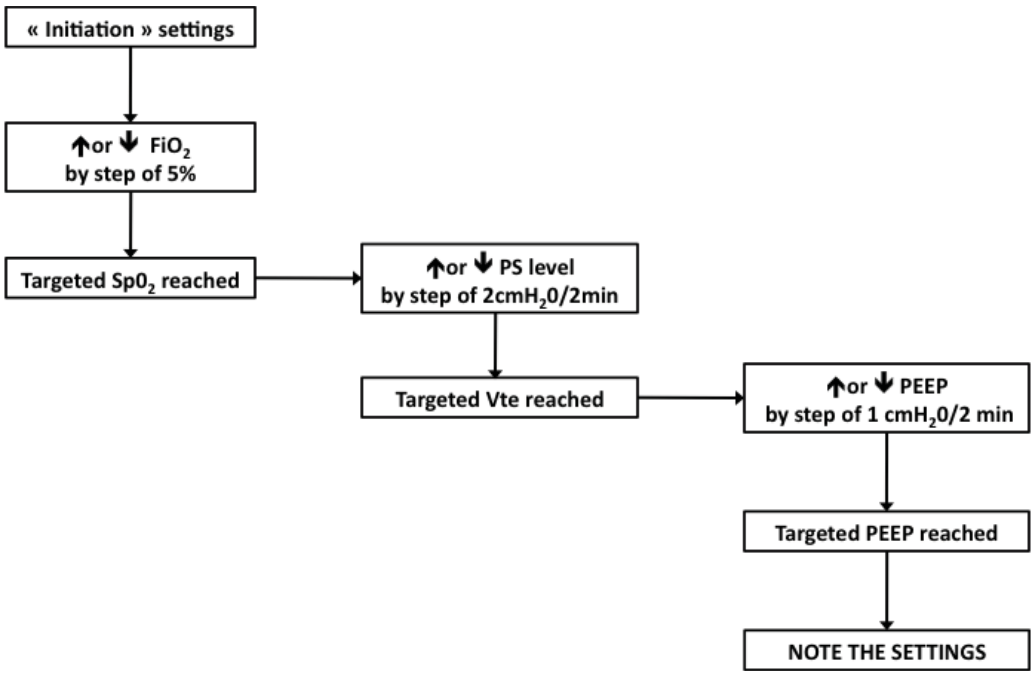
- Explain to the patient the course of the session
- Apply an artificial skin (Comfeel®) over the bridge of the nose to avoid nasal ulceration
- Check that heated humidifier is "on" in "NIV mode"
- Adjust the ventilator settings in accordance with those indicated on the first page
- Evaluate the potential risks before NIV session

Risky NIV session: when one of the four criteria is present before NIV session, there is a high risk of intubation and/or cardiac arrest. In this case, the patient must be transferred from the intermediate care unit to the ICU.

Monitoring codes

Tolerance:	0 (poor)	1 (bad)	2 (acceptable)	3 (excellent)
Leaks:	0 (none)	1 (few)	2 (many)	3 (major)

Settings adjustment:



What to do in case of leaks in PS mode?

1. Adjust mask
2. Reduce PEEP at 2 cmH_2O
3. Reduce PS level by step of 2 cmH_2O until the minimal expiratory volume is reached
4. Change the mask
5. Switch to BIPAP mode with:
    a. Inspiratory time 1 second
    b. Respiratory rate 10/min
    c. Start with a high pressure of 8 cm H_2O and gradually increase by step of 2cmH_2O to reach the targeted expiratory V_T

Session n°

Evaluation of risks before NIV session

RASS < -2: YES ❐/NO ❐

Abundant secretions: YES ❐/NO ❐

O_2>10L/min: YES ❐/NO ❐

Nor/epinephrine : YES ❐/NO ❐

Session n°

Evaluation of risks before NIV session

RASS < -2: YES ❐/NO ❐

Abundant secretions: YES ❐/NO ❐

O_2>10L/min: YES ❐/NO ❐

Nor/epinephrine : YES ❐/NO ❐

Session n°

Evaluation of risks before NIV session

RASS < -2: YES ❐/NO ❐

Abundant secretions: YES ❐/NO ❐

O_2>10L/min: YES ❐/NO ❐

Nor/epinephrine : YES ❐/NO ❐

Monitoring:

Hour	__H__	__H__	__H__	__H__	__H__	__H__	__H__	__H__	__H__	__H__	__H__	__H__
RASS												
BP												
HR												
RR												
SpO_2												
FiO_2												
PS level												
PEEP level												
V_T expiratory												
V_E (L/min)												
Tolerance	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3
Leaks	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3

NIV tolerance:

Duration of the session: _______

Premature NIV disconnection for intolerance:

NO ❐ YES ❐

Hypoxemia after NIV disconnection:

NO ❐ YES ❐ with SpO_2: |__|__| %

Tested masks:

The best: ________________

The worst: ________________

Why? Leaks YES ❐ NO ❐

Pain YES ❐ NO ❐

NIV tolerance:

Duration of the session: _______

Premature NIV disconnection for intolerance:

NO ❐ YES ❐

Hypoxemia after NIV disconnection:

NO ❐ YES ❐ with SpO_2: |__|__| %

Tested masks:

The best: ________________

The worst: ________________

Why? Leaks YES ❐ NO ❐

Pain YES ❐ NO ❐

NIV tolerance:

Duration of the session: _______

Premature NIV disconnection for intolerance:

NO ❐ YES ❐

Hypoxemia after NIV disconnection:

NO ❐ YES ❐ with SpO_2: |__|__| %

Tested masks:

The best: ________________

The worst: ________________

Why? Leaks YES ❐ NO ❐

Pain YES ❐ NO ❐

Session n°

Evaluation of risks before NIV session

RASS < -2: **YES ❒/NO ❒**

Abundant secretions: **YES ❒/NO ❒**

O_2>10L/min: **YES ❒/NO ❒**

Nor/epinephrine : **YES ❒/NO ❒**

Session n°

Evaluation of risks before NIV session

RASS < -2: **YES ❒/NO ❒**

Abundant secretions: **YES ❒/NO ❒**

O_2>10L/min: **YES ❒/NO ❒**

Nor/epinephrine : **YES ❒/NO ❒**

Session n°

Evaluation of risks before NIV session

RASS < -2: **YES ❒/NO ❒**

Abundant secretions: **YES ❒/NO ❒**

O_2>10L/min: **YES ❒/NO ❒**

Nor/epinephrine : **YES ❒/NO ❒**

Monitoring:

Hour	__H__	__H__	__H__	__H__	__H__	__H__	__H__	__H__	__H__	__H__	__H__	__H__
RASS												
BP												
HR												
RR												
SpO_2												
FiO_2												
PS level												
PEEP level												
V_T expiratory												
V_E (L/min)												
Tolerance	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3
Leaks	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3	0-1-2-3

NIV tolerance:

Duration of the session: _______

Premature NIV disconnection for intolerance:

NO ❒ YES ❒

Hypoxemia after NIV disconnection:

NO ❒ YES ❒ with SpO_2: |__|__| %

Tested masks:

The best: __________________

The worst: _________________

Why? Leaks YES ❒ NO ❒

Pain YES ❒ NO ❒

NIV tolerance:

Duration of the session: _______

Premature NIV disconnection for intolerance:

NO ❒ YES ❒

Hypoxemia after NIV disconnection:

NO ❒ YES ❒ with SpO_2: |__|__| %

Tested masks:

The best: __________________

The worst: _________________

Why? Leaks YES ❒ NO ❒

Pain YES ❒ NO ❒

NIV tolerance:

Duration of the session: _______

Premature NIV disconnection for intolerance:

NO ❒ YES ❒

Hypoxemia after NIV disconnection:

NO ❒ YES ❒ with SpO_2: |__|__| %

Tested masks:

The best: __________________

The worst: _________________

Why? Leaks YES ❒ NO ❒

Pain YES ❒ NO ❒

CHEST

Original Research

CRITICAL CARE

Patient-Ventilator Asynchrony During Noninvasive Ventilation

A Bench and Clinical Study

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Background: **Different kinds of ventilators are available to perform noninvasive ventilation (NIV) in ICUs. Which type allows the best patient-ventilator synchrony is unknown. The objective was to compare patient-ventilator synchrony during NIV between ICU, transport—both with and without the NIV algorithm engaged—and dedicated NIV ventilators.**

Methods: **First, a bench model simulating spontaneous breathing efforts was used to assess the respective impact of inspiratory and expiratory leaks on cycling and triggering functions in 19 ventilators. Second, a clinical study evaluated the incidence of patient-ventilator asynchronies in 15 patients during three randomized, consecutive, 20-min periods of NIV using an ICU ventilator with and without its NIV algorithm engaged and a dedicated NIV ventilator. Patient-ventilator asynchrony was assessed using flow, airway pressure, and respiratory muscles surface electromyogram recordings.**

Results: **On the bench, frequent auto-triggering and delayed cycling occurred in the presence of leaks using ICU and transport ventilators. NIV algorithms unevenly minimized these asynchronies, whereas no asynchrony was observed with the dedicated NIV ventilators in all except one. These results were reproduced during the clinical study: The asynchrony index was significantly lower with a dedicated NIV ventilator than with ICU ventilators without or with their NIV algorithm engaged (0.5% [0.4%-1.2%] vs 3.7% [1.4%-10.3%] and 2.0% [1.5%-6.6%], $P < .01$), especially because of less auto-triggering.**

Conclusions: **Dedicated NIV ventilators allow better patient-ventilator synchrony than ICU and transport ventilators, even with their NIV algorithm. However, the NIV algorithm improves, at least slightly and with a wide variation among ventilators, triggering and/or cycling off synchronization.**

CHEST 2012; 142(2):367–376

Abbreviations: AI = asynchrony index; ICUniv− = ICU ventilator with the noninvasive ventilation algorithm turned off; ICUniv+ = ICU ventilator with the noninvasive ventilation algorithm turned on; NIV = noninvasive ventilation; NIVv = dedicated noninvasive ventilation ventilator; PEEP = positive end-expiratory pressure; TD = triggering delay; TIexcess = insufflation time in excess; TIsim = simulated active inspiration time; TIvent = time between the beginning of a simulated inspiratory effort and the end of the ventilator's insufflation

Noninvasive ventilation (NIV) has become a standard of care for the management of many causes of acute respiratory failure.[1-3] During NIV, the unavoidable presence of leaks around the mask[4] can interfere with the ventilator performance. Expiratory leaks can mimic an inspiratory effort for the ventilator, leading to auto-triggering[5]; and inspiratory leaks can mimic a sustained inspiration, leading to delayed cycling.[6] Not surprisingly, patient-ventilator asynchronies have, therefore, been reported to occur with a high incidence during NIV in critically ill patients.[7]

Different ventilators are now used to conduct NIV in ICU: ICU ventilators,[2] dedicated NIV ventilators,[8]

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and also transport ventilators when needed.[9-11] Most ICU ventilators were initially built to work without any leak, at least in adults, and are prone to be disrupted

by the presence of leaks during NIV.[12] To address this issue, manufacturers have implemented NIV algorithms (so called "NIV modes") on the latest generation of ICU ventilators to compensate and better manage the leaks. Both bench[12,13] and clinical[14] studies assessing the performance of NIV algorithms on ICU ventilators have shown mixed results, partly due to large variations among the ventilators, making it difficult to draw an overall conclusion. Dedicated NIV ventilators stem from bilevel home ventilator technology, which has been particularly oriented toward leakage management and comfort. Some bench studies suggested that a dedicated NIV ventilator could produce better performance and synchronization than ICU ventilators in the presence of leaks.[13,15] However, no bench model concerning ventilator synchronization during NIV has been clinically validated, raising the question of their clinical relevance in critically ill patients. Consequently, the kind of ventilator that allows the best synchronization during NIV in the ICU is still unknown. In some areas, NIV is mainly delivered with dedicated NIV ventilators,[8] whereas in other countries ICU ventilators are almost exclusively preferred,[2] and this distribution reflects local habits rather than an evidence-based approach.

The purpose of this study was to compare patient-ventilator synchronization during NIV using ICU and transport ventilators with or without their NIV algorithm, and finally dedicated NIV ventilators. We designed a bench model to assess ventilator synchronization with a simulated inspiratory effort in different leak conditions, simulating the different challenges to be faced by the ventilator. Furthermore, we conducted a clinical study in critically ill patients to compare the incidence of patient-ventilator asynchrony between ICU ventilators with and without their NIV algorithm engaged, and a dedicated NIV ventilator.

Manuscript received September 7, 2011; revision accepted January 20, 2012.
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Funding/Support: This study was supported in part by a research grant from Philips Respironics (€10,000). This study was performed while Dr Carteaux was funded by an institutional grant, the Année Recherche, from the Ministère de l'éducation nationale, de l'enseignement supérieur et de la recherche (French Ministry for Education and Research).
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DOI: 10.1378/chest.11-2279

Materials and Methods

This study involved a bench part and a clinical part. An extensive description of both the bench and clinical protocols is provided in e-Appendix 1.

Bench Study

All 19 ventilators tested are reported in Table 1 and included eight ICU ventilators, five transport ventilators, and six dedicated NIV ventilators. The test lung, an Active Servo Lung 5000 (ASL 5000; IngMar Medical, Ltd), was used to simulate a moderate inspiratory effort in the presence of an 80 mL/cm H_2O respiratory system compliance and 10 cm H_2O/L/s resistance to mimic a mild obstructive condition. The simulated respiratory rate was 15 breaths/min and the inspiratory time 0.8 s. Three leak conditions were generated (Fig 1A): absence of leak, continuous leak (to reveal triggering asynchronies during expiratory leak), and inspiratory leak (to reveal cycling-off asynchronies). For this last experiment, the leak started at a pressure corresponding to a water column of 7 cm H_2O, as detailed in e-Appendix 1. The inspiratory leak was characterized by a nonlinear pressure-flow relationship with a flow varying from 0 to 22 L/min for a pressure from 7 to 15 cm H_2O. The continuous (expiratory) leak was characterized by a flow of 16 L/min at 5 cm H_2O pressure.

Ventilators were set in pressure support ventilation, with a pressure support level at 15 cm H_2O and a positive end-expiratory pressure (PEEP) at 5 cm H_2O. ICU and transport ventilators were tested with and without their NIV algorithm engaged, except the Elisee 250, whose NIV algorithm cannot be turned off. Data were acquired at 512 Hz from ASL 5000 and stored in a laptop computer for subsequent analysis (Acqknowledge 3.7.3; BIOPAC Systems, Inc). Inspiratory triggering synchronization was assessed using the triggering delay, the triggering pressure-time product, and the incidence of auto-triggering, expressed as a percentage and calculated as follows: auto-triggering incidence (%) = (auto-triggered cycles/total ventilator cycles) × 100. The pressurization was assessed using the pressure-time product at 300 milliseconds. Cycling synchronization was assessed by determining ventilator insufflation time in excess (TIexcess), expressed as a percentage and calculated as follows: TIexcess = [(TIvent − TIsim)/TIsim] × 100, where TIvent is the time between the beginning of the simulated inspiratory effort and the end of the ventilator's insufflation, and TIsim the simulated active inspiration time. Delayed cycling was defined by a TIvent ≥ 2 TIsim and premature cycling by a TIvent ≤ 2/3 TIsim.

Clinical Study

A prospective, randomized, crossover study was conducted in two university hospital ICUs. The protocol was approved by the ethics committee CPP-Ile-de-France IX (number: 08-021), and informed consent was obtained from all patients. We included 15 patients in the ICU receiving NIV in pressure support ventilation mode with PEEP via a standard oronasal mask. The ventilator settings chosen by the clinician in charge of the patient were kept identical for the study. Three consecutive NIV sessions were applied in a random order, using the same oronasal mask: (1) use of an ICU ventilator whose NIV algorithm has been turned off

Table 1—*Bench Study: Characteristics of the ICU, Transport, and NIV Ventilators Tested in the Bench Study*

Ventilator	Supplier	Use	Gas Source	Circuit	NIV Mode	ET Range	IT Range
Avea	CareFusion	ICU	Pressurized	Double	Manual	5%-45%	0.1-20 L/min
Engstrom	GE Healthcare	ICU	Pressurized	Double	Manual	5%-50%	1-9 L/min; −1 to −10 cm H_2O
Evita XL	Dräger	ICU	Pressurized	Double	Automatic	Automatic	0.3-15 L/min
G5	Hamilton Co	ICU	Pressurized	Double	Manual	5%-70%	0.5-15 L/min
PB840[a]	Covidien	ICU	Pressurized	Double	Manual	1%-80%	0.2-20 L/min
Servo-i	MAQUET GmbH & Co KG	ICU	Pressurized	Double	Manual	1%-40%	0%-100%; −20 to 0 cm H_2O
V500	Dräger	ICU	Pressurized	Double	Automatic/manual	Automatic; 5%-70%	Automatic; 0.2-15 L/min
Vela	CareFusion	ICU	Turbine	Double	Manual	5%-40%	1-8 L/min
Elisee 250	ResMed	Transport	Turbine	Double	Automatic/manual	Automatic; 1%-6%	Automatic
Medumat	Weinmann Medical Technology	Transport	Pneumatic	Single	Automatic	5%-50%	1-15 L/min
Oxylog 3000	Dräger	Transport	Pneumatic	Single	Automatic	Automatic	Automatic
Supportair	Covidien	Transport	Turbine	Single	Manual	5%-95%	01-05
T1	Hamilton Co	Transport	Turbine	Double	Manual	5%-80%	1-20 L/min
BiPAP Vision	Philips Respironics	NIV	Turbine	Single	Automatic	Automatic	Automatic
Carina	Dräger	NIV	Turbine	Single	Automatic	Automatic	Analogical (sensible/normal)
Trilogy 100	Philips Respironics	NIV	Turbine	Single	Automatic	Automatic	Automatic
V60	Philips Respironics	NIV	Turbine	Single	Automatic	Automatic	Automatic
Vivo 40	Breas	NIV	Turbine	Single	Automatic	Automatic	Automatic
VPAP 4	ResMed	NIV	Turbine	Single	Automatic	Automatic	Automatic

ET = expiratory trigger, expressed as a percentage of peak inspiratory flow; IT = inspiratory trigger; NIV = noninvasive ventilation.
[a]Version comprising both an NIV mode and leak compensation.

(ICUniv−), (2) use of an ICU ventilator whose NIV algorithm has been turned on (ICUniv+), and (3) use of a dedicated NIV ventilator (NIVv). Each session was 20 min long. ICU ventilators used in the clinical study were: Evita XL or EVITA 4 (Dräger) (n = 12) and Engstrom Carestation (GE Healthcare) (n = 3). The dedicated NIVv was the BiPAP Vision (Philips Respironics). We selected this ventilator because it is widely used in ICUs using NIV ventilators and also because it has been used in many clinical and physiologic studies concerning NIV. Flow, airway pressure, and diaphragmatic and inspiratory neck muscles surface electromyograms were continuously recorded throughout the three NIV sessions and stored in a laptop for subsequent analysis, as described in e-Appendix 1. All tracings were analyzed by one investigator (G. C.). The methodology used was previously described without noticing any interobserver difference,[7,14] and allowed the quantification of major asynchrony events (ineffective triggering, double-triggering, auto-triggering, premature cycling, and delayed cycling) (Fig 1B). A global asynchrony index (AI), expressed as a percentage, was computed as follows[16]: AI (%) = (number of asynchronies/[ineffective breaths + ventilator cycles]) × 100.

Statistics

Statistical analyses were performed with Statistical Package for the Social Sciences (version 16.0, SPSS). Continuous data are expressed as the median (25th-75th percentile). In both the bench and clinical study, the variables did not display a normal distribution, so only nonparametric tests, detailed in e-Appendix 1, were used. A P value of < 0.05 was considered statistically significant.

Results

Bench Study

Triggering Delay: The ICU and transport ventilators with their NIV algorithm turned off in the absence of leaks exhibited a total triggering delay (TD) of 117 milliseconds (99-131 milliseconds) and 143 milliseconds (114-174 milliseconds), respectively ($P = .37$) (Fig 2).The addition of inspiratory leaks did not significantly modify these values except for the Engstrom, G5, and T1, which had an increased TD, and the Medumat, which showed a reduced TD. Turning on the NIV algorithm while maintaining inspiratory leaks led to different behaviors among ICU and transport ventilators: TD significantly increased for five ventilators (Medumat, Evita XL, Servo-i, V500, Supportair), decreased for three (Engstrom, PB840, T1), and was not modified for the others. In this last condition, the TD of ICU, transport, and dedicated NIV ventilators were 107 (83-120), 126 (112-190), and 125 (102-145) milliseconds, respectively ($P > .05$ for every intergroup comparison). When NIV algorithms were used in the presence of inspiratory leaks, six ICU ventilators (Avea, Engstrom, PB840, Servo-i, V500, Vela), two transport ventilators (Elisee 250, Supportair), and two NIV ventilators (BiPAP Vision, V60) exhibited a TD < 117 milliseconds (ie, the median TD of ICU ventilators with the NIV algorithm turned off in absence of leaks). The additional assessment of the triggering pressure-time product is reported in e-Appendix 1 and e-Figure 1.

Auto-Triggering: Occurrence of auto-triggering was assessed during the presence of continuous leaks (Fig 3). Expiratory leaks induced an incidence of auto-triggering between 0% and 100% among ICU and transport ventilators when their NIV algorithm was

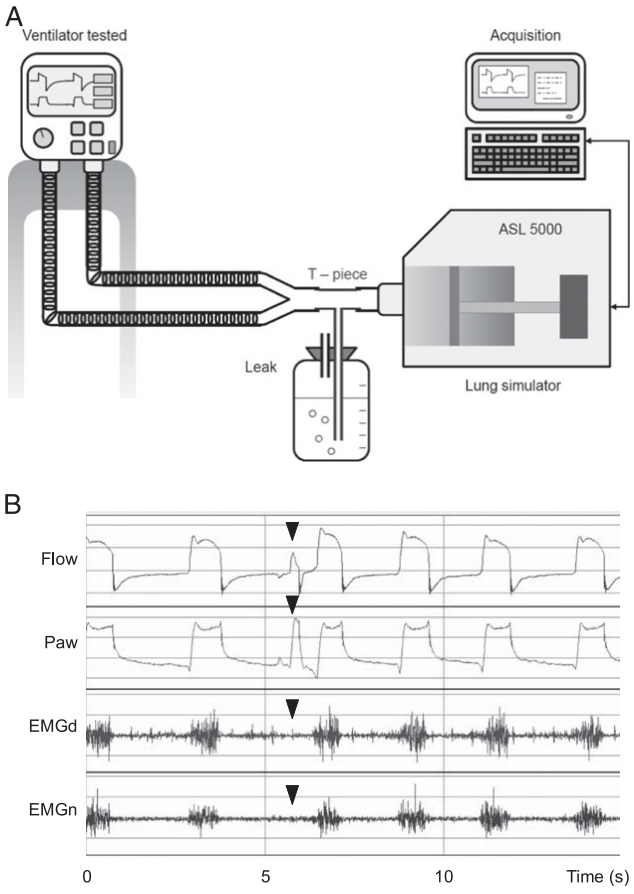

FIGURE 1. Experimental protocols. A, Bench study experimental design. To experimentally reproduce noninvasive ventilation (NIV) conditions with calibrated leaks, we placed a T-piece between the ASL5000 (lung simulator) and the ventilator circuit. Three situations were generated: no leak, in which the free extremity of the T-piece was closed; inspiratory leak, in which the free extremity of the T-piece was connected to a tube immersed in a 7 cm H_2O column, allowing leaks to occur during insufflation only when the pressure in the circuit was higher than the height of the water column; and continuous leak using the same experimental assembly without water in the receptacle, allowing leaks to occur during the whole respiratory cycle. B, Clinical study representative record of an auto-triggered cycle. EMGd = diaphragmatic electromyogram; EMGn = neck muscles electromyogram; Paw = airway pressure.

turned off. The activation of the NIV algorithm led to a heterogeneous response among these ventilators: the incidence of auto-triggering fell to or remained at 0% for three ICU ventilators (PB840, Servo-i, V500) and three transport ventilators (Elisee 250, Supportair, T1), was not modified for one ICU ventilator (Avea), and decreased slightly for the other ICU and transport ventilators. By contrast, no auto-triggering occurred with any NIV ventilator.

Cycling and Insufflation Time: ICU and transport ventilators without their NIV algorithm in the absence of leaks exhibited a TIexcess of 32% (30%-34%) and 49% (24%-75%), respectively ($P = .93$) (Fig 4). Inspiratory leaks led to a significant increase in insufflation time for six ICU ventilators (Avea, Engstrom, G5, PB840, Servo-i, Vela) and all four transport ventilators whose NIV algorithm can be turned off. The NIV algorithms generally minimized the insufflation time, which remained significantly higher than without leaks for only two ICU ventilators (Avea, G5) and three transport ventilators (Oxylog 3000, Supportair, T1). With NIV algorithm and inspiratory leaks, ICU, transport, and dedicated NIV ventilators exhibited a TIexcess of 34% (29%-43%), 37% (25%-43%), and 37% (18%-49%), respectively. In this condition, the TIexcess was<32% for four ICU ventilators (Engstrom, Evita XL, Servo-i, V500), two transport ventilators (Medumat, Supportair), and three dedicated NIV ventilators (BiPAP Vision, Trilogy 100, V60).

During inspiratory leaks when NIV algorithms were turned off, delayed cycling occurred with four ICU ventilators (Avea, G5, PB840, Vela) and three transport ventilators (Medumat, Oxylog 3000, T1). The activation of the NIV algorithm eliminated delayed cycling for all of these ventilators but one (G5). However, the NIV algorithm of the Servo-i overcorrected the TIexcess (−4%). Concerning dedicated NIV ventilators subjected to inspiratory leaks, one of them (VIVO 40) exhibited delayed cycling.

We also assessed the ability of the ventilators to pressurize the airway in the first 300 milliseconds with or without leaks. For the sake of simplicity, these data are only shown in e-Appendix 1 and e-Figure 2.

Clinical Study

Fifteen patients of median age 68 years old (61-76 years) were included, 13 men and two women, with a median BMI of 24 kg/m² (20-27 kg/m²). At inclusion, Simplified Acute Physiology Score II was 47 (32-62) and arterial blood gas levels were as follows: pH = 7.36 (7.29-7.42), $PaCO_2$ = 48 mm Hg

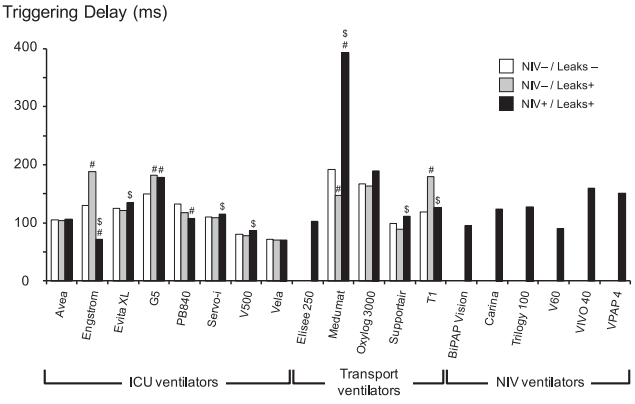

FIGURE 2. Bench study triggering delay. Representation of the triggering delay for ICU and transport ventilators with their NIV algorithm turned off in the absence of any leak (NIV−/Leaks−, white bars), then in the presence of inspiratory leaks (NIV−/Leaks+, gray bars); and for ICU and transport ventilators with their NIV algorithm turned on as well as for NIV ventilators in the presence of inspiratory leaks (NIV+/Leaks+, black bars). # $P<.05$ vs NIV−/Leaks−. $ $P<.05$ vs NIV−/Leaks+. See Figure 1 legend for expansion of abbreviation.

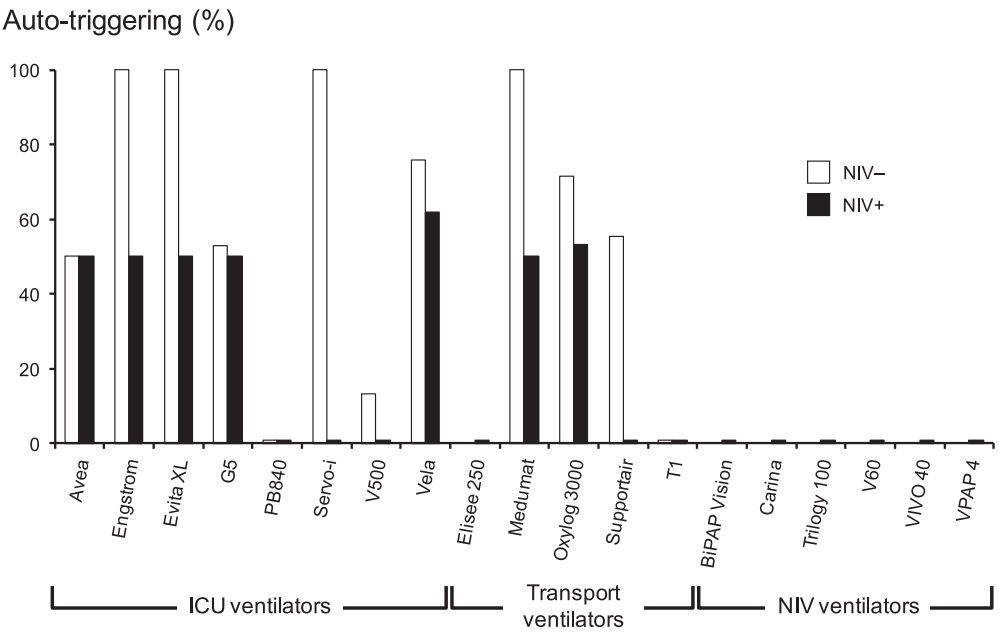

FIGURE 3. Bench study incidence of auto-triggering during continuous leaks. Incidence of auto-triggering is represented as a percentage of the total ventilator cycles ([Auto-triggered cycles]/[total ventilator cycles] × 100) during continuous leaks with ICU and transport ventilators without NIV algorithm (NIV−, white bar) and with the same ventilators with the NIV algorithm turned on, and with NIV ventilators (NIV+, black bar). The activation of the NIV algorithm on ICU and transport ventilators unequally led to an improvement in inspiratory triggering synchronization, whereas no auto-triggering occurred with any NIV ventilator. See Figure 1 legend for expansion of abbreviation.

(41-63 mm Hg), PaO_2/FIO_2 = 206 mm Hg (183-252 mm Hg). Patients had spent one median day (0.3-1.0 days) under NIV before inclusion. Indications for NIV were the following: to avert respiratory failure after extubation (n = 5), exacerbation of COPD (n = 4), cardiogenic pulmonary edema (n = 3), community-acquired pneumonia (n = 2), and post thoracic surgery (n = 1). Eight patients (53%) had COPD. Ventilator settings were pressure support level = 10 cm H_2O (8-11 cm H_2O), PEEP = 4 cm H_2O (4-5 cm H_2O), inspiratory trigger = 1 L/min (1-2 L/min), pressurization slope = 100 milliseconds (100-100 milliseconds), and FIO_2 = 40% (30%-50%). There was no significant difference between the three NIV sessions regarding ventilator settings, respiratory parameters, and the measured level of leaks (Table 2). ICU ventilators used in the clinical study had a similar response to leaks as during the bench study in terms of asynchrony: a propensity to auto-triggering with expiratory leaks, partially corrected by the NIV algorithm, but no delayed cycling with the NIV algorithm and inspiratory leaks (Figs 3, 4).

Patient-Ventilator Synchrony: The asynchrony index (AI) did not significantly differ when using ICU ventilators without (ICUniv−) or with (ICUniv+) their NIV algorithm engaged, 3.7% (1.4%-10.3%) vs 2.0% (1.5%-6.6%), respectively, P = .118. By contrast, AI was significantly lower with NIVv (0.5% [0.4%-1.2%]) than with both ICUniv− and ICUniv+ (P = .001 for both comparisons) (Fig 5). The incidence of each asynchrony during the three NIV sessions is represented in Figure 6. Auto-triggering had the highest incidence. The incidence of auto-triggering, however, was significantly lower with NIVv than with ICUniv− and ICUniv+, 0.1/min (0.1-0.1/min) vs 0.5/min (0.1-1.1/min) and 0.3/min (0.1-1.2/min), $P < .001$, and the proportion of patients who exhibited a high incidence of auto-triggering (> 1/min) was significantly lower with NIVv than with ICUniv− and ICUniv+ (Table 3). Four patients (27%) had an AI > 10% with ICUniv−, two (13%) with ICUniv+, and none with NIVv (P = .091). The level of leaks throughout the clinical study was noticeably high in these two last patients (14 and 16 L/min, respectively). The proportion of patients who exhibited at least one asynchrony with a high incidence (> 1/min) was significantly higher with ICUniv− and ICUniv+ than with NIVv (Table 3).

DISCUSSION

To our knowledge, this study is the first to compare patient-ventilator synchronization during NIV between ICU, transport, and dedicated NIV ventilators, with both a bench and a clinical evaluation. The observations made with these two approaches were consistent, offering a strong validation of the bench model, a logical explanation for the clinical data, and

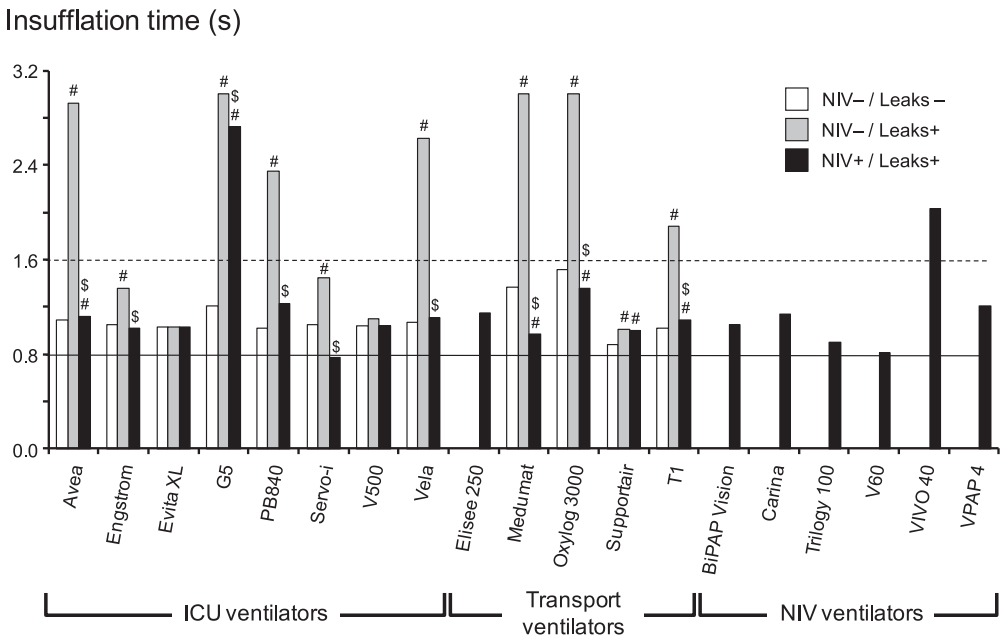

FIGURE 4. Bench study on the effect of inspiratory leaks on insufflation time. Representation of the insufflation time for ICU and transport ventilators without their NIV algorithm in the absence of leak (NIV−/Leaks−, white bars), then in the presence of inspiratory leaks (NIV−/Leaks+, gray bars); and for ICU and transport ventilators with their NIV algorithm turned on as well as for dedicated NIV ventilators in the presence of inspiratory leaks (NIV+/Leaks+, black bars). The simulated inspiratory time was 0.8 s (solid line). When insufflation time reached 1.6 s (dotted line) it corresponded to delayed cycling. For ICU and transport ventilators, the introduction of inspiratory leaks led to an increase in insufflation time when the NIV algorithm was turned off. This prolongation of insufflation due to leaks was partly and unequally minimized by the NIV algorithm. #$P < .05$ vs NIV−/Leaks−. \$$P < .05$ vs NIV−/Leaks+. See Figure 1 legend for expansion of abbreviation.

lending strength to the main results of this study, which are:

- In NIV conditions, most dedicated NIV ventilators allowed better patient-ventilator synchronization than ICU and transport ventilators, even when the NIV algorithm was engaged, especially regarding the risk of auto-triggering.
- Most of the dedicated NIV ventilators exhibited a synchronization performance in the presence of leaks equivalent to that of the ICU ventilators in absence of leaks.
- Synchronization performance in the presence of leaks remains heterogeneous among ICU as well as transport ventilators, and each machine should be considered individually.
- The NIV algorithm usually improved, at least slightly, the triggering and/or cycling synchronization of ICU and transport ventilators in the presence of leaks.

Table 2—*Clinical Study: Main Respiratory Parameters*

Respiratory Parameters	ICUniv−	ICUniv+	NIVv	*P* Value
RRp, per min	29 (22-31)	27 (22-31)	26 (24-30)	.982
TIp, ms	780 (599-914)	674 (558-957)	749 (629-923)	.057
TIexcess, %	14 (4-24)	12 (6-23)	13 (11-21)	.344
VTE, mL	467 (269-633)	465 (322-548)	487 (278-539)	.931
VTE, mL/kg	6.5 (4.3-9.4)	6.9 (4.6-8.3)	7.0 (4.6-9.0)	.797
V̇E, L/min	11.5 (8.7-15.5)	10.3 (9.2-16.7)	10.6 (8.6-14.0)	.683
Leaks, L/min	6.3 (4.3-10.8)	6.2 (2.6-12.1)	7.3 (3.0-11.7)	.947
Leaks, % V̇E	55 (39-101)	47 (26-113)	81 (16-121)	.612

Main respiratory parameters recorded throughout the three NIV sessions during the clinical study. ICUniv− = NIV session using an ICU ventilator whose NIV algorithm has been turned off; ICUniv+ = NIV session using an ICU ventilator whose NIV algorithm has been turned on; NIVv = NIV session using a dedicated NIV ventilator; RRp = patient's respiratory rate measured with the use of the electromyogram signal; TIexcess = percentage of insufflation time that exceeds the neural inspiratory time; TIp = patient's neural inspiratory time; V̇E = minute ventilation; VTE = expired tidal volume. See Table 1 legend for expansion of other abbreviation.

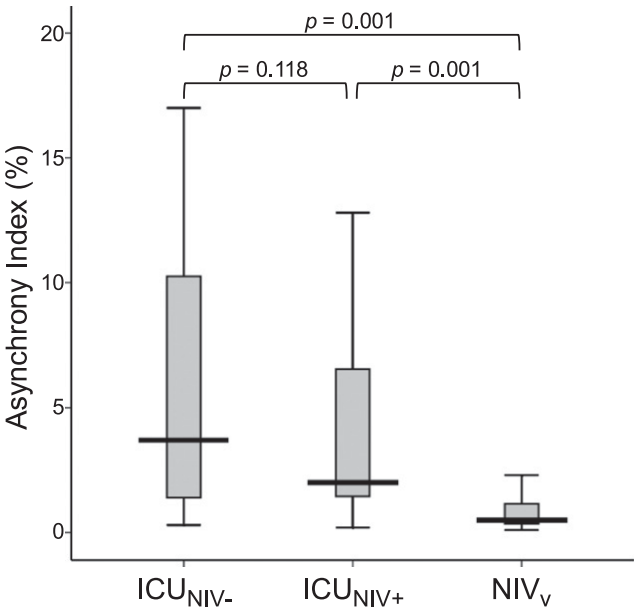

FIGURE 5. Clinical study asynchrony index during the three NIV sessions. The box plots represent the asynchrony index (thick horizontal bar: median; extremities of the boxes: 25th and 75th percentiles; thin horizontal bars: fifth and 95th percentiles) during each 20-min NIV session: ICU_{NIV-}, ICU_{NIV+}, and NIV_V. The asynchrony index was significantly lower with NIV_V than with ICU_{NIV-} and ICU_{NIV+}. ICU_{NIV-} = ICU ventilator with NIV algorithm turned off; ICU_{NIV+} = ICU ventilator with NIV algorithm turned on; NIV_V = dedicated NIV ventilator. See Figure 1 legend for expansion of abbreviation.

Patient-Ventilator Interactions During NIV

Patient-ventilator asynchrony is frequent during both invasive[16,17] and noninvasive[7,14] mechanical ventilation. However, the respective proportion of each type of major asynchrony markedly differs between these two techniques. During invasive mechanical ventilation, ineffective effort represents the most prevalent asynchrony.[16,18] Its occurrence is largely favored by overassistance and can frequently be avoided by reducing the amount of support both in terms of tidal volume and inspiratory time.[19,20] By contrast, during NIV, additional asynchronies, especially auto-triggering and delayed cycling, are induced by the presence of leaks around the mask[4,7] and reflect more the ventilator's ability to manage leaks than the settings chosen by the clinician. Our bench study showed a wide variation in this ability among ICU ventilators and their NIV algorithms, which is consistent with previous bench studies.[12,13] More interestingly, our bench results were also well reproduced during our clinical study. In fact, auto-triggering represented the most frequent asynchrony with ICU ventilators used in the clinical study, as predicted during their bench evaluation. Furthermore, there was a trend toward less asynchrony with the NIV algorithm, which usually minimized asynchronies during the bench study. Vignaux et al[14] assessed the impact of the NIV algorithm on the incidence of patient-ventilator asynchronies during NIV in a clinical study involving 65 patients and five ICU ventilators. Without the NIV algorithm engaged, 46% of the patients had an AI > 10%. The NIV algorithm permitted a decrease in the incidence of asynchronies due to leaks but without a decrease in the overall incidence of patient-ventilator asynchronies (38% vs 46%, $P = .69$), due to a high incidence of asynchronies not directly related to leaks. We report a lower proportion of patients exhibiting an AI > 10% due to a lower incidence of some major asynchronies. Several reasons explain this discrepancy. First, the level of assistance in our study was lower than the one observed in the study by Vignaux et al,[14] leading to a lower tidal volume, which might explain our low incidence of ineffective efforts.[20] Second, we have modified the definition of premature cycling, considering that the previous one was too sensitive in terms of clinical relevance and what can be considered as a "major" patient-ventilator asynchrony. This definition modification has automatically led to less recorded premature cycling, so to a lower AI. Third, the ICU ventilators used in our clinical assessment had the same behavior during our bench evaluation: a propensity to auto-triggering with expiratory leaks, but no delayed cycling in the presence of inspiratory leaks. Although the strength of our bench model was to assess separately the impact of expiratory and inspiratory leaks on triggering and cycling synchronizations, respectively, the originality of our clinical study was to use ICU ventilators that had the same behavior during their bench evaluation. This led to intelligible results and gave a mutual validation to the two assessments. In the meantime, as a part of this behavior was to avoid delayed cycling, this logically led to a decrease in the overall AI during the clinical study as compared with previous studies conducted with other ventilators. Finally, an AI > 10% in our clinical study was mainly related to a high incidence of auto-triggering, which reflects the ventilator's ability to manage leaks rather than the relevance of the settings chosen by the clinician.

As with ICU ventilators, our bench evaluation also showed very uneven performances of transport ventilators and their NIV algorithms in the presence of leaks. Such heterogeneity has also been previously reported with transport ventilators assessed in invasive conditions.[21,22]

On the whole, our results suggest that rather than being considered as belonging to a group of ventilators, each ICU and transport ventilator should be examined individually regarding its ability to manage NIV conditions. By contrast, dedicated NIV ventilators exhibited more homogeneous behavior during our bench evaluation, with an ability to avoid auto-triggering or delayed cycling while keeping a short

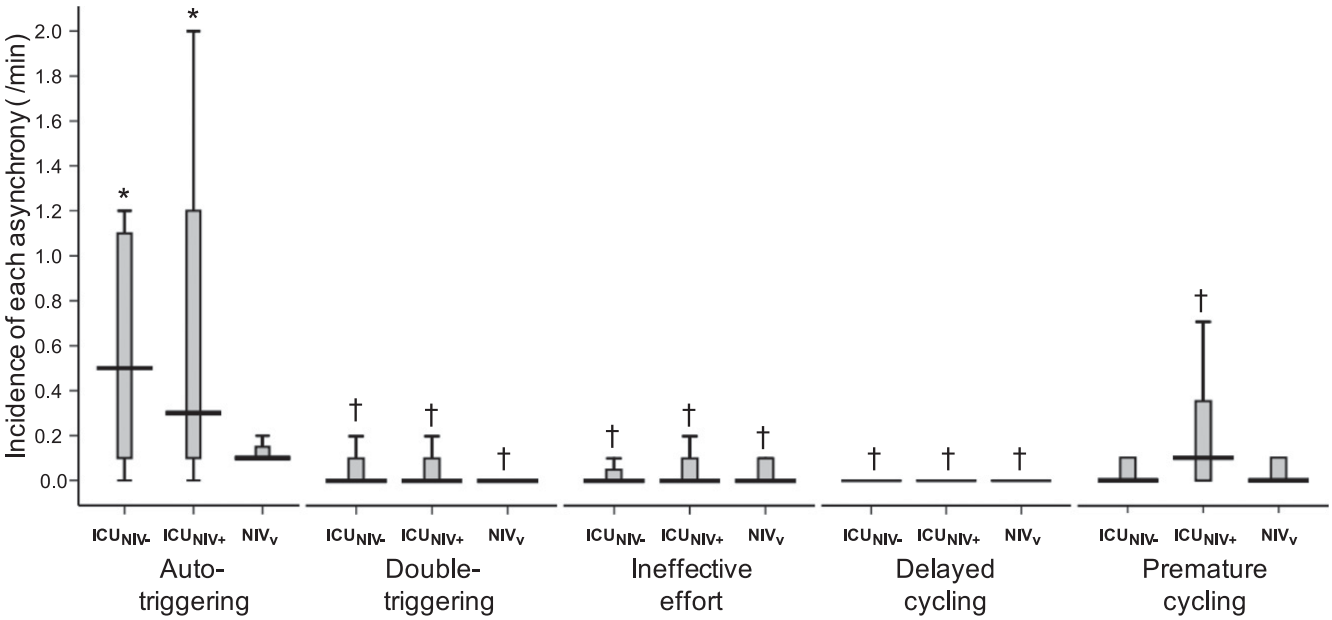

FIGURE 6. Clinical study incidence of each patient-ventilator asynchrony during the three NIV sessions. Each patient-ventilator asynchrony is represented as box plots (thick horizontal bar: median; extremities of the boxes: 25th and 75th percentiles; thin horizontal bars: fifth and 95th percentiles) for each 20-min NIV session: ICU_{NIV-}, ICU_{NIV+}, and NIV_V. *$P < .05$ vs NIV_V, †$P < .05$ vs auto-triggering. See Figure 1 and 5 legends for expansion of abbreviations.

triggering delay despite the presence of leaks. This is consistent with two previous bench studies that showed a better synchronization ability of a dedicated NIV ventilator as compared with several ICU ventilators without[15] or with[13] their NIV algorithm engaged. Our clinical study is the first to our knowledge to confirm that the use of a NIV ventilator to perform NIV in critically ill patients led to a significant decrease in the incidence of patient-ventilator asynchrony.

Limitations

Several limitations of this study should be underlined. First, during the bench study, only mild obstructive respiratory mechanics were simulated, as respiratory mechanics are known to affect the cycling delay. Our aim was to uncover delayed cycling in the presence of inspiratory leaks, which could be minimized in the case of restrictive respiratory mechanics.[12] In addition, COPD represents the most recognized indication for NIV in ICU.[23] Second, only one level of both inspiratory and expiratory leaks was designed. These experimental conditions may not reproduce what happens in clinical conditions. However, our clinical study showed that our bench model succeeded in capturing the kind of asynchronies that may occur in the presence of leaks with each ventilator in the clinical setting.

Clinical Relevance

It is currently unknown if patient-ventilator asynchronies, especially those due to leaks, can affect the clinical outcome of NIV and therefore influence ventilator choice by clinicians. However, several arguments favor the best possible synchronization during NIV. First, it seems reasonable to assume that auto-triggering and delayed cycling will reduce the tolerance of the procedure, an important key to NIV success.[24,25] Second, the occurrence of delayed cycling

Table 3—*Clinical Study Patients Presenting Each Type of Asynchrony With a High Incidence (> 1/min) or an Asynchrony Index > 10%*

Type of Asynchrony	ICUniv−	ICUniv+	NIVv	*P* Value
Auto-triggering	5 (33)	5 (33)	0	.016
Double-triggering	0	1 (7)	0	…
Ineffective effort	0	0	0	…
Delayed cycling	0	0	0	…
Premature cycling	3 (20)	1 (7)	0	.097
At least one asynchrony	6 (40)	5 (33)	0	.012
Asynchrony index > 10%	4 (27)	2 (13)	0	.091

Data are presented as No. (%). See Table 1 and 2 legends for expansion of abbreviations.

can lead to dynamic hyperinflation and contribute to the development of ineffective efforts,[6,19] which are associated with a prolongation of the ventilation during invasive mechanical ventilation.[26] Given the benefits of NIV when avoiding intubation,[23,25,27,28] each factor potentially involved in its success should logically be promoted. However, if no patient exhibited a high incidence of asynchrony with the NIV ventilator in our study, just a few had an AI > 10% with ICU ventilators. We cannot know to what extent this difference may be clinically relevant and further clinical studies addressing the impact of different devices on the outcome of different groups of patients under NIV are needed to formulate some recommendations.

Conclusion

In conclusion, our study shows that dedicated NIV ventilators allow a better patient-ventilator synchrony in the presence of leaks than ICU and transport ventilators, even if their NIV algorithm is engaged, especially for what concerns auto-triggering. When using an ICU or transport ventilator to perform NIV, the NIV algorithm usually improves, at least slightly and with variations among ventilators, triggering and/or cycling synchronization.

Acknowledgments

Author contributions: Dr Carteaux is the guarantor of the paper.
Dr Carteaux: contributed to the study design, patient enrollment, data collection, data analysis, data interpretation, and manuscript preparation, and read and approved the final manuscript.
Dr Lyazidi: contributed to the study design, patient enrollment, data collection, data analysis, data interpretation, and manuscript preparation, and read and approved the final manuscript.
Dr Cordoba-Izquierdo: contributed to the study design, patient enrollment, data collection, data analysis, data interpretation, and manuscript preparation, and read and approved the final manuscript.
Ms Vignaux: contributed to the study design, patient enrollment, and data collection, and read and approved the final manuscript.
Dr Jolliet: contributed to the study design and patient enrollment, and read and approved the final manuscript.
Dr Thille: contributed to the study design, data analysis, data interpretation, and manuscript preparation, and read and approved the final manuscript.
Dr Richard: contributed to reading and approving the final manuscript.
Dr Brochard: contributed to the study design, data analysis, data interpretation, and manuscript preparation, and read and approved the final manuscript.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Carteaux received reimbursement from Covidien for expenses relative to travel, accommodation, and registration for the 2010 American Thoracic Society annual meeting for a specific presentation that did not concern this study. Dr Jolliet received a research grant from MAQUET GmbH & Co KG and runs a laboratory that received research grants for specific research projects from Dräger and ResMed. Dr Brochard runs a laboratory that received research grants for specific research projects from Dräger, General Electric Company, MAQUET GmbH & Co KG, Covidien, and Fisher-Paykel. Drs Lyazidi, Cordoba-Izquierdo, Thille, and Richard and Ms Vignaux have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Role of sponsors: The sponsor had no role in the study design, the collection, analysis, interpretation of the data, the writing of the manuscript, or the decision to submit the paper for publication.
Other contributions: This work was performed at Réanimation Médicale, AP-HP, Centre Hospitalier Albert Chenevier-Henri Mondor, Créteil, France and the Department of Intensive Care, Geneva University Hospital, Geneva, Switzerland.
Additional information: The e-Appendix and e-Figures can be found in the "Supplemental Materials" area of the online article.

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CHEST Online Supplement

Patient-Ventilator Asynchrony During Noninvasive Ventilation

A Bench and Clinical Study

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METHODS

Bench study

Ventilators

We have assessed 19 ventilators (Table 1): Eight ICU ventilators, five transport ventilators, and six dedicated NIV ventilators. For each ventilator, the last version available by the time of the manuscript submission has been tested.

Lung Model

A lung simulator, comprising an active lung model Active Servo Lung 5000 (ASL 5000; Ingmar Medical, Pittsburgh, Pennsylvania) and a microprocessor, was used. The microprocessor was programmed with a script driver, using a mathematical model of the equation of motion of the respiratory system, to control the piston's movement in ASL 5000. The script driver was settled with a compliance of 80 ml/cm H_2O and a resistance of 10 cm $H_2O/l.s^{-1}$. The flow profile at the Y piece was 30 L/min. Respiratory rate and inspiratory time were 15 cycles/min and 0.8 s respectively.

Leak System

Three leak conditions have been designed: absence of leak, continuous leak (in order to reveal triggering asynchronies), and inspiratory leak (in order to reveal cycling-off asynchronies). Each ventilator was connected to the ASL 5000 with the manufacturer's circuit if provided, or a standard double-circuit (Intersurgical, Berkshire, UK). To create a calibrated leak we used a T-piece placed between the ASL 5000 and the ventilator circuit. The inspiratory leak was generated by connecting the free extremity of the T-piece to a tube immersed in a 7 cm water column (Fig. 1). In this situation, the leak occurred during the insufflation only when the pressure in the circuit exceeded 7 cm H_2O. For the generation of a continuous leak, the same system was used without water in the

 DOI: 10.1378/chest.11-2279

receptacle, allowing leaks to occur during the whole respiratory cycle. Using this experimental design, the inspiratory leak was characterized by a non-linear relationship of flow varying from 0 to 22 l/min when the pressure rose from 7 to 15 cm H_2O, while the expiratory leak during continuous leak was characterized by a flow of 16 l/min at 5 cm H_2O.

Ventilator setting

Ventilators were set in Pressure Support Ventilation mode, with a Pressure Support Level at 15 cm H_2O and a PEEP at 5 cmH_2O. The pressurization slope was set at the fastest value without overshooting. Inspiratory trigger, when adjustable, was set at the highest sensitivity while avoiding auto-triggering in the case of no leak and was maintained in an identical fashion during leaks. Expiratory trigger was adjusted at 25% of peak inspiratory flow when NIV algorithms were turned off on ICU and transport ventilators, and at 40% of peak inspiratory flow, otherwise automatic, when NIV algorithms were turned on. Some of the NIV ventilators can be used with a passive or active exhalation port. They were tested using the passive exhalation port. Maximal inspiratory time was set, when adjustable, at 3 seconds when assessing the ventilator cycling off synchronization (during inspiratory leak) and at 1 second when assessing the ventilator triggering synchronization (during continuous leak).

Measured Parameters

Each ventilator was assessed in each leak condition for two minutes after steady state. ICU and transport ventilators were tested twice: with and without their NIV algorithm engaged, except the Elisee 250 whose NIV algorithm cannot be turned off. Data were acquired at 512 Hz from the ASL 5000 and stored in a laptop computer for subsequent analysis (Acqknowledge 3.7.3, Biopac Systems, Goleta, CA, USA).

The measured parameters were defined as follows:

- The triggering delay (TD, ms) was the time from the beginning of the simulated inspiratory effort to the beginning of the ventilator's pressurization.
- The *triggering pressure-time product* (PTP_{Trig}, $cmH_2O.s$) was the area under the pressure-time curve from the onset of the simulated inspiratory effort to the return to pressure baseline.
- The *pressure-time product at 300 ms* (PTP_{300}, $cmH_2O.s$) was the area under the pressure-time curve during the first 300 ms after the onset of the inspiratory effort.
- The auto-triggerings were ventilator's insufflations without any previous simulated effort. They are reported as a percentage calculated as follows: Auto-triggering incidence (%) = (Auto-triggered cycles / total ventilator cycles) x 100.

 DOI: 10.1378/chest.11-2279

- Cycling (or expiratory trigger) synchronization was assessed by determining ventilator insufflation time in excess (Ti_{excess}), expressed as a percentage and calculated as follows: $Ti_{excess} = [(Ti_{vent} - Ti_{sim})/ Ti_{sim}] \times 100$, where Ti_{vent} is the time between the beginning of the simulated inspiratory effort and the end of the ventilator's insufflation, and Ti_{sim} the simulated inspiration time. A "delayed cycling" was defined by a $Ti_{vent} \geq 2\ Ti_{sim.}$ A "premature cycling" was defined by a $Ti_{vent} < 2/3\ Ti_{sim.}$

Clinical Study

***Study population*:**

The clinical study was conducted in two university hospital ICUs: one medical (Créteil, France), and one medical-surgical (Geneva, Switzerland).

ICU patients requiring NIV for the following indications were eligible:

1) Hypercapnic or non-hypercapnic respiratory failure, defined by at least two of the following[1-2]:
   a. Worsening dyspnoea over the last 10 days in patients with chronic respiratory failure;
   b. Respiratory rate > 25/min;
   c. Arterial pH < 7.35;
   d. $PaCO_2$ > 50 mm Hg;
   e. PaO_2 < 50 mm Hg.
2) To avert extubation failure in patients at risk, i.e. with one of these criteria at the time of extubation[3]:
   a. More than one failure of a weaning trial;
   b. Congestive heart failure;
   c. $PaCO_2$ > 45 mm Hg;
   d. Ineffective cough;
   e. Upper airways stridor at extubation not requiring immediate reintubation.

Non inclusion criteria were classical contraindications to NIV.

Furthermore, patients were included only if either a diaphragmatic (EMGd) or an inspiratory neck muscles (EMGn) surface electromyogram was available and of sufficient quality. Six patients have been excluded due to non reliable EMG signals.

The sample size was arbitrarily set at 15 patients.

 DOI: 10.1378/chest.11-2279

Additional settings information

The expiratory trigger was not adjustable on the NIV ventilator because it was automatically adjusted by the ventilator. It was set by default at 25% of the peak inspiratory flow and was not adjustable in the 11 patients with an Evita 4 or XL (Drager). For the remaining four patients with an Engstrom Carestation (GE Healthcare), it was set at 40% for three of them, and 25 % for the other one.

Measurements

Patients received in a random order three consecutive 20 minutes-sessions of NIV: 1) use of an ICU ventilator whose NIV algorithm has been turned off (ICU_{NIV-}), 2) use of an ICU ventilator whose NIV algorithm has been turned on (ICU_{NIV+}) and 3) use of a dedicated NIV ventilator (NIV_V).

Flow was measured with a non-heated pneumotachograph (Fleish No. 2, Lausanne, Switzerland) inserted between the mask and the Y-piece of the circuit and connected to a differential pressure transducer (Validyne MP45, ± 2cmH_2O, Northridge, CA, USA). Volume was obtained by integration of the flow signal. The leak around the mask was quantified as the difference between inspiratory and expiratory volumes. Airway pressure was measured with a differential pressure transducer (Validyne MP45, ± 70cmH_2O, Northridge, CA, USA) placed between the mask and the pneumotachograph. Signals were acquired online over the three NIV sessions (ICU_{NIV-}, ICU_{NIV+}, NIV_V) using an analog-digital converter (MP 100; Biopac systems, Goleta, CA, USA) sampled at 200 Hz, and stored in a laptop computer for subsequent analysis with the Acqknowledge 3.7.3 software (Biopac systems, Goleta, CA, USA). EMGd was recorded with two surface electrodes placed bilaterally over the costal margin, one reference electrode being placed over the sternum[4]. EMGn was recorded with two surface electrodes placed in the posterior triangle of the neck (aiming at recording mainly scalene EMG activity) or over the body of the sternocleidomastoid (aiming at recording mainly sternocleidomastoid activity), one reference electrode being placed over the sternum. The analogue signal was first filtered and digitized at a sampling rate of 1000 Hz by using a Biopac EMG module (Biopac systems, Goleta, CA, USA), then rectified and stored in a laptop computer for subsequent analysis (Acqknowledge 3.7.3; Biopac systems, Goleta, CA, USA).

Respiratory parameters were defined by analyzing these tracings as previously described[1-2]. For each parameter, a mean value of 10 consecutive cycles at 5, 10, 15 and 20 minutes of each NIV session was calculated.

The patient's neural inspiratory time (Ti_p) was measured as the interval between the initial increase in and the initial rapid decrease of electrical activity on the processed EMG signal[1-2, 5]. The difference between the end of Ti_p and the end of the ventilator's pressurization was measured as Ti_{excess}, expressed as a percentage of the Tip as follow: $Ti_{excess} = [(Ti_{vent} - Ti_p)/ Ti_p] \times 100$, where Ti_{vent} is the time between the beginning of the inspiratory effort and the end of the

 DOI: 10.1378/chest.11-2279

ventilator's insufflation. Major patient-ventilator asynchronies were defined and detected by visual inspection of the recordings as previously published[1-2, 6]:

Auto-triggering: a cycle delivered by the ventilator without a prior inspiratory EMG activity.

Double-triggering: two cycles separated by a very short expiratory time during the same inspiratory EMG activity.

Ineffective effort: presence of an inspiratory EMG activity not followed by an assisted cycle.

"Delayed cycling": a cycle where the ventilator's insufflation time is greater than twice the Ti_p.

"Premature cycling": a cycle where the ventilator's insufflation ended before the 2/3 of the Ti_p.

Each asynchrony event was considered as frequent if it occurred at an average of > 1/min over the 20 min recording period. A global asynchrony index (AI) was computed as previously published[1-2, 6], defined as the total number of the above events divided by the total number of triggered and non-triggered ventilator cycles. Therefore AI (%) = [number of events / (ineffective triggerings + ventilator cycles)] x 100.

Statistics

Statistical analyses were performed with Statistical Package for the Social Sciences (version 16.0, SPSS, Chicago, IL, USA). Continuous data are expressed as the median (25^{th}-75^{th} percentile). In both the bench and clinical study, the variables did not display a normal distribution, so only non parametric tests were used. A p value of less than 0.05 was considered statistically significant.

Continuous data from the test lung to assess the impact of leaks or NIV algorithm for each kind of ventilator were compared using a Wilcoxon test. Comparisons between different kinds of ventilators were made using a Kruskal-Wallis test then a Mann Whitney test for pairwise comparisons.

Continuous data between the three NIV sessions were compared using a Friedman test, then a Wilcoxon test for paired measures. Comparisons of the proportions of asynchronies between the three sessions were performed with the Cochran Q test, then a Mc Nemar test for pairwise comparisons.

ADDITIONAL RESULTS

Bench Study

Triggering pressure-time product (e-Figure 1)

ICU and transport ventilators with their NIV algorithm turned off in the absence of leaks exhibited a triggering pressure-time product (PTP_{Trig}) of -0.06 (-0.09--0.05) and -0.08 $cmH_2O.s$ (-0.16--0.06) respectively.

With inspiratory leaks, turning on the NIV algorithm led to either an improvement (Engstrom, G5, PB840) or no significant modification (Avea, Evita XL, Servo-i, V500, Vela) of the PTP_{Trig} with ICU ventilators, and to either an

improvement (T1) or a worsening (Medumat, Oxylog 3000, Supportair) of the PTP_{Trig} with transport ventilators. In this last condition, the PTP_{Trig} was -0.06 $cmH_2O.s$ (-0.08--0.04) with ICU ventilators, -0.10 $cmH_2O.s$ (-0.37--0.07) with transport ventilators, and -0.04 $cmH_2O.s$ (-0.06--0.02) with dedicated NIV ventilators. When NIV algorithms were used in the presence of leaks, three ICU ventilators (Avea, Engstrom, PB840), four dedicated NIV ventilators (BiPAP Vision, Trilogy 100, V60, VPAP 4), and one transport ventilator (Elisee 250) exhibited a PTP_{Trig} less than -0.06 $cmH_2O.s$, i.e., the median PTP_{Trig} of ICU ventilators in the absence of leaks (NIV algorithm turned off).

Pressure-time product at 300 ms (e-Figure 2)

In the absence of leaks, all ICU and transport ventilators without their NIV algorithm engaged exhibited a positive PTP_{300} except the Oxylog 3000. Thus, the median PTP_{300} was 1.6 $cmH_2O.ms$ (1.3-1.8) with ICU ventilators. The addition of inspiratory leaks led to a significant decrease in PTP_{300} for all ICU and transport ventilators except one (T1). With the NIV algorithm, the PTP_{300} remained lower than without leaks with all ICU and transport ventilators except three (Engstrom, PB840 and T1), and was even negative for two transport ventilators (Medumat, Oxylog 3000). With both inspiratory leaks and NIV algorithms, the PTP_{300} with ICU, transport and dedicated NIV ventilator was 1.4 (1.3-1.4), 0.3 (-0.2-0.9) and 0.5 $cmH_2O.ms$ (0.3-0.7) respectively. One dedicated NIV ventilator exhibited a negative PTP_{300} (VIVO 40).

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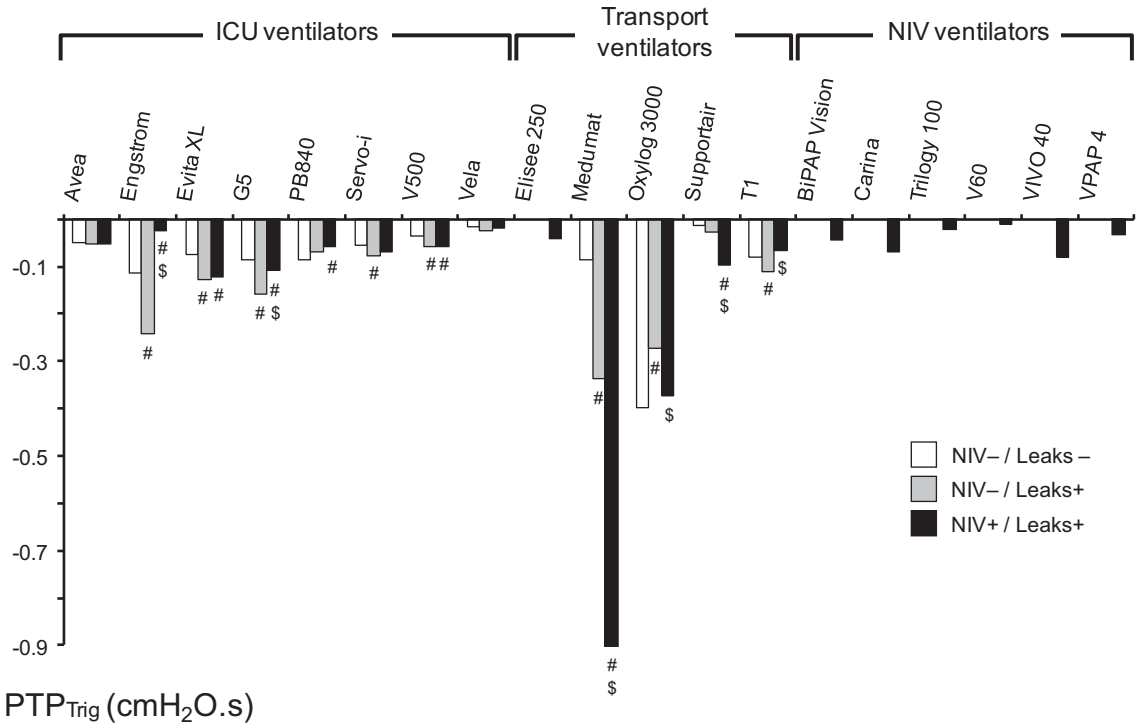
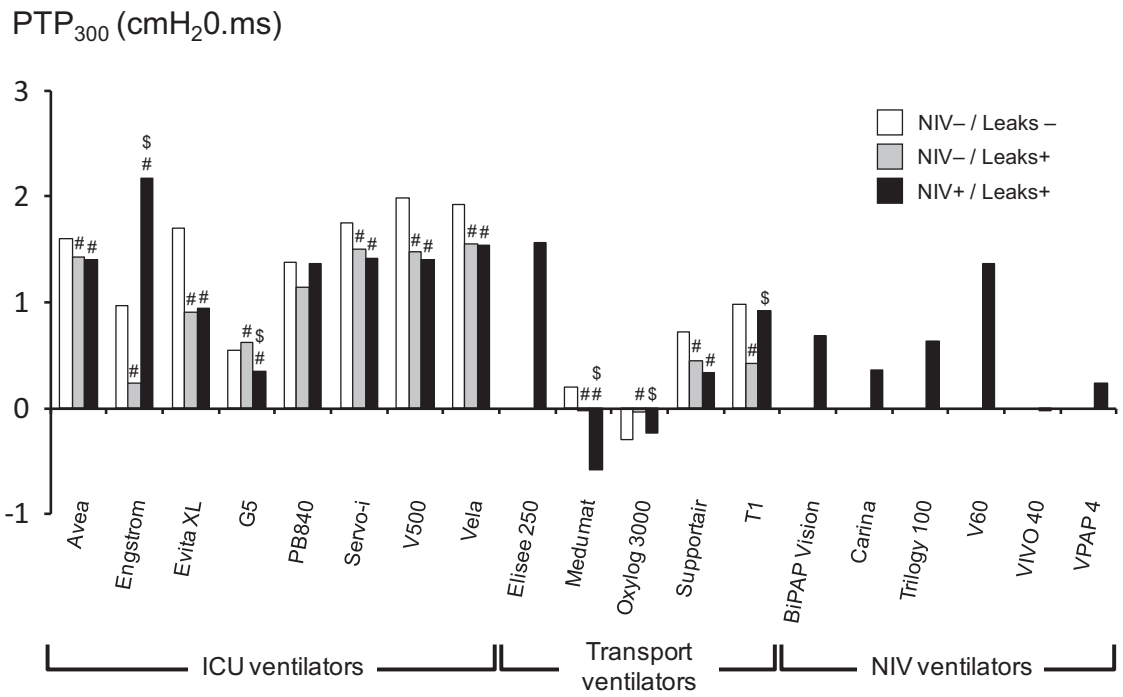
e-Figure 1.



e-Figure 1. ***Bench Study*** **– Triggering Pressure Time Product (PTP_{Trig}):** Representation of the PTP_{Trig} for ICU and transport ventilators with their NIV algorithm turned off in the absence of any leak (**NIV-/Leaks-**, white bars), then in the presence of inspiratory leaks (**NIV-/Leaks+**, grey bars); and for ICU and transport ventilators with their NIV algorithm turned on as well as for NIV ventilators in the presence of inspiratory leaks (**NIV+/Leaks+**, black bars). #: $p<0.05$ versus NIV-/Leaks-. $: $p<0.05$ versus NIV-/Leaks+.

 DOI: 10.1378/chest.11-2279

e-Figure 2.



e-Figure 2. ***Bench Study*** **– Pressure Time Product at 300 ms (PTP_{300})**: Representation of the PTP_{300} for ICU and transport ventilators with their NIV algorithm turned off in the absence of any leak (**NIV-/Leaks-**, white bars), then in the presence of inspiratory leaks (**NIV-/Leaks+**, grey bars); and for ICU and transport ventilators with their NIV algorithm turned on as well as for NIV ventilators in the presence of inspiratory leaks (**NIV+/Leaks+**, black bars). #: p<0.05 versus NIV-/Leaks-. $: p<0.05 versus NIV-/Leaks+.

Sleep in Hypercapnic Critical Care Patients Under Noninvasive Ventilation: Conventional Versus Dedicated Ventilators*

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Objective: To compare sleep quality between two types of ventilators commonly used for noninvasive ventilation: conventional ICU ventilators and dedicated noninvasive ventilators; and to evaluate sleep during and between noninvasive ventilation sessions in critically ill patients.
Design: Physiological sleep study with a randomized assessment of the ventilator type.
Setting: Medical ICU in a university hospital.
Patients: Twenty-four patients admitted for acute hypercapnic respiratory failure requiring noninvasive ventilation.
Interventions: Patients were randomly assigned to receive noninvasive ventilation with either an ICU ventilators ($n = 12$) or a dedicated noninvasive ventilators ($n = 12$), and their sleep and respiratory parameters were recorded by polysomnography from 4 PM to 9 AM on the second, third, or fourth day after noninvasive ventilation initiation.
Measurements and Main Results: Sleep architecture was similar between ventilator groups, including sleep fragmentation (number of arousals and awakenings/hr), but the dedicated noninvasive ventilators group showed a higher patient–ventilator asynchrony-related fragmentation (28% [17–44] vs. 14% [7.0–22]; $p = 0.02$), whereas the ICU ventilators group exhibited a higher noise-related fragmentation. Ineffective efforts were more frequent in the dedicated noninvasive ventilators group than in the ICU ventilators group (34 ineffective efforts/hr of sleep [15–125] vs. two [0–13]; $p < 0.01$), possibly as a result of a higher tidal volume (7.2 mL/kg [6.7–8.8] vs. 5.8 [5.1–6.8]; $p = 0.04$). More sleep time occurred and sleep quality was better during noninvasive ventilation sessions than during spontaneous breathing periods ($p < 0.05$) as a result of greater slow wave and rapid eye movement sleep and lower fragmentation.
Conclusions: There were no observed differences in sleep quality corresponding to the type of ventilator used despite slight differences in patient–ventilator asynchrony. Noninvasive ventilation sessions did not prevent patients from sleeping; on the contrary, they seem to aid sleep when compared with unassisted breathing. (*Crit Care Med* 2013; 41:60–68)
Key Words: acute respiratory failure; ICU; noninvasive ventilation; patient–ventilator asynchrony; polysomnography; sleep

***See also p. 338.**

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Supported, in part, by a research grant from Philips Respironics. This funding source had no role in the collection, analysis or interpretation of the data, or writing of the article. Dr. Ana Córdoba-Izquierdo received a grant from *Fundació La Caixa* and *Societat Catalana de Pneumologia*.

The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e31826764e3

Sleep is commonly disrupted in ICU patients, both in terms of alterations of circadian night/day distribution and architecture (1–3). A high sleep fragmentation with a marked reduction in the duration of rapid eye movement (REM) and slow wave sleep (SWS) has been described (1, 3, 4). Multiple factors contribute to these abnormalities such as the severity of illness (5), medications (6), noise (2, 3), patient care activities, (3) and mechanical ventilation (4, 7–9). The ventilatory mode (4, 7, 8), ventilatory settings (8, 9), and patient–ventilator synchronization (7, 9, 10) can have an impact on sleep quality. A high frequency of patient–ventilator asynchronies has been reported during noninvasive ventilation (NIV) in critically ill patients in the ICU (11). The choice of conventional ICU ventilators or dedicated ventilators for NIV delivery depends not only on the care setting and the etiology of the respiratory failure, but also on the geographical region and local protocols (12–14). ICU ventilators, initially conceived

for invasive ventilation, have been improved with algorithms aiming to minimize the impact of leaks on ventilation function and patient–ventilator synchronization. It has been shown that these algorithms partially correct this problem, albeit with variations between ventilators, both in bench (15, 16) and clinical studies (16, 17). Alternatively, dedicated NIV ventilators, derived from home ventilators, are usually very efficient in dealing with leaks, as has been suggested in both bench (16, 18, 19) and clinical (16) studies. In a recent short-term physiological study, Carteaux et al (16) showed a reduction in the frequency of patient–ventilator asynchronies, especially autotriggering, when a dedicated NIV ventilator was used compared with ICU ventilators either with or without their NIV mode engaged. Other studies have suggested that dedicated ventilators may be better tolerated: a study by Ferrer and colleagues (20) reports a mean of 18 hrs of continuous NIV administered with such ventilators in postextubated patients. Because comfort and patient–ventilator synchronization could influence sleep, comparing both types of ventilators was of clinical relevance. Additionally, intermittent or sequential delivery of NIV has often been advocated for ICU patients (21, 22), and this approach is often used even at night. A previous ICU study from our group conducted with patients under NIV showed that most of the sleep time over a 17-hr period occurred at night (23). In that study, however, no monitoring of NIV treatment delivery was performed. Because sleep induces a deleterious effect on respiratory failure by a decrease in ventilation compared with wakefulness (24), knowing whether NIV use at night in the ICU environment could favor or impede sleep may be important for clinical practice.

The goal of this study was to determine whether the type of ventilator used for NIV could influence sleep in critically ill patients with acute hypercapnic respiratory failure (AHRF) and second, whether patients slept correctly with ventilators at night.

MATERIALS AND METHODS

The study protocol was approved by the ethics committee of our institution (Comité de Protection des Personnes Ile-de-France IX, Créteil, France). This protocol complied with a French law provision concerning a category of clinical research with minimal risk, called research on usual care ("Recherche portant sur les soins courants" L. 1121-1 du Code de la Santé Publique, arrêté du 9 mars 2007), which does not require written consent from participants and simplifies administrative procedures (25). We were allowed to use this specific provision because we had already used the two types of ventilators in the unit and because we did not change our method of NIV delivery for the study. Patients or their surrogates were informed about the trial and their right to refuse participation. Patients who declined to participate were not treated differently.

Patients

All patients admitted to our medical ICU for AHRF over a 1-yr period and requiring NIV for >1 day were eligible for the study. AHRF was defined as respiratory distress with a respiratory rate ≥25 breaths/min, Pa_{CO_2} >45 mm Hg, and pH <7.35. Exclusion criteria included hypercapnic coma, use of medications that could alter sleep, previous home treatment with NIV or with continuous positive airway pressure (because they could be accustomed to home ventilators better than an ICU ventilator), the presence of central neurological disease, and hemodynamic instability.

Noninvasive Ventilation

Patients were evaluated between the second and the fourth day after NIV initiation and randomized to receive NIV treatment with either an ICU ventilator (NIV_{ICU}) or a dedicated NIV ventilator (NIV_D). The NIV_{ICU} used was either an Evita XL (Dräger, Lübeck, Germany) or an Engström Carestation (GE Healthcare, Fairfield, CT) with the NIV mode engaged. Both ventilators showed similar performances in the presence of leaks in a previous bench study (16). The NIV_D used was a V60 (Philips Respironics, Murrysville, PA). All patients were ventilated in the pressure support mode with a conventional oronasal mask. A heat humidifier was used for the NIV_{ICU} (26).

Ventilatory parameters were set as follows: a positive end expiratory pressure between 4 and 6 cm H_2O (up to 8 when obstructive sleep apnea syndrome was suspected); an adequate pressure support level to obtain an expiratory tidal volume of approximately 6–8 mL/kg and a respiratory rate <35 breaths/min; an inspiratory trigger sensitivity at either 3 L/min in the NIV_{ICU} or automatic in the NIV_D; a pressure ramp time between 100 and 150 msec in the NIV_{ICU} and at an equivalent qualitative value of 2 in the NIV_D; and a maximal inspiratory time of 1 sec in the NIV_{ICU} and set by default (not adjustable) to 3 secs for the NIV_D. Expiratory trigger was automatic for the Evita XL and the V60 and of 40% of maximal inspiratory flow for the Engström. During the study period, a 1- to 3-hr session of NIV was prescribed in the afternoon followed by a (preferably) longer session during the night based on clinical tolerance and/or a patient's need. Between periods of ventilation, patients received a minimal oxygen flow to achieve a hemoglobin oxygen saturation ≥90%. In all cases, arterial blood gases were obtained during unassisted spontaneous breathing (SB) between 5 AM and 7 AM.

Polysomnography

Standard polysomnography (Embla S7000; Embla ResMed, Denver, CO) was conducted from 4 PM to 9 AM in all patients. Seven electroencephalographic channels, right and left electrooculograms, and two electromyograms of the chin muscle were used for conventional sleep staging. Respiratory efforts were monitored by chest and abdominal movements using inductive plethysmography. The oxygen saturation of hemoglobin was continuously recorded with a finger pulse oxymeter. Flow and airway pressure were monitored with a pressure transducer connected to the mask during NIV sessions. During SB, the nasal pressure was measured through nasal prongs connected to a pressure transducer. Noise was simultaneously recorded near the patients' head (Quest Technologies, Oconomowoc, WI).

Sleep recordings were manually scored according to criteria of Rechtschaffen and Kales (27) by a physician blinded to

the study (X.D.). Sleep quantity was determined by total sleep time (TST). Sleep quality was assessed by calculating the sleep efficiency (defined as TST divided by total recording time), the percentage of TST spent in each sleep stage, and the fragmentation index (defined as the number of arousals and awakenings/TST). Arousals and awakenings were scored according to the criteria of the American Association of Sleep Medicine (28). Subcortical arousals, represented by low-frequency electroencephalographic changes (K-complex bursts and/or Δ wave burst) without α activity, were scored following patient–ventilator asynchronies as an index of sympathetic activity. Nighttime was considered to be from 11 PM, when lights are usually turned off, to 7:30 AM.

Patient–Ventilator Asynchrony and Respiratory Events

Patient–ventilator asynchronies (**Fig. 1**) were detected based on inductive plethysmography, flow, and airway pressure signals as previously reported (8, 9, 29) using the following definitions. An ineffective effort was defined as the presence of an inspiratory effort without an assisted ventilatory cycle. A prolonged cycle was defined as a ventilator cycle that spanned two inspiratory efforts; in this situation, the second effort was not considered as an ineffective effort. Double triggering was defined as the occurrence of two consecutive ventilator cycles during a single inspiratory effort. Autotriggering was defined as the occurrence of one to several consecutive and rapid ventilator-delivered breaths without a concomitant respiratory effort. Apnea was defined as the absence of ventilator insufflation lasting ≥10 secs. We analyzed all of the sleep time and a single 20-min period of quiet breathing during wakefulness for each patient. The patient–ventilator asynchrony index was expressed by the number of events/hr. All of these respiratory events were considered to be the cause of an arousal, an awakening, or a subcortical arousal when they occurred ≤10 secs before them (30).

During unassisted SB, apnea and hypopnea were scored following the current recommendations (28). Hypopnea was defined as a reduction in the nasal pressure signal by >50% followed by a desaturation >3% or an arousal (28). The presence of underlying sleep-related breathing disorders was considered if the apnea–hypopnea index during SB was ≥10/hr of sleep.

Noise

Noise recordings were available for all except one patient. The noise level is expressed in decibels (dB). Arousals and awakenings were associated with noise when they occurred 3 secs after or within a peak noise, defined as an increase in noise level ≥10 dB (2, 3).

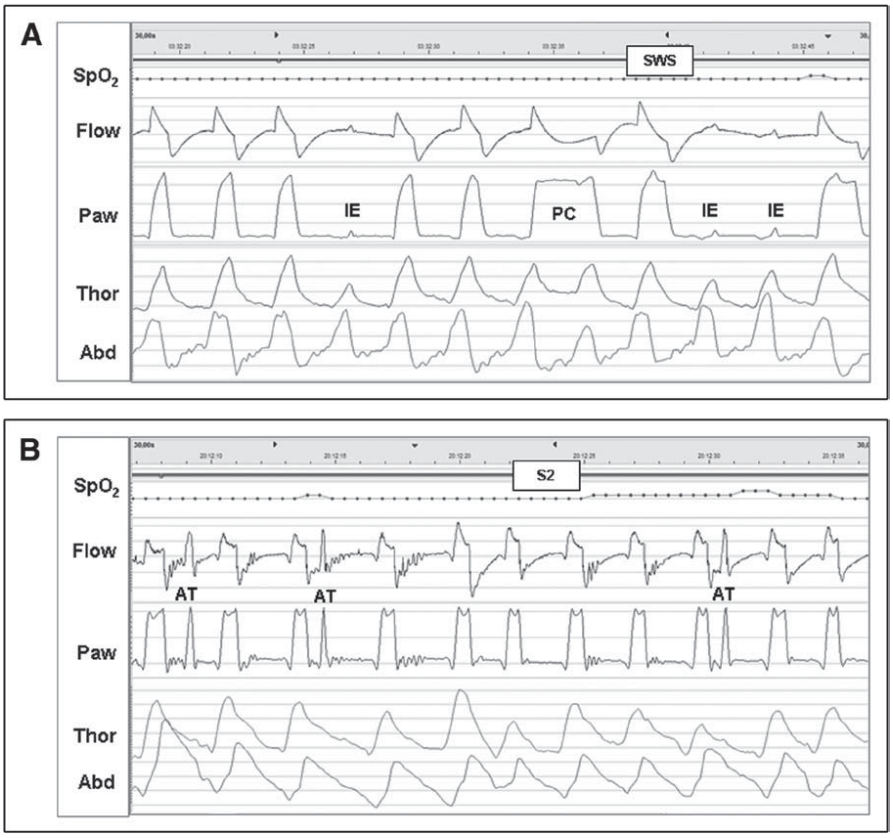

Figure 1. Two 30-sec tracings showing different patient–ventilator asynchronies with two different ventilators. **A**, Recording obtained with a dedicated noninvasive ventilation ventilator, positive end-expiratory pressure (PEEP) of 6 cm H_2O, and pressure support (PS) of 8 cm H_2O. **B**, Recording obtained with an ICU ventilator, PEEP of 5 cm H_2O, and PS of 10 cm H_2O. SWS = slow wave sleep stage; S2 = Stage 2 of sleep; S_{PO_2} = hemoglobin pulse oxygen saturation; Paw = airway pressure; Thor = thoracic plethysmography signal; Abd = abdominal plethysmography signal; IE = ineffective effort; PC = prolonged cycle; AT = autotriggering.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (Version 16.0; SPSS, Chicago, IL). Continuous data are expressed as medians and interquartile ranges. Both ventilator groups were compared using the Mann–Whitney *U* test, whereas the Wilcoxon's rank sum test was used for intragroup comparisons. Categorical data were compared using the χ^2 test or the Fisher's exact test where appropriate. A p value < 0.05 was considered significant for all tests.

RESULTS

Of the 64 patients screened, 29 were excluded and ten were not enrolled in the study (**Fig. 2**). The remaining 25 patients underwent randomization, 12 being allocated to the NIV_{ICU} group and 13 to the NIV_D group. One patient in the NIV_D group was excluded from the analysis as a result of technical problems during the recordings.

Characteristics of the Study Population

Patients' characteristics are provided in **Table 1**. There were no differences between groups, including the time under NIV previous to the study inclusion (19 hrs

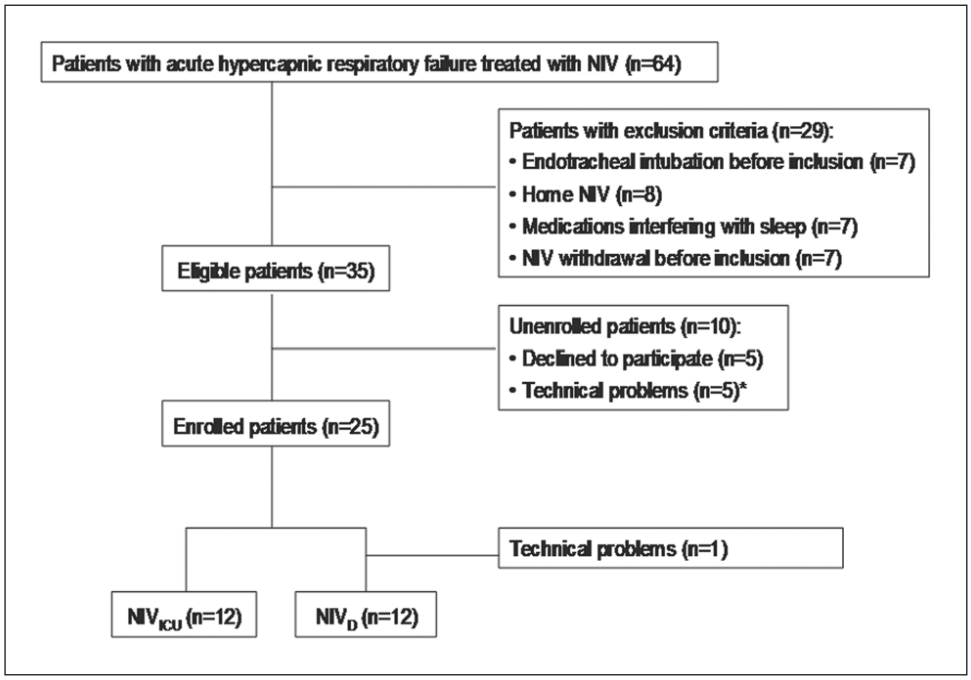

Figure 2. Flow diagram outlining the screening and enrollment of patients. NIV = noninvasive ventilation; NIV_{ICU} = intensive care unit ventilator; NIV_D = dedicated noninvasive ventilator. *Technical problems for patients' enrollment were nonavailability of the polysomnograph in two cases, planned diagnostic procedure out of the ICU in two cases, and nonavailability of the research physician in one case.

TABLE 1. Patient Characteristics

Characteristic	Total
Age, yrs	69 (65–77)
Male sex, *n* (%)	14 (58)
Body mass index, kg/m^2	29 (20–37)
Underlying chronic respiratory disease	
Chronic obstructive pulmonary disease, *n* (%)	11 (46)
Bronchiectasis, *n* (%)	1 (4.2)
Neuromuscular disease, *n* (%)	2 (8.3)
Rib cage disease, *n* (%)	3 (17)
Epworth sleepiness scale at baseline	9.5 (4.5–16)
At admission	
Simplified Acute Physiology Score-2	30 (25–35)
Pa_{O_2}/F_{IO_2}, mm Hg	228 (172–255)
pH	7.32 (7.28–7.33)
Pa_{CO_2}, mm Hg	73 (57–84)
At the time of inclusion	
Previous time on noninvasive ventilation, hrs	18 (12–22)
pH	7.37 (7.32–7.40)
Pa_{CO_2}, mm Hg	64 (55–72)

[17–21] in the NIV_D group vs. 13 hrs [9–23] in the NIV_{ICU} group; $p = 0.41$). The only difference was a higher Epworth sleepiness score in the NIV_D group than in the NIV_{ICU} group (14 [10–21] vs. 5 [2–9]; $p = 0.01$). The reasons for NIV treatment were acute on chronic respiratory failure ($n = 16$), cardiogenic pulmonary edema ($n = 3$), pneumonia ($n = 2$), and postextubation respiratory failure ($n = 3$). Three patients had already received NIV because of AHRF, and one patient had previously been studied by polysomnography.

Noninvasive Ventilation

Figure 3 represents the distribution of NIV sessions across the study period. The median overall ventilatory time was 7.4 hrs (6.5–8.9) distributed over 2.2 hrs (1.7–2.9) during the daytime and 5.8 hrs (4.6–6.5) during the night. Ventilatory settings other than F_{IO_2} were not modified during the study. NIV was poorly tolerated (unspecific complaints after optimizing mask fitting or airway pressure) by two patients in each group; in these cases, NIV was stopped and continued later. NIV time, ventilatory parameters, and breathing patterns were similar between groups (**Table 2**), with the exception of tidal volume per predicted body weight, which was higher in the NIV_D group than in the NIV_{ICU} group. Both groups showed a significant decrease in Pa_{CO_2} from inclusion to the end of the study period. NIV treatment was continued for 5.5 days (3.8–7.50). No differences in NIV time or ICU length of stay were found between groups.

Sleep Characteristics

No medications that interfere with sleep were administered. The sleep analysis during the 17-hr study period for the overall population showed a TST of 5.9 hrs (4.2–8.3). Stage 1 accounted for 8% (5.2–17) of TST, Stage 2 for 38% (25–60), SWS for 30% (17–46), and REM for 11% (5.7–17). Sleep fragmentation was high with 33 (16–42) arousals and awakenings/hr of sleep. Sixty-nine percent (59–81) of TST occurred during NIV periods, and sleep architecture was better during NIV compared with SB periods (**Fig. 4**) with less Stage 1, more SWS, more REM sleep, and a lower fragmentation index (26 arousals and awakenings/hr [14–35] vs. 39 [28–58]; $p = 0.002$). Concerning night–day distribution, 74% (64–77) of TST occurred during the night period. Sleep architecture was similar between both NIV_D and NIV_{ICU} groups during the entire study period and particularly during NIV periods (**Table 3**).

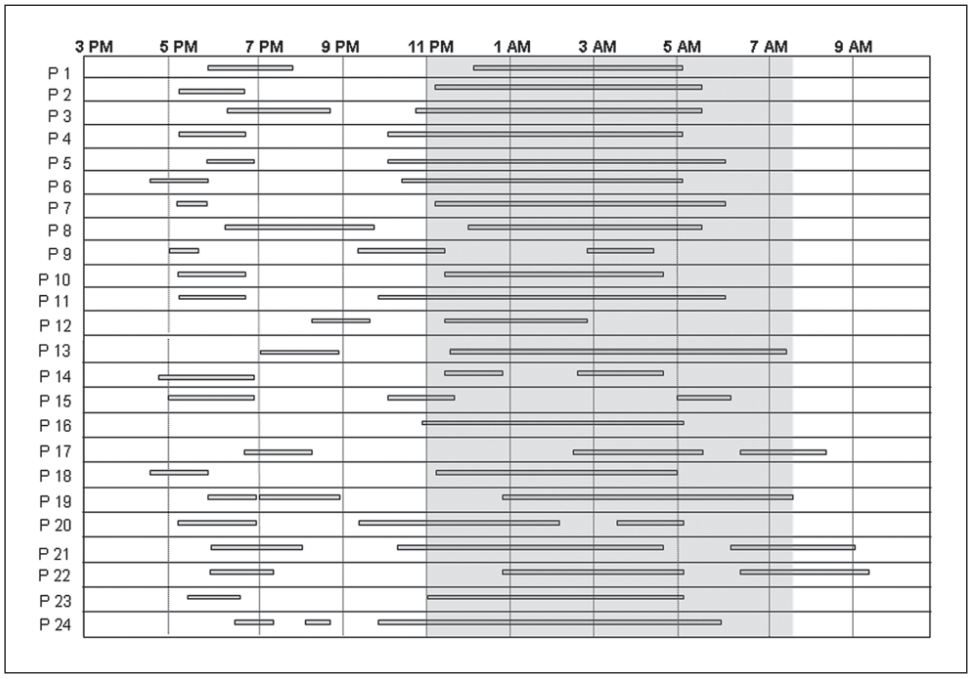

Figure 3. Noninvasive ventilation (NIV) session distribution during the study period for all patients included. Number and duration of NIV sessions are represented by *gray horizontal bars*. The *shaded area* represents the nighttime period (11 PM to 7:30 AM). Patients (P) one to 12 were ventilated with the dedicated noninvasive ventilator, and P 13 to 24 were ventilated with the intensive care unit ventilator.

Patient–Ventilator Asynchrony and Sleep-Related Breathing Disorders

Table 4 provides information on patient–ventilator asynchrony index in the NIV_D and NIV_{ICU} groups during sleep and wakefulness. Autotriggering was more frequent in the NIV_{ICU} group, reaching statistical significance only during wakefulness. Other asynchronies tended to be more frequent in the NIV_D group, but only ineffective effort achieved significant differences during wakefulness and during sleep. Prolonged cycles did not occur in the NIV_{ICU} group because the maximal inspiratory time was set at 1 sec, whereas this parameter was not adjustable in the NIV_D group. Apneas under NIV appeared in 13 patients while sleeping with an occurrence rate of 1.3 (0.7–7) apneas/hr without differences between groups.

Patient–ventilator asynchronies were responsible for 19% (11–30) of arousals and awakenings from sleep, ineffective effort the most frequent of them (50% [20–88]). Among asynchronies not related to sleep fragmentation, 7.6% (3.7–11) produced subcortical arousals.

Sleep fragmentation related to patient–ventilator asynchrony was more frequent in the NIV_D group than in the NIV_{ICU} group (28% of total arousals and awakenings [17–44] vs. 14% [7.0–22], respectively; $p = 0.02$). Low-frequency electroencephalographic changes related to patient–ventilator asynchrony showed no differences between groups.

The analysis of sleep-related breathing disorders during SB was possible for only 15 patients as a result of technical problems with the recording or to the absence of sleep. Five patients out of seven in the NIV_D group and three out of eight in the NIV_{ICU} group ($p = 0.32$) had an apnea–hypopnea index >10/hr.

Noise

During the 17-hr study period, the median noise value was 60 dB (58–61) with a maximum noise level of 101 dB (98–103) and 107 sound peaks/hr (86–123). The NIV_{ICU} group exhibited more frequent sound peaks (98 peaks/hr [89–121] vs. 39 [21–69]; $p = 0.001$) and a higher sleep fragmentation related

TABLE 2. Ventilator Settings and Respiratory Parameters During Noninvasive Ventilation Periods

	Dedicated Noninvasive Ventilator Group	ICU Ventilator Group	*p*
Time on noninvasive ventilator, hrs	7.6 (6.8–9.0)	7.6 (6.6–8.8)	0.95
Noninvasive ventilator sessions, *n*	2 (2–2)	2.5 (2–3)	0.13
Fractional inspired oxygen, %	30 (25–31)	28 (25–30)	0.25
Positive end-expiratory pressure, cm H_2O	6 (4–6)	5 (5–6)	0.55
Pressure support level, cm H_2O	10 (8–12)	10 (8–10)	0.39
Tidal volume, mL	475 (387–552)	398 (350–408)	0.12
Tidal volume, mL/kg of predicted body weight	7.2 (6.7–8.8)	5.8 (5.1–6.8)	0.04[a]
Respiratory rate, breaths/min	24 (16–30)	25 (21–27)	0.78
$Paco_2$ at the end of the study, mm Hg	61 (48–64)	60 (53–67)	0.71

[a]$p < 0.05$. The $Paco_2$ at the end of the study was obtained during spontaneous breathing.

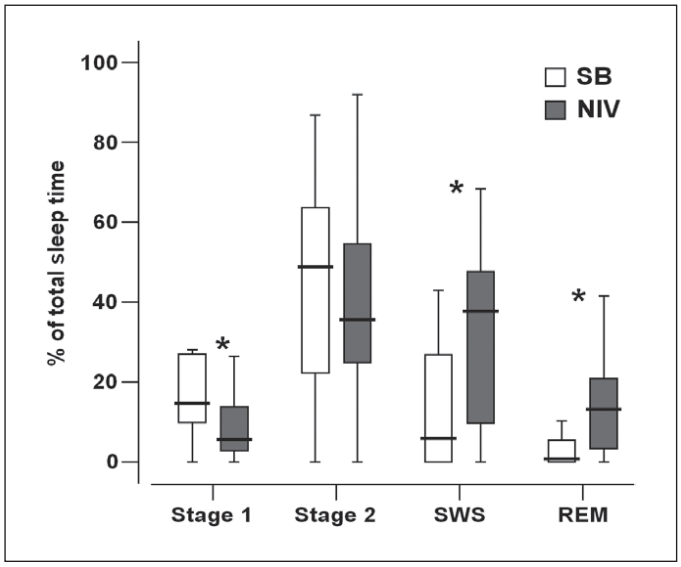

Figure 4. Differences in sleep architecture between noninvasive ventilation (NIV) and spontaneous breathing (SB) periods for the entire group of patients. *Box plots* represent sleep stages for each condition (*thick horizontal bar*: median; *extremities of the boxes*: 25th and 75th percentiles; *thin horizontal bars*: fifth and 95th percentiles). *$p < 0.05$. SWS = slow wave sleep; REM = rapid eye movement.

to noise (8.7% [4.7–12] vs. 1.8% [1.2–4.6]; $p < 0.01$) than the NIV_D group.

DISCUSSION

This is the first study in critical care patients with AHRF to evaluate 1) sleep under NIV; and 2) the impact on sleep of two types of ventilators widely used in the ICU to provide NIV. Patients can sleep during NIV, and no differences were found according to the type of ventilator used. Patient–ventilator asynchronies and asynchrony-related sleep fragmentation were more frequent in the NIV_D than in the NIV_{ICU} group, but noise peaks and noise-related fragmentation were more frequent in the NIV_{ICU} than in the NIV_D group with a similar number of total arousals and awakenings occurring in both groups.

Sleep Quality in the ICU

The patients studied showed a TST in the normal range, but they had impaired sleep quality with reduced REM sleep and a high sleep fragmentation. These results are in agreement with those obtained in other studies conducted in the ICU on intubated (1–3, 8) and nonintubated patients under NIV (23). However, similar to the aforementioned study on NIV patients (23), SWS was preserved and the circadian sleep cycle was relatively maintained because most of the sleep (74% of TST) occurred at night. Recordings were conducted for a 17-hr period with a lack of information occurring for the 7 hrs during which most of the care activities (toilet, diagnostic and therapeutic procedures, and meals) are usually carried out.

Sleep During NIV and SB

Our study also shows that critically ill patients can sleep while under NIV with most of their sleep, over a 17-hr period, occurring during NIV time. Furthermore, sleep quality seemed to be better during NIV than during unassisted SB in terms of the amount of SWS, REM sleep, and fragmentation. These interesting preliminary results should be considered cautiously because no randomization of such periods was done and several confounding factors may have contributed to this finding. First, most of NIV was provided during the nighttime when environmental factors interfering with sleep have less of a presence compared with daytime. Furthermore, most of the NIV sessions were performed at the beginning of the night, when the highest sleep drive is probably present. Second, patients may have profited from the short-term beneficial effects of NIV on sleep in cases with obstructive sleep apnea syndrome (31) and chronic respiratory failure of different etiologies (32, 33). Actually, eight among the 15 patients whose SB periods could be analyzed showed an apnea–hypopnea index >10/hr. Future studies evaluating the impact on sleep of the ventilatory support of critically ill patients should be performed to assess whether the strong association we observed can be confirmed.

TABLE 3. Comparison of Sleep Architecture Between Groups During the Noninvasive Ventilation Period

	Dedicated Noninvasive Ventilator Group	ICU Ventilator Group	*p*
TST-NIV, hr	4.7 (2.2–5.6)	3.9 (3.5–5.4)	0.64
Sleep efficiency, %	59 (46–74)	54 (48–61)	0.64
Stage 1, % of TST-NIV	4.4 (3–8)	8.3 (3.3–17)	0.30
Stage 2, % of TST-NIV	34 (24–54)	36 (28–51)	0.82
Slow wave sleep, % of TST-NIV	38 (5–45)	33 (21–50)	0.69
Rapid eye movement, % of TST-NIV	15 (2.7–21)	10 (3.7–20)	0.91
Fragmentation index	24 (10–32)	28 (17–36)	0.39

TST-NIV = total sleep time during noninvasive ventilation.
The fragmentation index is expressed as awakenings plus arousals/hr of sleep during noninvasive ventilation.

TABLE 4. Patient–Ventilator Asynchronies During Sleep and Wakefulness for Each Ventilator Group

Asynchronies (events/hr)	Dedicated Noninvasive Ventilator Group	ICU Ventilator Group	*p*
During sleep			
Autotriggering	2 (1–5)	2 (2–20)	0.49
Ineffective effort	34 (15–125)	2 (0–13)	< 0.01[a]
Double triggering	33 (14–52)	21 (7–60)	0.49
Prolonged cycle	0 (0–13)	0 (0–0)	0.10
Total asynchronies	174 (43–279)	34 (15–76)	0.02[b]
During wakefulness			
Autotriggering	0 (0–9)	15 (13–23)	< 0.01[a]
Ineffective effort	6 (2–14)	0 (0–0)	0.02[b]
Double triggering	54 (12–109)	11 (4–59)	0.27
Prolonged cycle	0 (0–1)	0 (0–0)	0.17
Total asynchronies	66 (18–129)	29 (20–81)	0.47

[a]$p < 0.01$.
[b]$p < 0.05$.

Patient–Ventilator Asynchrony

Our study showed a higher frequency of autotriggering with the NIV_{ICU} compared with the NIV_D ventilator. In agreement with our results, previous bench comparisons (16, 18, 19) and a clinical study (16) comparing these two types of ventilators in the presence of similar levels of leaks reported a higher autotriggering frequency with the NIV_{ICU} compared with the NIV_D ventilator.

The NIV_D group displayed more ineffective efforts than the NIV_{ICU} group. Several factors may have contributed to this difference. First, a significantly higher tidal volume was present in the former group compared with the NIV_{ICU} group. A high tidal volume has been shown to increase dynamic hyperinflation and intrinsic positive end-expiratory pressure, thereby producing ineffective efforts (34, 35). It is possible that these ineffective efforts were those producing arousals and awakenings because they are associated to a high inspiratory effort, which can reach the arousal threshold (36). Second, a less sensitive inspiratory trigger in the NIV_D compared with the NIV_{ICU} group could have been implicated in a lower occurrence of autotriggering with a higher occurrence rate of ineffective effort (29, 37). Nevertheless, the results of bench studies with these ventilators do not favor this hypothesis (16). Third, other factors that could contribute to ineffective triggering such as an increased inspiratory load resulting from augmented upper airway resistance (9) may have differed between groups. The higher, although nonsignificant, proportion of patients with obesity or showing sleep-related breathing disorders during SB periods in the NIV_D group compared with the NIV_{ICU} group could support this hypothesis. Although a crossover design might have been more appropriate by diminishing variability within patients, the need for a prompt discharge of patients from the ICU makes it difficult to conduct longer polysomnographic studies.

Sleep According to the Type of Ventilator

Previous studies have shown that patient–ventilator asynchrony may have a negative effect on sleep by favoring sleep fragmentation (4, 7, 9, 10). On the contrary, a recent study conducted by Fanfulla et al (38) in a stepdown unit comparing sleep patterns between patients breathing spontaneously and those on mechanical ventilation demonstrated a similar sleep quality between groups despite an ineffective effort index of 45 ± 66 events/hr associated with 10% of total arousals in the ventilated group (38). Similarly, our study showed no difference in sleep quality regarding the type of ventilator used. Even if a higher prevalence of patient–ventilator asynchrony and asynchrony-related sleep fragmentation was found in the NIV_D group compared with the NIV_{ICU} group, the total sleep fragmentation was similar. One possible explanation is the higher noise-related fragmentation in the NIV_{ICU} group compared with the NIV_D group. The higher number of noise peaks in the former group might be the result of a higher alarm noise in a group of ventilators generally used for invasive ventilation in severely ill patients, but the role of other external noncontrolled sources of noise cannot be determined. Apart from noise, many other noncontrolled factors such as pain, staff interruptions, or light (2, 3) might be implicated in this similar sleep disruption between groups. Furthermore, because critically ill patients have frequent arousals and awakenings, the possibility that some of them may mistakenly be attributed to noise or to patient–ventilator asynchrony cannot be excluded. Because the power of this study is quite limited, larger studies may be needed to definitively evaluate the impact of patient–ventilator

interactions on sleep and to establish the superiority of one type of ventilator over another for critically ill patients on NIV.

Clinical Implications

Our data suggest that patients admitted to the ICU for AHRF can sleep reasonably well during NIV sessions and that sleep is better preserved during NIV periods when compared with unassisted SB. With the nighttime being more conducive to sleep resulting from the occurrence of fewer environmental factors and the fact that sleep has a deleterious effect on respiratory failure (24), we suggest that ventilatory support should be given during the night in patients admitted for AHRF provided that it is well tolerated. The choice of the ventilator should be adapted individually, but either the NIV_{ICU} in the NIV mode or the NIV_D can be used.

CONCLUSIONS

We have shown that sleep quality was similar regardless of the type of ventilator used, although more sleep fragmentation related to patient–ventilator asynchrony was found in the NIV_D group compared with the NIV_{ICU} group. More importantly, patients admitted to the ICU with AHRF for NIV treatment can sleep when they are receiving NIV. Maintaining NIV treatment during the night does not impede sleep.

ACKNOWLEDGMENT

We appreciate the support and collaboration of the nursing staff.

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RESULTADOS

PUBLICACIÓN Nº1

Contou D, Fragnoli C, **Córdoba-Izquierdo A**, Boissier F, Brun-Buisson C, Thille AW. *Noninvasive ventilation for acute hypercapnic respiratory failure: intubation rate in an experienced unit.* Respiratory Care 2013;58(12):2045-2052.

Durante un periodo de 3 años se realizó VNI como primera intención en 242 pacientes con IRAH (excluidos los pacientes con orden de no intubación). Las causas de VNI fueron la descompensación de una patología respiratoria crónica (*AOCRF,* de *acute on chronic respiratory failure*) en 146 casos (60%), el edema pulmonar cardiogénico en 67 (28%) y la IRAH *de novo* en 29 (12%). La mayor parte de los pacientes con *AOCRF* tenían una AEPOC (n = 99) y la mayoría de los *de novo* tenían neumonía (n = 24).

La tasa de IET global fue del 15%. El grupo de pacientes con edema cardiogénico presentó la tasa más baja (4%) y el grupo con IRAH *de novo* la más alta (38%). El grupo de pacientes con *AOCRF* presentó una tasa de IET del 15%, sin diferencia entre las AEPOC y otras causas de *AOCRF*.

Los factores independientes asociados con un fracaso de VNI en el momento de la admisión fueron la causa *de novo* de la IRAH y la taquipnea (> 30 respiraciones/ minuto). Por el contrario, la disminución del nivel de conciencia previa al inicio de la VNI no se identificó como factor independiente de fracaso de la VNI en el análisis multivariado.

Los factores asociados con un fracaso de VNI tras 1 hora de ventilación fueron la hipoxemia severa (PaO_2/FiO_2 < 200 mmHg) y la acidosis severa (pH < 7.30).

No se obtuvieron diferencias entre los parámetros de ventilación, las variables respiratorias, el grado de fuga ni el nivel de tolerancia entre los pacientes que fracasaron y los que no fracasaron a la VNI. El volumen corriente fue discretamente menor en el grupo de pacientes que fracasó con la VNI con respecto a los que no (415 mL vs. 475 mL, p = 0.06) sin que la diferencia tuviera significación estadística.

PUBLICACIÓN Nº 2

Carteaux G, Lyazidi A, **Córdoba-Izquierdo A**, Vignaux L, Jolliet P, Thille AW, Richard JC, Brochard L. *Patient-ventilator asynchrony during noninvasive ventilation: a bench and clinical study.* Chest. 2012;142(2):367-376.

Este estudio consta de dos partes: una primera parte, realizada en laboratorio, en la que se evalúan diferentes tipos de ventiladores con un pulmón artificial y un modelo de fuga calibrada; y una segunda parte, clínica, cuyo objetivo es evaluar si las diferencias encontradas en el laboratorio se reproducen en clínica.

En el estudio de laboratorio se compararon 19 ventiladores en diferentes condiciones de fuga: 8 ventiladores convencionales de UCI, 5 ventiladores de transporte y 6 ventiladores específicos de VNI. La primera condición generaba una fuga continua, inspiratoria y espiratoria, que dio lugar a *auto-triggering* en la mayoría de los ventiladores de UCI y de transporte sin activación del *modo VNI.* Al activar el *modo VNI* la capacidad de corregir los *auto-triggerings* fue muy heterogénea de un ventilador a otro. Por el contrario, los ventiladores específicos de VNI no dieron lugar a *auto-triggering*. En la segunda condición se simuló una fuga únicamente inspiratoria en cuya presencia la mayoría de los ventiladores de UCI y transporte presentó un incremento en el tiempo de insuflación, que se corrigió parcial o totalmente al activar el modo VNI. La fuga inspiratoria también provocó un descenso en la capacidad de presurización (evaluada mediante el PTP_{300}) en todos los ventiladores de UCI y transporte (excepto uno) que la activación del *modo VNI* no corrigió en la mayoría de casos. En dos ventiladores de transporte la activación del *modo NIV* dio lugar a un PTP_{300} negativo; algo que también sucedió con un ventilador específico (Vivo 40).

En el estudio clínico se evaluaron 15 pacientes que recibieron 3 sesiones de VNI de 20 minutos de duración cada una, en orden aleatorio, con un ventilador convencional de UCI sin activar el *modo VNI,* el mismo ventilador con el *modo VNI* activado y un ventilador específico de VNI. Los dos ventiladores convencionales utilizados fueron Evita XL o Evita 4 (Dräger) o Engström Carestation (GE). El ventilador específico fue BiPAP Vision (Philips Respironics). No hubo diferencias en el índice de asincronías entre el uso del ventilador convencional sin activar o activando en modo VNI (3.7% vs. 2%, $p = 0.12$);

sin embargo, el uso del ventilador específico disminuyó de forma significativa el índice de asincronías (0.5%) con respecto a las dos situaciones anteriores (p = 0.001). La asincronía más frecuente fue el *auto-triggering*, y la reducción en la incidencia de asincronías con el ventilador específico se produjo fundamentalmente a expensas de la corrección de *auto-triggerings.*

PUBLICACIÓN Nº 3

Córdoba-Izquierdo A, Drouot X, Thille AW, Galia F, Roche-Campo F, Schortgen F, Prats-Soro E, Brochard L. *Sleep in hypercapnic critical care patients under noninvasive ventilation: conventional versus dedicated ventilators.* Critical Care Medicine. 2013;41(1):60-68.

Se estudiaron 24 pacientes que recibían VNI por IRAH, doce con un ventilador convencional con el *modo VNI* activado y 12 con un ventilador específico. Los dos ventiladores convencionales utilizados fueron Evita XL (Dräger) o Engström Carestation (GE). Ambos habían demostrado un funcionamiento similar en presencia de fuga en nuestro estudio previo de laboratorio y fueron los que se utilizaron en la parte clínica. El ventilador específico fue el V60 (Philips Respironics), que sustituye al modelo anterior BiPAP Vision utilizado en el estudio clínico previo y que presenta un funcionamiento similar a éste en banco de pruebas. Las características de los pacientes de ambos grupos fueron similares.

No hubo diferencias en la cantidad o la calidad del sueño entre los dos grupos. El tiempo de ventilación y los parámetros ventilatorios fueron también similares, excepto el volumen corriente por peso predicho que fue superior en el grupo con ventilador específico.

En cuanto a las asincronías paciente-ventilador, los pacientes con ventilador convencional presentaron más *auto-triggering*, aunque la diferencia sólo fue significativa en vigilia (0/hora vs. 16/hora, p <0.01) y no durante el sueño. Por el contrario, los esfuerzos ineficaces fueron más frecuentes con el ventilador específico, tanto durante el sueño (34/h vs. 2/h, $p< 0.01$) como durante la vigilia (6/hora vs. 0/hora, $p= 0.02$). La fragmentación del sueño asociada a asincronías fue mayor en los pacientes con ventilador específico que en los pacientes con ventilador convencional, con el 28% de los despertares y micro-despertares asociados a asincronías en primer grupo vs. 14% en el segundo grupo, $p= 0.02$. Sin embargo, la fragmentación del sueño asociada al ruido fue superior en el grupo de pacientes con ventilador convencional con un 8.7% de los despertares y micro-despertares asociados al ruido vs. 1.8% en los pacientes con ventilador específico ($p<0.01$).

La mayor parte del sueño se produjo durante los periodos de VNI (69% del tiempo total de sueño). La eficacia y la calidad del sueño durante estos periodos fueron superiores a los periodos de respiración espontánea, con más sueño profundo y sueño REM y menos despertares y microdespertares.

DISCUSIÓN

Publicación Nº 1: ***Noninvasive ventilation for acute hypercapnic respiratory failure: intubation rate in an experienced unit***

En este estudio evaluamos los resultados de la VNI durante un periodo de 3 años tras la instauración de un protocolo de VNI que permite al personal de enfermería ajustar los parámetros de ventilación y actuar en presencia de fuga importante. Durante el periodo analizado la tasa global de IET de los pacientes con IRAH se mantuvo por debajo del 15%. En el grupo de pacientes con edema pulmonar cardiogénico la tasa de fracaso de la VNI fue del 4%, cifra inferior al 24% reportado por Nouira[30] e idéntica a la reportada por Nava[29]. En el grupo de pacientes con AEPOC la tasa de IET fue del 15%, cifra también inferior al 20-30% descrita previamente en la literatura[5,24,27,28] y muy similar al 11% obtenida por el grupo de Carrillo y colaboradores en una publicación reciente[17]. En los pacientes con AOCRF no-AEPOC la tasa de IET fue también del 15%. Las tasas de IET reportadas en la literatura para este grupo de pacientes van del 0 al 40% cuando se analizan pacientes con hipoventilación asociada a obesidad[17,19,70,71] y pueden llegar hasta el 65% cuando se trata de otras patologías respiratorias crónicas que cursan con IRAH[21,28,31]. En los pacientes con IRAH *de novo* la tasa de IET fue marcadamente superior a la de los grupos anteriores (38%) y es concordante con los resultados de otros trabajos[28].

En cuanto a los factores predictivos de fracaso de la VNI, la severidad de la acidosis y la hipercapnia tras el inicio de la VNI ya habían sido identificadas anteriormente[25,26,31]. En nuestro estudio identificamos, además, la hipoxemia severa como un factor predictivo independiente de fracaso de VNI, probablemente porque incluimos pacientes con diferentes etiologías de IRAH como la neumonía. La tolerancia a la VNI había sido previamente identificada como un potente factor predictivo de fracaso de la VNI en una encuesta realizada en 70 UCIs de Francia[24]. En ese estudio sólo un 27% de los pacientes presentaban una buena tolerancia a la VNI y un 57% tenía una fuga importante. En nuestro estudio no hallamos relación entre tolerancia a la VNI o el nivel de fuga y el fracaso de la ventilación, probablemente porque la mayoría de nuestros pacientes (un 86% de ellos) presentaba una buena tolerancia a la VNI y sólo un 10% un alto grado de fuga.

En lo que respecta a los parámetros de ventilación como potenciales factores implicados en el éxito o fracaso de la VNI no hallamos diferencias entre los pacientes que fracasaron y los que no fracasaron con la VNI. Sin embargo el grupo "fracaso" presentó un volumen corriente discretamente menor, lo cual podría traducir la necesidad de fijar un objetivo de volumen corriente superior en los pacientes con alto riesgo de fracaso.

La presencia de un nivel de conciencia disminuido en el momento de la admisión no se estableció como un factor predictivo de fracaso de la VNI. De los 60 pacientes que presentaban disminución del nivel de conciencia en el momento de ingreso sólo un 23% requirió IET y de los 15 pacientes que ingresaron con coma (definido por una puntuación Glasgow ≤ 8) sólo 3 precisaron IET. Aunque la utilización de la VNI en estos pacientes está contraindicada por las guías internacionales[4] ningún estudio aleatorizado ha evaluado el papel de la VNI en los pacientes con depresión del nivel de conciencia, puesto que han sido sistemáticamente excluidos de los ensayos clínicos. Nuestros resultados y otras experiencias previas reportadas en la literatura[33-35] apoyan la utilización inicial de la VNI en pacientes IRAH y depresión del nivel de conciencia y recurrir a la IET si la evolución no es favorable en las horas siguientes a su inicio.

Es muy probable que el protocolo de actuación sea el responsable de la buena tolerancia de los pacientes a la VNI y de la baja tasa de fracaso de la VNI. Sería interesante descartar el papel que juega la dilatada experiencia del personal que conforma la unidad en la práctica de la VNI comparando estos resultados con los obtenidos por el mismo grupo los años previos a la instauración del protocolo. Es probable que de la misma manera que los protocolos de destete y de sedación durante la VMI han permitido reducir el tiempo de VMI[72] los protocolos de VNI permitan reducir la tasa de intubación.

Publicación Nº 2: ***Patient-ventilator asynchrony during noninvasive ventilation. A bench and clinical study***

En este estudio evaluamos de forma independiente el efecto de la fuga inspiratoria y espiratoria sobre el *trigger* inspiratorio, la presurización y el ciclado en diferentes tipos de ventiladores. En los ventiladores convencionales de UCI y en los ventiladores de transporte la fuga espiratoria provoca una alteración de la función del *trigger* y la fuga

inspiratoria una disminución de la capacidad de presurización y un retraso del ciclado en comparación con su evaluación en ausencia de fuga. La activación del *modo VNI* en estos ventiladores produce una respuesta heterogénea y diferente para cada ventilador, como ya mostraron estudios previos[44,46,73,74]. Esta heterogeneidad nos impide extraer conclusiones generales y nos obliga a considerar cada ventilador de forma individualizada. Por el contrario, los ventiladores específicos de VNI han demostrado un comportamiento más homogéneo durante su evaluación en laboratorio, con capacidad para evitar el *auto-triggering* o el retraso de ciclado pese a las fugas. Estos resultados están en consonancia con los obtenidos en dos estudios previos que mostraron una mejor capacidad de sincronización de un ventilador especifico (también BiPAP Vision) comparado con varios ventiladores de UCI con[44] o sin[45] la activación del *modo VNI*.

Hasta la fecha, ningún modelo de laboratorio que evalúe la sincronización paciente-ventilador durante la VNI ha sido validado clínicamente, lo cual pone en cuestión la relevancia clínica de sus resultados en los pacientes críticos. En nuestro estudio mostramos que los resultados que obtuvimos en el laboratorio se reprodujeron en el estudio clínico, probablemente porque los ventiladores que utilizamos en el estudio clínico mostraron el mismo comportamiento ante la fuga cuando se evaluaron en el laboratorio. Esta consistencia de los resultados clínicos y de laboratorio confiere una validez clínica al modelo de laboratorio.

El impacto del *modo VNI* en la incidencia de asincronías paciente-ventilador en clínica sólo ha sido evaluado anteriormente por otro estudio. Vignaux y colaboradores[49] evaluaron la incidencia de asincronías paciente ventilador en 65 pacientes usando ventiladores de UCI. Sin activar el *modo VNI* el 46% de pacientes presentaban una elevado índice de asincronías (definida como >10% de los ciclos). La activación del *modo VNI* no redujo de forma significativa la proporción de pacientes con asincronía grave, pero sí permitía disminuir la incidencia de asincronías relacionadas con la fuga. En nuestro estudio tampoco hallamos diferencias significativas en el índice de asincronías entre ambos grupos (ventiladores de UCI con y sin activación del *modo VNI*). Con respecto a los resultados del estudio previo la proporción de pacientes con asincronía severa fue menor (27% de los pacientes sin activación del *modo VNI* y 13% con activación del *modo VNI*) porque la incidencia de asincronías fue menor. Esta menor incidencia de asincronía severa podría explicarse por varias razones: 1. El nivel de

asistencia y el volumen corriente en nuestro estudio fueron inferiores, lo cual podría explicar la menor incidencia de esfuerzos ineficaces y ciclos prolongados. 2. La definición de ciclado prematuro fue modificada en nuestro estudio puesto que consideramos que la usada en el estudio de Vignaux y col. (cualquier tiempo de insuflación inferior al tiempo inspiratorio del paciente) era demasiado sensible en términos de relevancia clínica. Esto ha conducido a reconocer menos ciclos prematuros y a que el índice de asincronías sea menor. 3. Los ventiladores usados en nuestro estudio clínico son propensos al *auto-triggering* en presencia de fuga espiratoria pero no producen retraso de ciclado en presencia de fuga inspiratoria según los resultados laboratorio. Es probable por ello que la incidencia de ciclos prolongados sea menor (y con ella también el índice de asincronías global) que en los estudios que utilizan otros ventiladores. 4. La asincronía grave (índice de asincronías >10%) en nuestro estudio se debe fundamentalmente a la alta incidencia de *auto-triggering*, reflejando más la capacidad del ventilador de funcionar en presencia de fuga que a los parámetros de ventilación.

De acuerdo con los resultados obtenidos en este estudio el ventilador específico permite una mejor sincronización paciente-ventilador. Sin embargo, aunque ningún paciente mostró un índice de asincronía >10% con el ventilador específico, sólo unos pocos lo mostraron con los ventiladores convencionales. La relevancia clínica de estas diferencias se desconoce.

Publicación Nº 3: ***Sleep in acute hypercapnic critical care patients under noninvasive ventilation: conventional versus dedicated ventilators***

De acuerdo a los resultados obtenidos en el estudio anterior y sabiendo que la ventilación mecánica y las asincronías paciente-ventilador pueden afectar a la calidad del sueño de los pacientes ventilados[52,61,63,65] nos planteamos si el uso de un ventilador específico de VNI podía disminuir el número de asincronías paciente-ventilador y mejorar la calidad del sueño en comparación con los ventiladores convencionales. En el estudio que llevamos a cabo, sin embargo, no demostramos la superioridad del ventilador específico frente a los ventiladores convencionales en disminuir el número de asincronías ni en mejorar la calidad del sueño.

Los pacientes con ventilador convencional mostraron una mayor frecuencia de *auto-triggering* comparado con el grupo de ventilador específico. Este resultado es concordante con el estudio previo y con otros estudios de laboratorio[44,45]. Por el contrario, el grupo ventilado con el ventilador específico presentaba más esfuerzos ineficaces. Es posible que varios factores hayan contribuido a ello: 1. Un mayor volumen corriente puede dar lugar a hiperinsuflación dinámica, aumento de la PEEPi y consecuentemente esfuerzos ineficaces[51,75]. 2. Unas características técnicas del ventilador, con un *trigger* poco sensible, que para evitar el *auto-trigger* podría favorecer los esfuerzos ineficaces[53,76]. Sin embargo los resultados de nuestro estudio previo en el laboratorio no apoyan esta hipótesis. 3. Un aumento de la carga inspiratoria debido a una mayor resistencia de la vía aérea superior[52] podría haber sido diferente entre los dos grupos: los pacientes del grupo ventilador específico eran más obesos y tenían una mayor incidencia de trastornos respiratorios durante el sueño (ie, índice de apnea-hipopnea > 10 /hora) durante la respiración espontánea, aunque estas diferencias no fueron estadísticamente significativas. Desafortunadamente no se llevó a cabo un estudio cruzado que habría minimizado las diferencias inter-grupales al recibir cada paciente los dos tratamientos.

El número de asincronías paciente-ventilador en este tercer estudio es también bajo. Fanfulla reportó 62.5 esfuerzos ineficaces/hora de sueño en un grupo de 9 pacientes con enfermedad neuromuscular[52] y 48 esfuerzos ineficaces/hora en otro grupo de 48 pacientes con insuficiencia respiratoria crónica[77]. En ambos casos se trataba de pacientes en situación estable y usuarios crónicos de ventilación domiciliaria. Estas cifras son claramente superiores a nuestra incidencia mediana de esfuerzos ineficaces que es de 13.8 (1 - 41) eventos /hora para el total de 24 pacientes estudiados y que aumenta hasta 34 (15-125) esfuerzos ineficaces/hora en el grupo que mostró una incidencia más alta. En comparación con estudios que evalúan la incidencia de asincronías durante la vigilia en situación de insuficiencia respiratoria aguda nuestros valores son también bajos. Mulqueeny[78] reporta una incidencia de esfuerzos ineficaces de 180 ± 96 /hora y la comparación con otros estudios se antoja difícil puesto que muchos de ellos dan datos de índice de asincronías (definido como Nº de eventos/Nº ciclos ventilador+esfuerzos ineficaces)[49,54].

La ausencia de diferencias en la calidad del sueño entre los dos grupos de nuestro estudio puede deberse a varios factores: 1. El índice de fragmentación fue igual en los dos grupos, probablemente porque el grupo con el ventilador convencional presenta más picos de ruido ambiente y más despertares y microdespertares asociados, lo cual puede haber anulado las diferencias 2. Otros factores no controlados (dolor, luz, cuidados proporcionados por enfermería, etc.) pueden haber contribuido a la similitud en la fragmentación del sueño en los dos grupos. Es posible, incluso, puesto que los pacientes críticos presentan un sueño muy fragmentado, que hayamos atribuido erróneamente algunos de los despertares y microdespertares a los eventos "ruido" o "asincronía paciente-ventilador". 3. Cabe por último considerar la posibilidad que las asincronías paciente-ventilador no tengan un gran efecto sobre la calidad del sueño de los pacientes críticos. Fanfulla et al.[79] demostraron recientemente, en una unidad de post-agudos, que la ventilación mecánica no suponía la causa principal de la fragmentación del sueño. La calidad del sueño fue similar entre los pacientes ventilados y los pacientes no ventilados; y las asincronías paciente-ventilador (45 ± 66 esfuerzos ineficaces/hora) en el primer grupo suponían tan sólo un 10% de la fragmentación del sueño. De forma similar, Alexopoulou y colaboradores[80] tampoco lograron demostrar una mejor calidad del sueño en los pacientes ventilados con el modo PAV+ (*propoprtional asssist ventilation Plus*) pese a una mejor sincronización paciente-ventilador en comparación con la ventilación en modo presión de soporte.

El resultado más interesante del tercer estudio, sin embargo, es que los pacientes son capaces de dormir mientras reciben ventilación y la mayor parte del sueño acontece durante el periodo VNI. Incluso parece que la calidad del sueño en estos periodos es superior a la de los periodos de respiración espontánea. Este resultado, a pesar de su interés, tiene que ser considerado con reservas puesto que los periodos VNI y respiración espontánea no se aleatorizaron y existen varios factores de confusión que pueden haber favorecido una mejor calidad de sueño durante los periodos de VNI. El primero, que la VNI se administraba fundamentalmente durante la noche cuando las condiciones ambientales favorecen el sueño del paciente. El segundo, que los pacientes, muchos de ellos afectos de síndrome de apneas del sueño o insuficiencia respiratoria crónica de diversas etiologías, pueden haberse beneficiado del efecto que la VNI tiene sobre su sueño[81-83].

CONCLUSIONES

▪ Las tasas de fracaso de la VNI y necesidad de IET en pacientes con IRAH pueden reducirse por debajo del 15% cuando se lleva a cabo en una unidad experimentada y de acuerdo a un protocolo de actuación.

▪ La VNI debería intentarse en todos los pacientes con IRAH, incluso cuando el riesgo de fracaso es alto por la presencia de coma o la ausencia de una patología respiratoria subyacente.

▪ La activación del *modo VNI* en los ventiladores convencionales de UCI permite mejorar de forma parcial la sincronización con la respiración del paciente. Sin embargo cada ventilador debe ser considerado de forma individual dada la gran variabilidad en la capacidad de funcionamiento de estos algoritmos.

▪ Los ventiladores específicos de VNI permiten una mejor sincronización paciente-ventilador en presencia de fugas que los ventiladores convencionales de UCI cuando ambos tipos de ventiladores se comparan en un banco de pruebas y en un estudio fisiológico a corto plazo.

▪ La calidad del sueño de los pacientes críticos que reciben VNI por IRAH no se ve afectada por el tipo de ventilador utilizado.

▪ La VNI no impide el sueño de los pacientes críticos con IRAH e incluso podría contribuir a mejorar su calidad.

▪ Tanto los ventiladores convencionales como los ventiladores específicos pueden ser utilizados en los pacientes con IRAH, sin que nuestros resultados nos permitan recomendar uno más que otro.

VERSION RESUMÉE EN LANGUE FRANÇAISE

JUSTIFICATION

La ventilation non-invasive (VNI) s'est largement développée dans les services de réanimation et le nombre de patients traités pour insuffisance respiratoire aiguë (IRA) a augmenté de façon significative depuis les 20 dernières années. Plusieurs études ont cherché à identifier les facteurs d'échec de la VNI conduisant à l'intubation et la mise sous ventilation mécanique invasive. D'autres travaux se sont focalisés sur les réglages du ventilateur, afin d'optimiser la synchronisation avec le patient et favoriser la réussite de la technique, ou l'évaluation de la qualité du sommeil malgré la poursuite du traitement par VNI. En VNI, les asynchronies patient-ventilateur sont fréquentes et sont dues à la présence de fuites autour du masque de ventilation. Les ventilateurs ont développé des algorithmes afin de détecter puis de compenser ces fuites et enfin d'améliorer la synchronisation patient-ventilateur. Cependant, leurs performances sont très inégales d'un ventilateur à l'autre, aussi bien leur capacité de pressurisation que leur capacité de synchronisation. À ce jour, peu d'études se sont intéressées à montrer des différences entre les ventilateurs et surtout déterminer si un ventilateur plus performant pourrait améliorer le confort du patient.

Dans ce contexte, nous avons décidé d'évaluer la VNI sur 2 aspects. Premièrement d'un point de vue technique, afin de comparer les performances des ventilateurs en présence de fuites. Et deuxièmement d'un point de vue clinique, afin d'évaluer l'impact de la performance des ventilateurs sur des variables physiologiques comme la synchronisation patient-ventilateur et le sommeil. Finalement, nous avons également analysé le taux d'échec de la VNI et les facteurs prédictifs d'échec grâce à l'évaluation d'une cohorte de patients hypercapniques traités par de la VNI pour insuffisance respiratoire aiguë.

Cette thèse expose les résultats de ces différents travaux.

INTRODUCTION

I. VNI et insuffisance respiratoire aigue

L'insuffisance respiratoire aiguë (IRA) est caractérisée par une altération des échanges gazeux et une augmentation du travail respiratoire. La ventilation mécanique permet d'améliorer les échanges gazeux et de mettre au repos les muscles respiratoires. Elle peut être administrée de façon invasive après intubation par l'intermédiaire d'une sonde endotrachéale, ou de façon non-invasive (VNI) par l'intermédiaire d'un masque. La VNI permet de réduire les complications associées à la ventilation invasive, notamment les complications infectieuses et particulièrement les pneumonies qui sont fréquentes après l'intubation[1-3].

Tandis que chez les patients ayant une IRA hypoxémique par un syndrome de détresse respiratoire aiguë ou par une pneumonie l'utilisation de la VNI reste controversée[4], chez hypercapniques elle est largement utilisée. Les patients ayant une décompensation de bronchopathie chronique obstructive (BPCO) et qui présentent une IRA hypercapnique (IRAH) sévère sont ceux qui bénéficient le plus de la VNI[5-7]. Il a été montré que la VNI réduisait le taux d'intubation et améliorait la survie de ces patients[5,6]. Le traitement de première intention par VNI est donc une recommandation forte chez les patients qui présentent une décompensation de BPCO avec IRAH[4]. L'insuffisance cardiaque constitue la deuxième indication la plus fréquente pour la VNI dans la pratique clinique[11]. La pression positive délivrée par la VNI permet de rouvrir les alvéoles collabés (augmentation de la capacité résiduelle fonctionnelle du poumon), réduire le shunt et améliorer l'oxygenation[12]; et permet aussi d'améliorer les conditions hémodynamiques[12]. De plus, l'assistance ventilatoire fournit par le ventilateur permet également de réduire le travail des muscles respiratoires[13]. Plusieurs études randomisées ont comparé la pression positive continue (PPC) ou *continuous positive airway pressure* (CPAP) avec la VNI avec une assistance respiratoire à 2 niveaux de pression en aide inspiratoire sans montrer aucune différence dans le taux d'intubation ou la mortalité, même chez les patients hypercapniques[14-16]. D'autres maladies sont à l'origine d'une IRAH comme le syndrome d'hypoventilation obésité, les maladies restrictives de la caisse thoracique et les maladies neuromusculaires. Il n'y a pas d'études randomisées qui évaluent l'efficacité de la VNI pour les décompensations

aigues de ces maladies mais des études observationnelles et cas-contrôle soutiennent l'utilisation[17-21].

Malgré l'utilisation croissante de la VNI dans les unités de réanimation[22-24] le taux d'echec reste élevé: entre 20 et 30% chez les patients BPCO[5,25-28], entre 4 et 24% chez les patients avec un œdème pulmonaire cardiogénique[29,30] et plus de 30-40% chez les autres patients ayant une IRAH d'une étiologie différente[24,28,31]. La sévérité de l'hypercapnie et/ou l'acidose après le début de la VNI sont les facteurs prédictifs habituels d'échec de la VNI chez les patients BPCO[25,26,28,31,32]. Une diminution du niveau de conscience constitue aussi un risque d'échec pour les BPCO[25,26,28] et le coma est une contrindication classique de la VNI en raison du risque potentiel d'inhalation. Néanmoins, plusieurs publications récentes rapportent des résultats positifs quand la VNI est administrée chez des patients ayant une encéphalopathie et même un coma d'origine hypercapnique[33-35]. Cependant, ces résultats sont retrouvés par des équipes particulièrement entrainées dans un environnement de réanimation avec la possibilité d'intubation immédiate en cas de complication. La tolérance à la VNI a été aussi identifiée comme un facteur prédictif d'échec de la VNI[24,36].

II. Aspects techniques de la ventilation mécanique

Les deux principaux systèmes de pressurisation utilisés pour générer un débit de gaz sont les gaz muraux et les turbines. La plupart de ventilateurs de transport et les ventilateurs de domicile utilisent des turbines. Une turbine fonctionne comme un compresseur : elle génère une certaine pression qui dépend de sa vitesse de rotation. Ce système est particulièrement adapté pour les modes ventilatoires en pression puisqu'elle délivre une pression constante pour une vitesse donnée, mais aussi pour le transport des patients puisqu'elle ne dépend pas des gaz muraux. Les ventilateurs conventionnels de réanimation, par contre, utilisent du gaz muraux et la présence d'une servovalve en aval permet de contrôler le débit délivré.

Le mode de ventilation le plus fréquemment utilisé pour la VNI en réanimation est le mode aide inspiratoire (AI) en pression. C'est un mode spontané-assisté dans lequel chaque insufflation est activée avec l'effort inspiratoire du patient (spontané) et chaque respiration est assistée par une quantité de pression déterminée facilitée par le ventilateur (assisté). À chaque insufflation le ventilateur délivre un certain débit de gaz

pour atteindre la pression consigne (pression inspiratoire) puis il met fin à l'inspiration et permet l'expiration passive du patient. Le cycle d'un ventilateur en mode aide inspiratoire peut entre divisé par trois phases :

Première phase : le *trigger* inspiratoire. L'effort du patient est détecté par le ventilateur soit par une dépression (*trigger* en pression) soit par une variation de débit (*trigger* en débit) dans le circuit. Un délai de déclenchement rapide et une faible dépression sont le témoin d'un *trigger* performant (très sensible). En pratique clinique, les *triggers* en débit sont plus sensibles que les *triggers* en pressions, et permettent de réduire l'effort du patient[37,38]. Cependant, le travail respiratoire lié au *trigger* inspiratoire ne représente pas plus de 10 à 15% de l'effort du patient[38].

Deuxième phase : l'aide inspiratoire et la pente de montée en pression. Le niveau d'aide inspiratoire est l'assistance proportionnée par le ventilateur et le temps pour atteindre la pression réglée est la pente de montée en pression. Plus grand est le niveau d'aide inspiratoire[39,40] et plus rapide est la pente de montée en pression[41], plus l'effort du patient est réduit, mais aussi plus de fuite aérienne et plus d'inconfort[41,42].

Troisième phase : c'est la fin de l'inspiration (cyclage ou *trigger* expiratoire). La fin de l'inspiration survient quand le débit chute en dessous d'une valeur seuil qui correspond à un certain pourcentage du débit maximal insufflé (généralement 25% du débit maximal).

III. Effets des fuites et impact sur la synchronisation patient-ventilateur

Les fuites autour du masque sont quasiment inéluctables et sont une des caractéristiques intrinsèques de la VNI. D'une façon générale, les fuites provoquent un retard de détection de l'effort du patient (allongement du *trigger* inspiratoire), une altération de la capacité de pressurisation, et un retard à l'expiration. Les fuites inspiratoires peuvent provoquer des inspirations prolongées tandis que les fuites expiratoires peuvent produire des auto-déclenchements[43-47]. Des études réalisées sur banc ont montré que les ventilateurs dédiés à la VNI étaient plus performantes que les ventilateurs de réanimation[44,45,48]. Cependant, les nouvelles générations de ventilateurs de réanimation se sont adaptés et ont développés des algorithmes de fonctionnement intégrant un *mode VNI* qui permet de minimiser l'effet des fuites et d'améliorer la

synchronisation patient-ventilateur. Cependant, les résultats obtenus avec l'activation du *mode VNI* sur les ventilateurs de réanimation sont très hétérogènes[44,46,49].

Idéalement, le ventilateur devrait détecter l'effort du patient le plus rapidement possible, et lui délivrer une assistance ventilatoire synchronisée au cours du temps inspiratoire neural (véritable temps inspiratoire du patient). À l'heure actuelle, une synchronisation parfaite entre le patient et le ventilateur n'existe pas et voici les principales asynchronies qui peuvent être observées:

Les efforts inefficaces sont des efforts générés par le patient mais non détectés par le ventilateur. Ils sont favorisés par certaines caractéristiques liées au patient et par certains réglages. Il surviennent préférentiellement chez des patients ayant un trouble ventilatoire obstructif et qui présentent une pression expiratoire positive intrinsèque (PPEPi)[51]. Cette PEEPi augmente l'effort nécessaire pour déclencher le ventilateur et favorise la survenue d'efforts inefficaces. Ils peuvent survenir aussi en cas de faiblesse musculaire comme au cours des maladies neuromusculaires[52], ou d'une myopathie acquise en réanimation, ou lors d'une inhibition de la commande respiratoire centrale (sédation, alcalose, hyperventilation[53]). Les réglages du ventilateur peuvent aussi favoriser les efforts inefficaces. C'est le cas si le seuil de *trigger* inspiratoire est trop dur ou si le niveau d'assistance est trop élevé. En effet, la fréquence des efforts inefficaces augmente quand le niveau d'assistance ventilatoire augmente, du fait d'un plus grand volume courant (qui favorise la PEEPi) et d'une inhibition de la commande ventilatoire centrale (qui diminue l'intensité de l'effort)[51,53]. Les fuites autour du masque favorisent aussi la survenue d'efforts inefficaces. Il a été montré que le niveau de fuite était plus important chez les patients qui présentaient des efforts inefficaces[54]. Il est probable que les efforts inefficaces soient la conséquence des insufflations prolongées lors des fuites inspiratoires. En effet, lorsque l'insufflation se prolonge, le patient fait des efforts que le ventilateur n'est pas capable de détecter.

Les insufflations prolongées surviennent si le temps d'insufflation du ventilateur est pus long que le temps inspiratoire du patient. C'est l'asynchronie la plus fréquente en VNI[43,54] et survient en présence de fuite autour du masque en fin d'inspiration. Au cours de l'inspiration, le débit d'insufflation du ventilateur diminue progressivement et l'expiration survient quand la valeur du débit chute en dessous de la valeur du *trigger*

expiratoire. Si le débit de fuite est supérieur à celui du *trigger* expiratoire, alors le ventilateur n'atteint jamais le débit correspondant au *trigger* expiratoire et l'inspiration se prolonge jusqu'au temps inspiratoire maximal[43]. Limiter le temps inspiratoire maximal[43], augmenter le seuil de *trigger* expiratoire[55] et diminuer la fuite non-intentionnelle peuvent diminuer l'incidence de cycles prolongés.

Les auto-déclenchements sont des cycles délivrés par le ventilateur en absence d'effort du patient. Ils surviennent lorsqu'il existent des fuites expiratoires et quand la valeur du *trigger* inspiratoire est très sensible[47]. En effet, en cas de fuites télé-expiratoires, une dépression survient dans le masque, qui peut être reconnue par le ventilateur comme un effort du patient. Si cette dépression et donc cette variation de débit est supérieure au *trigger* inspiratoire réglé alors le ventilateur déclenche un cycle auto-déclenché.

Les double-déclenchements correspondent à deux cycles inspiratoires successifs séparés par un temps expiratoire inexistant ou très court. Ils surviennent quand la demande ventilatoire du patient est importante et que le temps d'insufflation du ventilateur est trop court, ou l'assistance insuffisante[53,54]. L'effort du patient n'est pas terminé à la fin du premier cycle et il déclenche donc un deuxième cycle ventilateur.

Le cycle prématuré ou cycle court c'est un cycle ventilateur qui se termine avant la fin du temps inspiratoire neural. Ils surviennent généralement chez des patients ayant une compliance du système respiratoire très abaissée[56]. Dans ce cas, le débit d'insufflation chute très rapidement en dessous de la valeur seuil du *trigger* expiratoire et le ventilateur ouvre sa valve expiratoire trop précocement.

IV. Incidence et conséquences des asynchronies patient-ventilateur

Les asynchronies patient-ventilateur sont très fréquentes au cours de la ventilation mécanique. Environ 25% des patients en ventilation invasive[53] et 43% des patients sous VNI pour IRA[54] présentent des asynchronies fréquentes (i.e., supérieure à 10% des cycles). Dans l'étude de Vignaux et al.[54] le niveau de fuite et le niveau d'aide inspiratoire étaient 2 facteurs associés à une incidence d'asynchronies élevée. Une étude ultérieure conduite par la même équipe a comparé l'index d'asynchronies chez un groupe de 65 patients sous VNI avec des ventilateurs de réanimation après l'activation ou non du *mode VNI*[49]. Le *mode VNI* permettait de réduire la fréquence des asynchronies liées aux

fuites, *i.e.* les auto-déclenchements, les efforts inefficaces et les cycles prolongés, mais la fréquence globale des asynchronies n'était pas significativement réduite, probablement parce que l'activation du *mode VNI* augmentait l'incidence des cycles prématurés.

Alors qu'en ventilation invasive, les patients qui présentent des asynchronies fréquentes ont une durée de ventilation prolongée[53], en VNI les effets potentiellement délétères des asynchronies n'ont jamais été identifiés. Dans l'étude de Vignaux et al.[54] le taux d'intubation et la mortalité étaient similaires entre les patients avec des asynchronies fréquentes et les autres. Cependant, dans cette étude et dans une autre plus récente[57], le confort et la tolérance des patients qui présentaient des asynchronies fréquentes étaient moins bons. Étant donné que la bonne tolérance à la VNI est un facteur déterminant de réussite[36] il est possible que la réduction des asynchronies puisse avoir un impact sur le succès de la technique.

V. Impact de la ventilation mécanique sur le sommeil

La qualité du sommeil est très altérée chez les patients de réanimation, aussi bien par sa distribution que par son architecture[58-60]. La ventilation mécanique est un des facteurs qui peut altérer la qualité du sommeil[52,61-63]. Certaines études ont montré que les asynchronies patient-ventilateur pouvaient également influencer la qualité du sommeil. Fanfulla et al.[52] ont retrouvé une corrélation directe entre la fréquence des efforts inefficaces et la quantité de sommeil paradoxal. L´optimisation des paramètres ventilatoires permettait de réduire les asynchronies et d'améliorer la qualité du sommeil. Bosma et al.[61] ont retrouvé chez des patients intubés une moindre incidence d'asynchronies patient-ventilateur et une meilleure qualité du sommeil en utilisant un mode assisté proportionnel. La qualité du sommeil des patients pourrait avoir une influence sur le pronostique. Roche Campo et al.[64] ont récemment montré chez des patients traités par VNI pour insuffisance respiratoire aiguë, une majeure incidence d'échec tardif de la VNI et de délirium chez ceux qui avait montré un sommeil de pire qualité avec moins de sommeil paradoxal. C'est alors possible que la diminution des asynchronies patient-ventilateur aie un effet positif sur la qualité du sommeil et sur le pronostique des patients.

HYPOTHÈSES Á L'ORIGINE DU TRAVAIL DE THÈSE

1. Dans une unité habituée à pratiquer la VNI, le taux d'intubation des patients admis pour une insuffisance respiratoire aigue hypercapnique est probablement plus faible que les 20 à 30% rapportés dans la littérature.

2. L'activation du mode VNI proposée par les ventilateurs conventionnels de réanimation ou l'utilisation de ventilateurs spécifiquement dédiés à la VNI pourraient permettre d'améliorer la synchronisation patient-ventilateur.

3. Les différences de performances entre les ventilateurs de réanimation et les ventilateurs spécifiques pourraient, via les asynchronies patient-ventilateur, avoir un impact sur la qualité de sommeil des patients admis pour une insuffisance respiratoire aigue hypercapnique.

OBJECTIFS DE LA THÈSE

1. Déterminer le taux d'échec de la VNI et les facteurs de risque d'intubation chez les patients admis en réanimation et traités par de la VNI pour une insuffisance respiratoire aigue hypercapnique.

2. Comparer les performances et l'incidence des asynchronies patient-ventilateur en fonction du type de ventilateur utilisé pour la VNI: ventilateurs conventionnels de réanimation avec ou sans activation du mode VNI, ventilateurs de transport et ventilateurs spécifiquement dédiés a la VNI. Évaluation d'abord sur banc à l'aide d'un poumon artificiel avec différentes conditions de fuite puis sur patients hospitalisés en réanimation dans le cadre d'une étude physiologique.

3. Comparer la qualité de sommeil chez les patients admis en réanimation et traités par de la VNI pour une insuffisance respiratoire aigue hypercapnique en fonction du type de ventilateur utilisé pour la VNI: ventilateur de réanimation ou ventilateur dédié à la VNI. Détecter les asynchronies patient-ventilateur et évaluer l'impact de ces asynchronies sur la qualité et notamment la fragmentation du sommeil. Comparer également la qualité du sommeil au cours des séances de VNI et au cours de la ventilation spontanée.

RÉSULTATS

La thèse repose sur les 3 travaux de recherche suivants:

PUBLICATION Nº1:

Contou D, Fragnoli C, **Córdoba-Izquierdo A**, Boissier F, Brun-Buisson C, Thille AW. *Noninvasive ventilation for acute hypercapnic respiratory failure: intubation rate in an experienced unit.* Respiratory Care 2013;58(12):2045-2052.

Nous avons analysé toutes les données recueillies après la mise en place d'un protocole infirmier dans notre service de réanimation pour la mise en route et le suivi de la VNI. Sur une période de 3 ans, 242 patients ont été admis et traités par de la VNI pour une IRAH (après exclusion des patients ayants un ordre de non intubation). Parmi eux, 146 patients avaient une maladie respiratoire chronique sous jacente (dont 99 BPCO et 48 ayant une autre maladie respiratoire), 67 patients (28%) étaient admis pour un œdème pulmonaire cardiogénique, et 29 patients (12%) pour une IRAH *de novo* sans maladie respiratoire chronique sous jacente, et dont la majorité (n = 24) présentaient une pneumonie.

Notre taux d'intubation global était de seulement 15% avec des différences significatives selon la cause de l'IRAH : 4% en cas d'œdème pulmonaire, 15% chez les patients avec une maladie respiratoire chronique sous jacente quelque soit la cause (pas de différence entre les patients BPCO et les non-BPCO), et 38% chez les patients avec une IRAH de novo.

Les facteurs indépendants associés à l'échec de la VNI à l'admission étaient la cause de l'IRHA (*de novo*) et la tachypnée (> 30 respirations /minute). Par contre, la diminution du niveau de conscience avant l'initiation de la VNI n'était pas un facteur indépendant d'échec du traitement en analyse multivariée. Après 1 heure de VNI, les facteurs indépendants associés à l'échec étaient l'hypoxémie sévère (PaO_2/FiO_2 < 200 mmHg) et l'acidose sévère (pH < 7.30). Les paramètres ventilatoires, l'importance des fuites et la tolérance à la VNI n'avaient pas d'influence sur la réussite de la VNI, excepté le volume courant discrètement inférieur dans le groupe échec (415 mL vs. 475 mL dans le groupe succès, p = 0.06).

PUBLICATION Nº 2

Carteaux G, Lyazidi A, **Córdoba-Izquierdo A**, Vignaux L, Jolliet P, Thille AW, Richard JC, Brochard L. *Patient-ventilator asynchrony during noninvasive ventilation: a bench and clinical study.* Chest. 2012;142(2):367-376.

Cette étude est constituée de 2 parties : une première étude sur banc avec un modèle de fuite calibrée pour comparer les différents types de ventilateurs, et une deuxième étude clinique pour évaluer si les différences retrouvées sur banc sont superposables en clinique.

L'étude sur banc comparait les performances de 19 ventilateurs avec différentes conditions de fuite : 8 ventilateurs de réanimation et 5 ventilateurs de transport ayant un mode VNI spécifique, et 6 ventilateurs dédiés pour la VNI. La première condition générant une fuite continue, inspiratoire et expiratoire, produisait des auto-déclenchements avec la plupart des ventilateurs de réanimation et transport quand le mode VNI n'était pas activé. Après activation du mode VNI, la correction des auto-déclenchements était très hétérogène d'un ventilateur à l'autre. Au contraire, les ventilateurs spécifiques dédiés pour la VNI ne produisaient pas d'auto-déclenchements. La deuxième condition simulant une fuite uniquement inspiratoire produisait un allongement du temps d'insufflation avec la plupart des ventilateurs de réanimation et de transport, en partie corrigées après activation du mode VNI. Les fuites inspiratoires provoquaient également une altération des capacités de pressurisation pour tous les ventilateurs de réanimation et de transport. L'activation du *mode VNI* ne permettait pas d'améliorer significativement leur capacité de pressurisation. Dans deux ventilateurs de transport l'activation du *mode VNI* a provoqué un PTP_{300} négatif; ce qui survient aussi avec un ventilateur spécifique (Vivo 40).

L'étude clinique a évalué 15 patients qui recevaient 3 séances de VNI de 20 minutes avec un ventilateur de réanimation sans activer le *mode VNI* (UCI_{VNI}-), le même ventilateur avec le *mode VNI* activé (UCI_{VNI+}) et un ventilateur spécifique dédié à la VNI (NIV_V).

Il n'y avait pas des différences en l'index d'asynchronies entre l'utilisation d'un ventilateur de réanimation sans ou avec activation du mode VNI (3.7% vs 2%, $p = 0.12$) ; néanmoins, le ventilateur dédié permettait de réduire d'une façon significative

l'incidence des asynchronies (0.5%) comparé avec un ventilateur de réanimation avec ou sans son mode VNI activé (*p*=0.001). Les auto-déclenchements étaient les asynchronies les plus fréquentes et la réduction de nombre d'asynchronies était essentiellement liée à la réduction des auto-déclenchements.

PUBLICATION Nº 3

Córdoba-Izquierdo A, Drouot X, Thille AW, Galia F, Roche-Campo F, Schortgen F, Prats-Soro E, Brochard L. *Sleep in hypercapnic critical care patients under noninvasive ventilation: conventional versus dedicated ventilators.* Critical Care Medicine. 2013;41(1):60-68.

Vingt-quatre patients traités par VNI pour une IRAH ont été étudiés. Douze étaient ventilés avec un ventilateur de réanimation avec son *mode* VNI activé, et 12 avec un ventilateur dédié pour la VNI. Les 2 ventilateurs de réanimation utilisés étaient soit un Evita XL (Dräger) ou un Engström Carestation (GE). Ces deux ventilateurs avaient montré des performances similaires dans notre étude sur banc et ce sont ceux qui sont utilisés en pratique clinique dans notre unité. Le ventilateur dédié à la VNI était le V60 de Philips (nouvelle version du modèle BiPAP Vision utilisé dans l'étude préalable sur banc et qui présente des performances similaires). Les 2 groupes de patients présentaient des caractéristiques similaires.

Concernant la quantité et la qualité du sommeil, aucune différence n'a été mise en évidence entre les 2 groupes. Le temps de ventilation et les paramètres ventilatoires étaient également identiques, excepté le volume courant expiré qui était supérieur parmi les patients ventilés avec un ventilateur dédié. Les auto-déclenchements étaient plus fréquents avec les ventilateurs de réanimation qu'avec les ventilateurs dédiés mais la différence n'était significative que pendant la veille (0/heure vs. 16/heure, p <0.01) et non pendant le sommeil. Les efforts inefficaces étaient au contraire plus fréquents avec les ventilateurs dédiés, et ce, aussi bien pendant le sommeil (34/heure vs. 2/heure, p<0.01) que pendant la veille (6/heure vs. 0/heure, p= 0.02). La fragmentation du sommeil liée aux asynchronies était plus fréquente avec les ventilateurs dédiés qu'avec les ventilateurs de réanimation (28% des éveils et micro-éveils étaient liés aux

asynchronies dans le groupe de patients ventilés avec un ventilateur dédié vs. 14% dans le groupe ventilateur de réanimation, p= 0.02). Cependant, la fragmentation du sommeil liée au bruit était supérieur chez les patients ventilés avec un ventilateur de réanimation qui montrait le 8.7% des éveils et micro-éveils liés au bruit vs. 1.8% chez les patients avec un ventilateur dédié, $p < 0.01$.

Soixante-neuf pourcent du temps total de sommeil survenait pendant les périodes de VNI. Dans ces périodes, l'efficacité et la qualité du sommeil étaient supérieures aux périodes de respiration spontanée, avec plus de sommeil profond et de sommeil paradoxal, et moins d'éveils et micro-éveils.

DISCUSSION

Publication Nº 1: ***Non-invasive ventilation for acute hypercapnic respiratory failure: intubation rate in an experienced unit***

Dans cette étude nous avons évalué les résultats de la VNI sur une période de 3 ans après la mise en place d'un protocole de VNI permettant aux infirmières d'optimiser les paramètres ventilatoires et d'agir en présence de fuites importantes. Pendant la période analysée le taux global d'IET des patients atteints par une IRAH s'est maintenu en dessous du 15%. Chez les patients avec un œdème pulmonaire cardiogénique le taux d'échec de la VNI était de 4%, chiffre inférieur au 24% rapporté par Nouira[30] et identique à cela rapporté par Nava[29]. Chez les DBPCO le taux d'IET était de 15%, chiffre aussi inférieur au 20-30% rapporté préalablement dans la littérature[5,24,27,28] et très similaire au 11% obtenue par le groupe de Carrillo et collaborateur dans une publication récente[17]. Dans ce travail[17] le taux d'échec chez les patients avec une hypoventilation-obésité a été du 6%, mais d'autres auteurs ont rapporté des taux qui vont du 0 au 40% chez ce type de patients[19,70,71], et il peut arriver au 65% quand il s'agit d'autres pathologies respiratoires chroniques qui se présentent avec une IRHA[21,28,31]. Chez les patients IRHA *de novo* le taux d'IET a été bien supérieur que chez les groupes précédents (38%) et ceci est concordant avec les résultats d'autres publications[28].

En ce qui concerne les facteurs prédictifs d'échec de la VNI, la sévérité de l'acidose et l'hypercapnie après le début de la VNI avait été déjà identifiés comme facteurs prédictifs d'échec de la VNI[25,26,31]. Dans notre étude nous avons identifié également l'hypoxémie sévère comme facteur prédictif indépendant d'échec de VNI, probablement parce que nous avons inclus des patients avec des étiologies différentes de l'IRHA notamment des pneumonies. La tolérance à la VNI avait été identifiée auparavant comme un facteur prédictif fort d'échec de la VNI dans une enquête réalisée dans 70 unités de réanimation en France[24]. Dans cette étude seulement le 27% des patients montraient une bonne tolérance à la VNI et 57% avaient des fuites importantes. Dans notre étude aucune relation n'a été trouvée entre la tolérance ou le niveau de fuite et l'échec de la VNI, probablement parce que la plupart des patients (86%) montrait une bonne tolérance à la VNI et seulement un 10% avait un haut niveau de fuite.

Concernant les paramètres ventilatoires comme possibles facteurs d'échec ou succès de la VNI, nous n'avons pas trouvé des différences entre les patients qui ont échoué et ceux qui no. Cependant, le groupe échec avait un volume courant discrètement inférieur ce qui pourrait traduire la nécessité de cibler un objectif de volume courant supérieur chez les patients à risque.

La présence d'un niveau de conscience diminué au moment de l'admission n'est pas identifiée comme facteur prédictif d'échec de la VNI. Parmi les 60 patients qui présentent une diminution du niveau de conscience au moment de l'admission seulement 23% d'entre eux nécessitaient une IET et parmi les 15 patients hospitalisés en état de coma (défini par une ponctuation Glasgow ≤ 8) seulement 3 ont nécessité de l'IET. Bien que l'utilisation de la VNI chez ces patients soit peu recommandé dans les guides internationaux[4] compte tenu du risque d'échec par la manque de collaboration et de protection des voies aériennes, aucune étude randomisée n'a comparé la VNI et la VMI dans ce type de patients qui sont systématiquement exclus des essais. Nos résultats et d'autres expériences précédentes rapportés dans la littérature[33-35] soutiennent l'utilisation de la VNI chez les patients hypercapniques avec une diminution du niveau de conscience suivie d'une intubation en seconde intention si l'évolution n'est pas favorable dans les heures qui suivent.

Il est très probable que le protocole soit responsable de la bonne tolérance des patients à la technique et du bas taux d'IET. Il est probable que, comme les protocoles de sevrage et de sédation qui ont permis de réduire le temps de VMI[72], les protocoles de VNI permettent de réduire le taux d'intubation.

Publication Nº 2: ***Patient-ventilator asynchrony during non-invasive ventilation. A bench and clinical study***

Dans cette étude nous avons évalué d'une façon indépendante l'effet de la fuite inspiratoire et expiratoire sur le cyclage et sur le *trigger*, respectivement, avec différents types de ventilateurs. La synchronisation des ventilateurs de réanimation et de transport avec le patient (ou le simulateur) est altérée en présence de fuite. D'une façon générale la performance du *trigger* est altérée, la capacité de pressurisation est diminuée et le cyclage est retardé. L'activation du *mode VNI* dans ces ventilateurs

produit une réponse hétérogène et différente pour chacun d'eux, comme il était déjà montré dans des études précédentes[44,46,73,74]. Ces résultats nous empêche d'extraire des conclusions générales et nous oblige à considérer chaque appareil individuellement. Au contraire, les ventilateurs spécifiques ont montré une performance plus homogène quand on les évalue au laboratoire, avec une capacité supérieure à éliminer l'*auto-triggering* ou les insufflations prolongées malgré la présence de fuites. Ces résultats sont similaires à deux études précédentes qui montrent une meilleure synchronisation d'un ventilateur spécifique (aussi le BiPAP Vision) par rapport à plusieurs ventilateurs de réanimation avec[44] ou sans[45] le *mode VNI* activé.

Jusqu'à ce jour, aucun modèle de laboratoire qui évalue la synchronisation patient-ventilateur pendant la VNI n'a été validée cliniquement, ce qui remet en question l'importance clinique des résultats de laboratoire sur les patients critiques. Notre étude montre que les résultats obtenus au laboratoire sont superposables à l'étude clinique. Cette consistance des résultats cliniques et de laboratoire confère au modèle de laboratoire une validité clinique.

L'impact du *mode VNI* sur les asynchronies patients-ventilateur a déjà été évalué. Vignaux et collaborateurs[49] ont évalué l'incidence d'asynchronies patient-ventilateur chez 65 patients sur VNI avec un ventilateur de réanimation. Sans activer le *mode VNI* le 46% des patients montrait un index d'asynchronies élevé (>10%). L'activation du *mode VNI* ne diminuait pas de façon significative la proportion de patients avec des asynchronies fréquentes, mais permettait de diminuer l'incidence des asynchronies liées aux fuites. Comme dans cette étude, nous n'avons pas trouvé que l'index d'asynchronies était significativement différent entre les deux groupes (UCI_{NIV}- et UCI_{NIV}+). Par rapport aux résultats de l'étude précédente, la proportion de patients avec asynchronies fréquentes était inférieure (27% des patients avec UCI_{NIV}- et 13% avec UCI_{NIV}+). Le fait que l'index d'asynchronies soit plus bas dans notre étude peut-être dû a plusieurs raisons: 1. Le niveau d'assistance et le volume courant dans notre étude sont inférieurs, ce qui pourrait expliquer une incidence inférieure d'efforts inefficaces et de cycles prolongés 2. La définition de cycle prématuré a été modifiée dans notre étude, et ça a conduit à reconnaitre moins d'asynchronies. 3. Les ventilateurs utilisés dans notre étude clinique sont enclins à l'*auto-triggering* en présence de fuite expiratoire mais ils ne produisent pas des retards de cyclage en présence de fuite inspiratoire selon les

résultats de laboratoire. C'est probable que l'incidence de cycles prolongés soit inferieure à cause de ça. 4. L'asynchronie grave (index d'asynchronies >10%) dans notre étude est due principalement à une haute incidence d'*auto-triggering*, ce qui reflète plus la capacité du ventilateur d'agir en présence de fuite que la conséquence des paramètres ventilatoires.

Pareil qu'avec les ventilateurs de réanimation, les ventilateurs de transport et leurs *modes VNI* ont montré une performance hétérogène en présence de fuite.

Nos résultats montrent que le VNI_v permet une meilleure synchronisation patients-ventilateur. Cependant, bien qu'aucun patient ne montre un index d'asynchronies supérieur à 10 % avec ce ventilateur, peu de patients le montrent avec le ventilateur de réanimation. La répercussion clinique de ces différences est méconnue.

Publication Nº 3: ***Sleep in acute hypercapnic critical care patients under noninvasive ventilation: conventional versus dedicated ventilators***

À partir des résultats de l'étude précédente et puisque la ventilation mécanique et les asynchronies patients-ventilateur peuvent altérer la qualité du sommeil des patients ventilés[52,61,63,65] on s'est demandé si l'utilisation d'un VNIv pourrait diminuer le nombre d'asynchronies patient-ventilateur et améliorer la qualité du sommeil par rapport à l'utilisation de ventilateurs de réanimation (UCI_{VNI+}). Cette troisième étude a failli à montrer la supériorité du VNI_v face aux ventilateurs de réanimation pour diminuer le nombre d'asynchronies patient-ventilateur et pour améliorer la qualité du sommeil.

Le groupe UCI_{VNI+} a montré une fréquence supérieure d'*auto-triggering* par rapport au groupe NIVv. Ces résultats sont dans la ligne de l'étude précédente et d'autres études de laboratoire[44,45]. Par contre, le groupe VNI_v a montré plus d'efforts inefficaces. Il est possible que plusieurs facteurs aient participé de ces résultats: 1. Un volume courant supérieur peut entrainer une hyperinsufflation dynamique, une augmentation de la PEEPi et conséquemment des efforts inefficaces[51,75]. 2. Des caractéristiques techniques du ventilateur, avec un *trigger* inspiratoire peu sensible qui favorise les efforts inefficaces pour éviter les *auto-triggers*[53,76]. Cependant, les résultats de notre étude de laboratoire ne soutiennent plus cette hypothèse. 3. Une augmentation de la charge inspiratoire due à une plus grande résistance des voies aériennes supérieures[52] pourrait

être différent entre les deux groupes: les patients du groupe VNIv étaient plus obeses et avaient une incidente supérieure de troubles respiratoires du sommeil (i.e., index d'apnée-hypopneée > 10/heure pendant la respiration spontanée) malgré l'absence de signification statistique pour ces différences. Malheureusement une étude croisée aurait éliminé les différences inter-groupales puisque chaque patient aurait reçu les deux traitements.

Le nombre d'asynchronies patients-ventilateur est aussi bas dans cette troisième étude. Fanfulla a rapporté 62.5 efforts inefficaces /heure chez 9 patients avec une maladie neuromusculaire[52] et 48 efforts inefficaces /heure chez 48 insuffisants respiratoires chroniques[77]. Dans les deux cas le patients étaient en situation de stabilité et utilisaient la VNI à domicile. Ces valeurs sont clairement supérieures à l'incidence d'efforts inefficaces dans notre groupe de 24 patients (13.8 [1-41] événements /heure) et qui monte jusqu'à 34 (15-125) efforts inefficaces /heure dans le groupe qui montre l'incidence la plus haute (groupe ventilateur dédié). Par rapport à d'autres études qui évaluent l'incidence d'asynchronies patient-ventilateur pendant la veille en situation de décompensation respiratoire nos valeurs sont aussi basses. Mulqueeny[78] rapporte une incidente d'efforts inefficaces de 180 ± 96 événements /heure. La comparaison avec d'autres études reste difficile parce qu'ils expriment le nombre d'asynchronies comme index, défini par Nº d'événements/Nº cycles ventilateur + efforts inefficaces[49,54].

Malgré une incidence d'asynchronies différente entre les deux groupes, la qualité du sommeil reste similaire. On peut considérer plusieurs facteurs à l'origine de ce résultat: 1. Un index de fragmentation pareil dans les deux groupes, probablement parce que le groupe avec le UCI_{VNI+} avait plus de hausses de bruit et plus d'éveils et micro-éveils associés, laquelle chose peut avoir annulé les différences en la qualité du sommeil. 2. D'autres facteurs non contrôlés comme la douleur, la lumière, les soins infirmière, etc., pourraient avoir contribué à une fragmentation similaire dans les deux groupes. 3. Etant donné l'importance de la fragmentation du sommeil en réanimation, on ne peut exclure que l'on ait attribué quelques éveils et micro-éveils aux événements « bruit » et « asynchronies » de façon erronée simplement par coïncidence. 4. Les asynchronies patient-ventilateur pourraient ne pas avoir un rôle important sur le sommeil des patients en réanimation. Selon une étude récente conduite par le groupe de Fanfulla[79] dans une unité de post-aiguë, les efforts inefficaces (45 événements/heure) étaient les

responsables de seulement 10% des micro-éveils et le sommeil était similaire chez les patients ventilés et ceux non-ventilés. Dans une autre étude, Alexopoulou[80] ne montrait pas de différence sur la qualité du sommeil malgré l'utilisation du mode PAV+ qui réduisait pourtant de façon significative l'incidence des asynchronies par rapport à l'aide inspiratoire.

Toutefois, le résultat le plus intéressant de cette troisième étude c'est que les patients sont capables de dormir pendant le temps qu'ils sont sous VNI et que la plupart du sommeil survient pendant les périodes de VNI. Même il paraît que la qualité du sommeil dans ces périodes est supérieure à ceux de respiration spontanée. Malgré son intérêt, ce résultat doit être considéré avec précaution puisque les périodes de VNI et de respiration spontanée n'étaient pas randomisées et ils existent plusieurs facteurs de confusion qui peuvent avoir favorisé une meilleure qualité du sommeil pendant les périodes de VNI. Le première que la VNI est administrée principalement pendant la nuit, période pendant lequel les conditions environnementales favorisent le sommeil des patients. Le deuxième, que plusieurs patients peuvent avoir profité de l'effet bénéfique que la VNI a sur le SAHS ou l'insuffisance respiratoire chronique[81-83].

CONCLUSIONS

▪ Les taux d'échec de la VNI et la nécessité d'IET chez les patients avec une IRHA peuvent être diminués au-dessous du 15% quand la VNI est conduite dans une unité expérimentée et conformément à un protocole de soins et de surveillance.

▪ La VNI devrait être tentée chez tous les patients avec une IRHA, même quand le risque d'échec est élevé, c'est-à-dire en présence d'une altération de la conscience ou en l'absence d'une pathologie respiratoire subjacente.

▪ L'activation du *mode VNI* des ventilateurs de réanimation permet d'améliorer partiellement, mais avec une grande variabilité entre ventilateurs, la synchronisation avec la respiration du patient. Dû à cette grande variabilité chaque ventilateur devrait être considéré de façon individuelle.

▪ Les ventilateurs spécifiques de VNI favorisent une meilleure synchronisation patient-ventilateur en présence de fuites que les ventilateurs de réanimation quand les deux sont comparés sur un banc-test et dans une étude physiologique à court terme.

▪ Le type de ventilateur utilisé pour le traitement de l'IRHA chez les patients critiques n'influence pas la qualité du sommeil.

▪ La VNI n'altère pas le sommeil des patients critiques avec une IRHA. Il est même possible que la VNI favorise la qualité du sommeil.

▪ Aussi bien les ventilateurs de réanimation que les ventilateurs spécifiques peuvent être utilisés chez les patients avec une IRHA. Nos résultats ne permettent pas de recommander un type de ventilateur particulier.

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