UNIVERSIDAD COMPLUTENSE DE MADRID

FACULTAD DE MEDICINA

TESIS DOCTORAL

Efecto de la ventilación mecánica no invasiva sobre el acoplamiento neurorrespiratorio y sincronía toracoabdominal durante el ejercicio en pacientes con enfermedad pulmonar obstructiva crónica grave

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

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DIRIGIDA POR

María Victoria Villena Garrido

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Programa de Doctorado en Investigación en

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EFECTO DE LA VENTILACIÓN MECÁNICA NO INVASIVA SOBRE EL ACOPLAMIENTO NEURORRESPIRATORIO Y SINCRONÍA TORACOABDOMINAL DURANTE EL EJERCICIO EN PACIENTES CON ENFERMEDAD PULMONAR OBSTRUCTIVA CRÓNICA GRAVE

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR JAVIER SAYAS CATALÁN

DIRECTORES DE TESIS

MARÍA VICTORIA VILLENA GARRIDO

MANEL LUJÁN TORNÉ

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Para la redacción de esta tesis, esta ha sido la primera sección en la que pensé.

Habitualmente se empieza dando las gracias a la familia más cercana por todo el apoyo que ha supuesto, y esta tesis no va a ser una excepción. Sin el apoyo constante, el ancla y línea de vida que supone mi esposa Cristina, desde hace más de 30 años presente en mi vida, ninguno de mis éxitos profesionales tendría sentido. Pero, más importante, tampoco habría superado los fracasos y malos momentos de la manera que lo hemos podido hacer. Y mis hijos, Miguel, Blanca y Ana, producto de este tiempo juntos, que suponen un orgullo por su compromiso, bondad y honestidad, siendo, de todos los eventos de nuestra vida, sin duda, del que más orgulloso puedo estar. Y por supuesto, mis padres y hermana, de los que he aprendido el compromiso por los demás, una educación basada en valores cristianos y de compasión, y un compromiso por hacer las cosas bien. Y a los que debo gran parte de esta tesis, por su insistencia en que la completase. En concreto, el empeño de mi padre, recientemente fallecido sin haber podido ver este momento de completar la tesis, ha sido un estímulo para finalizarla, y por lo tanto, esta constituye un homenaje a su memoria.

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Artículo	Revista	FI (2024)	Quartil 2024	Indexación	DOI
Measurement of thoraco-abdominal synchrony using respiratory inductance plethysmography(2)	Expert Review of Respiratory Medicine	2.48	Q2	Medline, SCI, Scopus	10.1080/17476348.2024.1834227
Thoracoabdominal Asynchrony in Very Severe COPD: Clinical and Functional Correlates During Exercise (3)	Archivos de Bronconeumología	9.2	Q1	Medline, SCI, Scopus	10.1016/j.arbres.2025.01.010
Muscle Unloading During Exercise: Comparative Effects of Conventional Oxygen, NIV, and HFNO on Neural Drive in Severe COPD(4)	Journal of Clinical Medicine	2.99	Q1	Medline, SCI, Scopus	10.3390/jcm140408150

RESUMEN

Efecto de la Ventilación Mecánica No Invasiva sobre el acoplamiento neurrespiratorio y sincronía toracoabdominal durante el ejercicio en pacientes con Enfermedad Pulmonar Obstructiva Crónica

Esta tesis doctoral investiga los mecanismos fisiopatológicos de la limitación al ejercicio en pacientes con EPOC severa, centrándose en la asincronía toracoabdominal (TAA) y el impulso neural respiratorio, evaluando el impacto de diferentes modalidades de soporte respiratorio no invasivo durante el ejercicio.

Sobre una población de 20 pacientes con EPOC muy grave, en lista de espera de trasplante pulmonar, se desarrolla este trabajo en torno a 3 artículos publicados.

La investigación se estructura en tres artículos científicos complementarios que abordan objetivos específicos. El primer estudio (2) desarrolla y valida el Global Phase Delay (GPD) como método mejorado para evaluar la TAA, superando las limitaciones del ángulo de fase tradicional mediante el análisis de 2290 ciclos respiratorios. El GPD proporciona un rango más amplio de medición (-179,75 a +178,54 grados) comparado con el ángulo de fase (-86,90 a +88,4 grados) y permite identificar que compartimento, torácico o abdominal, lidera el movimiento respiratorio. De esta manera identifica si la asincronía se produce por debilidad diafragmática, o por un mecanismo obstructivo.

El segundo artículo caracteriza los patrones de TAA durante el ejercicio (3). Se identificaron dos patrones distintos: rotación horaria (tórax adelantado) asociada con mayor severidad de la enfermedad, mayor disnea y mayor impulso neural respiratorio; y rotación antihoraria (abdomen adelantado) en pacientes con función pulmonar relativamente mejor preservada. Los pacientes con rotación horaria presentaron FEV1 significativamente menor (15,5% vs 20,54% del predicho) y mayor respuesta al soporte con ventilación no invasiva (VNI).

El tercer estudio evalúa comparativamente los efectos de la VNI y la terapia de alto flujo (TAF) sobre el impulso neural respiratorio durante el ejercicio (4). La VNI demostró superioridad significativa, reduciendo el impulso neural respiratorio en un 60% comparado con la oxigenoterapia convencional (488,81 µV vs 1180,63 µV), mientras que la TAF mostró efectos intermedios (807,8 µV). Adicionalmente, la VNI logró mayor

reducción en la frecuencia respiratoria, menor percepción del esfuerzo (disminución de 1,8 puntos en escala Borg) y reducción más pronunciada del CO2 transcutáneo (5,3 mmHg).

Las contribuciones principales incluyen: desarrollo metodológico del GPD para cuantificación precisa de la TAA; caracterización fisiopatológica de patrones específicos de TAA como biomarcadores de severidad; y la demostración de un efecto superior de la VNI sobre la TAF y el oxígeno convencional para la descarga muscular respiratoria durante el ejercicio, y también sobre la disnea y la hipercapnia.

Los hallazgos tienen implicaciones clínicas directas para la personalización de programas de rehabilitación respiratoria en EPOC severa. La monitorización de la TAA mediante GPD puede predecir la respuesta al soporte respiratorio y guiar la selección individualizada del tratamiento. El uso de la VNI durante el ejercicio puede ayudar a desarrollar programas de rehabilitación en pacientes con severas limitaciones al ejercicio, que de otra manera no desarrollarían una carga de trabajo eficaz por disnea y desacoplamiento neuroventilatorio.

ABSTRACT

Effect of Non-Invasive Mechanical Ventilation on Neuro-Respiratory Coupling and Thoracoabdominal Synchrony During Exercise in Patients with Severe Chronic Obstructive Pulmonary Disease

This doctoral thesis investigates the pathophysiological mechanisms underlying exercise limitation in patients with severe COPD, focusing on thoracoabdominal asynchrony (TAA) and neural respiratory drive. It evaluates the impact of different non-invasive respiratory support modalities during exercise.

The study was conducted on a cohort of 20 patients with very severe COPD, all awaiting lung transplantation, and is structured around three published scientific articles.

Research Structure and Key Findings

- Article 1 (2):
  Developed and validated the Global Phase Delay (GPD) as an improved method for assessing TAA, overcoming the limitations of the traditional phase angle by analyzing 2,290 respiratory cycles. The GPD offers a broader measurement range (−179.75 to +178.54 degrees) compared to the phase angle (−86.90 to +88.4 degrees) and enables identification of the leading compartment of movement.
- Article 2 (3):
  Characterized TAA patterns during exercise, identifying two distinct patterns:
  - Clockwise rotation (thorax leading): Associated with greater disease severity, increased dyspnea, and higher neural respiratory drive.
  - Counterclockwise rotation (abdomen leading): Observed in patients with relatively better preserved lung function.

Patients with clockwise rotation exhibited significantly lower FEV1 (15.5% vs. 20.54% predicted) and showed greater response to non-invasive ventilation (NIV) support.

- Article 3(4):
  Compared the effects of NIV and high-flow therapy (HFT) on neural respiratory drive during exercise. NIV demonstrated significant superiority, reducing neural respiratory drive by 60% compared to conventional oxygen therapy (488.81 µV

vs. 1180.63 µV), while HFT showed intermediate effects (807.8 µV). Additionally, NIV achieved greater reductions in respiratory rate, lower perceived exertion (1.8-point decrease on the Borg scale), and a more pronounced reduction in transcutaneous CO2 (5.3 mmHg).

Main Contributions

- Methodological development of GPD for precise quantification of TAA.
- Pathophysiological characterization of specific TAA patterns as biomarkers of disease severity.
- Demonstration of the superior effect of NIV over HFT and conventional oxygen for respiratory muscle unloading during exercise, as well as for reducing dyspnea and hypercapnia.

Clinical Implications

These findings have direct clinical implications for the personalization of respiratory rehabilitation programs in severe COPD. Monitoring TAA using GPD may predict response to respiratory support and guide individualized treatment selection. The use of NIV during exercise may facilitate the development of rehabilitation programs for patients with severe exercise limitations, who would otherwise be unable to achieve effective workloads due to dyspnea and neuroventilatory uncoupling.

1. INTRODUCCIÓN

1. INTRODUCCIÓN

La enfermedad pulmonar obstructiva crónica (EPOC) constituye un desafío sanitario global, siendo la tercera causa de muerte mundial con más de 3 millones de fallecimientos anuales, según la guía GOLD (5). En España, su prevalencia alcanza el 10,2% en mayores de 40 años (2,19 millones de casos), con marcadas diferencias geográficas: desde 47,4/1,000 en Valencia hasta 15.3/1,000 en Extremadura (6). Los costes económicos son significativos: en la UE representan el 6% del gasto sanitario total (7), mientras que en España superan los 750 millones anuales, distribuidos entre hospitalizaciones (40-45%), medicamentos (35-40%) y pruebas diagnósticas. Estudios regionales detallan un coste medio de 3.757€ por paciente, con impacto en productividad laboral (17,9% del total). La GOLD 2024 enfatiza la necesidad de diagnósticos precoces y enfoques terapéuticos personalizados para mitigar esta carga multidimensional.

En los pacientes con enfermedad pulmonar obstructiva crónica (EPOC), durante el ejercicio, la limitación del flujo espiratorio y el aumento de la frecuencia respiratoria pueden disminuir el tiempo espiratorio, lo que resulta en un aumento del volumen residual, una condición conocida como hiperinsuflación dinámica (8). La consecuencia inevitable de esta condición es el aumento de la presión positiva intrínseca tele espiratoria (PEEPi) y el aumento del trabajo respiratorio. Finalmente, el resultado es una disnea severa durante el esfuerzo físico que reduce la tolerancia al ejercicio (9-13). Incluso, esta hiperinsuflación dinámica tiene repercusiones a medio plazo en forma de un factor independiente de mal pronóstico. (14)

La limitación al ejercicio en pacientes con EPOC es multifactorial y constituye uno de los síntomas más incapacitantes de la enfermedad. La disnea de esfuerzo, la fatiga muscular periférica, las alteraciones del intercambio gaseoso y la disfunción cardiovascular contribuyen conjuntamente a la reducción progresiva de la capacidad funcional (15). Esta limitación no solo afecta la calidad de vida de los pacientes, sino que también se asocia con un aumento de la mortalidad, mayor frecuencia de hospitalizaciones y un incremento sustancial de los costes sanitarios (16).

La progresión de la enfermedad lleva a los pacientes a desarrollar un círculo vicioso en el que la limitación al ejercicio conduce a la inactividad física, lo que a su vez genera mayor desacondicionamiento, pérdida de masa muscular y deterioro funcional progresivo

(16). Este fenómeno de *círculo vicioso* o *espiral descendente de inactividad* representa uno de los aspectos más devastadores de la EPOC avanzada y justifica la necesidad de intervenciones terapéuticas específicas dirigidas a romper este ciclo (17).

1.1. Mecanismos fisiopatológicos en la limitación al ejercicio en EPOC grave

1.1.1. Desacoplamiento Neuroventilatorio

El desacoplamiento neuroventilatorio representa un mecanismo fundamental de limitación al ejercicio en la EPOC (18). Este fenómeno se caracteriza por la disociación entre el impulso neural respiratorio (*drive* neural respiratorio) y la respuesta ventilatoria mecánica resultante.

El desacoplamiento neuroventilatorio se manifiesta como un incremento desproporcionado del impulso neural respiratorio en relación con la respuesta ventilatoria obtenida (19). Esta disociación resulta de la combinación de múltiples factores: la hiperinsuflación dinámica, la alteración de la mecánica de los músculos respiratorios, el incremento de la resistencia de las vías aéreas y la fatiga de los músculos respiratorios.

El desacoplamiento neuroventilatorio puede cuantificarse mediante el registro de la electromiografía de los músculos respiratorios accesorios, particularmente los músculos paraesternales. Sus estudios han mostrado que el incremento del impulso neural respiratorio, medido a través de la actividad electromiográfica de estos músculos, se correlaciona significativamente con la intensidad de la disnea y la limitación al ejercicio (18, 20, 21).

Se ha propuesto que el desacoplamiento neuroventilatorio constituye un mecanismo adaptativo que intenta compensar la ineficiencia mecánica del sistema respiratorio mediante el incremento del impulso neural. Sin embargo, este mecanismo compensatorio tiene limitaciones y, cuando se agota, resulta en la terminación prematura del ejercicio.

También se han estudiado las implicaciones terapéuticas del desacoplamiento neuroventilatorio, demostrando que intervenciones dirigidas a reducir el impulso neural respiratorio o a mejorar la eficiencia mecánica del sistema respiratorio pueden mejorar la tolerancia al ejercicio.(22, 23) Estas observaciones han proporcionado la base científica para el desarrollo de estrategias de soporte respiratorio durante el ejercicio.

1.1.2. Disnea e Hipercapnia

La disnea representa el síntoma cardinal de la EPOC y constituye el principal factor limitante del ejercicio en la mayoría de los pacientes. La fisiopatología de la disnea en la EPOC es compleja y multifactorial, involucrando mecanismos periféricos y centrales.

La disnea en la EPOC resulta de la interacción entre múltiples factores: el incremento del impulso neural respiratorio, la alteración de la mecánica respiratoria, la hiperinsuflación dinámica, la fatiga de los músculos respiratorios y las alteraciones del intercambio gaseoso. La integración de estas señales a nivel del sistema nervioso central genera la sensación subjetiva de disnea (24).

La hipercapnia, definida como el incremento de la presión parcial de CO2 en sangre arterial por encima de 45 mmHg, constituye una complicación frecuente en la EPOC avanzada y un factor adicional de limitación al ejercicio. Durante el ejercicio, los pacientes con EPOC pueden desarrollar hipercapnia como resultado de la inadecuada eliminación de CO2 debido a la limitación ventilatoria.

Los mecanismos de la hipercapnia durante el ejercicio en la EPOC incluyen: el incremento de la producción de CO2 por el metabolismo muscular, la limitación ventilatoria que impide el incremento adecuado de la ventilación alveolar, el aumento del espacio muerto fisiológico y las alteraciones de la relación ventilación-perfusión. La hipercapnia durante el ejercicio se asocia con mayor disnea, reducción de la capacidad de ejercicio y peor pronóstico.

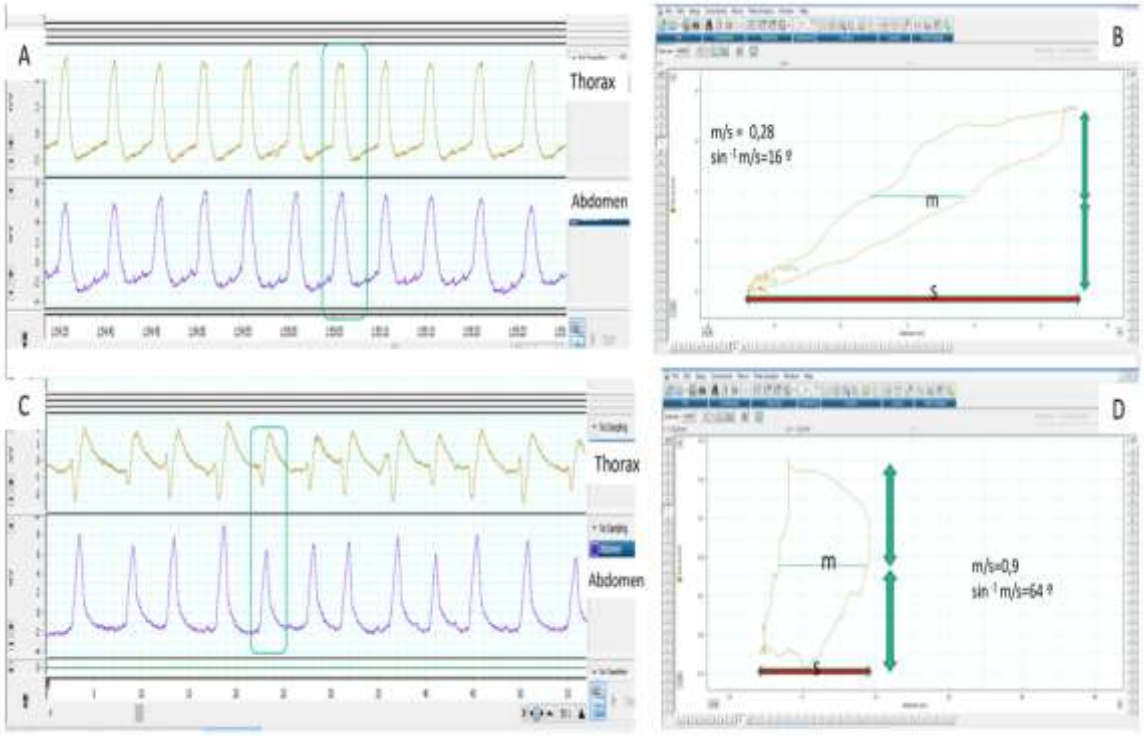
1.2. Sincronía toracoabdominal durante el ejercicio

En condiciones fisiológicas normales, la inspiración es el resultado de la contracción coordinada del diafragma y de los músculos inspiratorios accesorios, que provoca un aumento simultáneo del volumen torácico y abdominal. Al iniciar la inspiración, el diafragma se acorta e incrementa su tensión, desplazando el compartimento abdominal hacia abajo y afuera; al mismo tiempo, la expansión de la caja torácica se logra por la acción de los músculos intercostales externos y de los escalenos, que elevan las costillas y aumentan el diámetro anteroposterior y lateral del tórax. Ambos compartimentos (torácico y abdominal) se mueven en fase, de modo que el ángulo de fase (Φ), obtenido al trazar en un plano Lissajous desplazamiento abdominal en abscisas y torácico en

ordenadas, se aproxima a 0°, reflejando una sincronía casi perfecta (1, 25). Esta coordinación garantiza un mejor acoplamiento neuromecánico: el impulso neural respiratorio (drive) se traduce directamente en incremento de volumen corriente, minimizando el trabajo muscular y optimizando el intercambio gaseoso en los alvéolos (26). Durante la espiración, el retroceso elástico de pulmones y pared torácica, junto con el relajamiento muscular, permite el retorno simultáneo de ambos compartimentos a sus volúmenes de reposo, completando así un ciclo respiratorio sin desfases temporales ni asincronías apreciables.

Figura 1, sincronía toracoabdominal

(tomado de Rabec C, Luján M y Sayas J (1), con permiso de los otros dos coautores):



Determinación de la sincronía normal y patológica medida a partir de cintas toracoabdominales mediante el cálculo del ángulo de fase. (A) Los movimientos respiratorios del paciente son sincrónicos, con las cintas mostrando un desplazamiento simétrico y de la misma polaridad. (B) El ángulo de fase correspondiente se calcula comparando el movimiento torácico (eje vertical) con el desplazamiento abdominal (eje horizontal) en un mismo plano, utilizando una curva de Lissajous. Para cuantificarlo, se toma el ancho horizontal del lazo delimitado por la representación en el plano de ambos movimientos en el punto medio (m) del movimiento torácico y se compara con el movimiento abdominal total (s). Cuanto menor es la relación m/s, más próximo a cero es el ángulo de fase (que es el inverso del seno de dicha proporción) y mejor la sincronía toracoabdominal (16° en este caso). (C) En este caso, la banda abdominal comienza a moverse antes y la torácica termina antes, de modo que la sincronía toracoabdominal es peor que en el primer ejemplo, lo que se refleja en una mayor relación m/s y un ángulo de fase superior (D), en este caso 64°. Hay que tener en cuenta que, en situaciones de desajuste total u oposición de fase, el ángulo de fase puede alcanzar hasta 180°.

1.2.1. Uso de la TAA en estudios de sueño

La evaluación de la TAA mediante pletismografía de impedancia respiratoria (RIP) ha encontrado aplicaciones importantes en distintos ámbitos.

En la patología del sueño, la presencia de desacoplamiento toracoabdominal se ha utilizado como herramienta para objetivar eventos obstructivos de vía aérea, donde el abdomen se desplaza hacia afuera, por efecto de la contracción diafragmática, y "lucha" por insuflar un tórax que, debido a la obstrucción, no es capaz de insuflarse, y se deprime (se desplaza hacia adentro) (27). De hecho, constituye el método recomendado por la American Academy of Sleep Medicine (AASM) de evaluar el esfuerzo respiratorio en polisomnografías, junto con la manometría esofágica (28).

Incluso se ha podido utilizar como método alternativo para la estadificación del sueño (29).

1.2.2. Uso de la TAA en otras patologías, como la medicina crítica o en pediatría

En pacientes críticos, la TAA se utiliza como marcador de disfunción respiratoria y puede ayudar en la toma de decisiones respecto al soporte ventilatorio.

Los estudios en unidades de cuidados intensivos han demostrado que la TAA se asocia con mayor trabajo respiratorio, incremento del impulso neural respiratorio y mayor probabilidad de fracaso en el destete de la ventilación mecánica. La monitorización de la TAA durante el destete ventilatorio puede proporcionar información valiosa sobre la función de los músculos respiratorios y la capacidad del paciente para mantener una ventilación espontánea adecuada (30, 31).

En pediatría, la TAA es un hallazgo común en recién nacidos con distrés respiratorio, displasia broncopulmonar y otras patologías respiratorias (32). La evaluación de la TAA en esta población es particularmente importante debido a la inmadurez del sistema respiratorio y la mayor susceptibilidad a la fatiga de los músculos respiratorios.

Se ha demostrado que la TAA en neonatos se correlaciona con la severidad de la enfermedad respiratoria, la necesidad de soporte ventilatorio y el pronóstico a largo plazo. La monitorización no invasiva de la TAA mediante RIP puede ayudar en la optimización

del soporte respiratorio y en la reducción de complicaciones asociadas a la ventilación mecánica.

1.2.3. Impacto de la Asincronía Toracoabdominal en la EPOC en reposo y en ejercicio

La asincronía toracoabdominal (TAA) representa un hallazgo característico en pacientes con EPOC avanzada y constituye un marcador de disfunción respiratoria grave.

En la EPOC, múltiples factores contribuyen al desarrollo de TAA: la hiperinsuflación pulmonar que altera la geometría del diafragma, la disfunción de los músculos respiratorios, el incremento del trabajo respiratorio y la fatiga muscular.

La TAA en la EPOC puede manifestarse en diferentes patrones. Sin embargo, son escasas las evidencias sobre el papel de estos patrones bajo ejercicio o en agudizaciones de pacientes con EPOC.

La TAA durante el ejercicio en pacientes con EPOC se asocia con múltiples consecuencias adversas: incremento del trabajo respiratorio, reducción de la eficiencia ventilatoria, mayor disnea, limitación prematura del ejercicio y deterioro de la calidad de vida. Además, la presencia de TAA severa se ha identificado como un marcador de mal pronóstico en la EPOC.

El ejercicio físico tiene un impacto significativo en la sincronía toracoabdominal, particularmente en pacientes con EPOC. Durante el ejercicio, el incremento de las demandas ventilatorias puede exacerbar la TAA preexistente o precipitar su desarrollo en pacientes que presentan sincronía en reposo.

Los mecanismos mediante los cuales el ejercicio influye en la TAA incluyen: el incremento de la ventilación que acorta el tiempo espiratorio y favorece la hiperinsuflación dinámica, el aumento del trabajo respiratorio que puede precipitar la fatiga de los músculos respiratorios, la alteración de la mecánica respiratoria por cambios posturales y el incremento del impulso neural respiratorio.

La evaluación de la TAA durante el ejercicio podría tener valor pronóstico y ayudar en la identificación de pacientes que se beneficiarían de estrategias específicas de soporte respiratorio. Además, el patrón de TAA durante el ejercicio puede proporcionar

información sobre los mecanismos fisiopatológicos predominantes en cada paciente individual.

1.2.4. Bases matemáticas y limitaciones en la medición de la TAA

La evaluación de la TAA tradicionalmente se ha realizado mediante la pletismografía de inductancia respiratoria (RIP), utilizando el ángulo de fase como parámetro principal.

Otros métodos, como las bandas piezoeléctricas o las de fluoropolivinilindeno presentan limitaciones, como la falta de linearidad en su respuesta, o los artefactos por atrapamiento de las bandas con los movimientos del paciente. (33)

La pletismografía inductiva se basa en los principios electromagnéticos fundamentales establecidos por las leyes de Faraday y Lenz. Una corriente aplicada a través de una espira metálica genera un campo magnético de orientación normal (perpendicular) a la orientación de la espira. Durante la respiración, los cambios en el área del cuerpo del individuo modifican la forma del campo magnético, creando una corriente directamente proporcional al cambio en dicha área. (Figura 2)

En detalle, la **Ley de Faraday** establece que una corriente aplicada a través de una espira metálica genera un campo magnético de orientación normal (perpendicular) a la orientación de la espira. Matemáticamente se expresa como: $\boldsymbol{\varepsilon = -d\Phi/dt}$, donde:

- ε = fuerza electromotriz inducida
- Φ = flujo magnético
- dt = cambio en el tiempo

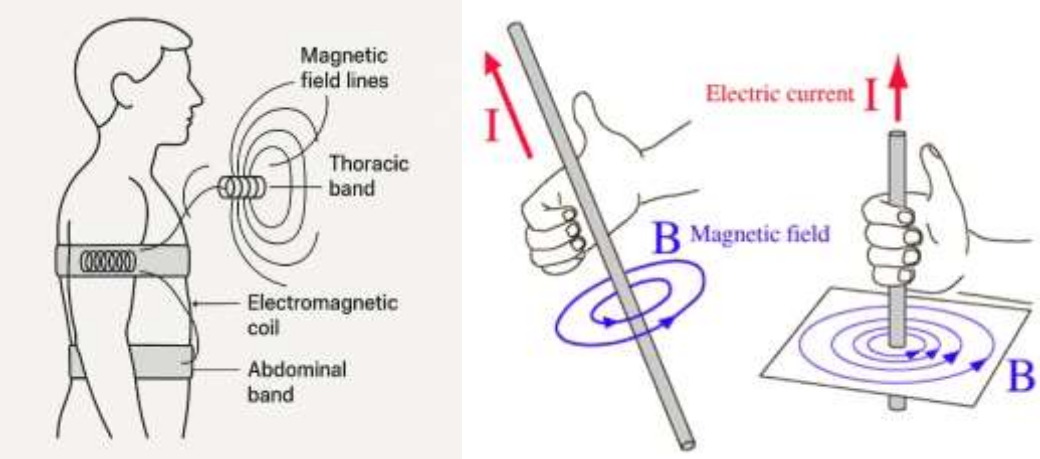
En el contexto de las bandas respiratorias, cada banda funciona como una espira inductiva que crea un campo magnético alrededor del área que delimita.

La Ley de Lenz complementa la ley de Faraday estableciendo que un cambio en el área delimitada por la espira crea una corriente directamente proporcional al cambio en dicha área. Esta ley determina la dirección de la corriente inducida, que siempre se opone al cambio que la produce.

Durante la respiración, los cambios volumétricos en los compartimentos torácico y abdominal modifican el área delimitada por cada banda. Este cambio de área altera la

inductancia de cada espira, generando variaciones en la señal eléctrica que pueden ser detectadas y amplificadas.

Figura 2, principios electromagnéticos de las bandas de inductancia (RIP), *basadas en las leyes de Faraday y Lenz*

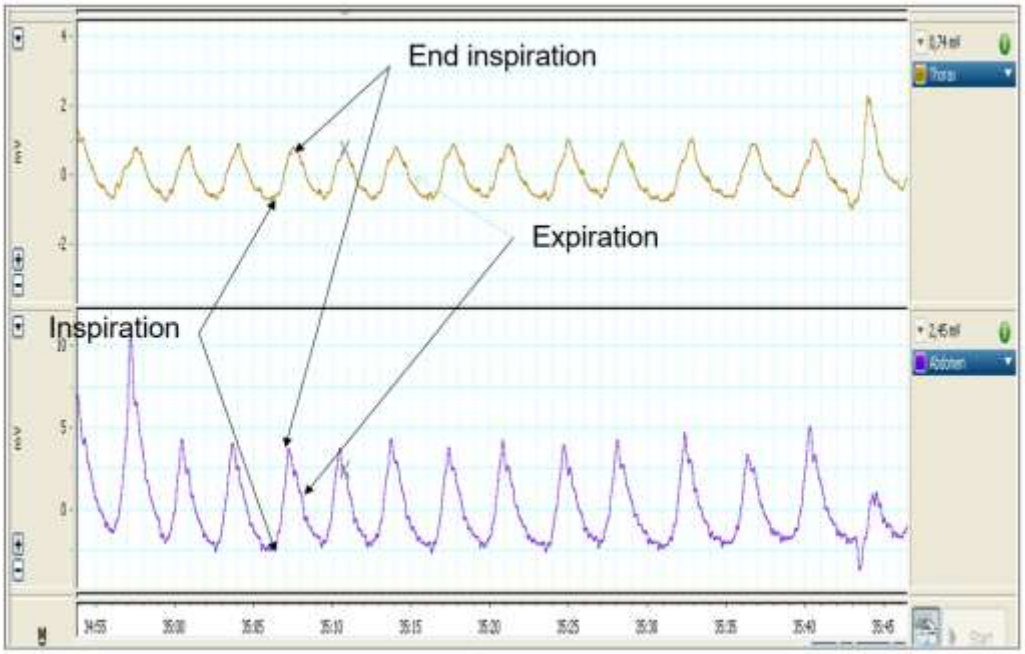


El ángulo de fase se calcula a partir de las figuras de Lissajous, que representan gráficamente la relación entre los movimientos torácicos y abdominales.

Sin embargo, el ángulo de fase presenta importantes limitaciones metodológicas que deben evaluarse mediante una aproximación nueva. Estas limitaciones incluyen: 1) la asunción de que los movimientos respiratorios siguen un patrón sinusoidal, lo cual no es cierto en pacientes con EPOC severa; 2) la limitación matemática del cálculo del ángulo de fase a un rango entre 0 y 90 grados, lo que impide la detección de asincronías severas; 3) la incapacidad para identificar qué compartimento (torácico o abdominal) lidera el movimiento; y 4) la dificultad para detectar movimientos paradójicos.

La figura 3 puede aclarar estos distintos patrones de movimiento y sincronía toracoabdominal.

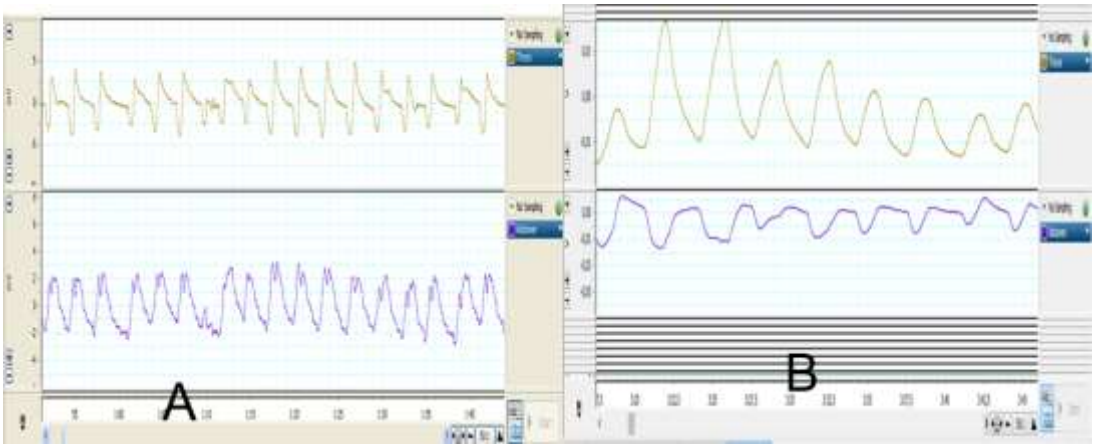
Figura 3, Sincronía toracoabdominal y fases de la respiración



Los picos del movimiento torácico y abdominal, cuando están sincronizados, marcan el final de la inspiración y el inicio de la espiración.

La figura 4 muestra en la imagen A el efecto en la sincronía toracoabdominal de un paciente con un atrapamiento aéreo severo, en el cual el diafragma "empuja" el abdomen sin poder insuflar el tórax, generando el "hundimiento" de la base del tórax (Signo de Hoover), En contraste, la imagen B muestra un paciente con debilidad diafragmática, en el que el tórax se insufla por efecto del uso de musculatura accesoria, y el abdomen se dirige hacia el interior del tórax ("aspirado" por el efecto de la musculatura accesoria y la ausencia de tono muscular diafragmático).

Figura 4. Sincronía toracoabdominal



A) paciente con hiperinsuflación y signo de Hoover. B) paciente con parálisis frénica.

1.3. Soporte ventilatorio no invasivo

En la última década ha aumentado el interés en el uso de la ventilación mecánica no invasiva (VNI) para aumentar la capacidad física durante el ejercicio (12, 34-36), por la evidencia de que la ventilación asistida reduce la carga muscular, lo que permitiría al paciente entrenarse con ejercicios de mayor intensidad.

Durante el ejercicio físico de pacientes con EPOC, que tienen un trabajo respiratorio incrementado, puede haber una redistribución del flujo sanguíneo desde las extremidades hacia los músculos respiratorios, lo que induciría a una fatiga muscular precoz en las extremidades, una causa reconocida de interrupción del ejercicio. Esta redistribución podría, al menos en parte, reducirse si se asiste la ventilación durante el ejercicio (37), y en algunos estudios ya se demuestra la prevención del agotamiento diafragmático inducido por el ejercicio mediante la VNI (38).

Como la presión positiva al final de la espiración intrínseca (PEEPi) y el agotamiento de la musculatura inspiratoria en los pacientes con EPOC contribuyen al desarrollo de la disnea, es posible que la VNI proporcione un beneficio al menos sintomático mediante la descarga muscular y la disminución del trabajo respiratorio. Mediante la descarga de los músculos respiratorios, estos podrían necesitar menor flujo sanguíneo y con esto evitar la redistribución proveniente de las extremidades que limita la capacidad física del paciente (37, 39).

El mensaje de estos estudios fisiológicos es claro: la VNI durante el ejercicio podría reducir el trabajo respiratorio y la disnea, aumentando la tolerancia al ejercicio, pero la evidencia disponible es controvertida. Algunos estudios no han encontrado beneficios de la VNI durante el ejercicio usando un modo ventilatorio híbrido de presión positiva proporcional al esfuerzo del paciente y no una presión de soporte fija (40), mientras que otros han objetivado un aumento en la intensidad del ejercicio en pacientes bajo VNI incluso con el mismo modo ventilatorio (41), en comparación con pacientes con ventilación espontánea. Sin embargo, dos metaanálisis sobre el tema concluyen que, dado el escaso número de estudios disponibles y el escaso tamaño muestral, son necesarios estudios clínicos aleatorizados para determinar los efectos reales de la VNI en EPOC y validar su recomendación generalizada en programas de rehabilitación (42, 43). Dado que la mayoría de los pacientes con EPOC moderado y grave son candidatos para programas

de rehabilitación, y la rehabilitación es un componente importante en el manejo de la disnea (37, 44) la utilización de VNI durante el ejercicio es un tema de gran relevancia.

Otro estudio (13) demostró el efecto de realizar la rehabilitación en tapiz rodante con la ayuda de VNI. Aunque las presiones inspiratorias eran discretas (IPAP media 12cmH2O) se demostró una mejoría en la presión espiratoria máxima, una mejoría en el consumo de oxígeno y en la capacidad de ejercicio, frente al programa de rehabilitación con ventilación espontánea.

Por lo tanto, el uso de la VNI se ha propuesto como una herramienta para aumentar la capacidad de los pacientes con EPOC grave para realizar ejercicio. Si bien los estudios iniciales mostraron resultados contradictorios y un metaanálisis inicial no mostró evidencia de beneficio (43), existe una amplia heterogeneidad en la selección de pacientes, los protocolos, las medidas de resultado y la titulación de la VNI. Así, algunos estudios se han centrado en usuarios *naïve* de VNI, con malos resultados (45), otros han evaluado modos ventilatorios alternativos (40, 46), otros se han centrado en las mejoras fisiológicas (por ejemplo, en el flujo sanguíneo muscular (47) o en el perfil inflamatorio (48, 49)), en la mejora de la eficiencia ventilatoria y de la capacidad de ejercicio (50) o en los efectos a largo plazo (13, 36, 37, 51).

Por otro lado, la terapia nasal de alto flujo TAF es una técnica ya establecida que proporciona un alto flujo (generalmente >30-40 lpm) de gas acondicionado (mezcla de aire y oxígeno con FiO2 seleccionado, calentado y humificado al 100% de humedad relativa) (52). También se ha estudiado como herramienta para aumentar la capacidad de ejercicio en pacientes con EPOC. Si bien hay mucha menos evidencia de sus beneficios, y la mayoría de los estudios son limitados, parece ser una herramienta prometedora, con mejor tolerancia, que la VNI, para mejorar la capacidad de ejercicio (53). Los metaanálisis más recientes han demostrado la capacidad de la VNI para mejorar la tolerancia al ejercicio y muchas medidas fisiológicas, como el consumo de oxígeno y la disnea, en comparación con la TAF (54). Si bien ha habido varios estudios que identifican los efectos fisiológicos de agregar VNI durante el ejercicio, el efecto de la terapia de alto flujo sobre el impulso respiratorio neural, en comparación con la VNI, no se ha investigado directamente. La evidencia disponible indica que la ventilación no invasiva (VNI) produce consistentemente una mayor descarga de los músculos respiratorios,

medida como una reducción del impulso respiratorio neural (NRD), durante el ejercicio en la EPOC grave que la terapia nasal de alto flujo (TAF).

Aunque está ampliamente aceptado que la conciencia de un aumento del trabajo respiratorio muscular por parte de los centros respiratorios centrales es importante para la sensación de la disnea, la identificación de una medición fisiológica fiable del drive neural respiratorio (DNR) representa un reto significativo. Además, la disnea aumenta de forma desproporcionada cuando la respuesta ventilatoria está limitada por alteraciones mecánicas pulmonares (55), como las que se presentan en la EPOC, fenómeno al que se denomina desacoplamiento o "uncoupling" neuro ventilatorio (18, 56).

Las mediciones relacionadas con la ventilación no reflejan adecuadamente el drive neuroventilatorio (DNR) en los pacientes con EPOC, porque sus alteraciones en la mecánica respiratoria modifican la relación entre el DNR y el flujo inspiratorio. Tampoco puede ser relacionado con las variables relativas a las presiones del sistema respiratorio, porque estas varían en función de la capacidad contráctil de los músculos respiratorios y de su tensión, propiedades independientes del DNR, sobre todo en presencia de hiperinsuflación pulmonar (57).

El acceso a la medición de la activación eléctrica diafragmática se puede realizar mediante una sonda esofágica con electrodos, (EMGdi) (22, 23, 58, 59), que permite la cuantificación precisa del DNR, ya que se obtiene una medida que está, desde el punto de vista neurofisiológico, más cerca de la generación del impulso respiratorio que los cambios de presión pleural (56, 60). La medición del DNR mediante el EMGdi ha permitido demostrar una estrecha relación entre el incremento de la disnea, medida por la escala Borg, y del DNR. La medida del volumen minuto respiratorio se relaciona mal con la disnea ya que, bajo el esfuerzo físico, y una vez superado el punto de desacoplamiento, a pesar del incremento compensatorio de la frecuencia respiratoria y del esfuerzo muscular y "drive" respiratorio, el volumen minuto alcanza una meseta. A pesar del incremento paralelo de la disnea y del "drive neural", no se consigue obtener un incremento del volumen minuto (18, 56).

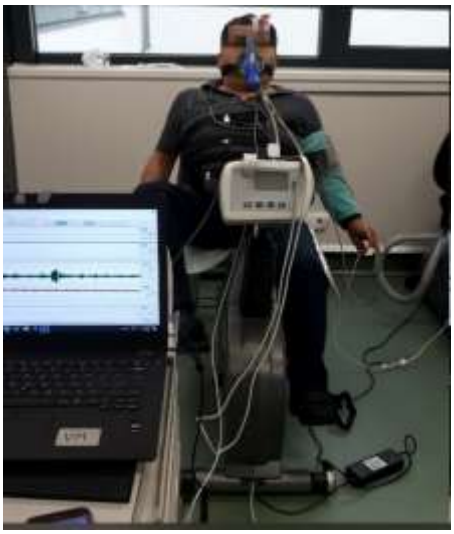
El estudio del comportamiento del DNR, como se ha descrito previamente, se ha realizado en pacientes con EPOC grave en situación de reposo y durante el ejercicio físico (18, 56), pero no se ha estudiado tan extensamente en pacientes con VNI. Es posible que la VNI,

al aumentar la ventilación alveolar y el volumen corriente, modifique las características mecánicas respiratorias responsables del DNR.

La medición del drive neural a partir de electromiografía diafragmática (EMGdi) se considera el método "gold standard" pero cuenta con una serie de problemas asociados. Quizá el más relevante es la invasividad del método: requiere el uso de una sonda esofágica con múltiples electrodos, cuya inserción puede resultar incómoda para el paciente.

Se ha propuesto el uso de electromiografía paraesternal como un marcador subrogado de la actividad eléctrica muscular diafragmática con una buena correlación con la electromiografía diafragmática a través de catéter esofágico (52, 61-73). Su uso, en pacientes en reposo, parece prometedor para obtener una señal con relevancia clínica, habiéndose propuesto como marcador de esfuerzo muscular respiratorio aumentado en EPOC estable y agudizado (22, 74), en población pediátrica con Fibrosis Quística (22, 23) y en otros pacientes respiratorios. Su uso durante el ejercicio es controvertido, dado que a activación muscular de la cintura escapular que se produce al agarrar el manillar de la bicicleta condiciona una interferencia en el registro de la musculatura paraesternal(20). Se propone el uso de bicicletas recumbentes para mantener los brazos en reposo y limitar esta interferencia (Figura 5).

Figura 5, Paciente en bicicleta recumbente



Paciente en bicicleta recumbente con un sistema de monitorización durante el esfuerzo de electromiografía paraesternal (EMGpara) y de esternocleidomastoideo (EMGscm), junto bandas pletismográficas de inductancia para evaluar la sincronía toracoabdominal, y monitorización de flujo inspiratorio, presión en mascarilla, y oxicapnografia transcutánea. Nótese que los brazos relajados evitan la contracción de pectorales y deltoides que podrían "contaminar" la señal de EMGpara.
(Imagen reproducida con permiso del paciente).

2. JUSTIFICACIÓN DE LA INVESTIGACIÓN

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La presente tesis doctoral se fundamenta en la necesidad de abordar las limitaciones del conocimiento actual sobre los mecanismos fisiopatológicos de la limitación al ejercicio en pacientes con EPOC severa y el desarrollo de estrategias terapéuticas optimizadas. A pesar de los avances significativos en la comprensión de la EPOC y el desarrollo de intervenciones de rehabilitación respiratoria, persisten importantes lagunas en el conocimiento que limitan la capacidad de proporcionar tratamientos individualizados y efectivos.

La limitación al ejercicio en la EPOC es un fenómeno complejo que involucra múltiples mecanismos fisiopatológicos interrelacionados. Aunque se han identificado los principales mecanismos, incluyendo la hiperinsuflación dinámica, el desacoplamiento neuroventilatorio y la TAA, la comprensión de cómo estos mecanismos interactúan y se modifican con diferentes intervenciones terapéuticas sigue siendo limitada.

La TAA representa un aspecto particularmente importante pero insuficientemente estudiado de la limitación al ejercicio en la EPOC. Aunque se reconoce que la TAA contribuye significativamente a la disnea y la limitación al ejercicio, los métodos tradicionales de evaluación presentan limitaciones importantes que han impedido una caracterización adecuada de este fenómeno.

El uso de soporte respiratorio durante el ejercicio en pacientes con EPOC ha demostrado beneficios significativos, pero la optimización de estas estrategias requiere un mejor entendimiento de los mecanismos de acción y la identificación de predictores de respuesta. La VNI y la TAF representan modalidades prometedoras, pero la selección entre diferentes opciones y la individualización del tratamiento siguen siendo desafíos clínicos importantes.

La monitorización de la respuesta al ejercicio y al soporte respiratorio en pacientes con EPOC requiere herramientas que puedan proporcionar información objetiva sobre los mecanismos fisiopatológicos subyacentes. El desarrollo de métodos mejorados para la evaluación de la TAA y el impulso neural respiratorio puede facilitar la optimización del tratamiento y la identificación de pacientes que se beneficiarían de estrategias específicas.

3. HIPÓTESIS DE TRABAJO

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3.1. Hipótesis Principal

El soporte respiratorio no invasivo durante el ejercicio en pacientes con EPOC severa reduce significativamente el impulso neural respiratorio y mejora la sincronía toracoabdominal, con efectos diferenciales entre la VNI y la TAF.

3.2. Hipótesis Secundarias

- Hipótesis metodológica: El Global Phase Delay (GPD) es superior al ángulo de fase tradicional para la detección y cuantificación de asincronías toracoabdominales severas y movimientos paradójicos.
- Hipótesis fisiopatológica: Los pacientes con EPOC severa presentan patrones específicos de TAA durante el ejercicio que se correlacionan con la severidad de la enfermedad y el grado de disfunción respiratoria.
- Hipótesis terapéutica: La VNI es superior a la TAF en términos de reducción del impulso neural respiratorio durante el ejercicio, pero ambas modalidades mejoran la tolerancia al ejercicio comparadas con la terapia convencional con oxígeno.
- Hipótesis pronóstica: Los patrones de TAA durante el ejercicio pueden predecir la respuesta al soporte respiratorio no invasivo y ayudar en la selección individualizada del tratamiento.

4. OBJETIVOS DE LA TESIS

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4.1. Objetivo General

Investigar los mecanismos fisiopatológicos de la limitación al ejercicio en pacientes con EPOC severa, con especial énfasis en la TAA y el impulso neural respiratorio, y evaluar el impacto de diferentes modalidades de soporte respiratorio no invasivo (VNI y TAF) en estos mecanismos.

4.2. Objetivos Específicos

1. **Evaluar el impacto del soporte respiratorio no invasivo en el impulso neural respiratorio:** Comparar los efectos de la VNI y la TAF en el impulso neural respiratorio durante el ejercicio en pacientes con EPOC severa.
2. **Desarrollar y validar métodos mejorados para la evaluación de la TAA:** Superar las limitaciones metodológicas del ángulo de fase tradicional mediante el desarrollo del Global Phase Delay (GPD) como parámetro alternativo para la cuantificación de la TAA.
3. **Caracterizar los patrones de TAA durante el ejercicio en EPOC severa**: Identificar y describir los diferentes patrones de TAA que se presentan durante el ejercicio en pacientes con EPOC severa y establecer sus correlaciones con parámetros clínicos y funcionales.
4. **Identificar predictores de respuesta al soporte respiratorio:** Determinar qué características clínicas, funcionales y fisiopatológicas predicen una respuesta favorable al soporte respiratorio durante el ejercicio.

5. MATERIAL Y MÉTODOS

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5.1. Diseño del Estudio

La presente tesis doctoral se basa en un diseño experimental, longitudinal, prospectivo y controlado que incluye tres estudios complementarios:

- **Estudio metodológico**: Desarrollo y validación de un nuevo método (Global Phase Delay, GPD) como método mejorado para la evaluación de la TAA.
- **Estudio observacional**: Caracterización de los patrones de TAA durante el ejercicio en pacientes con EPOC severa y sus correlaciones clínicas y funcionales.
- **Estudio experimental**: Evaluación comparativa de los efectos de la VNI y la TAF en el impulso neural respiratorio durante el ejercicio.

5.2. Población de Estudio

La población de estudio incluye pacientes con EPOC severa en lista de espera para trasplante pulmonar, evaluados en la Unidad de Trasplante Pulmonar del Hospital Universitario 12 de Octubre. Esta población fue seleccionada por presentar limitaciones ventilatorias severas que permiten estudiar los mecanismos fisiopatológicos de interés en su expresión más intensa. Además, la extensa evaluación pre-trasplante permite descartar factores de confusión como la presencia de comorbilidades cardiovasculares que contribuyan a la limitación al esfuerzo. Por lo tanto, es una población cuya limitación al esfuerzo es puramente respiratoria.

Los criterios de inclusión fueron los siguientes:

- Diagnóstico de EPOC según criterios GOLD, evidencia de atrapamiento aéreo (volumen residual > 120% del predicho).
- Pacientes registrados en la lista de espera de trasplante pulmonar en el Hospital Universitario 12 de Octubre de Madrid, superando toda la evaluación previa a su inclusión.
- Limitación al flujo espiratorio durante el ejercicio.
- Adaptación previa a VNI domiciliaria.

- Capacidad para realizar protocolos de ejercicio.

Los criterios de exclusión compenden:

- Comorbilidades incontrolables que limiten la capacidad de ejercicio.
- Rechazo a participar en el estudio.
- Incapacidad para realizar ejercicio de pedaleo por limitaciones motrices.
- Incapacidad para generar señales electromiográficas de suficiente calidad para su interpretación.

5.3. Medidas

La instrumentación utilizada incluye equipos avanzados de monitorización fisiológica: sistema de adquisición de datos PowerLab (ADInstruments@), bandas de pletismografía de inductancia respiratoria (Braebon RIP), electrodos de superficie para electromiografía de músculos respiratorios, sensores de CO2 transcutáneo y oximetría de pulso (Sentec), y ventiladores de alto rendimiento (Astral 150, ResMed). El detalle completo de estos métodos se aborda en profundidad en los artículos que componen esta tesis.

La electromiografía de músculos paraesternales se utiliza para la cuantificación del impulso neural respiratorio, siguiendo protocolos estandarizados previamente validados. La pletismografía de inductancia respiratoria se emplea para la evaluación de la TAA, con análisis automatizado mediante algoritmos desarrollados específicamente para el estudio.

5.4. Protocolos de Ejercicio

Los protocolos de ejercicio incluyen pruebas de entrenamiento en cicloergómetro semirreclinado a carga constante al 75% de la carga máxima tolerada. En concreto, el protocolo para fijar la carga máxima tolerada (“ramp test”) se establece en los siguientes pasos:

- Se inicia con el paciente tranquilo, descansado tras la fase de calentamiento y fisioterapia respiratoria. Se explica detalladamente al paciente la prueba, indicándole que debe realizar el máximo esfuerzo posible hasta que se detenga

cuando no pueda continuar por disnea o fatiga, así como cualquier malestar que presente durante el esfuerzo.

- Se adapta el cicloergómetro recumbente para obtener la mejor ergonomía.
- Se monitoriza con electrocardiograma y oximetría continua, y tensión arterial sistémica no invasiva cada 3 minutos.
- Se asegura la oxigenación mediante gafas nasales para obtener SpO2 92-94%.
- Se inicia el pedaleo con una carga de 10 watios (W) con un progresivo ascenso de 15W cada minuto.
- Se finaliza la prueba cuando el paciente se detiene por fatiga, por SpO2 <85% a pesar de oxígeno, aumento de frecuencia cardiaca (FC) por encima de la FC máxima estimada (220-edad), o respuesta hipertensiva (con tensión arterial sistólica >200 mmHg) o hipotensión, o bien si se presentan arritmias.
- Al finalizar la prueba de ramp test, el paciente sigue pedaleando sin resistencia para recuperar la FC y saturación de oxígeno del reposo, disminuir la TA del esfuerzo, normalizar patrón ventilatorio y relajar los músculos tras el esfuerzo con ejercicio suave.

La carga máxima tolerada en esta prueba se registra, y en las posteriores sesiones se establecerá como carga el 75% de los watios desarrollados. Los pacientes realizan sesiones de 10 minutos de ejercicio seguidos de 5 minutos de recuperación bajo tres condiciones diferentes: terapia convencional con oxígeno (COT), VNI y TAF.

La secuencia de los protocolos se realiza en días consecutivos, con titulación individualizada de los parámetros de soporte respiratorio. Para la VNI, se ajustan las presiones inspiratoria y espiratoria para lograr una reducción del impulso neural respiratorio de al menos 20%. Para la TAF, se utiliza un flujo de 40 L/min con ajuste de la FiO2 para mantener SpO2 > 92%.

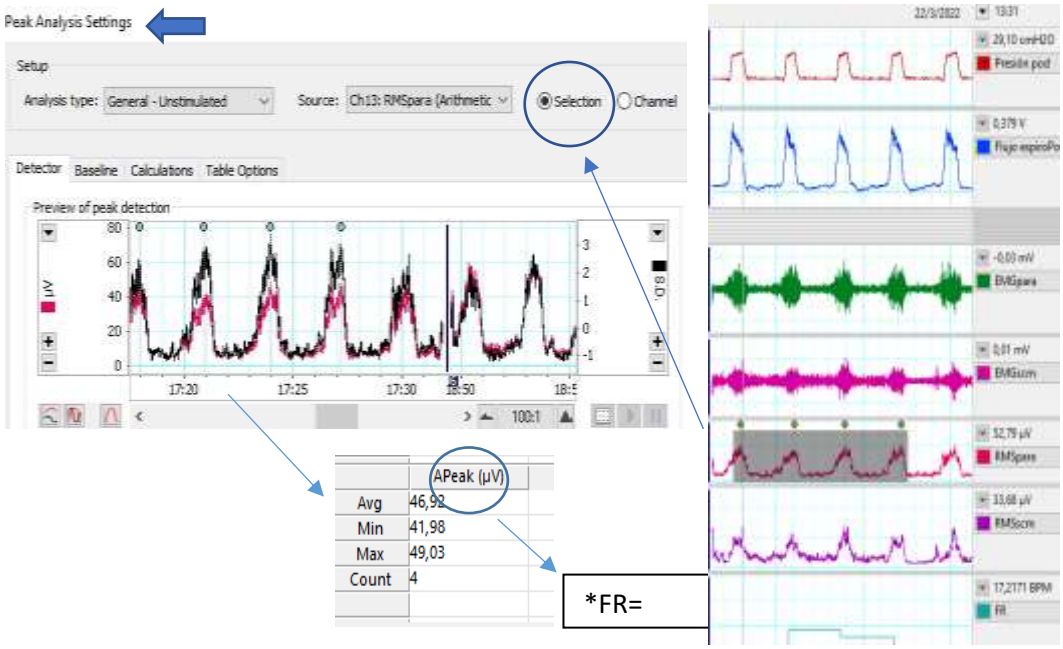
5.5. Procesamiento de señales

5.5.1. Procesamiento de la señal de electromiografía para el cálculo del drive neuroventilatorio

El procesamiento de la señal de electromiografía (EMG) para el cálculo del drive neuroventilatorio (NRD) en este estudio se realizó siguiendo protocolos validados en la literatura. Durante las pruebas de ejercicio, se emplearon electrodos de superficie ubicados en el segundo espacio intercostal parasternal y sobre el músculo esternocleidomastoideo, conforme a lo descrito previamente por Jolley et al. La señal EMG fue adquirida a una frecuencia de muestreo de 2000 Hz, aplicando un filtro de paso alto de 80 Hz para eliminar artefactos y ruido de baja frecuencia. Posteriormente, la señal fue rectificada y procesada mediante el método de raíz cuadrada media (RMS), normalizándola respecto al valor máximo obtenido durante maniobras inspiratorias máximas (MIP) realizadas antes del ejercicio. Con el objetivo de evitar artefactos tónicos no respiratorios, se utilizó la señal de los cinturones de pletismografía inductiva toracoabdominal para identificar el inicio de la inspiración, asegurando que el análisis del EMG correspondiera únicamente a la actividad inspiratoria. Finalmente, el NRD se calculó como el producto de la frecuencia respiratoria y el valor pico RMS normalizado de la EMG para cada músculo analizado, aunque también se hizo un análisis del valor del área bajo la curva del RMS.

De acuerdo a la literatura publicada, el EMG de los músculos respiratorios, especialmente la intercostal parasternal, es un biomarcador robusto del drive respiratorio central y de la carga muscular inspiratoria, y puede interpretarse como un subrogado no invasivo de la activación diafragmática (75). La activación del esternocleidomastoideo (EMGscm) es más tardía en el esfuerzo, reflejando el reclutamiento de musculatura accesoria.

Figura 6. Procesamiento de la señal de EMG. Identificación de los valores pico y área bajo curva mediante la función "Peak Analysis " de Labchart 8



$$DNR = \sqrt{\frac{EMG_{paraesternal} + EMG_{esternocleidomastoideo}}{2}} x\ FR$$

5.5.2. Procesamiento de la señal de las bandas pletismográficas

Las señales de las bandas pletismográficas (tórax y abdomen) se adquirieron mediante un transductor pletismográfico (Braebon RIP®, BRAEBON Medical Corporation, ON, Canadá) y adquiridas mediante un conversor analógico-digital (PowerLab 16/35, AD Instruments®, Australia) a una frecuencia de muestreo de 500 Hz. Antes del análisis matemático, se aplicó un filtro "*band-pass*" de 0,5-3 Hz para limpiar la señal. Posteriormente, mediante un script personalizado en MATLAB, se realizó la normalización de la amplitud de ambas señales (asignando valores entre 0 y 1) y se identificaron automáticamente los inicios y finales de los ciclos respiratorios (inspiración/espiración) detectando los máximos y mínimos locales, con una verificación manual posterior para asegurar la precisión ante posibles artefactos.

5.6. Análisis Estadístico

El análisis estadístico incluye métodos descriptivos e inferenciales apropiados para el diseño del estudio. Se utiliza ANOVA de medidas repetidas para la comparación entre condiciones, con corrección post-hoc de Bonferroni para comparaciones múltiples. La

correlación entre variables se evalúa mediante regresión lineal. El nivel de significación se establece en $p < 0,05$.

De acuerdo con los trabajos previamente publicados (18, 56), todos los pacientes con EPOC expresaron desacoplamiento neuro-respiratorio. Asumiendo un descenso del 10% de DNR como clínicamente significativo, con un nivel de confianza del 95% (error alfa 5%) y un poder del 80% (1-beta), asumiendo un 5% de pérdidas, se calculó una n necesaria de 18 pacientes. Se ha empleado la calculadora de tamaño muestral para ANOVA proporcionada por http://powerandsamplesize.com/ .

5.7. Aspectos éticos

El protocolo de estudio ha sido aprobado por el Comité Ético de Investigación del CEIC del Hospital 12 de Octubre (resolución 18/025). La participación en este estudio fue totalmente voluntaria, y no afectó a la valoración del paciente en la lista de espera de trasplante. Desde el punto de vista de la confidencialidad se aseguró el cumplimiento de lo recogido en la LOPD 15/1999. En concreto, se generó una base de datos con un número consecutivo, como único dato identificativo del paciente. La correlación entre el número de inclusión en el estudio y el número de historia clínica (como único identificador) se almacenó en una base de datos ubicada en la carpeta del servicio de Neumología en el servidor "Y", de acceso protegido mediante contraseña, únicamente autorizado a dos investigadores del trabajo (Sayas y Hernández-Voth).

La intervención sobre los pacientes no supuso ningún riesgo (derivado de la determinación de electromiograma de superficie) y solo consiste en la medición de la actividad muscular durante el esfuerzo basal, con VNI y con gafas nasales de alto flujo, de manera similar a como se realiza actualmente la rehabilitación de estos pacientes, y dentro del programa de rehabilitación habitual.

Previo a la inclusión de cualquier paciente, este protocolo de estudio fue registrado en ClinicalTrials.gov con el número NCT04597606 (https://clinicaltrials.gov/study/NCT04597606).

6. RESULTADOS

6. RESULTADOS

6.1. Organización de la Tesis

La presente tesis doctoral se organiza en formato de compendio de publicaciones, incluyendo tres artículos científicos originales que abordan los objetivos específicos de la investigación.

Artículo 1: "Measurement of thoraco-abdominal synchrony using respiratory inductance plethysmography: technical aspects and a proposal to overcome its limitations"

Este artículo aborda el objetivo metodológico de la tesis, presentando el desarrollo y validación del Global Phase Delay como método mejorado para la evaluación de la TAA. El estudio incluye el análisis de 2290 ciclos respiratorios de diferentes poblaciones clínicas y demuestra la superioridad del GPD sobre el ángulo de fase tradicional para la detección de asincronías severas.

Artículo 2: "Thoracoabdominal Asynchrony in Very Severe COPD: Clinical and Functional Correlates During Exercise"

Este artículo presenta la caracterización de los patrones de TAA durante el ejercicio en pacientes con EPOC severa. El estudio identifica dos patrones distintos de TAA (rotación horaria y antihoraria) y establece sus correlaciones con parámetros clínicos y funcionales. Los resultados demuestran que el patrón de rotación horaria se asocia con mayor severidad de la enfermedad y mayor impulso neural respiratorio.

Artículo 3: "Muscle Unloading During Exercise: Comparative Effects of Conventional Oxygen, NIV, and High-Flow Therapy on Neural Drive in Severe COPD"

Este artículo evalúa los efectos comparativos de la VNI y la TAF en el impulso neural respiratorio durante el ejercicio. Los resultados demuestran que la VNI es superior a la TAF en términos de reducción del impulso neural respiratorio, con una reducción del 60% comparada con la terapia convencional con oxígeno.

6.2. Pacientes incluidos

Durante el período de estudio, se incluyeron 47 pacientes con EPOC en el programa de trasplante pulmonar. Solo 23 pacientes, previamente bajo VNI domiciliaria, cumplieron los criterios de inclusión. Un paciente fue sometido a trasplante pulmonar antes de que se pudiera realizar el ensayo y 2 de ellos no presentaron señales de EMG fiables a pesar de varios intentos.

Se reclutaron 20 pacientes con EPOC grave (7 mujeres). Los datos antropométricos, las pruebas de función pulmonar y los parámetros del ventilador para toda la cohorte se muestran en la Tabla1.

Tabla1: datos antropométricos, función pulmonar y parámetros del ventilador:

Categoría	**Parámetro**	**Media**	**Desviación estándar**
Datos antropométricos	Edad (años)	60	3,9
	Sexo (F)	6 (30%)	
Pruebas de función pulmonar	FEV1 (ml)	568,2	131,1
	FEV1 (%)	19,05	4,18
	FVC (ml)	1934,5	760,5
	FVC (%)	50,75	17,8
	RV (ml)	6023,56	1180,4
	RV (%)	283,4	74,54
	TLC (ml)	8280,89	1143,9
	TLC (%)	141,2	27,1

Tabla1: datos antropométricos, función pulmonar y parámetros del ventilador:

Categoría	Parámetro	Media	Desviación estándar
Gases arteriales	PaO2 (mm Hg)	62,5	10,91
	PaCO2 (mm Hg)	50,36	6,56
	pH	7,38	0,04
Parámetros en el ventilador	IPAP (cm H2O)	20,4	4,62
	EPAP (cm H2O)	8,8	2,2

6.3. Artículos

6.3.1. Artículo 1: Measurement of thoraco-abdominal synchrony using respiratory inductance plethysmography: technical aspects and a proposal to overcome its limitations

Sayas J, Lalmolda C, Corral M, Flórez P, Hernández-Voth A, Janssens JP, et al. Measurement of thoraco-abdominal synchrony using respiratory inductance plethysmography: technical aspects and a proposal to overcome its limitations. Expert Rev Respir Med. 2024;18:227-36.

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ORIGINAL RESEARCH

Measurement of thoraco-abdominal synchrony using respiratory inductance plethysmography: technical aspects and a proposal to overcome its limitations

Javier Sayas[a], Cristina Lalmolda[b], Marta Corral[a], Pablo Flórez[b], Ana Hernández-Voth[a], Jean Paul Janssens[c,d], Claudio Rabec[e], Bruno Langevin[f], Frédéric Lofaso[g,h], Annalisa Carlucci[i], Claudia Llontop[j], Joao Carlos Winck[k], Jesús González Bermejo[l] and Manel Lujan[b,m]on behalf of the SOMNO-NIV group

[a]Pulmonology Service, Hospital Universitario 12 de Octubre, Universidad Complutense de Madrid, Madrid, Spain; [b]Servei de Pneumologia, Parc Taulí Hospital Universitari. Institut d'Investigació i Innovació Parc Taulí (I3PT-CERCA), Universitat Autònoma de Barcelona, Sabadell, Spain; [c]Division of Pneumology, Geneva University Hospitals, Geneva, Switzerland; [d]Medicine, University of Geneva, Geneva, Switzerland; [e]Department of Pulmonary Medicine and Intensive Care Unit. Constitutive Reference Center for Rare Pulmonary Diseases, University Hospital of Dijon Bourgogne, Dijon, France; [f]Réanimation, Pôle Soins Aigus, Centre Hospitalier Alès, Alès, France; [g]INSERM-UMR 1179, Versailles Saint-Quentin University, Paris Saclay University, France; [h]Department of Physiology, AP-HP, Hôpital Raymond Poincaré, Garches, France; [i]Dipartimento di Medicina e Chirurgia, Università Insubria Varese-Como. Pneumologia Riabilitativa. Istituti Clinici Scientifici Maugeri-Pavia, Pavia, Italy; [j]Unité ambulatoire d'appareillage respiratoire de domicile. Département R3S (Respiration Réanimation, Réhabilitation, Sommeil), Groupe hospitalier Pitié-Salpétrière, Paris, France; [k]UniC Cardiovascular R&D Centre, Faculdade de Medicina da Universidade do Porto, Porto, Portugal; [l]Sorbonne Université, INSERM, UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique; AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpétrière, Département R3S (Respiration, Réanimation, Réadaptation respiratoire, Sommeil), Service de médecine de readaptation respiratoire, Paris, France; [m]CIBERES, Madrid, Spain

ABSTRACT

Background: Thoraco-abdominal asynchrony (TAA) is usually assessed by respiratory inductance plethysmography. The main parameter used for its assessment is the calculation of the phase angle based on Lissajous plots. However, there are some mathematical limitations to its use.

Research design and methods: Sequences of five breaths were selected from a) normal subjects, b) COPD patients, both at rest and during exercise, and c) patients with obstructive apnea syndrome. Automated analysis was performed calculating phase angle, loop rotation (clockwise or counterclockwise), global phase delay and loop area. TAA severity was estimated quantitatively and in subgroups.

Results: 2290 cycles were analyzed (55% clockwise rotation). Phase angle ranged from −86.90 to + 88.4 degrees, while global phase delay ranged from −179.75 to + 178.54. Despite a good correlation with global phase delay ($p < 0.01$, ANOVA test), phase angle and loop area were not able to correctly classify breaths with severe deviation and paradoxical movements (p=ns, Bonferroni post hoc test).

Conclusions: Global phase delay covers the whole spectrum of TAA situations in a single value. It may be a relevant parameter for diagnosis and follow-up of clinical conditions leading to TAA.

Clinical trial registration: The trial from which the traces were obtained was registered at ClinicalTrials.gov ;(identifier: NCT04597606).

ARTICLE HISTORY
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KEYWORDS
Global phase delay; paradox; phase angle; COPD; Obstructive sleep apnea

1. Introduction

Thoracic-abdominal asynchrony (TAA) is defined as the presence of a delay between the movement of the thoracic rib cage (RC) and the abdomen (Abd) during the respiratory cycle [1]. As the inspiratory cycle begins, the contraction of the diaphragm pushes the abdomen outwards, while almost simultaneously the start of an inspiratory flow inflates the chest, increasing its volume. Thus, the abdomen and chest increase (and decrease) in volume almost simultaneously throughout the respiratory cycle. Asynchrony occurs when there is a lag time between the movements of these two compartments. When this lag reaches its maximum, complete asynchrony (or paradox, referred to the movement of the compartments in opposite directions) is present [2].

TAA has been studied using various methods. In recent research, non-contact methods such as structured light plethysmography [3], or skin electrode respiratory impedance [4], have been proposed. However, respiratory inductance plethysmography (RIP) remains the most widely used and tested method in the study of TAA [5]. RIP is a technique based on Faraday's and Lenz's laws that allows the qualitative or quantitative study of the individual's thoracic and abdominal movements in different clinical situations (sleep, exercise, rehabilitation) using two belts attached to the thoracic and abdominal surfaces. It is a technique validated by the American Academy of Sleep as a surrogate for effort in sleep studies [5]. Several authors have validated the RIP signal to identify respiratory effort in sleep apnea, allowing differentiation between central and obstructive apnea [6]. It is also considered a surrogate for tidal volume and has been used to monitor respiratory patterns in infants and critical care patients [7,8]. From a quantitative point of view, the contribution of each compartment to the tidal volume (RC/VT, AB/VT) was also analyzed [9,10]

CONTACT Manel Lujan mlujan@tauli.cat Servei de Pneumologia, Parc Taulí Hospital Universitari. Institut d'Investigació i Innovació Parc Taulí (I3PT-CERCA), Universitat Autònoma de Barcelona. C. Parc Taulí, Sabadell 1 08208, Spain

More interesting is the use of both thoracic and abdominal belts to analyze the synchrony of movement between the thorax and the abdomen. The technical approach to this analysis was first established by Konno and Mead using the Lissajous figure approach, plotting abdominal motion on the x-axis against thoracic motion on the y-axis [11]. It assumes that both the thorax and abdomen move in a pure sinusoidal pattern ('simple harmonic motion'). TAA can be easily identified, measured, and objectively monitored by examining the phase shift (or phase angle) between the thoracic and abdominal signals. The following equation can be used to calculate the phase angle (Φ):

$$\sin\Phi = m/s$$

In this equation, 'm' denotes a line on the Chest-Abdomen plot. This line is parallel to the horizontal axis and is positioned midway between the maximum perpendicular to the chest and the origin. Additionally, 's' represents the length of a line extending from the maximum perpendicular to the abdomen to the origin, as illustrated in Figure 1.

In addition, the resultant loop when chest and abdominal movements are plotted continuously on an X-Y graph, provide visual insight into changes in the shape and rotation direction of the loop. Synchronous expansion and contraction of the chest and abdomen will result in a closed or very narrow loop with a positive slope on the X-Y plot. In TAA, however, the loop becomes progressively wider as the phase difference between the RC and ABD movements increases until a phase angle of 90 degrees is reached. Beyond a phase angle of 90 degrees, the loop starts to narrow again, but with a negative slope. Different patterns of TAA are shown in Table 1. However, there are some limitations to this approach: firstly, its calculation is based only on the ratios between thoracic and abdominal displacement at a single point in the respiratory cycle (the midpoint of the thoracic excursion), and the ratio may change, especially for aberrant loop shapes. Furthermore, there is a mathematical limit to simply calculating the ratio of the m and s vectors, as the range of the ratio can only be between 0 and 1 (m can never be higher than 1 or lower than 0, see Figure 1), which means that the $\sin^{-1}$ values would be between 0 and 90 degrees. Finally, and more relevant, it would not inform which belt (thoracic or abdominal) is ahead, since the XY plot would be identical in both cases.

Various concepts have been added to this mathematical method to increase the information provided by the phase angle. For example, the index of thoracic and abdominal asynchrony, depending on the inspiratory and expiratory ranges delimited by the Lissajous figure, and the concept of paradox, to describe the inversion of one of the two belts during the inspiratory phase, distinguishing between the thoracic paradox and the abdominal paradox, depending on the involvement of one or the other belt [12]. Finally, more recent studies have assigned a positive sign to clockwise rotation (thorax ahead over the abdomen) and a negative sign when the abdominal compartment was ahead (counterclockwise) [13]. However, the phase angle often remains the tool most used for the estimation of the lag time between the two compartments.

The aim of the present work is to validate new indices derived from the analysis of RIP signals that could improve or potentially simplify the information provided by the phase angle.

2. Patients and methods

2.1. Patients

Sequences of ventilatory cycles from healthy individuals and patients with severe chronic obstructive pulmonary disease (COPD) at rest and in semi-recumbent exercise in a cycloergometer, as well as patients with obstructive apnea syndrome (OSA), were included for the present analysis. The reason for the selection of such a diversity of patients was to achieve the greatest range in the thorax-abdomen relationships.

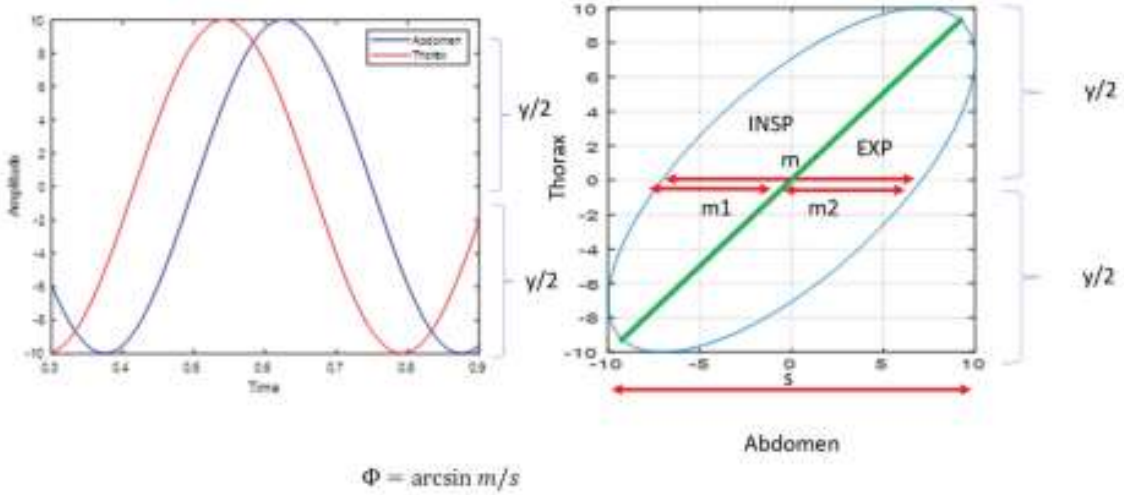
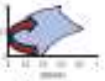
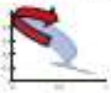
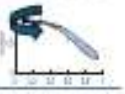


Figure 1. Example of phase angle calculation using an automatically generated function offset by 60°. Note that the red (thoracic) belt is ahead, producing the figure on the right, with a clockwise rotation. If the blue (abdominal) belt had been ahead, the same figure would have been generated on the XY axis, but with a counterclockwise rotation. The vector 'm' could actually be considered as two different vectors, m1 and m2, where m1 is the distance from the plot to the bisector in the Lissajous plot in the inspiratory phase and m2 is the same distance in the expiratory phase. The bisector line would represent the 'ideal state' where the two signals are in phase.

Table 1. Different TAA patterns (collected from clinical samples).

Thoracoabdominal asynchrony	Rotation direction	Image in amplitude/time axis	Lissajous figure
No TAA or minimum TAA	Can be clock or counterclockwise		
Moderate (thorax ahead)	Clockwise		
Severe (thorax ahead)	Clockwise		
Abdominal paradox	Clockwise		
Moderate (abdomen ahead)	Counterclockwise		
Severe (abdomen ahead)	Counterclockwise		
Thoracic paradox	Counterclockwise		

TAA was assessed using two different plots (columns 3 and 4): amplitude/time axis (blue: abdomen, red: thorax) and Lissajous figure. In the Lissajous figure, the abdomen is on the horizontal axis and the thorax is on the vertical axis. The direction of rotation is indicated in column 4 by red (clockwise) or blue (counterclockwise) arrows.

- Inclusion criteria: For the normal group, absence of cardiac and respiratory disease and a normal spirometry were required. For the COPD group, smoking history (>20 packs/year and spirometry with forced vital capacity > 80% and FEV1/FVC ratio < 70% was required). Finally, for patients with sleep apnea, normal spirometry and apnea/hypopnea index > 30/min were required. All cycles were obtained in the recumbent or semi-recumbent position. The criteria for systematic inclusion of specific tracings were as follows: For healthy subjects and COPD patients, belt tracings at baseline (no exercise) and after 1, 4, 7 and 10 minutes of constant load submaximal exercise in a cycloergometer were selected. To select the most representative cycles of each phase of the exercise, the last five cycles of each phase were analyzed. For patients with upper airway obstruction, belt recordings corresponding to episodes (1 per hour of recording) of apnea were selected. Apneic episodes were defined as peak flow reductions of > 90% from pre-event baseline for ≥10 seconds with belt movements in phase opposition during the event [5].
- For healthy subjects and COPD patients, belt tracings at baseline (no exercise) and after 1, 4, 7 and 10 minutes of constant load submaximal exercise in a cycloergometer were selected. To select the most representative cycles of each phase of the exercise, the last five cycles of each phase were analyzed.
- For patients with upper airway obstruction, belt recordings corresponding to episodes (1 per hour of recording) of apnea were selected. Apneic episodes were defined as peak flow reductions of > 90% from pre-event baseline for ≥10 seconds with belt movements in phase opposition during the event [5].
- Exclusion criteria: Lack of written consent. Patients with central events (absence of movement in the belts during apneic episodes) were also excluded.

Informed consent was required, with protocols approved by the ethics committee of the hospital that performed the recordings (CEIM Hospital Universitario 12 de Octubre, resolution 18/025) The trial from where traces were retrieved was registered as NCT04597606).

2.2. Procedures

The tracings were acquired using two belts (Braebon RIP belts, Braebon Inc, Ontario, Canada) attached to the thorax (around the upper part of the chest, just below the armpits and above the nipples) and the abdomen (around the waistline) of the individuals [5]. Belts were connected to an analogue-digital converter (PowerLab 16/35; AD instruments, Bella Vista, NSW 2153, Australia) by means of a standard BNC connector. The signal acquisition frequency was set at 500 Hz, and a low-pass filter (2 Hz) was set before mathematical analysis.

2.2.1. Mathematical analysis

Data were stored in.m format for automated analysis. A MATLAB script was developed *ad hoc* for the study. The functions implemented in the script were as follows:

- Normalization of abdomen and thoracic signal amplitude (between 0 and 1)
- Identification of the leading belt (thorax ahead of abdomen or vice versa) on the time axis.

- Automatic identification of the start and end of the inspiratory and expiratory phases by determining local maxima and minima for each of the two belts. The accuracy of the start point identification had to be checked by the operator. If the identification was not appropriate because of artifacts, especially in the traces under effort, the sensitivity of the local maxima and minima was modified accordingly, or a safety window (condition of minimum distance between the start and end points of the cycle) was added (Figure 2).
- Automated calculation of the following variables, breath by breath and in groups of five breaths each:

a. Phase angle (Φ), using the method proposed from the Konno and Mead plots, by applying the formula on Equation 1 (see examples in Figure 3).

$$\Phi = \sin^{-1} m/s \quad (1)$$

b. Global phase delay (GPD). Based on the ratio of two different vectors each representing one of the belts. These vectors (Abd and Tho) were determined by joining the minimum and maximum excursion points of each of the belts in the XY plot (Figure 4). GPD was calculated from the slopes of both vectors (m1 -Abd- and m2 -Tho-) and correspond to the angle between both vectors, assigning a positive sign if the advanced belt was the thoracic and a negative sign if it was the abdominal. The formula for the GPD (Equation 2) was:

$$\text{Global phase delay} = Arctg\frac{(m2 - m1)}{1 + m1 * m2} \quad (2)$$

c. Area inside the Lissajous figure as a surrogate for TAA: since the greater the asynchrony, the greater the area inside the loop, a global measure of the area inside the loop can reflect the degree of TAA.

2.2.2. Groups based on Φ and GPD

Ventilatory cycles were distributed into the following groups based on phase angle and GPD:

Phase angle (Φ): Normal: between −30 and 30 degrees. Moderate phase lag: between 30/-30 and 60/-60 respectively, and severe phase lag between 60/-60 and 90/-90 respectively.

GPD groups were defined as follows: Normal: between + 45 and −45 degrees. Moderate clockwise lag: between 45 and 90 degrees. Mild abdominal paradox, between 90 and 135 degrees and severe abdominal paradox, between 135 and 180 degrees. The same criteria were applied to counterclockwise rotation (moderate counterclockwise lag, mild and severe rib cage paradox).

2.3. Statistical analysis

Mean, standard deviation and range of all numerical values studied were provided. The analysis of values for each of the subgroups (when more than two subgroups were present) was performed by ANOVA test, with post hoc Bonferroni correction to identify differences between groups. Correlation between numerical variables was studied by linear regression (R^2, coefficient of determination). The significance level was set at $p < 0.05$. Statistical analyses were performed using SPSS version 25.

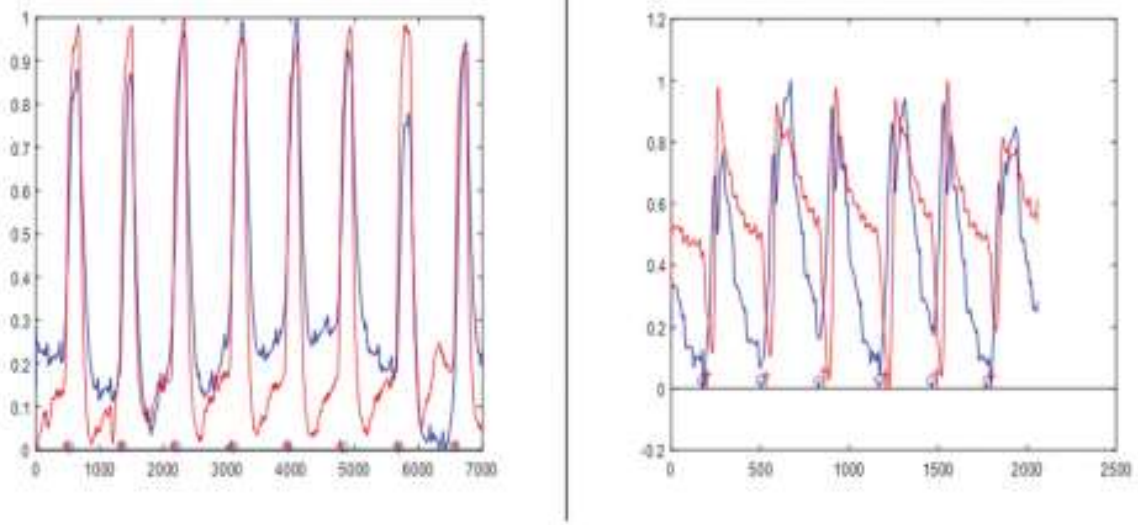


Figure 2. Standardized sequence of thoraco-abdominal belts with automated indication of cycle start. Blue dot, beginning of abdomen (blue signal, abdominal belt). Red cross, start of thorax (red signal, thoracic belt). In addition, the raw belt signals were normalized for amplitude (between 0 and 1, see vertical axis). X axis: number of points. The specific points with blue and red marks were used for later loop analysis. Two different examples are provided, with good synchrony (example on the left) and bad synchrony (on the right).

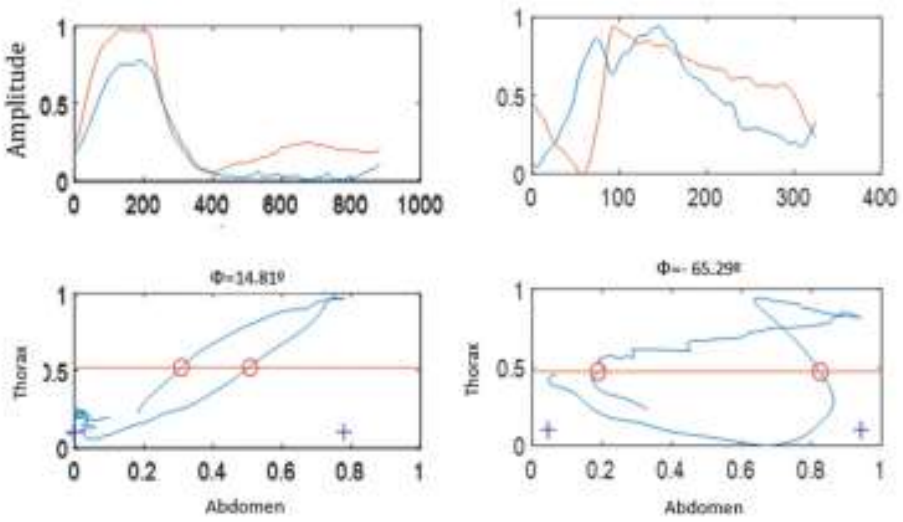


Figure 3. Two different examples of phase angleΦ calculation. In the left panel, the synchronization between the two belts is quite good, with the thoracic belt (red) slightly more advanced than the abdominal belt (blue). The phase angle is 14.81°. On the other hand, in the model on the right, the abdominal belt is clearly ahead with a phase angle of − 65.29°.

Table 2. Mean, standard deviation and range of all the studied parameters. Note that the range of the phase angle is smaller than that of the GPD.

Parameter	Mean (SD)	Range
Phase angle (in degrees)	10.41 (38.97)	−86.90 to + 88.4
Global phase delay (in degrees)	15.89 (74.67)	−179.75 to + 178.54
Area inside the loop (in %)	18 (12)	1 to 66

3. Results

3.1. Descriptive analysis

A total of 2290 ventilatory cycles were included, 1251 (54.6%) with clockwise rotation (thorax ahead) and 1039 (45.4%) with counterclockwise rotation (abdomen ahead).

Table 2 displays the mean and range of values of the main parameters. Whereas the range of phase angle was −86.90 to + 88.4 degrees, GPD range was between −179.75 to + 178.54 degrees.

Figure 5 shows the percentage distribution (histogram) of ventilatory cycles between each of the groups into which the phase angle and GPD were classified. Normal synchronization was found in most cycles, according to both classification criteria.

3.2. Relationships between Φ and other variables

Phase angle showed a good correlation with GPD in a linear regression, but only for the normal and mild deviation groups, both thoracic and abdominal. For severe deviations in Φ, linear regression showed no significant association (see Figure 6).

There was a linear relationship (Figure 7) between phase angle and loop area as far as the groups of values (clockwise or counterclockwise) are concerned. Correlation of absolute values (without considering the sign indicating direction of rotation) of the phase angle with the loop area was highly significant. (R^2 0.403, $p < 0.0001$).

3.3. Relationships between global phase delay groups, Φ and loop area

Using the GPD groups as a reference (including paradox groups), as shown in Figure 8, there was a significant difference of Φvalues ($p < 0.01$ ANOVA test). However, the differences were found only for the normal and mild clockwise and anticlockwise groups. In other words, Φ was not able to predict severe deviations and paradoxes (neither thoracic nor abdominal, p=ns in Bonferroni post hoc test).

Concerning loop area, Figure 9 shows the relationship between GPD and loop area. Similarly to Φ values, differences were found between the groups ($p < 0.01$, ANOVA test), but the differences were also restricted to normal and mild deviation groups, without significant differences for the remaining groups (p=ns, Bonferroni post hoc test).

4. Discussion

The main finding of this study is that the angle formed by the thoracic and abdominal vectors of the plethysmographic belts on the XY axis offers a more accurate information to categorize the phase difference between the two movements as compared to other currently published index (such as the phase angle or the loop area). While phase angle and GPD show good agreement for mild to moderate TAA, GPD is superior for detecting and identifying paradoxical motion. In addition, GPD not only quantifies lagtime but also identifies the responsible compartment being ahead (thorax or abdomen), leading to the diagnosis of different medical conditions.

Asynchronous or paradoxical thoracic movement (anticlockwise) occurs when the chest is pulled in or retracted while abdominal expansion occurs. In other words, the abdominal expansion precedes the inward movement of the chest. This is the most observed pattern and serves as a typical clinical indicator of upper airway obstruction. This pattern is

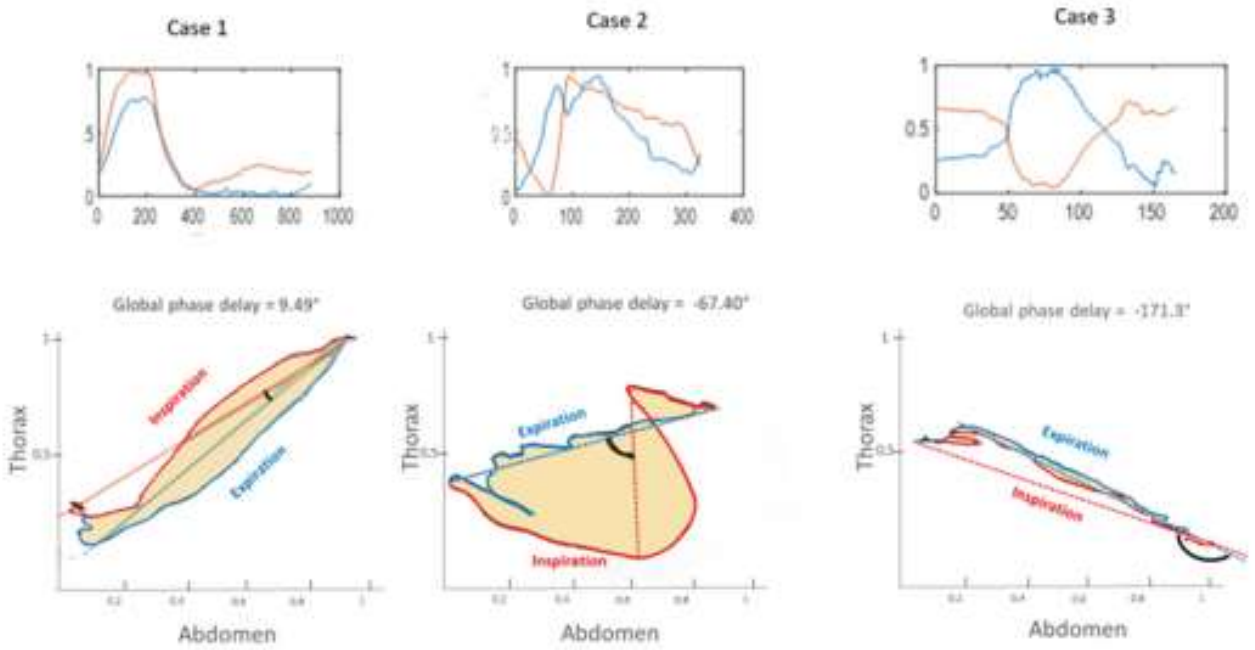


Figure 4. Examples of three cycles with different lags and their Global Phase Delay (GPD) estimates. In case 1 (from a healthy volunteer) the thoracic belt is slightly ahead, but the synchronization is good. In case 2, from a severe COPD patient, the abdominal belt is ahead at the start of the exercise and the thoracic belt starts to rise after 90 msec. Note that when the abdominal belt starts, the thoracic belt moves inwards in a kind of 'Hoover sign.' The cross of the abdominal and thoracic belts before the end of inspiration forms a kind of 'eight.' Finally, in case 3, which corresponds to an obstructive event, the abdominal belt is ahead, with a severe chest paradox.

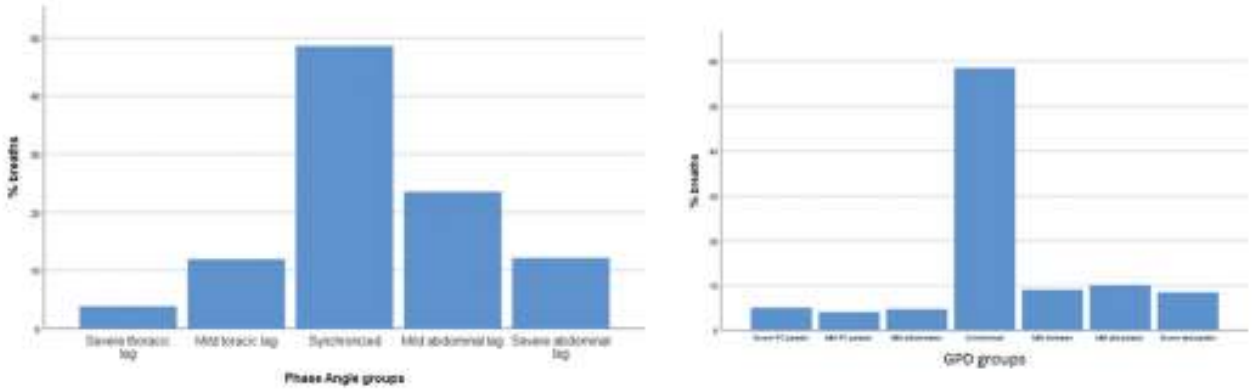
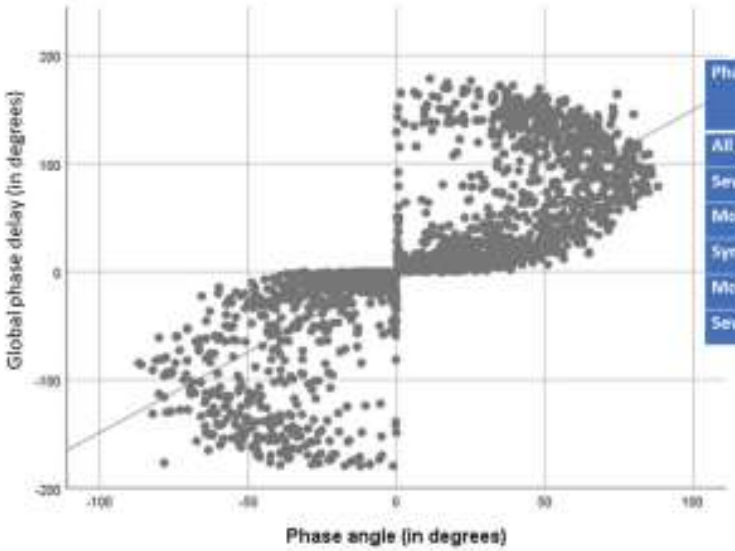


Figure 5. Histogram of breath cycle distribution in each category defined for phase angle and Global phase delay (GPD).

the result of high negative intrathoracic pressure variations caused by diaphragmatic contraction during obstructed inspiration. The same pattern can also be seen in patients with obstructive lower airway disease, dynamic hyperinflation with high lung compliance and low chest wall compliance, such as in emphysema [14]. Analysis of thoracoabdominal synchrony can complement other techniques that have been shown to be useful in determining pulmonary hyperinflation in COPD and its effect on ventilatory pattern [15].

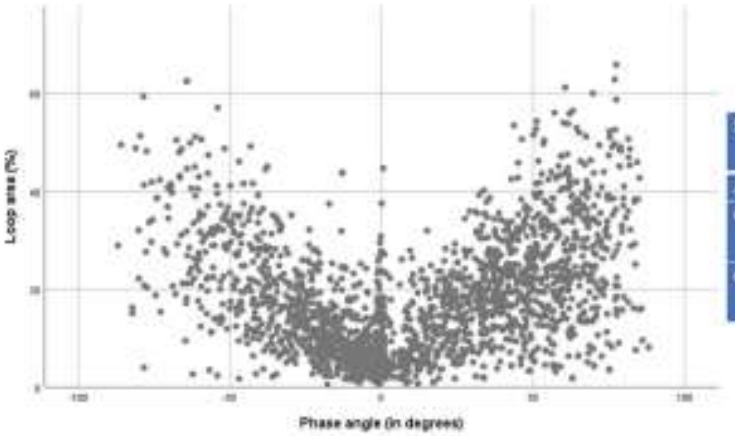
Another factor contributing to paradoxical chest motion is weakness or paralysis of the intercostal muscles, which prevents the chest from stabilizing or expanding during inhalation. As a result, the thoracic cage is pulled inward instead of expanding as it should. This condition is often seen in patients with neuromuscular disorders or with tetraplegia due to spinal cord injury in the lower cervical region.

In contrast, asynchronous or paradoxical abdominal movement is seen in patients primarily affected by diaphragmatic weakness. In such cases, the primary force for inspiration relies on the intercostal muscles, and the diaphragm is passively pulled into the chest, causing inward abdominal motion that is contrary to the typical pattern. This phenomenon is a classic clinical indicator of diaphragmatic paralysis and is often seen in adult patients with COPD who experience acute respiratory failure, suggesting underlying diaphragmatic weakness (and use of accessory muscles) [16].



Phase angle group	R^2	p value
All groups	0.606	<0.01
Severe thoracic lag	0.008	ns
Moderate thoracic lag	0.06	<0.05
Synchronized	0.257	<0.01
Moderate abdominal lag	0.05	<0.05
Severe abdominal lag	0.003	ns

Figure 6. Linear regression between phase angle and Global phase delay (GPD) values. Although the overall R2 value (0.606) was significant, for the subgroups with higher deviation, the association was not significant.



Phase angle group	R^2	p value
All groups	0.403	<0.01
Clockwise breaths	0.483	<0.001
Counterclockwise breaths	0.306	<0.001

Figure 7. Linear regression for the relationship between phase angle and loop area, achieving statistical significance especially when phase angles are taken as a function of rotation (clockwise or counterclockwise). The relationship is also significant when absolute values of phase angle are correlated with area (see text for details).

Estimating the delay or phase lag between plethysmographic belts by calculating the phase angle has been the most widely used strategy in many published studies [10,13,17–20]. However, it is important to note that the calculation of the phase angle has mathematical drawbacks: firstly, it assumes that the waveform is sinusoidal. The sinusoidal function operates on the principles of simple harmonic motion, where position is predictable as a function of amplitude (A) and angular velocity (ω) is, by definition, constant. This analogy could be valid for a normal individual, but in patients with chronic obstructive pulmonary disease (i.e. COPD), the rate of emptying of the thoracic compartment is much slower because of high intrapulmonary resistance, and therefore the basic condition for considering the phase angle valid (the need of a constant angular velocity, ω) is no longer met. In fact, the presence of loops with an abnormal morphology is often due to this phenomenon of inconstant angular velocity. Loops with an '8' shape are common in COPD patients [14] and may distort calculations (Figure 2).

The '8' morphology occurs when there is an initial delay between abdominal activation and thoracic activation. This delay is usually caused by air trapping: as the abdomen increases, there is an initial inverted deflection in the thoracic belt. Once the thoracic motion is initiated, the angular velocity of the thoracic motion increases relative to the abdominal motion, creating the '8' shape. This figure has been described by Konno and Mead and may disappear during REM sleep when inspiratory or expiratory effort becomes more subtle [21].

Secondly, it is important to remember that the relationship between vectors m and s is always between 0 and 1, and therefore, without further calculations, the phase angle should be between 0 and 90 degrees. Studies published in the 1980s

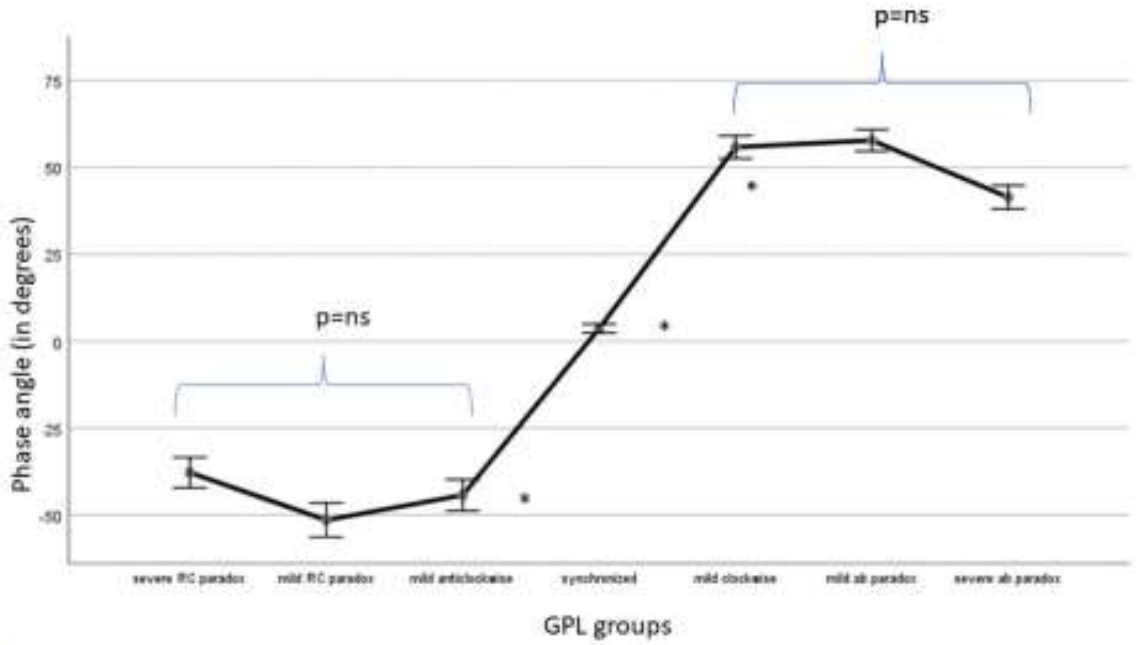


Figure 8. Relationship between Global phase delay (GPD) groups and phase angle. As shown in graph, the phase angle values tend to peak in the group between ±90/135 degrees and then decrease again ($p < 0.01$ ANOVA test, differences only in the groups labeled with an asterisk).

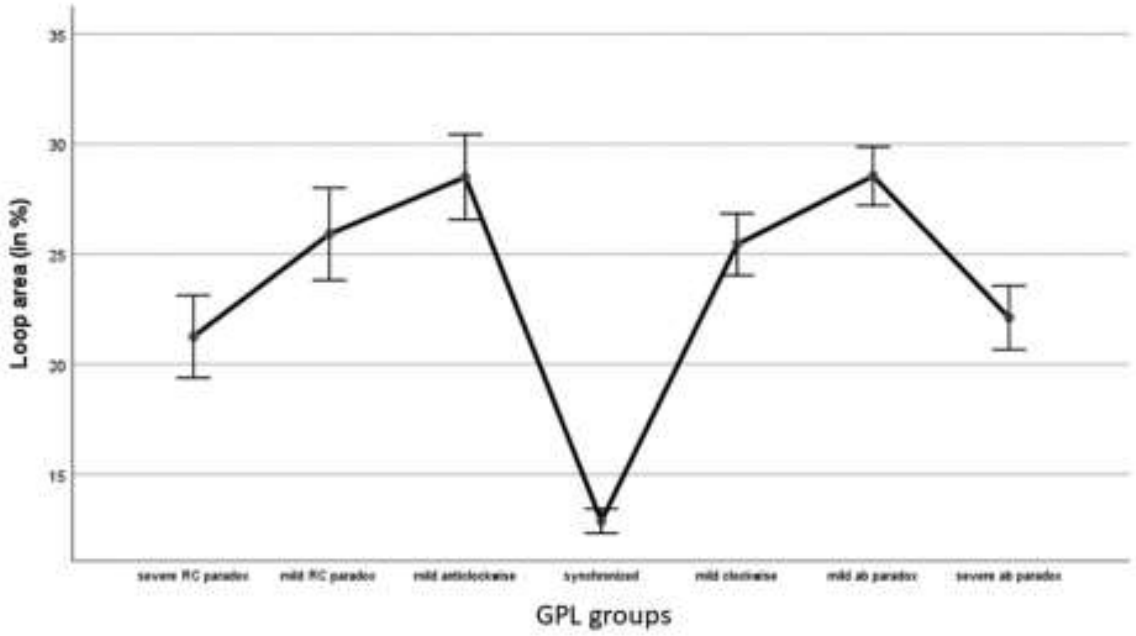


Figure 9. Relationship between groups and loop area. The only significant differences were between the synchronized group and the other groups. In contrast, there were no differences between the severe paradox, mild paradox and mild deviation groups (ANOVA test and Bonferroni post hoc test).

introduced, in addition to the phase angle, the terms thoracic paradoxical movement and abdominal paradoxical movement, which are calculated in a different way than the phase angle [9], perhaps indirectly assuming the limits of the Φ calculation. Interestingly, some authors reported that the phase angle range studied was between 0 and 180 degrees, but most reported phase angle values between 0 and 60 degrees. However, it seems important to highlight that most of them did not perform exercise in a recumbent or semi-recumbent position [10,17–20]. The present study may favor the presence of a thoracic or abdominal paradox, as all studies were performed in the decubitus or semi-recumbent position. For future studies, this is probably the correct position for analysis of TAA by RIP.

Finally, as mentioned above, the phase angle can be the same regardless of whether the thoracic belt or the abdominal belt is ahead in the movement. Some recent studies [13] have introduced a distinction between clockwise rotation (thorax starts movement ahead of abdomen) and counterclockwise rotation(abdomen starts movement ahead of thorax) by assigning a negative value to counterclockwise rotation. However, several studies do not make this distinction while missing a relevant clinical significance of what is the mechanism of TAA [19,22,23]. The advanced component can also have important clinical implications. Significant advancement of the abdominal component may indicate air trapping, whereas significant advancement of the thoracic component may indicate recruitment of accessory muscles. In the present study, the slight predominance of clockwise cycles (55 vs 45%) would be consistent with the fact that many of the cycles analyzed were obtained from patients undergoing exercise.

The loop area has been also analyzed in this study as a parameter of interest and seems to have the same limitations as the phase angle. The loop area tends to be maximal at angles of 90 and 270 degrees and minimal at 0 and 180 degrees, making it impossible to distinguish between a normal loop and a paradox.

Using the measure of GPD as the main parameter overcomes many of the above disadvantages by providing an idea of the total loop offset, not just at a particular point in the cycle. In addition, the range of TAA measured by GPD is wider than that of phase angle, allowing the thoracic and abdominal paradoxes to be included in the estimate. As can be seen in Figures 6 and 7, both area and phase angle are not enough to discriminate loops with severe paradoxes. The only mathematical modification in the GPD was the assignment of a positive sign if the rotation of the loop was clockwise, such as in diaphragm dysfunction and a negative sign if it was counterclockwise, such in COPD patients.

The study has limitations that need to be mentioned. Firstly, no correlation was made with the clinical status or exercise capacity of each of the synchrony-based groups into which the cohort was divided. As mentioned above, all the cycles included were in the supine or semi-recumbent position, both at baseline and during exercise. Theoretically, the supine position would favor the occurrence of clockwise rotation and, in situations of diaphragm fatigue or abdominal paradox. It is therefore possible that this fact might lead to some differences in the results with other similar studies in the literature, not carried out in a recumbent position. Finally, and despite the inclusion of patients with respiratory disease, most cycles had a low TAA.

5. Conclusions

The measurement of the global phase delay, based on the angle formed in the horizontal plane by the two thoracic and abdominal slopes, covers the whole spectrum of thoraco-abdominal asynchrony situations in a single value, thus simplifying its measurement and eliminating some of the drawbacks associated with the classical phase angle measurement. It may be a relevant parameter for the diagnosis and follow-up of clinical conditions leading to TAA.

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Declaration of interest

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Author contributions

J Sayas, and M Luján performed the study conception and design. M Luján, P Flórez, and C Lalmolda developed the software. J Sayas, C Lalmolda, M Corral, P Flórez, and A Hernández-Voth performed the recruitment and data analysis. J Sayas, and M Luján drafted the paper. JP Janssens, C Rabec, B Langevin, F Lofaso, C Llontop, A Carlucci, JC Winck, and J González-Bermejo performed the critical revision of the manuscript for intellectual content.

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6.3.2. Artículo 2: Thoracoabdominal Asynchrony in Very Severe COPD: Clinical and Functional Correlates During Exercise

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Original Article

Thoracoabdominal Asynchrony in Very Severe COPD: Clinical and Functional Correlates During Exercise

Javier Sayas Catalán[a,f,*], Cristina Lalmolda[b,c], Ana Hernández-Voth[a], Marta Corral Blanco[a], Patrick Murphy[d], Laura Gonzalez-Ramos[a], Pablo Florez-Solarana[b], Berta Lloret-Puig[b], Manel Lujan[b,e]

[a] Hospital Universitario 12 de Octubre, Pneumology Service, Madrid, Spain
[b] Consorci Corporació Sanitària Parc Taulí, Pneumology Service, Sabadell, Spain
[c] Centro de Investigación Médica en Red de Enfermedades Respiratorias (CIBERES), Respiratory Research, Spain
[d] Guy's & St. Thomas' NHS Foundation Trust, Lane Fox Respiratory Unit, London, United Kingdom
[e] Pneumology Department, Universitat Autònoma de Barcelona, Spain
[f] Universidad Complutense de Madrid, Spain

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ABSTRACT

Introduction: Patients with severe Chronic Obstructive Pulmonary Disease (COPD) often experience breathlessness and exercise limitations due to expiratory flow limitation. Pulmonary rehabilitation programmes, including exercise with non-invasive ventilation (NIV) or high-flow nasal therapy (HFT), aims to improve quality of life and exercise tolerance. This study investigates the relationship between thoracoabdominal asynchrony (TAA) during supported (NIV and HFT) and unsupported (conventional oxygen therapy – COT) exercise and clinical and functional parameters in severe COPD patients awaiting lung transplantation.

Methods: This experimental, longitudinal, prospective, controlled study included 20 severe COPD patients on the lung transplant waiting list. Patients underwent three constant load exercise tests under COT, NIV, and HFT conditions. TAA was measured using respiratory inductance plethysmography, and neurorrespiratory drive (NRD) was assessed via parasternal electromyography.

Results: Patients exhibited distinct TAA patterns during exercise. Clockwise rotation (thorax ahead) was associated with worse baseline lung function, higher peak exercise dyspnoea and higher peak exercise NRD compared to counterclockwise rotation (abdomen ahead). No significant differences in TAA were observed between the three exercise conditions (COT, NIV, HFT). However, patients with clockwise TAA were more likely to have reduction in breathlessness with NIV compared to COT than those with counterclockwise rotation.

Conclusions: TAA patterns during exercise in severe COPD patients can indicate the severity of lung function impairment and predict severity of exercise induced dyspnoea. Analysis of TAA may predict response to respiratory support modalities and therefore monitoring TAA and NRD should be further studied to allow better tailoring of respiratory support during rehabilitation.

Introduction

Patients with severe Chronic Obstructive Pulmonary Disease (COPD) experience breathlessness and exercise limitation due to expiratory flow limitation.[1] Pulmonary rehabilitation programmes are key components of care for stable COPD, improving quality of life, preventing exacerbations, and being cost-effective. Outpatient programmes include regular training sessions (3–5 times per week) at 60–80% of peak exercise capacity.[2]

Exercise rehabilitation can be supported by conventional oxygen therapy (COT), non-invasive ventilation (NIV), or high-flow

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; COT, conventional oxygen therapy; NIV, non-invasive ventilation; HFT, high-flow nasal therapy; EMG, electromyography; TAA, thoracoabdominal asynchrony; OEP, optoelectronic plethysmography; RIP, respiratory inductance plethysmography; NRD, neurorrespiratory drive; RMS, root mean square.

* Corresponding author.
E-mail address: javier.sayas@salud.madrid.org (J. Sayas Catalán).

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nasal therapy (HFT). NIV improves acute exercise capacity by reducing the work of breathing but requires expertise, and its long-term impact is uncertain. Current data indicates NIV is optimal for augmenting exercise performance in stable COPD.[2,3]

NIV monitoring during exercise includes techniques such as oxygen saturation, transcutaneous CO_2,[4] pulmonary function testing, respiratory muscle electromyography (EMG)[5] or thoracoabdominal asynchrony (TAA) evaluation using optoelectronic or respiratory inductance plethysmography (RIP).[6] TAA, caused by impaired airway obstruction, increases work of breathing and dyspnoea and reduces exercise capacity. A new method proposes the use of Global Phase Delay (GPD) for improved accuracy.[7]

This study aims to determine the relationship between TAA (using GPD) during supported (NIV and HFT) and unsupported (COT) exercise and clinical and functional parameters in severe COPD patients who are candidates for lung transplantation.

Methods

The study design was an experimental, longitudinal, prospective, non randomized controlled study with three sequential protocols (exercise testing supported by: COT, NIV and HFT). The before/after comparison of the same individuals was conducted. Exercise testing was performed in a single centre (Hospital Universitario 12 de Octubre), and the signal processing and calculations were made by the team at Hospital Universitari Parc Tauli (Sabadell) and Hospital 12 de Octubre.

Population

Inclusion Criteria

- The study included patients with severe COPD (with an obstructive pattern and air trapping, according to GOLD criteria, and a residual volume > 120% of predicted), admitted on the lung transplant waiting list. These patients were evaluated by the Lung Transplant Unit between September 2019 and November 2022. Comorbidities as confounding factors were excluded as a thorough evaluation was made to be included in lung transplant list.
- Patients had expiratory flow limitation by the analysis of flow/volume curves during exercise. This fact was assessed subjectively by 2 experienced operators while performing initial adaptation to NIV during exercise.
- Patients were already adapted and compliant with home NIV as a bridge to transplantation.

Exclusion Criteria

- The patient must not have any uncontrollable comorbidities that limit their ability to exercise. These include uncontrolled ischaemic heart disease, severe pulmonary hypertension and neuromuscular pathology.
- Refusal of treatment with NIV or enrolment in the study.
- Inability to perform the proposed exercise under baseline conditions and with ventilation.
- Lung transplantation during the study resulted in incomplete exercise sessions.

Protocol

In a first visit, a "ramp test" with incremental loads up to maximal tolerated was performed. Then, a 75% load of that maximal tolerated one was selected to perform the tests. Patients were already included in the exercise protocol for lung transplantation programme, so they all have previously performed at least three sessions of exercise in cycloergometer under COT. Three constant load exercise tests were performed over three consecutive days. The first day was performed under COT, and at the end of the exercise testing, a 5 min trial with NIV, cycling with no strict protocol, was performed to titrate pressures. The NIV and the HFT trials were then randomly performed in subsequent days. All of the patients underwent exercise with an Astral 150® ventilator (Resmed, Ca, USA®) under ST mode, as it has been tested previously capable of providing enough pressurization support and capable of different programs.[8] Expiratory pressure was titrated to avoid ineffective efforts and trigger delay, and Inspiratory pressure was titrated in order to diminish at least 20% of neurorrespiratory drive (NRD) as measured by parasternal EMG. To avoid cross contamination with pectoral muscle activity (due to grip over the handlebar[9]), a recumbent cycloergometer (SanaComfort 1000, Ergosana GmbH, Blitz, Germany) was used for the all three exercise tests. The subjects were instructed to cycle with their arms relaxed along their trunk and avoid grasping the handlebars or support bars.

The exercise tests comprised 10 min of exercise and 5 min of recovery. They were conducted under the following conditions:

- COT: Patients will start under their home COT flow and then titrated to maintain an $SpO_2 > 92\%$ through all the exercise.
- NIV: titrated as described above, with supplemental oxygen if needed, to maintain $SpO_2 > 92\%$.
- HFT (Airvo 2®, Fisher & Paykel, Auckland, NZ): A flow of 40 l per minute was selected. Supplemental O_2 flow was initially set – before starting exercise – to maintain an estimated FiO_2 similar to that obtained to achieve a $SpO_2 > 92\%$ with COT.[10]

Before the exercise, we performed three inhalation manoeuvres to measure maximum inspiratory pressure with simultaneous EMG recording for calibration (see below). No other pulmonary function was measured during or after the exercise.

Signal Recording

During the test, patients were connected to a recording system equipped with the following sensors:

- Parasternal surface EMG is performed with electrodes placed on both sides of the second parasternal space, as previously described.[3]
- Combined transcutaneous CO_2 and pulse oximetry oxygen saturation sensor (Sentec TCM®, Therwill, Switzerland).
- Chest and abdominal RIP belts (Braebon QZ-RIP, Braebon Medical Corp, Ontario, Canada).

All sensors were connected to a digital-to-analogue converter (PowerLab SP, ADInstruments, Australia). The sampling frequency was set to 2000 Hz.

Data Processing

- RIP signal was filtered with a 2 Hz low-pass filter to eliminate the artefact caused by the cycling activity over the abdominal belt. The filtered signals were exported to Matlab® to compute GPD[7] (See online supplement for details).
- Parasternal EMG signal: An 80 Hz high-pass filter was applied. The root mean square (RMS) was calculated as previously described.[11] We avoided non-respiratory tonic artefacts in the EMG by estimating the onset of inspiration from the RIP signal. Finally, we related both the peak and the area under the peak of the RMS signal to the mean baseline EMG activity, expressing the result as a percentage of it.[12]

Variables

The following variables were collected. Anthropometric data and pulmonary function tests were conducted (maximum, three months prior to the exercise test). These included forced spirometry, whole-body plethysmography and arterial blood gases. The BODE index and prescribed ventilator parameters were also recorded.

The following variables were recorded during the exercise test at baseline, 1, 4, 7 and 10 min of exercise and after 3 and 5 min of recovery:

- Dyspnoea, measured by the Borg scale.
- Global Phase Delay (mean value of the last 5 cycles of each of the previously stated stages).
- EMG variables: A maximal inspiratory manoeuvre was performed before each day of testing. The parasternal EMG signal was defined as a fraction of the 100% maximal EMG signal obtained during the maximal inspiratory pressure manoeuvre.

Definitions

- Clockwise rotation: advance of the thoracic belt and assign a positive sign to GPD.
- Anticlockwise rotation: abdominal belt was advanced over the thoracic belt, and a negative sign was assigned to GPD.
- Thoracic paradox: anticlockwise rotation with a GPD between −90 and −180° in any step of the exercise.
- Abdominal paradox: clockwise rotation with a GPD between +90 and +180° in any step of the exercise.

We calculated the NRD as the product of the respiratory rate and both the peak and area under the peak RMS as described by Jolley et al.[13]

Statistical Analysis

The Kolmogorov–Smirnov test analyzed the normality of quantitative variables. For normal distributions, the mean and standard deviation were provided; otherwise, the median and interquartile range were given. The Student *t* test for non-paired measures compared TAA groups. A mixed ANOVA for repeated measures assessed performance across exercise tests. The *F* score, mean differences, and observed power ($\beta - 1$) were provided. Significance was set at $p < 0.05$. Statistical analyses were performed using SPSS version 25.

Results

Through the study period, 47 patients with COPD were included in the lung transplant programme of whom 23 were on home NIV and suitable for inclusion. One patient underwent lung transplantation before the trial could be conducted and 2 did not have reliable EMG signals despite several attempts. The study population therefore included 20 patients with severe COPD (6 women). The anthropometric data, pulmonary function tests and ventilator parameters for the entire cohort are shown in Table 1.

The study population had a median maximum workload of 25 W (range 7–60 W) as determined in the baseline ramp test. All patients had a BODE index of 7 or more (median 9, range 7–12). Extensive cardiac examinations, including cardiac ultrasound and coronariography, excluded significant cardiovascular disease. Mean MIP was −65 cm H_2O, suggesting diaphragm weakness was not the primary cause of exercise limitation. All patients exhibited air trapping, with a mean FEV_1 of 19 ± 4% and a mean residual volume of 283 ± 75%. All of the patients had stable condition hypercapnia.

Table 1
Anthropometric and Lung Function Data for the Entire Cohort.

	Mean	Standard Deviation
Anthropometric data		
Age	60	3.9
Gender (F)	6 (30%)	
Pulmonary function tests		
FEV_1 ml	568	131
FEV_1 %	19	4.2
FVC ml	1935	761
FVC %	51	18
RV ml	6024	1180
RV %	283	75
TLC ml	8281	1144
TLC %	141	27
Arterial blood gases		
PaO_2 (mm Hg)	62.5	10.91
$PaCO_2$ (mm Hg)	50.4	6.56
pH	7.38	0.04
Ventilator parameters		
IPAP (cm H_2O)	20.4	4.62

Thus, dynamic hyperinflation was suspected as the main driver of exercise limitation.

Baseline mean GPD: 14 patients had counterclockwise rotation (abdomen ahead) with a mean GPD of −14.24 ± 15.56 and 6 had clockwise rotation (thorax ahead) with a mean GPD of 23.47 ± 22.69. Patients with clockwise rotation had a lower percent predicted FEV_1 and FVC than patients with counterclockwise rotation, with no significant differences in the other lung function parameters (FEV_1 15.5% ± 3.44% vs. 20.54 ± 3.85%, $p < 0.05$ and FVC 37.5 ± 13.86 vs. 54.50 ± 18.14, $p < 0.05$).

Exercise Tests With COT

During exercise on COT 9 patients change the pattern of breathing to counterclockwise rotation (2 with thoracic paradox at some point during exercise), while 11 had clockwise rotation (7 with abdominal paradox at some point during exercise), see Fig. 1. Significant differences were observed between groups ($F = 23.47$, $p < 0.01$, mean difference between groups 88.4°, 95% CI 50.07–123.76, ($\beta - 1$) = 0.99 mixed ANOVA for repeated measures). Table 2 shows the differences in lung function between patients with clockwise and counterclockwise rotation, and in patients with and without abdominal paradox.

As shown in Fig. 2, patients with clockwise rotation (thorax ahead) had a higher degree of dyspnoea during unsupported exercise than patients with counterclockwise rotation ($F = 11.598$, $p < 0.05$, mean difference 2.53 Borg points, CI 95% 1–4.08, ($\beta - 1$) = 0.91), general linear model for repeated measures.

Patients with clockwise rotation also had higher NRD: peak RMS was higher ($F = 11.35$, $p < 0.01$, mean difference 456 microV/RR, CI 95% 170.7–742.3, ($\beta - 1$) = 0.77) but not RMS area ($F = 4.35$, $p = 0.05$, mean difference 368 microV/RR, CI 95% 264.7–472.3, ($\beta - 1$) = 0.44). When the subgroups based on the abdominal paradox were analyzed, patients with abdominal paradox showed higher NRD, both peak ($F = 27.49$, $p < 0.01$, mean difference 835 microV/RR, CI 95% 716–955 ($\beta - 1$) = 0.99) and area ($F = 10.72$, $p < 0.01$, mean difference 423 microV/RR, CI 95% 328–518, ($\beta - 1$) = 0.87). See Fig. 3A–D.

Exercise Under NIV

Under NIV 13 patients had clockwise rotation (9 with paradox) and 7 had predominantly counterclockwise rotation (3 with paradox), i.e. there were four patients who changed the direction of rotation (3 from counterclockwise to clockwise and one from

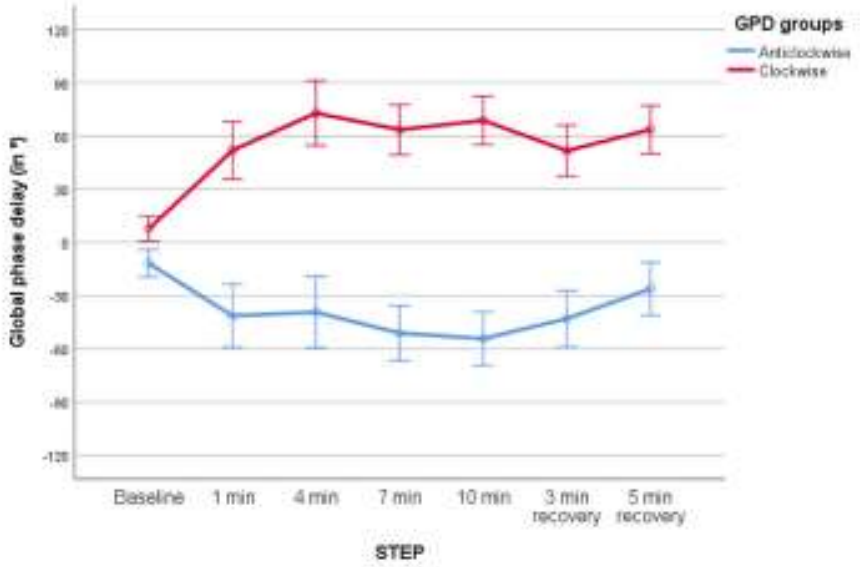


Fig. 1. Global Phase Delay (GPD) performance during exercise with conventional oxygen therapy in the study population. Two distinct groups were identified: (1) a group with predominant anticlockwise rotation (abdomen ahead, blue line), and (2) a group with clockwise rotation (thorax ahead, red line), showing higher absolute deviations compared to the former ($p < 0.01$, ANOVA for repeated measures).

Table 2
Thoracoabdominal Synchrony During Exercise With Conventional Oxygen Therapy and Group Correlation Based on TAA and Pulmonary Function Tests.

Parameter	Anticlockwise $N = 9$		Clockwise $N = 11$		*P* Value	No Abdominal Paradox ($N = 13$)		Abdominal Paradox ($N = 7$)		*P* Value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
FEV_1 ml	620.91	156.23	527.11	94.18	0.11	581	148	546	98	0.5
FEV_1 %	22.11	3.62	16.72	2.76	<0.01	20.62	3.92	16.43	3.15	<0.05
FVC ml	2265.3	708.8	1662.4	677.2	0.07	2048	776	1848	673	0.6
FVC %	63.56	8.06	41.09	16.19	<0.01	58.08	13.2	38.43	17.1	<0.05
RV ml	5758.8	846.5	6380.55	1543.1	0.28	5635	839	6936	1403	<0.05
RV %	259.3	62.63	302.75	79.02	0.2	269.1	80.2	308.2	59.4	0.27
TLC ml	8061.43	851.3	8685.73	1700.2	0.3	7926	879	9188	1795	0.05
TLC %	138.75	25.96	143.00	29.316	0.5	140	29	151	23	0.5

Two comparisons are presented: (1) clockwise (thorax ahead) vs anticlockwise (abdomen ahead) in columns 2 and 3, and (2) abdominal paradox (indicative of extreme diaphragm weakness/fatigue) vs no abdominal paradox in columns 5 and 6.
Abbreviations: FEV_1: forced expiratory volume in the first second, FVC: forced vital capacity, RV: residual volume; TLC: total lung capacity; SD: standard deviation.

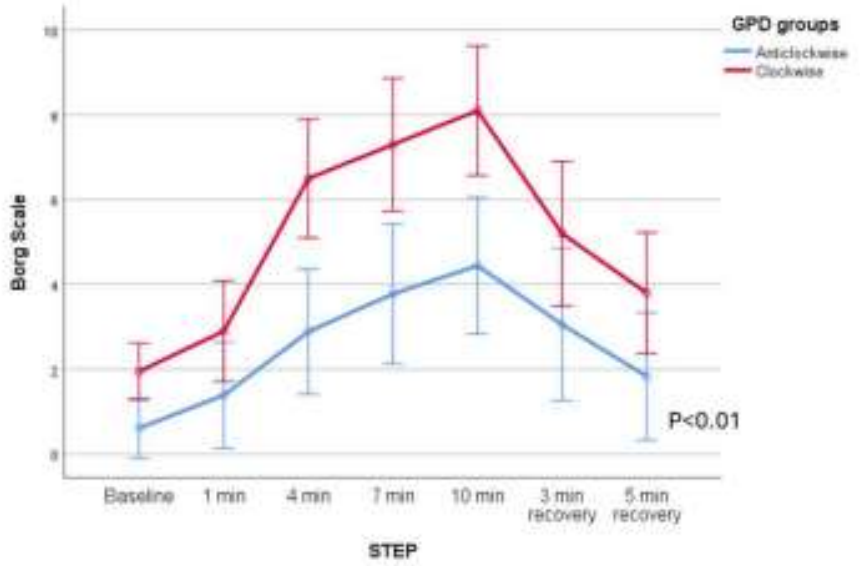


Fig. 2. Borg Scale scores for both groups (patients with predominantly counterclockwise or clockwise rotation) during exercise with low-flow oxygen. As shown in the figure, patients with clockwise rotation exhibited higher dyspnoea levels compared to those with predominantly counterclockwise rotation ($p < 0.01$, ANOVA for repeated measures).

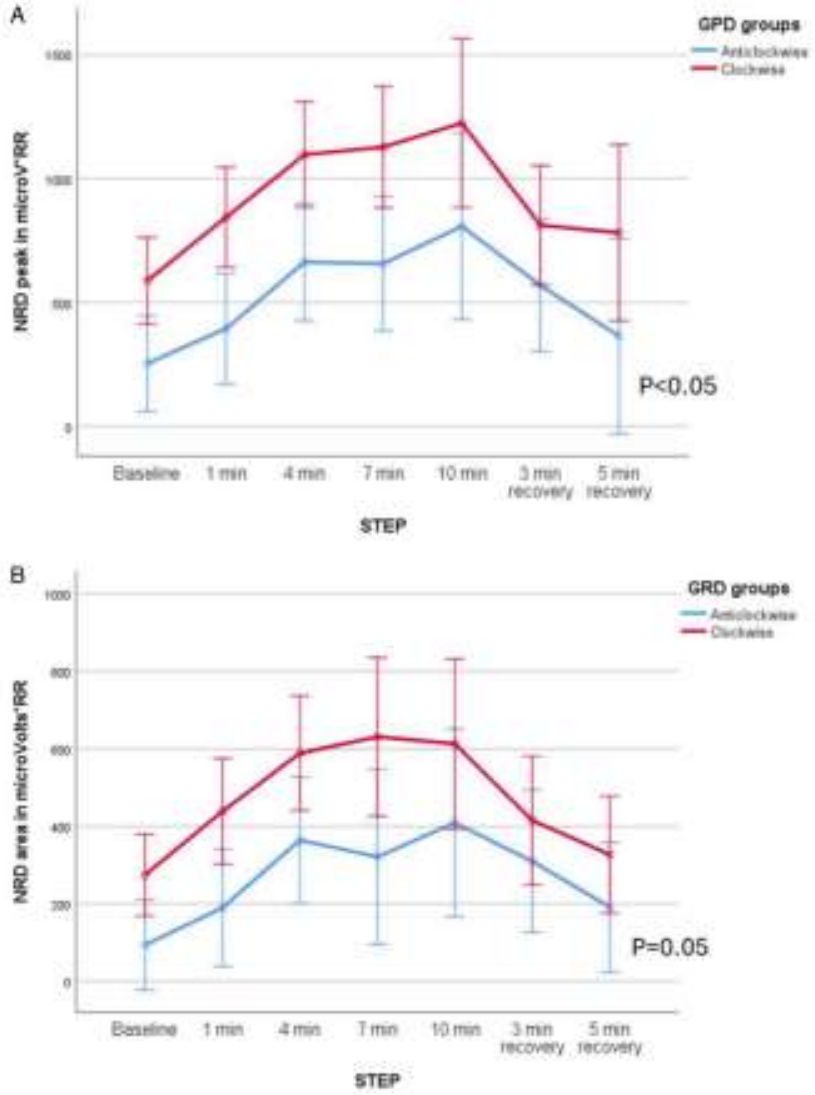


Fig. 3. (A–D) Neurorespiratory drive (NRD peak and area in microV*RR), in patients with clockwise and counterclockwise rotation (A and B), and with and without abdominal paradox (C and D) during low-flow oxygen exercise. Comparisons were made through ANOVA for repeated measures.

clockwise to counterclockwise, see Table 3). No differences were observed in the degree of dyspnoea during exercise with NIV when the groups (clockwise or anticlockwise, abdominal paradox or no abdominal paradox) were compared. There were also no differences between groups in the ventilator parameters used to perform the test (inspiratory pressure, expiratory pressure and pressure support).

NRD was higher in patients with abdominal paradox both in peak ($F = 12.28$, $p < 0.01$, mean difference 406 microV/RR, CI 95% 324–488, $(\beta - 1) = 0.91$), and area ($F = 7.01$, $p < 0.05$, mean difference 199 microV/RR, CI 95% 144–254, $(\beta - 1) = 0.7$), but no differences were found when the groups based on clockwise/counterclockwise were compared (Fig. 4A–D).

Exercise Under HFT

Eleven patients had clockwise rotation (7 with paradox) and 9 had predominantly counterclockwise rotation (3 with paradox). No differences were observed in the degree of dyspnoea as measured by the Borg scale during exercise with HFT when both groups (clockwise and anticlockwise) were compared.

NRD was higher in patients with clockwise rotation for the EMG peak ($F = 10.19$, $p < 0.01$, mean difference 555 microV/RR, CI 95% 438–671, $(\beta - 1) = 0.85$) and area ($F = 7.31$, $p < 0.05$, mean difference 255 microV/RR, CI 95% 184–326, $(\beta - 1) = 0.72$). When the group of patients with abdominal paradox were analyzed, they presented a higher NRD than patients without abdominal paradox: Peak: $F = 6.59$, $p < 0.05$, mean difference 660 microV/RR, CI 95% 517–803, $(\beta - 1) = 0.68$ Area: $F = 13.19$, $p < 0.01$, mean difference 328 microV/RR, CI 95% 254–402, $(\beta - 1) = 0.92$ (see Fig. 5A–D).

Comparing COT, NIV and HFT

No significant differences in the degree of TAA were observed when comparing the three interventions (COT, NIV and HFT). Three patients changed direction of rotation and development of paradox between interventions.

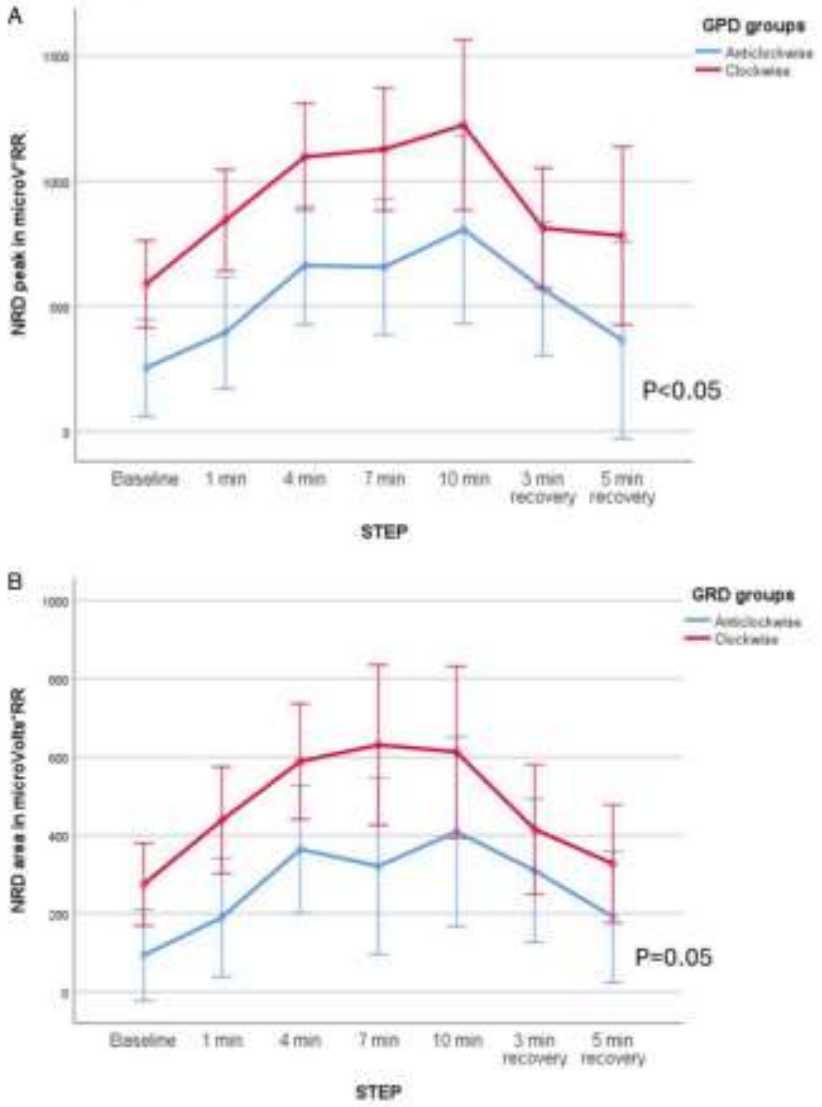


Fig. 3. (A–D) Neurorespiratory drive (NRD peak and area in microv*RR), in patients with clockwise and counterclockwise rotation (A and B), and with and without abdominal paradox (C and D) during low-flow oxygen exercise. Comparisons were made through ANOVA for repeated measures.

clockwise to counterclockwise, see Table 3). No differences were observed in the degree of dyspnoea during exercise with NIV when the groups (clockwise or anticlockwise, abdominal paradox or no abdominal paradox) were compared. There were also no differences between groups in the ventilator parameters used to perform the test (inspiratory pressure, expiratory pressure and pressure support).

NRD was higher in patients with abdominal paradox both in peak ($F = 12.28$, $p < 0.01$, mean difference 406 microV/RR, CI 95% 324–488, $(\beta - 1) = 0.91$), and area ($F = 7.01$, $p < 0.05$, mean difference 199 microV/RR, CI 95% 144–254, $(\beta - 1) = 0.7$), but no differences were found when the groups based on clockwise/counterclockwise were compared (Fig. 4A–D).

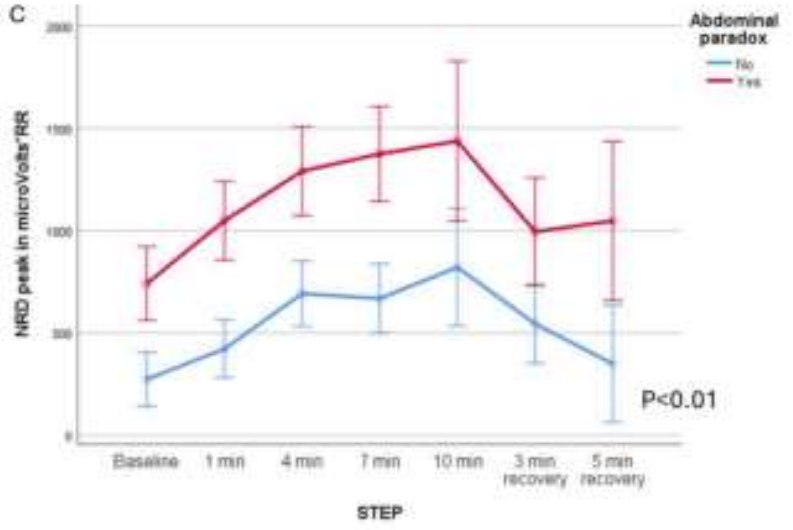
Exercise Under HFT

Eleven patients had clockwise rotation (7 with paradox) and 9 had predominantly counterclockwise rotation (3 with paradox). No differences were observed in the degree of dyspnoea as measured by the Borg scale during exercise with HFT when both groups (clockwise and anticlockwise) were compared.

NRD was higher in patients with clockwise rotation for the EMG peak ($F = 10.19$, $p < 0.01$, mean difference 555 microV/RR, CI 95% 438–671, $(\beta - 1) = 0.85$) and area ($F = 7.31$, $p < 0.05$, mean difference 255 microV/RR, CI 95% 184–326, $(\beta - 1) = 0.72$). When the group of patients with abdominal paradox were analyzed, they presented a higher NRD than patients without abdominal paradox: Peak: $F = 6.59$, $p < 0.05$, mean difference 660 microV/RR, CI 95% 517–803, $(\beta - 1) = 0.68$ Area: $F = 13.19$, $p < 0.01$, mean difference 328 microV/RR, CI 95% 254–402, $(\beta - 1) = 0.92$ (see Fig. 5A–D).

Comparing COT, NIV and HFT

No significant differences in the degree of TAA were observed when comparing the three interventions (COT, NIV and HFT). Three patients changed direction of rotation and development of paradox between interventions.



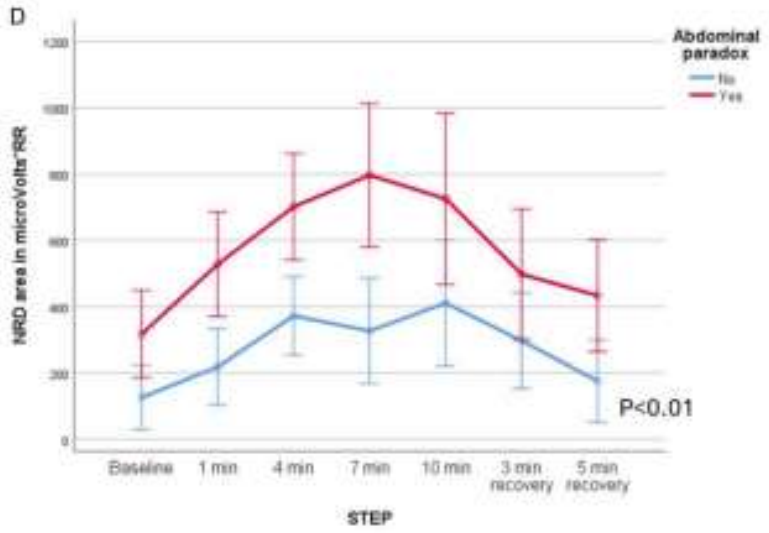


Fig. 3. (Continued)

Table 3
Predominant Direction of Rotation (Clockwise or Counterclockwise) for Each Individual Patient and Each Exercise Condition.

Patient Number	COT (Belt Ahead)	NIV (Belt Ahead)	High Flow (Belt Ahead)
1	Thorax	Abdomen (P)	Abdomen(P)
2	Abdomen	Thorax (P)	Thorax
3	Abdomen	Thorax (P)	Abdomen
4	Thorax (P)	Thorax (P)	Thorax (P)
5	Thorax (P)	Thorax (P)	Thorax (P)
6	Abdomen	Abdomen	Abdomen
7	Thorax (P)	Thorax (P)	Thorax (P)
8	Abdomen (P)	Abdomen	Abdomen (P)
9	Abdomen (P)	Abdomen (P)	Abdomen (P)
10	Thorax (P)	Thorax (P)	Thorax (P)
11	Abdomen	Thorax (P)	Thorax (P)
12	Abdomen	Abdomen	Abdomen
13	Thorax (P)	Thorax	Thorax (P)
14	Thorax	Thorax (P)	Thorax
15	Thorax (P)	Thorax	Thorax
16	Abdomen	Abdomen	Abdomen
17	Thorax (P)	Thorax (P)	Thorax (P)
18	Abdomen	Abdomen (P)	Abdomen
19	Thorax	Thorax	Abdomen
20	Thorax	Thorax	Thorax

P: Paradox.

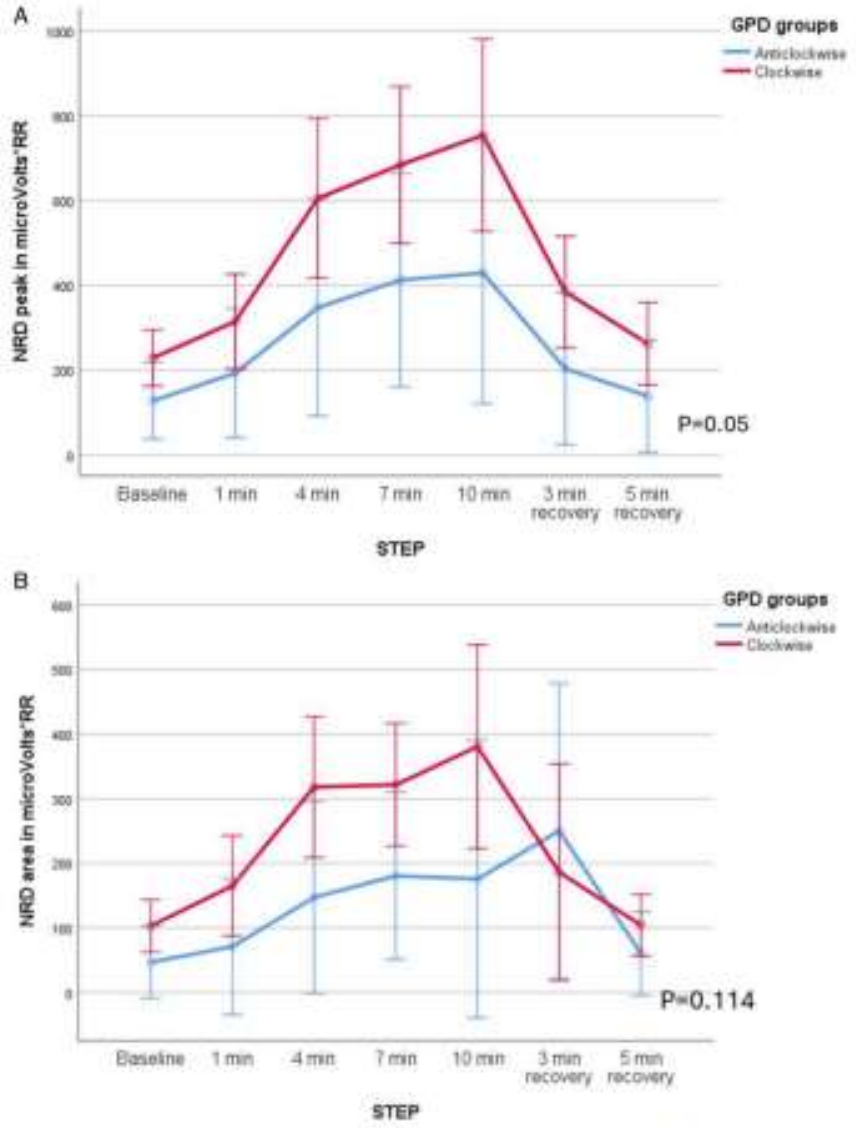


Fig. 4. (A–D) Neurorespiratory drive (NRD peak and area in microV*RR) in patients with clockwise and counterclockwise rotation (A and B) and abdominal paradox (C and D) during exercise with NIV. Comparisons were made through ANOVA for repeated measures.

Dyspnoea, Respiratory Support and TAA

Comparing dyspnoea response to NIV and HFT in patients with clockwise or counterclockwise rotation showed no significant difference. However, patients with clockwise rotation showed a significant improvement in dyspnoea under NIV compared with COT ($F = 5.52$, $p < 0.05$, mean difference: 4.27, 95% CI: 3.58–4.95 (beta – 1) = 0.68). No improvement in dyspnoea was found between COT and HFT in any of the 2 different patterns of TAA. Figure E3 A to D (online supplement) reflect the effect in dyspnoea of COT vs NIV and HFT between those 2 patterns of TAA.

Discussion

Two distinct patterns of TAA were identified during exercise in patients with advanced COPD: abdomen ahead (counterclockwise) and thorax ahead (clockwise). Notably, patients with severely impaired lung function exhibited an extreme clockwise pattern characterized by abdominal paradoxical breathing during exercise. This pattern was associated with greater hyperinflation, increased dyspnoea during COT exercise testing, and higher NRD, regardless of the type of respiratory support used (COT, NIV, or HFT). These findings suggest a compensatory activation of the parasternal muscles to counterbalance the diaphragm's inability to meet the increased respiratory demand.

Defining TAA as a delay between chest and abdominal movements highlights its role in ineffective respiratory mechanics, a subtype of dysfunctional breathing. It occurs in asthma, COPD, and neuromuscular diseases, with the most severe form being paradoxical (completely out-of-phase) movement.[14–16] The abdominal paradox (abdomen moving inward during inspiration) is a classic sign of muscle fatigue, detectable via physical exam, and linked

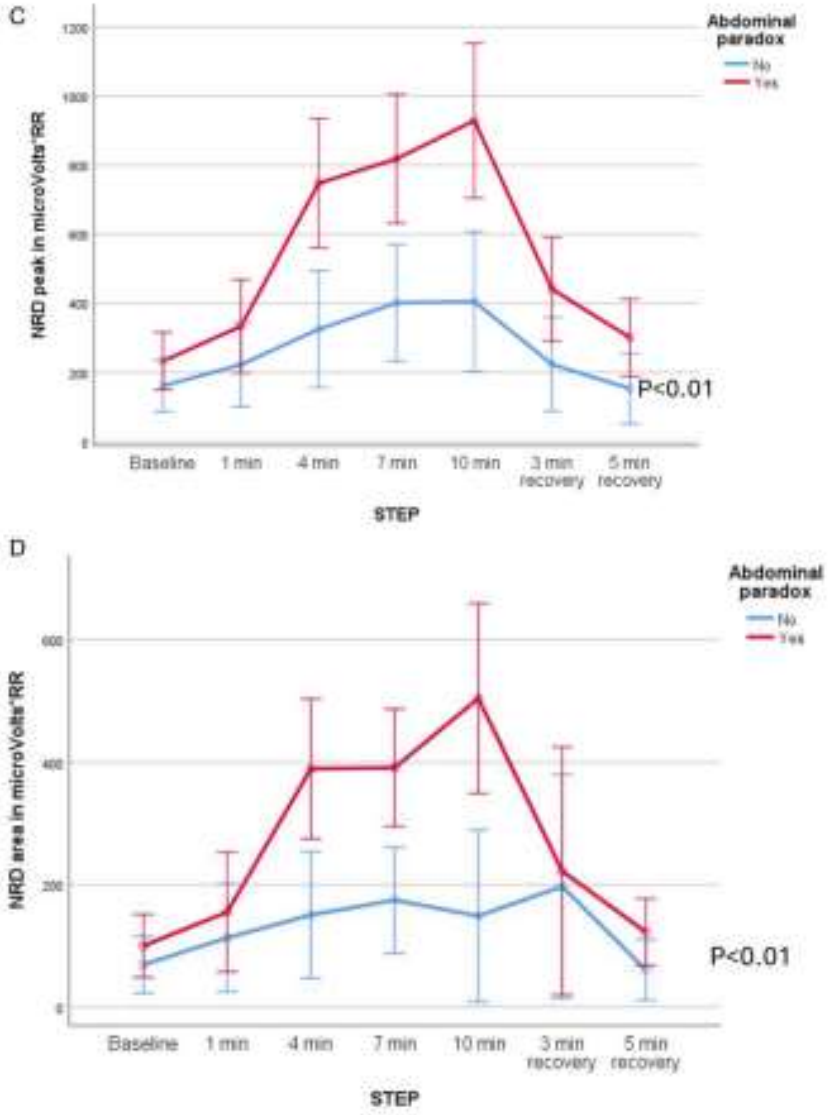


Fig. 4. (Continued)

to severe diaphragmatic dysfunction, seen in 20% of COPD outpatients and 80% of acute respiratory failure cases. This pattern stands in clear contrast to the pattern observed in patients with air trapping but more preserved diaphragmatic function, who exhibit counterclockwise rotation with delayed thoracic expansion, known as "Hoover's sign."[17]

It is difficult to compare our results with previous studies on TAA, as the calculation methods used in earlier research were not the same. For example, Alves et al. studied 22 COPD patients with an average FEV_1 of 45% (much higher than in the present cohort) and evaluated synchrony at rest and during exercise. The reported phase angle values (not GPD) were 10° at rest and 22° during exercise, presumably indicating counterclockwise rotation.[18] Chien et al. examined the impact of TAA on 6-min walk distance, but, like the study by Alves et al., they did not specify the leading compartment, and phase angle values remained below 35°, even in patients with severe COPD.[15] Finally, Pereira et al. utilized RIP and OEP to analyze individuals with and without lung disease during exercise. Among COPD patients, the phase angle was predominantly negative and significantly narrower compared to the present study. Notably, previous studies did not establish a connection between RIP findings and clinical or respiratory function, which stands out as a key strength of the current study.[6]

The results of the present study should be understood from a pathophysiological perspective and may have implications for monitoring and designing exercise protocols: patients with worse lung function and more air trapping at rest often exhibit a well-defined clockwise pattern during exercise, suggesting fatigue or a loss of diaphragmatic efficiency caused by flattening and a decrease in the zone of apposition. Additionally, this pattern is associated with greater activation of the parasternal muscles and increased dyspnoea and may eventually contribute to evaluating the response to rehabilitation programmes. Interestingly, the most severe pattern (abdominal paradox) has not been previously reported or studied during exercise. Two reasons could be behind this fact: the way the RIP signal is analyzed, which may not show the pres-

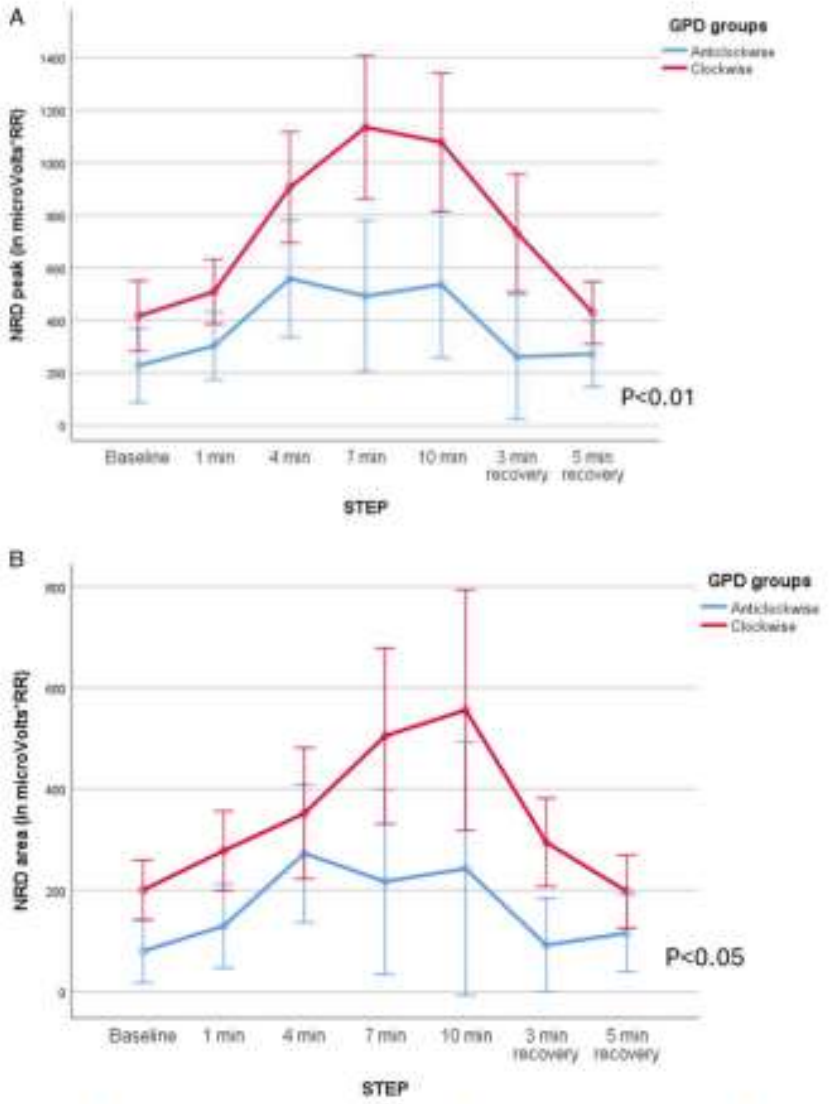


Fig. 5. (A–D) Neurorespiratory drive (NRD peak and area in microV*RR), in patients with clockwise and counterclockwise rotation (A and B) and abdominal paradox (C and D) during exercise with HFT. Comparisons were made through ANOVA for repeated measures.

ence of paradox, or the use of a recumbent cycloergometer, which may increase intra-abdominal pressure and make it harder for the diaphragm to contract.

One key aspect of the study is the response to non-invasive support techniques. A consistent decrease in TAA might be expected with NIV or HFT, but it's crucial to analyze these modes separately. No significant differences in TAA with NIV were found across the cohort, though responses varied widely (see Table 3). Patients with clockwise rotation may benefit most from exercise under NIV in terms of dyspnoea relief. Some patients showed an abdominal paradox with NIV before exercise, possibly due to excessive support (mean pressure support of 16 cm H_2O), which could worsen hyperinflation and lead to issues like deventilation syndrome.[19]

Despite the common practice of using NIV during exercise and its even recommendation in guidelines,[20,21] there is a lack of objective data on the superiority of high-pressure support values (high-intensity ventilation) during exercise. In a randomized controlled trial, Schneeberger et al. found no significant difference in exercise capacity in patients receiving high-intensity ventilation.[22] It remains to be demonstrated whether RIP monitoring can discriminate between patients who respond to high pressures and those who do not benefit from high pressures.

On the other way, the evidence supporting the benefits of HFT in the context of COPD rehabilitation programmes is limited.[23] A recent meta-analysis found no significant difference in quality of life, exercise capacity and breathlessness between those who received HFT and those who received COT. In an experimental model, Adams et al.[24] demonstrated that there was an increase in expiratory resistance that was directly proportional to flow and cannula size.

The results of the present study may have clinical implications for the management of patients with advanced COPD who are candidates for rehabilitation. Firstly, RIP can be used as a non-invasive monitoring method of the effects of rehabilitation programmes. Secondly, it can inform the titration of non-invasive respiratory support. In the event of paradoxical breathing (particularly abdom-

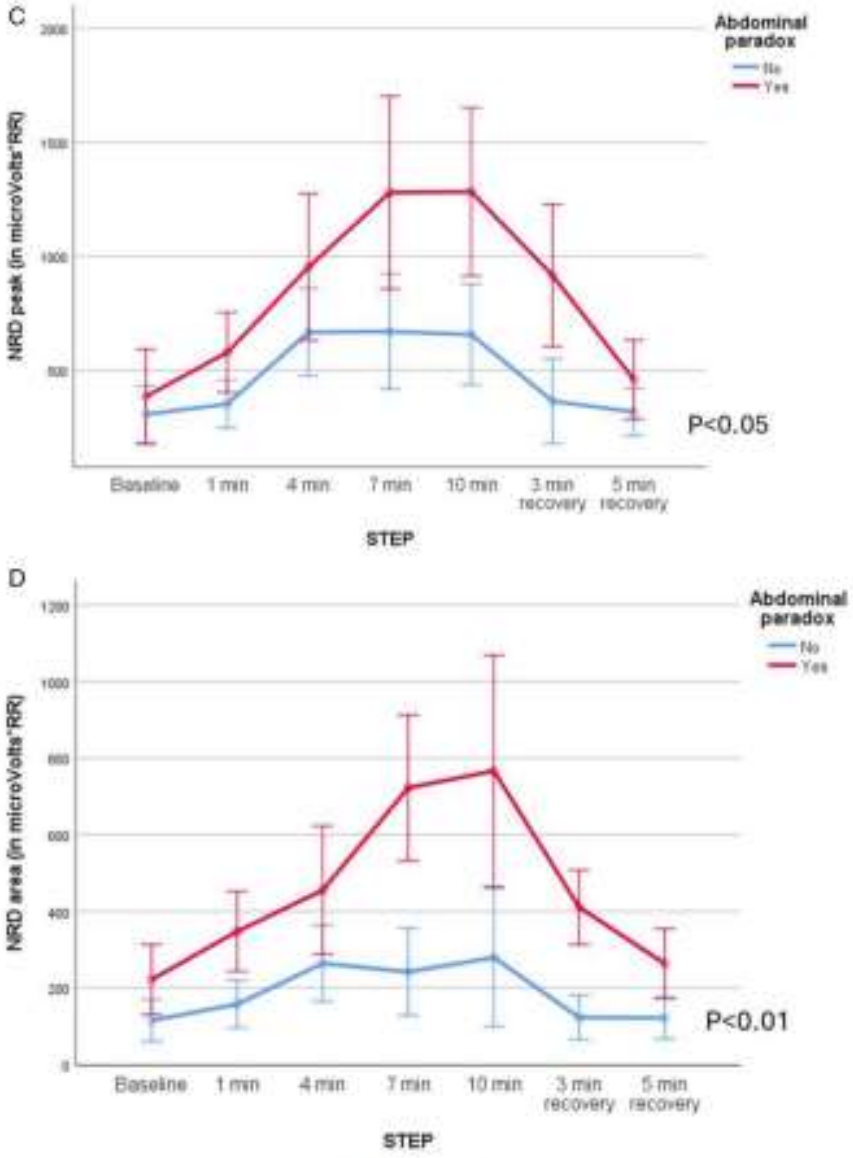


Fig. 5. (*Continued*)

inal) occurring in patients undergoing previously home NIV, the programmed parameters should be checked and readjusted if necessary. Ultimately, this approach can assist in identifying patients with severe clockwise rotation or abdominal paradox, who may require tailored rehabilitation programmes, particularly following an acute exacerbation.[25]

This study has relevant limitations. The sample size was limited and the study utilized a non-randomized design. It must be acknowledged that the conclusions of this study may not be applicable to other rehabilitation protocols, such as conventional cycloergometry or treadmill ergometry. Furthermore, the findings cannot be extrapolated to patients with less severe COPD or those with additional comorbidities, such as cardiovascular impairment.

In conclusion, the information provided by RIP allows the description of two distinct patterns of exertional TAA in patients with COPD. The thoracic advancement pattern is associated with increased NRD and greater dyspnoea. This finding may facilitate the personalization of exercise rehabilitation protocols and subsequent evaluation of their efficacy.

Authors' Contributions

All authors have significantly contributed to the entirety of the research process, including the conceptualization, data collection, analysis, and manuscript writing. Each author has approved the final version of the manuscript and agrees to be accountable for all aspects of the work.

Generative AI

No use of artificial intelligence have been made in any phase of the work related this manuscript.

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Conflicts of Interest

The authors declare that any of the following COI statements may be considered to influence directly or indirectly the content of the manuscript:

- Javier Sayas Catalán reports lecture fees from Philips, ResMed and Chiesi. Advisory board fees from Philips in the field of NIV, ResMed in the field of home care High flow therapy and Inogen in the field of oxygen therapy.
- Cristina Lalmolda reports lecture fees from Philips.
- Ana Hernández Voth reports fees from Chiesi and ResMed for lecture fees and research funding from Sanofi in the field of metabolic diseases.
- Marta Corral Blanco reports no competing interests or conflict of interests.
- Patrick Murphy reports lecture honoraria from Philips Respironics, Resmed, Fisher & Paykel, Chiesi, Genzyme.
- Laura González-Ramos reports lecture honoraria from Philips.
- Pablo Florez reports no conflict of interests.
- Berta Lloret-Puig reports no conflict of interests.
- Manel Lujan reports no conflict of interests.

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Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2025.01.010.

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6.3.3. Artículo 3: Muscle Unloading During Exercise: Comparative Effects of Conventional Oxygen, NIV, and High-Flow Therapy on Neural Drive in Severe COPD.

Sayas-Catalán J, Villena Garrido V, Lalmolda C, Hernández-Voth A, Corral-Blanco M, Jiménez-Gómez M, et al. Muscle Unloading During Exercise: Comparative Effects of Conventional Oxygen, NIV, and High-Flow Therapy on Neural Drive in Severe COPD. Journal of Clinical Medicine. 2025;14:8150.

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Article

Muscle Unloading During Exercise: Comparative Effects of Conventional Oxygen, NIV, and High-Flow Therapy on Neural Drive in Severe COPD

Javier Sayas-Catalán [1,2], Victoria Villena Garrido [1,2,*], Cristina Lalmolda [3,4], Ana Hernández-Voth [1], Marta Corral-Blanco [1], Miguel Jiménez-Gómez [1], Laura González-Ramos [1] and Manel Luján [3,4,*]

[1] Hospital Universitario 12 de Octubre, 28041 Madrid, Spain; javier.sayas@salud.madrid.org (J.S.-C.); m.corralblanco@gmail.com (M.C.-B.); migueljimenezgomez@gmail.com (M.J.-G.)
[2] Facultad de Medicina, Universidad Complutense de Madrid, 28040 Madrid, Spain
[3] Corporació Sanitària Parc Taulí, 08208 Sabadell, Spain
[4] Facultad de Medicina, Universitat Autonoma de Barcelona, 08193 Barcelona, Spain
* Correspondence: vvillena@separ.es (V.V.G.); mlujan@tauli.cat (M.L.)

Abstract

Objectives: This study aimed to evaluate how non-invasive ventilation (NIV) and high-flow nasal cannula therapy (HFT) versus conventional oxygen therapy (COT) affect neural ventilatory drive during exercise in patients with severe chronic obstructive pulmonary disease (COPD). **Methods**: We conducted an experimental, controlled study with one arm and three different conditions for the same cohort. After initial testing on conventional oxygen therapy (COT), patients exercised under NIV and HFT in sequential days and a random order. **Participants**: Twenty patients (mean age 60 years old (SD 3.9), 6 female) with severe COPD (30% women) on home NIV as a bridge to lung transplantation were enrolled in this study, with a mean FEV_1 of 19.78% predicted and marked hyperinflation. **Protocol**: Participants performed constant-load cycling exercises at 75% maximum tolerated workload under three conditions: COT, NIV, and HFT. Neuro-respiratory drive (NRD) was measured using surface parasternal and sternocleidomastoid electromyography, and mixed ANOVA was performed to analyze repeated measures across conditions. **Results**: In total, 20 patients were included in this study. NIV demonstrated superior performance, with 60% lower NRD compared to COT (488.81 μV vs. 1180.63 μV, $p < 0.05$). HFT showed intermediate effects (807.8 μV). NIV also achieved greater reduction in respiratory rate (4.2 breaths/min), lower perceived exertion (Borg score decrease: 1.8 points), and more pronounced CO_2 reduction (5.3 mmHg) compared to both COT and HFT. **Conclusions**: NIV significantly reduces NRD during exercise in severe COPD patients compared to HFT and COT. This supports its use as a valuable adjunct to pulmonary rehabilitation in severe COPD.

Keywords: chronic obstructive pulmonary disease; exercise therapy; high-flow therapy; neural drive; non-invasive ventilation

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1. Introduction

Chronic obstructive pulmonary disease (COPD) carries a high burden of mortality and morbidity worldwide [1]. Patients with severe COPD experience exercise limitation due to multiple mechanisms, including ventilatory constraints, impaired gas exchange, and haemodynamic limitation [2]. Among these, expiratory flow limitation may be a key

component of developing breathlessness and exercise intolerance [3], worsening as exercise progresses and patients attempt to increase their respiratory rate (RR) at the expense of shortening expiratory time. This situation inevitably leads to dynamic hyperinflation and the development of intrinsic end-expiratory positive pressure (iPEEP) [4–7].

The final consequence of this exercise-induced dynamic hyperinflation is the development of a "neuro-ventilatory uncoupling" [6]. Despite an increase in inspiratory effort, trying to meet the breathing demands induced by exercise, patients are unable to proportionally increase tidal volume. Thus, dyspnoea and inspiratory muscle activity (both closely linked) rise while breathing efficiency reaches a plateau, limiting exercise capacity [8].

Non-invasive ventilation (NIV) has been extensively studied as a means to improve ventilation in severe COPD by reducing neural respiratory drive uncoupling through inspiratory muscle unloading, intrinsic PEEP reduction, and increased tidal volume at rest [9–11] and during exercise.

Therefore, NIV has been proposed as a strategy to enhance the exercise capacity of severe COPD patients. While early reports showed conflicting results and an initial meta-analysis did not show evidence of NIV's benefit [12], there is wide heterogenicity in terms of patient selection, protocols, outcome measures, and NIV titration. Some studies have focused on naïve NIV users, with limited, poor results [13], while others have evaluated alternative ventilatory modes [14,15] or improvements in physiological markers (for example, in muscle blood flow [16] or inflammatory profile [17,18]), ventilatory efficiency and exercise capacity [19], or long-term effects.

On the other hand, high-flow therapy (HFT) is a relatively established technique that provides high flow rates (usually >30–40 L/min) of conditioned gas (air and oxygen mixture with a selected fraction of inspired oxygen (FiO_2), heated and humidified to 100% relative humidity) [20] that has also been studied as a tool to increase exercise capacity in COPD patients. While there is much less evidence of its benefits, and most of the studies investigating it are limited, it seems a promising tool for improving exercise capacity, with better tolerance than NIV [21].

More recent meta-analyses have demonstrated the ability of NIV to improve exercise tolerance and many physiological measures, such as oxygen consumption and dyspnoea, over HFT [22,23].

While there have been several studies identifying the physiological effects of administering NIV during exercise, the effect of HFT on NRD compared with NIV has not been directly researched. A recent study by Bonnevie et al. [24] assessed the physiological effects of HFT during exercise in severe COPD, including an exploratory evaluation of neuromechanical uncoupling, and found partial improvement with some uncertainty. Unlike previous studies using fixed NIV settings, we aim to compare the effects on neural respiratory drive (NRD) during exercise between real-time electromyography (EMG)-guided NIV with high-flow therapy (HFT) support and unsupported exercise with conventional oxygen therapy (COT). To our knowledge, this is the first study to directly compare EMG-derived NRD responses across NIV, HFT, and COT. The aim of this study was therefore to compare NRD during constant-load exercise across three different conditions: COT, respiratory support with NIV, and HFT.

2. Materials and Methods

2.1. Population

The inclusion criteria for the study consisted of patients with COPD who were on the lung transplant waiting list and already evaluated by the Lung Transplant Unit at 12 de Octubre University Hospital, with the lung transplant waiting list inclusion criteria determined according to national guidelines [25]. COPD was diagnosed according to

Global Obstructive Lung Disease (GOLD) guidelines, with plethysmography confirming air trapping (a Residual Volume greater than 120% of the predicted value). Evidence of dynamic air trapping during exercise was required, confirmed by flow–volume curve analyses and the visual identification of expiratory flow limitation as previously described [26]. Additionally, patients needed to be already adapted and adherent to home non-invasive ventilation (NIV) as a bridge to transplantation. A minimum use of >4 h/day for more than 20 out of 30 days of the previous month was required.

Exclusion criteria included the presence of uncontrollable comorbidities that limited the ability to perform physical exercise (such as uncontrolled ischemic heart disease, severe pulmonary hypertension, or neuromuscular disorders), refusal to participate in the study, inability to carry out the proposed exercise protocol under baseline conditions or with ventilatory support, and the absence of reliable EMG signals for analysis.

2.2. Ethical and Data Management Protocol

The study protocol was approved by the Ethics Committee of Hospital 12 de Octubre (Resolution 18/025) and complied with the Spanish Organic Law on Data Protection 15/1999. All participants provided informed consent, and their inclusion in this study did not affect their status on the lung transplant waiting list.

An anonymized database, linked to clinical records through consecutive codes, was stored on a secure server within the Pneumology Department, accessible only to the principal investigator.

The trial was registered at ClinicalTrials.gov (identifier: NCT04597606).

2.3. Study Design

We conducted an experimental, cross-sectional, controlled study, with one arm and three different conditions (NIV, COT, HFT) for the same cohort.

2.4. Protocol

For the exercise testing, a semi-recumbent cycloergometer was used. The subjects were instructed to cycle with their arms relaxed along their trunk and avoid grasping the handlebars or support bars to avoid cross-contamination with pectoral muscle activity (due to gripping the handlebars) [27]. Each exercise session was planned for a maximum of 10 min of constant-load cycling, followed by a 5-min recovery (unloaded cycling at a gradually decreasing pace until stopping). Participants were strongly encouraged to continue pedaling throughout the 10-min period; however, some were unable to do so due to exertion and stopped early. Nevertheless, for all participants—regardless of whether they completed the full period without stopping pedaling, the prescribed duration of the exercise phase was set at 10 min for data analysis purposes. Testing was conducted on three separate days under the following conditions:

- COT: Patients started on their usual home oxygen flow, which was then adjusted to maintain a peripheral oxygen saturation (SpO_2) between 92% and 96% [28]. Continuous pulse oximetry was monitored, although mean SpO_2 values were not recorded for later analysis.
- NIV: Patients were titrated as described below, with supplemental oxygen if needed, to maintain their SpO_2 > 92% avoiding SpO_2 values over 96%.
- HFT (Airvo 2®, Fisher &Paykel, Auckland, New Zealand): A flow of 40 litres per minute was selected. Supplemental O_2 flow was initially set—before starting exercise—to maintain an estimated FiO_2 similar to that required to achieve an SpO_2 > 92% with COT [29], avoiding SpO_2 values over 96%.

Each day, before starting the exercise, each patient performed three maximum inspiratory maneuvers with simultaneous EMG recording to allow calibration and normalization. No other pulmonary function was measured during or after the exercise.

At baseline, participants underwent a "ramp test" with incremental loads up to their maximum tolerated workload, and 75% of that maximal tolerated load was selected for the tests [30,31]. Patients were already included in the exercise protocol for the lung transplantation programme, so they had all previously performed at least three sessions of exercise on a cycloergometer under COT and could thus already be considered acclimated. Three constant-load exercise tests were performed over three consecutive days. The first day was performed under COT, and at the end of the exercise testing, a 5 min trial with NIV, cycling under a free protocol for pressure titration, was performed to titrate pressures. All of the patients underwent exercise with an Astral 150® ventilator (Resmed©, San Diego, CA, USA) in spontaneous/timed mode (ST mode), as it had been previously shown to be capable of providing enough pressurization support across different programmes [32]. Expiratory pressure was titrated to avoid ineffective efforts and trigger delay in online flow/pressure control, and inspiratory pressure was titrated in order to reduce neural respiratory drive (NRD) by at least 20% as measured by parasternal EMG (online EMG Root Mean Square (RMS) traces were continuously monitored to obtain that decrease, with no subsequent offline calculations in that phase).

The ≥20% visual EMG RMS peak for parasternal muscle reduction was employed exclusively as a pre-exercise titration target during a brief unloaded cycling trial to standardize NIV support (intervention step). These titration data were not analyzed as outcomes.

2.5. Signal Recording

During the tests, patients were connected to a recording system equipped with the following sensors:

- Electrodes placed on both sides of the second parasternal space to conduct parasternal and sternocleidomastoid surface EMG, as previously described [33].
- A combined transcutaneous CO_2 and pulse oximetry oxygen saturation sensor (Sentec TCM®, Therwill, Switzerland).
- Chest and abdominal respiratory inductance plethysmography (RIP) belts (Braebon QZ-RIP, Braebon Medical Corp, Ottawa, ON, Canada) for determining inspiratory and expiratory onset.
- In the NIV condition, airflow was recorded as a raw signal from a calibrated pneumotachograph placed between the tubing and usual oronasal mask and connected to a differential pressure transducer (Powerlab Spirometer FE141, AD Instruments, Sydney, Australia) and pressure mask (Powerlab MLT844, AD Instruments, Australia).

All sensors were connected to a digital-to-analogue converter (PowerLab SP, AD Instruments, Australia), and the sampling frequency was set to 2000 Hz.

EMG signals were processed to calculate NRD as previously described [34]. Briefly, an 80 Hz high-pass filter was applied, the RMS method was employed to normalize the signals, and they were referenced to the maximum peaks obtained in an MIP maneuver. Both the peak and area under the curve (AUC) of EMG contraction were used to calculate NRD. We avoided non-respiratory tonic artefacts in the EMG by estimating the onset of inspiration from the belts' signals. NRD was calculated as the product of the respiratory rate and both the peak and area under the peak RMS, as described by Jolley et al. [35]. Respiratory rate was determined from RIP signals, independently of the ventilator's trigger detection, ensuring that all inspiratory efforts were accounted for.

2.6. Data Collection

Anthropometric variables were collected, data were taken from the last spirometry and arterial blood gas analysis, and lung function tests were performed according to current national guidelines [36], with the closest test to the exercise day selected (all within the previous 6 months).

Data were collected at different time points during the exercise test: at baseline; 1, 4, 7, and 10 min into exercise; and 3 and 5 min into the recovery period. Before each constant-load exercise, participants underwent a 5-min stabilization period under their assigned ventilatory support, and values collected at the end of this period served as baseline data for each condition.

- Respiratory variables: RR; dyspnoea perception, as measured by the BORG test scale; breathless sensation, as asked; and transcutaneously monitored CO_2 ($tcCO_2$, mmHg).
- NRD was measured as described by Jolley et al. [35]. Briefly, we choose to measure parasternal (EMGpara) and sternocleidomastoid (EMGscm) EMG signals by attaching 2 electrodes, as described previously [37]. These signals were normalized and transformed through an RMS protocol, and non-respiratory tonic artefacts in the EMG were avoided in calculations as inspiration was also signalled by the inductive plethysmography belts, and peaks were referenced to the mean baseline EMG RMS activity [38]. The RMS peak and AUC of both the EMGpara and EMGscm (μV) signals were analysed at every time step by LabChart ® Software, Version 8.0 (AD Instruments, Australia).

2.7. Statistical Analysis

Quantitative variables were described using means and standard deviations. A general linear model with repeated measures (mixed ANOVA) was used to analyze NRD variables, including the maximum parasternal RMS value across all measurements, with the signal normalized by transmissibility—both for the peak and the AUC EMGpara signal.

The same linear model was applied to repeated measures of the maximum sternocleidomastoid RMS value, also normalized, for both the peak and the area of the EMG signal. For the ANOVA, the F value, degrees of freedom, and corresponding p-value were recorded to assess the statistical significance of differences across conditions.

It was considered that, in the whole-sample analysis, the global EMG signal amplitude might have been underestimated due to patients who paused during exercise. Therefore, the same mixed factorial repeated-measures ANOVA was performed on a subset of patients who did not stop pedalling during the tests.

The level of significance was set at $p < 0.05$, and statistical analyses were performed using SPSS, Version 25 (Chicago, IL, USA).

3. Results

3.1. Descriptive Analysis

During the study period, 47 patients with COPD were enrolled in the lung transplant programme. Of these, 23 were receiving home NIV and met the criteria for inclusion. One patient underwent lung transplantation before the trial commenced, and two others were excluded due to consistently unreliable EMG signals despite multiple attempts. As a result, the final study cohort consisted of 20 patients with severe COPD, 30% of whom were women. Detailed anthropometric measurements, pulmonary function test results, and arterial blood gas values are presented in Table 1.

Table 1. Patient characteristics and ventilator parameters.

Patient Characteristics	
Variable	**Mean ± SD**
Age (years)	60.0 ± 3.9
FEV_1 (mL; % predicted)	580 ± 129; 19.3 ± 4.1
FVC (mL; % predicted)	2038.5 ± 739.6; 51.5 ± 18.0
RV (mL; % predicted	6240.6 ± 1242.5; 286.4 ± 28.2
TLC (mL; % predicted)	8563.9 ± 1358.9; 140.9 ± 28.2
RV/TLC ratio (%)	73.4 ± 7.8
pO_2 (mmHg)	60.7 ± 14.2
pCO_2 (mmHg)	51.1 ± 6.8
pH (units)	7.40 ± 0.1
Ventilator Parameters	
IPAP at baseline (cmH_2O)	19.3 ± 5.0
IPAP during exercise (cmH_2O)	21.9 ± 5.7
EPAP at baseline (cmH_2O)	9.0 ± 2.7
EPAP during exercise (cmH_2O)	9.5 ± 3.1

FEV_1: Forced Expiratory Volume in 1 s (mL = absolute value; % = percent predicted); FVC: Forced Vital Capacity (mL = absolute value; % = percent predicted); RV: Residual Volume (mL = absolute value; % = percent predicted); TLC: Total Lung Capacity (mL = absolute value; % = percent predicted); RV/TLC: Residual Volume to Total Lung Capacity ratio (%); pO_2: baseline partial pressure of oxygen in arterial blood (mmHg) under room air or home continuous oxygen; pCO_2: baseline partial pressure of carbon dioxide in arterial blood (mmHg); pH: arterial blood pH measured under room air conditions (FiO_2 = 0.21, Fraction of Inspired Oxygen 21%); IPAP: Inspiratory Positive Airway Pressure (cmH_2O); EPAP: Expiratory Positive Airway Pressure (cmH_2O); baseline: home NIV parameters; exercise: pressure values after titration, while performing constant-load cycling at 75% of maximum tolerated workload.

Comparative analysis showed that ventilatory pressure parameters differed significantly between home NIV settings and exercise testing conditions. Specifically, the mean Inspiratory Positive Airway Pressure (IPAP) increased from 19.57 ± 5.02 cmH_2O during home use to 21.93 ± 5.73 cmH_2O during exercise ($p < 0.01$), indicating a clinically meaningful rise in pressure requirements during physical activity, as outlined in Table 1.

3.2. Comparative Study of Respiratory Variables

A comparative analysis of respiratory interventions revealed distinct physiological effects. NIV showed superior performance, with a greater reduction in RR (mean difference: 4.2 breaths/min), lower perceived exertion (Borg score decrease: 1.8 points), and a more pronounced reduction in $tcCO_2$ (decrease: 5.3 mmHg) compared to both COT and HFT during exercise testing ($p < 0.05$ for all comparisons). HFT demonstrated intermediate efficacy between COT and NIV. These findings are illustrated in Figure 1, and a summary of intra- and intercondition statistics is presented in Table 2.

3.3. Comparative Study of Neuroventilatory Variables

During exercise, significant within-subject differences were observed in the degree of respiratory muscle activation. In the intercondition analysis, NIV resulted in the greatest muscular unloading compared to COT, with HFT showing an intermediate effect. When analyzing NRD (expressed as μV × RR) across the three exercise conditions (COT, NIV, and HFT), a mixed repeated-measures ANOVA including the full cohort demonstrated significant differences. Specifically, peak EMGpara activity was lowest with NIV, indicating the most effective reduction in respiratory muscle load during exercise. However, the analysis of the EMG area (AUC RMS for both EMGpara and EMGscm) showed no significant intercondition muscle differences, although significant within-subject changes were detected. Table 2 also summarizes NRD findings for EMGpara and EMGscm, while Table 3 reflects the average RD values for each condition.

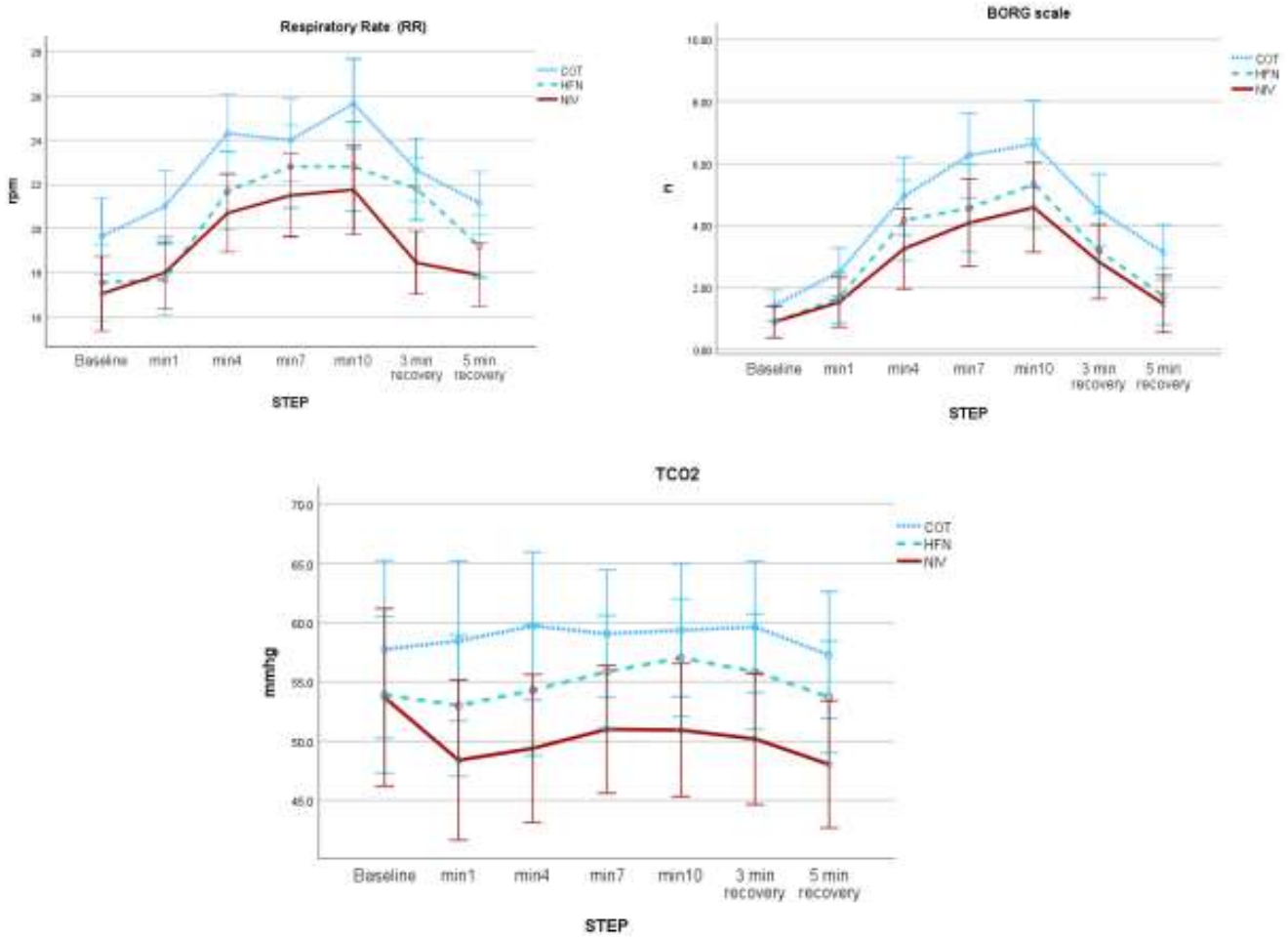

Figure 1. Evolution of respiratory rate (RR), dyspnea perception (Borg scale), and transcutaneous CO_2 ($tcCO_2$) during constant-load exercise under three ventilatory conditions (conventional oxygen therapy, high-flow therapy, and non-invasive ventilation). Mean ± SD values are shown for each time point (baseline; minutes 1, 4, 7, and 10 of exercise; and 3- and 5-min recovery). Results from mixed repeated-measures ANOVA show significant intra- and intercondition effects.

Table 2. Statistical analysis of respiratory and neural respiratory variables.

Parameter	F-Statistic	*p*-Value	Effect Size (η^2)	Power (β^{-1})
Respiratory Rate (RR)				
Intrasubject	12.00	$p < 0.05$	0.20	0.88
Intersubject	6.07	$p < 0.01$	0.20	0.86
Borg Scale				
Intrasubject	26.08	$p < 0.001$	0.77	1.00
Intersubject	4221.59	$p < 0.001$	0.76	1.00
$TcCO_2$ (mmHg)				
Intrasubject	1191.23	$p < 0.001$	0.96	1.00
Intersubject	26.08	$p = 0.1$	0.10	0.43
Parasternal peak EMG				
Intrasubject	25.95	$p < 0.001$	0.68	1
Intersubject	2.56	0.05	0.09	0.56

Table 2. *Cont.*

Parameter	F-Statistic	*p*-Value	Effect Size (η^2)	Power (β^{-1})
Parasternal area EMG				
Intrasubject	15.21	$p < 0.001$	0.61	0.99
Intersubject	2.52	$p = 0.08$	0.1	0.48
SCM peak EMG				
Intrasubject	6.53	0.08	0.2	0.67
Intersubject	2.57	0.1	0.05	0.35
SCM area EMG				
Intrasubject	28.04	$p < 0.001$	0.32	1
Intersubject	2.77	0.07	0.1	0.52

Table 3. Mean neural respiratory drive variable analysis across exercise conditions.

Parameter	Condition	Mean ± SD	95% CI
Parasternal NRD in µV (peak)	COT	1180.00 ± 200.10	781.68 to 1579.58
	NIV	488.81 ± 199.09	89.80 to 887.70
	HFT	807.80 ± 204.32	398.50 to 1217.15
SCM NRD in µV (peak)	COT	1434.24 ± 265.17	903.30 to 1965.24
	NIV	758.90 ± 265.17	227.80 to 1289.80
	HFT	1256.10 ± 265.17	725.15 to 1787.10

COT: Conventional oxygen therapy; NIV: non-invasive ventilation; NRD: neural respiratory drive; HFT: high-flow therapy; SCM: sternocleidomastoid; SD: standard deviation; CI: confidence interval.

Finally, Figure 2 presents the whole-cohort NRD analysis.

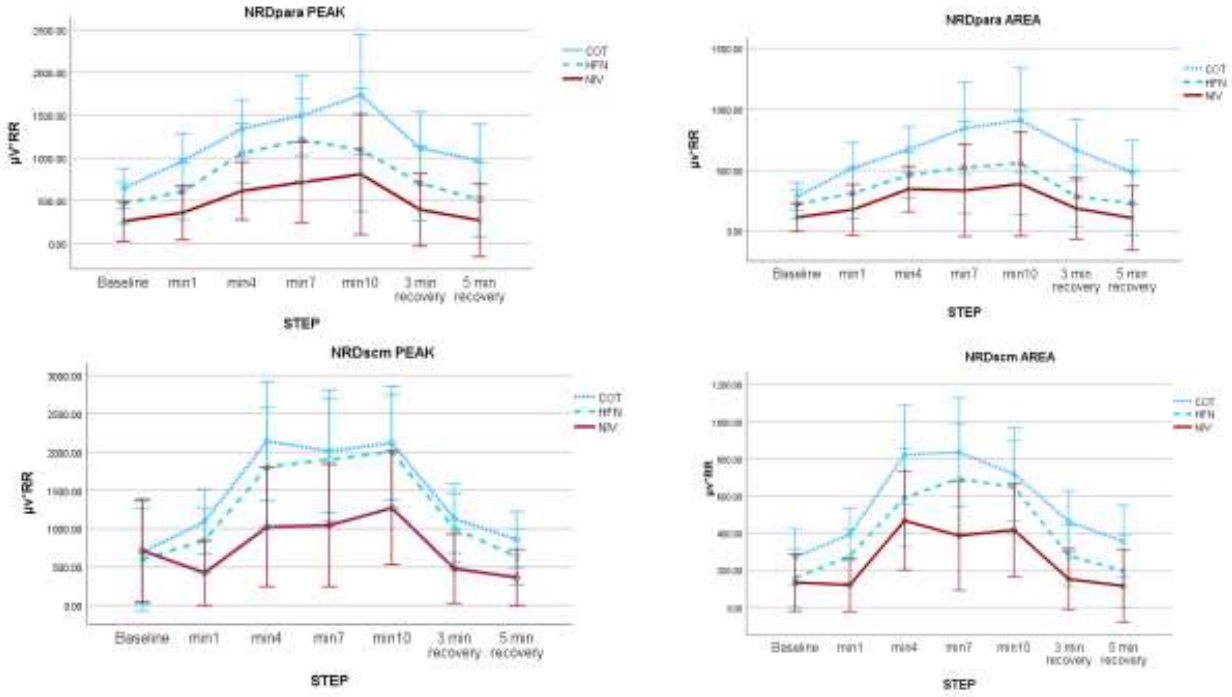

Figure 2. "All sample with STOPs" Peak and area values of parasternal (NRDpara) and sternocleidomastoid (NRDscm) EMG activity during constant-load exercise under three ventilatory conditions (conventional oxygen therapy, high-flow therapy, and non-invasive ventilation). Results from the full cohort are shown as mean ± SD. Mixed repeated-measures ANOVA revealed significant intra- and intercondition effects.

3.4. Subgroup Analysis: Exercise Non-Limited Cohort (Patients Who Did Not Stop Pedalling, N = 7)

Significant time- and condition-related differences were observed in peak NRD (μV × RR) in both muscle groups analyzed, with effects observed both within and between subjects. Among the three experimental conditions, NIV was associated with the greatest reduction in respiratory muscle effort during exercise, reflected in highly significant decreases in both peak and area NRD values for the EMGpara compared with COT and HFT:

- EMGpara NRD peaks:
  - Within-subject: $F(6,14) = 8.970$, $p < 0.001$, $\eta^2 = 0.79$, $\beta^{-1} = 0.99$.
  - Between-subject: $F(2,18) = 9.116$, $p < 0.01$, $\eta^2 = 0.50$, $\beta^{-1} = 0.94$.
- EMGscm NRD peaks:
  - Within-subject: $F(6,33) = 23.142$, $p < 0.001$, $\eta^2 = 0.41$, $\beta^{-1} = 0.99$.
  - Between-subject: $F(2,33) = 4.760$, $p < 0.01$, $\eta^2 = 0.22$, $\beta^{-1} = 0.75$.

For the patients who did not stop, the differences did not reach statistical significance. When only taking normalized EMG RMS values into account (both parasternal and sternocleidomastoid, independent of RR), no significant differences were obtained between the three modalities (COT, HFT, and NIV) across the whole cohort.

4. Discussion

This study demonstrates that NIV significantly reduces NRD during exercise in patients with severe COPD when compared to HFT and COT. NRD, quantified as the product of RR and normalized EMGpara (EMGpara%max), was 60% lower with NIV than with COT (488.81 μV vs. 1180.63 μV, $p < 0.05$), with HFT showing intermediate effects (807.8 μV). These results are consistent with previous meta-analyses indicating the superiority of NIV over HFT in improving exercise tolerance and alleviating dyspnoea [22,39–44]. The physiological basis for this advantage lies in NIV's ability to unload inspiratory muscles by counteracting iPEEP, reducing dynamic hyperinflation, and increasing tidal volume—mechanisms that are only modestly engaged by HFT, which primarily enhances oxygenation and comfort.

The limited impact of HFT on NRD likely reflects its inability to provide sufficient and consistent positive pressure under high ventilatory demand. Although HFT can generate a degree of airflow-dependent positive airway pressure (~4 cmH_2O at 40 L/min), this is typically inadequate to overcome the elevated inspiratory threshold load encountered during exercise in severe COPD [21]. In contrast, NIV offers adjustable inspiratory pressures, effectively reducing inspiratory effort, as demonstrated by decreases in both EMGpara and EMGscm activity. In post hoc analyses, we observed that while some patients exhibited reductions in EMG amplitude alone, others showed minimal EMG changes but marked decreases in RR. Only the composite NRD measure (EMG × RR) revealed consistent and statistically significant differences across the cohort, underscoring the dual contribution of both respiratory muscle unloading and rate reduction to the overall ventilatory relief provided by NIV. This slowing of RR represents an additional mechanism contributing to NRD reduction and is functionally coupled with the unloading of inspiratory muscles. These findings reinforce the concept that pressure support, rather than flow delivery alone, is essential for effective respiratory muscle unloading in patients with significant expiratory flow limitation [45].

Patient characteristics likely influenced the observed efficacy of NIV. Participants presented with severe airflow limitation with a predicted first-second Forced Expiratory Volume (FEV_1) of 19.78% and marked hyperinflation (Residual Volume/Total Lung Capacity 160%), making them particularly suitable for NIV-assisted training.

Another key contributor to NIV's success was participants' prior acclimatization to home NIV. This familiarity likely enhanced both tolerance and adherence, in contrast to NIV-naïve patients, who frequently experience mask-related discomfort and patient–ventilator asynchrony, often resulting in early discontinuation [13]. In our cohort, acclimatized patients achieved optimal synchrony, allowing sustained pressure delivery even during peak exercise, which likely contributed to improved alveolar ventilation and lower transcutaneous CO_2 levels.

The use of a high-performance ventilator, with rapid pressurization capabilities (rise time < 50 ms), also played a pivotal role in matching the ventilator's response to patients' inspiratory demands during exercise. Unlike older or less responsive devices [13], this technology minimized flow demand and ensured consistent patient–ventilator synchrony even under rapidly changing ventilatory loads. This likely contributed to the consistent achievement of the study's target of at least a 20% NRD reduction, a result that would be harder to obtain with suboptimal equipment. In this context, it is worth noting that proportional assist ventilation shares these physiological principles and has been shown to allow higher-intensity exercise training and greater physiological adaptation compared with conventional or unassisted exercise in severe COPD [30].

Finally, individualized inspiratory pressure titration was key to achieving physiological optimization. IPAP was adjusted prior to testing to ensure a $\geq$20% reduction in NRD during unloaded cycling, thereby tailoring support to each patient's needs [13,14,46]. Comparisons of NRD reported in this study refer to the constant-load exercise phase, and real-time feedback from EMG allowed for the fine-tuning of pressure support, maximizing inspiratory muscle unloading.

The improved ventilatory pattern and lower dyspnoea with NIV suggest better exercise tolerance, in line with previous studies reporting increased endurance with ventilatory support, consistent with previous findings, such as those by Xie et al. [47], who reported a 59% improvement in dyspnoea-adjusted exercise capacity using comparable protocols. In contrast, the absence of significant benefits with HFT diverges from the review by Candia et al. [21], who observed functional improvements in patients with milder COPD. This contrast underscores HFT's potential utility in moderate disease stages, while reinforcing the specific advantage of NIV in patients with more severe airflow limitation and hyperinflation.

These findings must also be interpreted in light of the practical demands associated with implementing NIV in clinical settings. The complete experimental setup—including EMG preparation, calibration, and transcutaneous CO_2 stabilization—required approximately 45 min per session (for only 10 min of active, loaded exercise and 5 min of cold down), while the actual pressure titration phase lasted about 5 min and was performed by experienced personnel. This requirement poses a significant barrier in rural or resource-limited environments where access to both equipment and trained professionals may be limited. The development of automated pressure adjustment algorithms and simplified EMG monitoring techniques could play a key role in facilitating broader implementation. Moreover, future research should aim to develop simplified titration strategies that do not rely on complex monitoring. Easily measurable surrogates such as RR, dyspnoea scores, or ventilator-derived parameters could serve as practical alternatives to guide NIV initiation and adjustment in routine rehabilitation settings. But, at the same time, technological developments may offer easier approaches to these complex measurements. For example, automated expiratory flow limitation compensation may serve to titrate EPAP, or cheaper wearable devices may allow for a better understanding of respiratory muscle response during exercise [48]. Additionally, cost considerations remain an important factor, and future research should focus on evaluating whether the higher upfront costs of NIV and EMG

monitoring are offset by long-term healthcare savings, particularly through reductions in hospital admissions following rehabilitation.

Accordingly, while our data provide mechanistic support—namely a robust, acute reduction in NRD during exercise—we consider it premature to recommend routine incorporation of NIV into standard pulmonary rehabilitation outside specialized settings until pragmatic trials demonstrate sustained improvements in function, symptoms, and quality of life after program completion and address real-world implementation barriers.

This study has some limitations that warrant consideration. The relatively small sample size (n = 20) constrains statistical power, and although this is comparable to previous single-centre physiological trials, it limits the generalizability of the findings to broader COPD populations. Another limitation concerns the characteristics of our study population. All participants were lung transplant candidates with very severe, "pure" COPD and minimal comorbidities, which limits the generalizability of our findings. To minimize the potential impact of comorbidities on study outcomes, all participants underwent a comprehensive pre-transplant evaluation, which, combined with the extensive pre-transplant assessment, ruled out the presence of comorbidities that confound the response to ventilatory support, and patients who are older and have milder disease or common comorbidities such as heart failure, pulmonary hypertension, or muscle dysfunction may respond differently. Furthermore, the inclusion of patients previously acclimatized to home NIV may have introduced a selection bias, potentially overestimating tolerance and benefit during exercise sessions. Another limitation concerns the HFT condition, which was applied at a fixed flow of 40 L/min without individual titration. This setting was chosen based on tolerability in severe COPD, the flow rates most commonly used in chronic home settings [49], current clinical recommendations for home HFT [50], and the potential physiological adverse effects reported with higher flows [51]. Future studies should explore EMG-guided flow titration to better define the physiological ceiling of HFT in this population. To confirm the reproducibility and external validity of these results, larger multicentre studies involving more heterogeneous patient groups and varying levels of disease severity are essential. Another important limitation is that the NIV systems used in this and previous studies are stationary and restricted to supervised settings. Attempts to develop truly portable ventilatory support for ambulation have faced major technical barriers, mainly related to battery life, device weight, and the need for high-pressure oxygen sources. Early studies using backpack-mounted ventilators [52] showed no improvement in dyspnoea or walking distance, and newer lightweight devices, such as the Philips VitaBreath, provided only intermittent support and have since been discontinued [53]. Therefore, the applicability of our findings remains limited to controlled, stationary rehabilitation environments until substantial technological advances occur.

Future research should focus on several key areas to build on these findings. First, the development of personalized ventilatory support algorithms that could enable automatic pressure adjustments during exercise, enhancing both precision and feasibility. Second, rigorous cost–benefit analyses comparing the long-term outcomes of NIV and HFT across healthcare systems with differing resource availability are needed to inform clinical and policy decisions. Third, the potential of hybrid protocols—such as sequential HFT-NIV strategies—should be investigated to determine whether they could offer an optimal balance between patient comfort and physiological efficacy, particularly in populations with variable tolerance or access to equipment.

5. Conclusions

This study confirms that EMG-titrated NIV significantly reduces NRD during exercise in patients with severe COPD compared to HFT and COT. These benefits are particularly evident in patients previously acclimatized to NIV and with no other comorbidities.

Author Contributions: J.S.-C., C.L. and M.L. conceived and designed the study protocol, developed the analysis plan, and drafted the initial version of the manuscript. A.H.-V., M.J.-G., M.C.-B. and L.G.-R. contributed substantially to the setup and optimization of the signal processing protocols, conducted preliminary tests to refine the experimental procedures, performed all exercise trials, provided medical supervision during these sessions, contributed to the revision of the manuscript, and approved the final version. V.V.G. provided essential infrastructure and logistical support for the execution of the study, contributed to the initial drafting of the manuscript, and participated in the critical revision and approval of the final version, enhancing its clarity and overall quality. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was approved by the Medical Research Ethics Committee of the Hospital Universitario 12 de Octubre under approval number 18/025, approval date 13 March 2018. The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: Due to the biological nature of the signals and information related to inclusion in the lung transplant list, data are not publicly available. Upon justified request, authors may share the raw flow/pressure/EMG data and other biological variable tracings.

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Abbreviations

The following abbreviations are used in this manuscript:

COPD	Chronic Obstructive Pulmonary Disease
COT	Conventional Oxygen Therapy
NIV	Non-Invasive Ventilation
HFT	High-Flow Nasal Cannula Therapy (High-Flow Therapy)
NRD	Neural Respiratory Drive
iPEEP	Intrinsic End-Expiratory Positive Pressure
EMG	Electromyography
EMGpara	Parasternal Electromyography
EMGscm	Sternocleidomastoid Electromyography
SCM	Sternocleidomastoid Muscle
RIP	Respiratory Inductance Plethysmography
SpO_2	Peripheral Oxygen Saturation
$tcCO_2$	Transcutaneous Carbon Dioxide
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
RV	Residual Volume
TLC	Total Lung Capacity
RV/TLC	Residual Volume to Total Lung Capacity Ratio

IPAP	Inspiratory Positive Airway Pressure
EPAP	Expiratory Positive Airway Pressure
FiO_2	Fraction of Inspired Oxygen
MIP	Maximal Inspiratory Pressure
RMS	Root Mean Square
AUC	Area Under the Curve
RR	Respiratory Rate
SD	Standard Deviation
CI	Confidence Interval
ST mode	Spontaneous/Timed Mode (Ventilator Setting)

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7. DISCUSIÓN CONJUNTA

7. DISCUSIÓN CONJUNTA

7.1. Visión General y Contribución Científica

7.1.1. Contribución Metodológica

La presente tesis doctoral contribuye significativamente al avance metodológico en la evaluación de la función respiratoria mediante el desarrollo del Global Phase Delay (GPD) como método mejorado para la cuantificación de la asincronía toracoabdominal (TAA). Este desarrollo metodológico supera las limitaciones del ángulo de fase tradicional y permite una caracterización más precisa de los patrones de asincronía respiratoria.

El GPD, basado en el ángulo formado por los vectores torácico y abdominal en el plano horizontal, cubre todo el espectro de situaciones de asincronía toracoabdominal en un único valor, simplificando así su medición y eliminando algunos de los inconvenientes asociados con la medición clásica del ángulo de fase. Los resultados demuestran que el GPD es superior al ángulo de fase para detectar desviaciones severas y movimientos paradójicos, con un rango de -179,75 a +178,54 grados comparado con -86,90 a +88,4 grados del ángulo de fase.

La medición de la asincronía toracoabdominal mediante el ángulo de fase presenta importantes limitaciones metodológicas que han sido identificadas y estudiadas sistemáticamente en esta investigación. Estas limitaciones incluyen varios aspectos fundamentales:

- Limitaciones matemáticas inherentes: El cálculo del ángulo de fase se basa únicamente en las relaciones entre el desplazamiento torácico y abdominal en un único punto del ciclo respiratorio (el punto medio de la excursión torácica), y esta relación puede cambiar, especialmente para formas de bucle aberrantes (distintas velocidades de movimiento angular del componente torácico y el abdominal). Además, existe un límite matemático para calcular simplemente la relación de los vectores m y s, ya que el rango de la relación solo puede estar entre 0 y 1, lo que significa que los valores $\sin^{-1}$ estarían entre 0 y 90 grados.

- Asunción de movimiento sinusoidal: El ángulo de fase asume que tanto el tórax como el abdomen se mueven en un patrón puramente sinusoidal ("movimiento armónico simple"). Esta analogía podría ser válida para un individuo normal, pero en pacientes con EPOC, la tasa de vaciado del compartimento torácico es mucho más lenta debido a la alta resistencia intrapulmonar, y por lo tanto, la condición básica para considerar válido el ángulo de fase (la necesidad de una velocidad angular constante, **ω**) ya no se cumple.
- Incapacidad para identificar el compartimento que lidera el movimiento ("tórax adelantado" vs "abdomen adelantado"): El ángulo de fase no informa qué banda (torácica o abdominal) está adelantada. Esta limitación es particularmente relevante desde el punto de vista clínico, ya que el compartimento avanzado puede tener importantes implicaciones clínicas, traduciendo uso de musculatura accesoria por debilidad diafragmática en el caso de "tórax adelantado, giro horario" vs. obstrucción o marcado atrapamiento aéreo en el caso de "abdomen adelantado, giro antihorario".
- Limitaciones en la detección de paradojas toracoabdominales severas: El ángulo de fase y el área del bucle no son suficientes para discriminar bucles con paradojas severas. Solo se encontraron diferencias significativas entre los grupos de sincronización normal y desviación leve, sin diferencias significativas para los grupos restantes.

Desarrollo del Global Phase Delay como Solución

Para superar estas limitaciones, se desarrolló el GPD como parámetro alternativo basado en la relación de dos vectores diferentes que representan cada uno de los cinturones. El GPD se calculó a partir de las pendientes de ambos vectores (m1 -Abd- y m2 -Tho-) y corresponde al ángulo entre ambos vectores, asignando un signo positivo si el cinturón avanzado era el torácico y un signo negativo si era el abdominal.

Los resultados demuestran que el GPD supera las limitaciones del ángulo de fase tradicional al:

- Proporcionar información sobre la totalidad del desplazamiento del bucle, no solo en un punto particular del ciclo
- Permitir un rango más amplio de TAA medida (de -179,75 a +178,54 grados)

- Incluir las paradojas torácicas y abdominales en la estimación
- Identificar claramente qué compartimento lidera el movimiento

Implicaciones Clínicas de las Mejoras Metodológicas

La implementación del GPD tiene implicaciones para la práctica clínica. La capacidad de detectar y cuantificar patrones paradójicos permite una mejor caracterización de la disfunción respiratoria, especialmente en situaciones donde el ángulo de fase tradicional fallaría en identificar asincronías severas.

Además, la identificación del compartimento líder proporciona información valiosa sobre los mecanismos fisiopatológicos subyacentes. El avance significativo del componente abdominal puede indicar atrapamiento aéreo, mientras que el avance significativo del componente torácico puede indicar reclutamiento de músculos accesorios.

7.1.2. Contribución Fisiopatológica

Los resultados del primer artículo presentado han contribuido al posterior entendimiento de los mecanismos fisiopatológicos de la limitación al ejercicio en la EPOC, particularmente en relación con la TAA y el impulso neural respiratorio. Esta herramienta aplicada a la población de EPOC estudiada ha permitido caracterizar los patrones específicos de TAA durante el ejercicio y sus correlaciones con parámetros clínicos y funcionales.

Se identificaron dos patrones distintos de TAA durante el ejercicio: el patrón de rotación horaria (tórax adelantado, propio de predominio de la musculatura accesoria sobre el diafragma) y el patrón de rotación antihoraria (abdomen adelantado, propio de actividad diafragmática intensa que no consigue superar la hiperinsuflación). El patrón de rotación horaria se asoció con peor función pulmonar basal, mayor disnea de ejercicio pico y mayor impulso neural respiratorio comparado con la rotación antihoraria, sugiriendo una activación compensatoria de los músculos paraesternales para contrarrestar la incapacidad del diafragma de satisfacer la demanda respiratoria aumentada.

7.1.3. Contribución Terapéutica

La evaluación comparativa de diferentes modalidades de soporte respiratorio no invasivo durante el ejercicio contribuye al desarrollo de estrategias terapéuticas optimizadas para pacientes con EPOC severa. Los resultados demuestran que la VNI es superior a la terapia de alto flujo (TAF) en términos de reducción del impulso neural respiratorio, con una reducción del 60% comparada con la terapia convencional con oxígeno. Y de acuerdo al estudio sobre TAA, aquellos pacientes con tórax adelantado se benefician más del soporte con VNI que los que adelantan el abdomen.

7.1.4. Contribución Clínica

Los hallazgos de esta investigación tienen implicaciones clínicas directas para el manejo de pacientes con EPOC severa sometidos a ejercicio para su rehabilitación. El desarrollo de métodos mejorados de monitorización y la identificación de predictores de respuesta al tratamiento pueden mejorar la atención clínica y los resultados de los pacientes.

TAA como Marcador de Respuesta a la VNI Durante el Ejercicio

Los resultados de este estudio revelan que los patrones de TAA durante el ejercicio en pacientes con EPOC severa pueden indicar la severidad del deterioro de la función pulmonar y predecir la severidad de la disnea inducida por el ejercicio. Se identificaron dos patrones distintos:

- Patrón de rotación horaria (tórax adelantado): Este patrón se caracterizó por una mayor severidad de la enfermedad, con pacientes presentando menor FEV1 y FVC predicha comparado con aquellos con rotación antihoraria (FEV1 15,5% ± 3,44% vs. 20,54 ± 3,85%, $p < 0,05$). Estos pacientes también experimentaron mayor disnea durante el ejercicio con terapia convencional de oxígeno y mayor impulso neural respiratorio.
- Patrón de rotación antihoraria (abdomen adelantado): Este patrón se observó en pacientes con función pulmonar relativamente mejor preservada y menor grado de disfunción respiratoria durante el ejercicio.

La paradoja abdominal, caracterizada por el movimiento hacia adentro del abdomen durante la inspiración, representa la forma más severa de TAA y sirve como marcador

clínico de disfunción diafragmática severa y fatiga muscular. Los pacientes con paradoja abdominal mostraron mayor impulso neural respiratorio tanto en pico como en área bajo la curva comparado con aquellos sin paradoja abdominal.

Respuesta Diferencial a la VNI Según el Patrón de TAA

Una observación clave de este estudio es que la respuesta al soporte respiratorio no invasivo varía según el patrón de TAA presente. Los pacientes con rotación horaria fueron más propensos a experimentar reducción de la disnea con VNI comparado con la terapia convencional de oxígeno, en contraste con aquellos con rotación antihoraria.

Este hallazgo sugiere que la TAA puede servir como un biomarcador para predecir la respuesta al soporte respiratorio durante el ejercicio. La identificación previa del patrón de TAA podría permitir una selección más precisa de pacientes que se beneficiarían de estrategias específicas de soporte respiratorio.

Limitaciones en la Respuesta Global a la VNI

Aunque se esperaba una disminución consistente de la TAA con VNI o TAF, no se observaron diferencias significativas en el grado de TAA al comparar las tres intervenciones (terapia convencional, VNI y TAF). Las respuestas variaron ampliamente entre individuos, y tres pacientes cambiaron la dirección de rotación y desarrollo de paradoja entre intervenciones.

Esta variabilidad en la respuesta sugiere que la TAA es un fenómeno complejo influenciado por múltiples factores, incluyendo el grado de soporte proporcionado, la configuración del ventilador y las características individuales del paciente. Algunos pacientes mostraron paradoja abdominal con VNI antes del ejercicio, posiblemente debido a soporte excesivo que podría empeorar la hiperinsuflación.

Valor Predictivo y de Monitorización de la TAA

Los resultados sugieren que la pletismografía de inductancia respiratoria puede proporcionar una herramienta no invasiva para identificar pacientes que más probablemente respondan a intervenciones específicas, incluyendo configuraciones de VNI de alta presión. Además, podría ayudar a asegurar configuraciones apropiadas de

VNI durante el ejercicio basándose en asincronías registradas y podría ser una herramienta efectiva para el seguimiento de pacientes.

La monitorización de la TAA durante el ejercicio puede proporcionar información valiosa sobre la eficacia del soporte respiratorio y permitir ajustes en tiempo real de los parámetros ventilatorios para optimizar la sincronía paciente-ventilador.

7.1.5. Efectos Superiores de la VNI en la Descarga Muscular, CO2 y Disnea

Los resultados de este estudio demuestran de manera concluyente que la VNI es superior a la TAF en términos de reducción del impulso neural respiratorio durante el ejercicio en pacientes con EPOC severa. La VNI redujo el impulso neural respiratorio pico en un 60% comparado con la terapia convencional de oxígeno (488,81 µV vs. 1180,63 µV, $p<0,05$), mientras que la TAF mostró efectos intermedios (807,8 µV).

Esta superioridad se explica por los diferentes mecanismos de acción de ambas modalidades. La VNI proporciona soporte inspiratorio activo mediante presión positiva ajustable, reduciendo efectivamente el trabajo de los músculos respiratorios al contrarrestar la PEEP intrínseca y aumentar el volumen corriente. En contraste, la TAF, aunque puede generar un grado de presión positiva dependiente del flujo (~4 cmH_2O a 40 L/min), es típicamente inadecuada para superar la carga umbral inspiratoria elevada encontrada durante el ejercicio en EPOC severa.

La VNI demostró una reducción más pronunciada en la CO2 transcutánea (disminución de 5,3 mmHg) comparada tanto con la terapia convencional como con la TAF durante el esfuerzo. Esta mejora en la eliminación de CO2 refleja varios mecanismos:

- Mejora de la ventilación alveolar: La VNI facilita el incremento del volumen corriente y reduce la frecuencia respiratoria, mejorando la eficiencia ventilatoria y reduciendo el espacio muerto fisiológico.
- Reducción de la hiperinsuflación dinámica: Al proporcionar presión espiratoria (EPAP) que contrarresta la PEEP intrínseca, la VNI facilita el vaciado pulmonar y reduce el atrapamiento aéreo.
- Optimización de la relación ventilación-perfusión: La mejora en la mecánica respiratoria con VNI resulta en una distribución más homogénea de la ventilación, optimizando el intercambio gaseoso.

La VNI logró una mayor reducción en la percepción del esfuerzo (disminución de 1,8 puntos en la escala de Borg) comparada con ambas modalidades de control (TAF y oxígeno convencional). Esta reducción superior en la disnea se atribuye a varios factores:

- Reducción del impulso neural respiratorio: La disminución significativa del impulso neural respiratorio con VNI se traduce directamente en una menor percepción del esfuerzo respiratorio. Existe una elevada y sólida evidencia que correlaciona el drive neuro ventilatorio (NRD) con la disnea percibida (11, 18, 22, 23, 56, 76-80).
- Mejora de la eficiencia neuromecánica: La VNI reduce el desacoplamiento entre el impulso neural y la respuesta mecánica del sistema respiratorio, fundamental en la génesis de la disnea en EPOC.
- Reducción de la fatiga muscular: Al aliviar la carga de los músculos respiratorios, la VNI previene o retrasa el desarrollo de fatiga muscular, un factor importante en la limitación del ejercicio.

Varios factores específicos del estudio contribuyeron a la eficacia superior de la VNI observada:

- Aclimatación previa: Los participantes tenían familiaridad previa con VNI domiciliaria, lo que mejoró tanto la tolerancia como la adherencia, en contraste con pacientes *näive* a VNI que frecuentemente experimentan incomodidad relacionada con la mascarilla y asincronía paciente-ventilador. En este sentido existen trabajos previos con pacientes más leves, previamente sin adaptación a ventilación domiciliaria (40). que encontraron incluso empeoramiento de la tolerancia al ejercicio empleando VNI (45). El paciente además realizaba el ejercicio con su propio equipamiento (mascarilla, tubuladura) con la que ya estaba familiarizado.
- Uso de ventilador de alto rendimiento: Se utilizó un ventilador con capacidades de presurización rápida (tiempo de elevación <50 ms), que minimizó la demanda de flujo y aseguró sincronía paciente-ventilador consistente incluso bajo cargas ventilatorias que cambian rápidamente. La presurización de estos equipos es óptima en situaciones de muy alta demanda. Nuestro grupo conjunto entre el Hospital Parc Taulí y el Hospital 12 de Octubre ya demostró en un relevante

estudio previo publicado por C Lalmolda (81) sobre pacientes EPOC estables cómo las diferencias en la capacidad de presurización de los equipos domiciliarios influían no solo en parámetros propios de banco de pruebas (como el PTP300) sino también en la descarga muscular en pacientes estables. Esto se exacerba en pacientes bajo situaciones de muy alta demanda, como durante el esfuerzo. Incluso en algunos trabajos citados (45) los pacientes incluidos llegaban a superar el flujo máximo de respiradores de generaciones anteriores (150lpm) produciendo una intensa demanda de flujo y evitando el efecto de descarga muscular buscado.

- Titulación individualizada: La presión inspiratoria se ajustó para asegurar una reducción ≥20% en el impulso neural respiratorio durante el ciclismo sin carga, maximizando así la descarga de los músculos inspiratorios mediante retroalimentación en tiempo real del EMG. Esto permitió partir de unos parámetros más ajustados al inicio del ejercicio, que cubriesen la demanda del paciente desde el inicio. Y de manera más relevante, se puso interés en el ajuste de la presión espiratoria (EPAP) para compensar la limitación al flujo espiratorio evitando retrasos de disparo (*trigger)* y esfuerzos ineficaces. Algunos trabajos han tratado de titular la EPAP realizando medidas repetidas durante el ejercicio de capacidad inspiratoria, sin encontrar diferencias entre una EPAP empírica y la titulada (5cmh2O) ya que en ambos casos mejoraba la hiperinsuflación (82). Otros autores han empleado el concepto de ventilación de alta intensidad aplicado al esfuerzo (83), empleando presiones inspiratorias altas, pero, sorprendentemente, tiempos inspiratorios fijos y frecuencias respiratorias elevadas, tratando de "capturar" al paciente durante el esfuerzo. Fisiopatológicamente es difícil de entender, dado el impacto en la limitación del tiempo espiratorio y la dificultad de "capturar" y descargar muscularmente a un paciente taquipneico con altas demandas mediante una ventilación controlada y no asistida. Más sorprendente en este estudio es el uso de EPAP relativamente bajas, lo que puede impedir una adecuada corrección de la limitación al flujo espiratorio.
- Selección de aquellos pacientes más graves: La severidad de la enfermedad influye significativamente en la respuesta a la VNI durante el ejercicio. Los pacientes con EPOC muy severa, como los incluidos en nuestro estudio (FEV1 medio 19,78% predicho), presentan características que los hacen particularmente adecuados para el entrenamiento asistido con VNI:

- Limitación ventilatoria marcada: Pacientes con obstrucción severa al flujo aéreo y hiperinsuflación marcada (volumen residual/capacidad pulmonar total 160%) se benefician más del soporte de presión para superar la resistencia de las vías aéreas.
- PEEP intrínseca elevada: La presencia de auto-PEEP significativa en estos pacientes permite que la EPAP proporcionada por la VNI tenga un efecto más pronunciado en la reducción del trabajo respiratorio.
- Reserva ventilatoria limitada: En pacientes con EPOC muy severa, incluso pequeñas mejoras en la eficiencia respiratoria pueden traducirse en mejoras sustanciales en la tolerancia al ejercicio.

- Ausencia de Comorbilidades no controladas: la presencia de comorbilidades cardiovasculares, musculoesqueléticas o neurológicas puede confundir los efectos de la VNI durante el ejercicio. Nuestro estudio incluyó pacientes en lista de espera para trasplante pulmonar, quienes habían sido sometidos a evaluaciones exhaustivas (incluyendo coronariografía, evaluación cardiológica extensa, etc) que descartaron comorbilidades significativas. Esta selección estricta, aunque limita la generalización, permite una evaluación más pura de los efectos de la VNI en la limitación ventilatoria. En poblaciones menos seleccionadas, los efectos de la VNI pueden verse atenuados por factores no respiratorios que limitan el ejercicio.

7.1.6. Papel del alto flujo

Finalmente, tras demostrarse la superioridad (en EPOC) del ejercicio soportado con VNI vs TAF, cabe plantear cual es el papel del alto flujo como ayuda en el ejercicio. Una revisión reciente (53), y un documento de posicionamiento de la Sociedad Española de Neumología (SEPAR) (84), dejan clara la escasez de estudios comparados con los disponibles para la VNI. Los beneficios, superiores a los del oxígeno convencional, vienen probablemente determinados por la capacidad de mantener una FiO_2 constante durante todo el ejercicio, más que por el limitado efecto PEEP (que se pierde en pacientes que durante el ejercicio suelen respirar con la boca abierta), o por la capacidad de humidificación. Sin embargo, al disminuir el drive neuro ventilatorio de manera superior al oxígeno convencional, tal y como se demuestra en los presentes trabajos, puede ser de utilidad como alternativa a la VNI en pacientes intolerantes.

7.2. Limitaciones del Estudio

7.2.1. Derivadas de la muestra de pacientes

Una limitación importante de esta investigación es el tamaño muestral relativamente pequeño (n=20) y la población altamente seleccionada de pacientes en lista de espera para trasplante pulmonar. Esta selección estricta, aunque permite el estudio de los mecanismos fisiopatológicos en su expresión más intensa, limita significativamente la generalización de los resultados. Los pacientes en lista de trasplante representan una población muy específica con EPOC en estadio terminal, sin comorbilidades cardiovasculares significativas y con un estado funcional que les permite someterse a protocolos de ejercicio intensivos. Si bien hay datos de metaanálisis sobre la eficacia del soporte ventilatorio en pacientes con insuficiencia cardiaca en rehabilitación (85), la interacción respiratoria y hemodinámica en estos pacientes puede complicar la titulación y la interpretación de los resultados, no siendo por tanto extrapolables nuestros hallazgos a otras poblaciones. De igual manera, son pacientes con un sesgo de edad, por lo que se desconoce como pueden responder pacientes más ancianos a este tipo de entrenamiento.

Aunque el tamaño de cohorte es comparable a otros estudios fisiológicos unicéntricos previos, limita el poder estadístico para detectar diferencias menores entre grupos y para análisis de subgrupos. De especial interés sería una evaluación por subgrupos según los niveles de atrapamiento aéreo (por ejemplo, segmentados según capacidad pulmonar total o volumen residual). Sin embargo, lo limitado de la muestra impide realizar este estudio de subgrupos.

7.2.2. Derivadas de requerimientos Técnicos y Económicos

La implementación de los protocolos utilizados en esta investigación presenta importantes barreras técnicas y económicas:

Sistema de monitorización costoso: La configuración de EMG y la titulación de presiones requirieron aproximadamente 45 minutos por sesión e involucraron personal con experiencia especializada. El costo de los equipos de monitorización EMG y la necesidad de personal altamente entrenado pueden ser prohibitivos en entornos rurales o con recursos limitados.

En el caso concreto de la titulación de presiones, el desarrollo de algoritmos automatizados de ajuste de presión, basadas por ejemplo en oscilometría de impulsos acoplada al respirador (86) o en el análisis de la señal de flujo del respirador (como propuso el codirector de esta tesis junto con nuestro grupo (87)), pueden permitir disminuir la experiencia necesaria en la titulación y el tiempo requerido para ello, automatizando el proceso. No obstante, algunos estudios previos con sistemas automáticos de soporte (ventilación asistida proporcional) no encontraron diferencias con presiones inspiratorias "fijas" (41, 88).

Aunque estudios previos han demostrado que la rehabilitación pulmonar resulta en una intervención altamente costo efectiva (74), los costos iniciales más altos de la VNI y monitorización EMG requieren evaluación adicional para determinar si son compensados por ahorros a largo plazo en el sistema de salud.

7.3. Líneas Futuras de Investigación

En el campo de la asistencia a la rehabilitación se pueden plantear varias líneas que mejorarían las actuales limitaciones:

Mejora en sistemas de monitorización: La complejidad técnica y los frecuentes problemas de señales derivados de la electromiografía de superficie pueden limitar su uso. La alternativa de EMG diafragmático a través de una sonda esofágica multicanal aporta señales de mucha más fidelidad a costa de mucha mayor complejidad técnica y sobre todo, mayor invasividad. En los últimos años ha aumentado el interés en sistemas no invasivos de monitorización tanto de la ventilación (sobredistensión, reclutamiento, etc) con equipos como la tomografía de impedancia eléctrica (EIT) (89), o en el uso de técnicas destinadas a evaluar la sincronía toracoabdominal sin contacto, como la pletismografia de luz estructurada (90). Sin embargo, ambos métodos presentan como limitación los artefactos inducidos por el movimiento parásito del pedaleo, requiriendo complejos algoritmos para minimizar este impacto. De manera paralela, el desarrollo de sistemas wearables de electromiografía, integrados en chalecos es una prometedora vía para "democratizar" el uso de EMG en la guía de la titulación del soporte ventilatorio (91).

Automatización de la titulación: Si bien trabajos previos con sistemas de presión de soporte automatizados, como la presión asistida proporcional, no demostraron superioridad sobre la presión de soporte tradicional en su uso en ejercicio, la posibilidad de un autoajuste de EPAP para compensar la progresiva limitación al flujo espiratorio que se produce durante el esfuerzo. Así, algunos fabricantes están desarrollando, con grandes limitaciones, sistemas que integran oscilómetros en respiradores, empleando una oscilación a 5Hz tanto en inspiración como en espiración para la detección de limitación al flujo espiratorio (86). Estos equipos incluyen un algoritmo de ”auto-EPAP” que puede ser una forma de simplificar la titulación en un futuro. Si además se desarrollan sistemas que integren un autoajuste del nivel de soporte y de la presurización de manera más sencilla y explicable que el algoritmo previo de la presión asistida proporcional, puede ser de una gran utilidad para simplificar el proceso de adaptación del soporte al nivel de esfuerzo.

Telerrehabilitación: La necesidad de hacer llegar estos programas a áreas más remotas o menos dotadas tecnológicamente ha hecho que exista un progresivo interés en el desarrollo de programas de telerrehabilitación y “telecoaching” (92). Estos programas, combinados con tecnologías de “wearables”, tal y como comentábamos en este editorial (93), suponen una oportunidad para expandir los beneficios de la rehabilitación asistida con VNI. Cabe soñar con un futuro cercano en que se integren los datos de dispositivos comerciales (tipo Fitbit®) con los datos que aporta el respirador, permitiendo un ajuste remoto de parámetros, e idealmente, la alimentación con estos datos de sistemas de inteligencia artificial que automaticen el proceso.

8. CONCLUSIONES

8. CONCLUSIONES

- La ventilación no invasiva genera una descarga muscular respiratoria (mejoría del drive neuroventilatorio) estadística y clínicamente significativa superior a la terapia de alto flujo y al oxígeno convencional.
- La ventilación no invasiva mejora la disnea, la tolerancia al ejercicio y la hipercapnia de manera superior a la terapia de alto flujo y a la oxigenoterapia convencional.
- El cálculo de Global Phase delay (GPD) es una técnica que mejora la capacidad de identificar asincronía toracoabdominal de manera superior al cálculo del ángulo de fase.
- Los patrones de asincronía toracoabdominal observados durante el ejercicio en pacientes con EPOC muy grave reflejan la severidad de la obstrucción e hiperinsuflación pulmonar y se correlacionan con la intensidad de la disnea inducida.
- El registro continuo de la sincronía toracoabdominal permitió identificar dos patrones claramente diferenciados: adelantamiento torácico (rotación horaria) y adelantamiento abdominal (rotación antihoraria). La presencia de adelantamiento torácico o de un patrón paradójico abdominal se asocia a mayores valores de NRD y mayor disnea.

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10. ÍNDICE DE ABREVIATURAS

- **CEIC**: Comité Ético de Investigación Clínica
- **COT**: Terapia convencional con oxígeno
- **DNR**: Drive Neural Respiratorio (impulso neural respiratorio)
- **EMG**: Electromiografía
- **EMGdi**: Electromiografía diafragmática
- **EMGpara**: Electromiografía paraesternal
- **EMGscm**: Electromiografía esternocleidomastoideo
- **EPOC**: Enfermedad Pulmonar Obstructiva Crónica (COPD en inglés)
- **FEV1**: Volumen Espiratorio Forzado en el primer segundo
- **FiO2**: Fracción inspirada de oxígeno
- **FR**: Frecuencia Respiratoria
- **FVC**: Capacidad Vital Forzada
- **GOLD**: Global Initiative for Chronic Obstructive Lung Disease
- **GPD**: Global Phase Delay (Retardo de Fase Global)
- **IPAP**: Presión Inspiratoria Positiva en las Vías Aéreas
- **LOPD**: Ley Orgánica de Protección de Datos
- **MIP**: Maniobra Inspiratoria Máxima
- **NIV**: Non-Invasive Ventilation (Ventilación Mecánica No Invasiva)
- **PaCO2**: Presión Parcial Arterial de CO2
- **PaO2**: Presión Parcial Arterial de O2
- **PEEPi**: Presión Positiva al Final de la Expiración Intrínseca
- **RIP**: Respiratory Inductance Plethysmography (Pletismografía de Inductancia Respiratoria)
- **RV**: Volumen Residual
- **SpO2**: Saturación de Oxígeno Pulmonar
- **TAF**: Terapia de Alto Flujo (High-Flow Therapy)
- **TAA**: Thoracoabdominal Asynchrony (Asincronía Toracoabdominal)
- **TLC**: Capacidad Pulmonar Total
- **VNI**: Ventilación Mecánica No Invasiva