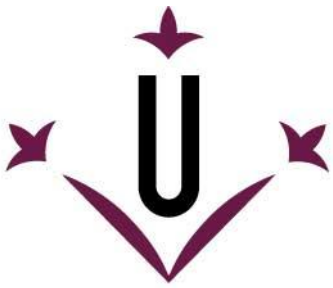
Estudio del efecto del síndrome de apneas-hiponeas del sueño y su tratamiento con CPAP en diferentes fenotipos de presión arterial

Esther Sapiña Beltrán



Universitat de Lleida

TESI DOCTORAL

Estudio del efecto del síndrome de apneas-hipopneas del sueño y su tratamiento con CPAP en diferentes fenotipos de presión arterial

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"El futuro pertenece a quienes
creen en la belleza de sus sueños"

- Eleanor Roosevelt

A mi padre, Enrique

Allí donde estés, gracias

A mi madre, Susi

A mis hermanas, Elena y Raquel

A Dani

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2. Sapiña-Beltrán E, Torres G, Benitez I, Fortuna-Gutiérrez AM, Márquez PP, Masa JF, Corral-Peñafiel J, Drager LF, Cabrini M, Félez M, Vázquez S, Abad J, Lee CH, Aung AT, García-Río F, Casitas R, Sanchez-de-la-Torre M, Gaeta AM, Barbé F, Dalmases M. *Prevalence, Characteristics, and Association of Obstructive Sleep Apnea with Blood Pressure Control in Patients with Resistant Hypertension.* Ann Am Thorac Soc. 2019;16(11):1414-1421. Factor de impacto (2019): 4.836. Q1.

3. Sapiña-Beltrán E, Santamaria-Martos F, Benítez I, Torres G, Masa JF, Sánchez-de-la-Torre M, Barbé F, Dalmases M. *Normotensive patients with obstructive sleep apnoea: changes in 24-h ambulatory blood pressure monitoring with continuous positive airway pressure treatment.* J Hypertens. 2019;37(4):720-727. Factor de impacto (2019): 4.171. Q1.

4. Sapiña-Beltrán E, Torres G, Benítez I, Santamaría-Martos F, Durán-Cantolla J, Egea C, Sánchez-de-la-Torre M, Barbé F, Dalmases M; on behalf of the Spanish Sleep and Breathing Group. *Differential blood pressure response to continuous positive airway pressure treatment according to the circadian pattern in hypertensive patients with obstructive sleep apnoea*. Eur Respir J. 2019;54(1). Factor de impacto (2019): 12.339. D1.

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APÉNDICE

GLOSARIO DE ABREVIATURAS

AMPA	Automedida de la presión arterial en el domicilio
CPAP	Presión positiva continua en vía aérea
CI	Intervalo de confianza. Confidence interval
DM	Diabetes mellitus
DR	Dipping ratio
ECG	Electrocardiograma
HTA	Hipertensión arterial
HR	Hipertensión resistente
HVI	Hipertrofia ventricular izquierda
IAH	Índice de apneas/hipopneas
IMC	Índice de masa corporal
MAPA	Monitorización ambulatoria de la presión arterial
PA	Presión arterial
PAD	Presión arterial diastólica
PAM	Presión arterial media
PAS	Presión arterial sistólica
PCR	Poligrafía cardiorrespiratoria
PSG	Polisomnografía convencional
RAAS	Sistema renina-angiotensina-aldosterona
SAHS	Síndrome de apneas-hipopneas del sueño
SNS	Sistema nervioso simpático

RESUMEN

RESUMEN

El síndrome de apneas-hipopneas del sueño (SAHS) se ha asociado a la presencia de hipertensión arterial (HTA), especialmente con la hipertensión resistente (HR). Además, se ha descrito que el tratamiento del SAHS con presión positiva continua en la vía aérea (CPAP) consigue reducciones en la presión arterial (PA), pero existe una gran variabilidad en la respuesta observada y no hay evidencia a largo plazo. Por lo tanto, los cuatro estudios de esta tesis tienen cómo objetivo contribuir al conocimiento sobre la relación de ambas patologías, y establecer el efecto del tratamiento del SAHS sobre la PA en distintos fenotipos de PA.

En este sentido, se desarrolló e implementó un estudio prospectivo para evaluar el impacto del SAHS y su tratamiento en el pronóstico cardiovascular en pacientes con HR.

En el segundo estudio, se evaluó la prevalencia de SAHS en sujetos con HR, así cómo el impacto de esta patología sobre el control de la PA, observándose una prevalencia de SAHS del 83.5%, además de, una asociación dosis-respuesta entre la gravedad del SAHS y los valores de la PA, especialmente la PA nocturna.

En el tercer estudio, se evaluó el efecto de la CPAP en sujetos normotensos. Los resultados muestran que el patrón circadiano de la PA o la presencia de hipertensión enmascarada tiene un papel importante en el efecto de la CPAP sobre la PA, siendo los sujetos con patrón circadiano non-dipper y aquellos con hipertensión enmascarada los que más se benefician del tratamiento con CPAP, en términos de reducción de la PA. Además, en pacientes normotensos con patrón circadiano dipper, el tratamiento con CPAP podría incrementar la PA nocturna, por lo que estos resultados muestran la necesidad de llevar a cabo una monitorización de la PA previamente a la prescripción de CPAP con el fin de definir subgrupos de respuesta al tratamiento. Finalmente, y de continuidad con este estudio, se evaluó el efecto del tratamiento con CPAP en pacientes con HTA según el patrón circadiano basal, y los resultados muestran de nuevo que sólo los pacientes en tratamiento con CPAP y con un patrón circadiano non-dipper reducen los valores de PA.

En definitiva, los resultados expuestos en la presente tesis doctoral son de relevancia e interés en la práctica clínica habitual dado que pueden ayudar a mejorar el manejo e indicación del tratamiento con CPAP en pacientes con SAHS y contribuir a establecer una indicación más individualizada y coste-efectiva.

RESUM

La síndrome d'apnees-hipopnees de la son (SAHS) s'ha associat a la presència d'hipertensió arterial (HTA), especialment amb la hipertensió resistent (HR). A més, s'ha descrit que el tractament del SAHS amb pressió positiva contínua en la via aèria (CPAP) aconsegueix reduccions en la pressió arterial (PA), però, hi ha una gran variabilitat en la resposta observada i no hi ha evidència a llarg termini. Per tant, els quatre estudis que composen la present tesi doctoral tenen com a objectiu contribuir al coneixement sobre la relació entre ambdues patologies, i establir l'efecte del tractament del SAHS sobre la PA en diferents fenotips de PA.

En aquest sentit, es va desenvolupar i implementar un estudi prospectiu per avaluar l'impacte del SAHS i el seu tractament en el pronòstic cardiovascular en pacients amb HR.

En el segon estudi, es va avaluar la prevalença de SAHS en subjectes amb HR, així com l'impacte d'aquesta patologia sobre el control de la PA, observant-se una prevalença de SAHS del 83.5%, i una associació dosi-resposta entre la gravetat del SAHS i els valors de la PA, especialment de la PA nocturna.

En el tercer estudi, es va avaluar l'efecte de la CPAP en subjectes normotensos. Els resultats mostren que el patró circadià de la PA o la presència d'hipertensió emmascarada tenen un paper important en l'efecte de la CPAP sobre la PA, sent els pacients amb un patró circadià non-dipper i aquells amb hipertensió emmascarada els que més es beneficien del tractament amb CPAP, en termes de reducció de la PA. A més, en pacients normotensos amb patró circadià dipper, el tractament amb CPAP podria incrementar la PA nocturna, per tant aquests resultats mostren la necessitat de dur a terme un monitoratge de la PA prèviament a la prescripció de CPAP per tal de definir subgrups de resposta al tractament. Finalment, i de continuïtat amb aquest estudi, es va avaluar l'efecte del tractament amb CPAP en pacients amb HTA segons el patró circadià basal, i els resultats mostren de nou, que només els pacients amb tractament amb CPAP i un patró circadià non-dipper redueixen els valors de PA.

En definitiva, els resultats exposats en la present tesi doctoral són de rellevància i interès en la pràctica clínica habitual donat que poden ajudar a millorar el maneig i indicació del tractament amb CPAP en pacients amb SAHS i contribuir a establir una indicació més individualitzada i cost-efectiva.

ABSTRACT

Obstructive sleep apnea syndrome (OSAs) has been associated with arterial hypertension (HTN), especially with resistant hypertension (RH). In addition, it has been described that the treatment of OSAs with continuous positive airway pressure (CPAP) produces reductions in blood pressure (BP), nevertheless there is a great variability in the BP response and there is no evidence at long-term. Despite the relation between both pathologies, some aspects remain unclear due to the limited available evidence and the controversy in the published studies. Therefore, the four studies that shape this doctoral thesis aim to contribute to the knowledge about the relation between both pathologies, and to determine the effect of CPAP treatment on BP in different BP phenotypes.

In this sense, a prospective study was carried out and implemented to evaluate the impact of OSAs and its treatment on cardiovascular prognosis in patients with RH.

In the second study, we evaluate the prevalence of OSAs and its impact on BP in subjects with RH, and a prevalence of 83.5% was found. Moreover, we found a dose-response association between OSAs' severity and BP values, especially with nocturnal BP.

In the third study, the effect of CPAP on normotensive subjects was evaluated. The results show that the circadian BP pattern or the presence of masked hypertension could determine the effect of CPAP on BP. It was observed that patients with a non-dipper circadian pattern and those with masked hypertension benefited the most from CPAP treatment, in terms of BP reduction. Moreover, an increase in nocturnal BP with CPAP treatment was observed in normotensive subjects with a dipper circadian pattern. These results show the necessity to perform a BP monitoring prior to CPAP prescription in order to define subgroups of treatment response. Finally, we evaluated if there is a differential effect of CPAP treatment on BP in patients with HTN according to the baseline circadian BP pattern. The results of this study showed again that only patients with CPAP treatment and non-dipper circadian pattern reduce BP.

In conclusion, the results presented in this doctoral thesis could be of relevance and interest in the clinical practice because they can help to improve the management and indication of CPAP treatment in patients with OSAs and contribute to establishing a more individualized and cost-effective indication of the CPAP treatment.

INTRODUCCIÓN

1. SÍNDROME DE APNEAS-HIPOPNEAS DEL SUEÑO (SAHS)

1.1. Definición y prevalencia

El síndrome de apneas-hipopneas del sueño (SAHS) es el trastorno respiratorio del sueño más común. Se caracteriza por episodios repetidos de obstrucción total (apnea) o parcial (hipopnea) de la vía aérea superior durante el sueño. Los eventos asociados al cierre de la vía aérea superior producen cambios en la presión intratorácica, hipoxia intermitente, hipercapnia y microdespertares encefalográficos o arousals, y estos cambios conllevan, un patrón de respiración con pausas respiratorias cíclicas y un sueño fragmentado [1–3].

El SAHS es una enfermedad prevalente en la población general, y en los últimos años su prevalencia ha ido en aumento debido al incremento de la obesidad y al envejecimiento de la población [4–7]. En población de mediana edad, es el doble de prevalente en el género masculino, aunque esta distribución varía con la edad, ya que tras la menopausia existe un aumento de la prevalencia en las mujeres [6,7].
En la actualidad, se estima que podría afectar cerca de mil millones de adultos entre 30-69 años de todo el mundo. Concretamente, en España, la prevalencia de SAHS en este mismo rango de edad se sitúa en entorno al 35.2% [8].

1.2. Etiología y factores de riesgo

La etiología del SAHS es multifactorial y las causas pueden variar entre sujetos. En general, en la fisiopatología del SAHS se considera que juega un papel importante la interacción entre la anatomía de la vía aérea superior, el tono muscular de la zona y factores genéticos [1,3,9]. Existen diversos factores de riesgo asociados cómo son la edad, la obesidad, el género masculino, el envejecimiento, la menopausia, la obstrucción nasal y anomalías craneofaciales y orofaríngeas, entre otros. De entre todos estos factores de riesgo mencionados, la obesidad es considerado el factor que contribuye de manera más destacada[1,3,9,10].

1.3. Signos y síntomas

Clínicamente, el SAHS puede manifestarse mediante una variedad de síntomas que se presentan durante el día o la noche. Entre los síntomas más comunes se encuentran los ronquidos, las apneas presenciadas, sensación de ahogo, excesiva somnolencia diurna, mala calidad del sueño, nicturia, irritabilidad, pérdida de memoria y cefalea matutina. Además de estos síntomas, el SAHS también se asocia a cambios en el estado de ánimo y cognición, disminución del rendimiento laboral, aumento de los accidentes de tráfico, disminución de la calidad de vida y mayor riesgo de enfermedades cardiovasculares. No obstante, un pequeño porcentaje de pacientes permanece asintomático [5,11].

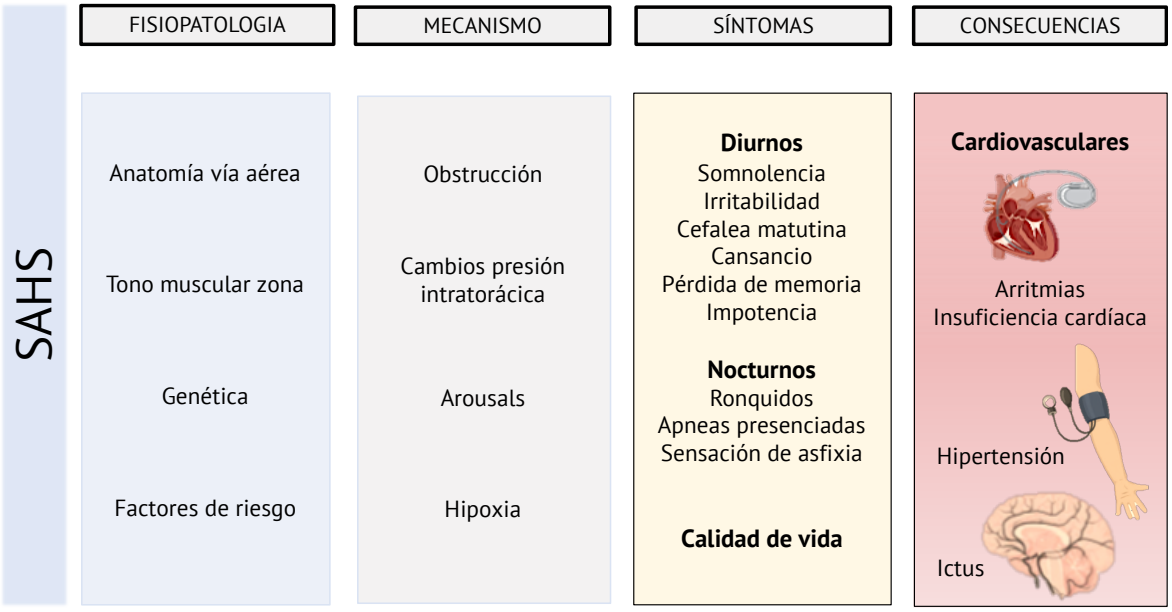


Figura 1. Fisiopatología, presentación y consecuencias del SAHS.

1.4. Métodos diagnósticos

Para la detección del SAHS se debe valorar la clínica y las comorbilidades asociadas, por ello, es importante llevar a cabo una evaluación clínica detallada. No obstante, la confirmación del diagnóstico requiere valorar la respiración durante el sueño.

La prueba de elección *gold standard*, para el diagnóstico de SAHS y otros trastornos del sueño es la polisomnografía convencional (PSG), prueba en la que se registran las señales neurofisiológicas (electroencefalograma, electrooculograma, electromiograma), cardíacas (electrocardiograma), y respiratorias (flujo respiratorio, saturación arterial de oxígeno, esfuerzo torácico y abdominal, ronquido), del paciente durante toda la noche. Estas señales permiten identificar las fases del sueño e identificar si el paciente hace eventos respiratorios. Se trata de una prueba compleja, además de costosa, que requiere de la vigilancia nocturna de un técnico de laboratorio del sueño. Por ello, con el fin de simplificar este proceso, y en los casos de sospecha clínica de SAHS, sin indicios de otros trastornos del sueño ni comorbilidades asociadas, el diagnóstico se puede realizar mediante poligrafía cardiorrespiratoria (PCR). Se trata de una prueba válida, sencilla y que se puede llevar a cabo en el domicilio del paciente.

A diferencia de la PSG convencional, en la PCR únicamente se registran señales respiratorias, por lo que no permite detectar trastornos del sueño de no respiratorios, evaluar la calidad del sueño, y además, dado que no se conoce el tiempo de sueño se puede infravalorar el índice de apneas-hipopneas (IAH) del sueño [12–14].

1.5. Criterios diagnósticos

Los criterios diagnósticos del SAHS están basados en la presencia de clínica y en los eventos repetitivos de obstrucción de la vía aérea superior que tienen lugar durante el sueño, que se miden con el IAH por hora de sueño (horas de cama si se utiliza PCR).

El IAH es la medida utilizada para definir la enfermedad y clasificar la gravedad. El diagnóstico de SAHS se establece con un IAH superior o igual a 5 eventos/h asociado a los síntomas típicos de la enfermedad o con un IAH ≥ 15 eventos/h con ausencia de sintomatología [13] . En relación a la gravedad del SAHS, se clasifica según el IAH en: leve, moderado, grave (Tabla 1) [12–14].

Gravedad	Índice de apneas-hipopneas (IAH)
Leve	5-14.9
Moderado	15-29.9
Grave	⩾ 30

Tabla 1. Clasificación de la gravedad del SAHS.

1.6. Tratamientos del SAHS

En cuánto al tratamiento del SAHS, existen diversas opciones terapéuticas entre las que se encuentran: el tratamiento conservador que hace referencia a una serie de medidas higiénico-dietéticas y posturales, el tratamiento con presión positiva continua en vía aérea (CPAP) considerado *gold standard*, y otros tratamientos cómo el dispositivo de avance mandibular e intervención quirúrgica. De estas opciones, el tratamiento conservador y el tratamiento con CPAP constituyen las opciones terapéuticas fundamentales del SAHS.

1.6.1. Tratamiento conservador

El tratamiento conservador engloba una serie de medidas higiénico-dietéticas y posturales, y se debe indicar de forma general a todos los pacientes diagnosticados de SAHS, independientemente de la gravedad que presenten. Estas medidas incluyen: tener una buena higiene de sueño (dormir un número de horas adecuado y mantener un horario regular, entre otras pautas de sueño saludable); perder peso en el caso que el paciente en el momento del diagnóstico presente un índice de masa corporal (IMC)>25 kg/m^2 [14]; evitar el consumo de alcohol entre 4-6 h antes de acostarse, ya que el alcohol reduce el tono del músculo geniogloso y predispone o exacerba la obstrucción de la vía aérea [15]; levantar el cabecero de la cama y dormir en decúbito

lateral, ya que dormir en posición supina produce cambios en la forma de la faringe y puede exacerbar el colapso de la vía aérea [5,14].

1.6.2. Presión positiva continua en vía aérea (CPAP)

El tratamiento con CPAP es un tratamiento que consiste en un generador de aire que, mediante una tubuladura conectada a una mascarilla oral, introduce de forma continua aire con presión positiva a la vía aérea, con el fin de evitar que se produzca la obstrucción en la vía aérea superior [13,14,16]. La CPAP es el tratamiento de elección para pacientes diagnosticados de SAHS moderado/grave. En los casos con SAHS leve/moderado su prescripción está sujeta a la presencia de sintomatología y/o enfermedad cardiovascular [14](Figura 2). El tratamiento con CPAP se considera un tratamiento crónico de manera que la utilización de este dispositivo conlleva la aparición de nuevo de las apneas durante el sueño.

El tratamiento con CPAP es efectivo para mejorar la somnolencia, la función diurna y la calidad de vida, y estos beneficios se observan pocos días después del inicio del tratamiento [1,17,18] . No obstante, la adherencia al tratamiento supone un aspecto clave en la efectividad de éste, y generalmente se requiere un mínimo de 4 h/noche para obtener una mejoría clínica significativa, sin embargo el número de horas de uso de la CPAP necesario para obtener mejoras en otras esferas es superior [19,20]. Diversos factores podrían influir en la adherencia al tratamiento con CPAP, pero la importancia de muchos de los determinantes sigue sin estar clara. En un trabajo reciente [21] se identificaron la gravedad del SAHS, la somnolencia diurna y no fumar cómo determinantes de la adherencia al tratamiento con CPAP.

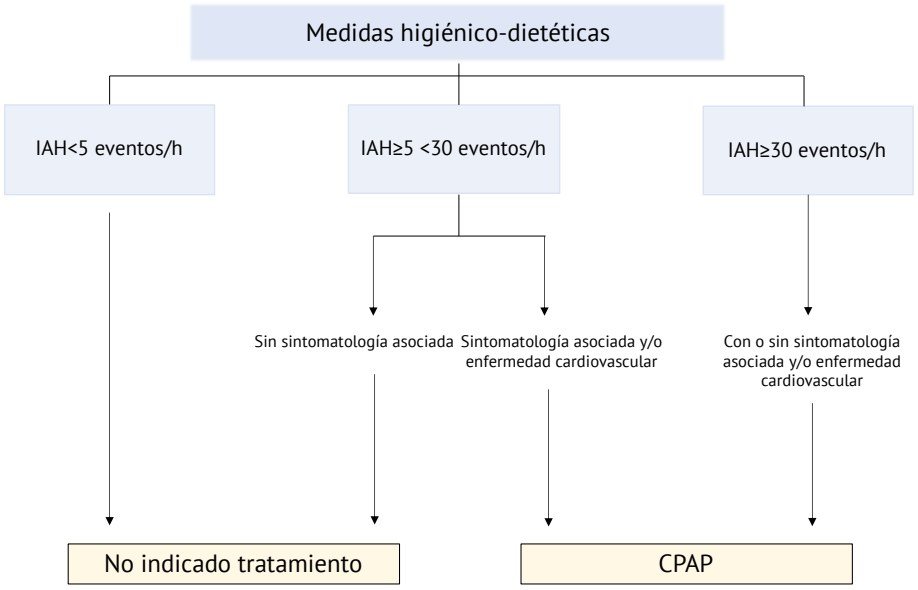


Figura 2. Indicación del tratamiento con CPAP

1.6.3. Otros tratamientos

La primera indicación en los casos de SAHS moderado/grave suele ser el tratamiento con CPAP. No obstante, se pueden indicar otras opciones terapéuticas dependiendo de la gravedad del SAHS, las comorbilidades asociadas, las características anatómicas del paciente, su ocupación y sus preferencias. En los casos de SAHS leve-moderado o de intolerancia a la CPAP, se puede indicar el dispositivo oral (el más conocido es el dispositivo de avance mandibular) Y intervención quirúrgica, en casos de anomalías craneofaciales u orofaríngeas. En personas con obesidad mórbida, está indicada la cirugía bariátrica [5,13,14].

2. LA HIPERTENSIÓN ARTERIAL (HTA)

2.1. Definición, prevalencia y diagnóstico

La hipertensión arterial (HTA) es el factor de riesgo cardiovascular más importante y representa una elevada morbilidad y mortalidad en la población general [22,23]. Según la medición de la presión arterial (PA) en consulta, la HTA se define cómo una presión arterial sistólica (PAS) ≥ 140 mmHg o una presión arterial diastólica (PAD) ≥ 90 mmHg, no obstante, estas cifras pueden variar según el método utilizado para realizar la medición de la PA [24] (Tabla 2).

La prevalencia de HTA es elevada, debido principalmente al crecimiento y envejecimiento de la población. En 2015, la prevalencia global estimada de hipertensión era de 1.13 mil millones [25]. En España, se sitúa en torno al 43% [26] y aumenta progresivamente con la edad, siendo la prevalencia superior al 60% en personas mayores de 60 años, originado por los cambios en el estilo de vida que se producen en esta etapa [27,28].

		PAS (mmHg)		*PAD (mmHg)*
PA consulta	**Normal**	120-129	y/o	80-84
	Hipertensión	⩾ 140	y/o	⩾ 90
MAPA	**Normal**	<130	y/o	<80
	Hipertensión			
	Media 24h	⩾ 130	y/o	⩾ 80
	Media diurna	⩾ 135	y/o	⩾ 85
	Media nocturna	⩾ 120	y/o	⩾ 70

PA: presión arterial; MAPA: monitorización ambulatoria de la presión arterial; PAS: presión arterial sistólica; PAD: presión arterial diastólica.

Tabla 2. Definición de hipertensión en consulta y domiciliaria. (Criterios para jóvenes, adultos de mediana edad y ancianos).(Adaptada de Guía ESC/ESH 2018)[24].

Para confirmar el diagnóstico de HTA, es necesario realizar diferentes medidas de PA debido a la variabilidad de ésta. La última guía europea para el manejo de la HTA, establece algunos cambios en las recomendaciones para confirmar el diagnóstico de HTA respecto a la anterior. En la actualidad, se recomienda que el diagnóstico de la HTA se realice en base a, diversas mediciones de la PA en consulta y en diferentes días, o mediante monitorización ambulatoria de la presión arterial durante 24 horas (MAPA). En el caso que no sea posible realizar la MAPA, el diagnóstico podría establecerse mediante la automedida de la presión arterial en el domicilio (AMPA). No obstante, la MAPA aporta mayor información en cuanto a la PA nocturna y permite identificar diversos fenotipos de PA [24]. De acuerdo al método utilizado para establecer el diagnóstico de HTA, las guías determinan diferentes intervalos de PA (Tabla 2).

2.2. Fenotipos de la presión arterial

La información obtenida con la MAPA, junto con la AMPA y las mediciones de PA en consulta, ha permitido determinar diferentes fenotipos de PA: Normotensión verdadera, hipertensión arterial de bata blanca, hipertensión arterial enmascarada y hipertensión arterial sostenida [24,29] (Tabla 3).

- **Normotensión verdadera:** Este término hace referencia a aquellos pacientes que presentan valores de PA dentro de la normalidad tanto en las mediciones en consulta*(<140/90 mmHg)*, cómo en las domiciliarias: MAPA *(PA media 24 <130/80 mmHg; PA diurna <135/85 mmHg; PA nocturna <120/70 mmHg)* o *AMPA (<135/85 mmHg)* [24].

- **Hipertensión arterial de bata blanca:** Se trata de un fenotipo común utilizado para definir a aquellos sujetos con (HTA no controlada de bata blanca) o sin tratamiento farmacológico que presentan la PA elevada en las

mediciones en consulta *(≥140/90 mmHg)*, pero, sin embargo, los resultados obtenidos en las mediciones en domicilio (MAPA o AMPA) son normales [24]. Comúnmente, se conoce el efecto de bata blanca cómo la respuesta vasopresora ante la situación de alerta al entrar en una consulta médica y que, de forma transitoria, produce un aumento de la frecuencia cardiaca y la PA [30,31].

La prevalencia de la HTA de bata blanca es elevada, entorno al 30-40%, siendo más frecuente en edades avanzadas, sexo femenino y no fumadores [24]. El riesgo cardiovascular asociado a este fenotipo sigue en estudio, pero los resultados de dos importantes metaanálisis muestran un aumento del riesgo cardiovascular y de problemas metabólicos en las personas diagnosticadas de hipertensión de bata blanca en comparación con pacientes normotensos [32,33]. Además, existe un elevado riesgo de que las personas con este fenotipo de PA desarrollen con el tiempo HTA sostenida.

- **Hipertensión arterial enmascarada:** La HTA enmascarada define a aquellos sujetos con o sin tratamiento farmacológico que tienen la PA controlada en consulta *(<140/90 mmHg)*, pero presentan valores elevados en la MAPA *(PA media 24 ≥ 130/80 mmHg; PA diurna ≥135/85 mmHg; PA nocturna ≥120/70 mmHg)* o AMPA *(≥135/85 mmHg)*[24,29]. Su prevalencia se sitúa entre el 10-23% [34], dependiendo de la población estudiada y suele ser más frecuente en hombres y en población de temprana edad [34,35].

  En diversos estudios, se ha observado que la incidencia de eventos cardiovasculares en este fenotipo hipertensivo es elevada, mayor que la observada en la HTA de bata blanca y similar a la sostenida [36–39], también destaca una elevada prevalencia de trastornos metabólicos, sobrepeso, hipertrofia ventricular izquierda (HVI), y diabetes mellitus (DM) [38,40] en estos pacientes.

- **Hipertensión arterial sostenida o verdadera:** Se utiliza este término para designar a aquellas personas que presentan niveles PA elevados tanto en consulta como en las mediciones domiciliaras. Se trata del fenotipo hipertensivo asociado a mayor morbimortalidad cardiovascular [36,37].

	PA consulta	⊕	MAPA* o AMPA
Normotensión verdadera	< 140/90		< 130/80; < 135/85
Hipertensión de bata blanca	⩾ 140/90		< 130/80; < 135/85
Hipertensión enmascarada	< 140/90		⩾ 130/80; ⩾ 135/85
Hipertensión sostenida	⩾ 140/90		⩾ 130/80; ⩾ 135/85

PA: presión arterial; MAPA: monitorización ambulatoria de la presión arterial; AMPA: automedición de la PA
*PA media 24h

Tabla 3. Fenotipos de presión arterial basados en la medición de consulta y la MAPA/AMPA.

2.3. Patrón circadiano de la presión arterial

La presión arterial (PA) sigue un patrón circadiano, es decir, fisiológicamente las cifras de PA, varían a lo largo de 24h. Estas variaciones que se producen entre la PA diurna y nocturna observables en la MAPA, han permitido establecer diferentes patrones circadianos.

Durante la noche se produce un descenso de la PA, si este descenso de la presión arterial media (PAM) nocturna respecto a la PAM diurna es superior al 10%, se denomina patrón circadiano dipper o "normal". Por el contrario, se habla de patrón circadiano non-dipper cuando el descenso de la PAM nocturna es inferior al 10% respecto a la diurna [38,41].

A la clasificación de los patrones circadianos, han sido añadidos dos patrones más, dipper extremo y raiser. Se conoce cómo dipper extremo, a la caída excesiva de la PAM nocturna (>20%) respecto a la PAM diurna. Sin embargo, el patrón raiser hace

referencia a aquellos sujetos en los que no se observa un descenso de la PA nocturna o incluso hay una elevación [38,41].

Para determinar cuál es el patrón circadiano de la PA de cada sujeto, se utiliza el cociente entre la PAM nocturna y la PAM diurna, conocido como dipping ratio (DR), con diferente valor de corte para cada patrón (Tabla 3). En la actualidad, el patrón circadiano de PA es considerado un importante factor pronóstico cardiovascular, y los resultados de diferentes estudios muestran que el patrón non-dipper está asociado a un mayor riesgo cardiovascular [42,43].

Patrones circadianos	Dipping ratio (DR)
Dipper extremo	< 0.7
Dipper "normal"	⩾ 0.8 < 0.9
Non-dipper	⩾ 0.9 < 1
Raiser	⩾ 1

Tabla 3. Patrones circadianos de presión arterial.

3. LA HIPERTENSIÓN RESISTENTE (HR)

3.1. Definición, prevalencia y diagnóstico

La hipertensión resistente (HR) es considerada cómo una de las formas de hipertensión severa, y en la que frecuentemente se agotan las opciones terapéuticas antes de lograr un adecuado control de la PA.

Su definición ha sufrido varios cambios a lo largo de los años, y con discrepancias entre la guía de la American Heart Association (AHA) y la europea (ESC/ESH) [44]. Según la última guía de la AHA, la definición de HR contempla dos situaciones, hipertensión resistente no controlada e hipertensión resistente controlada [45,46]:

- La hipertensión se define cómo resistente no controlada, cuando los valores de PA se encuentran por encima del rango de normalidad a pesar del tratamiento con 3 fármacos antihipertensivos de diferentes clases, incluyendo un diurético y todos ellos prescritos a dosis óptimas.

- La condición de hipertenso resistente controlado, engloba a aquellos sujetos que presentan valores de PA dentro de la normalidad, pero requieren 4 o más fármacos antihipertensivos para alcanzar un adecuado control de la presión.

Este tipo de hipertensión se asocia con la edad avanzada, obesidad, sexo masculino, ingesta excesiva de sodio en la dieta, raza negra, daño en órganos diana (hipertrofia ventricular izquierda o enfermedad renal crónica), rigidez aórtica, enfermedad vascular aterosclerótica y hipertensión crónica no controlada [47–49]. También, con peor pronóstico cardiovascular, debido a que los pacientes con HR

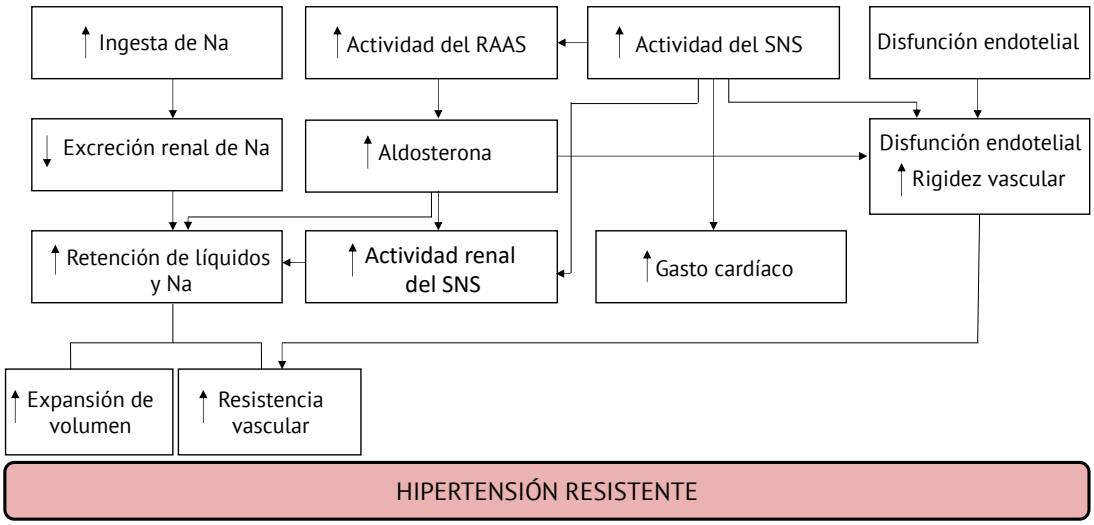
presentan mayor riesgo de desarrollo de eventos cardiovasculares adversos en comparación con sujetos sin HR [50,51].

En la actualidad, existen diversos estudios que evalúan la prevalencia de HR, sin embargo, la información es limitada y variable debido, a las características de la población estudiada y a la falta de uniformidad en la definición utilizada. No obstante, los resultados de un metaanálisis reciente que engloba las diferentes definiciones de HR, sitúa alrededor del 10% la prevalencia global de HR verdadera en población hipertensa [52].

Para establecer su diagnóstico, es necesario realizar una anamnesis para conocer factores y estilo de vida del paciente, confirmar el mal control de PA mediante diversas medidas en consulta, AMPA o MAPA, descartar la presencia de hipertensión de bata blanca, excluir la presencia de causas secundarias de HR, y comprobar que existe una adecuada adherencia al tratamiento farmacológico [24,44,46,53].

3.2. Fisiopatología

La fisiopatología de la HR es compleja e intervienen diversos mecanismos, entre los cuáles se encuentran la hiperactividad del sistema nervioso simpático (SNS), el consumo excesivo de sodio y en consecuencia la retención de líquidos y sodio, la hiperactividad del sistema renina-angiotensina-aldosterona (RAAS), y las alteraciones vasculares. De todos estos mecanismos, se considera que el consumo en exceso de sodio y la retención de líquidos tienen un papel principal en la fisiopatología de la HR [54,55] (Figura 3).



Na: Sodio; RAAS: Sistema renina- angiotensina- aldosterona; SNS: Sistema nervioso simpático.

Figura 3. Esquema de los mecanismos implicados en el desarrollo de la HR (Adaptado de Hwang [55]).

4. El SAHS Y LA HIPERTENSIÓN ARTERIAL

4.1. Mecanismos que relacionan el SAHS y la hipertensión

El SAHS y la HTA son dos patologías estrechamente relacionadas y se considera que diversos mecanismos fisiopatológicos podrían explicar la relación entre ambas. Las consecuencias de los eventos obstructivos repetitivos que tienen lugar en el SAHS a lo largo de toda la fase de sueño, promueven la activación de mecanismos intermedios como estrés oxidativo, inflamación, hiperactividad simpática, hipercoagulabilidad, desregulación metabólica y disfunción endotelial. La activación de estos mecanismos predispone a su vez, el desarrollo de enfermedades cardíacas, entre las cuáles se encuentran las arritmias, ictus, insuficiencia cardíaca, isquemia miocárdica, muerte súbita e hipertensión [9,56–59].

Entre las enfermedades cardíacas citadas anteriormente, la asociación entre el SAHS y la hipertensión ha sido ampliamente estudiada [60–63]. Peppard et al [60] en un estudio prospectivo con seguimiento a 4 años mostraron que los sujetos con un SAHS moderado/grave presentaban mayor riesgo (odds ratio 2.89 (CI 95%; 1.46, 5.64))

de desarrollar hipertensión durante el seguimiento, respecto a los pacientes sin SAHS. Los resultados de otro estudio observacional de 12 años de seguimiento fueron similares, observándose también una asociación entre el SAHS y un aumento del riesgo de hipertensión [62].

En la actualidad, las guías clínicas establecen el SAHS como una de las principales causas identificables de hipertensión, observándose una elevada prevalencia (38%-56%) de esta patología entre la población hipertensa [64,65].

4.2. El SAHS como causa secundaria de hipertensión resistente

Entre todas las causas secundarias de hipertensión resistente, el SAHS se ha establecido como la causa principal. El estudio llevado a cabo por Logan et al [66] fue el primero en mostrar la estrecha relación entre estas dos enfermedades, observándose una prevalencia de SAHS en sujetos con HR del 83%. Esta relación ha sido confirmada posteriormente, ya que son diversos los estudios que han evaluado dicha prevalencia, situándose entre el 64-83%, dependiendo del criterio utilizado para definir el SAHS [61,66–70]. Los resultados de los diferentes estudios han contribuido a identificar el SAHS cómo principal causa secundaria de HR y, así es considerado desde el 2017 en las guías de hipertensión [46].

La estrecha relación entre ambas patologías podría explicarse por la retención de líquidos, originada principalmente por el hiperaldosteronismo. Durante el sueño, tiene lugar una redistribución de líquido de las piernas hacia la parte superior del cuerpo, principalmente hacía el cuello y el tejido perifaríngeo. Este hecho favorecería el colapso de la vía aérea, y podría explicar la elevada prevalencia de SAHS en esta población [71].

Actualmente, y debido a la elevada prevalencia reportada, las guías sobre el manejo de la HTA recomiendan evaluar la presencia de SAHS en esta población, para reducir su impacto en el control de la PA.

5. EFECTO DEL TRATAMIENTO DEL SAHS SOBRE LA PRESIÓN ARTERIAL

En los últimos años se ha convertido en un tema de especial relevancia conocer la efectividad del tratamiento con CPAP en la reducción de la PA en pacientes hipertensos con SAHS, puesto que ambas enfermedades se asocian con frecuencia. La efectividad del tratamiento ha sido evaluada en diferentes fenotipos de PA. Estos estudios se recogen a continuación:

5.1. Efecto del tratamiento del SAHS en la hipertensión arterial

El efecto del tratamiento del SAHS con CPAP sobre la PA en pacientes con hipertensión ha sido evaluado en diversos estudios [20,72–76].

La evidencia científica publicada hasta el momento, muestra un efecto moderado pero relevante del tratamiento del SAHS sobre la PA en pacientes con HTA, no obstante, existe una gran variabilidad en los efectos observados (Tabla 4).

Duran-Cantolla et al [74], en un estudio con 340 pacientes con SAHS e HTA de reciente diagnóstico y sin tratamiento farmacológico, observaron una reducción moderada de 1.5 mmHg en la PA de 24h en el grupo tratado con CPAP respecto al grupo control. Los resultados de otro estudio, mostraron tras 12 meses de tratamiento, que la CPAP producía una leve disminución de la PAS (1.89 mmHg) y de la PAD (2.19 mmHg), aunque el cambio en la PAS no alcanzó la significación estadística. Además, la disminución de la PA fue más evidente en aquellos pacientes que utilizaron la CPAP más de 5.6 horas/noche [20]. Campos-Rodríguez et al [72], en un estudio aleatorizado con pacientes diagnosticados de SAHS e HTA, no observó una reducción estadísticamente significativa de la PA en el grupo tratado con CPAP. Este mismo autor, en un estudio observacional, evaluó el efecto del tratamiento con CPAP a largo plazo, y los resultados mostraron únicamente una disminución significativa de la PAD. No obstante, se observó que la reducción de la PAM de 24h era mayor, en valores basales elevados de PAS, PAD y con mayor adherencia al tratamiento con CPAP [73].

Los resultados de dos metaanálisis muestran un efecto moderado del tratamiento con CPAP sobre la PA, observándose mayores reducciones de la PA durante la noche.

La literatura existente coincide en que la CPAP produce una reducción moderada de la PA en pacientes con HTA, alrededor de 2 mmHg, identificándose en algunos estudios cómo predictores de respuesta favorable: niveles de PA basales elevados, y fundamentalmente, la adherencia al tratamiento con CPAP (≥ 4h/noche). Sin embargo, en la actualidad, no se ha demostrado todavía que el tratamiento con CPAP resulte efectivo cómo medida de prevención cardiovascular secundaria [18].

Tabla 5: Características y principales resultados de estudios aleatorizados en los que se observa el efecto del tratamiento con CPAP en pacientes con SAHS e HTA.

Estudio	Sujetos incluidos (Fin seguimiento)	Duración	Edad	IMC	IAH	Efecto PA (mmHg)	CPAP (h/noche)
Campos-Rodríguez et al.[72]	34 CPAP 34 control	4 semanas	55.3 (9.6) CPAP 58.0 (7.0) control	35.7 (5.6) CPAP 33.8 (6.3) control	58.3 (24.6) CPAP 59.5 (21.7) control	PAM 24h: -1.1 (7.9)* *No se observaron cambios estadísticamente significativos	4.7 (1.7)
Durán-Cantolla et al.[73]	137 CPAP 135 control	3 meses	52.4 (10.5)	31.9 (5.7)	43.5 (24.5)	PAM 24h: 1.5 (95% CI, 0.4, 2.7) PAS 24h: 2.1 (95% CI 0.4,3.7) PAD 24h: 1.3 (95% CI 0.2, 2.3) PAM nocturna: 2.1 (95% CI 0.5, 3.6)	4.5 (1.7) CPAP 4.2 (1.8) Sham CPAP
Barbé et al.[20]	178 CPAP 181 control	12 meses	56 (10)	33 (5)	45 (20)	PAS: -1.89 (95% CI, -3.90, 0.11)* PAD: -2.19 (95% CI -3.46, -0.93) *Cambio estadísticamente no significativo	4.7 (2)

Valores expresados como media (DE), excepto en los casos especificados. Abreviaturas: IMC: índice de masa corporal; IAH: índice de apneas/hipopneas; PA: presión arterial; CPAP: presión positiva continua en vía aérea; PSG: polisomnografía convencional; PCR: poligrafía cardiorespiratoria; PA: presión arterial; PAD: presión arterial diastólica; PAS: presión arterial sistólica; PAM: presión arterial media.

5.2. Efecto del tratamiento del SAHS en la hipertensión resistente

Hasta la fecha, son numerosos los estudios y metaanálisis que han evaluado el efecto del tratamiento con CPAP sobre la PA en pacientes con HR [77–88].

En 2003, Logan et al [77] llevaron a cabo el que es considerado, el primer estudio en evaluar el efecto del tratamiento con CPAP en pacientes con SAHS e HR. Los resultados de este estudio mostraron una reducción de la PA, especialmente significativa en la PAS y PAD nocturna. Tras la publicación de este estudio, se han llevado a cabo diversos estudios aleatorizados con el fin de confirmar estos resultados (Tabla 5). Lozano et al [78], realizaron el primer estudio aleatorizado con pacientes diagnosticados de SAHS e HR. Tras 3 meses de tratamiento con CPAP, y en los pacientes con HR confirmada, se observó una reducción de la PA diastólica media de 24h respecto a los pacientes con tratamiento convencional. Evidenciándose, mayor reducción de la PA en aquellos sujetos con una adherencia al tratamiento con CPAP >5.8h/noche. Los resultados del estudio HIPARCO [82] mostraron, tras 3 meses de tratamiento, que el grupo en tratamiento con CPAP en comparación con el grupo control, logró una disminución significativa de 3.1 mmHg en la PA media de 24h y de 3.2 mmHg en la PAD de 24h, aunque no se observó una disminución significativa de la PAS de 24h. También, se observó una mejora del patrón nocturno de PA en el grupo CPAP respecto al grupo control. Al igual que en otros estudios, Martínez-García et al [82] observaron una relación favorable entre el número de horas de uso de la CPAP y la disminución de la PA. Sin embargo, Pedrosa et al [81] no encontraron una correlación entre el cumplimiento de la CPAP y los cambios de PA. Los resultados de este mismo estudio, mostraron una disminución significativa de la PA diurna, tanto sistólica cómo diastólica. No obstante, los cambios en la PA sólo se observaron en el período diurno y no en el nocturno.

El último metaanálisis publicado y que incluye 6 estudios aleatorizados, muestra que la estimación del cambio en la PAS de 24h fue de 5.40 mmHg y de 3.86 mmHg en la PAD de 24h[79].

La evidencia muestra reducciones clínicamente significativas de la PA, especialmente en aquellos pacientes con buena adherencia al tratamiento con CPAP. Además, se ha observado que el efecto del tratamiento con CPAP, en cuánto a la reducción de la PA en pacientes con SAHS e HR, es mayor que el reportado hasta la fecha en población con HTA.

Tabla 6: Características y principales resultados de estudios aleatorizados en los que se observa el efecto del tratamiento con CPAP en pacientes con SAHS e HR.

Estudio	Sujetos incluidos (Fin seguimiento)	Duración	Edad	IMC	IAH/Estudio del sueño	Efecto de CPAP sobre PA (mmHg)	CPAP (h/noche)
Lozano et al.[77]	29 CPAP 35 control	3 meses	59.2 (9.9)	30.8 (5)	52.67 (21.5)	PAD 24h: -4.9 (6.4) (Efecto observado en pacientes con HR confirmada 20 CPAP; 21 control)	5.67 (1.52)
Martínez-García et al.[81]	98 CPAP 96 control	3 meses	56.0 (9.5)	34.1 (5.4)	40.4 (18.9)	PAM 24h: - 3.1 (95% CI, 0.6, 5.6) PAD 24h - 3.2 (95% CI, 1.0,5.4)	5 (1.9)
Pedrosa et al.[80]	19 CPAP 16 control	6 meses	56 (1)	32 (28-39) Mediana (IQR)	29 (24-48)	PAS diurna: - 6.5 (3.3) PAD diurna: - 4.5 (1.9)	6.01 (0.20)
Lloberes et al.[82]	36 CPAP 42 control	3 meses	58.3 (9.4)	31.4 (4.9)	50.1 (21.6)	*1 PAS diurna: - 5.4 (11.8) PAD diurna: - 3.3 (6.5) PAD nocturna: - 5.1 (8.5) PAD 24h: - 4.4 (6.0) (Efecto observado en pacientes con HR confirmada)	5.6 (1.5)
de Oliveira et al.[85]	24 CPAP 23 control	8 semanas	59.4 (7.7)	29.8 (4.4)	20 (18–31) Mediana (IQR)	PAS 24h: -9.3 (95% CI, -17.9, -0.4) PAD 24h: -4.4 (95% CI, -9.4,0.4)	5.3 (4.1-7.1) Mediana (IQR)
Muxfeldt et al.[86]	57 CPAP 60 control	6 meses	60.5 (8.2)	33.4 (5.3)	41 (21)	*1PAS nocturna: 4.7 (95% CI, –11.3, +3.1) (Efecto observado en pacientes con HR no controlada, no estadísticamente significativo)	4.8 (Media)
Joyeux-Faure et al.[79]	17 CPAP 16 control	3 meses	60 (10)	29.6 (3.9)	-	PAD nocturna: 8.10 (–13.91, –2.29) PAM: –9.09 (–16.75, –1.43) (Efecto solo observado en pacientes con valores basales ≥ la mediana)	3.90 (0.60; 5.82) Media (IQR)

Valores expresados como media (DE), excepto en los casos especificados. *1 Análisis por protocolo. Abreviaturas: IMC: índice de masa corporal; IAH: índice de apneas/hipopneas; PA: presión arterial; CPAP: presión positiva continua en vía aérea; PSG: polisomnografía convencional; PCR: poligrafía cardiorespiratoria; PA: presión arterial; PAD: presión arterial diastólica; PAS: presión arterial sistólica; PAM: presión arterial media.

5.3. Efecto del tratamiento del SAHS en población normotensa

La mayor parte de los esfuerzos investigadores para evaluar el efecto del tratamiento con CPAP se han centrado en los pacientes hipertensos, por lo que los efectos del tratamiento con CPAP sobre la PA en pacientes normotensos han sido poco explorados y la información de la que se dispone al respecto es limitada.

La mayor parte de la evidencia publicada evalúa los efectos del tratamiento en población hipertensa o con prehipertensión, y la información disponible proviene de dos estudios con un número bajo de sujetos. Faccenda et al [89] llevó a cabo durante 8 semanas un estudio aleatorizado con 78 pacientes sin tratamiento antihipertensivo. Los resultados mostraron únicamente una disminución de 1.5 mmHg en la PAD de 24h en el grupo en tratamiento con CPAP. En otro estudio llevado a cabo en 24 pacientes normotensos sin tratamiento, se observó tras 12 semanas de tratamiento con CPAP una reducción moderada de la PA tanto diurna como nocturna. En los pacientes con SAHS grave, se observó también que la CPAP revertía el patrón circadiano de PA de non-dipper a dipper [90].

6. CONTEXTO DE ESTA TESIS DOCTORAL

En la sociedad actual, la hipertensión y el SAHS son dos patologías de prevalencia creciente, el estudio de las cuáles ha mostrado una asociación entre ambas que podría explicarse por diversos mecanismos fisiopatológicos comunes, aunque su relación sigue en estudio. Diversas investigaciones han observado que el tratamiento del SAHS con CPAP, resulta efectivo en el control de la PA en sujetos con hipertensión esencial o con HR. No obstante, los efectos de la CPAP sobre la reducción de la PA no se observan en la totalidad de los sujetos, y se ha reportado una variabilidad en la respuesta. Esta elevada variabilidad en la respuesta de la PA al tratamiento con CPAP, ha suscitado el interés en identificar aquellos sujetos que realmente podrían experimentar efectos positivos en términos de PA. Por lo tanto, estudios dirigidos a conocer el impacto del SAOS en el control tensional, así como a identificar las características clínicas que se asocian a una respuesta favorable en términos de PA en los diferentes fenotipos, son de especial trascendencia, por las importantes implicaciones sanitarias y económicas que esto podría conllevar. Esto resulta especialmente relevante en aquellos sujetos en los cuáles es difícil conseguir un adecuado control de la PA. Asimismo, resulta necesario conocer con detalle el efecto del tratamiento con CPAP en los niveles de PA en pacientes normotensos.

Cómo consecuencia y, en este contexto, la presente tesis está centrada en evaluar la prevalencia e impacto del SAHS sobre la PA en sujetos con HR, y evaluar los efectos que puede tener el tratamiento con CPAP en sujetos hipertensos y normotensos, dada la escasa evidencia en este último grupo poblacional. Todo ello con el objetivo contribuir a una mejora en el manejo de la presión arterial, y permitir una indicación más personalizada del tratamiento con CPAP.

HIPÓTESIS Y OBJETIVOS

ESTUDIO 1

Justificación y metodología del estudio SARAH: Eventos cardiovasculares a largo plazo en pacientes con hipertensión resistente y apnea obstructiva del sueño

Este estudio corresponde con el siguiente artículo:

Sapiña-Beltrán E, et al. Rationale and Methodology of the SARAH Trial: Long-Term Cardiovascular Outcomes in Patients With Resistant Hypertension and Obstructive Sleep Apnea. *Arch Bronconeumol. 2018.*

HIPÓTESIS

El tratamiento con CPAP en pacientes con SAHS y HR puede disminuir la morbilidad y mortalidad cardiovascular a largo plazo.

OBJETIVO

1. Diseñar y dar a conocer el protocolo de un estudio observacional, prospectivo, multicéntrico e internacional, que tiene como objetivo principal evaluar el impacto del SAHS y su tratamiento en el control tensional y pronóstico cardiovascular (morbilidad y mortalidad) en sujetos con HR.

ESTUDIO 2

Prevalencia, características y asociación de la apnea obstructiva del sueño con el control de la presión arterial en pacientes con hipertensión resistente

Este estudio corresponde con el siguiente artículo:

Sapiña-Beltrán E, et al. Prevalence, Characteristics, and Association of Obstructive Sleep Apnea with Blood Pressure Control in Patients with Resistant Hypertension. *Ann Am Thorac Soc. 2019.*

HIPÓTESIS

Los pacientes diagnosticados de HR pueden presentar una elevada prevalencia de SAHS y éste podría asociarse con mal control de la presión arterial en estos sujetos.

OBJETIVOS

1. Determinar la prevalencia de SAHS en una cohorte de sujetos con HR.
2. Evaluar si existe asociación que entre el SAHS y el control de la presión arterial en sujetos con HR.

ESTUDIO 3

Pacientes normotensos con apnea obstructiva del sueño: cambios en la monitorización ambulatoria de la presión arterial de 24 h con el tratamiento de presión positiva continua en vía aérea

Este estudio corresponde con el siguiente artículo:

Sapiña-Beltrán E, et al. Normotensive patients with obstructive sleep apnoea: changes in 24-h ambulatory blood pressure *monitoring with continuous positive airway pressure treatment. J Hypertens. 2019.*

HIPÓTESIS

En sujetos normotensos y diagnosticados de SAHS, el tratamiento con CPAP podría disminuir la presión arterial tras 6 meses de tratamiento.

OBJETIVOS

1. Evaluar cambios en la presión arterial con el tratamiento con CPAP en sujetos con SAHS y normotensión.
2. Analizar cambios de presión arterial en sujetos con SAHS en tratamiento con CPAP y con diagnóstico de hipertensión enmascarada o normotensión verdadera.
3. Determinar cambios de presión arterial en sujetos normotensos y con SAHS en tratamiento con CPAP, en función del patrón circadiano de presión arterial (dipper/non-dipper).

ESTUDIO 4

Respuesta diferencial de la presión arterial al tratamiento de presión positiva continua en vía aérea según el patrón circadiano en pacientes hipertensos con apnea obstructiva del sueño

Este estudio corresponde con el siguiente artículo:

Sapiña-Beltrán, et al. Differential blood pressure response to continuous positive airway pressure treatment according to the circadian pattern in hypertensive patients with obstructive sleep apnoea. *Eur Respir J. 2019*.

HIPÓTESIS

Podría existir una respuesta diferencial del tratamiento con CPAP sobre la presión arterial en sujetos con HTA dependiendo del patrón circadiano de presión arterial.

OBJETIVO

1. Evaluar el efecto del tratamiento con CPAP sobre la presión arterial en función del patrón circadiano (dipper/non-dipper) en sujetos con HTA no tratada.

ARTÍCULOS

RATIONALE AND METHODOLOGY OF THE SARAH TRIAL: LONG-TERM CARDIOVASCULAR OUTCOMES IN PATIENTS WITH RESISTANT HYPERTENSION AND OBSTRUCTIVE SLEEP APNEA.

Sapiña-Beltrán E, Torres G, Martínez-Alonso M, Sánchez-de-la-Torre M, Franch M, Bravo C, Masa JF, Felez M, Fortuna-Gutierrez AM, Abad J, García-Río F, Drager LF, Lee Chi-Hang R, Martínez-García MÁ, Barbé F, Dalmases M.

Arch Bronconeumol.2018;54(10):518-523.

Factor de impacto: 4.214 (2018). Q1.

Summary

Introduction: Patients with resistant hypertension (RH) have a high risk of developing cardiovascular events; therefore, new therapeutic approaches to better control blood pressure may be useful in improving cardiovascular outcomes. The prevalence of obstructive sleep apnea (OSA) is very high among patients with RH. Continuous positive airway pressure (CPAP) has been shown to be an effective treatment for reducing blood pressure in patients with RH. Nevertheless, the long-term effect of CPAP treatment on cardiovascular outcomes has not been explored.

The main objective of the SARAH study is to assess the impact of OSA and its treatment on cardiovascular outcomes (morbidity and mortality) in patients with RH.

Methods: This study is a multi-center, prospective, observational cohort study. A total of 1,371 patients with RH will be enrolled in the study and followed once a year for five years. At inclusion, ambulatory blood pressure monitoring (ABPM) and a sleep study will be performed in all subjects. Socio-demographic, clinical and cardiovascular variables will be collected at baseline and follow-up. Subsequently, subjects with OSA will be managed according to local standard practice. Based on the OSA diagnosis and its treatment, three cohorts of subjects with RH will be defined: non-OSA, treated OSA and non-treated OSA.

Conclusions: This study will contribute to elucidating the long-term impact of OSA treatments on blood pressure control and cardiovascular outcomes in patients with RH. These results will contribute to improve the cardiovascular prognosis of patients with RH.

Keywords

Ambulatory blood pressure monitoring; continuous positive airway pressure; resistant hypertension; sleep apnea.

Introduction

According to the American Heart Association, resistant hypertension (RH) is defined as a clinical condition in which the blood pressure (BP) remains above the goal, despite lifestyle changes and pharmacologic treatments with optimal doses of 3 antihypertensive drugs (including a diuretic) or patients whose BP is controlled by no less than 4 antihypertensive agents [1,2]. The prevalence of RH is estimated to be approximately 12-15% in subjects being treated for hypertension [2-4]. Patients with RH have a high risk of developing cardiovascular events such as myocardial infarction, stroke or even cardiovascular death, and the ratio of cardiovascular events is approximately 50% higher in patients with RH than in patients with other types of hypertension [5]. Therefore, therapeutic strategies facilitating BP control in these patients might achieve a great benefit in decreasing the incidence of cardiovascular events.

Based on epidemiological data, systemic hypertension is strongly associated with obstructive sleep apnea (OSA) [6,7], which has important implications for cardiovascular outcomes.

OSA is characterized by recurrent episodes of upper airway obstruction that result in intermittent hypoxia, hypercapnia, increased respiratory effort, sympathetic activation and disruption of the sleep architecture. These events lead to a state of inflammation, hypercoagulability, oxidative stress, endothelial dysfunction and metabolic dysregulation. OSA has a negative impact on patients' quality of life and is

related to several adverse cardiovascular, metabolic and cognitive consequences [6].

The prevalence of OSA in the middle-aged population is 24-26% in men and 17%-28% in women [8]. However, its prevalence increases in hypertensive subjects (30-80%) and reaches 70-83% in patients with RH [9-12]. Although OSA is a main cause of RH, with effects greater than other known causes [7,12], the development of new strategies to treat patients with RH is primarily focused on expensive and aggressive techniques, such as sympathetic renal denervation, rather than treating OSA [13].

According to data from randomized clinical trials, treatment of OSA with continuous positive airway pressure (CPAP) induces -6.7 mmHg and -5.9 mmHg decreases in systolic and diastolic blood pressure, respectively, in patients with RH [14-17]. Nevertheless, the benefits of the CPAP treatment in BP reduction have not been assessed. Moreover, despite good CPAP compliance, high variability in the BP reduction has been described among patients. A recent study developed a predictive tool, the HIPARCO-Score, which is based on the micro-ribonucleic profile, to identify subjects with a favorable BP response to CPAP treatment. Although the tool is highly sensitive and specific, data on its implementation in the management of patients with RH are not available [18].

Therefore, in the current study, we aim to determine the impact of OSA and its treatment on BP control and cardiovascular outcomes in patients with coexisting RH and OSA. The BP reduction reported in short-term trials has been hypothesized to be associated with a reduction in the incidence of cardiovascular events; nevertheless, long-term studies are lacking.

Methodology

Primary objective

The main objective of the SARAH study is to determine the impact of OSA and its treatment on cardiovascular outcomes (morbidity and mortality) in patients with RH.

Secondary objectives

The secondary objectives are listed below. 1) Evaluate subclinical organ damage and determine whether treating OSA improves BP control and reduces the number of medications required for long-term BP control. 2) Identify epigenetic profiles and clinical, biological and polygraphic variables with value in predicting cardiovascular outcomes in patients with both RH and OSA and determine epigenomic changes related to cardiovascular disease that can be modified by time or CPAP treatment. 3) Validate the use of the HIPARCO-Score in men from an independent cohort and identify a singular cardiovascular system-specific miRNA biomarker profile that reliably distinguishes patients with favorable BP responses to CPAP among female patients with RH and OSA. 4) Perform a cost-effectiveness analysis to evaluate the impact of OSA diagnosis and treatment in patients with RH.

Design and population

This multi-center, prospective, observational, cohort study includes 1,371 subjects with RH. Participants will be recruited consecutively in the Hypertension or

Nephrology Unit of each participating center.

The estimated duration of the study is 7 years (the recruitment is expected to be completed in two years). The study is led by the coordinating center (Hospital Arnau de Vilanova-Hospital Santa María, Lleida), which has the overall responsibility for the study design and follow-up.

RH will be diagnosed based on the American Heart Association guidelines [1] and confirmed by 24 h of ambulatory blood pressure monitoring (ABPM). Patients who meet all inclusion criteria and none of the exclusion criteria will be invited to participate in the study (Table 1). All enrolled will undergo a sleep test using either polysomnography (PSG) or a respiratory polygraph (RP). Apnea is defined as an absence of airflow lasting ≥ 10 seconds. Hypopnea is defined as a reduction in airflow lasting ≥ 10 seconds associated with arousal or oxygen desaturation (considered a decrease in oxygen saturation (SaO_2) ≥ 4%). The Apnea Hypopnea Index (AHI) is defined as the number of apneas plus hypopneas per hour of sleep or recording, depending on whether the PSG or RP is used, respectively. According to the AHI, OSA will be classified as mild (AHI 5-14), moderate (AHI 15-29) or severe (AHI ≥ 30) [19]. Treatment recommendations will be based on the guidelines of each country according to usual clinical practice.

The study will consider 3 cohorts distributed as follows: (i) non-OSA (patients without OSA); (ii) treated OSA (patients who are treated with CPAP or a mandibular advancement device or who have undergone surgery) and (iii) non-treated OSA

(because of a medical decision, refusal of treatment or intolerance/poor adherence). The general framework of the SARAH project is shown in (Fig 1).

Patient follow-up

All patients will be evaluated at baseline, and a minimum follow-up of 5 years has been established. During the follow-up period, an annual programmed visit will be conducted for all participants.

Study variables and data collection

The following variables will be collected at baseline: i) socio-demographic characteristics; ii) clinical variables: toxic habits, comorbidity, BP, pharmacological treatment related to hypertension, and therapeutic compliance; iii) variables related to OSA: PSG or RP variables, Epworth Sleepiness Scale (ESS) and other symptoms; iv) quality of life (EuroQol-5D) and costs; v) fasting blood and urine samples and 24-h urine analysis; and vi) asymptomatic organ damage. Blood and urine samples will be obtained with the support of IRB-Lleida Biobank (B.0000682) and Biobanks' Platform PT13/0010/0014. More detailed information regarding the recorded variables is provided in the supplemental material.

In each follow-up visit, blood and urine samples will be obtained, and anthropometric data, BP variables, the use of antihypertensive treatments (number of drugs and compliance) and the incidence of new cardiovascular events will be assessed. Moreover, patients treated with CPAP will be monitored for compliance. The degree of compliance will be determined by dividing the number of hours of use

(obtained from the internal clock of the CPAP device) by the number of days of treatment. Adequate compliance is defined as CPAP use ≥ 4 h/day.

Additionally, costs will be recorded at every visit. Direct costs will be estimated based on the clinical records of each participating center using standard fees provided by the corresponding Department of Health in each of the study areas.

Clinical outcomes

The primary outcome will be a composite of the cardiovascular endpoints of death from any cardiovascular cause, cardiac events (non-fatal myocardial infarction, heart failure, atrial fibrillation, or hospitalization for unstable angina), cerebrovascular events (non-fatal stroke and transient ischemic attack (TIA)), hypertensive crises and emergencies, peripheral arteriopathy or revascularization procedures. These outcomes will be collected from the subjects' interviews at each yearly follow-up visit in the office and from computed medical records. All cardiovascular events will be independently evaluated by two physicians to establish a diagnosis. In cases with a disagreement, a third external physician will assess the case. The date of each event will be recorded. Other secondary endpoints, such as kidney disease and all-cause death, will also be assessed.

A more detailed description of the outcome variables that will be assessed is provided in the supporting information (see section 2).

Sample size calculation

The inclusion of 1.029 OSA patients with RH achieves a 80% of statistical power (β=0.2) to detect a reduction of at least 35% in the incident/recurrent cardiovascular events at 5-year follow-up in OSA treated patients vs OSA non-treated patients. We assume an incident/recurrent cardiovascular event rate at 5-year follow-up of 25% for non-treated OSA patients, an anticipated dropout rate of 5% and the proportion of OSA patients expected to be treated with CPAP is around 65% [20],

To detect significant differences in cardiovascular outcomes relative risk between OSA and non-OSA patients, we will include a control group of 342 non-OSA patients. We assume a 12% incident/recurrent cardiovascular event rate at 5-year follow-up in the non-OSA patients and a dropout rate of 5% [21].

An interim analysis is planned to be performed when half of the sample of each group had completed the 5 years follow-up to test the main hypothesis, it is, to compare the incidence/recurrence of cardiovascular events applying a significance level of 0.003, which has been penalized using the O'Brien-Fleming method to maintain a global type I error of 5%.

Statistical analysis

First, a comparability analysis among the three groups (non-OSA, treated OSA and non-treated OSA groups) will be performed with respect to clinical and anthropometric, biochemical, and baseline OSA-related variables. For this purpose, means and standard deviations, as well as medians and interquartile ranges for

quantitative variables and the absolute frequencies and percentages for qualitative variables. Parametric (ANOVA) or non-parametric (Kruskal-Wallis) tests will be used to compare quantitative variables between groups, depending on the distribution of the variables (if a normal distribution is assumed, a parametric test will be performed). For qualitative variables, the chi-squared test will be used to compare differences between groups, unless the expected frequencies below are less than 5, in which case, the Fisher test will be preferred. The Benjamini-Hochberg ("BH" or its alias false discovery rate ("fdr")) correction for multiple tests will be used as appropriate whenever comparisons between pairs of groups are performed. Second, Kaplan-Meier curves and a log-rank test will be used to assess the relationship between the time to the development of a new cardiovascular event (incident or recurrence) with each one of the qualitative variables and the tertiles of the quantitative variables, both independently and combined with the group definition, thus allowing for a possible interaction between OSA and its treatment. Third, the time to the development of a new cardiovascular event (incident or recurrence) will be analyzed by considering non-cardiovascular deaths as competing risks in a Fine and Gray model and in a cause-specific multivariate regression model. All variables showing a significant contribution to the model and variables showing a confounding effect over other significant contributing variables in the model will be included. The interactions among each of these variables and the group (non-OSA, treated OSA and non-treated OSA group) will be assessed and included in the model if significant. When multiple interactions with the group are observed, a stratified regression analysis for each

group will be performed. Finally, the same analytical strategy will be used to model the time until cardiovascular death. Overall survival will be modeled by fitting a Cox proportional-hazards regression model. All analyses will be performed with the R package, using a significance level of $\alpha = 0.05$.

An interim analysis of the results will be performed when half of the targeted numbers of patients have completed the five-year follow-up. The results may lead to the discontinuation of the study if either (i) statistically significant results (implying a greater than hypothesized effect of OSA diagnosis and treatment) are observed or (ii) the results do not reach the expected magnitude (regardless of whether they are statistically significant) and a continuation of the study would clearly be insufficient to detect any significant differences in cardiovascular outcomes among the groups. For this analysis, the main hypothesis will be tested using a threshold for significance of 0.003 with the O'Brien-Fleming method to calculate this penalization of the p-value, which maintains a global type I error of 5%.

Cost analysis

Upon completion of the follow-up study, a cost-effectiveness analysis will be performed. The aim of this analysis is to compare the effectiveness ratios among study groups and to compare the cost of health care utilization between two years before and after the beginning of the study for the study groups. The costs will be estimated based on the clinical records of each participating center and standard fees provided by the corresponding Department of Health in each of the study areas. Direct costs

will be recorded in a costs questionnaire at baseline and at each follow-up visit and the overall costs will be computed. Only direct costs will be considered. Analyses will include an estimation of the quality-adjusted life-years (QALYs) gained. Costs incurred by each group will be evaluated based on the effectiveness of the provided health care related to the above-mentioned primary outcome (a composite of CV endpoints) using Bayesian cost-effectiveness techniques.

Ethical considerations

The study will be managed according to the guidelines and principles of the Declaration of Helsinki and standard ethical conduct for research involving humans. Moreover, the study will also guarantee the Protection of Personal Data (Law 15/1999-Spanish Government) during the study. It will preserve the confidentiality of the participating subjects, and the protection of their information will be guaranteed. The Ethics and Clinical Research Committees of all participating centers have approved this study. All study subjects will provide informed consent before participating in the study. This study is registered at ClinicalTrials.gov (Identifier: NCT03002558).

Trial organization

The coordinating center (Hospital Arnau de Vilanova-Hospital Santa María, Lleida) will elaborate the protocol to standardize the procedures and data collection and will train participating personnel in methods to implement these protocols.

The center will provide instructions for entering data into a specific database, guaranteeing the data protection.

The SARAH study has a clinical events committee (CEC) that will be responsible for evaluating all reported primary and secondary outcomes.

Justification of the study design and limitations

There are previous published studies reporting BP reductions with CPAP treatment in patients with RH and OSA [14,16-17,22-23]. Moreover, there is also evidence that reductions in systolic blood pressure could lead to a decrease of cardiovascular risk [24]. Therefore, based on the existing literature, it would be unethical to performance a randomized trial and that is why an observational cohort design was considered.

It is important to note that the previously published studies evaluated the effect of CPAP on BP reduction at short-term without any follow-up period longer than 6 months. Thus, there is a lack of studies evaluating the effects on BP at long-term and the impact of CPAP treatment on cardiovascular outcomes. Therefore, the SARAH study will fill this existing gap involving a large number of patients and with a long follow-up.

Moreover, the observational design will allow for “real life” results, not biased by any special procedures beyond the standard care provided in each centre and it will be more feasible to extrapolate the results to the clinical practice.

The observational design presents limitations that deserve mention. First, two different methods for the OSA diagnosis are used. Nevertheless, both methods are validated and implemented in clinical practice. Second, OSA patients who refused CPAP treatment will be considered into the non-treated group, regardless, these patients could have a different profile form those in whom treatment is not offered.

Relevance of the study

This prospective observational multi-center study aims to assess the impact of OSA and its treatment on cardiovascular outcomes in patients with RH. Significant impacts on two different areas are expected.

On one hand, the SARAH study will shed light on the clinical implications of the association between OSA and RH and will assess the impact of OSA treatment on cardiovascular outcomes. According to several studies and meta-analyses, CPAP treatment improves BP control in patients with both hypertension and OSA, although the effect is mild. However, in patients with RH, CPAP treatment have yielded a significant decrease in BP [25-26]. Nevertheless, most of these studies evaluated BP over a short period and did not perform a long-term evaluation [19]. Furthermore, the use of a greater number of antihypertensive medications, even in patients with good BP control, did not ameliorate the long-term risk of adverse cardiovascular events in a cohort study [20]. Therefore, the implementation of non-pharmacological strategies that simultaneously reduce BP and act through different mechanisms may be helpful in improving outcomes.

On the other hand, this study will also contribute to the identification of epigenetic profiles and clinical, biological and polygraphic variables with value in predicting cardiovascular outcomes in patients with both RH and OSA. Thus, individuals who are more susceptible to developing cardiovascular events would be able to be identified. Therefore, the SARAH study will also contribute to the validation and development of new tools to predict the BP response to CPAP treatment in patients with RH and will enable the development of new tools that might influence the management of patients with RH in daily clinical practice.

Despite the reported association between OSA and RH and the described short-term effect of CPAP treatment on BP, the diagnosis of OSA in these patients is not standardized. Thus, acceptance of the relevance of the results of the SARAH study would influence clinical practice and might consequently require changes in the current recommendations and guidelines for the diagnostic assessment and treatment of patients with RH.

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TABLES

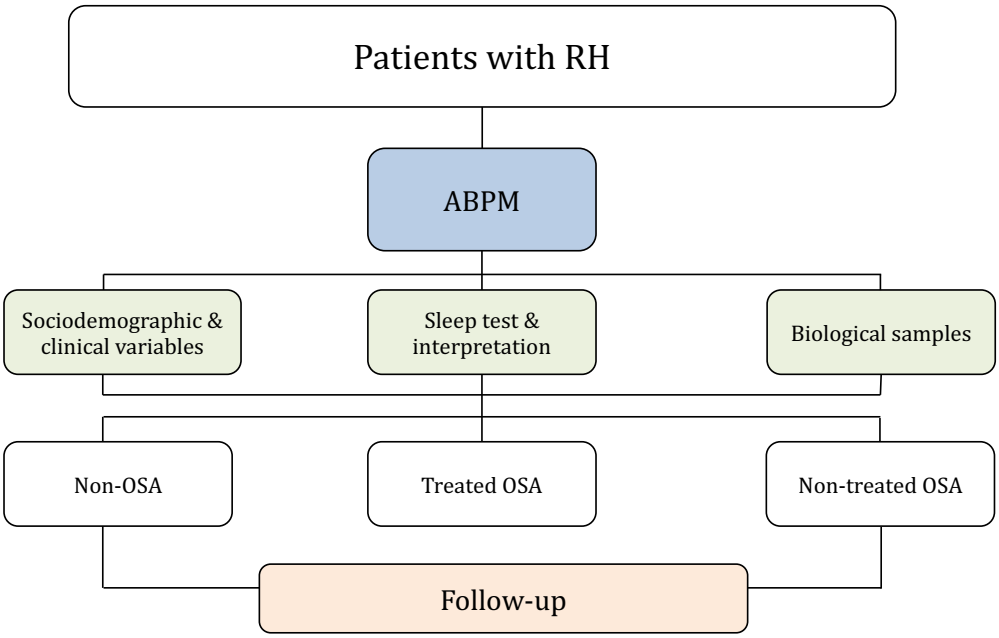
Table 1: Inclusion and exclusion criteria

Inclusion Criteria
Patients diagnosed with RH according to the AHA guidelines
Patients aged 18 to 75 years
Patients who provide informed consent
Exclusion criteria
RH secondary to other causes
Any process that limits the life expectancy to less than one year
Previously diagnosed with OSA and currently receiving active treatment
Abbreviations: AHA, American Heart Association; OSA, obstructive sleep apnea; RH, resistant hypertension

Abbreviations: AHA, American Heart Association; OSA, obstructive sleep apnea; RH, resistant hypertension

FIGURE LEGENDS

Figure 1: General framework of the study



Abbreviations: ABPM, ambulatory blood pressure monitoring; OSA, obstructive sleep apnea; RH, resistant hypertension

MATERIAL SUPLEMENTARIO: RATIONALE AND METHODOLOGY OF THE SARAH TRIAL: LONG-TERM CARDIOVASCULAR OUTCOMES IN PATIENTS WITH RESISTANT HYPERTENSION AND OBSTRUCTIVE SLEEP APNEA.

1. Data Collection and study variables

1.1. Baseline study variables

1.1.1 Date of inclusion

1.1.2 Date of diagnosis of resistant hypertension (RH)

1.1.3 Sociodemographic variables: age and sex

1.1.4 Anthropometric Variables: weight, height, body mass index (BMI), neck circumference, waist circumference, and hip circumference. The current recommended waist circumference thresholds for abdominal obesity are > 102 cm in men and > 88 cm in women, with the exception of Asian and South American populations, for whom > 90 cm in men and > 80 cm in women are used [1].

1.1.5 EuroQoL- 5D test and costs [2].

1.1.6 Clinical Variables:

a) Toxic habits:

a-1. Smoking habit: The number of cigars/cigarettes/pipes smoked and duration of smoking will be collected (for both current and former smokers). Current smoking is defined as an active daily smoking habit within the past month of any number of pipes or cigarettes.

a-2. Alcohol consumption: The consumption of 1 unit of alcohol an average of three times a week will be considered significant consumption.

b) Comorbidity (prior to inclusion in the study and the date of diagnosis):

b- 1. General comorbidity: Charlson index (adapted to age).

b- 2. Cardiovascular risk factor comorbidity:

b-2.1. Abnormal fasting glucose levels: glucose levels > 110 mg/dl or ≥ 126 mg/dl without pharmacological treatment.

b-2.2. Diabetes mellitus: Medical diagnosis or treatment with anti-diabetic drugs or insulin.

b-2.3. Hypercholesterolemia: Medical diagnosis or treatment with statins or resins.

b-2.4. Hypertriglyceridemia: Medical diagnosis or treatment with fibrates.

b-2.5. Mixed dyslipidemia: Medical diagnosis or treatment with statins, resins, or fibrates.

c) Blood pressure (BP) variables:

c-1. Date of the diagnosis of hypertension (and date of the diagnosis of RH, if it is registered).

c-2. Office BP (the mean of the last 2 of 3 measurements with a 2-min lapse).

c-3. ABPM that allows RH to be diagnosis:

- Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) (24 h).
- Mean SBP and DBP (day-time).
- Mean SBP and DBP (night-time).
- Maximum day-time SBD and DBP.
- Maximum night-time SBD and DBP.
- Minimum day-time SBD and DBP.
- Minimum night-time SBD and DBP.

d) Pharmacological treatment at the time of inclusion:

d-1. Number of drugs used to treat hypertension.

d-2. Agent group: Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers, beta blockers, diuretics, alpha receptor blockers, antialdosterones and others (dose and frequency).

d-3. Use of antialdosterone drugs (yes or no).

e) Therapeutic compliance:

e- 1. Morisky-Green test (3).

e- 2. Haynes-Sackett test.

e-3. Optimal compliance based on pharmacy databases: Based on the electronic prescription record, optimal compliance is considered when the patient has picked up >80% of the antihypertensive medications from the pharmacy within a predefined period (1 month for the inclusion visit and 1 year for the follow-up visits).

1.1.7. Respiratory variables

- Epworth Sleepiness Scale score (ESS) [4].
- Type of sleep test: respiratory polygraph (RP) or polysomnography (PSG).
- Test date and location.
- Apnea-Hypopnea index (AHI).
- Postural apnea-hypopnea index (in the supine position and non-supine position).
- % Supine.
- % Obstructive and mixed events.
- Number of apneas.
- Apnea Index.
- Number of hypopneas.
- Hypopnea Index.
- Total time in apnea/hypopnea.
- Mean oxygen saturation (SaO_2).
- Minimum oxygen saturation.
- TC90 in minutes and percentage. TC90 is defined as the minutes or percentage of time with SaO_2 less than 90%.
- Oxygen Desaturation Index (ODI) of at least 4% and 3%.

Obstructive sleep apnea (OSA) treatment:

- Continuous positive airway pressure (CPAP) (yes or no).

- Surgery (yes or no).
- Mandibular advancement device (yes or no).
- Date of treatment initiation.

- When polysomnography is performed, the following additional data will be collected:

- General sleep parameters:
  - Total sleep time (TST).
  - Sleep efficiency (total sleep time/time in bed).
  - Sleep latency.
  - Rapid eye movement (REM) sleep latency.
  - Wake after sleep onset (WASO) sleep stages.
  - STAGE I: record time; % of TST.
  - STAGE II: record time; % of TST.
  - STAGE III: record time; % of TST.
  - REM: record time; % of TST.
- General analysis of leg movements:
  - Total leg movements during sleep.
  - Index of leg movements per h of sleep.
- Arousals.
  - Total number of arousals.
  - Index of arousals per h of sleep.
  - Index of arousals associated with leg movements.
  - Index of arousals associated with respiratory events.
  - Index of non-specific arousals.

1.1.8 Biochemical variables:

a) Biological parameters in the blood samples: (at baseline) hemoglobin, fasting plasma glucose, urea, calcium, creatinine, glomerular filtration rate (GFR), potassium,

sodium, total cholesterol, triglycerides, high-density cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and uric acid levels.

3.1.9 Asymptomatic organ damage variables:

- Heart:

a) Left ventricular hypertrophy (LVI): In echocardiography, left ventricular hypertrophy is defined as a posterior wall (PW) or septum > 11 mm, or left ventricular mass (LVM) calculated according to the American Society of Echocardiography formula that is greater than 115 g/m2 in men and greater than 95 g/m2 in women.

b) Left atrial diameter enlargement in the echocardiogram (mm).

c) Atrial fibrillation: paroxysmal, permanent or persistent according to the electrocardiogram (EKG).

- Kidney:

a) Persistent microalbuminuria: defined as albuminuria of 20-300 mg/g creatinine in two urine samples collected at an interval of 6 months.

b) Proteinuria: defined as albuminuria greater than 300 mg in 24 h.

- Fundoscopy: Grade of hypertensive retinopathy according to the classification reported by Keith Wagener and Baker [5].

- Peripheral arteriopathy: ankle-brachial index (ABI). An ankle-brachial index < 0.9 is considered low and has predictive value for cardiovascular events [6].

- Carotid ultrasound: presence of a plaque.

3.1.10 Biological samples

At the inclusion and follow-up visits, blood samples will be collected to obtain plasma,

serum, buffy coat, and total blood for RNA extraction. Blood samples and data collected from them will be stored in the IRB Lleida Biobank.

3.2 Follow-up variables

1.2.1 BP variables:

a) The home-measured blood pressure will be calculated at the medical visit. It is the mean of the last 4 measurements obtained at home (namely, 2 before breakfast and 2 before dinner whenever possible).

b) ABPM:

- Mean SBP and DBP (24 h).
- Mean SBP and DBP (day-time).
- Mean SBP and DBP (night-time).
- Maximum day-time SBD and DBP.
- Maximum night-time SBD and DBP.
- Minimum day-time SBD and DBP.
- Minimum night-time SBD and DBP.

c) BP control will be defined as:

1. Optimal control: home BP < 140/90 mmHg or normal ABPM.
2. Uncontrolled: patients who do not meet the above criteria.

1.2.2 Management:

- Number of drugs used to treat hypertension.
- Agent group: Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta blockers, alpha receptor blockers, antialdosterone and others (dose and frequency).
- Use of antialdosterone drugs (yes or no).

1.2.3 Anthropometric variables: weight, height, body mass index, abdominal fat, and neck, waist and hip circumferences.

1.2.4 Compliance with CPAP (in CPAP-treated patients with obstructive sleep apnea):

a) Number of hours/night. Adherence to CPAP will be objectively assessed by reading the time counter of the device. If the average cumulative use is ≥ 4 h per night, the patient will be considered compliant.
b) Tolerance (optimal, bad, intolerant).
c) Type of mask.
d) Side effects and complications.

1.2.5 Biochemical and biological samples

1.2.6 Costs

4. Study outcomes

The primary endpoint will be a composite of death from any cardiovascular cause, cardiac events (non-fatal myocardial infarction, hospitalization for unstable angina, hospitalization for heart failure, and new onset atrial fibrillation), cerebrovascular events (non-fatal stroke and transient ischemic attack (TIA)), hypertensive crises and emergencies, peripheral arteriopathy or revascularization procedures. All cardiovascular events will be independently evaluated by two physicians to establish a diagnosis. In cases with a disagreement, a third external physician will assess the case. The date of each event will be recorded.

4.1 Other endpoints

The following secondary endpoints will be recorded:

- Kidney disease:
  - Renal event: defined as the occurrence of renal insufficiency (Ccr < 60 ml/m) confirmed in two blood sample analyses collected at approximately 6-month intervals that is related to hypertensive nephroangiosclerosis.

- Persistent microalbuminuria: defined as albuminuria of 20-30 mg/g creatinine in two urine samples collected at an interval of 6 months.
- Proteinuria: defined as albuminuria greater than 300 mg in 24 h.

- Death from any cause.

All endpoints will be assessed at baseline and at each follow-up visit.

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PREVALENCE, CHARACTERISTICS, AND ASSOCIATION OF OBSTRUCTIVE SLEEP APNEA WITH BLOOD PRESSURE CONTROL IN PATIENTS WITH RESISTANT HYPERTENSION.

Sapiña-Beltrán E, Torres G, Benitez I, Fortuna-Gutiérrez AM, Márquez PP, Masa JF, Corral-Peñafiel J, Drager LF, Cabrini M, Félez M, Vázquez S, Abad J, Lee CH, Aung AT, García-Río F, Casitas R, Sanchez-de-la-Torre M, Gaeta AM, Barbé F, Dalmases M.

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Factor de impacto: 4,836 (2019). Q1

Abstract

Rationale: Obstructive sleep apnea (OSA) is associated with poor blood pressure (BP) control and resistant hypertension (RH). Nevertheless, studies assessing its prevalence, characteristics and association with BP control in RH patients are limited.

Objective: The aim of this multicenter study was to assess the prevalence of OSA in a large cohort of RH subjects and to evaluate the association of OSA with BP control.

Methods: We recruited consecutive RH subjects from 3 countries. A formal sleep test and blood pressure measurements, including 24-h ambulatory blood pressure monitoring (ABPM) were performed in all participants. .

Results: In total, 284 RH subjects were included in the final analysis. Of these, 83.5% (CI 95%; 78.7 to 87.3) had OSA (apnea-hypopnea index (AHI) ≥5 events/h); 31.7% (26.5 to 37.3) had mild OSA, 25.7% (21 to 31.1) had moderate OSA and 26.1% (21.3 to 31.5) had severe OSA. Patients with severe OSA had higher BP values than mild-moderate or non-OSA subjects. A greater effect was observed on the average nighttime BP, with an adjusted effect of 5.72 (1.08 to 10.35) mmHg in severe OSA compared to non-OSA participants. A dose-response association between the severity of OSA and BP values was observed. The prevalence of severe OSA was slightly higher in uncontrolled participants (adjusted OR 1.69 (0.97 to 2.99)) but was not statistically significant.

Conclusions: The present study confirms the high prevalence of OSA in RH participants. Furthermore, it shows a dose-response association between OSA severity and BP measurements, especially in the nighttime.

Clinical Trial Registration: NCT03002558

Primary source of funding: This work was supported by ISCIII y fondos FEDER "Una manera de hacer Europa" (PI16/00489), the Spanish Respiratory Society (SEPAR) ResMed Foundation and Societat Catalana d'Hipertensió Arterial (SCHTA), Philips and FENIN.

Introduction

Hypertension represents an important and prevalent cardiovascular risk factor and it is considered an important topic in public health [1-3]. Among all hypertensive phenotypes, resistant hypertension (RH) is considered to confer the highest cardiovascular risk [1-4]. Among all hypertensive subjects, the estimated prevalence of RH ranges from 12-15% [5-7].

RH is defined as blood pressure (BP) that remains above the goal in spite of the use of 3 different antihypertensive drugs including a diuretic, prescribed at the optimal dose or as those in whom require 4 or more medications for BP control [8]. Patients with RH have the worst prognosis of all hypertensive patients, as they presented with the highest rates of target organ damage and cardiovascular events in long-term follow-up; these rates are estimated to be 50% higher than in patients with controlled hypertension [9-14].

Moreover, it has been described that among all RH patients, those who presented with uncontrolled BP on the 24-hour ambulatory blood pressure monitoring (ABPM) measurements are at a higher risk of experiencing cardiovascular events, especially those subjects with the masked phenotype (normal office BP measures but above the normal range on the 24-hour ABPM) [11-15].

Obstructive sleep apnea (OSA) is a disorder characterized by recurrent episodes of

upper airway collapse that result in intermittent hypoxia, sleep fragmentation, intrathoracic negative pressure and the disruption of sleep architecture. OSA is associated with daytime symptoms, a decrease in the quality of life and an increase in morbidity and mortality from cardiovascular alterations [16-17]. The prevalence of OSA in middle-aged population is 24-26% in men and 17%-28% in women [18-20]. However, its prevalence increases in hypertensive subjects (30-80%) and previous studies have indicated that it could reach 64-83% in patients with RH [1,12,21-23]; the prevalence of OSA has also been reported to be 100% in refractory hypertensive patients (hypertension that remains uncontrolled despite the administration of at least 5 antihypertensive drugs, preferably including a long-acting thiazide-like diuretic and a mineral-corticoid receptor antagonist) [24-26]. Beyond this, it has been described that OSA could be associated with poor BP control and its treatment with continuous positive pressure (CPAP) could be an effective means of controlling BP in this population [27-32].

Nevertheless, studies evaluating the prevalence of OSA in RH patients and its association with BP control are scarce. These studies have usually been single-centre studies, which limit the generalizability of their results. Therefore, the aim of this study was to assess the prevalence of OSA in a large cohort of RH participants, identify the clinical variables associated with severe OSA and evaluate the association of OSA with BP control. All these issues are particularly relevant considering that the traditional screening questionnaires for OSA are not useful in patients with RH [33].

MATERIAL AND METHODS

Study design and population

This is an ancillary study of the SARAH study (Long-term Cardiovascular Outcomes in Patients With RH and OSA With or Without Treatment With CPAP), which is a multicenter, international, prospective, observational cohort study (registered trial NCT03002558), evaluating the impact of OSA and continuous positive airway pressure (CPAP) treatment on cardiovascular outcomes (morbidity and mortality) in subjects with RH.

Briefly, the study included consecutive subjects aged between 18-75 years who were diagnosed with RH confirmed by 24-hour ABPM, as defined later (see Blood Pressure measurements). The exclusion criteria for the study were RH secondary to endocrinological cause (pheochromocytoma, Conn disease, Cushing´s Syndrome, hyperparatiroidism), drug treatment (nonsteroidal anti-inflammatory drugs or cortisone, inmunodepressants) renal artery stenosis, aortic coarctation or intracranial tumours; life expectancy less than 1 year and current treatment with CPAP. Subjects were evaluated for participation in the study in 6 teaching hospitals in Spain, 1 in Singapore and 1 in Sao Paulo. The methodology of the SARAH trial is published elsewhere[34]. The ethics committee of each participating centre approved the study and all participants provided informed consent.

For the current study, we included 284 participants consecutively recruited between April 2016 and July 2018. Information regarding eligibility and exclusions is provided in Figure 1. We analysed the presence and severity of OSA in the RH subjects, their clinical characteristics and the association of OSA with BP control.

Based on the results obtained on the sleep test, participants were classified as non-OSA (apnea-hypopnoea index (AHI) < 5/h) or OSA. Moreover, OSA subjects were classified as having mild (AHI 5-14.9/ h), moderate (AHI 15-29.9/ h) or severe (AHI ≥ 30/ h) OSA. Based on the results of the ABPM, participants with RH were classified as having controlled (average 24-hour ambulatory BP < 130/80 mmHg) or uncontrolled (average 24-hour ambulatory BP ≥130/80 mmHg) RH.

Procedures

Baseline visit

At the initial visit, all participants completed a detailed medical interview regarding their sociodemographic characteristics, cardiovascular risk factors, cardiovascular disease and medication. Self-reported sleepiness (analysed by the Spanish version of the Epworth Sleepiness Scale) and anthropometric measures were also recorded.

Sleep evaluation

A sleep test, consisting of either a cardio-respiratory polygraphy or polysomnography, was performed in all included participants. Of all the subjects included, 250 underwent cardiorespiratory polygraphy and 34 underwent polysomnography. Approximately 84% of the sleep studies were performed using an Embletta® sleep monitor. The rest of the studies were performed using: Compumedics E. Profusion 3.4; Sibelmed Exea Serie 5; Philips Respironics Alice 6 LDx; Somnomedics. Somnoscreen plus Versión 2.7.0; and ApneaLink Resmed.

Apnea was defined as an interruption in or reduction of oronasal airflow ≥ 90% that lasted at least 10 seconds. An apnea was scored as obstructive when it was associated with continued

or increased inspiratory effort. It was scored as mixed when there was a lack of inspiratory effort in the initial portion of the event followed by the resumption of inspiratory effort in the second portion of the event. Central apnea was scored when the apnea was associated with a lack of inspiratory effort throughout the entire period of absent airflow. Hypopnoea was defined as a 30% to 90% reduction in oronasal airflow for at least 10 seconds associated with oxygen desaturation of at least 4% or an arousal. The AHI was defined as the number of apnea and hypopnoea events per hour of recording or sleep depending on the study (cardio-respiratory polygraphy or polysomnography, respectively). CT90 was defined as the percentage of time with an oxygen saturation lower than 90%. The diagnosis of central sleep apnea was made when at least 50% of the respiratory events were without respiratory effort. Central sleep apnea diagnosis was not considered an exclusion criterion. OSA diagnosis and treatment recommendations were based on the guidelines of each country according to usual clinical practice [35].

Blood pressure measurements

Office BP and 24-hour ABPM measurements were performed in all participants at the beginning of the study. During the initial visit, office BP was obtained in all participants according to the guidelines. Office BP was determined by the average of three recordings of systolic and diastolic BP obtained at 5-minute intervals after subjects had been seated on a chair with their feet on the floor and arms supported at heart level for at least 5 minutes [36]. ABPM measurement was performed following international guidelines[36]. Before the ABPM monitor was fitted, the BP was measured in both arms to determine whether there were differences in BP between them. If there were differences, the cuff was placed on the arm with the higher BP values. If there were no differences in BP values between arms, the cuff was

placed in the non-dominant arm to interfere as little as possible in the daily activities of participants. All participants were instructed to perform their usual activities during the test [37].

During ABPM, a BP measurement was taken every 20 minutes during the daytime and every 30 minutes during the night. All recruited subjects were asked about their sleep habits. The waking and sleeping periods were determined by the times that each individual reported awakening and going to bed, respectively. ABPM recordings were considered successful when the percentage of the measurements was > 70%, with at least one measurement every hour. Data related to the average 24-hour ambulatory BP, daytime and nighttime systolic BP (SBP) and diastolic BP (DBP) and heart rate were recorded.

The monitors used were Spacelabs 90207/90217A devices (Spacelabs® Inc. Richmond, Washington, United States), Mortara Ambulo 2400 (Milwaukee, EE.UU), Microlife WatchBP (Microlife AG, Switzerland), and Dyna-MAPA (Cardios Sistemas Coml. Indl. Ltda, Sao Paulo, Brasil)

The 24-hour ABPM criteria used to define RH were a BP that remained above the target (average SBP ≥ 130 mmHg, average DBP ≥ 80 mmHg or both) in spite of the use of three antihypertensive drugs (one of those should be a diuretic) or a BP in the optimal range with 4 or more antihypertensive medications (therefore these participants were included regardless of the BP values recorded during the ABPM). Subjects treated with three antihypertensive drugs who had normal ABPM measurements (<130/80 mmHg) were excluded from the study.

The circadian dipping pattern of each participant was established according to the dipping ratio (DR) which is the quotient between the nighttime mean arterial pressure (MAP) and the

daytime MAP. According to the quotient obtained, subjects were classified as non-dippers if the DR was higher than 0.9 and dippers if it was ≤ 0.9.

Considering ABPM values, daytime hypertension was defined as at least 135/85 mmHg for the daytime average and at least 120/70 mmHg for the nighttime average [36].

BP control was defined based on the ABPM measurements. Thus, participants were considered controlled when the average 24-hour ambulatory BP was < 130/80 mmHg and uncontrolled when average 24-hour ambulatory BP was ≥130/80 mmHg.

All participants maintained their prescribed antihypertensive treatment during office and ABPM measurements. To evaluate adequate compliance with the antihypertensive treatment, the Morisky [38] and Haynes [39] tests were assessed. Moreover, participants must have retrieved from the pharmacy more than 80% of their prescribed antihypertensive treatment.

Statistical analyses

With regard to descriptive statistics, the means (standard deviation) and medians (interquartile range) were estimated for quantitative variables with normal or nonnormal distributions, respectively. The absolute and relative frequencies were used for qualitative variables. The normality of the distribution was analysed using the Shapiro–Wilk test. The Agresti–Coull intervals [40] (95%CI) were generated for the prevalence estimations. The demographic and clinical data of the participants were compared among the OSA severity groups (non-OSA, mild-moderate and severe) using the appropriate tests (ANOVA or Kruskal-Wallis) for quantitative variables and Fisher's exact test for qualitative variables. The p-value for trend was computed from the Spearman's rank correlation coefficient when the

variable was continuous and χ^2 test for trend if it was categorical [41]. ABPM parameters were compared among OSA severity groups with the Kruskal-Wallis test. In addition, the comparison was evaluated by ANOVA with linear models adjusted by confounding factors (age, sex and body mass index) and an unadjusted linear model. Trend tests were conducted, treating OSA categories as an ordinal variable by using the median AHI of each category. The same analysis was carried out to evaluate the sleep parameters according to BP control. R statistical software, version 3.3.1, was used for all the analyses [42].

Results

Cohort characteristics

In total, 284 subjects with RH were included. The main socio-demographic and clinical characteristics of the population are shown in Table 1. Briefly, the median age (IQR) was 64 (57.0; 69.0) years, and the participants were predominantly male gender and obese. The most prevalent co-morbidity was diabetes (129 patients; 46.9%).

Prevalence of OSA characteristics in RH patients

In the whole cohort, 83.5% (95%CI; 78.7 to 87.3) of the included participants had an AHI greater than or equal to 5 events/h. With regard to OSA severity, 31.7% (26.5 to 37.3) of participants had mild OSA, 25.7% (21 to 31.1) had moderate OSA and 26.1% (21.3 to 31.5) had severe OSA.

The OSA prevalence was slightly higher in males than in females (86.3% (80.8 to 90.4) versus 76% (65.8 to 84.3)), respectively. Moreover, the prevalence of severe OSA was more than twice as high in men as it was in women (30.4%vs 15%). A high body mass index was also associated

with a higher prevalence of OSA (70.6% in normal weight, 77.5% in overweight and 88.5% in obese subjects) and severe OSA was more prevalent by increasing weight (11.8% in normal weight, 16.7% in overweight and 33.3% in obese subjects). Among the participants with severe OSA (AHI≥30 events/h), there was a larger proportion of men and they had higher body mass index, waist circumference and neck circumference values than those with mild-moderate OSA.

Regarding the sleep parameters, the median AHI (IQR) was 16.6 (7.88; 30.2) events/hour and the median 4% oxygen desaturation index (IQR) was 11.6 (5.75; 23.1) per hour. The percentage of time with an oxygen saturation < 90% was 11% (2.20; 35.8). The median Epworth sleepiness scale score was 6 (4.00; 10.0). None of the included participants was diagnosed with central sleep apnea. More detailed information is provided in Table 1.

ABPM parameters stratified by OSA severity

In general, ABPM parameters increased as the severity of OSA increased (Figure 2) and a statistically significant dose-response association was found (p for trend in Table 2). Higher values for all average 24-hour ambulatory BP parameters, daytime and nighttime average ambulatory BP and the daytime and nighttime diastolic BP were observed in severe OSA than in non-OSA participants. The effect was greater on nocturnal blood pressure, with an adjusted effect on the average nighttime ambulatory BP of 5.72 (1.08 to 10.35) mmHg in severe OSA compared to non-OSA participants. The adjusted and unadjusted effects of OSA severity on ABPM parameters are detailed in Table 2.

Furthermore, the adjusted OR (95% CI) of having nocturnal hypertension in severe OSA group compared with the non-OSA group was 2.7 (1.15 to 6.43). There was no statistically

significant difference in the proportion of non-dippers according to OSA severity (56.4% in mild-moderate OSA and 70.3% in severe OSA).

OSA prevalence in the different BP control groups

No significant differences in sleep parameters were observed between subjects with controlled or uncontrolled BP. More detailed information is provided in Table 3. Moreover, similar OSA prevalence was observed between the groups; however, the results show that severe OSA was slightly more prevalent in participants with uncontrolled RH than in participants with controlled RH, with an adjusted OR of 1.69 (0.97 to 2.99), although the difference is not statistically significant (e-Table 1).

Discussion

The present multicenter study confirms that the prevalence of OSA in RH subjects is high. Moreover, it shows that there is a dose-response association between the severity of OSA and the blood pressure values observed, with greater effects on nighttime BP.

Our study shows that the total prevalence of OSA is 83.5%; the prevalence of mild OSA is 31.7%, the prevalence of moderate OSA is 25.7%, and the prevalence of severe OSA is 26.1%. This prevalence is probably underestimated because 34 subjects were excluded from the SARAH study because they were currently with CPAP treatment. Therefore, considering these subjects, the estimated OSA prevalence would be around 95.4%.

Data from previous studies already reported a high prevalence of OSA in RH subjects, nevertheless, it is difficult to compare results among studies due to different or unspecified criteria used to define hypopnea, the use of different AHI cut off values to diagnose OSA and the use of different sleep tests as well.

Previous published studies, such as those by Logan et al. [12] and Florczak et al. [23] reported an OSA prevalence rates of 83% and 72% respectively. Nevertheless, these authors did not indicate the criteria used to define hypopnea, making a comparison difficult. Moreover, in the study by Logan et [12] all participants included had refractory hypertension. Comparing our results with those of the studies that indicating the oxygen desaturation criteria used, we observed that our results are consistent with those of Muxfeldt et al. [22] who reported an OSA prevalence of 82.2 % using the same criteria to define hypopnea (at least 4% oxygen desaturation) and participants with similar characteristics to those included in our study. However, in Muxfeld's study, only polysomnography was performed. The prevalence reported by Pedrosa et al. [1], who used polysomnography and a 3% oxygen desaturation criteria to define hypopnea, was 64%, which is lower than in our study. This could be related with to the fact that the subjects included were younger, and they used a more conservative cut off value to diagnose OSA (AHI ≥15/h).

The prevalence of OSA was higher in men than in women, and severe OSA was twice as prevalent in males as in females. This male predominance had been previously described in the general population, hypertensive patients and RH [1-22]. Moreover, as described in previous studies, OSA presence and severity increased as BMI increased [1,12]. Moreover, our data also show that the most frequent comorbidity was diabetes, which has been strongly associated with antihypertensive drug resistance [8,43].

A dose-response association between OSA severity and BP values was found. OSA severity was related to worse BP control with higher values for all 24-hour ambulatory blood pressure variables, the average daytime BP, daytime diastolic BP, average nighttime BP and nighttime diastolic BP values. Moreover, the prevalence of nocturnal hypertension was significantly

greater in participants with severe OSA. It is important to highlight the association of OSA with high nighttime BP values because it has been previously demonstrated that nocturnal BP is a better risk predictor than the daytime BP, and an elevated nighttime BP has been associated with an increased risk of cardiovascular events and worse cardiovascular prognosis [11]. It has also been described that the circadian pattern provides additional prognostic information beyond that possible with just average 24-hour BP levels, and a non-dipping pattern has also been associated with worse cardiovascular outcomes [44-45].Our results are in line with those of Muxfeld et al. [22], who described a worse nocturnal BP profile and a higher prevalence of a non-dipping patterns in subjects with severe OSA than in those without severe OSA, although in our study this last factor did not reach statistical significance. Therefore, as previously described [22], our results already show that beyond age, gender and anthropometric characteristics, ABPM measurements could also be associated with OSA severity, especially nighttime measures. The results suggest that identifying underlying causes, such as OSA and treating them may be helpful when attempting to improve BP control, especially during the nighttime, and may suggest new treatment approaches beyond pharmacology. Nevertheless, further studies should address the impacts of OSA treatment on BP parameters and cardiovascular outcomes in the long term.

Although we found a high OSA prevalence and a dose-response association between the severity of OSA and blood pressure values, no differences in sleep parameters were observed between the controlled or uncontrolled RH groups; which were defined based on average 24-hour ambulatory BP. This could be related to the fact that the greatest impact of OSA on BP has been observed on nocturnal pressure and that the nighttime period only represents approximately one-third of the 24-hour. In addition, the results suggest that the decision to explore OSA in subjects with RH should not be based on the BP control parameters proposed

in the hypertension guidelines and that it could be especially important to assess OSA in subjects with RH who have high BP values at nighttime even if they have values in the normal ranges for the 24-hour measurements.

The main strength of our study is its multicenter and international design, with the inclusion of a large number of patients with RH diagnosed based on ABPM measurements. Therefore, unlike other previous published studies, we only included subjects with true RH. Furthermore, unlike other studies, we used indirect methods to estimate treatment compliance and ensure that at least 80% of the antihypertensive treatment was retrieved from the pharmacy.

This study has some limitations that should be acknowledged. First, it has a cross-sectional design; thus, only associations and not causality should be inferred. Second, two different methods were used for OSA diagnosis; cardiorespiratory polygraphy and polysomnography. Both methods have been validated and are commonly implemented in clinical practice. Nevertheless, the severity of OSA can be underestimated using cardiorespiratory polygraphy; therefore, the mild-moderate and severe OSA participants may have been misclassified. Third, OSA prevalence may have been underestimated due to the exclusion of subjects who were undergoing CPAP treatment. However, an estimated prevalence including those subjects has been included. Fourth, the study included RH subjects, and the reported prevalence results should not be generalized to a population with less severe hypertension.

Conclusions

Our study confirms that RH subjects have a high prevalence of OSA and shows a dose-response association between OSA severity and blood pressure measurements. The results highlight the importance of identifying OSA in RH subjects to reduce its impact on blood pressure control through appropriate treatment.

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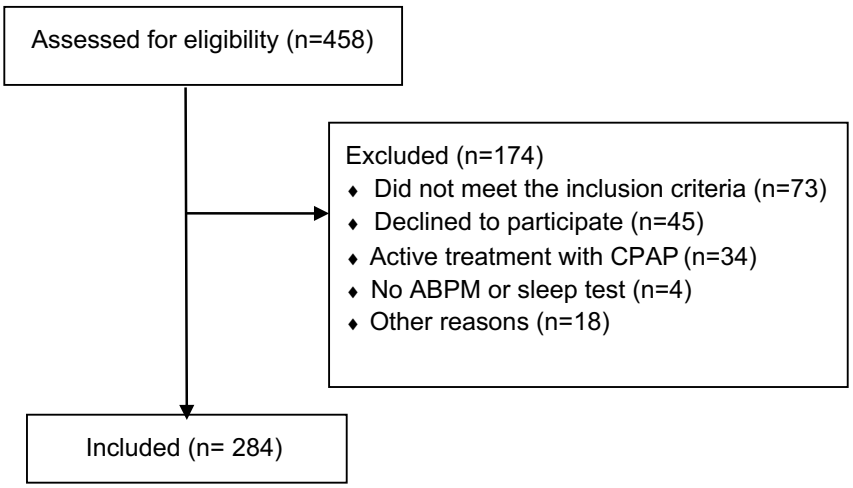
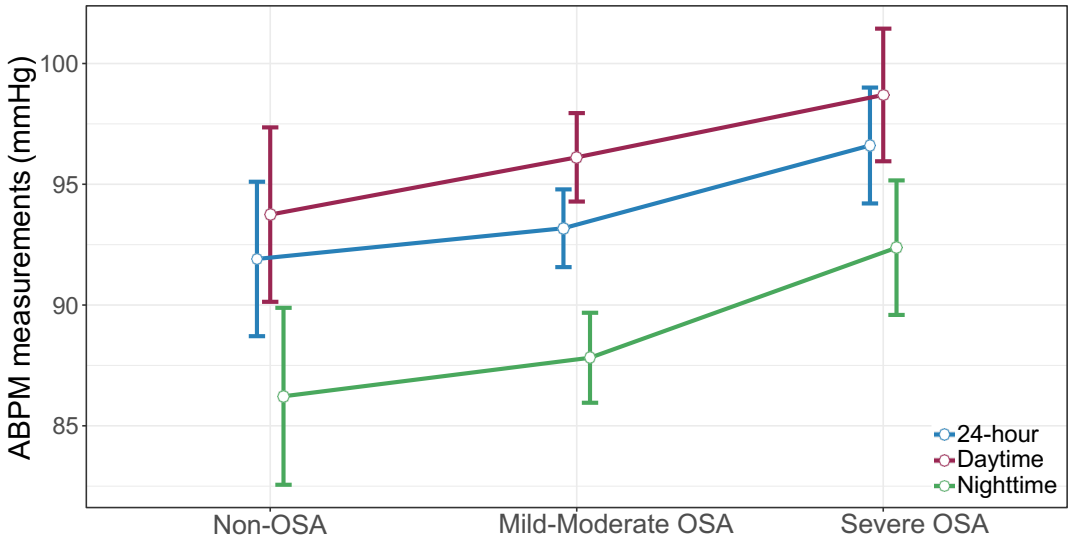
FIGURE LEGENDS

Figure 1: Flow diagram of the study



Abbreviations: ABPM= Ambulatory blood pressure monitoring; CPAP= Continuous positive airway pressure

Figure 2: Least squares means and 95% confidence intervals for the ABPM parameters according to OSA severity.



Abbreviations: ABPM= Ambulatory blood pressure monitoring; OSA= Obstructive sleep apnea

TABLES

Table 1. Characteristics of the study cohort stratified by OSA severity

	Global (n=284)	Non-OSA (n=47)	Mild-Moderate OSA (n=163)	Severe OSA (n=74)	p value for trend
Sociodemographic characteristics					
Age (years) -*Me[p25;p75]*-	64.0 [57.0;69.0]	61.0 [52.0;69.0]	65.0 [59.0;69.0]	63.0 [55.5;68.0]	0.892
Sex (male) -*n (%)*-	204 (71.8%)	28 (59.6%)	114 (69.9%)	62 (83.8%)	0.003
Tobacco use -*%*-					0.367
Current smoker	36 (13.2%)	8 (18.2%)	18 (11.5%)	10 (13.9%)	
Former smoker	109 (39.9%)	12 (27.3%)	69 (43.9%)	28 (38.9%)	
Non-smoker	128 (46.9%)	24 (54.5%)	70 (44.6%)	34 (47.2%)	
Anthropometric characteristics					
BMI (kg/m^2) -*Me[p_{25};p_{75}]*-	31.1 [28.2;34.1]	29.2 [27.0;32.6]	30.8 [27.6;33.4]	32.8 [29.9;35.1]	<0.001
Waist circumference (cm) -*Me[p25;p75]*-	105 [99.0;113]	100 [97.0;108]	103 [97.0;112]	109 [102;118]	<0.001
Abdominal circumference (increased) -n%-	144 (50.7%)	22 (46.8%)	77 (47.2%)	45 (60.8%)	0.009
Hip circumference (cm) -*Me[p25;p75]*-	107 [101;113]	106 [102;113]	106 [100;112]	108 [102;116]	0.108
Neck circumference (cm) -*Me[p25;p75]*-	41.0 [38.0;44.0]	40.5 [36.0;42.0]	41.0 [38.0;44.0]	42.0 [40.9;44.0]	<0.001
Clinical variables					
Diabetes (yes) -*n (%)*-	129 (46.9%)	17 (38.6%)	79 (50.0%)	33 (45.2%)	0.66
Dyslipidaemia (yes) -*n (%)*-	43 (15.7%)	8 (18.6%)	24 (15.2%)	11 (15.1%)	0.639
Stroke (yes) -*n (%)*-	5 (1.81%)	0 (0.00%)	4 (2.55%)	1 (1.37%)	0.729
Coronary heart disease (events) -*n (%)*-	38 (13.8%)	4 (9.09%)	26 (16.5%)	8 (10.8%)	0.969
Sleep parameters -*Me[p25;p75]*-					
Apnea-Hypopnea index (events/h)	16.6 [7.88;30.2]	2.80 [1.50;4.25]	14.1 [9.55;20.6]	44.3 [35.8;63.0]	<0.001
Hypopnea Index (events/h)	10.4 [4.60;20.2]	2.10 [0.90;3.45]	10.4 [5.95;15.9]	22.2 [10.2;30.9]	<0.001
Apnea Index (events/h)	5.50 [1.30;14.7]	0.60 [0.05;1.70]	4.40 [1.40;9.15]	28.2 [12.2;46.4]	<0.001
ODI 4%	11.6 [5.75;23.3]	2.60 [1.18;4.07]	11.5 [7.80;17.7]	38.0 [31.2;53.5]	<0.001
CT90 (%)	11.0 [2.20;35.8]	0.50 [0.00;3.40]	10.8 [2.62;25.7]	31.9 [13.0;47.1]	<0.001
Obstructive + mixed events (%)	83.0 [20.0;100]	50.0 [0.00;100]	92.5 [28.8;100]	79.0 [34.0;97.0]	0.394
Mean. O_2 saturation (%)	91.8 [90.0;93.1]	93.5 [92.0;94.1]	92.0 [90.5;93.0]	90.1 [89.2;92.0]	<0.001
Min. O_2 saturation (%)	80.0 [74.0;84.0]	86.0 [84.0;88.5]	81.0 [76.0;84.0]	72.5 [65.2;79.0]	<0.001
ESS	6.00 [4.00;10.0]	6.00 [4.00;9.00]	6.00 [4.00;10.0]	6.00 [4.00;10.0]	0.653

Abbreviatons:BMI=Body mass index;ESS: Epworth sleepiness scale; ODI= Oxygen desaturation index; OSA=Obstructive sleep apnea; CT90= Percentage of time with an oxygen saturation lower than 90%. Note: Prevalence Non OSA(AHI<5); Mild (5≥AHI<15); Moderate (15≥AHI<30); Severe (30≥AHI). The apnea index is the total number of apneas per hour (including obstructive, mixed and central apneas). Obstructive+mixed events: percentage corresponding to obstructive and mixed apneas of the total number of apneas.

Table 2. Association of OSA severity with ABPM parameters

	Non-OSA (n=47)	Mild-Moderate OSA (n=163)	Severe OSA (n=74)	p value for trend
ABPM - average 24-h BP (mean SD) -mmHg-	93.2 (9.06)	93.3 (10.3)	96.0 (12.0)	0,108
Mean difference (95% CI)	0 (Ref)	0.1 (-3.41 to 3.61)	2.8 (-1.14 to 6.74)	0,0665
Adjusted mean difference (95% CI)	0 (Ref)	1.74 (-1.76 to 5.25)	**4.73 (0.71 to 8.76)**	**0,0139**
ABPM - 24-h systolic BP (mean SD) -mmHg-	128 (12.6)	130 (15.1)	133 (17.0)	0,05
Mean difference (95% CI)	0 (Ref)	2.18 (-2.79 to 7.16)	5.38 (-0.23 to 10.98)	0,0513
Adjusted mean difference (95% CI)	0 (Ref)	2.52 (-2.59 to 7.63)	**6.14 (0.22 to 12.05)**	**0,0361**
ABPM - 24-h diastolic BP (mean SD) -mmHg-	74.6 (9.21)	72.7 (10.2)	76.1 (11.1)	0,255
Mean difference (95% CI)	0 (Ref)	-1.89 (-5.24 to 1.47)	1.48 (-2.3 to 5.26)	0,0851
Adjusted mean difference (95% CI)	0 (Ref)	0.65 (-2.41 to 3.72)	**4 (0.45 to 7.55)**	**0,0073**
ABPM - average daytime BP (mean SD) -mmHg-	95.5 (9.03)	96.2 (13.3)	98.0 (11.8)	0,249
Mean difference (95% CI)	0 (Ref)	0.61 (-3.44 to 4.65)	2.45 (-2.1 to 7)	0,2214
Adjusted mean difference (95% CI)	0 (Ref)	2.66 (-1.34 to 6.65)	**5.06 (0.45 to 9.66)**	**0,0422**
ABPM - daytime systolic BP (mean SD) -mmHg-	131 (12.6)	132 (15.2)	135 (17.2)	0,104
Mean difference (95% CI)	0 (Ref)	1.52 (-3.48 to 6.52)	4.42 (-1.22 to 10.05)	0,0964
Adjusted mean difference (95% CI)	0 (Ref)	2.13 (-3.01 to 7.26)	5.51 (-0.43 to 11.45)	0,0565
ABPM - daytime diastolic BP (mean SD) -mmHg-	77.2 (9.83)	75.1 (10.7)	78.0 (11.6)	0,472
Mean difference (95% CI)	0 (Ref)	-2.12 (-5.65 to 1.41)	0.78 (-3.19 to 4.76)	0,2064
Adjusted mean difference (95% CI)	0 (Ref)	0.67 (-2.53 to 3.86)	**3.57 (-0.13 to 7.27)**	**0,0233**
ABPM - average nighttime BP (mean SD) -mmHg-	86.9 (11.6)	87.7 (12.2)	**91.6 (11.7)**	**0,021**
Mean difference (95% CI)	0 (Ref)	0.82 (-3.12 to 4.76)	**4.73 (0.3 to 9.15)**	**0,0115**
Adjusted mean difference (95% CI)	0 (Ref)	1.54 (-2.49 to 5.57)	**5.72 (1.08 to 10.35)**	**0,0061**
ABPM - nighttime systolic BP (mean SD) -mmHg-	121 (14.6)	124 (17.8)	127 (15.6)	0,05
Mean difference (95% CI)	0 (Ref)	2.99 (-2.48 to 8.46)	6.07 (-0.11 to 12.24)	0,0613
Adjusted mean difference (95% CI)	0 (Ref)	2.51 (-3.11 to 8.12)	5.89 (-0.62 to 12.39)	0,0708
ABPM - nighttime diastolic BP (mean SD) -mmHg-	68.8 (9.65)	66.9 (10.6)	71.2 (10.8)	0,098
Mean difference (95% CI)	0 (Ref)	-1.85 (-5.28 to 1.58)	**2.43 (-1.43 to 6.3)**	**0,0214**
Adjusted mean difference (95% CI)	0 (Ref)	0.05 (-3.27 to 3.36)	**4.12 (0.29 to 7.95)**	**0,0052**

The adjusted models included the confounding factors age, sex and body mass index. Statistically significant p values (<0.05) are shown in bold. Abbreviatons: ABPM = Ambulatory blood pressure monitoring; OSA=Obstructive sleep apnea. Note: Prevalence Non OSA (AHI<5); Mild-Moderate OSA (5≥AHI<30); Severe OSA(30≥AHI).

Table 3. Sleep characteristics in groups with controlled and uncontrolled BP groups

	Controlled (n=132)	Uncontrolled (n=152)	p value
Apnea-Hypopnea Index (median [p_{25};p_{75}]) -events/h-	17.6 [8.35;28.4]	15.4 [7.55;33.3]	0.964
Mean difference (95% CI)	0 (Ref)	0.78 (-3.91 to 5.47)	0.7429
Adjusted mean difference (95% CI)	0 (Ref)	2.2 (-2.28 to 6.69)	0.3344
Hypopnea Index (median [p_{25};p_{75}]) -events/h-	11.7 [4.95;20.2]	9.30 [4.35;21.9]	0.451
Mean difference (95% CI)	0 (Ref)	-1.28 (-6.29 to 3.72)	0.6144
Adjusted mean difference (95% CI)	0 (Ref)	-1.68 (-6.63 to 3.28)	0.5058
Apnea Index (median [p_{25};p_{75}]) -events/h-	5.60 [1.60;14.7]	5.15 [1.10;14.8]	0.82
Mean difference (95% CI)	0 (Ref)	0.72 (-3.43 to 4.86)	0.7341
Adjusted mean difference (95% CI)	0 (Ref)	1.48 (-2.64 to 5.59)	0.4808
ODI 4% (median [p_{25};p_{75}]) -%-	13.3 [5.90;22.4]	11.2 [5.80;24.7]	0.585
Mean difference (95% CI)	0 (Ref)	-0.07 (-4.17 to 4.04)	0.9751
Adjusted mean difference (95% CI)	0 (Ref)	1.32 (-2.55 to 5.2)	0.5013
Obstructive + mixed events (median [p_{25};p_{75}]) -%-	89.0 [22.0;100]	81.5 [19.2;100]	0.282
Mean difference (95% CI)	0 (Ref)	-3.33 (-12.65 to 5.99)	0.4822
Adjusted mean difference (95% CI)	0 (Ref)	0.61 (-8.24 to 9.46)	0.8922
CT90 (median [p_{25};p_{75}]) -%-	14.5 [4.00;40.1]	6.60 [1.95;24.8]	**0.024**
Mean difference (95% CI)	0 (Ref)	-5.03 (-10.59 to 0.53)	0.0759
Adjusted mean difference (95% CI)	0 (Ref)	-2.64 (-7.87 to 2.59)	0.3217
Mean. O_2 saturation (median [p_{25};p_{75}]) -%-	91.2 [90.0;93.0]	92.0 [90.4;93.1]	0.042
Mean difference (95% CI)	0 (Ref)	0.49 (-0.05 to 1.04)	0.0765
Adjusted mean difference (95% CI)	0 (Ref)	0.23 (-0.27 to 0.74)	0.3657
Min. O_2 saturation (median [p_{25};p_{75}]) -%-	80.0 [73.0;84.0]	81.0 [74.8;85.0]	0.208
Mean difference (95% CI)	0 (Ref)	1.33 (-0.9 to 3.56)	0.241
Adjusted mean difference (95% CI)	0 (Ref)	0.75 (-1.45 to 2.94)	0.5045
Total sleep time[§]	338 [278;368]	316 [256;381]	0.868
Mean difference (95% CI)	0 (Ref)	20.82 (-61.43 to 103.08)	0.6093
Adjusted mean difference (95% CI)	0 (Ref)	13.42 (-75.86 to 102.7)	0.7604
Sleep efficiency[§]	80.5 [66.3;85.7]	71.1 [59.7;84.0]	0.225
Mean difference (95% CI)	0 (Ref)	-6.7 (-16.71 to 3.32)	0.1816
Adjusted mean difference (95% CI)	0 (Ref)	-7.48 (-18.05 to 3.08)	0.1569

The adjusted models included the confounding factors age, sex and body mass index. Statistically significant p values (<0.05) are shown in bold. Abbreviatons: ODI= Oxygen desaturation index; CT90 = Percentage of time with a oxigen saturation lower than 90%.[§] patients diagnosed by polysomnography (n = 34).The apnea index is the total number of apneas per hour (including obstructive, mixed and central apneas). Obstructive+mixed events: percentage corresponding to obstructive and mixed apneas of the total number of apneas.

NORMOTENSIVE PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA: CHANGES IN 24-H AMBULATORY BLOOD PRESSURE MONITORING WITH CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT.

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Abstract

Background: Continuous positive airway pressure (CPAP) treatment reduces blood pressure (BP) in obstructive sleep apnoea (OSA) and hypertensive patients, but there is a lack of data about the effects of CPAP on the BP in normotensive patients.

Objective: The aim of the study was to evaluate BP changes in normotensive OSA subjects receiving CPAP treatment.

Methods: We selected 131 normotensive outpatients with an apnoea/hypopnoea index (AHI)≥ 15 events/hour who required CPAP treatment. All patients underwent a sleep study and 24-hour ambulatory blood pressure monitoring (ABPM) at baseline and after 6 months. In addition, the patients were assessed for the presence of baseline masked hypertension (MH), defined as office BP <140/90 mmHg and increased BP on 24-h ABPM (mean 24-h BP ≥130/80 mmHg).

Results: After 6 months of CPAP treatment, a mild reduction in all 24-h ABPM variables was observed, but only the mean 24-h diastolic BP (-1.39 mmHg, CI 95%, -2.50 to -0.27), mean daytime diastolic BP (-1.39 mmHg, CI 95% -2.56 to -0.22), and the mean 24-h ambulatory BP (-1.80 mmHg, CI 95%, -3.16 to -0.44) reached statistical significance.

The reduction was primarily due to BP changes in subjects with MH who displayed a mean BP reduction of -4.78 mmHg (-7.25 to -2.30 mmHg). Consistent with a circadian

BP pattern, a reduction in mean nocturnal BP of -4.73 mmHg (-7.39 to -2.06 mmHg) was observed at 6 months in non-dippers; in contrast, the mean nocturnal BP in dippers increased by 2.61 mmHg (0.60 to 4.62 mmHg).

Conclusion: Our findings suggest that the CPAP effects may be different in normotensive outpatients depending on the presence of undiagnosed MH and the dipping pattern. Therefore, it is important to consider measuring ABPM in this type of patient.

KEYWORDS

Ambulatory blood pressure monitoring; blood pressure; continuous positive airway pressure; masked hypertension; normotensive; obstructive sleep apnoea

Introduction

Obstructive sleep apnoea (OSA) is a common disorder characterized by recurrent episodes of upper airway collapse during sleep that produce intermittent hypoxaemia and hypercapnia, brain arousal, sympathetic activation and haemodynamic changes that lead to sleep disturbances, daytime somnolence and poor quality of life [1,2]. The prevalence of OSA in middle-aged individuals is 24-26% in men and 17%-28% in women [3].

OSA is associated with an increased risk of cardiovascular comorbidities, and hypertension is one of the most well-established consequences of OSA [3–7]. The relationship between OSA and hypertension has been associated with sympathetic nervous system activation, oxidative stress, systemic inflammation, endothelial dysfunction and metabolic dysregulation due to arousal and hypoxaemia [1,8]. OSA has been associated with two unfavourable conditions related with the BP. First, OSA patients exhibit a higher rate of masked hypertension [9], which is defined as a normal office BP <140/90 mmHg and an abnormally increased 24-h mean BP on ambulatory blood pressure monitoring (ABPM). This hypertension phenotype, exhibited by 8-20% of the total normotensive outpatient population, increases to a rate of 30% in OSA patients and is associated with a higher risk of cardiovascular events and target organ damage [10]. In addition, OSA individuals exhibit a higher prevalence of alterations in 24-hour BP circadian patterns [11].

Two different circadian patterns of BP have been established related to changes in BP during sleep compared with the awake period. The dipper pattern is observed when the BP decreases at least 10% during sleep. Otherwise, the pattern is defined as non-dipping [12]. The non-

dipping BP circadian pattern has been related to an adverse cardiovascular prognosis regardless of BP status, i.e., hypertensive or normotensive [13,14]. Specifically in normotensive individuals, it has been estimated that each 5% decrease in the reduction of nocturnal BP is associated with an approximate 20% greater risk of cardiovascular mortality [13]. The dipping pattern directly correlates with the amount of deep sleep and is inversely correlated with sleep fragmentation [10,14].

Continuous positive airway pressure (CPAP) is the gold standard treatment for severe and symptomatic OSA [2]. The effect of CPAP on hypertension has been widely investigated, and several studies have demonstrated that CPAP significantly reduces BP in patients with OSA and hypertension [15,16]; this reduction is more evident in patients with resistant hypertension [2,6,15,17,18]. Recent evidence has demonstrated high BP variability in patients treated with CPAP, which could be explained by the heterogeneity of patients studied and the multifactorial nature of systemic hypertension. This variability has triggered an interest in identifying subgroups of patients who are most likely to benefit from CPAP treatment [2,19]. Nevertheless, the effects of CPAP treatment on BP in normotensive patients is poorly explored, and an overall lack of data on this phenomenon exists [20,21].

The aim of the present study was to evaluate BP changes in normotensive individual with CPAP, focusing on the influence of criteria used for diagnosing normal BP, ambulatory BP and baseline circadian BP patterns.

MATERIAL AND METHODS

Design and study population

This ancillary study included individuals who participated in two different studies (ClinicalTrials.gov: NCT01752556). These studies have been approved by the ethics committees of the respective hospitals (number 1153/1411). Briefly, one study evaluated the efficacy of therapeutic decisions for cardiorespiratory polygraphy (CRP) versus polysomnography (PSG) in individuals with suspected OSA, and the second study evaluated the cardiovascular risk in different OSA populations. For the current analysis, we selected normotensive patients who had an apnoea/hypopnoea index (AHI) > 15 events/hour and required CPAP treatment. Patients were included in the analysis regardless of adherence to CPAP treatment. Good CPAP compliance was defined as a use ≥ 4 hours/night.

We defined normotensive as an office BP measurement of <140/90 mmHg that was obtained according to international guidelines [22]. Individuals with a history of previous hypertension or who received antihypertensive treatment were excluded. Patients without BP recordings at baseline and after 6 months and those who reported previous use of CPAP at enrolment were also excluded from the analysis. For detailed information, see Figure 1.

Variables

BP measurements

Office BP and 24-h ABPM (Mortara Ambulo 2400, Milwaukee, USA) were routinely measured at the sleep unit in all patients at the beginning of the study period and after 6 months of CPAP treatment, according to the internationally recommended procedures [22–24].

Moreover, all patients included had an office BP measurement in the normal range at a primary care visit.

Hypertension was defined as the use of antihypertensive drugs or was based on the office BP measurement [23] as usual clinical practice. In 24-h ABPM, the dipping pattern was defined by a drop in BP at night. A subject was considered a dipper if the reduction in BP was at least 10% during sleep compared with the awake period and as a non-dipper if the reduction in BP was <10% [12]. Circadian patterns were classified based on the dipping ratio (nighttime/daytime BP ratio): non-dipper >0.9 and dipper ≤0.9 [3]. Masked hypertension is a clinical condition in which the office BP level is <140/90 mmHg but ambulatory or home BP readings are in the hypertensive range. According to the guidelines, the cut-off that we used to define masked hypertension was a mean BP ≥130/80 mmHg during 24-h ABPM [23,25].

Sleep evaluation

All patients underwent a sleep study consisting of either cardiorespiratory polygraphy or polysomnography. For more detailed information, see the supplemental materials.

Statistical analysis

Descriptive statistics of the mean (standard deviation) or median (interquartile range) were estimated for quantitative variables with a normal or non-normal distribution, respectively. The absolute and relative frequencies were used for qualitative variables. The normality of the distribution was analysed using the Shapiro-Wilk test. The baseline characteristics of the participants in each group were compared using Student's t-test or a non-parametric Mann-Whitney U-test for quantitative variables and Fisher's exact test for qualitative variables depending on the distribution of the data. Differences in ABPM parameters between groups

at six months were assessed by means ordinary least-squares linear models after adjusting for the baseline values, age, sex, BMI, AHI and CPAP compliance. The direction of change of the dipping ratio at six months relative to baseline values (decrease or increase) between groups (dipper or non-dipper) was compared with Pearson's Chi-square test. All statistical analyses and data processing were performed using R software-version 3.3.1, Vienna, Austria.

Results

Baseline patient characteristics

On the basis of the office measurements of BP, a total of 131 normotensive patients with a diagnosis of OSA who were scheduled for CPAP therapy were included in the analysis. A total of 92 (78.6%) patients used the CPAP ≥ 4 hours per night. The mean CPAP pressure was 9.97 cmH20. The primary characteristics of the included patients were male gender (84%), middle-aged (49.2 years (9.3)), and slightly obese with severe OSA.

At baseline, there were no significant differences between the true normotensive group and the masked hypertensive group, except for a higher percentage of males and slightly higher office BP values in the masked hypertension group. Nevertheless, both groups were in the normal BP range. For more detailed information, see Table 1.

Changes in the ABPM parameters

The changes in the ABPM parameters between the beginning of the study and 6 months after CPAP treatment are presented in Table 2. Briefly, a mild reduction in all ABPM variables (24-h mean BP, daytime BP and nighttime BP) was observed, although only the mean 24-h ambulatory BP, mean 24-h diastolic BP and mean daytime diastolic BP reached statistical

significance. The reduction observed in the mean 24-h ambulatory BP was -1.80 mmHg (CI 95%, -3.16 to -0.44; p-value = 0.01).

The evolution of ABPM parameters for masked hypertensive patients

We observed that 34.3% of patients exhibited a diagnosis of masked hypertension by ABPM. Thus, according to ABPM, patients were classified as true normotensive or masked hypertension, and we compared the changes in BP parameters at 6 months between the groups (Table 3). The proportion of compliers (average use of CPAP ≥ 4h/night) was 75.3% and 85% (p-value = 0.33) for the true normotensive and masked hypertensive groups, respectively. Moreover, no significant differences were observed in changes in BMI between true normotensive and masked hypertensive groups. The results revealed a marginal change in the mean 24-h ambulatory BP of -0.25 (-1.79 to 1.29 mmHg) in the true normotensive patients and a relevant decrease in masked hypertensive patients (-4.78 (-7.25 to -2.30) mmHg). The adjusted difference between the groups with respect to the mean change was -3.65 (-6.76 to -0.54) mmHg (p-value = 0.021). The change in mean daytime and nighttime BP was not significantly different in masked hypertension with respect to the true normotensive patients. After 6 months of CPAP treatment, 50% of masked hypertensive patients became true normotensive patients.

The evolution of ABPM parameters by circadian pattern

The change in BP with respect to the circadian pattern in patients with an office BP <140/90 mmHg is presented in Table 4. A reduction in the mean nocturnal BP occurred at 6 months in non-dippers

(-4.73 mmHg (-7.39 to -2.06 mmHg)). However, we observed that the mean nocturnal BP in dippers was significantly increased by 2.61 mmHg (0.60 to 4.62 mmHg). The adjusted difference between the groups with respect to the mean change in nocturnal BP was -4.05 mmHg (-7.99 to -0.11 mmHg) (p-value = 0.044). The change in the mean 24-h ambulatory BP and mean daytime BP did not significantly differ between non-dipper and dipper patients.

We classified patients as true normotensive or as having MH according to ABPM, and we observed that the true normotensive subjects with a non-dipping pattern exhibited a significant reduction in mean nocturnal BP that was not observed in dippers (mean difference in change between groups -4.99 mmHg (-9.42 to -0.55 mmHg), p-value = 0.028) (e-Table 1 and e-Figure 1 in the supplementary information). This difference was not observed when comparing patterns in masked hypertensive patients (e-Table 2 and e-Figure 1 in the supplementary information).

Evolution of the circadian pattern

Moreover, our results also revealed changes in the BP circadian pattern. Although 75% of patients who were dippers at baseline exhibited increased dipping ratio, only 31% of non-dippers exhibited increased dipping ratio (p-value < 0.001). The proportion of compliers (average use of CPAP ≥ 4h/night) was 77.4% and 80% (p-value = 0.909) for the dippers and non-dippers, respectively.

When continuously observed, the mean dipping ratio changes increased by 0.05 (95% CI, 0.03 to 0.06) for dippers and decreased by -0.04 (95% CI, -0.07 to -0.016) for non-dippers (Figure 2). A comparison of the change between groups demonstrated a difference of -0.087 (95% CI, -0.12 to -0.05; p-value < 0.001) in the mean dipping ratio changes between the non-dippers and dippers.

Discussion

This study demonstrated that in normotensive OSA patients, who were identified as such based on office BP measurements, CPAP treatment produced a significant reduction in mean 24-h ambulatory BP, mean 24-h diastolic BP and mean daytime diastolic BP. A mild reduction in all other ABPM variables was observed. The reduction in ABPM was primarily the effect of CPAP on the subgroup of patients with MH. Furthermore, the results also revealed that in non-dippers, CPAP treatment was associated with a reduction in the mean 24-h ambulatory BP and nocturnal BP. In contrast, in dipper patients, CPAP treatment was associated with an increase in nocturnal BP and in the dipping ratio.

Studies that assess the effect of CPAP on BP exclusively in normotensive subjects are lacking, but several studies have been designed to evaluate the effect of CPAP treatment on BP that include both hypertensive and normotensive patients [26–29].

A recent meta-analysis including more than 1100 patients based on randomized clinical trials (RCTs) that evaluated the effect of CPAP on BP concluded that CPAP treatment promotes significant but small reductions in BP in patients with OSA [30]. Nevertheless, a differentiation between the study subjects based on their baseline BP status was not conducted. The heterogeneity of individuals, mixing normotensive and hypertensive patients, may have influenced the results.

The available evidence centres on a select number of studies designed to evaluate the cardiovascular effect of treating OSA independent of the effects of BP. Faccenda et al. [31] analysed the effect of CPAP on patients taking no medications who had a baseline BP close to the normal range. The authors observed very minor effects of CPAP on BP, which were limited

to small decreases in the diastolic BP. Yorgun et al. [21] investigated predictors of BP changes in normotensive patients with OSA who underwent CPAP treatment for 12 weeks. The authors concluded that CPAP reduced daytime and nighttime BP, even in the absence of overt hypertension, and improved the dippig ratio in severe OSA patients. Moreover, a similar trend of switching to the dipper BP pattern was observed in non-dippers. The frequency of the non-dipper circadian pattern changed from 50% to 12.5% [21]. Nevertheless, this study was limited due to its short follow-up and small sample size.

Furthermore, another RCT that included normotensive patients but was designed to evaluate insulin sensitivity [32] concluded that BP was reduced by CPAP treatment in normotensive patients based on office BP values. These results are consistent with our findings; however, the authors did not describe the presence of masked hypertension, which could have affected the results.

To our knowledge, only one study has specifically assessed the effect of CPAP treatment in OSA patients with prehypertension or masked hypertension. In this study [33], the authors concluded that the use of CPAP resulted in a significant reduction in office systolic BP and in diurnal and nocturnal BP in ABPM. However, the lack of a separate analysis of the masked hypertensive individuals did not allow the authors to explain the influence of this BP phenotype on the observed results.

In addition, Castro-Grattoni et al. [34] performed a study that included patients with or without a prior history of hypertension for identifying variables that predict BP response to CPAP, and their results suggest that nocturnal hypertension, circadian BP pattern and nighttime heart rate could be clinical predictors of the BP response to CPAP and support the usefulness of 24-h ABPM for OSA patients before treatment initiation.

The present study demonstrates for the first time that the reduction in mean 24-h ambulatory BP reported with CPAP in normotensive outpatients is primarily due to the different BP responses in individuals with masked hypertension. As observed in our study, this condition is estimated to be present in at least one-third of patients with OSA who are considered normotensive based on office BP measurements [9]. Moreover, masked hypertension has been associated with cardiovascular risk [35]. Our results suggest that in patients with severe OSA who are considered normotensive in the office, ABPM should be performed to evaluate the presence of masked hypertension.

This study also suggests that normotensive individuals with a dipper BP circadian pattern might exhibit increases in nighttime BP with CPAP that may unfavourably affect the circadian BP pattern, whereas non-dippers exhibit reductions in BP. The circadian BP pattern is a variable that possesses proven cardiovascular predictive value in normotensive patients [13,36], and Ohkubo et al. reported that reductions in dipping ratio through a decline in nighttime BP strongly decreases the risk of cardiovascular events and mortality [13]. Based on our results, those benefits may be expected in non-dipper patients. Moreover, each 5% decrease in the decline in nocturnal BP was associated with a 20% greater risk of cardiovascular mortality [13]. Furthermore, of all the measures of BP, nighttime BP is the strongest predictor and exhibits the highest prognostic value of cardiovascular risk [37,38]. Therefore, absolute changes in nighttime BP should be carefully assessed in OSA patients [14].

The explanation for why normotensive individuals who are dippers tend to exhibit increased nighttime BP with CPAP might be that these patients develop adaptive responses to the pathophysiologic changes triggered by apnoea, and these mechanisms may be affected by

CPAP treatment. Before CPAP treatment, these subjects may have exhibited a balance between sympathetic activity, which exerts a pressor effect, and the production of natriuretic peptides (NPs) that decrease BP. When CPAP treatment is started, intermittent hypoxaemia and intrathoracic pressure disappear; therefore the level of natriuretic peptides my decrease even in normotensive patients [39,40]. However, in addition to this suggested hypothesis, the important influence of regression to the mean with the repetition of ABPM should also be considered.

The main strength of this study was that it is one of the first studies to evaluate the effect of CPAP treatment in normotensive outpatients, including those with masked hypertension. Furthermore, the present study evaluated the effect of CPAP on nighttime BP and the BP circadian pattern. The limitations of the study are as follows: First, due to the relatively modest sample size, differences may not have been observed secondary to limited statistical power. Second, the effect of regression to the mean should be considered; some results suggest that other factors in addition to a regression effect are responsible for the results. Third, ABPM variability was estimated to be approximately 50%. Therefore, we cannot exclude the possibility that some of the effects could be related to this variability [36]. Fourth, patients were diagnosed using either polysomnography or respiratory polygraphy. Nevertheless, respiratory polygraphy is accepted and validated for use in the diagnosis of OSA [41]. Fifth, we do not have information regarding residual AHI on CPAP treatment. Sixth, we demonstrated associations and not causality between CPAP treatment and BP changes because this study lacked controls. However, due to ethical issues, it is not possible to conduct a study involving untreated patients with severe OSA.

In conclusion, our findings suggest that in normotensive outpatients with OSA, CPAP treatment is associated with a decrease in BP that is primarily driven by the decrease in BP in subjects with undiagnosed masked hypertension. CPAP treatment was associated with a decrease in nocturnal BP in patients with a non-dipping pattern, whereas an increase in nocturnal BP was observed in dipper patients. The results suggest that CPAP effects may differ in normotensive patients depending on their dipping pattern and the presence of masked hypertension and highlight the importance of performing ABPM in these patients. Moreover, our results indicate the necessity of an RCT to evaluate the effect of CPAP in normotensive patients.

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FIGURE LEGENDS

FIGURE 1. Study flowchart

A total of 131 patients were included. A sleep study at baseline and 24-h ambulatory blood pressure monitoring (ABPM) at baseline and at 6 months of the inclusion were performed. According to the results of ambulatory blood pressure monitoring, patients were classified as either true normotensive or masked hypertensive.

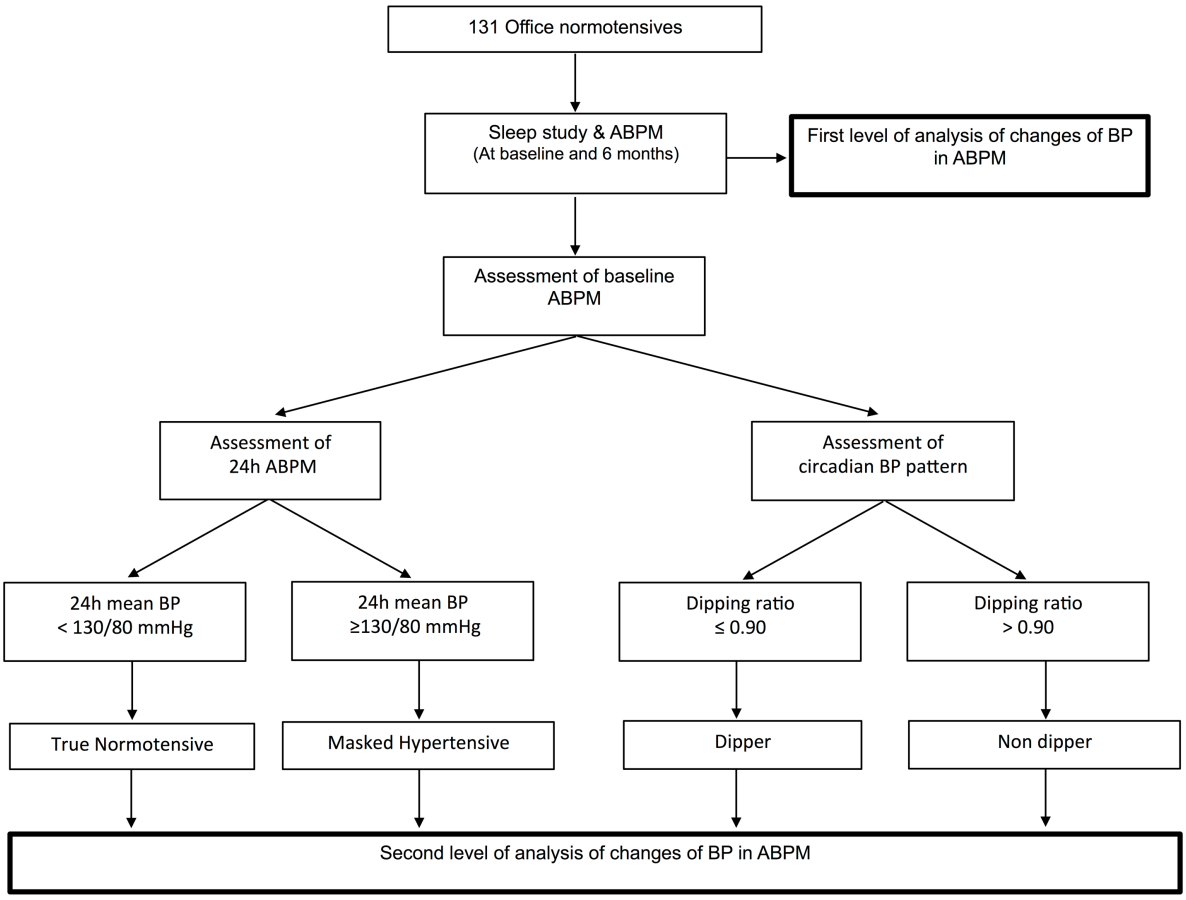
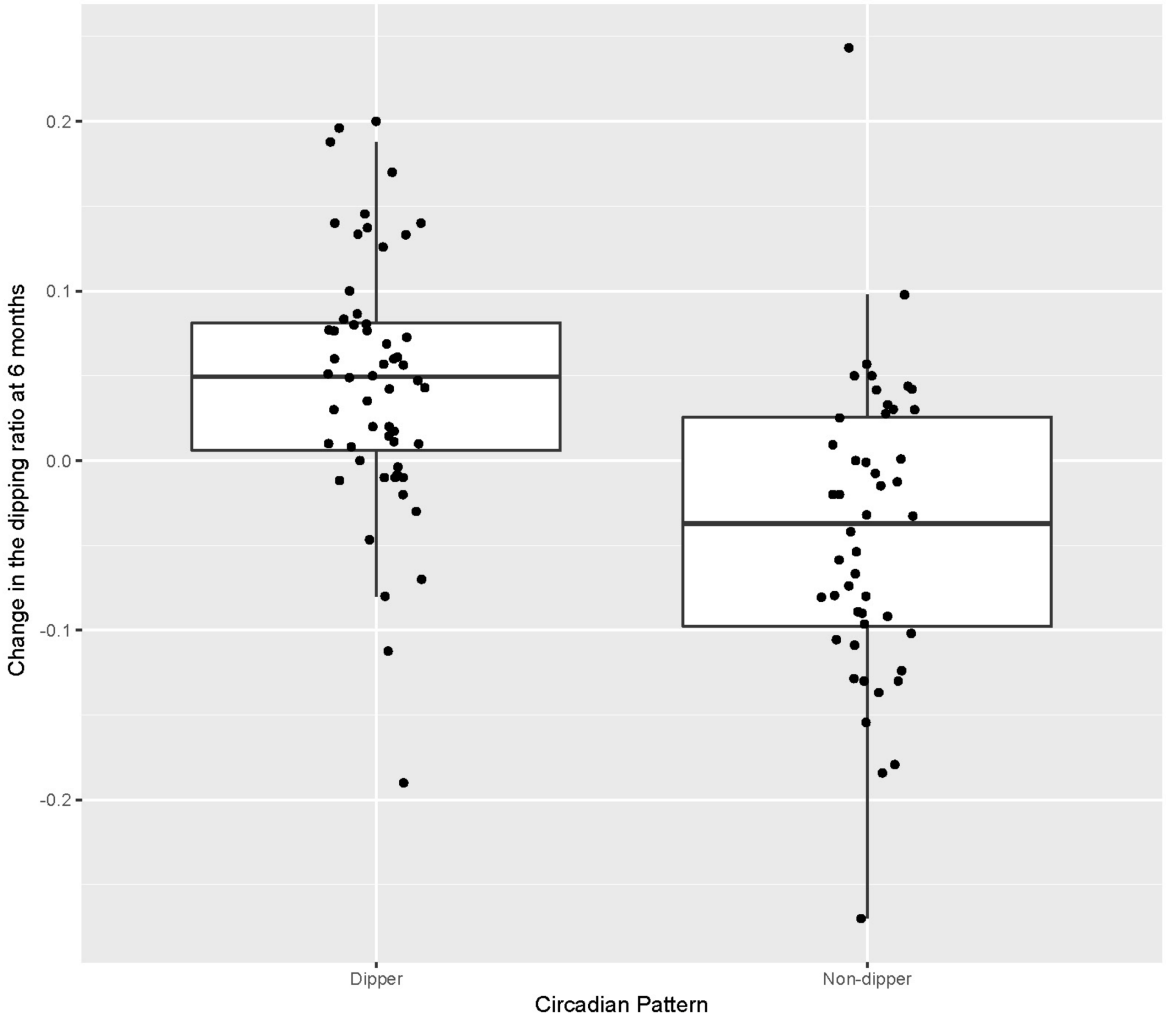


FIGURE 2. Change in the dipping ratio after 6 months of continuous positive airway pressure treatment.

Blood pressure (BP) was assessed with 24-h ABPM before and after 6 months of CPAP treatment. The bars represent the change in the dipping ratio at 6 months of CPAP treatment between dippers and non-dippers.



TABLES

Table 1. Baseline characteristics of participants

	All n=131	True normotensive n=86	Masked hypertensive n=45	p-value
Clinical variables				
Age (years)-*mean (SD)*	49.2 (9.33)	49.5 (9.78)	48.7 (8.49)	0,622
Gender:				0,018
Male- *n (%)*	110 (84.0%)	67 (77.9%)	43 (95.6%)	
Female- *n (%)*	21 (16.0%)	19 (22.1%)	2 (4.44%)	
BMI (kg/m^2)- *median [IQR]*	30.9 [28.2;35.3]	30.5 [27.8;35.6]	31.0 [28.7;34.5]	0,493
Smoking status- *n (%)*:				0,71
Non-smoker	86 (67.2%)	55 (65.5%)	31 (70.5%)	
Smoker	42 (32.8%)	29 (34.5%)	13 (29.5%)	
Dyslipidaemia-*n (%)*:	23 (22.8%)	13 (20.3%)	10 (27.0%)	0,597
Glucose (mg/dL)-*median [IQR]*	95.0 [87.0;103]	95.0 [87.2;102]	96.0 [87.0;106]	0,387
Office SBP (mmHg)- *median [IQR]*	121 [117;129]	120 [115;128]	125 [120;130]	0,022
Office DBP (mmHg)- *median [IQR]*	79.0 [72.0;82.2]	77.0 [70.0;81.0]	80.0 [75.0;84.5]	0,013
ABPM variables				
Heart rate (beats/min)- *mean (SD)*	72.9 (10.3)	71.6 (8.95)	75.2 (12.2)	0,103
Dipping ratio- *mean (SD)*	0.90 (0.08)	0.89 (0.07)	0.91 (0.09)	0,262
Respiratory parameters				
AHI (events/h)- *median [IQR]*	40.9 [30.2;62.3]	39.1 [30.4;59.0]	48.5 [28.5;72.1]	0,168
$TSat_{90}$ (%)-*median [IQR]*	7.10 [2.00;30.1]	5.30 [1.50;25.9]	12.0 [4.62;35.0]	0,073
ESS (0-24)- *mean (SD)*	12.7 (4.35)	12.6 (4.34)	12.8 (4.42)	0,824
CPAP compliance (≥4h/night)- *n (%)*:	92 (78.6%)	58 (75.3%)	34 (85.0%)	0,33

TABLE 2. Change in ambulatory blood pressure monitoring parameters at 6 months in normotensive patients with continuous positive airway pressure treatment

	Mean BP *Mean (95% CI)*	Systolic BP *Mean (95% CI)*	Diastolic BP *Mean (95% CI)*
ABPM – mean 24-h ambulatory BP (mmHg)	n = 131	n = 131	n = 131
Baseline	91.69 (90.09 to 93.30)	119.90 (117.64 to 122.16)	75.54 (74.16 to 76.91)
6-months	89.89 (88.37 to 91.42)	119.12 (116.79 to 121.44)	74.15 (72.88 to 75.42)
Change	-1.80 (-3.16 to -0.44)§	-0.78 (-2.58 to 1.02)	-1.39 (-2.50 to -0.27)§
ABPM - mean daytime (mmHg)	n = 131	n = 131	n = 131
Baseline	94.85 (93.17 to 96.53)	123.67 (121.43 to 125.91)	78.55 (77.10 to 79.99)
6-months	94.01 (91.76 to 96.26)	123.22 (120.72 to 125.72)	77.16 (75.70 to 78.62)
Change	-0.84 (-2.72 to 1.05)	-0.45 (-2.26 to 1.35)	-1.39 (-2.56 to -0.22)§
ABPM – mean nighttime (mmHg)	n = 131	n = 130	n = 131
Baseline	84.40 (82.50 to 86.31)	111.56 (108.88 to 114.24)	68.94 (67.26 to 70.62)
6-months	83.63 (81.81 to 85.44)	111.08 (108.48 to 113.69)	68.21 (66.87 to 69.55)
Change	-0.78 (-2.54 to 0.98)	-0.47 (-2.90 to 1.96)	-0.73 (-2.23 to 0.77)

ABPM, ambulatory blood pressure monitoring; CI, confidence interval.
§ P<0.05 for paired comparison of outcome measures examining change from baseline to 6 months

Table 3. Change in ambulatory blood pressure monitoring parameters at 6 months in true normotensive and masked hypertensive groups

	True normotensive *Mean (95% CI)*	Masked hypertensive *Mean (95% CI)*	Difference in group adjusted for age, BMI, sex, AHI and CPAP compliance *Mean (95% CI)*	*P-value*
ABPM - mean 24-h ambulatory BP, (mmHg)	*n=69*	*n=36*		
Baseline	87,47 (86,23 to 88,71)	99,79 (97,39 to 102,19)		
6-months	87,22 (85,62 to 88,81)	95,02 (92,45 to 97,59)		
Change	-0,25 (-1,79 to 1,29)	-4,78 (-7,25 to -2,30)§	-3.65 (-6.76 to -0.54)	**0,021**
ABPM - mean daytime BP, (mmHg)	*n=69*	*n=37*		
Baseline	90,62 (89,30 to 91,94)	102,74 (100,02 to 105,46)		
6-months	90,36 (88,70 to 92,02)	100,82 (95,71 to 105,92)		
Change	-0,25 (-1,86 to 1,35)	-1,92 (-6,57 to 2,72)	-0.96 (-5.65 to 3.73)	0,685
ABPM - mean nighttime BP, (mmHg)	*n=68*	*n=36*		
Baseline	80,34 (78,61 to 82,08)	92,08 (88,83 to 95,32)		
6-months	80,76 (79,06 to 82,46)	89,04 (85,39 to 92,69)		
Change	0,42 (-1,41 to 2,25)	-3,04 (-6,81 to 0,73)	-2.05 (-6.31 to 2.20)	0,341

Change computed as the difference of the 6-months values with respect to the baseline values. Difference in mean change computed as the difference of masked hypertensive regard to true normotensive. The statistically significant p values (p values lower than 0.05) are bolded. ABPM, ambulatory blood pressure monitoring; AHI, apnoea/hypopnoea index CI, confidence interval; CPAP, continuous positive airway pressure. § P<0.05 for paired comparison of outcome measures examining change from baseline to 6 months.

Table 4. Change in ambulatory blood pressure monitoring parameters at 6 months by circadian pattern groups

	Dipper	Non-dipper	Difference in group adjusted for baseline BP, age, BMI, sex, AHI and CPAP compliance.	
	Mean (95% CI)	*Mean (95% CI)*	*Mean (95% CI)*	*P-value*
ABPM - mean 24-h ambulatory BP, (mmHg)	*n=57*	*n=48*		
Baseline	91,19 (88,83 to 93,56)	92,29 (90,09 to 94,48)		
6-months	90,36 (88,14 to 92,58)	89,33 (87,21 to 91,45)		
Change	-0,83 (-2,74 to 1,07)	-2,96 (-4,92 to -0,99)§	-1.73 (-4.31 to 0.85)	0,186
ABPM - mean daytime BP, (mmHg)	*n=58*	*n=48*		
Baseline	96,09 (93,58 to 98,60)	93,35 (91,20 to 95,50)		
6-months	95,15 (91,78 to 98,52)	92,64 (89,70 to 95,58)		
Change	-0,94 (-3,65 to 1,77)	-0,71 (-3,40 to 1,98)	-0.69 (-4.87 to 3.49)	0,742
ABPM - mean nighttime BP, (mmHg)	*n=56*	*n=48*		
Baseline	79,69 (77,57 to 81,81)	89,90 (87,30 to 92,50)		
6-months	82,30 (80,12 to 84,49)	85,17 (82,14 to 88,20)		
Change	2,61 (0,60 to 4,62)§	-4,73 (-7,39 to -2,06)§	-4.05 (-7.99 to -0.11)	**0,044**

Change was computed as the difference in the 6-month values with respect to the baseline values. The difference in the mean change was computed as the difference between non-dipper and dipper values. The statistically significant p-values (p-values lower than 0.05) are bolded.

ABPM, ambulatory blood pressure monitoring; AHI, apnoea/hypopnoea index CI, confidence interval; CPAP, continuous positive airway pressure. § P<0.05 for the paired comparison of outcome measures examining the change from baseline to 6 months.

DIFFERENTIAL BLOOD PRESSURE RESPONSE TO CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT ACCORDING TO THE CIRCADIAN PATTERN IN HYPERTENSIVE PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA.

Sapiña-Beltrán E, Torres G, Benítez I, Santamaría-Martos F, Durán-Cantolla J, Egea C, Sánchez-de-la-Torre M, Barbé F, Dalmases M; on behalf of the Spanish Sleep and Breathing Group.

Eur Respir J. 2019;54(1).

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A este artículo se le ha dedicado un editorial en el mismo número de la revista.
Eur Respir J. 2019; 54(1): 1901219.

Abstract

Introduction: Continuous positive airway pressure (CPAP) has a heterogeneous effect on blood pressure (BP) in hypertensive patients. However, the effect of CPAP on BP in hypertensive subjects regarding to circadian BP pattern has never been explored. This study aimed to assess the effect of CPAP on BP considering the circadian BP pattern in untreated hypertensive patients.

Methods: This study is a post hoc analysis of the Spanish Cohort for the Study of the Effect of CPAP in Hypertension (CEPECTA), a multicentre, randomized trial of CPAP versus sham-CPAP in patients with new-onset systemic hypertension and an apnea/hypopnea index >15 events/h. We included patients for whom 24-h ambulatory BP monitoring (ABPM) data were available at baseline and 12 weeks after the intervention. Subjects were classified based on the dipping ratio (dipper/nondipper). We evaluated the effect of CPAP on ABPM parameters after 12 weeks of treatment.

Results: Overall, 272 hypertensive subjects were included in the analysis (113 dippers/159 nondippers). Baseline clinical and polysomnographic variables were similar between the groups. CPAP treatment in nondipper patients was associated with reductions in 24-h ambulatory BP variables and nighttime ambulatory BP measurements. However, a nonsignificant effect was reported in the dipper group. The differential effects of CPAP between the groups were -2·99 mmHg (-5·92 to -0·06) for the mean 24-h ambulatory BP and -5·35 mmHg (-9·01 to -1·69) for the mean nighttime ambulatory BP.

Conclusions: Our results show a differential effect of CPAP treatment on BP in hypertensive patients depending on the circadian pattern. Only nondipper patients benefited from CPAP treatment in terms of BP reduction.

Introduction

Obstructive Sleep Apnea (OSA) is a common sleep disorder characterized by partial (hypopnea) or complete (apnea) episodes of collapse in the upper airway during sleep. This collapse causes intermittent hypoxia, hypercapnia, negative intrathoracic pressure and arousals, resulting in excessive daytime sleepiness and poor quality of life. OSA is associated with a higher cardiovascular risk due to several pathogenic factors, and hypertension has been established as one of the main causes of these cardiovascular complications [1–4]. Moreover, OSA can reportedly affect the circadian blood pressure (BP) pattern by increasing the prevalence of patients with a nondipper circadian BP pattern, which has been related to a poor cardiovascular prognosis [5–7].

Several randomized clinical trials and meta-analyses have indicated that continuous positive airway pressure (CPAP) can produce a modest but consistent reduction in BP, with greater reductions observed in resistant hypertension (RH) subjects [8–15]. Thus, severe OSA, hypersomnolence, higher BP values and adherence to CPAP are variables that have been associated with a greater improvement in BP in several studies [8,12,15]. Nevertheless, even in RH patients with moderate to severe OSA and good compliance, the effect of CPAP treatment on BP is highly variable [8].

Recently, our group published a study on office normotensive patients who showed a differential BP response to CPAP depending on the dipping ratio (DR) category. The results of this study indicate that several factors may contribute to modulating the effect of CPAP on BP [16] and highlight the importance of better characterizing OSA patients in terms of the BP response to CPAP treatment.

Therefore, due to the high variability of the results observed, using a precision medicine approach and identifying and differentiating subgroups of patients in whom BP could be reduced to a greater extent and who could benefit from CPAP treatment from those with low or no effects of CPAP on BP is necessary [8,17]. Determining which patients could benefit from this intervention could have important implications in clinical practice and for resource consumption.

The effects of CPAP treatment on BP in hypertensive subjects with respect to the circadian BP pattern have never been explored [18]. Thus, as previous results suggest, we hypothesize that the BP response in hypertensive patients could vary depending on the dipping ratio (DR) category. Therefore, the aim of the present study was to assess the effect of CPAP treatment on BP considering the baseline circadian BP pattern in untreated hypertensive patients.

MATERIALS AND METHODS

Design and study population

This study is a post hoc analysis of the Spanish Cohort for the Study of the Effect of CPAP in Hypertension (CEPECTA). This was a multicentre, randomized, prospective, double-blind and parallel study controlled by a placebo that evaluated the effect of CPAP treatment on BP in patients with OSA and untreated systemic hypertension diagnosed based on office BP measurements [19].

Briefly, patients aged between 18 and 75 years with untreated new-onset systemic hypertension were included between December 2004 and June 2007. Patients were excluded if they met any of the following criteria: had secondary hypertension, a BP greater than 180/100 mmHg, had cognitive impairment, were professional drivers or handled dangerous machinery, were shift workers, were pregnant, had severe chronic disease or were previously treated with CPAP, or had any contraindication for prescribing CPAP. Patients treated with antihypertensive, psychotropic, stimulant or antidepressant drugs and those consuming illicit drugs were also excluded.

All patients underwent polysomnography and 24-h ambulatory blood pressure monitoring (ABPM) (Spacelabs model 90207, EEUU) at baseline and after 6 and 12 weeks of treatment. Subjects with an apnea/hypopnea index (AHI) >15 events/hour were randomized to CPAP treatment or sham-CPAP and evaluated at 12 weeks.

Systemic hypertension was not treated with drugs during the study. More detailed information on the inclusion and exclusion criteria and the methodology of the CEPECTA study is published elsewhere [19].

The CEPECTA trial was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics committee. All participants provided written informed consent. The trial is registered with ClinicalTrials.gov (NCT00202527).

For the present study, we selected 272 patients who completed CEPECTA trial and for whom 24-h ABPM data were available at baseline and after 12 weeks. The included patients were classified as dippers or nondippers based on the DR. (Figure 1)

Procedures

Definition of hypertension

Systemic hypertension was diagnosed according to standard criteria and defined as an office systolic blood pressure (SBP) ≥140 mmHg, a diastolic blood pressure (DBP) ≥90 mmHg, or both.

Sleep evaluation

All included subjects underwent polysomnography according to recommended guidelines. The sleep evaluation was considered valid if it lasted for >180 minutes of total sleep.

24-h ambulatory blood pressure monitoring

Twenty-four-hour ABPM (Spacelabs model 90207, EEUU) was performed for all patients at baseline and after 6 and 12 weeks of treatment.

During ABPM, BP measurements were recorded every 20 minutes during the daytime (from 6 am to 10 pm) and every 30 minutes during the nighttime (between 10 pm and 6 am). The diagnosis of true systemic hypertension was determined based on 24-h ABPM results following guidelines and standard criteria. The cut-off for systemic hypertension was defined as an SBP ≥135 mmHg, DBP ≥85 mmHg or both during the awake period [19]. Circadian patterns were defined based on the DR (nighttime/daytime BP ratio): non-dipper >0·9 and dipper ≤0·9.

The mean blood pressure was calculated using the formula (SBP + 2×DBP)/3.

Office blood pressure measurements

Office BP measurements were performed following guidelines. Before BP measurement, the patient should rest for at least 5 minutes in a seated position with the feet on the floor and the arm supported at the heart level. Caffeine, exercise, and smoking should be avoided for at least 30 minutes prior to measurement. The seated BP was recorded as the average of at least 2 replicate measurements [19,20].

CPAP treatment

Patients with CPAP treatment were titrated with an auto-CPAP (Autoset- T; ResMed, Sydney, Australia) according to a previously described protocol [19]. The optimal pressure was determined visually from the raw data, and the patient was treated with this pressure for 12 weeks. Furthermore, the patients receiving sham-CPAP also received the treatment at home for 12 weeks.

Statistical analysis

Baseline bivariate analysis was carried out using a t-test (or an equivalent nonparametric test) or χ^2 test depending on whether the variables were quantitative or categorical, respectively. The differential CPAP effect on BP according to the circadian pattern was assessed using linear models. The models included the treatment (CPAP or Sham), circadian pattern (dipper or nondipper) and the interaction between them. All models were adjusted according to baseline measurements. Furthermore, the CPAP effect was evaluated using a linear model adjusted for age, sex, body mass index (BMI) and AHI. The assumptions of the model were assessed using residual analysis. All tests were two tailed, and p values <0.05 were considered indicative of statistical significance.

RESULTS

Patient characteristics

A total of 272 hypertensive subjects with untreated hypertension and an AHI>15/h^{-1} events were included in the analysis. Of all the patients included, 113 (42%) were dippers, and 159 (58%) were nondippers.

The baseline characteristics of the enrolled subjects are shown in Table 1. No significant differences were observed in the baseline variables between the groups. Mainly, the

subjects included were male with a median [IQR] age of 53·0 years [46·0; 60·0], a BMI of 30·8 kg/m² [28·1; 34·9], a median AHI of 38·0 [22·0; 58·0] events/h. No differences were observed in polysomnographic and sleep variables between the groups. The mean systolic and diastolic office blood pressures of the subjects were 150 (9·66) and 93.4 (6·60) mmHg, respectively

Effect of CPAP treatment on BP by circadian pattern

The mean CPAP compliance was 4·08 hours, without significant differences across the different groups. Changes in ABPM parameters after 12 weeks of treatment (CPAP or sham-CPAP) were evaluated in each circadian pattern group (dipper or nondipper). In the dipper group, we observed nonsignificant effects of CPAP on the mean 24-h ambulatory BP (0·11 mmHg; 95% CI -2·13 to 2·34), the mean daytime ambulatory BP (-0·21 mmHg; 95% CI -2·65 to 2·23) and the mean nighttime ambulatory BP (0·95 mmHg; 95% CI -1·84 to 3·73). In contrast, significant effects of CPAP were observed on the mean 24-h ambulatory BP (-2·88 mmHg; 95% CI -4·74 to -1·02) and the mean nighttime ambulatory BP (-4·40 mmHg; -6·73 to -2·08) in the nondipper group. The differential effects of CPAP between the circadian pattern groups revealed a better response in nondippers of -2·99 mmHg (-5·92 to -0·06) for the mean 24-h ambulatory BP and -5·35 mmHg (-9·01 to -1·69) for the mean nighttime ambulatory BP (see Figure 2 and Table 2). Moreover, more detailed information on absolute BP values and changes in each treatment and dipping category group is described in the supplemental material (e-Table 1). The model adjusted only for baseline measurements showed similar results (see e-Table 2).

When the analysis was performed only with patients diagnosed with systemic hypertension based on the results of 24-h ABPM, similar results were observed. A differential effect of CPAP was also observed between dippers and nondippers. Nondipper patients exhibited significantly reduced blood pressure, especially nighttime blood pressure (e-Table 3), while no significant changes were observed in the dipper group (e-Table 3).

Discussion

This study suggests that the BP response to CPAP treatment in hypertensive patients depends on the circadian blood pressure pattern. The results show significant reductions in the mean 24-h ambulatory BP, 24-h systolic BP, 24-h diastolic BP and nighttime ambulatory BP variables in nondipper patients, whereas no significant changes were observed in the dipper group after 12 weeks of CPAP treatment. Therefore, in relation to BP, only nondipper patients benefited from CPAP treatment.

Several studies have evaluated the effect of CPAP treatment on BP in hypertensive patients, and a reduction in BP has been described previously [19,21,22]. Data from a meta-analysis indicate a mild effect of CPAP treatment on BP in OSA patients, which has been reported to be approximately 2 mmHg [13–15,23,24], with greater reductions observed in subjects with RH [8–11]. Notably, the BP response to CPAP treatment has been found to be highly variable. Some authors noted that factors such as higher BP values, CPAP use or OSA severity could be related to a better BP response [10,12,25]; nevertheless, the causes of this variability have not been well established.

Therefore, this considerable variability in the BP response to CPAP treatment highlights the importance of differentiating patients who will effectively respond to CPAP treatment from those who will not. In recent years, some published studies have identified clinical and molecular profiles that may predict the BP response to CPAP treatment. Sanchez-de-la Torre et al. [17] reported a circulating miRNA profile that could predict BP responses to CPAP treatment in patients with RH and OSA. Moreover, in an observational study with severe OSA patients, Castro-Grattoni et al. [26] suggested that the circadian BP pattern, nocturnal hypertension and the nighttime heart rate could be predictors of the BP response to CPAP treatment. Furthermore, data from an observational study recently published by our group showed that in normotensive subjects, the BP circadian pattern may influence the BP response to CPAP treatment [16]. Although several authors have suggested that certain clinical characteristics may predict the BP response to treatment, no randomized studies have confirmed these findings, which could be very useful in clinical practice.

In our study, the decrease observed in the mean 24-h ambulatory BP was –2.99 mmHg. Moreover, when analysing nocturnal BP, the decrease was -5·35 mmHg in the mean nighttime ambulatory BP, -6·45 mmHg in the mean systolic ambulatory BP and -4·87 mmHg in the mean diastolic ambulatory BP.
In previous studies with systemic hypertension and RH patients, decreases in the mean 24-h ambulatory BP of approximately -1.5 mmHg [19] and -3 mmHg, respectively, were observed [8,9]. Our results show that blood pressure decreases are greater in nondipper patients than those in dipper patients, and nondipper patients would therefore benefit the most from CPAP treatment in terms of BP reduction.

Multiple studies have indicated that sleep alterations, such as duration changes, fragmentation or blunted BP declines, which are frequent in OSA, are associated with atherosclerosis, hypertension and an increased incidence of cardiovascular events [27,28]. Previous studies have highlighted the importance of reducing nighttime blood pressure and have suggested that decreasing nocturnal BP has higher prognostic value for reducing cardiovascular outcomes than reducing daytime blood pressure [29,30]. Furthermore, the fact that these reductions in BP are observed in nondipper subjects is especially important since this circadian pattern category has been related to a worse cardiovascular prognosis, a higher prevalence of organ damage and less favourable outcomes compared to the dipper category [31,32]. Moreover, international guidelines indicate even minimal reductions in BP levels may be clinically effective in reducing cardiovascular mortality [20].
Therefore, identification of bedtime chronotherapy strategies to reduce BP in hypertensive patients, especially at night, has received increasing interest [33], and some authors have even combined these strategies with CPAP treatment in hypertensive patients with OSA [34]. However, the results are not fully consistent, and more evidence is required to confirm the beneficial effect of combining both methods.

This study shows a differential BP response based on the circadian pattern category in hypertensive patients and demonstrated the importance of performing ABPM in hypertensive subjects before prescribing CPAP. The results support the recommendation of performing ABPM for the management of patients with office hypertension and suspected OSA. However, this recommendation was based on the assessment of the cardiovascular risk [35,36] whereas in our study is based on identifying patients who could benefit the most from CPAP treatment in terms of BP. Our study indicates that the BP circadian pattern at baseline may determine differences in the BP response to CPAP

treatment. Therefore, performing ABPM may contribute to identify subgroups of hypertensive patients with OSA in whom blood pressure is expected to be reduced to a greater extent and highlights the utility of individual characteristics, such as the blood pressure circadian pattern, as factors to consider in the management of these patients.
In addition, the results suggest that the BP circadian pattern can be used when selecting the optimal therapeutic approach for each patient, and that CPAP treatment may be the first treatment approach in untreated hypertensive patients with OSA who are nondippers.
Future studies should determine the role of ABPM in managing these patients and clarify whether ABPM should be routinely performed for patients with hypertension and OSA before deciding to prescribe CPAP.

The main strength of this study is that to our knowledge, it is the first to confirm that the effect of CPAP on BP varies depending on the circadian pattern and to identify the dipping category as a clinical variable that allows differentiation between hypertensive OSA patients with a good BP response to CPAP treatment and those without a good response. Moreover, this study included a large sample size an implemented ABPM, and OSA was diagnosed by polysomnography. In addition, the included patients did not receive antihypertensive drugs and were treated only with conservative measures[19], thus enabling evaluation of the effects of CPAP without interference from changes in BP induced by pharmacological treatments. Nevertheless, the study presents several limitations that should be mentioned. This study encompasses the inherent limitations of a post hoc analysis. In our analysis, the included patients were classified according to the DR, which was not considered before randomization. However, dippers and nondippers were fully comparable at the baseline evaluation, and when we assessed the effect of CPAP, a fully adjusted model showed similar results. Second, the subjects presented moderate to severe OSA, and the results may not be generalizable to less severe OSA patients. Third, the included patients had recently been diagnosed with hypertension, exhibited mild hypertension, and were untreated. Thus, the results should be interpreted with caution when addressing patients receiving antihypertensive drugs. Fourth, the categorization of the circadian BP pattern with single 24-h ABPM is only moderately reproducible.

Conclusions

In conclusion, our findings show that in patients with moderate to severe OSA who are newly diagnosed with hypertension, only those with a nondipper BP circadian pattern experience significant benefit for BP with CPAP treatment, especially nocturnal BP.

Author contribution

ESB, GT, JD-C, CE, MST, FB, and MD participated in the study conception and design.
IB and FSM participated in the analysis of the data.
ESB, GT, IB, FSM, MST, FB, and MD participated in the interpretation of the data for the work.
All authors drafted the manuscript, revised it critically and provided final approval of the version to be published. MD is the guarantor.

Declaration of interests

The authors have reported no conflicts of interest with organizations or companies to the European Respiratory Journal.

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TABLES

Table 1. Baseline characteristics of the studied groups

	Global N = 272	Dipper		Nondipper		p value
		Sham N=62	CPAP N=51	Sham N=73	CPAP N=86	
Demographic and Clinical variables						
Age (years) -median [IQR]-	53·0 [46·0;60·0]	51·5 [46·0;59·8]	50·0 [45·0;57·0]	55·0 [46·0;60·0]	54·0 [49·0;61·8]	0·108
Male: -n (%)-	223 (82·0%)	50 (80·6%)	42 (82·4%)	64 (87·7%)	67 (77·9%)	0·544
BMI (kg/m2) -median [IQR]-	30·8 [28·1;34·9]	30·4 [28·4;33·4]	32·4 [28·4;34·9]	31·8 [28·7;35·2]	30·5 [27·4;34·6]	0·356
Smoking status: -n(%)-						0·607
Non smoker	90 (34·2%)	25 (41·7%)	15 (29·4%)	25 (35·7%)	25 (30·5%)	
Former smoker	103 (39·2%)	21 (35·0%)	23 (45·1%)	29 (41·4%)	30 (36·6%)	
Smoker	70 (26·6%)	14 (23·3%)	13 (25·5%)	16 (22·9%)	27 (32·9%)	
Alcohol consumption (g/day) -median [IQR]-	15·0 [0·00;32·0]	15·0 [0·00;30·0]	15·0 [0·00;35·0]	12·5 [0·00;30·0]	15·0 [0·00;40·0]	0·867
Polysomnographic and sleep parameters						
Stage 1 (min) -median [IQR]-	32·0 [13·0;60·0]	32·0 [19·8;53·5]	36·5 [11·5;80·0]	29·0 [13·0;39·0]	31·5 [12·5;83·8]	0·557
Stage 2 (min) -median [IQR]-	216 [166;257]	224 [177;285]	224 [166;254]	200 [149;255]	212 [170;252]	0·432
Stage 3 (min) -median [IQR]-	31·5 [13·0;58·0]	30·0 [13·0;53·0]	34·0 [11·0;77·5]	30·0 [13·0;51·0]	29·5 [10·0;63·2]	0·351
REM Stage (min) -median [IQR]-	50·5 [33·0;70·0]	51·0 [41·5;70·2]	47·0 [21·2;71·2]	48·5 [30·8;68·8]	51·0 [39·2;70·5]	0·783
Total sleep time (min) -median [IQR]-	357 [314;400]	390 [337;411]	358 [316;415]	353 [303;390]	354 [314;382]	0·152
AHI (events/h) -median [IQR]-	38·0 [22·0;58·0]	41·0 [25·2;58·0]	48·0 [22·5;67·0]	35·0 [20·0;56·0]	31·0 [22·0;52·0]	0·245
Mean saturation (%) -median [IQR]-	93·5 [92·0;95·0]	94·0 [92·0;95·0]	94·0 [92·0;95·0]	93·0 [92·0;94·0]	93·0 [92·0;95·0]	0·137
TSat90 (%) -median [IQR]-	3·00 [1·00;16·8]	3·00 [0·00;18·5]	2·50 [1·00;15·5]	2·00 [0·00;13·0]	3·50 [1·00;13·8]	0·754
Arousals Index (events/h) -median [IQR]-	31·5 [19·0;49·8]	32·0 [21·0;45·0]	41·5 [25·0;54·0]	26·0 [18·5;49·0]	29·5 [19·0;48·0]	0·374
ESS (0-24) -median [IQR]-	10·0 [8·00;13·0]	9·50 [6·50;13·0]	10·0 [7·50;13·0]	10·0 [8·00;12·0]	10·0 [8·00;12·0]	0·699
CPAP compliance (h/night) -median [IQR]-	4·08 [4·02;5·09]	4·08 [3·07;5·07]	4·40 [4·02;6·05]	4·07 [4·03;5·02]	4·17 [4·02;6·00]	0·289
Blood pressure (mmHg) -mean(SD)-						
Office SBP	150 (9·66)	151 (10·3)	150 (8·55)	150 (10·2)	150 (9·38)	0·821
Office DBP	93·4 (6·60)	93·1 (7·97)	93·8 (7·83)	94·2 (5·15)	92·8 (5·82)	0·527
Mean 24-h ambulatory BP	98·2 (8·12)	95·9 (9·56)	98·5 (8·94)	99·6 (7·37)	98·5 (6·77)	0·060
Mean daytime ambulatory BP	101 (8·41)	101 (9·96)	104 (9·53)	101 (7·28)	100 (6·99)	0·037
Mean nighttime ambulatory BP	91·8 (9·87)	85·2 (9·66)	86·8 (8·83)	96·9 (8·96)	95·3 (7·02)	<0·001

Statistically significant p values (p values less than 0·05) are shown in bold. Abbreviations: BMI = Body Mass Index; AHI =Apnoea-Hypoapnoea Index; TSat90 = nighttime with oxygen saturation less than 90%; CPAP = Continuous Positive Airway Pressure; ESS= Epworth Sleepiness Scale; REM= Rapid Eye Movement; SBP= Systolic Blood Pressure; DBP= Diastolic Blood Pressure; BP= Blood Pressure

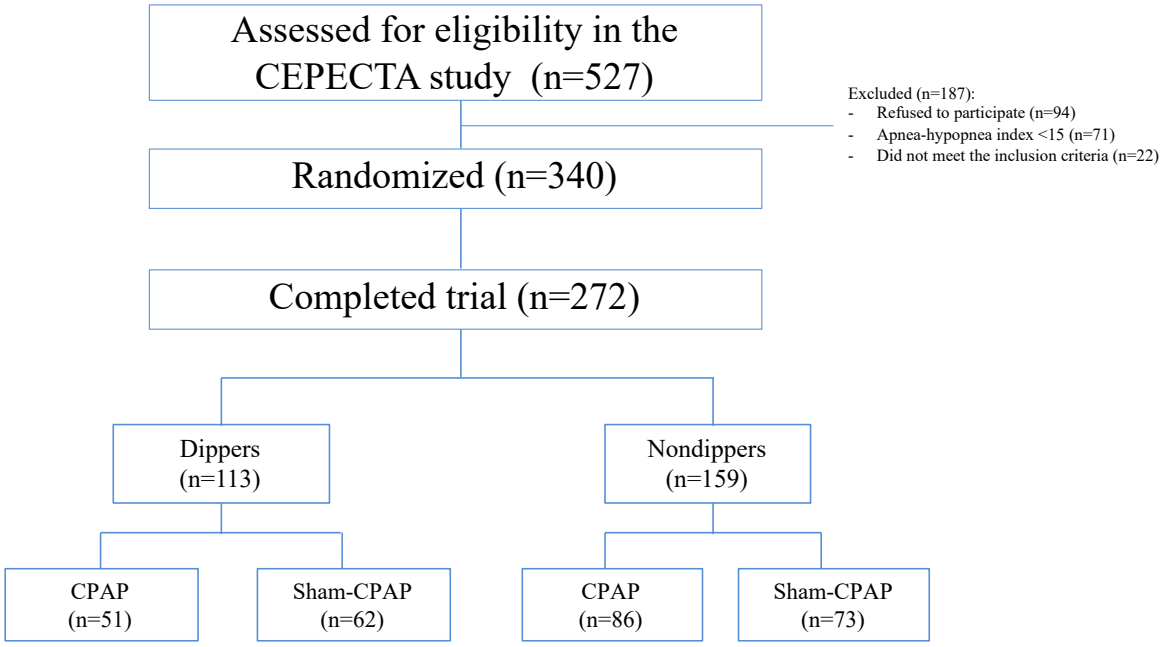
Table 2. Changes in blood pressure by circadian pattern groups adjusted by confounding factors

	Dipper (Sham=62/CPAP=51)		Nondipper (Sham=73/CPAP=86)		Difference	
Blood Pressure	*CPAP effect mean (95% CI)*	*p value*	*CPAP effect mean (95% CI)*	*p value*	*CPAP effect mean (95% CI)*	*p value*
24h- ABPM (mmHg)						
Mean	0·11 (-2·13 to 2·34)	0·9997	-2·88 (-4·74 to -1·02)	**0·0139**	-2·99 (-5·92 to -0·06)	**0·0458**
Systolic	-0·11 (-3·22 to 2·99)	0·9999	-3·63 (-6·21 to -1·04)	**0·032**	-3·52 (-7·58 to 0·55)	0·0898
Diastolic	0·16 (-1·92 to 2·25)	0·9987	-2·49 (-4·23 to -0·76)	**0·0267**	-2·66 (-5·4 to 0·08)	0·0573
Daytime- ABPM (mmHg)						
Mean	-0·21 (-2·65 to 2·23)	0·9982	-2·16 (-4·18 to -0·14)	0·1574	-1·95 (-5·14 to 1·25)	0·2308
Systolic	-0·3 (-3·55 to 2·95)	0·9979	-2·45 (-5·15 to 0·25)	0·2846	-2·15 (-6·4 to 2·1)	0·3195
Diastolic	-0·24 (-2·56 to 2·09)	0·9971	-2·01 (-3·93 to -0·08)	0·1762	-1·77 (-4·81 to 1·28)	0·2538
Nighttime- ABPM (mmHg)						
Mean	0·95 (-1·84 to 3·73)	0·9097	-4·4 (-6·73 to -2·08)	**0·0014**	-5·35 (-9·01 to -1·69)	**0·0043**
Systolic	0·48 (-3·5 to 4·45)	0·9955	-5·97 (-9·29 to -2·65)	**0·0028**	-6·45 (-11·66 to -1·23)	**0·0155**
Diastolic	1·21 (-1·33 to 3·74)	0·788	-3·66 (-5·78 to -1·54)	**0·0046**	-4·87 (-8·2 to -1·53)	**0·0044**

Estimated CPAP effects using a linear model adjusted for baseline measurements, age, sex, BMI, and AHI. The model includes treatment, circadian pattern and their interaction. Statistically significant p values (p values less than 0·05) are shown in bold.
Abbreviations: CPAP = Continuous Positive Airway Pressure; ABPM= Ambulatory Blood Pressure Monitoring.

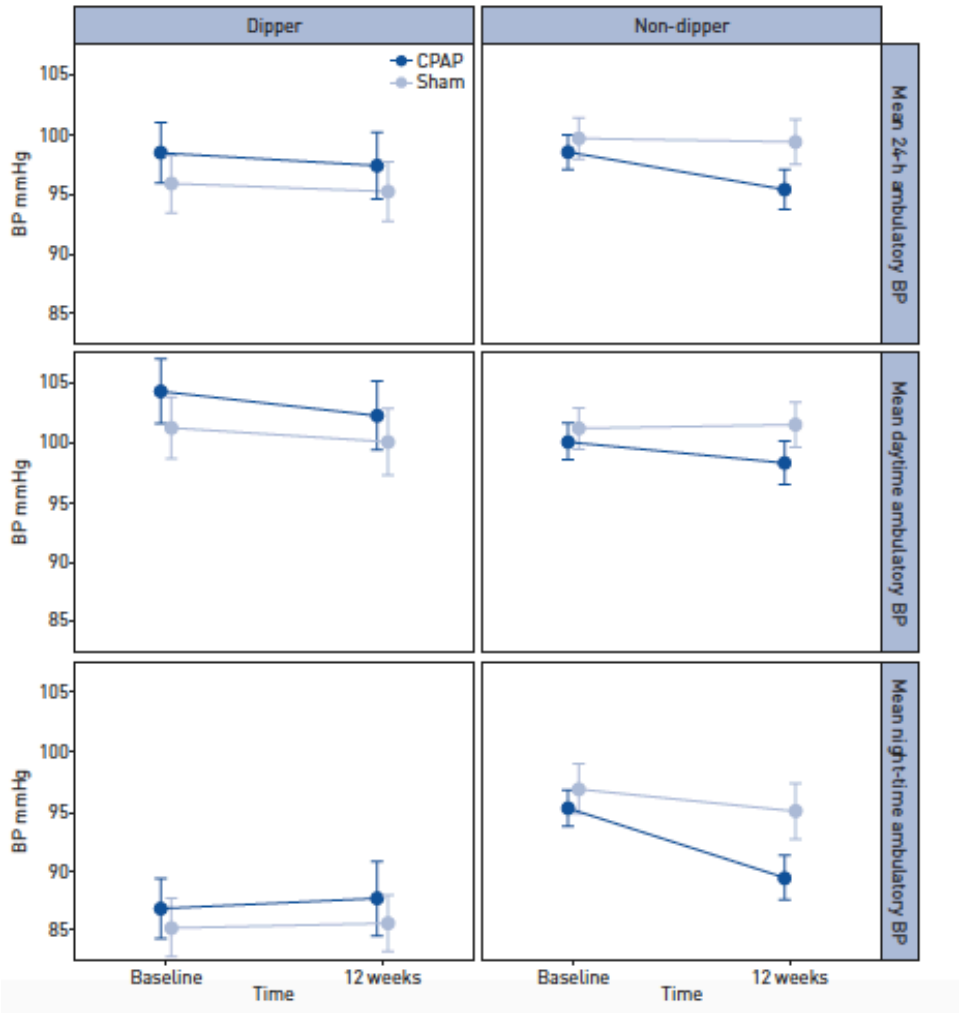
FIGURE LEGENDS

Figure 1. Flow diagram of the study



Abbreviations: CPAP=Continuous Positive Airway Pressure

Figure 2. Changes in BP parameters at twelve weeks according to the circadian pattern



The figure shows the means (95% CIs) of the observed values for 24-h ambulatory BP, daytime BP and nighttime BP at baseline and after 12 weeks of treatment according to the circadian pattern. In the nondipper group, the figure shows a greater reduction in BP in patients with CPAP compared with those receiving sham-CPAP treatment. In the dipper group, no differential effect was observed.

MATERIAL SUPLEMENTARIO: DIFFERENTIAL BLOOD PRESSURE RESPONSE TO CONTINUOUS POSITIVE AIRWAY PRESSURE TREATMENT ACCORDING TO THE CIRCADIAN PATTERN IN HYPERTENSIVE PATIENTS WITH OBSTRUCTIVE SLEEP APNOEA.

Table S1. Changes in blood pressure at twelve weeks according to the circadian pattern.

	Dipper		Nondipper	
	Sham	CPAP	Sham	CPAP
	N=62	N=51	N=73	N=86
24h- ABPM				
Mean (mmHg)				
Baseline	95·9 (93·47 to 98·33)	98·51 (95·99 to 101·02)	99·62 (97·9 to 101·34)	98·5 (97·05 to 99·95)
3 months	95·24 (92·74 to 97·75)	97·41 (94·62 to 100·2)	99·36 (97·47 to 101·24)	95·38 (93·73 to 97·02)
Change	-0·66 (-2·13 to 0·81)	-1·1 (-2·78 to 0·57)	-0·26 (-1·61 to 1·08)	**-3·12 (-4·53 to -1·71)**
Systolic (mmHg)				
Baseline	127·65 (124·42 to 130·88)	130·67 (127·03 to 134·31)	130·83 (128·68 to 132·97)	130·84 (128·98 to 132·71)
3 months	126·51 (123·24 to 129·78)	128·9 (125·12 to 132·68)	130·48 (127·77 to 133·19)	126·6 (124·34 to 128·86)
Change	-1·14 (-3·01 to 0·73)	-1·77 (-4·23 to 0·69)	-0·35 (-2·08 to 1·38)	**-4·24 (-6·31 to -2·17)**
Diastolic (mmHg)				
Baseline	80·03 (77·78 to 82·27)	82·42 (80·21 to 84·64)	84·02 (82·25 to 85·79)	82·33 (80·77 to 83·88)
3 months	79·61 (77·08 to 82·13)	81·66 (79·08 to 84·24)	83·79 (82·1 to 85·49)	79·76 (78·08 to 81·45)
Change	-0·42 (-2·01 to 1·17)	-0·76 (-2·26 to 0·73)	-0·22 (-1·46 to 1·01)	**-2·56 (-3·77 to -1·35)**
Daytime- ABPM				
Mean (mmHg)				
Baseline	101·24 (98·71 to 103·77)	104·34 (101·66 to 107·02)	100·99 (99·29 to 102·69)	100·11 (98·61 to 101·61)
3 months	100·06 (97·28 to 102·84)	102·27 (99·42 to 105·13)	101·54 (99·71 to 103·37)	98·34 (96·54 to 100·15)
Change	-1·18 (-2·94 to 0·58)	**-2·07 (-3·89 to -0·25)**	0·55 (-0·8 to 1·89)	**-1·76 (-3·32 to -0·21)**
Systolic (mmHg)				
Baseline	133·76 (130·43 to 137·08)	137·57 (133·72 to 141·42)	132·4 (130·47 to 134·33)	132·49 (130·64 to 134·33)
3 months	131·98 (128·35 to 135·62)	134·75 (130·9 to 138·59)	132·7 (130·25 to 135·14)	129·9 (127·59 to 132·21)
Change	-1·77 (-3·95 to 0·4)	**-2·82 (-5·43 to -0·22)**	0·3 (-1·42 to 2·02)	**-2·59 (-4·73 to -0·46)**
Diastolic (mmHg)				
Baseline	84·98 (82·6 to 87·37)	87·73 (85·34 to 90·11)	85·29 (83·48 to 87·1)	83·92 (82·3 to 85·54)
3 months	84·1 (81·33 to 86·87)	86·04 (83·39 to 88·69)	85·96 (84·24 to 87·68)	82·57 (80·69 to 84·45)
Change	-0·89 (-2·75 to 0·97)	**-1·69 (-3·32 to -0·05)**	0·67 (-0·59 to 1·93)	-1·35 (-2·74 to 0·05)
Nighttime- ABPM				
Mean (mmHg)				
Baseline	85·22 (82·77 to 87·67)	86·84 (84·36 to 89·33)	96·88 (94·79 to 98·97)	95·28 (93·77 to 96·78)
3 months	85·61 (83·27 to 87·95)	87·67 (84·53 to 90·81)	94·99 (92·66 to 97·32)	89·44 (87·59 to 91·28)
Change	0·39 (-1·1 to 1·87)	0·83 (-1·41 to 3·07)	**-1·89 (-3·73 to -0·05)**	**-5·84 (-7·63 to -4·06)**
Systolic (mmHg)				
Baseline	115·44 (112·16 to 118·71)	116·88 (113·29 to 120·48)	127·68 (124·78 to 130·59)	127·56 (125·43 to 129·68)
3 months	115·56 (112·57 to 118·56)	117·22 (112·92 to 121·51)	126·04 (122·34 to 129·74)	120·01 (117·38 to 122·64)
Change	0·13 (-1·84 to 2·1)	0·33 (-3·01 to 3·68)	-1·64 (-4·17 to 0·89)	**-7·55 (-10·12 to -4·97)**
Diastolic (mmHg)				
Baseline	70·11 (67·89 to 72·33)	71·82 (69·65 to 74)	81·48 (79·36 to 83·6)	79·14 (77·59 to 80·69)
3 months	70·63 (68·25 to 73)	72·9 (70·06 to 75·74)	79·47 (77·49 to 81·44)	74·15 (72·39 to 75·91)
Change	0·52 (-1·05 to 2·08)	1·08 (-0·86 to 3·02)	**-2·01 (-3·82 to -0·21)**	**-4·99 (-6·52 to -3·46)**

Note: statistically significant p values (p values less than 0·05) are shown in bold. Abbreviations: ABPM=Ambulatory Blood Pressure Monitoring ; CPAP=Continuous Positive Airway Pressure

Table S2. Changes in blood pressure by circadian pattern group.

Blood Pressure	Dipper (Sham=62/CPAP=51)		Nondipper (Sham=73/CPAP=86)		Difference	
	CPAP effect mean (95% CI)	*p value*	*CPAP effect mean (95% CI)*	*p value*	*CPAP effect mean (95% CI)*	*p value*
24h- ABPM (mmHg)						
Mean	0·06 (-2·13 to 2·25)	0·9999	-3·08 (-4·91 to -1·24)	**0·0064**	-3·14 (-6·02 to -0·26)	**0·0328**
Systolic	-0·07 (-3·12 to 2·98)	1	-3·89 (-6·45 to -1·34)	**0·0163**	-3·83 (-7·82 to 0·17)	0·0606
Diastolic	0·07 (-1·97 to 2·11)	0·9999	-2·63 (-4·35 to -0·92)	**0·0152**	-2·71 (-5·4 to -0·02)	**0·0486**
Daytime- ABPM (mmHg)						
Mean	-0·25 (-2·66 to 2·16)	0·9969	-2·49 (-4·51 to -0·48)	0·0754	-2·24 (-5·4 to 0·93)	0·1648
Systolic	-0·28 (-3·49 to 2·93)	0·9982	-2·88 (-5·56 to -0·19)	0·1568	-2·6 (-6·8 to 1·61)	0·2257
Diastolic	-0·3 (-2·58 to 1·99)	0·9942	-2·27 (-4·19 to -0·35)	0·0959	-1·97 (-4·98 to 1·03)	0·1974
Nighttime- ABPM (mmHg)						
Mean	0·87 (-1·84 to 3·58)	0·9229	-4·37 (-6·66 to -2·09)	**0·0012**	-5·24 (-8·81 to -1·67)	**0·0042**
Systolic	0·55 (-3·33 to 4·44)	0·9923	-5·93 (-9·2 to -2·67)	**0·0025**	-6·49 (-11·58 to -1·39)	**0·0128**
Diastolic	1·04 (-1·44 to 3·52)	0·8447	-3·63 (-5·73 to -1·53)	**0·0045**	-4·67 (-7·94 to -1·39)	**0·0054**

Estimated CPAP effects using a linear model adjusted for baseline measurements. The model includes treatment, circadian pattern and their interaction. Statistically significant p values (p values less than 0·05) are shown in bold. Abbreviations: ABPM= Ambulatory Blood Pressure Monitoring; CPAP= Continuous Positive Airway Pressure.

Table S3. CPAP effect on blood pressure according to the circadian pattern in true hypertensive subjects adjusted by confounding factors.

Blood Pressure	Dipper (Sham=33/CPAP=43)		Nondipper (Sham =58/CPAP=62)		Difference	
	CPAP effect mean (95% CI)	*p value*	*CPAP effect mean (95% CI)*	*p value*	*CPAP effect mean (95% CI)*	*p value*
24h- ABPM (mmHg)						
Mean	0·01 (-2·86 to 2·88)	0·9999	-3·27 (-5·4 to -1·14)	**0·016**	-3·28 (-6·88 to 0·33)	0·0745
Systolic	0·78 (-3·17 to 4·72)	0·9804	-4·8 (-7·72 to -1·88)	**0·0083**	-5·58 (-10·54 to -0·62)	**0·0277**
Diastolic	-0·32 (-3·1 to 2·45)	0·9957	-2·52 (-4·58 to -0·46)	0·0821	-2·19 (-5·68 to 1·29)	0·2162
Daytime- ABPM (mmHg)						
Mean	-0·98 (-4·13 to 2·17)	0·9294	-2·7 (-5·04 to -0·36)	0·1115	-1·72 (-5·68 to 2·24)	0·3924
Systolic	-0·32 (-4·45 to 3·8)	0·9987	-3·72 (-6·79 to -0·66)	0·0841	-3·4 (-8·59 to 1·79)	0·1977
Diastolic	-1·3 (-4·4 to 1·8)	0·8445	-2·19 (-4·49 to 0·11)	0·2459	-0·89 (-4·79 to 3)	0·6516
Nighttime - ABPM (mmHg)						
Mean	1·8 (-1·7 to 5·31)	0·7441	-4·55 (-7·15 to -1·95)	**0·0042**	-6·35 (-10·74 to -1·97)	**0·0048**
Systolic	2·61 (-2·57 to 7·79)	0·7572	-6·92 (-10·75 to -3·09)	**0·0028**	-9·53 (-16·02 to -3·04)	**0·0042**
Diastolic	1·44 (-1·78 to 4·66)	0·8164	-3·51 (-5·91 to -1·1)	**0·0242**	-4·95 (-8·99 to -0·91)	**0·0167**

Estimated CPAP effects using a linear model adjusted for baseline measurements, age, sex, BMI, and AHI. The model includes treatment, circadian pattern and their interaction. Statistically significant p values (p values less than 0.05) are shown in bold. Abbreviations: ABPM= Ambulatory Blood Pressure Monitoring; CPAP= Continuous Positive Airway Pressure

DISCUSIÓN

Los estudios que componen esta tesis doctoral han contribuido a ampliar el conocimiento de la relación entre el SAHS y la PA, así como en el efecto del tratamiento con CPAP en diferentes fenotipos de PA.

De este modo, dos de los estudios que la forman se han centrado en el efecto del SAHS en sujetos con HR. En el primero se presenta al diseño de un estudio para evaluar el impacto del SAHS y su tratamiento sobre el pronóstico cardiovascular en estos pacientes. En el segundo, se evalúa la prevalencia de SAHS en población con HR y su impacto en el control de la PA.

Por otro lado, se ha evaluado el efecto del tratamiento con CPAP en diferentes grupos en función de su tensión arterial. Dada la escasa información existente sobre los efectos del tratamiento del SAHS en sujetos normotensos, se decidió evaluar los efectos del tratamiento con CPAP en esta población. Por último, por la evidencia de gran variabilidad en la respuesta tensional, y de continuidad con los resultados obtenidos en este artículo, se evaluaron los efectos del tratamiento con CPAP sobre la PA en sujetos con HTA no tratada teniendo en cuenta el patrón circadiano.

La discusión de los resultados se ha estructurado en los dos aspectos clave en los que se centra la presente tesis doctoral**.**

Evaluación de la prevalencia de SAHS y su impacto sobre el control de la presión arterial en la hipertensión resistente.

En uno de los estudios que forma parte esta tesis doctoral, se evaluó la prevalencia de SAHS y su impacto en el control de la PA en población con diagnóstico de HR. Para ello, se llevó a cabo un estudio observacional con 284 sujetos con HR, anidado al proyecto SARAH, del cuál su metodología ha sido publicada y forma parte también de la presente tesis doctoral [91].

De acuerdo con la literatura existente, los resultados confirman una estrecha relación entre el SAHS y la HR. La prevalencia total de SAHS (IAH ≥ 5/H) observada

en nuestro estudio fue del 83.5%. En cuánto a la gravedad del SAHS, el 31.7 % de los sujetos presentaba SAHS leve, el 25.7% SAHS moderado y el 26.1% SAHS grave. A pesar de que la prevalencia reportada en nuestro estudio es elevada, los datos encontrados podrían estar infra-estimados debido a que no se incluían pacientes que ya habían iniciado tratamiento con CPAP. Teniendo en cuenta los pacientes que no se incluyeron por este motivo, la prevalencia de SAHS en esta población alcanzaría aproximadamente el 96%.

Los estudios publicados previamente ya mostraban una elevada prevalencia de SAHS en sujetos con HR, no obstante, existe una disparidad en los resultados y resulta difícil la comparación entre estudios debido, al uso de diferentes pruebas del sueño y puntos de corte de IAH para definir SAHS, así como la falta de uniformidad o no se especifican los criterios utilizados para definir hipopnea.

Los resultados de estudios como los de Logan et al [66] y Florczak et al [68] mostraron una prevalencia de SAHS del 83% y 72.1%, respectivamente. Sin embargo, en estos estudios los autores no indicaron los criterios que utilizaron para definir hipopnea, hecho que dificulta su comparación. Nuestros resultados son consistentes con otro estudio publicado previamente, en el que utilizaron los mismos criterios de desaturación [69], y en el que informaron de una prevalencia de SAHS del 82.2%. Además, los sujetos tenían características similares a los incluidos en nuestro estudio, aunque, en este estudio se llevó a cabo PSG a todos los participantes [69].

Por el contrario, en otro estudio [61] reportaron una prevalencia del 64%, a pesar de utilizar cómo prueba diagnóstica PSG y el 3% cómo índice de desaturación para definir hipopnea. Este resultado tan bajo respecto a nuestro estudio podría explicarse por dos motivos; los autores utilizaron un valor de corte más conservador para diagnosticar SAHS (IAH> 15/h), y los sujetos incluidos eran más jóvenes.

La prevalencia de SAHS observada en nuestro trabajo fue superior en hombres que, en mujeres, siendo el doble de prevalente en hombres en SAHS grave. Este

predominio del sexo masculino ha sido descrito con anterioridad en población general [6], y en población con HR [66,67].

De acuerdo con otros trabajos [61], tanto la presencia cómo la gravedad de SAHS aumentó a medida que aumentaba el IMC. Entre todas las comorbilidades recogidas, se observó que la más frecuente era la DM, la cuál ha sido relacionada con la resistencia al tratamiento antihipertensivo [49,92]

Además, en nuestro estudio, se encontró una asociación dosis-respuesta entre la gravedad del SAHS y los valores de PA. La gravedad se relacionó con valores elevados de PA en algunas de las variables de la MAPA, siendo también significativamente mayor la prevalencia de hipertensión nocturna en sujetos con SAHS grave. Cabe destacar estos hallazgos que relacionan el SAHS con valores de PA nocturna elevados, ya que previamente ha sido demostrado que la PA nocturna es mejor predictor de riesgo que la PA diurna. La PA nocturna elevada se relaciona con un aumento del riesgo y peor pronóstico cardiovascular, estimándose tanto en población con HTA cómo en población normotensa, que una reducción del 5% de la PA nocturna está asociada con un 20% más de riesgo de mortalidad cardiovascular [42].

Es conocida la importancia que tiene el patrón circadiano de PA cómo factor pronóstico, y tal y cómo se ha mencionado en la introducción, es el patrón non-dipper el que se ha asociado con peores resultados cardiovasculares [42,93]. Nuestros resultados están en línea con los publicados por Muxfeldt el al [69], quienes encontraron valores de PA nocturnos más elevados y mayor prevalencia de patrón circadiano non-dipper en sujetos con SAHS grave que en aquellos con SAHS leve o sin SAHS, aunque en este último aspecto en nuestro estudio no se alcanzó significación estadística.

Por lo tanto, tal y cómo se ha descrito anteriormente [69], nuestros resultados muestran que más allá de la edad, el sexo y las características antropométricas, las variables de la MAPA (especialmente las mediciones nocturnas) podrían estar asociadas con la gravedad del SAHS.

Estos resultados sugieren que en pacientes con HR, es importante identificar las causas secundarias, cómo el SAHS, puesto que su tratamiento puede ser efectivo para mejorar el control de la PA, especialmente durante la noche, en estos pacientes en los que resulta difícil lograr un adecuado control de la tensión arterial. Además, estos resultados pueden ayudar a establecer nuevas estrategias de tratamiento más allá del farmacológico y de técnicas agresivas y costosas, cómo la denervación renal. No obstante, es necesario llevar a cabo más estudios para abordar el impacto del tratamiento del SAHS sobre la PA y también, los eventos cardiovasculares a largo plazo en estos pacientes, en los que, el uso de un mayor número de medicamentos antihipertensivos, no disminuye el riesgo de eventos cardiovasculares sino todo lo contrario [51]. En este sentido, serán importantes los resultados que se obtengan en el estudio SARAH [91].

Efecto del tratamiento con CPAP sobre la presión arterial en diferentes poblaciones.

En el tercer estudio de esta tesis doctoral, se decidió evaluar el efecto del tratamiento con CPAP en 131 pacientes normotensos. Tras 6 meses de tratamiento con CPAP e independientemente de la adherencia al tratamiento, los resultados de este estudio muestran que, en estos pacientes, el tratamiento con CPAP produce una reducción significativa en la PA media de 24h, PAD media de 24h y la PAD media diurna. En el resto de variables de la MAPA, se observó una reducción leve. Esta reducción de la PA fue principalmente el efecto de la CPAP en el subgrupo de pacientes con hipertensión enmascarada, observándose de hecho que tras 6 meses de tratamiento el 50% de los pacientes con hipertensión enmascarada se convirtieron en normotensos.

En este mismo estudio, se evaluó también el efecto de la CPAP teniendo en cuenta el patrón circadiano de PA. Los resultados mostraron que, en pacientes con patrón circadiano non-dipper, el tratamiento con CPAP se asoció con una reducción

en la PA media de 24 h y la PA nocturna. Por el contrario, en pacientes con patrón circadiano dipper, el tratamiento con CPAP se asoció con un aumento de la PA nocturna y del DR.

Son escasos los estudios que evalúan el efecto de la CPAP sobre la PA, únicamente en pacientes normotensos, no obstante, hay varios estudios que han estudiado dicho efecto incluyendo sujetos hipertensos y normotensos [94–98]. Esta heterogeneidad de los individuos, es decir, mezclar poblaciones de pacientes normotensos e hipertensos, podría haber influenciado los resultados de los estudios publicados.

Los datos que se disponen sobre el efecto de la CPAP en sujetos normotensos provienen de dos estudios comentados anteriormente en la introducción. Faccenda et al. [89] encontraron un efecto leve de la CPAP sobre la PA en sujetos normotensos, limitándose únicamente a una reducción de 1.5 mmHg en la PAD. Yorgun et al. [90] investigaron predictores de cambio de PA en pacientes normotensos en tratamiento con CPAP. Tras 12 semanas, observaron que la CPAP producía una reducción de la PA diurna, nocturna y una mejora en el patrón circadiano de PA. Al inicio del estudio, el 50% de los sujetos incluidos tenían un patrón circadiano non-dipper, mientras que 12.5% al final del estudio [90]. No obstante, los resultados de este estudio son limitados debido al tamaño de la muestra y al corto seguimiento de los pacientes.

Además, otro estudio aleatorizado [99] con pacientes normotensos, diseñado para evaluar la sensibilidad a la insulina, concluyó que el tratamiento con CPAP producía una disminución de la PAS y PAD en sujetos normotensos, definidos por PA en consulta. Nuestros resultados son consistentes con los de este estudio; sin embargo, los autores no determinaron la presencia de hipertensión enmascarada, aspecto que podría haber influenciado los resultados.

Por lo que sabemos, sólo un estudio [100] ha investigado específicamente el efecto de la CPAP en pacientes con SAHS y pre-hipertensión o hipertensión enmascarada y este efecto sólo fue evaluado en hombres. En este estudio aleatorizado,

los autores concluyeron que el uso de la CPAP producía una reducción significativa de la PAS observada en las mediciones en consulta, y de la PA nocturna y diurna de la MAPA. Aunque, la falta de un análisis separado con los sujetos con hipertensión enmascarada no permitió a los autores explicar la influencia de este fenotipo de PA en los resultados observados.

Nuestro estudio demuestra por primera vez que la reducción de la PA media de 24h reportada tras el uso de CPAP en pacientes normotensos se debe principalmente a las diferentes respuestas de la PA en individuos con hipertensión enmascarada, y que tras 6 meses de tratamiento con CPAP.

Tal y cómo observamos en nuestro estudio, se estima que el fenotipo de hipertensión enmascarada, está presente en al menos un tercio de los pacientes con SAHS, y que son considerados normotensos teniendo en cuenta la PA en consulta [101]. Asimismo, este fenotipo se ha asociado con riesgo cardiovascular [102]. En este sentido, nuestros resultados sugieren que en los pacientes con SAHS grave que se consideran normotensos por las mediciones en consulta, se debe realizar la MAPA para evaluar la presencia de hipertensión enmascarada.

Por otro lado, lo resultados sugieren que los sujetos normotensos en tratamiento con CPAP y con patrón circadiano de PA, dipper, podrían experimentar aumentos en la PA nocturna, mientras que en los sujetos non-dipper se observan reducciones de PA. Estos resultados adquieren especial relevancia, ya que, cómo se ha comentado anteriormente, el patrón circadiano es una variable que posee un valor predictivo cardiovascular [42,93].

En cuánto a la explicación de porque los pacientes normotensos dipper tienden a sufrir un aumento de la PA nocturna con la CPAP puede deberse a que estos pacientes desarrollan respuestas adaptativas a los cambios fisiopatológicos desencadenados por la apnea, y estos mecanismos pueden verse afectados por el tratamiento con CPAP. Antes del tratamiento con CPAP, estos individuos pueden haber exhibido un equilibrio entre la actividad simpática, la cuál ejerce un efecto

presor, y la producción de péptidos natriuréticos que disminuyen la PA. Cuando se inicia el tratamiento con CPAP, desaparece la hipoxia intermitente y la presión intratorácica, por consiguiente, el nivel de péptidos natriuréticos disminuye incluso en pacientes normotensos [103,104].No obstante, además de esta hipótesis, se debe tener en cuenta la influencia de la regresión a la media por lo que se debería considerar repetir la MAPA. Por lo tanto, este estudio indica que en pacientes normotensos en consulta seria necesario realizar un MAPA para identificar aquellos que si, se podrían beneficiar del tratamiento con CPAP, de aquellos en los que el tratamiento podría no tener efecto o ser incluso perjudicial (dippers).

Con la hipótesis que establece que el patrón circadiano basal podría influir en la respuesta de la PA al tratamiento con CPAP y en continuidad con el trabajo anterior, se evaluó el efecto de la CPAP en pacientes con HTA no tratada, según su patrón circadiano, con la finalidad de identificar a los pacientes que podrían beneficiarse más del tratamiento con CPAP en términos de reducción de la PA.

Los resultados de este estudio sugieren que la respuesta de la PA al tratamiento con CPAP en sujetos hipertensos depende del patrón circadiano, observándose una reducción significativa en la PA media de 24h, PAS de 24h, PA diastólica de 24h y en las variables de la PA nocturna en los pacientes non-dippers, mientras que en los pacientes dippers no se observaron cambios de PA significativos tras 12 semanas de tratamiento con CPAP.

El efecto del tratamiento con CPAP sobre la PA en pacientes hipertensos, ha sido evaluado en diversos estudios, describiéndose un efecto leve del tratamiento con CPAP sobre la PA en pacientes con SAHS, [76,84,88,105,106], con mayores reducciones de PA en sujetos con HR [78,81,82,87]. No obstante, se ha observado en diferentes estudios que la respuesta de la PA al tratamiento con CPAP es muy variable. Algunos autores, han señalado factores que podrían estar relacionados con una mejor respuesta de la PA, tales como: valores de PA más altos, adherencia a la CPAP o la

gravedad del SAHS [73,75,78,107]; sin embargo, las causas de esta variabilidad todavía no han sido bien establecidas.

Esta variabilidad considerable en la respuesta de la PA al tratamiento con CPAP destaca la importancia de diferenciar aquellos pacientes que responderán de forma favorable al tratamiento con CPAP de aquellos que no. En este sentido, en los últimos años, se han llevado a cabo diversos estudios con la intención de identificar perfiles clínicos y moleculares que puedan predecir la respuesta de la PA al tratamiento con CPAP [108,109]. En nuestro trabajo anterior [110], se identificó el patrón circadiano de PA, cómo factor que puede influir en la respuesta de la PA al tratamiento con CPAP.

Aunque diversos autores también sugirieron que ciertas características clínicas pueden predecir la respuesta de la PA al tratamiento con CPAP, no hay estudios aleatorizados que hayan confirmado estos hallazgos, lo cuál resultaría muy útil en la práctica clínica.

En nuestro estudio, se observó una disminución en la PA media de 24 h de -2,99 mmHg. En cuánto a la PA nocturna, la disminución fue -5.35 mmHg en la PA media nocturna, -6.45 mmHg en la PAS media y –4.87 mmHg en la PAD media. En estudios previos llevado a cabo en pacientes con HTA y pacientes con HR, la disminución de la PA media de 24 h fue aproximadamente de -1,5 mmHg [74] y -3 mmHg, respectivamente [81,82].

Nuestros resultados muestran que la reducción de la PA es mayor en los sujetos con patrón circadiano non-dipper que en los sujetos dippers, y, por lo tanto, los pacientes non-dippers se beneficiarían más del tratamiento con CPAP en términos de reducción de la PA. El hecho de que estas reducciones de la PA se observen en sujetos non-dippers es de especial relevancia, debido a la relación de este patrón con un mayor riesgo cardiovascular [42,93].

No obstante, los sujetos incluidos en el presente estudio eran pacientes hipertensos no tratados; por lo tanto, los resultados pueden ser diferentes para los pacientes hipertensos que toman medicamentos antihipertensivos, ya que varios

factores pueden influir en el efecto del tratamiento con CPAP sobre la PA. Por lo tanto, los resultados deben interpretarse con cautela considerando otros perfiles clínicos.

Nuestro estudio indica que el patrón circadiano de PA al inicio del estudio puede determinar diferencias en la respuesta de la PA al tratamiento con CPAP. Por lo tanto, la recomendación se basa en el hecho de que realizar la MAPA en sujetos hipertensos previamente al inicio del tratamiento con CPAP e identificar el patrón circadiano de PA puede ayudar a identificar subgrupos de pacientes con SAHS en los que se espera una mayor reducción de la PA.

Además, nuestros resultados destacan la utilidad de las características individuales, como el patrón circadiano de la PA, como factores a considerar en el manejo de estos pacientes, factor que permitirá indicar de forma más individualizada el tratamiento con CPAP.

CONCLUSIONES

Las conclusiones más relevantes de los estudios presentados y que componen la presente tesis doctoral son:

1. En pacientes con HR se observa una elevada prevalencia de SAHS, además de, una asociación dosis-respuesta entre la gravedad del SAHS y la PA.

2. En pacientes definidos como normotensos, el tratamiento del SAHS con CPAP produce una disminución de la PA, principalmente en aquellos sujetos con hipertensión enmascarada no diagnosticada.

3. En pacientes normotensos, el tratamiento con CPAP produce una disminución de la PA nocturna en aquellos sujetos con un patrón circadiano de PA non-dipper. Sin embargo, en los pacientes con patrón circadiano dipper, se observa un aumento de la PA nocturna.

4. En pacientes con SAHS moderado/grave e HTA sin tratamiento farmacológico, sólo aquellos con un patrón circadiano de PA non-dipper experimentan beneficios significativos en la PA, especialmente en la PA nocturna.

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APÉNDICE

Durante el desarrollo de la presente tesis doctoral, la doctoranda ha participado en otros proyectos de investigación, de los cuales han derivado las siguientes publicaciones científicas:

1. Posadas T, Campos-Rodriguez F, Sapiña-Beltrán E, Oscullo G, Torres G, Martinez-Garcia MA. Obstructive Sleep Apnea and Arterial Hypertension: Implications of Treatment Adherence. Curr Hypertens Rep. 2020;22(2):12. Review.

2. Benítez I, Roure N, Pinilla L, Sapiña-Beltran E, Buysse DJ, Barbé F, de Batlle J. Validation of the Satisfaction, Alertness, Timing, Efficiency and Duration (SATED) Questionnaire for Sleep Health Measurement. Ann Am Thorac Soc. 2020;17(3):338-343.

3. Oscullo G, Torres G, Campos-Rodriguez F, Posadas T, Reina-González A, Sapiña-Beltrán E, Barbé F, Martinez-Garcia MA. Resistant/Refractory Hypertension and Sleep Apnoea: Current Knowledge and Future Challenges. J Clin Med. 2019;8(11). Review

4. Oscullo G, Sapiña-Beltrán E, Torres G, Zaldivar E, Barbé F, Martinez-Garcia MA. The Potential Role of Obstructive Sleep Apnoea in Refractory Hypertension. Curr Hypertens Rep. 2019;21(8):57. Review.

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