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Special article

Rationale and Methodology of the SARAH Trial: Long-Term Cardiovascular Outcomes in Patients With Resistant Hypertension and Obstructive Sleep Apnea

Esther Sapiña-Beltrán^a, Gerard Torres^a, Montserrat Martínez-Alonso^b, Manuel Sánchez-de-la-Torre^{a,c}, Maria Franch^d, Carmen Bravo^d, Juan F. Masa^{c,e}, Miquel Felez^f, Ana Maria Fortuna-Gutierrez^g, Jorge Abad^{c,h}, Francisco García-Río^{c,i}, Luciano F. Drager^j, Ronald Lee Chi-Hang^k, Miguel Ángel Martínez-García^{l,c}, Ferran Barbé^{a,c}, Mireia Dalmases^{a,c,*}

^a Hospital Universitari Arnau de Vilanova and Santa Maria, Group of Translational Research in Respiratory Medicine, IRBLleida, Lleida, Cataluña, Spain

^b University of Lleida, IRBLleida, Biostatistics Unit, Lleida, Cataluña, Spain

^c Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain

^d Hospital Santa Maria, Internal medicine department, Lleida, Cataluña, Spain

^e Hospital San Pedro de Alcantara, Respiratory Dept, Cáceres, Extremadura, Spain

^f Hospital del Mar, Unit of Sleep Breathing Disorders, Respiratory Dept, Barcelona, Cataluña, Spain

^g Hospital de la Santa Creu i Sant Pau, Respiratory Dept, Barcelona, Cataluña, Spain

^h Hospital Universitari Germans Trias i Pujol, Respiratory Dept, Badalona, Cataluña, Spain

ⁱ Hospital Universitario La Paz-IdiPAZ, Respiratory Dept, Madrid, Spain

^j University of São Paulo Medical School, Heart Institute(InCor), Sao Paulo, Brazil

^k National University Heart Centre Singapore, Department of Cardiology, Singapore

^l Hospital Universitario y Politécnico La Fe, Respiratory Department, Valencia, Spain

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ABSTRACT

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 1371 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.

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* Corresponding author.

E-mail address: mdalmases.lleida.ics@gencat.cat (M. Dalmases).

Justificación y metodología del ensayo clínico SARAH: evolución cardiovascular a largo plazo en pacientes con hipertensión resistente y apnea obstructiva del sueño

R E S U M E N

Palabras clave:
Monitorización ambulatoria de la presión arterial
Presión positiva continua de las vías respiratorias
Hipertensión resistente
Apnea del sueño

Introducción: Los pacientes con hipertensión resistente (HR) tienen un elevado riesgo de desarrollar eventos cardiovasculares; así, las nuevas estrategias terapéuticas para el control de la presión arterial podrían ser útiles para mejorar los resultados cardiovasculares. La prevalencia de la apnea obstructiva del sueño (AOS) es muy elevada entre los pacientes con HR. Se ha demostrado que la presión positiva continua en la vía aérea (CPAP) constituye un tratamiento efectivo para reducir la presión arterial en pacientes con HR. Sin embargo, todavía no se han estudiado los efectos a largo plazo del tratamiento con CPAP sobre los resultados cardiovasculares. El principal objetivo del estudio SARAH es evaluar el impacto de la AOS y su tratamiento en los resultados cardiovasculares (morbilidad y mortalidad) en pacientes con HR.

Métodos: Este es un estudio observacional prospectivo multicéntrico en el que se incluirán 1.371 pacientes con HR, a los cuales se les realizará seguimiento una vez al año durante 5 años. En el momento de la inclusión se realizará a todos los pacientes monitorización ambulatoria de la presión arterial (MAPA), así como un estudio de sueño. Se recogerán las variables sociodemográficas, clínicas y cardiovasculares tanto al inicio del estudio como durante el seguimiento. Posteriormente, los individuos con AOS serán tratados de acuerdo con la práctica clínica estándar de cada centro. Se definirán 3 grupos en función del diagnóstico de AOS y su tratamiento: sin AOS, con AOS en tratamiento, con AOS sin tratar.

Conclusiones: Este estudio contribuirá a averiguar el impacto a largo plazo del tratamiento de la AOS en el control de la presión arterial y los resultados cardiovasculares en pacientes con HR. Asimismo, estos resultados contribuirán a mejorar el pronóstico cardiovascular de los pacientes con HR.

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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.

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