JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 9, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.06.1315

Precision Medicine in Patients With Resistant Hypertension and Obstructive Sleep Apnea

Blood Pressure Response to Continuous Positive Airway Pressure Treatment

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ABSTRACT

BACKGROUND In patients with resistant hypertension (RH) and obstructive sleep apnea (OSA), the blood pressure response to continuous positive airway pressure (CPAP) treatment is highly variable and could be associated with differential micro-ribonucleic acid (miRNA) profiles. Currently, no available methods exist to identify patients who will respond favorably to CPAP treatment.

OBJECTIVES The aim of this study was to identify plasma miRNA profiles that predict blood pressure responses to CPAP treatment.

METHODS Cardiovascular system–focused circulating miRNA expression was evaluated in plasma samples using an 84-miRNA array among patients with RH and OSA at baseline and after 3 months of adherent CPAP use. Pathway analysis and miRNA target gene enrichment were performed in silico. Plasma levels of peptides and hormones related to cardiovascular function were also measured.

RESULTS The OSA responder group exhibited blood pressure decreases exceeding the observed median (>4.5 mm Hg) after CPAP, which were not present in the nonresponder group (≤4.5 mm Hg) ($p < 0.01$). Three miRNAs provided a discriminatory predictive model for such a favorable blood pressure response to CPAP (area under the curve: 0.92; $p = 0.01$). Additionally, CPAP treatment significantly altered a total of 47 plasma miRNAs and decreased aldosterone-to-renin ratios in the responder group ($p = 0.016$) but not in the nonresponder group.

CONCLUSIONS A singular pre-CPAP treatment cluster of 3 plasma miRNAs predicts blood pressure responses to CPAP treatment in patients with RH and OSA. CPAP treatment is accompanied by changes in cardiovascular system–related miRNAs that may potentially influence the risk for cardiovascular disease among patients with OSA and RH. (Effect of Continuous Positive Airway Pressure [CPAP] Treatment in the Control of Refractory Hypertension; NCT00616265) (J Am Coll Cardiol 2015;66:1023–32) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

BP = blood pressure

CI = confidence interval

CPAP = continuous positive airway pressure

CVD = cardiovascular disease

miRNA = micro-ribonucleic acid

OSA = obstructive sleep apnea

qRT-PCR = quantitative real-time reverse transcription polymerase chain reaction

RH = resistant hypertension

Cardiovascular disease (CVD) is the leading cause of death throughout the world. Among all risk factors associated with CVD development, hypertension is likely the most important; it is also among the most treatable cardiovascular risk factors (1). Between 12% and 27% of all patients with hypertension are considered to have resistant hypertension (RH) (2), defined as blood pressure (BP) higher than therapeutic goals (i.e., average systolic BP ≥130 mm Hg, average diastolic BP ≥80 mm Hg, or both) despite concurrent use of at least 3 antihypertensive agents prescribed at doses that provide optimal benefit, with 1 of these drugs ideally being a diuretic agent (3). Patients with RH are approximately 50% more likely to experience cardiovascular events than patients with hypertension but not RH, and the incidence of RH is anticipated to increase in the coming years (4).

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Obstructive sleep apnea (OSA), a common disorder that affects approximately 10% of the middle-age population (5), is associated with increased CVD and overall mortality risks (6–9). OSA is a common cause of systemic hypertension and should be suspected in patients with hypertension (10–13), particularly those with RH (14,15). Indeed, more than 70% of patients with RH have OSA (16). Although continuous positive airway pressure (CPAP) treatment reduces BP levels in patients with OSA (17–24), its beneficial effects are related to patient adherence as well as to baseline BP levels (25,26). However, BP responses are highly variable, even when adherent use of CPAP is documented, with some patients exhibiting major reductions in BP (>10 mm Hg) and others showing either unchanged or worsening BP levels (16,25,27). In fact, 25% to 30% of patients who use CPAP treatment for >4 h/night do not experience a positive effect on BP (25,26). The underlying causes of patient variability in response to continuous adherent use of CPAP are unknown. More important, no tools are available to date that enable clinicians to identify those patients who will respond favorably to CPAP treatment (i.e., reduced BP levels).

Micro-ribonucleic acids (miRNAs) are a class of small (19- to 25-nucleotide), noncoding RNAs that regulate gene expression at the post-transcriptional level by binding to a target messenger RNA, thereby leading to either degradation or translational repression (28). Evidence suggests that miRNAs control development and are critically involved in many biological processes related to health and disease, including CVD (29–31). Consequently, miRNAs have emerged as major protagonists for managing CVD in an era of evolving precision medicine.

We hypothesized that among patients with RH and OSA, a singular cardiovascular system–focused miRNA biomarker profile might reliably discriminate those patients with favorable BP responses to CPAP. Additionally, we posited that adherence to CPAP treatment might modify the miRNA profiles and plasma levels of peptides and hormones related to cardiovascular function. Some of these study results have been previously reported in abstract form (32,33).

METHODS

Study participants were part of a larger multicenter, randomized, controlled trial (NCT00616265) conducted at 24 Spanish teaching hospitals to evaluate the effect of 3 months of CPAP treatment on the BP levels of patients with RH and OSA; the patient characteristics have been provided in detail elsewhere (26). In this study, we included male patients who used CPAP for at least 4 h/day. CPAP adherence was objectively examined on the basis of the number of hours of CPAP use per day, according to the device's internal clock. Patients with reductions in mean BP greater than the observed median of 4.5 mm Hg were classified as responders to CPAP treatment.

To identify plasma miRNA profiles that predict BP response to CPAP treatment, we screened an initial group of 8 subjects with the best and 8 subjects with the worst BP responses to adherent CPAP use who were matched for age, sex, ethnicity, body mass index, and participant center (**Figure 1**). The initial set of differentially expressed miRNAs from these experiments was then used in a subsequent complete training set (n = 24), divided equally between responders and nonresponders, enabling final selection of the minimum number of miRNAs that specifically differentiate

Valenciana de Neumología, Fundació Catalana de Neumología, Agència de Gestió d'Ajuts Universitaris i de Recerca, and Centro de Investigación Biomédica en Red de Enfermedades Respiratorias. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.
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Manuscript received April 10, 2015; revised manuscript received June 12, 2015, accepted June 19, 2015.