Current Hypertension Reports (2019) 21: 57
https://doi.org/10.1007/s11906-019-0963-6

RESISTANT HYPERTENSION (LUCIANO DRAGER, SECTION EDITOR)

The Potential Role of Obstructive Sleep Apnoea in Refractory Hypertension

Grace Oscullo[1] · E. Sapiña-Beltrán[2,3] · Gerard Torres[2,3] · Enrique Zaldivar[1] · Ferran Barbé[2,3] · Miguel Angel Martinez-Garcia[1]

Published online: 10 June 2019

Abstract

Purpose of Review This review seeks to present an overview of the recently found association between refractory hypertension (RfH) and obstructive sleep apnoea (OSA).

Recent Findings RfH was recently defined as an extreme phenotype of resistant hypertension characterized by the lack of blood pressure control despite using ≥ 5 antihypertensive drugs at optimal doses. Current data support that the pathophysiological pathway of both types of hypertension is different. The main mechanism involved in resistant hypertension is fluid retention whereas in the case of RfH is the sympathetic over-activity. OSA is now recognized as a cause of hypertension (especially in the case of difficult-to-treat hypertension). It seems that the biological mechanism linking OSA and arterial hypertension is the sympathetic over-activity related to the respiratory events (apnoeas and hypopnoeas) during the night. So, it is not surprising that, although the literature is scarce, some studies have found a very high prevalence of OSA and an excess of sympathetic activity in patients with RfH. Finally, a very recent study demonstrated that continuous positive airway pressure (CPAP) treatment, which controls sympathetic activation in OSA patients, achieves very significant reductions in blood pressure levels in RfH patients, even greater than in those with resistant (non-refractory) hypertension.

Summary The prevalence of OSA in patients with RfH is very high. CPAP treatment achieves a clinically significant reduction in blood pressure levels in those patients with RfH (especially in night readings). Patients with RfH must be sent to a sleep unit for a study.

Keywords Sleep apnoea · Resistant hypertension · Refractory hypertension · Continuous positive airway pressure

Introduction

Resistant hypertension (RH) is defined as blood pressure (BP) that remains uncontrolled in spite of a combination of three or more antihypertensive drugs, including a diuretic agent, prescribed at an optimal dose. RH is also applied to subjects who require four or more drugs to achieve adequate BP control [1••]. In the overall treated hypertensive population, the prevalence of RH ranges between 12 and 15%, depending on whether the measurement used for the diagnosis was office or ambulatory BP [2–4, 5•].

An unfavourable prognosis is associated with this hypertensive phenotype and several studies have reported that RH subjects present the most unfavourable cardiovascular prognosis of all hypertensive patients in terms of the rate of cardiovascular events [2, 6–9]. Furthermore, in recent years, a subgroup of RH patients has been shown to exhibit the highest cardiovascular risk of all: this phenomenon has come to be known as refractory hypertension (RfH) [10••, 11, 12••, 13•].

RfH was originally defined by Acelajado et al. as a form of hypertension that cannot be controlled by any pharmacological treatment. This clinical situation implied that the

This article is part of the Topical Collection on *Resistant Hypertension*

✉ Miguel Angel Martinez-Garcia
mianmartinezgarcia@gmail.com

[1] Pneumology Department, Hospital Universitario y Politécnico La Fe, Bulevar Sur s/n, 46012 Valencia, Spain

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

[3] Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain

patients affected were taking an average of six drugs [14••]. In the last few years, the definition became subtler and incorporated not only treatment with five or more antihypertensive drugs but also treatment with a diuretic thiazide (or thiazide-like drug) and a mineral-corticoid receptor antagonist [15•]. The recognized superiority of the thiazide-type diuretic chlorthalidone over hydrochlorothiazide in reducing BP has spurred some authors to consider adding to the definition of RfH compliance with an intensive diuretic therapy including chlorthalidone and a mineral receptor antagonist (spironolactone) [16•]. Depending on the definition taken as a reference, the prevalence of RfH ranges from 9.5%, in the less restrictive definition [14••], to 3% if all the criteria, including intensive diuretic therapy (chlorthalidone and spironolactone), are taken into account [15•]. Several differences between the two phenotypes have been described, and although there is currently no evidence about the cardiovascular prognosis with respect to RH and RfH, one recent study showed a poorer circadian profile and higher nocturnal BP levels in RfH subjects, compared with RH subjects. Both these physiological factors have been related to a poorer cardiovascular prognosis and greater organ damage [16•].

Obstructive sleep apnoea (OSA) is a disease characterized by repetitive collapse of the upper airway during sleep, which leads to intermittent hypoxia, arousals, oxygen desaturation and sleep disturbance and contributes to daytime sleepiness and a poor quality of life. In the middle-aged population (30–70 years), the prevalence of OSA ranges from 26 to 34% in men and 17 to 28% in women, and this prevalence increases in line with age and the body mass index [17, 18]. OSA is considered one of the secondary causes associated with the development of hypertension, particularly RH, and cardiovascular events [18, 19]. In the last 10 years, numerous studies have explored the implications of the close relationship between OSA and RH [20–22, 23••, 24–26], but new evidence has emerged to highlight the key role of OSA in RfH. The present review seeks to present an overview of this relationship.

Pathophysiological Aspects

Pathophysiology of RH

The main mechanisms involved in the pathophysiology of RH are sodium, fluid retention and sympathetic over-activity [27, 28]. Excessive fluid retention is associated with old age, obesity and chronic kidney disease, but the biggest contributor is hyperaldosteronism derived from chronically increased activity of the renin-angiotensin-aldosterone system (RAAS). This excess of fluid is considered to be the main mechanism of RH. In this respect, the key role of intensive diuretic treatment, including a mineral-corticoid receptor antagonist, in achieving BP control in a multiple drug regimen in these patients is considered proof of this mechanism [29].

Specific Pathophysiological Aspects of Refractory Hypertension: the Hypothesis of Sympathetic Over-activity

RfH patients cannot achieve BP control despite taking five or more antihypertensive drugs, even at the optimal dose for the most effective treatment of fluid overload. Although RfH has been considered an extreme phenotype of RH, different pathophysiological factors have been described in each of them. RfH seems to be less closely related to fluid retention and more closely linked to greater sympathetic activity. Patients with RfH are characterised as being younger, more obese and with greater organ damage and a higher prevalence of diabetes mellitus and metabolic syndrome [30, 31] (Table 1).

Table 1 Clinical characteristics of patients with refractory hypertension compared with patients with resistant hypertension)

Clinical characteristics	Resistant hypertension	Refractory hypertension
Age	Older	Younger
Sex (male/female)	(+)	(++)
Comorbidity		
Obesity	(+)	(++)
Diabetes	(+)	(++)
Dyslipidemia	(+)	(++)
OSA	(+)	(++)
Target organ damage		
Previous cardiovascular disease	(+)	(+++)
Left ventricular hypertrophy	(+)	(+++)
Kidney damage (decreased GFR/increased albuminuria)	(+)	(++)

GFR glomerular filtration rate, *OSA* obstructive sleep apnoea

Data from an important study carried out by Dudenbostel et al. support this particular pathophysiology in RfH patients. This study undertook a thorough comparison of 29 patients diagnosed with controlled RH and 15 patients with RfH. The following variables were measured in all the participants: 24-h urinary normetanephrine levels, office resting and ambulatory heart rate (HR), and its variability, and arterial stiffness (using pulse waves). Furthermore, an impedance cardiography study was performed to assess thoracic fluid content and systemic vascular resistance. The results suggested a lower implication of fluid overload in RfH subjects, who showed a lower sodium dietary intake and a lower thoracic fluid content in the impedance cardiography study [15•].

In addition to these findings, Dudenbostel et al. [15•] also found data indicative of an elevated sympathetic tone in RfH patients. Subjects with RfH, compared to those with controlled RH, presented higher resting and ambulatory HR, higher levels of 24-h urinary normetanephrine and greater arterial stiffness and peripheral vascular resistance. This was not the first time that an increased clinical HR had been reported in RfH patients, compared with controlled RH subjects. The same authors had themselves reported this finding in a previous retrospective study [14••]. These data therefore suggest that any therapeutic strategy for RfH should primarily focus on reducing sympathetic over-activity (Fig. 1).

The Close Relationship Between OSA and RfH

Several intermediate mechanisms link OSA with hypertension and cardiovascular disease, particularly oxidative stress, inflammation, hypercoagulability, endothelial dysfunction, metabolic alterations and sympathetic activation. Subjects with OSA have presented greater activation of the sympathetic system (especially while asleep), due to respiratory events, and this activation causes an increase in BP [18, 32, 33]. Data from various studies suggest that sympathetic hyperactivation—presumed to be the main mechanism responsible for RfH—could be considered the primary pathophysiological mechanism for explaining the association between OSA and the high incidence and prevalence of hypertension [32, 33, 34••]. Beyond this common pathophysiology between OSA and RfH, the two diseases are linked by shared epidemiological data. There is an increase in OSA prevalence in hypertensive subjects, and the severity of their hypertension increases accordingly. In this respect, the prevalence of hypertension in OSA subjects is situated at between 30 and 50% [35–37], but this figure rises considerably to 70–83% in patients with resistant hypertension [38–40] and can even reach 100% in patients with a diagnosis of RfH, according to the results of one recent study [34••] (Fig. 1).

All these data therefore suggest that OSA has a closer relationship with RfH than with RH, and that sympathetic overactivation might be the underlying mechanism that explains this link. Despite this hypothesis, it is not yet known whether OSA can influence RH patients to eventually develop the RfH phenotype (Fig. 2).

Prevalence of OSA in RfH Patients

To date, only two studies [14••, 15•] with only a limited number of patients (15 and 29) have evaluated the presence of OSA in patients with RfH. OSA was found in, respectively, 31 and 41.6% of the patients included, although neither study

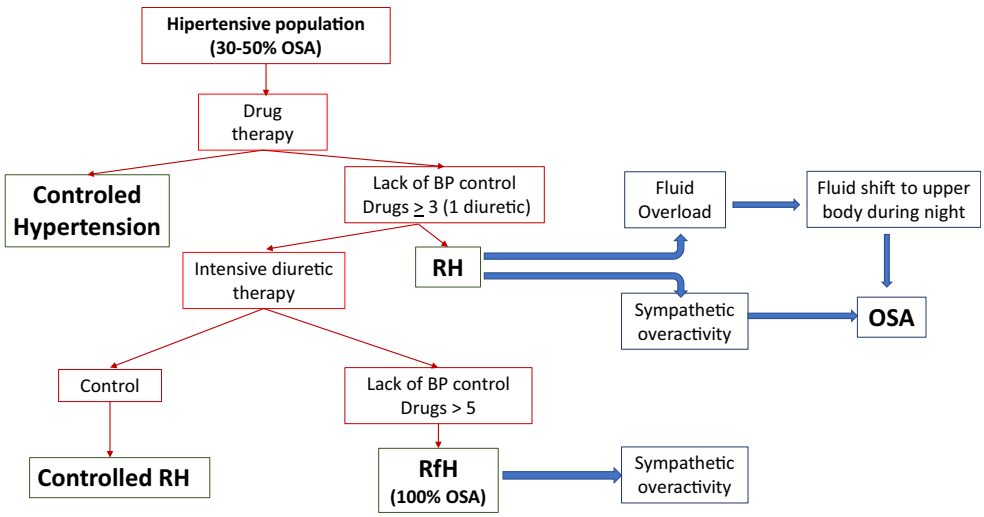

Fig. 1 Pathophysiological mechanisms linking resistant hypertension, refractory hypertension and sleep apnoea. BP blood pressure, OSA obstructive sleep apnoea, RfH refractory hypertension, RH resistant hypertension

RH: Resistant hypertension, RfH: Refractory hypertension, OSA: Obstructive sleep apnea.

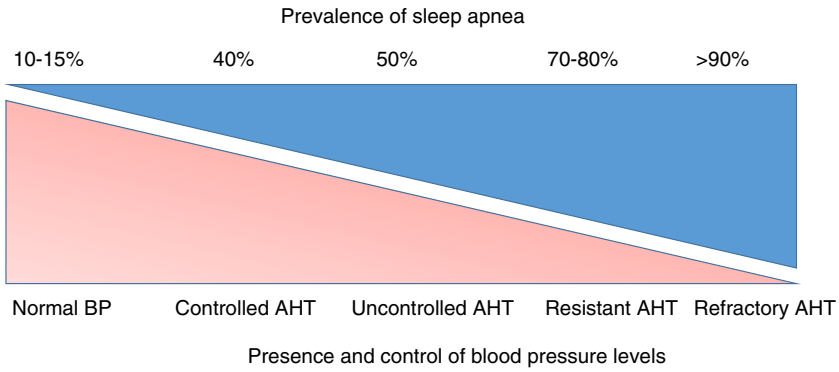

Fig. 2 Prevalence of sleep apnoea depending of the presence, control and severity of arterial hypertension. BP blood pressure, AHT arterial hypertension

specified the cut-off point used to define OSA or the diagnostic method used (Table 2).

Recently, Martinez-Garcia et al. [34••] published the only study so far to deal specifically with this topic. This study included 42 patients with RfH and 187 with RH, diagnosed by means of 24-h ABPM. All the patients underwent a sleep study involving cardiorespiratory polygraphy or complete polysomnography, and a diagnosis of OSA was established as an AHI ≥ 5; the OSA was considered severe when the AHI > 30, and as OSAS if it was accompanied by secondary symptoms, particularly daytime hypersomnia evaluated by the Epworth Sleepiness Scale (Epworth > 10). All the patients with RfH presented OSA, as compared with 89% of those with RH ($p = 0.027$). As regards severe OSA (AHI ≥ 30) in particular, its prevalence was higher in patients with RfH versus RH, at 64.3% and 48.6%, respectively ($p = 0.044$). If we consider the symptoms associated with the diagnosis of OSA syndrome (IAH ≥ 5 + Epworth > 10), 52.4% of the subjects with RfH presented OSAS versus 33.7% of those with RH ($p = 0.023$). Overall, however, RfH patients were not characterised by a high clinical pre-test probability of OSA (mean Epworth score of 9.1). These authors also found that this higher prevalence of OSA in RfH patients was independent of age, gender and the presence of obesity. Furthermore, RfH patients presented a greater variability in BP and mean cardiac frequency than those with RH, supporting the notion that sympathetic hyperstimulation provides the pathophysiological basis for this hypertensive phenotype.

Therefore, in the light of the high prevalence of OSA in patients with RfH, regardless of the associated symptoms, they (like their counterparts with RH) must be referred to a sleep unit for a diagnostic evaluation and, if necessary, appropriate therapy.

Effect of CPAP Treatment on BP in Refractory Hypertension

Numerous meta-analyses have demonstrated that CPAP is capable of reducing BP levels in patients with OSA, in both clinical and statistically significant terms [24, 25, 40–42].

Table 2 Published studies evaluating refractory hypertensive patients

		Clinical characteristics			
Author	Sample size (RfH)	Age (years)	Sex (% men)	BMI (kg/m^2)	OSA prevalence
Martinez-García MA et al. 2018 [34••]	42 (true RfH)	58.4 (8.5)	61.9	34.7 (6.25)	100% (AHI ≥ 5)
Armario P et al. 2017 [16•]	700 (true RfH)	63.9 (11)	58.4	31.6 (4.9)	–
Modolo R et al. 2015 [11]	36 (true RfH)	58 (11)	33	32.1 (5.6)	–
Dudenbostel T et al. 2015 [15•]	15 (true RfH)	48 (13.3)	20	32.4 (7.1)	41.6%
Calhoun D et al. 2014 [10••]	78	66.0 (1.0)	53.8	33.6 (0.8)	–
Acelajado M et al. 2012 [14••]	29	51.4 (14.9)	45	33.2 (6.2)	31%

Values are expressed as mean ± SD or *n* (%)

AHI Apnea/Hypopnea Index, *BMI* body mass index, *RfH* refractory hypertension, *true RfH* based on a 24-h ambulatory blood pressure monitoring diagnosis

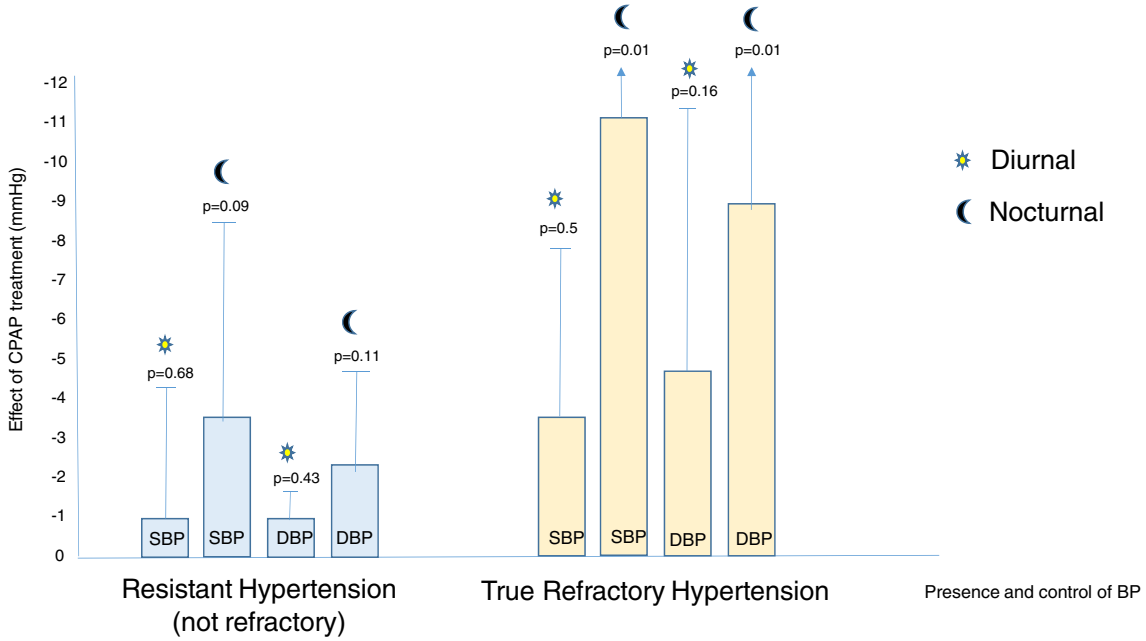

Fig. 3 Effect of continuous positive airway pressure on patients with resistant (non-refractory) hypertension and true refractory hypertension. SBP systolic blood pressure, DBP diastolic blood pressure, CPAP continuous positive airway pressure. Based on [34••]

Moreover, CPAP treatment is capable of increasing the percentage of hypertensive subjects who present a circadian BP dipper pattern [23••, 43], a factor associated with an improved cardiovascular prognosis, independent of the diurnal BP levels.

As regards the effect of CPAP on BP, although this is modest in hypertensive patients as a whole (a drop of 2–2.5 mmHg in the mean 24-h systolic and diastolic BP readings) [40–43], it seems to be more substantial in patients with more severe OSA [40] and in those with poorer control of their BP levels [41, 42].

This effect is also greater in patients with RH [23••, 24, 25]. In a recent meta-analysis Iftikhar et al. [24] found that CPAP treatment in patients with RH can reduce 24-h BP readings by 5.9–6.7 mmHg. This drop seems to be bigger in those patients with higher baseline BP levels and, more particularly, in those presenting good compliance with CPAP (at least 4–6 h per night).

Only very recently, the only study to specifically analyse the effect of CPAP in patients with RfH, compared to those with RH, was published [44••] (Fig. 3). This was a post hoc randomized controlled HIPARCO trial (the biggest of its kind for the analysis of the effect of CPAP on patients with HR). The HIPARCO sample of 194 patients with RH was divided into two: 41 patients with RfH versus 154 patients with RH, randomized to receive CPAP or no CPAP for 3 months if they presented an AHI > 15 events/h. Both the initial and final evaluations were undertaken in all the patients with 24-h ABPM. The following table shows the main results of the study in an intention-to-treat analysis. Although there was only a limited number of RfH patients ($n = 42$), a very significant drop was observed in both the 24-h systolic and diastolic BP readings (− 9 mmHg and − 7.3 mmHg, respectively), especially during the night (− 11.3 mmHg and − 8.8 mmHg, respectively). Moreover, there was also a near-significant reduction in the mean cardiac frequency and variability in BP readings; this was greater in RfH patients than in RH patients, which again supports the notion of sympathetic activation as a key pathophysiological factor in this type of hypertension, and the mechanism by which CPAP achieves a drop in BP and thereby reduces this activation. A comparison of the magnitudes of the reduction in BP achieved with CPAP treatment in patients with RH and RfH showed that CPAP obtained a statistically significant greater drop in BP in RfH patients, adjusted for the initial values of BP and OSA severity (− 7.4 mmHg of 24-h systolic BP, SBP), while the drops in 24-h diastolic BP, DBP (− 5 mmHg), nocturnal DBP (− 6.6 mmHg), mean cardiac frequency and the variability in BP readings all remained within the limits of statistical significance. This suggests that the effect of CPAP was statistically higher in RfH patients than in RH patients in the 24-h SBP readings, and near-significantly higher in the 24-h DBP, nocturnal DBP, HR and BP variability readings. Finally, in both groups, the clinical picture associated with OSA improved significantly (3.2 vs 3.9 points on the Epworth scale), with no significant differences between the two hypertensive groups.

Future Challenges

The description of this special phenotype of hypertensive patients (RfH) has only recently been formulated, and that of its association with OSA is even more recent, and so a fascinating line of research has now opened up, with more questions than answers at the moment. However, in the light of the results obtained to date, particularly the high prevalence of OSA and the considerable hypotensive effect of CPAP in these patients, it is worth continuing to delve into this relationship, as it could provide results that would improve our management of patients with RfH, who have an extremely poor prognosis and little possibility of being controlled by a primarily pharmacological strategy.

Although RfH is not highly prevalent, it is seemingly on the rise, and so future studies need to recruit a greater number of patients on a multicentre basis in order to undertake RCTs specifically focusing on RfH, as well as longitudinal studies that analyse the effect of CPAP in the longer term and examine whether it has any impact on the vital prognosis and incidence of cardiovascular events in RfH patients.

Conclusions

According to the results that have recently been published, the prevalence of OSA (including moderate-severe OSA) is very high in patients with RfH, even more than in those with RH. The pathophysiological mechanism mediating this relationship seems to be the hyperactivation of the sympathetic nervous system, and this is probably linked to the fact that CPAP treatment, which controls sympathetic activation very effectively in OSA patients, achieves very significant reductions in these patients' BP levels.

Clinical Remarks (Bullets)

1. The evidence available to date seems to indicate that the difficulties in controlling BP levels in patients with RH and RfH can be explained by two different pathophysiological mechanisms. Thus, while the dysfunction of the renin-angiotensin-aldosterone axis seems to play a leading role in RH, RfH is more closely linked to sympathetic hyperstimulation, which in its turn coincides with the mechanism by which OSA is capable of raising BP.
2. The prevalence of OSA and OSA syndrome is extraordinarily high in RfH patients, even though the probability of their incidence is usually not very high in the pre-test clinical picture. These circumstances mean that patients with RfH must be sent to a sleep unit for a study.
3. CPAP treatment achieves a clinically and statistically significant reduction in BP in RfH patients (even more than in RH patients). These reductions are more marked in the night-time BP readings.

Author Contribution All authors have access to the data and a role in writing the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1.•• Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008;117(25):e510–26. **This is the most important specific guidelines on resistant hypertension.**
2. Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC Jr, Crowley K, et al. Resistant hypertension: a frequent and ominous finding among hypertensive patients with atherothrombosis. Eur Heart J. 2013;34(16):1204–14.
3. Persell SD. Epidemiology/population studies prevalence of resistant hypertension in the United States, 2003–2008. Hypertension. 2011;57:1076–80.
4. Egan BM, Zaho Y, Axon RN, Brezinsky WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988-2008. Circulation. 2011;124:1046–58.
5.• de la Sierra A, Segura J, Banegas JR, Gorostidi M, de la Cruz JJ, Armario P, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. Hypertension. 2011;57:898–902. **The largest series of patients analized with resistant hypertension.**
6. Pierdomenico SD, Lapenna D, Bucci A, Di Tommaso R, Di Mascio R, Manente BM, et al. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. Am J Hypertens. 2005;18(11):1422–8.
7. Daugherty SL, Powers JD, Magid DJ, Tavel HM, Masoudi FA, Margolis KL, et al. Incidence and prognosis of resistant hypertension in hypertensive patients. Circulation. 2012;125(13):1635–42.
8. Tsioufis C, Kasiakogias A, Kordalis A, Dimitriadis K, Thomopoulos C, Tsiachris D, et al. Dynamic resistant hypertension patterns as predictors of cardiovascular morbidity. J Hypertens. 2014;32(2):415–22.
9. Holmqvist L, Boström KB, Kahan T, Schiöler L, Hasselström J, Hjerpe P, et al. Cardiovascular outcome in treatment-resistant hypertension: results from the Swedish Primary Care Cardiovascular Database (SPCCD). J Hypertens. 2018;36(2):402–9.
10.•• Calhoun DA, Booth JN III, Oparil S, Irvin MR, Shimbo D, Lackland DT, et al. Refractory hypertension: determination of

prevalence, risk factors, and comorbidities in a large, population-based cohort. Hypertension. 2014;63:451–8. **A comprehensive review on the new refractory hypertensive phenotype in a large series of patients.**

11. Modolo R, de Faria AP, Sabbatini AR, Barbaro NR, Ritter AM, Moreno H. Refractory and resistant hypertension: characteristics and differences observed in a specialized clinic. J Am Soc Hypertens. 2015;9(5):397–402.
12.•• Dudenbostel T, Siddiqui M, Oparil S, Calhoun DA. Refractory hypertension: a novel phenotype of antihypertensive treatment failure. Hypertension. 2016;67:1085–92. **Other interesting paper adding more evidence and comments on the exitence of a refractory hypertensive phenotype.**
13.• Acelajado M, Hughes Z, Oparil S, Calhoun DA. Treatment of resistant and refractory hypertension. Circ Res. 2019;124:1061–70. **Paper describing the comparative similitudes and differences between the treatment of resistant and refractory hypertension.**
14.•• Acelajado MC, Pisoni R, Dudenbostel T, Dell'Italia LJ, Cartmill F, Zhang B, et al. Refractory hypertension: definition, prevalence, and patient characteristics. J Clin Hypertens (Geenwich). 2012;14(1):7–12. **One of the first papers describing the new refractory hypertension phenotype of patients.**
15.• Dudenbostel T, Acelajado MC, Pisoni R, Li P, Oparil S, Calhoun DA. Refractory hypertension: evidence of heightened sympathetic activity as a cause of antihypertensive treatment failure. Hypertension. 2015;66:126–33. **An interesting paper describing the most likely pathophisiological mechanisms related to refractory hypertension.**
16.• Armario P, Calhoun DA, Oliveras A, Blanch P, Vinyoles E, Banegas JR, et al. Prevalence and clinical characteristics of refractory hypertension. J Am Heart Assoc. 2017;6(12):e007365. https://doi.org/10.1161/JAHA.117.007365. **One more key paper on the prevalencia and clinical characteristics of refractory hypertensive patients.**
17. Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population based sample of subjects aged 30–70 yr. Am J Respir Crit Care Med. 2001;163(3 Pt1):685–9.
18. Peppard PE, Young TY, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013;177:1006–14.
19. Sánchez-de-la-Torre M, Campos-Rodriguez F, Barbé F. Obstructive sleep apnoea and cardiovascular disease. Lancet Respir Med. 2013;1(1):61–72.
20. Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK, Amaro AC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. Hypertension. 2011;58(5):811–7.
21. Friedman O, Bradley TD, Chan CT, Parkes R, Logan AG. Relationship between overnight rostral fluid shift and obstructive sleep apnea in drug-resistant hypertension. Hypertension. 2010;56:1077–82.
22. Demede M, Pandey A, Zizi F, Bachmann R, Donat M, Mcfarlane SI, et al. Resistant hypertension and obstructive sleep apnea in the primary-care setting. Int J Hypertens. 2011;2011:240929.
23.•• Martínez-García MA, Capote F, Campos-Rodriguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension. The HIPARCO randomized clinical trial. JAMA. 2013;310(22):2407–15. **The largest randomized clinial trial on the positive effect of continuous positive airway pressure on blood pressure levels in patients with resistant hypertension.**
24. Iftikhar IH, Valentine CW, Bittencourt LR, Cohen DL, Fedson AC, Gislason T, et al. Effect of continuous positive airway pressure on blood pressure in patients with resistant hypertension and obstructive sleep apnea: a meta-analysis. J Hypertens. 2014;32(12):2341–50.
25. Liu L, Cao Q, Guo Z, et al. Continuous positive airway pressure in patients with obstructive sleep apnea and resistant hypertension : a meta-analysis of randomized controlled trials. J Clin Hypertens (Greenwich). 2016;18(2):153–8.
26. Martínez-García MA, Gómez-Aldaraví R, Soler-Cataluña JJ, Martínez TG, Bernácer-Alpera B, Román-Sánchez P. Positive effect of CPAP treatment on the control of difficult-to-treat hypertension. Eur Respir J. 2007;29:951–7.
27. Hwang AY, Dietrich E, Pepine CJ, Smith SM. Resistant hypertension: mechanisms and treatment. Curr Hypertens Rep. 2017;19(7):56.
28. Tsioufis C, Kordalis A, Flessas D. Pathophysiology of resistant hypertension: the role of sympathetic nervous system. Int J Hypertens. 2011;2011:642416.
29. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, cross-over trial. Lancet. 2015;386(10008):2059–68.
30. Dudenbostel T, Siddiqui M, Gharpure N, Calhoun DA. Refractory versus resistant hypertension: novel distinctive phenotypes. J Nat Sci. 2017;3(9):e430.
31. Muxfeldt ES. Prevalence of obstructive sleep apnea in refractory hypertension. Hypertension. 2018;72(3):592–3.
32. Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. J Am Coll Cardiol. 2017;69(7):841–58.
33. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. Physiol Rev. 2010;90(1):47–112.
34.•• Martínez-García MA, Navarro-Soriano C, Torres G, Barbé F, Caballero-Eraso C, Lloberes P, et al. Beyond resistant hypertension relationship between refractory hypertension and obstructive sleep apnea. Hypertension. 2018;72(3):618–24. **First study published on the relationship between obstructive sleep apnea and refractory hypertension.**
35. Fletcher EC, DeBehnke RD, Lovoi MS, Gorin AB. Undiagnosed sleep apnea in patients with essential hypertension. Ann Intern Med. 1985;103(2):190–5.
36. Silverberg DS, Oksenberg A. Are sleep-related breathing disorders important contributing factors to the production of essential hypertension? Curr Hypertens Rep. 2001;3(3):209–15.
37. Ahmad M, Makati D, Akbar S. Review of and updates on hypertension in obstructive sleep apnea. Int J Hypertens. 2017;2017:1848375.
38. Logan AG, Perlikowski SM, Mente A, et al. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J Hypertens. 2001;19(12):2271–7.
39. Gonçalves SC, Martinez D, Gus M, et al. Obstructive sleep apnea and resistant hypertension: a case-control study. Chest. 2007;132(6):1858–62.
40. Montesi SB, Edwards BA, Malhorta A, Baker JP. The effect of continuous positive airway pressure treatment on blood pressure: a systematic review and meta-analysis of randomized controlled trials. J Clin Sleep Med. 2012;8(5):587–96.
41. Fava C, Dorignoni S, Dalle Vedove F, Danese E, Montagnana M, et al. Effect of CPAP on blood pressure in patients with OSA/hypopnea. A systematic review and meta-analysis. Chest. 2014;145(4):762–71.
42. Bakker J, Edwards B, Gautam S, Montesi S, Duran-Cantolla J, Aizpuru F, et al. Blood pressure improvement with continuous positive airway pressure is independent of obstructive sleep apnea severity. J Clin Sleep Med. 2014;10(4):365–9.
43. Duran-Cantolla AF, Montserrat JM, Ballester E, Terán-Santos J, Aguirregomoscorta JI, et al. Continuous positive airway pressure

as treatment for systemic hypertension in people with obstructive sleep apnoea: randomised controlled trial. BMJ. 2010;341:c5991. https://doi.org/10.1136/bmj.c5991.

44.•• Navarro-Soriano C, Martínez-García MA, Torres G, Barbé F, Caballero-Eraso C, Lloberes P, et al. Effect of continuous positive airway pressure in patients with true refractory hypertension and sleep apnea: a post-hoc intention-to-treat analysis of the HIPARCO randomized clinical trial. J Hypertens. 2019;37:1269–75. https://doi.org/10.1097/HJH.0000000000002053. **First study published on the positive effect of continuous positive airway pressure on patients with refractory hypertension, compared wth those with resistent (non-refractory) hypertension.**