

OSA and Resistant Hypertension: A Literature Review

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Abstract

Resistant hypertension is a serious condition in which blood pressure remains uncontrolled despite using three or more antihypertensive medications in different classes. Resistant hypertension can lead to chronic kidney disease and cardiovascular diseases. One of the main causes of resistant hypertension is OSA. Based on research study, prevalence of OSA in resistant hypertension patients up to 83%. After reviewing previous research articles, it was found that there is an association between OSA and resistant hypertension.

Keywords : OSA, Resistant Hypertension, Blood Pressure, Cardiovascular Risk Factor

1. Introduction

Based on JNC VIII, hypertension is a condition when systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, or on antihypertensive medication [1]. Data from WHO (2021), showed an increase of hypertensive patients from 594 million to 1,13 billion people in the whole wide world [2]. In Indonesia, the prevalence of hypertensive people is up to 34,1% of the entire Indonesian population but only 8,8% are diagnosed with hypertension [3]. From Institute for Health Metrics and Evaluation data on 2017, 23,7% from 1,7 million deaths in Indonesia caused by hypertension [4]. Hypertension can be controlled by antihypertensive medication, even though some people may be resistant to antihypertensive drugs.

Resistant hypertension is a condition where blood pressure remains uncontrolled while using three antihypertensive drugs in different classes, one should include diuretic [5]. Studies showed the prevalence of resistant hypertension was 10% out of patients treated with hypertension [6]. If it is not treated right, resistant hypertension potentially leads to organ damage such as chronic kidney disease and cardiovascular diseases [7].

OSA is one of the causes of secondary hypertension and has been associated with resistant hypertension by many studies [8]. Prevalence of OSA in resistant hypertension patients is relatively high ranging from 70% to 83% [9]. Study using the Berlin questionnaire to determine risk of OSA found that the resistant hypertension group was 78% at high risk of OSA compared to the controlled hypertension group [10]. Unfortunately, research data of OSA and resistant hypertension is still limited in Indonesia.

Hence, it is important to do further research about OSA and resistant hypertension in order to know more about the association between OSA and resistant hypertension. The purpose of this paper is to review and explore the association of OSA and resistant hypertension, whether they are related or not.

2. Resistant Hypertension

2.1. Definition of Resistant Hypertension

Based on consensus of ESC/ESH 2018, hypertension defines as resistant when systolic blood pressure above 140 mmHg and diastolic blood pressure above 90 mmHg, respectively, despite using 3 or more antihypertensive drugs (ACE inhibitor or ARB, CCB, and diuretic) with optimal doses and appropriate lifestyle modification. Adherence to drug-treatment and ABPM (ambulatory blood pressure measurement) or HBPM (home blood pressure measurement) should be confirmed [11].

On the other hand, AHA 2018 defines resistant hypertension as elevated blood pressure despite the use of 3 antihypertensive drug classes, including long-acting calcium channel blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and one should be diuretic. Drugs should be administered at optimal or best-tolerated doses. Definition of resistant hypertension also applied to those whose systolic and diastolic blood pressure controlled on 4 or more antihypertensive drugs [12].

2.2. Epidemiology of Resistant Hypertension

Epidemiology of resistant hypertension varies based on the definition used. A meta-analysis study from 91 studies between 1991 and 2017 with 3.207.911 patients with treated-hypertension found that the prevalence of true-resistant hypertension was as much as 10,3% [6]. Besides that, another systematic review and meta-analysis found the prevalence of resistant hypertension based on observational study was 13,72% and based on RCTs was 16,32% [13].

In Brazil, medical records of patients treated with hypertension medication assessed and grouped into resistant hypertension and non-resistant hypertension. Out of 104 patients included, criteria for resistant hypertension found in 33 patients (31,7%). Based on genders, females suffered the most of resistant hypertension (75,7%) [14]. Another study conducted in the Asian population among hypertensive patients in a hospital in Karachi, Pakistan. From 515 patients, 62 patients (12%) had resistant hypertension. The resistant hypertension patient was more often female, had an older age, and higher BMI [15].

In Indonesia, the prevalence of resistant hypertension is still unknown because of the lack of data and research. There was one study conducted in a hospital of Christian University of Indonesia involving 1.030 hypertensive patients. From the study, the prevalence of resistant hypertension patients was 139 patients (13,49%). There was no big difference between male and female in resistant hypertension patients and the most ages was >65 years [16].

2.3. Etiology of Resistant Hypertension

There are several factors that contribute to resistant hypertension. The most common cause of resistant hypertension is poor adherence to antihypertensive drugs. The reason for poor adherence is not always because of lack of patient awareness but also can be caused by expensive drug prices, medications are not available, or difficult to keep doctor appointments. Besides that, whitecoat phenomena can be false negative of resistant hypertension. Lifestyle factors such as obesity, alcohol consumption, smoking, and excessive dietary sodium also will contribute to resistant hypertension. Another factor is drug-induced resistant hypertension including NSAIDs, oral contraceptives, sympathomimetics, adrenal steroids, and antineoplastic drugs [17].

Moreover, resistant hypertension can be caused by secondary hypertension. The most common secondary causes are OSA, renal artery stenosis, renal parenchymal disease, and primary aldosteronism [17]. OSA as a common condition in patients with resistant hypertension had prevalence between 70% up to 90% [18]. The uncommon secondary causes are pheochromocytoma, Cushing's disease, thyroid and parathyroid dysfunction, and aortic coarctation [17].

2.4. Treatment for Resistant Hypertension

Management therapy for resistant hypertension has been stated based on AHA 2018 guidelines [12]. The management therapy should be combined between lifestyle intervention and pharmacological treatment. The management of resistant hypertension are as follows:

1. The combination of 3 antihypertensive drugs from different classes (ACE-i or ARB, CCB, and diuretic) should be administered at maximally tolerated doses. Patients with resistant hypertension should be screened from secondary causes and excluded from white-coat effect or nonadherence to antihypertensive medication. Patients should implement lifestyle modification such as >6 hours uninterrupted sleep, low sodium diet (<2400 mg/day), weight loss, and exercise.
2. If blood pressure is still not at target, substitute optimally dozed thiazide like-diuretics such as chlorthalidone or indapamide.
3. If blood pressure is still not at target, mineralocorticoid receptor antagonists such as spironolactone or eplerenone.
4. If blood pressure is still not at target, add beta-blocker or combined alfa-beta blocker (only if patient heart rate is more than 70 beats/minute).
5. If blood pressure is still not at target, add hydralazine 25 mg thrice a day and titrated carefully.
6. If blood pressure is still not at target, substitute hydralazine to minoxidil 2.5 mg two to three times daily.
7. And if blood pressure remains uncontrolled, consider referral to a hypertension specialist.

3. OSA (Obstructive Sleep Apnea)

3.1. Definition of OSA

OSA also known as obstructive sleep apnea is a sleep disorder defined as total obstruction (apnea) or partial obstruction (hypopnea) of the upper airway, repeatedly [19]. During apnea, reduction of airflow occurs by 90% for at least 10 seconds. Meanwhile, hypopnea is defined as airflow reductions at least 30% and causes arterial oxygen saturation of at least 3% [20].

The gold standard for OSA diagnosis is polysomnography [21]. Polysomnography examination will produce AHI (apnea-hypopnea index) namely the occurrence apnea and hypopnea per hour during sleep [22]. Based on ICSD-3, the diagnosis of OSA is made when AHI ≥ 15 even without symptoms or AHI ≥ 5 followed by one of the following symptoms: 1) daytime sleepiness, 2) gasping or choking while sleeping at night, 3) tiredness, 4) insomnia, 5) sleep partners conveyed snoring or saw respiratory arrest during sleep or both, 6) unrefreshing sleep [23].

American academy of Sleep classified OSA into three based on apnea-hypopnea index. OSA is classified as mild when AHI 5 to <15, moderate with AHI 15 – 30, and severe with AHI >30 [24].

3.2. Epidemiology of OSA

A literature analysis study was done using studies reporting prevalence of OSA based on polysomnography examination. The results showed that 936 million adults have mild to severe OSA and as much as 425 million have moderate to severe OSA. From this study, the highest OSA prevalence with an AHI 5/h were China, USA, Brazil, and India [25]. Another study using the Berlin Questionnaire as a screening tool for risk of OSA was done. High risk of OSA was 18,1% from subjects untreated with sleep apnea and 20,9% from subjects treated with sleep apnea [26].

In Indonesia, OSA risk levels assessed by STOP-BANG questionnaire in general population age from 35 to 75 years found that the prevalence of high risk of OSA was 49,5% with the majority was male [27]. Similar study using the Berlin questionnaire performed on traffic polices in Jakarta, it was found that 17,2% of the subjects were at high risk of OSA [28].

3.3. Treatment for OSA

The American Academy of Sleep Medicine published guidelines for treatment of OSA. The medical therapy of OSA including weight reduction, pharmacologic agents consumption, supplemental oxygen, agents to improve nasal patency, and positional therapies. Dietary weight loss may improve AHI in obese OSA patients. The pharmacologic agent with a clinical certainty is protriptyline and oxygen supplementation improves oxygenation parameters in OSA patients but both are not recommended as a primary treatment for OSA. Topical nasal steroid may improve AHI in patients with concurrent rhinitis and OSA, and thus can be useful for primary therapies for OSA. The positional therapy consists of a method that keeps the patient in a non-supine position [29].

PAP or positive airway pressure is strongly recommended by the American Academy of Sleep Medicine to treat OSA patients with excessive sleepiness. Patients with ongoing treatment of OSA strongly recommended to use CPAP (continuous positive airway pressure) or APAP [30]. CPAP is still the gold standard treatment for OSA. CPAP reduces the number of AHI to normal or nearly normal state and reduces the nocturnal arousals. This treatment will also improve quality of sleep and nocturnal SaO₂ [31].

Oral appliances can be applied to patients who request treatment for primary snoring without OSA. In OSA patients, oral appliances can be an alternative for patients with intolerant CPAP. Patients with OSA and oral appliances should visit hospitals periodically to get follow-up [32].

The other treatment for OSA is by surgery. The surgery can be done to patients with OSA and BMI <40kg/m² who are intolerant with CPAP. Bariatric surgery also can be done by patients with OSA and obesity class II or III who are unaccepting CPAP. Moreover, patients with OSA and upper airway anatomic abnormality may undergo surgery for initial therapy [33].

4. OSA and Resistant Hypertension

4.4. Association between OSA and Resistant Hypertension

A study conducted in 41 patients with resistant hypertension and underwent polysomnographic study. OSA incidence was defined as an AHI ≥ 10 /h. Based on the research study, it was found that the incidence of OSA is 83% of all patients with resistant hypertension. The OSA prevalence in men was higher than in women [34].

In South China, 668 snorer patients filled in questionnaire and underwent polysomnography examinations. From the multivariate analysis, presence of OSA syndrome ($p=0,03$), apnea ($p=0,015$), and Epworth Sleepiness Scale results were the independent risk factors for resistant hypertension [35].

Meta-analysis study found that OSA is associated with resistant hypertension. This study includes 26 studies with 51.632 patients. Six studies result in significant association between OSA and resistant hypertension ($OR=2,842$, $p<0,05$). Another 20 studies presented significant results ($p<0,05$) between OSA and essential hypertension. This study also showed that OSA patients had 4 times increased risk of resistant hypertension with $OR=4,16$ (3,07, 5,64) [36].

Another systematic review and meta-analysis were done by searching studies from 2000 to January 2022 demonstrating the association between OSA and resistant hypertension. The study includes seven studies of 2,541 patients. The results from six studies showed that patients with OSA and with risk factors (age, gender, and obesity) were at increased risk of resistant hypertension and in OSA patients without risk factors also showed increased risk of resistant hypertension. It was shown in this study that patients with OSA with or without predisposing risk factors will increase risk of resistant hypertension [37].

4.5. Mechanisms of Disease

Mechanisms underlying between OSA and hypertension have not been well studied. Several potential mechanisms explanations may help to understand OSA and resistant hypertension better.

OSA induces intermittent hypoxemia, similarly to hypoxia or reperfusion injury [36]. This hypoxia condition will stimulate activation of central and peripheral chemoreflexes due to decreased oxygen levels in the body. The decrease of baroreflex sensitivity, indirectly, will contribute to acute and chronic activation of the sympathetic nervous system. The activation of the sympathetic nervous system affects the increase in heart rate and peripheral vasoconstriction, resulting in an increase of blood pressure [8]. From study, patients with OSA are likely to have a higher sympathetic nervous system activity while asleep and during the day [38].

In the meantime, hypoxia will also activate adrenal and result in hyperaldosteronism. Hyperaldosteronism effect in fluid retention in the body [19]. Aldosterone excess leads to salt and water retention resulting in parapharyngeal edema and worsening the OSA condition [39]. Besides that, hypoxia induces endothelial dysfunction causing decrease the production of NO (nitric oxide). NO helps vascular cells to be able to vasodilate, decrease in NO production causing decreased vasodilation ability [8].

Arousal that happens during the episode of OSA is a mechanism to maintain airway and prevention of asphyxia [38]. When arousal happens, there has been an increase of the sympathetic nervous system exceeding wakefulness. This condition will induce a significant spike of heart rate and blood pressure. Intermittent arousal will affect the sympathetic nervous system in the long-term and potentially develop into hypertension [40], especially resistant hypertension.

5. Conclusion

Evidence has supported the association between OSA and resistant hypertension. OSA causes resistant hypertension by various mechanisms such as activation of the sympathetic nervous system, aldosterone excess, and endothelial dysfunctions.

References

- [1] James, P. A., Oparil, S., Carter, B. L., Cushman, W. C., Dennison-Himmelfarb, C., Handler, J., Lackland, D. T., LeFevre, M. L., MacKenzie, T. D., Ogedegbe, O., Smith, S. C., Jr, Svetkey, L. P., Taler, S. J., Townsend, R. R., Wright, J. T., Jr, Narva, A. S., & Ortiz, E. 2014. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*, 311(5), 507–520. <https://doi.org/10.1001/jama.2013.284427>
- [2] Who.int. 2021. Hypertension. [online] Available at: <<https://www.who.int/news-room/fact-sheets/detail/hypertension>> [Accessed 20 June 2022].
- [3] Kementerian Kesehatan RI, 2018. Hasil Utama RISKESDAS 2018. [online] Kesmas.kemkes.go.id. Available at: <https://kesmas.kemkes.go.id/assets/upload/dir_519d41d8cd98f00/files/Hasil-risikesdas-2018_1274.pdf> [Accessed 20 June 2022].
- [4] Anitasari. 2019. Hari Hipertensi Dunia 2019: “Know Your Number, Kendalikan Tekanan Darahmu dengan CERDIK.” Retrieved April 17, 2020, from Direktorat Pencegahan dan Pengendalian Penyakit Tidak Menular website: <http://p2ptm.kemkes.go.id/kegiatanp2ptm/pusat/hari-hipertensi-dunia-2019-knowyour-number-kendalikan-tekanan-darahmudengan-cerdik>
- [5] Yaxley, J. P., & Thambar, S. V. (2015). Resistant hypertension: an approach to management in primary care. *Journal of family medicine and primary care*, 4(2), 193–199. <https://doi.org/10.4103/2249-4863.154630>
- [6] Noubiap, J. J., Nansseu, J. R., Nyaga, U. F., Sime, P. S., Francis, I., & Bigna, J. J. 2019. Global prevalence of resistant hypertension: a meta-analysis of data from 3.2 million patients. *Heart (British Cardiac Society)*, 105(2), 98–105. <https://doi.org/10.1136/heartjnl-2018-313599>
- [7] Braam, B., Taler, S., Rahman, M., Fillaus, J., Greco, B., Forman, J., Reisin, E., Cohen, D., Saklayen, M. & Hedayati, S. 2016. Recognition and Management of Resistant Hypertension. *Clinical Journal of the American Society of Nephrology*, 12(3), pp. 524–535.
- [8] Parati, G., Ochoa, J. E., Bilo, G., Mattaliano, P., Salvi, P., Kario, K., & Lombardi, C. (2014). ‘Obstructive sleep apnea syndrome as a cause of resistant hypertension’. *Hypertension research: official journal of the Japanese Society of Hypertension*, 37(7), 601–613.
- [9] Pedrosa, R. P., Drager, L. F., Gonzaga, C. C., Sousa, M. G., de Paula, L. K., Amaro, A. C., Amodeo, C., Bortolotto, L. A., Krieger, E. M., Bradley, T. D., & Lorenzi-Filho, G. 2011. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. *Hypertension*, 58(5), 811–817. <https://doi.org/10.1161/HYPERTENSIONAHA.111.179788>
- [10] Gus, M., Gonçalves, S. C., Martinez, D., de Abreu Silva, E. O., Moreira, L. B., Fuchs, S. C., & Fuchs, F. D. 2008. Risk for Obstructive Sleep Apnea by Berlin Questionnaire, but not daytime sleepiness, is associated with resistant hypertension: a case-control study. *American journal of hypertension*, 21(7), 832–835.
- [11] Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., Clement, D. L., Coca, A., de Simone, G., Dominiczak, A., Kahan, T., Mahfoud, F., Redon, J., Ruilope, L., Zanchetti, A., Kerins, M., Kjeldsen, S. E., Kreutz, R., Laurent, S., Lip, G. Y. H., McManus, R., Narkiewicz, K., Ruschitzka, F., Schmieder, R.E., Shylakhto, E., Tsioufis, C., Aboyans, V., & Desormais, I. 2018. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *European heart journal*, 39(33), 3021–3104. <https://doi.org/10.1093/eurheartj/ehy339>
- [12] Carey, R.M., Calhoun, D.A., Bakris, G.L., Brook, R.D., Daugherty, S.L., Dennison-Himmelfarb, C.R., Egan, B.M., Flack, J.M., Gidding, S.S., Judd, E., Lackland, D.T., Laffer, C.L., Newton-Cheh, C., Smith, S.M., Taler, S.J., Textor, S.C., Turan, T.N., White, W.B. 2018. Resistant hypertension: Detection, evaluation, and management: A scientific statement from the American Heart Association. *Hypertension*, 72(5). doi:10.1161/hyp.0000000000000084.
- [13] Achelrod, D., Wenzel, U., & Frey, S. 2015. Systematic review and meta-analysis of the prevalence of resistant hypertension in treated hypertensive populations. *American journal of hypertension*, 28(3), 355–361. <https://doi.org/10.1093/ajh/hpu151>
- [14] Moura, A. F., Moura-Neto, J. A., Rodrigues, C. I. S., Miranda, M. O., Carvalho, T. C., Paschoalin Carvalho, N. P., Souza, E., Moura-Jr, J. A., & Cruz, C. M. S. 2021. Resistant hypertension: Prevalence and profile of patients followed in a university ambulatory. *SAGE open medicine*, 9, 20503121211020892. <https://doi.org/10.1177/20503121211020892>
- [15] Naseem, R., Adam, A. M., Khan, F., Dossal, A., Khan, I., Khan, A., Paul, H., Jawed, H., Aslam, A., Syed, F. M., Niazi, M. A., Nadeem, S., Khan, A., Zia, A., & Arshad, M. H. 2017. Prevalence and characteristics of resistant hypertensive patients in an Asian population. *Indian heart journal*, 69(4), 442–446. <https://doi.org/10.1016/j.ihj.2017.01.012>
- [16] Suling, F. R.W., Hutabarat, H., Kramasanjaya, I. B. U., & Agustian, Z. 2020. ‘2-2 profile of resistant hypertension in the university christian of indonesia general hospital in 2019’. *Journal of Hypertension*, 38, e3.
- [17] Sarwar M.S., Islam M.S., Al Baker S.M., & Hasnat A. 2013. Resistant hypertension: underlying causes and treatment. *Drug Research*, 63(5): 217–223. doi:10.1055/s-0033-1337930
- [18] Dybiec, J., Julia K., Ewa R., Magdalena S., Magdalena W., Ewelina M., Jacek R., and Beata F. 2023. Advances in the Pathogenesis and Treatment of Resistant Hypertension. *International Journal of Molecular Sciences*, 24, no. 16: 12911. <https://doi.org/10.3390/ijms241612911>

- [19] Oscullo, G., Torres, G., Campos-Rodriguez, F., Posadas, T., Reina-González, A., Sapiña-Beltrán, E., Barbé, F., & Martinez-Garcia, M. A. 2019. Resistant/Refractory Hypertension and Sleep Apnoea: Current Knowledge and Future Challenges. *Journal of clinical medicine*, 8(11), 1872. <https://doi.org/10.3390/jcm8111872>
- [20] Arnaud C, Bochaton T, Pépin JL, & Belaidi E. 2020. Obstructive sleep apnoea and cardiovascular consequences: Pathophysiological mechanisms. *Arch Cardiovasc Dis*, 113(5):350-358. doi: 10.1016/j.acvd.2020.01.003
- [21] Gottlieb, D. & Punjabi, N., 2020. Diagnosis and Management of Obstructive Sleep Apnea. *JAMA*, 323(14), p.1389.
- [22] Franklin, K., & Lindberg, E. 2015. Obstructive sleep apnea is a common disorder in the population—a review on the epidemiology of sleep apnea. *Journal Of Thoracic Disease*, 7(8), 1311-1322
- [23] Sateia M. J. 2014. International classification of sleep disorders-third edition: highlights and modifications. *Chest*, 146(5), 1387–1394.
- [24] Kapur, V. K., Auckley, D. H., Chowdhuri, S., Kuhlmann, D. C., Mehra, R., Ramar, K., & Harrod, C. G. 2017. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of clinical sleep medicine*, 13(3), 479–504. <https://doi.org/10.5664/jcsm.6506>
- [25] Benjafield, A. V., Ayas, N. T., Eastwood, P. R., Heinzer, R., Ip, M. S. M., Morrell, M. J., Nunez, C. M., Patel, S. R., Penzel, T., Pépin, J. L., Peppard, P. E., Sinha, S., Tufik, S., Valentine, K., & Malhotra, A. 2019. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *The Lancet. Respiratory medicine*, 7(8), 687–698. [https://doi.org/10.1016/S2213-2600\(19\)30198-5](https://doi.org/10.1016/S2213-2600(19)30198-5)
- [26] Balagny, P., Vidal-Petiot, E., Renuy, A., Matta, J., Fria-Masson, J., Steg, P. G., Goldberg, M., Zins, M., d'Ortho, M. P., & Wiernik, E. 2023. Prevalence, treatment and determinants of obstructive sleep apnoea and its symptoms in a population-based French cohort. *ERJ open research*, 9(3), 00053-2023. <https://doi.org/10.1183/23120541.00053-2023>
- [27] Gunawan P.Y., Haris, S., & Octaviana, F. 2013. Prevalensi risiko obstructive sleep apnea menggunakan kuesioner STOP-BANG dan hubungannya dengan faktor risiko stroke lain pada populasi normal. *Neurona*, 30(4):1-9.
- [28] Susanto, A.D., Yunus, F., Antarksa, B., Fitriani, F., Luthfi, A., & Harlivasari AD. 2016. Prevalensi obstructive sleep apnea berdasarkan Kuesioner Berlin pada polisi lalu lintas di Jakarta Timur. *Jurnal Respirologi Indonesia*, 36:67-72.
- [29] Morgenthaler, T., Kramer, M., Alessi, C. et al. 2006. Practice parameters for the psychological and behavioral treatment of insomnia: an update. An American Academy of Sleep Medicine report. *SLEEP*; 29(11): 1415-1419.
- [30] Patil, S. P., Ayappa, I. A., Caples, S. M., Kimoff, R. J., Patel, S. R., & Harrod, C. G. 2019. Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of clinical sleep*, 15(2), 335–343. <https://doi.org/10.5664/jcsm.7640>
- [31] Spicuzza, L., Caruso, D., & Di Maria, G. 2015. Obstructive sleep apnoea syndrome and its management. *Therapeutic advances in chronic disease*, 6(5), 273–285. <https://doi.org/10.1177/2040622315590318>
- [32] Ramar, K., Dort, L. C., Katz, S. G., Lettieri, C. J., Harrod, C. G., Thomas, S. M., & Chervin, R. D. 2015. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. *Journal of clinical sleep medicine*, 11(7), 773–827. <https://doi.org/10.5664/jcsm.4858>
- [33] Kent, D., Stanley, J., Aurora, R. N., Levine, C., Gottlieb, D. J., Spann, M. D., Torre, C. A., Green, K., & Harrod, C. G. 2021. Referral of adults with obstructive sleep apnea for surgical consultation: an American Academy of Sleep Medicine clinical practice guideline. *Journal of clinical sleep medicine*, 17(12), 2499–2505. <https://doi.org/10.5664/jcsm.9592>
- [34] Logan, A. G., Perlikowski, S. M., Mente, A., Tisler, A., Tkacova, R., Niroumand, M., Leung, R. S., & Bradley, T. D. 2001. High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. *Journal of hypertension*, 19(12), 2271–2277. <https://doi.org/10.1097/00004872-200112000-00022>
- [35] Wu, Y., Hu, G., Pan, F., Liu, J., Mo, X., Xie, Y., Liang, D., Lei, Z., & Liang, B. 2016. Obstructive sleep apnea hypopnea syndrome was a risk factor for uncontrolled hypertension in adult snorers in South China. *Clinical and experimental hypertension*, 38(5), 429–434. <https://doi.org/10.3109/10641963.2016.1151525>
- [36] Hou, H., Zhao, Y., Yu, W., Dong, H., Xue, X., Ding, J., Xing, W., & Wang, W. 2018. Association of obstructive sleep apnea with hypertension: A systematic review and meta-analysis. *Journal of global health*, 8(1), 010405. <https://doi.org/10.7189/jogh.08.010405>
- [37] Ahmed AM, Nur SM, Xiaochen Y. 2023. Association between obstructive sleep apnea and resistant hypertension: Systematic review and meta-analysis. *Frontiers in Medicine*, Vol 10. doi:10.3389/fmed.2023.1200952
- [38] Antarksa B, Santoso RM, & Astuti P. 2010. Obstructive Sleep Apnea (OSA) dan Penyakit Kardiovaskular. *Jurnal Respirologi Indonesia*.
- [39] Loh, H. H., & Sukor, N. 2022. Primary aldosteronism and obstructive sleep apnea: What do we know thus far?. *Frontiers in endocrinology*, 13, 976979. <https://doi.org/10.3389/fendo.2022.976979>
- [40] Mansukhani, M. P., Kara, T., Caples, S. M., & Somers, V. K. 2014. Chemoreflexes, sleep apnea, and sympathetic dysregulation. *Current hypertension reports*, 16(9), 476.