Relationship Between Obstructive Sleep Apnoea and AF

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Abstract

With the growing obesity epidemic, the global burden of AF and obstructive sleep apnoea (OSA) is increasing at an alarming rate. Obesity, age, male gender, alcohol consumption, smoking and heart failure are common risk factors for both AF and OSA and they are independently associated with adverse cardiovascular outcomes. Weak evidence from observational studies link OSA to the development of AF. Hypoxia/hypercapnia, systemic inflammation and autonomic nervous system modulation are biological mechanisms that link OSA to AF. Patients with OSA have a poor response to catheter ablation of AF and often suffer recurrences. Observational data shows that continuous positive airway pressure is associated with a reduction in AF burden and a better response to catheter ablation of AF. However, prospective randomised studies are needed to confirm the usefulness of continuous positive airway pressure in the treatment of AF in patients with OSA.

Keywords

AF, catheter ablation, inflammation, continuous positive airway pressure, obstructive sleep apnoea, outcomes, sleep-disordered breathing

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Prevalence of AF and Obstructive Sleep Apnoea

Nonvalvular AF is the most common sustained arrhythmia, affecting nearly 3 million adult Americans.[1–4] By 2050, nearly 12–15 million adults in the US will have AF.[1] The global prevalence of obstructive sleep apnoea (OSA) is also increasing. OSA is the most common form of sleep-disordered breathing, affecting 10–15% of the general population (6–9% in women; 17–31% in men).[5,6] Nearly 5 million adults in the US will have OSA by 2020.[5,6] Hence, both AF and OSA are global public health problems.

Risk Factors Common to AF and Obstructive Sleep Apnoea

OSA and AF share multiple risk factors. Obesity seems to be the metabolic disease that strongly links OSA to AF. With nearly 35% of adult Americans being obese, it is estimated that both OSA and AF will increase exponentially in its prevalence.[5–7] In addition, other risk factors, including increasing age, male gender, alcohol consumption, cigarette smoking, hypertension and heart failure, increase the risk of developing AF and OSA.[8–10] Hence, OSA and AF have a lot in common and it is possible there may be pathophysiological mechanisms that operate to cause both AF and OSA.

Cardiovascular Outcomes Common to AF and Obstructive Sleep Apnoea

AF confers a three- to five-fold increase in the risk of stroke, MI and heart failure (HF).[11–13] The association between OSA and cardiovascular (CV) outcomes have also been clearly established. OSA is independently associated with an increased risk of stroke.[7] In the Wisconsin Sleep Cohort, among 1,522 patients followed for 18 years, patients with untreated OSA had five times the risk of CV events when compared with those without OSA.[14] In the Sleep Heart Health Study (SHHS), a cross-sectional analysis involving 6,424 patients with sleep studies, OSA was identified as an independent risk factor for CV disease.[15] Furthermore, OSA is associated with a higher risk of hypertension, left ventricular hypertrophy and early atherosclerosis.[16–18] Among patients with heart failure, OSA and AF are associated with a poor response to cardiac resynchronisation therapy and increased mortality.[19,20]

Is Obstructive Sleep Apnoea a Risk Factor for AF in the General Population?

OSA and AF share common risk factors and are independently associated with similar adverse outcomes, but it has not been proved that OSA causes AF. Several prospective analyses have assessed the association between OSA and AF. In the SHHS, it was observed that OSA/sleep-disordered breathing increased AF risk fourfold, after adjusting for confounders.[15] These findings were confirmed by a recent meta-analysis of patients who had coronary artery bypass surgery.[21] In another analysis of 3,542 patients who received a sleep study, Gami et al. demonstrated a relationship between OSA severity and AF.[22] OSA was associated with a 1.3-fold increase in the risk of AF for every 1-point increase in apnoea-hypopnea index (AHI). This association remained robust in people over the age of 65 years.[22] Previous studies have also reported an association between OSA severity and AF frequency, AF persistence and treatment efficacy.[23–25]

Is Obstructive Sleep Apnoea a Risk Factor for AF in Patients with Heart Failure?

Although multiple studies have assessed the association between OSA and AF in patients with HF, most patients in these studies had central

sleep apnoea (CSA) and only some had OSA. Two studies, one involving 81 patients with HF (40% CSA and 11% OSA) and the other with 450 HF patients, reported a robust association between sleep apnoea and AF, but most patients had CSA and the link between OSA and AF was weak.[26,27] Similar associations have been reported in patients with systolic HF and in patients with compensated and ambulatory CHF.[28,29] However, there also was an over-representation of CSA in these studies, making conclusions about the relationship between OSA and AF non-definitive.

Several methodological considerations need to be taken into account when assessing the association between OSA and AF. The diagnosis of OSA in a majority of studies was based on patient reports and screening questionnaires. Hence under- or over-diagnosis of OSA could have been possible. Most studies did not use polysomnography to confirm OSA. Also, inferring a causal association should be avoided because of the possibility of confounding variables that were not taken into account in these observational studies.

Mechanism of AF in Patients with Obstructive Sleep Apnoea

There are several possible explanations for the triggers and substrate of AF: the multiple wavelet theory where multiple wavelets of activation coalesce and spread across the atrium; spontaneous pulmonary vein ectopy; atrial sources of repetitive spiralling activity referred to as rotors; and focal sources of rapid activation.[30–34] Intramural micro re-entry enabled by discontinuous atrial myocardial fibres and anatomic or functional conduction barriers help to explain the substrate that maintains AF.[35–37]

Several other factors such as hypoxia, hypercapnia, fluctuations in autonomic tone, atrial stretch and inflammatory factors may contribute to the pathogenesis of AF alongside OSA.

Hypoxia/Hypercapnia as Triggers to AF in Patients with Obstructive Sleep Apnoea

Patients with poorly controlled OSA have repetitive episodes of hypoxia/hypercapnia while experiencing apnoea, and then normal oxygenation when woken up by the episode. These repetitive episodes form an electrophysiological milieu for AF generation. Animal studies have shown that hypoxic periods enable slow atrial conduction and increased atrial refractoriness.[38,39] Hypercapnia that accompanies hypoxic episodes accentuates these atrial conduction changes.[38]

Clinical studies have shown that the magnitude of nocturnal desaturation is proportional to the risk of AF, and there is a relationship between the severity of OSA and the risk of AF (AHI 5–15 is associated with a twofold higher risk of AF, whereas AHI >15 is associated with an almost sixfold higher risk of AF).[40,41] These data add strength to the hypoxia/hypercapnia theory of AF in patients with OSA.

Autonomic Nervous System Modulation in AF

Repetitive episodes of apnoea which wake up patients with OSA stimulates the sympathetic nervous system and can cause catecholamine surges.[42] This stimulates the renin–angiotensin–aldosterone system which in turn leads to fluid retention. Parapharyngeal fluid collection seems to accentuate OSA.[42] Hence, patients with OSA go through a vicious circle of autonomic nervous system stimulation, fluid retention and worsening OSA.

In our previous work, in support of this hypothesis, we showed that renal sympathetic denervation, a therapeutic modality that severs sympathetic nerves around the kidney, had the potential to reduce the AHI and hence improve OSA.[42] The autonomic nervous system perturbations also increase blood pressure and cardiac afterload. These changes lead to diastolic dysfunction and significant atrial stretch.[43] Atrial stretch leads to slow conduction, areas of low voltage denoting atrial scar, decreased sinus node reserve, and pockets of excitability, predisposing to both AF initiation and maintenance.[44–47] In addition, the negative tracheal pressure that occurs during episodes of apnoea is known to modify the atrial effective refractory period and increase AF inducibility.[48]

Role of Inflammation in AF and Obstructive Sleep Apnoea

Patients with OSA are known to have enhanced systemic inflammation. Inflammatory markers including C-reactive protein, tumour necrosis factor-alpha and interleukin-6 are elevated in patients with OSA and are known to correlate with OSA severity.[49–51] Likewise, there are clinical and histological data to support the role of inflammation in promoting AF.[52–54] Inflammation seems to correlate with the quantity of atrial scar and remodelling.

Obesity and Adiposity in AF and Obstructive Sleep Apnoea

As mentioned above, an obesity epidemic runs in parallel to the increasing prevalence of AF and OSA. Obesity is a state of sympathetic excess and significant systemic inflammation and several mechanisms have been identified.[55] Hence, obesity plays a central link between OSA and AF. Sustained weight loss abates these pathogenic pathways. Weight loss consistently reduces OSA severity and improves AF burden, AF symptom scores and potentially reverses cardiac remodelling.[56,57]

Negative Thoracic Pressure, Obstructive Sleep Apnoea and AF Pathogenesis

Observations from studies using animal models show that negative intrathoracic pressure (NTP) created by an obstructed upper airway, has the potential to increase AF susceptibility.[58,59] NTP is associated with a profound shortening of atrial effective refractory period and increases AF susceptibility. Further, recurrent and chronic NTP may lead to atrial remodelling by altering connexin junctions in atrial myocytes leading to conduction abnormalities and AF susceptibility.

Obstructive Sleep Apnoea Treatment and AF Burden

Continuous positive airway pressure (CPAP) is the most common treatment modality for OSA. Multiple small observational studies have assessed the utility of CPAP in reducing AF burden.[60–63] Although limited by methodology issues and small sample sizes, these studies largely support the view that CPAP therapy improves AF burden. This is independent of the modality used for rhythm control, including antiarrhythmic drug therapy, direct current cardioversion or catheter ablation.[64–66]

In the Outcomes Registry for Better Informed Treatment for Atrial Fibrillation (ORBIT-AF) registry, 1,841 of the 10,132 AF patients had OSA.[63] These patients had worse symptoms and required more hospitalisations. CPAP therapy reduced the risk of transition from paroxysmal to persistent AF (HR 0.66). However, large randomised studies are needed before firm conclusions can be made regarding the effects of CPAP on AF.

Catheter Ablation for AF in Patients with Obstructive Sleep Apnoea

OSA is a risk factor for AF recurrence after catheter ablation (CA) of AF independent of comorbid conditions including obesity and left atrial size.[60,61] In a study by Anter et al., 43 patients with paroxysmal AF and recently diagnosed, previously untreated, moderate-to-severe OSA underwent pulmonary vein isolation and ablation of residual triggers.[67] A similar ablation approach was used in a group of 43 patients with paroxysmal AF who had a recent normal sleep study. These two groups were compared with control groups of patients with and without OSA in whom only pulmonary vein isolation was performed without any attempt to eliminate residual AF triggers. The authors found a high prevalence of low voltage areas and abnormal electrograms in both atria in patients with OSA. An increased amount of atrial fibrosis in patients with OSA has been reported in other clinical and experimental studies.[68,69]

CPAP therapy is noted to improve outcomes after CA of AF. A prospective evaluation of 62 patients with OSA undergoing CA of AF showed that CPAP therapy showed superior single (66% versus 33%) and multiple (72% versus 37%) procedure success rates.[70] Furthermore, the higher the severity of OSA, the higher the rate of AF recurrence at 1 year (mild OSA 66% versus moderate OSA 58%, versus severe OSA 82%).[23] CPAP appears to improve outcomes in patients with all grades of OSA severity. Pooled analyses shows that patients with OSA have nearly a 30% increased risk of recurrence after CA of AF compared with those without OSA.[71,72] CPAP use reduced risk of recurrent AF by 55–58%.[71,72] Another interesting observation is that in patients with AF and OSA undergoing cavo-tricuspid isthumus ablation of typical atrial flutter, the AF recurrence rate was significantly reduced in the group of CPAP users.[73] Since it is believed that AF and atrial flutter may have common triggers, this study may support the idea that CPAP use may reduce AF triggers. However, these were observational cohort studies, not prospective randomised studies, hence the strength of the evidence is not strong.

Unresolved Issues

Recent evidence has shown that patients with OSA tend to have a hypercoagulable state.[74] Hence, it may be worthwhile to assess if OSA should be considered an independent risk factor for stroke in patients with AF and if the efficacy and safety of oral anticoagulants in patients with AF is affected by OSA. Guidelines conflict on the use of screening tools, with the American College of Physicians recommending the use of tools such as the STOP-Band and Berlin questionnaires to screen for OSA while the United States Preventative Services Task Force guidelines do not. However, the screening tools do have significant predictive accuracy (sensitivity for moderate-to-severe OSA [AHI >15] is 93%, with negative predictive value of 90%).[75,76] The sensitivity to detect severe OSA (AHI >30) is 100%). Future studies should try to assess the predictive accuracy of these tools to screen for OSA in patients with AF because they represent a high-risk population. ■

Clinical Perspective

- The global burden of AF and obstructive sleep apnoea are increasing as the obesity epidemic worsens.
- AF and obstructive sleep apnoea have common risk factors.
- AF and obstructive sleep apnoea are independently associated with adverse cardiovascular outcomes.
- Biological mechanisms link obstructive sleep apnoea to the development of AF.
- Patients with obstructive sleep apnoea have a poor response to catheter ablation of AF.

1. Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol* 2009;104:1534–9. https://doi.org/10.1016/j.amjcard.2009.07.022; PMID: 19932788.
2. Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation. *J Am Coll Cardiol* 2011;57:e101–98. https://doi.org/10.1161/CIR.0b013e318214876d; PMID: 21392637.
3. Stewart S, Hart CL, Hole DJ, et al. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med* 2002;113:359–64. https://doi.org/10.1016/S0002-9343(02)01236-6; PMID: 12401529.
4. Friberg L, Hammar N, Pettersson H, et al. Increased mortality in paroxysmal atrial fibrillation: report from the Stockholm Cohort-Study of Atrial Fibrillation (SCAF). *Eur Heart J* 2007;28:2346–53. https://doi.org/10.1093/eurheartj/ehm308; PMID: 17670754.
5. Duran J, Esnaola S, Rubio R, et al. Obstructive sleep apnea–hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med* 2002;163:685–9. https://doi.org/10.1164/ajrccm.163.3.2005065; PMID: 11254524.
6. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008;5:136–43. https://doi.org/10.1513/pats.200709-155MG; PMID: 18250205.
7. Loke YK, Brown JW, Kwok CS, et al. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcome* 2012;5:720–8. https://doi.org/10.1161/CIRCOUTCOMES.111.964783; PMID: 22828826.
8. Chamberlain AM, Alonso A, Gersh BJ, et al. Multimorbidity and the risk of hospitalization and death in atrial fibrillation: a population-based study. *Am Heart J* 2017;185:74–84. https://doi.org/10.1016/j.ahj.2016.11.008; PMID: 28267478.
9. Alonso A, Krijthe BP, Aspelund T, et al. Simple risk model predicts incidence of atrial fibrillation in a racially and geographically diverse population: the CHARGE-AF consortium. *J Am Heart Assoc* 2013;2:e000102. https://doi.org/10.1161/JAHA.112.000102; PMID: 23537808.
10. Schnabel RB, Sullivan LM, Levy D, et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009;373:739–45. https://doi.org/10.1016/S0140-6736(09)60443-8; PMID: 19249635.
11. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983–88. https://doi.org/10.1161/01.STR.22.8.983; PMID:1866765.
12. Friberg L, Hammar N, Pettersson H, et al. Increased mortality in paroxysmal atrial fibrillation: report from the Stockholm Cohort-Study of Atrial Fibrillation (SCAF). *Eur Heart J* 2007;28:2346–53. https://doi.org/10.1093/eurheartj/ehm308; PMID: 17670754.
13. Violi F, Soliman EZ, Pignatelli P, et al. Atrial fibrillation and myocardial infarction: a systematic review and appraisal of pathophysiologic mechanisms. *J Am Heart Assoc* 2016;5:e003347. https://doi.org/10.1161/JAHA.116.003347; PMID: 27208001.
14. Young T, Finn L, Peppard PE, et al. Sleep disordered breathing and mortality: Eighteen-year follow-up of the Wisconsin Sleep Cohort. *Sleep* 2008;31:1071–78. PMID: 18714778.
15. Shahar E, Whitney CW, Redline S, et al. Sleep-disordered breathing and cardiovascular disease: Cross-sectional results of the sleep heart health study. *Am J Respir Crit Care Med* 2001;163:19–25. https://doi.org/10.1164/ajrccm.163.1.2001008; PMID: 11208620.
16. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA* 2000;283:1829–36. https://doi.org/10.1001/jama.283.14.1829; PMID: 10770144.
17. Hedner J, Ejnell H, Caidahl K. Left ventricular hypertrophy independent of hypertension in patients with obstructive sleep apnoea. *J Hypertens* 1990;8:941–6. https://doi.org/10.1097/00004872-199010000-00009; PMID: 2174947.
18. Koehler U, Schafer H. Is obstructive sleep apnea (OSA) a risk factor for myocardial infarction and cardiac arrhythmias in patients with coronary heart disease (CHD)? *Sleep* 1996;19:283–86. PMID: 8776784.
19. Rickard J, Michtalik H, Sharma R, et al. Predictors of response to cardiac resynchronization therapy: A systematic review. *Int J Cardiol* 2016;225:345–52. https://doi.org/10.1016/j.ijcard.2016.09.078; PMID: 27756040.
20. Shantha G, Mentias A, Pothineni NVK, et al. Role of obstructive sleep apnea on the response to cardiac resynchronization therapy and all-cause mortality. *Heart Rhythm* 2018;15:1283–8. https://doi.org/10.1016/j.hrthm.2018.06.016; PMID: 30170662.
21. Qaddoura A, Kabali C, Drew D, et al. Obstructive sleep apnea as a predictor of atrial fibrillation after coronary artery bypass grafting: A systematic review and meta-analysis. *Can J Cardiol* 2014;30:1516–22. https://doi.org/10.1016/j.cjca.2014.10.014; PMID: 25475456.
22. Gami AS, Hodge DO, Herges RM, et al: Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. *J Am Coll Cardiol* 2007;49:565–71. https://doi.org/10.1016/j.jacc.2006.08.060; PMID: 17276180.
23. Szymanski FM, Filipiak KJ, Platek AE, et al. Presence and severity of obstructive sleep apnea and remote outcomes of atrial fibrillation ablations-a long-term prospective, cross-sectional cohort study. *Sleep Breath* 2015;19:849–56. https://doi.org/10.1007/s11325-014-1102-x; PMID: 25566942.
24. Stevenson IH, Teichtahl H, Cunnington D, et al. Prevalence of sleep disordered breathing in paroxysmal and persistent atrial fibrillation patients with normal left ventricular function. *Eur Heart J* 2008;29:1662–9. https://doi.org/10.1093/eurheartj/ehn214; PMID: 18515807.
25. Monahan K, Brewster J, Wang L, et al. Relation of the severity of obstructive sleep apnea in response to anti-arrhythmic drugs in patients with atrial fibrillation or atrial flutter. *Am J Cardiol* 2012;110:369–72. https://doi.org/10.1016/j.amjcard.2012.03.037; PMID: 22516529.
26. Javaheri S, Parker TJ, Liming JD, et. al. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. *Circulation* 1998;97:2154–9. https://doi.org/10.1161/01.CIR.97.21.2154; PMID: 9626176.
27. Sin DD, Fitzgerald F, Parker JD, et al. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. *Am J Respir Crit Care Med* 1999;160:1101–6. https://doi.org/10.1164/ajrccm.160.4.9903020; PMID: 10508793.
28. Javaheri S. Sleep disorders in systolic heart failure: A prospective study of 100 male patients. The final report. *Int J Cardiol* 2006;106:21–8. https://doi.org/10.1016/j.ijcard.2004.12.068; PMID: 16321661.
29. Ferrier K, Campbell A, Yee B, et al. Sleep-disordered breathing occurs frequently in stable outpatients with congestive heart failure. *Chest* 2005;128:2116–22. https://doi.org/10.1378/chest.128.4.2116; PMID: 16236863.

30. Allessie M, Lammers W, Bonke F, et al. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J (eds). *Cardiac Electrophysiology and Arrhythmias*. NY: Grune & Stratton, 1985;265–75.
31. Haïssaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;339:659–66. https://doi.org/10.1056/NEJM199809033391003; PMID: 9725923.
32. Sanders P, Nalliah CJ, Dubois R, et al. Frequency mapping of the pulmonary veins in paroxysmal versus permanent atrial fibrillation. *J Cardiovasc Electrophysiol* 2006;17:965–72. https://doi.org/10.1111/j.1540-8167.2006.00546.x; PMID: 16948740.
33. Narayan SM, Baykaner T, Clopton P, et al. Ablation of rotor and focal sources reduces late recurrence of atrial fibrillation compared with trigger ablation alone: Extended follow-up of the confirm trial (conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation). *J Am Coll Cardiol* 2014;63:1761–8. https://doi.org/10.1016/j.jacc.2014.02.543; PMID: 24632280.
34. Haissaguerre M, Hocini M, Denis A, et al. Driver domains in persistent atrial fibrillation. *Circulation* 2014;130:530–8. https://doi.org/10.1161/CIRCULATIONAHA.113.005421; PMID: 25028391.
35. Hansen BJ, Zhao J, Csepe TA, et al. Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. *Eur Heart J* 2015;36:2390–401. https://doi.org/10.1093/eurheartj/ehv233; PMID: 26059724.
36. Shamsuzzaman AS, Winnicki M, Lanfranchi P, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation* 2002;105:2462–4. https://doi.org/10.1161/01.CIR.0000018948.95175.03; PMID: 12034649.
37. Tanigawa T, Yamagishi K, Sakurai S, et al. Arterial oxygen desaturation during sleep and atrial fibrillation. *Heart* 2006;92:1854–5. https://doi.org/10.1136/hrt.2005.081257; PMID: 17105888.
38. Stevenson IH, Roberts-Thomson KC, Kistler PM, et al. Atrial electrophysiology is altered by acute hypercapnia but not hypoxemia: Implications for promotion of atrial fibrillation in pulmonary disease and sleep apnea. *Heart Rhythm* 2010;7:1263–70. https://doi.org/10.1016/j.hrthm.2010.03.020; PMID: 20338265.
39. Iwasaki YK, Kato T, Xiong F, et al. Atrial fibrillation promotion with long-term repetitive obstructive sleep apnea in a rat model. *J Am Coll Cardiol* 2014;64:2013–23. https://doi.org/10.1016/j.jacc.2014.05.077; PMID: 25440097.
40. Mehra R, Benjamin EJ, Shahar E, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. *Am J Respir Crit Care Med* 2006;173:910–6. https://doi.org/10.1164/rccm.200509-1442OC; PMID: 16424443.
41. Tanigawa T, Yamagishi K, Sakurai S, et al. Arterial oxygen desaturation during sleep and atrial fibrillation. *Heart* 2006;92:1854–5. https://doi.org/10.1136/hrt.2005.081257; PMID: 17105888.
42. Shantha GP, Pancholy SB. Effect of renal sympathetic denervation on apnea-hypopnea index in patients with obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Breath* 2015;19:29–34. https://doi.org/10.1007/s11325-014-0991-z; PMID: 24839239.
43. Arias MA, Garcia-Rio F, Alonso-Fernandez A, et al. Obstructive sleep apnea syndrome affects left ventricular diastolic function: Effects of nasal continuous positive airway pressure in men. *Circulation* 2005;112:375–83. https://doi.org/10.1161/CIRCULATIONAHA.104.501841; PMID: 16009798.
44. Sanders P, Morton JB, Davidson NC, et al. Electrical remodeling of the atria in congestive heart failure: Electrophysiological and electroanatomic mapping in humans. *Circulation* 2003;108:1461–8. https://doi.org/10.1161/01.CIR.0000090688.49283.67; PMID: 12952837.
45. Sanders P, Morton JB, Kistler PM, et al. Electrophysiological and electroanatomic characterization of the atria in sinus node disease: Evidence of diffuse atrial remodeling. *Circulation* 2004;109:1514–22. https://doi.org/10.1161/01.CIR.0000121734.47409.AA; PMID: 15007004.
46. Sanders P, Kistler PM, Morton JB, et al. Remodeling of sinus node function in patients with congestive heart failure: Reduction in sinus node reserve. *Circulation* 2004;110:897–903. https://doi.org/10.1161/01.CIR.0000139336.69955.AB; PMID: 15302799.
47. Morton JB, Sanders P, Vohra JK, et al. Effect of chronic right atrial stretch on atrial electrical remodeling in patients with an atrial septal defect. *Circulation* 2003;107:1775–82. https://doi.org/10.1161/01.CIR.0000058164.68127.F2; PMID: 12665497.
48. Linz D, Schotten U, Neuberger HR, et al. Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation. *Heart Rhythm* 2011;8:1436–43. https://doi.org/10.1016/j.hrthm.2011.03.053; PMID: 21457790.
49. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. *J Clin Endocrinol Metab* 1997;82:1313–6. https://doi.org/10.1210/jcem.82.5.3950; PMID: 9141509.
50. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Sleep apnea and daytime sleepiness and fatigue: Relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* 2000;85:1151–8. https://doi.org/10.1210/jcem.85.3.6484; PMID: 10720054.
51. Zouaoui Boudjeltia K, Van Meerhaeghe A, Doumit S, et al. Sleep apnoea hypopnea index is an independent predictor of high-sensitivity creactive protein elevation. *Respiration* 2006;73:243–6. https://doi.org/10.1159/000090201; PMID: 16549947.
52. Boldt A, Wetzel U, Lauschke J, et. al. Fibrosis in left atrial tissue of patients with atrial fibrillation with and without underlying mitral valve disease. *Heart* 2004;90:400–5. https://doi.org/10.1136/hrt.2003.015347; PMID: 15020515.
53. Platonov PG, Mitrofanova LB, Orshanskaya V, et al. Structural abnormalities in atrial walls are associated with presence and persistency of atrial fibrillation but not with age. *J Am Coll Cardiol* 2011;58:2225–32. https://doi.org/10.1016/j.jacc.2011.05.061; PMID: 22078429.
54. Swartz MF, Fink GW, Sarwar MF, et al. Elevated pre-operative serum peptides for collagen I and III synthesis result in post-surgical atrial fibrillation. *J Am Coll Cardiol* 2012;60:1799–806. https://doi.org/10.1016/j.jacc.2012.06.048. PMID: 23040566.
55. Guarino D, Nannipieri M, Iervasi G, et al. The role of the autonomic nervous system in the pathophysiology of obesity. *Front Physiol* 2017;8:665–7. https://doi.org/10.3389/fphys.2017.00665; PMID: 28966594.
56. Iftikhar IH, Bittencourt L, Youngstedt SD, et al. Comparative efficacy of CPAP, MADs, exercise-training, and dietary weight loss for sleep apnea: a network meta-analysis. *Sleep Med* 2017;30:7–14. https://doi.org/10.1016/j.sleep.2016.06.001; PMID: 28215266.
57. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: The ARREST-AF cohort study. *J Am Coll Cardiol* 2014;64:2222–31. https://doi.org/10.1016/j.jacc.2014.09.028; PMID: 25456757.
58. Linz D, Wirth K. Intrathoracic pressure oscillations during obstructive apneas disturb ventricular repolarisation. *Eur J Appl Physiol* 2012;112:4181–4. https://doi.org/10.1007/s00421-012-2485-7; PMID: 22949051.
59. Iwasaki YK, Kato T, Xiong F, et al. Atrial fibrillation promotion with long-term repetitive obstructive sleep apnea in a rat model. *J Am Coll Cardiol* 64:2013–23. https://doi.org/10.1016/j.jacc.2014.05.077; PMID: 25440097.
60. Jongnarangsin K, Chugh A, Good E, et al. Body mass index, obstructive sleep apnea, and outcomes of catheter ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2008;19:668–72. https://doi.org/10.1111/j.1540-8167.2008.01118.x; PMID: 18363693.
61. Patel D, Mohanty P, Di Biase L, et al. Safety and efficacy of pulmonary vein antral isolation in patients with obstructive sleep apnea: The impact of continuous positive airway pressure. *Circ Arrhythm Electrophysiol* 2010;3:445–51. https://doi.org/10.1161/CIRCEP.109.858381; PMID: 20689107.
62. Fein AS, Shvilkin A, Shah D, et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. *J Am Coll Cardiol* 2013;62:300–5. https://doi.org/10.1016/j.jacc.2013.03.052; PMID: 23623910.
63. Holmqvist F, Guan N, Zhu Z, et al. Impact of obstructive sleep apnea and continuous positive airway pressure therapy on outcomes in patients with atrial fibrillation – results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J* 2015;169:647–54. https://doi.org/10.1016/j.ahj.2014.12.024; PMID: 25965712.
64. Monahan K, Brewster J, Wang L, et al. Relation of the severity of obstructive sleep apnea in response to anti-arrhythmic drugs in patients with atrial fibrillation or atrial flutter. *Am J Cardiol* 2012;110:369–72. https://doi.org/10.1016/j.amjcard.2012.03.037; PMID: 22516529.
65. Kanagala R, Murali NS, Friedman PA, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation* 2003;107:2589–94. https://doi.org/10.1161/01.CIR.0000068337.25994.21; PMID: 12743002.
66. Mohanty S, Mohanty P, Di Biase L, et al. Long-term outcome of catheter ablation in atrial fibrillation patients with coexistent metabolic syndrome and obstructive sleep apnea: impact of repeat procedures versus lifestyle changes. *J Cardiovasc Electrophysiol* 2014;25:930–8. https://doi.org/10.1111/jce.12468; PMID: 24903158.
67. Anter E, Di Biase L, Contreras-Valdes FM, et al. Atrial substrate and triggers of paroxysmal atrial fibrillation in patients with obstructive sleep apnea. *Circ Arrhythm Electrophysiol* 2017;10:e005407. https://doi.org/10.1161/CIRCEP.117.005407; PMID: 29133380.
68. Dimitri H, Ng M, Brooks AG, et al. Atrial remodeling in obstructive sleep apnea: implications for atrial fibrillation. *Heart Rhythm* 2012;9:321–7. https://doi.org/10.1016/j.hrthm.2011.10.017; PMID: 22016075.
69. Ramos P, Rubies C, Torres M, et al. Atrial fibrosis in a chronic murine model of obstructive sleep apnea: mechanisms and prevention by mesenchymal stem cells. *Respir Res* 2014;15:54–8. https://doi.org/10.1186/1465-9921-15-54; PMID: 24775918.
70. Fein AS, Shvilkin A, Shah D, et al. Treatment of obstructive sleep apnea reduces the risk of atrial fibrillation recurrence after catheter ablation. *J Am Coll Cardiol* 2013;62:300–5. https://doi.org/10.1016/j.jacc.2013.03.052; PMID: 23623910.
71. Li L, Wang ZW, Li J et al. Efficacy of catheter ablation of atrial fibrillation in patients with obstructive sleep apnoea with and without continuous positive airway pressure treatment: A meta-analysis of observational studies. *Europace* 2014;16:1309–14. https://doi.org/10.1093/europace/euu066; PMID: 24696222.
72. Shukla A, Aizer A, Holmes D, et al. Effect of obstructive sleep apnea treatment on atrial fibrillation recurrence: A meta-analysis. *J Am Coll Cardiol* 2015;1:41–51. https://doi.org/10.1016/j.jacep.2015.02.014; PMID: 29759338.
73. Bazan V, Grau N, Valles E, et al. Obstructive sleep apnea in patients with typical atrial flutter: Prevalence and impact on arrhythmia control outcome. *Chest* 2013;143:1277–83. https://doi.org/10.1378/chest.12-0697; PMID: 23117936.
74. Hong SN, Yun HC, Yoo JH, et al. Association between hypercoagulability and severe obstructive sleep apnea. *JAMA Otolaryngol Head Neck Surg* 2017;143:996–1002. https://doi.org/10.1001/jamaoto.2017.1367; PMID: 28817760.
75. Farney RJ, Walker BS, Farney RM, et al. The STOP-Bang equivalent model and prediction of severity of obstructive sleep apnea: relation to polysomnographic measurements of the apnea/hypopnea index. *J Clin Sleep Med* 2011;7:459–65. https://doi.org/10.5664/jcsm.1306 PMID: 22003340.
76. Khan A, Patel J, Sharma D, et al. Obstructive sleep apnea screening in patients with atrial fibrillation: missed opportunities for early diagnosis. *J Clin Med Res* 2018;11:21–5. https://doi.org/10.14740/jocmr3635; PMID: 30627274.