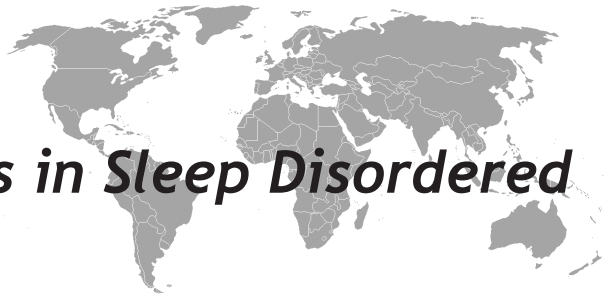
Review Article



The Right Heart Diaries in Sleep Disordered Breathing

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ABSTRACT

Epidemiologic studies show that sleep apnea increases risks for cardiovascular disease independently of individuals' demographic characteristics or risk markers i.e., smoking, alcohol, obesity, diabetes, dyslipidemia, atrial fibrillation, and hypertension. Individuals with severe sleep apnea are at increased risk for pulmonary arterial hypertension. The underlying mechanisms explaining associations between obstructive sleep apnea and pulmonary arterial hypertension are not entirely delineated. Several intermediary mechanisms might be involved including sustained sympathetic activation, intrathoracic pressure changes, and oxidative stress. Other abnormalities such as disorders in coagulation factors, endothelial damage, platelet activation, and increased inflammatory mediators might also play a role in the pathogenesis of pulmonary hypertension and cardiovascular disease. Linkage between obstructive sleep apnea and pulmonary arterial hypertension is corroborated by evidence that treatment of sleep apnea with continuous positive airway pressure reduces systolic blood pressure, improves left ventricular systolic function, and diminishes platelet activation. Several systematic studies are necessary to explicate complex associations between sleep apnea and pulmonary hypertension.

Key words: *Sleep apnea, pulmonary arterial hypertension, right heart*

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Uykudaki Solunum Bozukluğunda, Sağ Kalp Günlükleri

Epidemiyolojik çalışmalar, uyku apnenin, bireylerin demografik özelliklerinden ve risk markörlerinden yani sigara, alkol, obesite, diabet, dislipidemi, atrial fibrilayon ve hipertansiyondan bağımsız olarak kardiovasküler riski artırdığını gösterir. Ciddi uyku apneli bireyler artmış pulmoner arteriyel hipertansiyon riski altındadır. Tıkayıcı uyku apne ile pulmoner hipertansiyon ilişkisi altında yatan mekanizma tam anlamıyla tanımlanmamıştır. Uzamış sempatik aktivasyon, intratorasik basınç değişiklikleri ve oksidatif stress gibi bazı ara mekanizmalar katılabilir. Koagülasyon faktörü, endotel hasarı, trombosit aktivasyonu ve artmış inflamasyon mediatörleri ile ilgili hastaliklar gibi diğer anomalilerde pulmoner hipertansiyon ve kardiovasküler hastalıkların patogenezinde rol oynayabilir. Tıkayıcı uyku apneli hastaların pozitif yüksek hava yolu basıncı ile tedavisi sonucunda sistolik kan basıncında düşmesi, sol venrikül sistolik fonksiyonunda düzelmesi ve trombsosit aktivasyonunda azalmasi gibi kanıtlar, tıkayıcı uyku apne ile pulmoner hipertansiyon arasında ilişki olduğunu destekler. Pulmoner hipertansiyon ile uyku apne sendromu arasındaki kompleks ilişkinin gösterilmesi için daha fazla sistematik çalışmaya ihtiyaç vardır.

***Anahtar kelimeler**: Uyku apne, pulmoner arteriyel hipertansiyon, sağ kalp*

INTRODUCTION

Sleep state induced reduction and/or complete cessation of airflow characterizes sleep disordered breathing (SDB) (1). It is estimated that 17% of US adults (1), experience variations in blood gases, intrathoracic pressure and sleep/wake cycle due to SDB (2). These variations stress the cardiovascular system (3) and lead to increase in morbidity and mortality(4). Pulmonary vasculature vasoconstricts in an autoregulatory response to hypoxemia (5). Such vasoconstrictive response chronically, however can promote vascular remodelling and lead to pulmonary hypertension (PH) defined as mean pulmonary artery pressure (PAP) >25 mm Hg at rest or > 30 mm Hg with exercise as measured with right heart catheterization (RHC) (6). This PH is present in 30% to 40% of patients with SDB without any other cardiopulmonary disorders (7). Conversely, 82.6 % of PH patients have also been found to have SDB (8). This high rate of SDB among PH patients may be due to concurrent ventilatory instability causing oscillatory changes in breathing and oxygen desaturation and eventually vascular remodeling. This two way pathophysiologic link makes the relationship between these two disorders very intriguing. Purpose of this article: A-To understand ; hemodynamic changes in normal sleep and sleep disordered breathing, B-To understand; pulmonary vascular changes due to sleep disordered breathing. C-To understand: pathophysiology of Pulmonary Hypertension due to Sleep apnea, D-To show the relationship between sleep apnea and pulmonary hypertension.

Hemodynamics During Normal Sleep

Systemic and pulmonary circulation undergo not only circadian changes but also have discrete patterns during the various stages of normal sleep .Veerman et al determined the 24 hour hemodynamic profile in 8 healthy ambulatory subjects and found that in Non-Rapid eye movement (NREM)-sleep , there is a decline in blood pressure (9 mmHg), heart rate (18 beat / minute), stroke volume (7%) , cardiac output (29%) and a decrease in total peripheral resistance (22%) due to increased parasympathetic tone and decreased sympathetic tone when compared to daytime values (10,13). However Rapid eye movement (REM) sleep is characterized by a decrease in parasympathetic and an increase in sympathetic tone due to augmented baroreflex activity, resulting in an elevation of blood pressure and heart rate to levels similar to those registered during wakefulness although less than wakefulness (14). Blood pressure falls to its lowest level during the first few hours of sleep, followed by a marked surge in the morning hours coinciding with the transition from sleep to wakefulness. The average difference between waking and sleeping systolic and diastolic pressure is 10% to 20% (11). In the post wake up, there is a rise in cardiac output and stroke volume leading to high blood pressure. The absence of physical activity during the night is instrumental in the genesis of cardio-vascular (CV) circadian rhythm. When subjects rest during the daytime instead of being ambulant, the circadian variation in blood pressure and heart rate is significantly decreased (11,12).

Short Term Pulmonary Vascular Changes Due To SDB

When compared to controls(15), nocturnal systemic circulation in SDB shows a decline in cardiac output (22%) and cardiac index (24 %) while a rise in systemic vascular resistance (18%) . The inspiratory efforts to overcome the upper airway obstruction generate markedly negative intrathoracic pressure and increase the cardiac afterload

contributing to acute changes in pulmonary artery pressure (PAP) (16). In NREM- SDB: systolic and diastolic PAP decline at the beginning of the respiratory event and begin to rise again at the resumption of airflow (17). In REM-SDB; PAP is higher during REM than NREM SDB, and the difference can be related to the more profound falls in SaO2 observed during REM sleep (18).

Long Term Pulmonary Vascular Changes Due To SDB

Repetitive cycles of hypoxia and reoxygenation due to SDB promotes alterations in endothelial function (19) which in turn causes diminished nitric oxide release (20). This contributes to increased vascular smooth muscle tone and vascular remodeling which is proportional to the severity and duration of nocturnal desaturations. In a necropsy study on 20 obese subjects, half of whom had presented with SDB, Ahmed et al. found muscularisation of arterioles with a diameter of <100 μm and moderate hypertrophy of muscle cells of the pulmonary arterial media (21). The finding of mild hypoxemia in PH patients with SDB without any apparent lung disease is intriguing (22). One possibility is that it may be because of subtle changes in small airway function associated with obesity and chest wall mass loading; however, a recent study of nocturnal desaturation and daytime hypoxemia in patients with SDB suggests that the direction of association may be from nocturnal desaturation to awake hypoxemia and not the reverse (22). One possible explanation raised by the authors of the latter study is that repeated nocturnal desaturation may lead to recurrent PH and pulmonary vascular injury that in turn may lead to mild hypoxemia. Severity of SDB and nocturnal desaturation have also been linked with an increased hematocrit levels (23), although not into the polycythemia range. When compared to controls, SDB patients demonstrate increased blood viscosity with the greatest differences on first rising in the morning (24). These observations are supported by findings that PH appears to worsen across the course of the night (25).

Obstructive Sleep Apnea And Pulmonary Hypertension

Currently, PH due to SDB is placed in group 3 of World Health Organization (WHO) classification (table 1) (9). PH is common in patients with OSA, with reported estimates ranging between 16% and 42% (26,27). Discrepancies in prevalence estimates result from differences in study methodology. For example, most studies include only a small number of patients often unselected for comorbidities, and use varying definitions of pulmonary hypertension as well as modalities to measure pulmonary arterial pressure (Table 2). Most experts, however, estimate the prevalence of PH in uncomplicated OSA patients to be about 20%. The occurrence of PH in OSA patients is associated with obesity, poor lung function, degree and duration of hypoxemia, and hypercapnia, and does not appear to be associated with age, gender, or OSA severity as measured by the apnea-Hypoapnea index (AHI) (28-30). When pulmonary hypertension does occur with OSA, mean pulmonary artery pressure is generally only mildly elevated (20–52 mm Hg), unless there is underlying lung or heart disease, or chronic daytime hypoxemia or hypercapnia, in which case pulmonary hypertension may be severe (31).

Obstructive Sleep Apnea And Right And Left Heart

Moderated-severe OSA (AHI≥ 15) has been shown to have a deleterious effect over right (32,33) and left ventricular contractility (34) independently of other risk factors such as obesity, and pulmonary and arterial systolic pressure respectively (35). Of importance is that global and diastolic myocardial function of the left ventricle is impaired in OSA, even when systolic function is not. Concomitant atrial enlargement has also been reported in this population (36). The increase in atrial volume index could explain the predisposition of these patients to develop atrial fibrillation (37) with concomitant complications and/or perpetuation of heart failure. OSA is associated with increased right ventricular wall thickening but, contrary to left ventricular hypertrophy, right ventricular hypertrophy has not been confirmed as an independent predictor of adverse cardiovascular outcomes (38,39).

Pathophysiology of OSA in Pulmonary Arterial Hypertension

A. Effects of hypoxia: A significant inverse correlation between PAP and SaO2 has been documented in most SDB patients, suggesting an integral role of hypoxia in the pathogenesis of nocturnal PH (40). Patients with PH tend to be more hypoxemic during daytime wakefulness than patients without PH, a finding that could either contribute to or result from PH (41). However administration of O2 to maintain SaO2 ≥90% has only prolonged the SDB without affecting the mean PAP or the amplitude of PAP swings (42). These findings can be explained by the counteractive vasoconstrictive effects of hypercapnia caused by prolonged SDB (43). PAP during O2 administration has been shown to decrease in younger patients with minor rises in transcutaneous carbon dioxide tension suggesting

that structural vascular remodeling influences the pulmonary haemodynamic response to SDB(42). An additional possibility is that pulmonary hypoxic vasoconstriction may develop slowly, requiring repetitive and profound desaturations to significantly increase PAP (41). SDB during NREM sleep recurs with relatively constant characteristics in each patient, making the analysis of a slow effect of hypoxia difficult. In animal model of SDB by means of repetitive airway obstructions of different duration, CV changes were analyzed over a wide range of SaO2 values (42). At the release of airway occlusion, PAP progressively increased as SaO2 decreased, but oxygen administration prevented the occurrence of the pulmonary hypertensive peaks (42).

B. Mechanical Effects: SDB -induced mechanical changes may also affect the pulmonary circulation (44). The lower intrathoracic pressure during NREM-SDB episode is found out to be associated with increased pulmonary vascular resistance (PVR) but lower pulmonary flow (RVSV) (45). This increase in PVR could not be ascribed to lung volume changes, absent during apneas, but may reflect the effects of negative intrathoracic pressure on the left heart. Limitation of left ventricle (LV) filling and emptying (46) could at least contribute to increase PVR during SDB by increasing pulmonary venous pressure and blood volume (47). This hypothesis is further supported by the high pulmonary arterial wedge pressure documented during SDB (47) and by the possible, albeit infrequent, clinical presentation of obstructive sleep apnea (OSA) as nocturnal pulmonary edema (48) Thus, mechanical changes affect PVR during the apneic phase, while the pulmonary hypertensive peaks seem to be related mostly to hypoxemia, since they occur when intrathoracic pressure returns towards normal values and are blunted by oxygen administration (49)

C. Autonomic Effects: However, hypoxia may not be the only pathogenic factor responsible for the post-apneic increase in PAP. At the resolution of SDB, the similar behaviour of the pulmonary and systemic circulations (decrease in right ventricular stroke volumes (RVSV) and left ventricular stroke volumes (LVSV) and increase in pulmonary and systemic vascular resistance) may lead to the hypothesis that a generalized CV reflex may also play some role (50). The data available would not confirm the hypothesis of major, reflex-induced pulmonary circulatory changes, since PAP increased similarly during SDB in patients with or without the Shy-Drager syndrome. However, studying reflex mechanisms is difficult, especially for the pulmonary circulation which can only be approached invasively. Preliminary results obtained during repetitive airway obstruction in dogs suggested that an α-adrenergic pathway through the carotid body played only a minor role in the pathogenesis of pulmonary hypertension (49,51). On the other hand, in anaesthetized dogs, stimulation of peripheral chemoreceptors may inhibit hypoxic pulmonary vasoconstriction, whereas sympathetic activation would reduce pulmonary vascular tone during both hypoxia and hyperoxia (52).

D. Oxidative stress and systemic inflammation: The intermittent hypoxia (IH) due to SDB is implicated in vasoconstriction (53,54) and oxidative stress. Increased sympathetic surges associated with IH as compared to the continuous hypoxia (55) may reflect the oxidative stress produced by rebound hyperemia. Oxidative insult promotes the release of proinflammatory mediators, such as cyclo-oxygenase-2, tumor necrosis factor-alpha, and interleukins (56-58) leading to systemic inflammation, endothelial dysfunction and culminating in vascular non compliance (59). The dysfunctional endothelium has been observed in SDB patients without any overt vascular disease and is a precursor to atherogenesis, thrombogenesis, and reduced vascular lumen (54,55,60). Following the initial vasoconstrictive response, the restorative reperfusion generates shear stresses inhibiting complete recovery and eventually leads to persistent vasoconstriction (61). This combined with the reduced production of Nitric Oxide (NO) a potent vasodilator and increasing vascular sensitivity to endothelin-1 in SDB may result in the hemodynamic changes preceding the development of PH (54,62,63). In fact the vascular and endothelial dysfunction markers (endotelin-1 ,Thrombomodulin and ICAM) have recently been described to have a linear relationship with the severity of SDB (64).

Management

There is no doubt that effective treatment of SDB eliminates nocturnal PAH, Positive pressure therapy is considered the most effective and widely used therapy for SDB. CPAP treatment has recently been shown to result in improvement of cardiac output by 10%, cardiac index by 9%, and a reduction in the systemic vascular resistance by 18% (65). Peripheral arterial blood flow, estimated by tonometry has also been shown to improve with CPAP therapy suggesting reversal of endothelial dysfunction in SDB patients (66). There is limited evidence for the effectiveness of CPAP treatment for SDB on PAP. In a study

of 29 SDB patients (with no cardiopulmonary disease), Alchanatis and colleagues compared doppler echocardiographic determined PAP measurements with 12 healthy controls before and after 6-month of CPAP treatment. A total of 20% of the SDB patients had PH that was clinically mild (mean PAP= 25.6 mm Hg). Greater age and increased BMI distinguished these from the patients with OSA without PH; 6 months of CPAP treatment was associated with reductions in mean PAP in both SDB patients with PH (25.6 ± 4.0 to 19.5 ± 1.5 mm Hg) and those without PH (14.9± 2.2 to 11.5 ± 2.0 mm Hg) (67). Sajkov and colleagues treated 20 patients with SDB and free of any cardiopulmonary disease with 4 months of CPAP therapy (68). Only 5 patients met criteria for PH, with a mean PAP for the whole group of 16.8 mmHg. To assess the reversibility of PH in these patients, PAP was measured by echocardiography at three levels of inspired oxygen (50%, 21% and 11%). After 4 months of CPAP therapy, PAP (for all patients) decreased to a mean of 13.9 mm Hg.

CPAP may also affect vasoreactivity, as the pulmonary artery pressure response to hypoxia was attenuated. Finally, in the first placebo-controlled trial of treatment of OSA in PH, Arias and colleagues recently reported the results of a randomized cross-over trial of CPAP and sham CPAP over 12 weeks in 23 patients with OSA (69). A total of 10 patients with PH (defined as pulmonary artery systolic pressure (PASP)≥ 30 mm Hg by Doppler echocardiography) were more obese, had more ventilatory limitation (reduced FVC), and more severe sleep apnea (by AHI and mean oxygen saturation) than the 13 patients without PH. CPAP therapy reduced PASP in all patients with OSA, though more so in those with PH at baseline (mean reductions, 8.5 vs. 2.6 mm Hg) .

Conclusion

The increasing prevalence of SDB in the population suggests that the population attributable risk percent (the percentage of the total risk of cardiovascular disease due to sleep apnea) is high, making this an important public health issue; this is particularly true given that sleep apnea is a potentially modifiable risk factor. Short-term randomized controlled trials of CPAP in cardiovascular end points and long term observational cohort studies with follow-up of cardiovascular outcomes suggest a clinically significant cardiovascular risk reduction associated with the use of CPAP As a result; treatment of OSA may represent a novel target to reduce cardiovascular health outcomes.

REFERENCES

1. *Young T, Palte M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993; 328:1230-1235*
2. *Rafanan AL, Golish JA, Dinner DS. Nocturnal hypoxemia is common in primary pulmonary hypertension.Chest 2001; 120:894-899*
3. *Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995:1897-1904*
4. *Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005; 305:1046-1053*
5. *Motley HL, Cournand A, Werko L, Himmelstein A, Dresdale D. The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. Am J Physiol 1947;150:315-320*
6. *Barst RJ, McGoon M, Torbicki A, et al. Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2004; 43:40S-47S*
7. *Marrone O, Bonsignore MR. Pulmonary haemodynamics in obstructive sleep apnoea. Sleep Med Rev 2002; 6*
8. *Krishnan V, Hassaun P, Hummers L, Collop NA. Sleep disordered breathing and pulmonary hypertension. Sleep. 2005;20:A300.*
9. *Simonneau G, Galiè N,Rubin LJ, et al. Clinical classification of pulmonary hypertension. Am Coll Cardiol 2004 Jun 16;43:5-12*
10. *Veerman DP, İmholz BP, Wieling W, Wesseling KH, van Montfrans GA. Circadian profile of systemic hemodynamics. Hypertension 1995;26:55-9.*
11. *Rowlands DB ST, Watson RDS, Littler WA. The influence of physical activity on arterial pressure during ambulatory recordings in man. Clin Sci 1980; 58:115-117*
12. *Mann S, Craig MW, Melville DI, Balasubramanian V, Raftery EB. Physical activity and the circadian rhythm of blood pressure. Clin Sci 1979; 57:291-294*
13. *Somers VK Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med 1993; 328:303-307*
14. *Mancia G. Autonomic modulation of the cardiovascular system during sleep. N Eng J Med 1993; 328*
15. *Bakshi MS, Hoskere G, Mehta JB, Chidambaram B, Ponder M, Girish MR. Circulatory response in sleep apnea patients during sleep before and after CPAP treatment. Sleep. 2005;20:A194*
16. *Bonsignore MR, Marrone O, Insalaco G, Bonsignore G. The cardiovascular effects of obstructive sleep apnoeas: analysis of pathogenic mechanisms. Eur Respir J 1994; 7:786-805*
17. *Marrone O, Bellia V, Ferrara G, et al. Transmural pressure measurements. İmportance in the assessment of pulmonary hypertension in obstructive sleep apneas. Chest*

1989; 95:338-342

18. Marrone O, Romano S. Pulmonary artery pressure in obstructive apneas: influence of intrathoracic pressure and hypoxia. Am Rev Respir Dis 1993; 147:1017

19. Phillips BG, Narkiewicz K, Pesek CA, Haynes WG, Dyken ME, SomersVK. Effects of obstructive sleep apnea on endothelin-1 and blood pressure. J Hypertens. 1999;17:61-66.

20. Carpagnano GE, Spanevello A, Sabato R, et al. Exhaled pH, exhaled nitric oxide, and induced sputum cellularity in obese patients with obstructive sleep apnea syndrome. Transl Res. 2008 Jan;151(1):45-50.

21. Ahmed Q, Chung-Park M, Tomashefski J. Cardiopulmonary pathology in patients with sleep apnea/obesity hypoventilation syndrome. Hum Pathol 1997;28:264-269

22. Sajkov D, Cowie RJ, Thornton AT, Espinoza HA, McEvoy RD Pulmonary hypertension and hypoxemia in obstructive sleep apnea syndrome.. Am J Respir Crit Care Med. 1994 Feb;149:416-22.

23. Sajkov D, Wang T, Saunders NA, Bune AJ, Neill AM, Douglas MR. Daytime pulmonary hemodynamics in patients with obstructive sleep apnea without lung disease. Am J Respir Crit Care Med. 1999 ;159:1518-26.

24. Dikmenoğlu N, Ciftçi B, İleri E, et al. Erythrocyte deformability, plasma viscosity and oxidative status in patients with severe obstructive sleep apnea syndrome. Sleep Med. 2006 Apr;7:255-61

25. Reinhart WH, Oswald J, Walter R, Kuhn M. Blood viscosity and platelet function in patients with obstructive sleep apnea syndrome treated with nasal continuous positive airway pressure. Clin Hemorheol Microcirc. 2002;27:201-7.

26. Podszus T, Mayer J, Penzel T, et al. Nocturnalhemodynamics in patients with sleep apnea. Eur J Respir Dis 1986;146:435-42.

27. Hawrylkiewicz I, Palasiewicz G, Plywaczewski R,et al. Pulmonary hypertension in patients with pure obstructive sleep apnea]. Pol Arch Med Wewn 2004;111:449-54

28. Chaouat A, Weitzenblum E, Krieger J, et al. Pulmonary hemodynamics in the obstructive sleep apnea syndrome. Results in 220 consecutive patients.Chest 1996;109:380-6.

29. Bradley TD, Rutherford R, Grossman RF, et al. Role of daytime hypoxemia in the pathogenesis of right heart failure in the obstructive sleep apnea syndrome. Am Rev Respir Dis 1985;131:835-9.

30. Weitzenblum E, Krieger J, Apprill M, et al. Daytime pulmonary hypertension in patients with obstructive sleep apnea syndrome. Am Rev Respir Dis 1988;138:345-9.

31. Chaouat A, Weitzenblum E, Krieger J, et al. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. Am J Respir Crit Care Med 1995;151:82-6.

32. Dursunoglu N, Dursunoglu D, Kilic M. Impact of obstructive sleep apnea on right ventricular global function: sleep apnea and myocardial performance index. Respiration 2005;72:278-84.

33. Sanner BM, Konermann M, Sturm A, et al. Right ventricular dysfunction in patients with obstructive sleep apnoea syndrome. Eur Respir J 1997;10:2079-83.

34. Dursunoglu D, Dursunoglu N, Evrengul H, et al.Impact of obstructive sleep apnoea on left ventricular mass and global function. Eur Respir J 2005;26:283-8.

35. Romero-Corral A, Somers VK, Pellikka PA, et al.Decreased right and left ventricular myocardialperformance in obstructive sleep apnea. Chest2007;132:1863-70.

36. Otto ME, Belohlavek M, Romero-Corral A, et al.Comparison of cardiac structural and functional changes in obese otherwise healthy adults with versus without obstructive sleep apnea. Am J Cardiol 2007;99:1298-302.

37. 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.

38. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med 1990;322:1561-6.

39. Guidry UC, Mendes LA, Evans JC, et al. Echocardiographic features of the right heart in sleep-disorderedbreathing: the Framingham Heart Study. Am J Respir Crit Care Med 2001;164:933-8.

40. Marrone O Bollero V, Ferrara G, et al. Transmural pressure measurements. İmportance in the assessment of pulmonary hypertension in obstructive sleep apneas. Chest 1989; 95:338-342

41. Sajkov D CR, Thornton AT, Espinoza HA, McEvoy RD. Pulmonary hypertension and hypoxemia in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 1994; 149:416-422

42. Marrone O, Bollero V, Pieri D, Salvaggio A, Bonsignore, G. M. Acute effects of oxygen administration on transmural pulmonary artery pressure in obstructive sleep apnea. Chest 1992; 101:1023-1027

43. Emery C SP, Mohammed F, Barer G. The action of hypercapnia during hypoxia on pulmonary vessels. Bull Eur Physiopathol Respir 1977;

44. Shivalkar B, Van De Heyning C, Kerremans M, Rinkevich D, Verbraecken J, De Backer W, et al. Obstructive Sleep Apnea Syndrome. Journal of the Am Coll Cardiol 2006;47(7):1433-9.

45. Robotham J LW, Holland L, MacGregor D, Bryan, A RJ. Effects of respiration on cardiac performance. J Appl Physiol: Respirat Environ Exercise Physiol 1978; 44:703-709

46. Scharf SM. Cardiovascular effects of airways obstruction. Lung 1991; 169:1-23

47. Bradley TD. Right and left ventricular function impairment and sleep apnea. Clin Chest Med 1992; 13:459-479

48. Chaudary B, Ferguson D, Speir W. Pulmonary edema as a presenting feature of sleep apnea syndrome. Chest 1982; 82:122-124

49. Iwase N, Kikuchi Y, Hida W, et al. Effects of repetitive air-

way obstruction on O2 saturation and systemic and pulmonary arterial pressure in anesthetized dogs. Am Rev Respir Dis 1992; 146:1402-1410

50. *Garpestad E Katayama H, Parker J, et al. Stroke volume and cardiac output decrease at termination of obstructive apneas. J Appl Physiol 1992;73:1743-1748*

51. *Iwase N Kikuchi Y, Hida W, et al. Effects of phentolamine and carotid body resection on pulmonary artery and systemic artery pressure during repetitive airway obstruction. Am Rev Respir Dis 1989; 39:A181*

52. *Naeije R, Lejeune P, Leeman M, Melot C, Closset J. Pulmonary vascular responses to surgical chemodenervation and chemical sympathectomy in dogs. J Appl Physiol Rev 1989; 66:42-50*

53. *Prabhakar NR, Peng YJ, Jacono FJ, Kumar GK, Dick TE. Cardiovascular alterations by chronic intermittent hypoxia: importance of carotid body chemoreflexes. Clin Exp Pharmacol Physiol. 2005;32:447-449.*

54. *Allahdadi KJ, Walker BR, Kanagy NL. Augmented endothelin vasoconstriction in intermittent hypoxia-induced hypertension. Hypertension. 2005;45:705-709.*

55. *Rodway GW, Sethi JM, Hoffman LA, et al. İntermittent hypoxia (İH) versus continuous hypoxia (CH): impact on hemodynamic variables and iNOS expression. Sleep. 2005;20:A211*

56. *Yamauchi M, Nakano H, Maekawa J, et al. Oxidative stress in obstructive sleep apnea. Chest. 2005;127:1674-1679.*

57. *Teramoto S, Yamamoto H, Yamaguchi Y, Namba R, Ouchi Y. Obstructive sleep apnea causes systemic inflammation and metabolic syndrome. Chest. 2005;127:1074-1075.*

58. *Kataoka T, Enomoto F, Kim R, et al. The effect of surgical treatment of obstructive sleep apnea syndrome on the plasma TNF-alpha levels. Tohoku J Exp Med. 2004;204:267-272.*

59. *Hawrylkiewicz I, Sliwinski P, Gorecka D, Plywaczewski R, Zielinski J. Pulmonary haemodynamics in patients with OSAS or an overlap syndrome. Monaldi Arch Chest Dis. 2004;61:148-52.*

60. *Hung TH, Charnock-Jones DS, Skepper JN, Burton GJ. Secretion of tumor necrosis factor-alpha from human placental tissues induced by hypoxia-reoxygenation causes endothelial cell activation in vitro: a potential mediator of the inflammatory response in preeclampsia. Am J Pathol. 2004;164:1049-1061.. Monaldi Arch Chest Dis. 2004;61:148-152.*

61. *Sharafkhaneh H, Hirshkowitz M, Sharafkhaneh A, Bozkurt B. Endothelial dependent vascular dilation is abnormal in patients with obstructive sleep apnea. Sleep. 2005;20:A210.*

62. *Lopez-Ramos JC, Martinez-Romero R, Molina F, et al. Evidence of a decrease in nitric oxide-storage molecules following acute hypoxia and/or hypobaria, by means of chemiluminescence analysis. Nitric Oxide. 2005 ;13:62-7.*

63. *Naughton MT. .The link between obstructive sleep apnea and heart failure: underappreciated opportunity for treatment. Curr Cardiol Rep. 2005;7:211-215.*

64. *Poyares D, Guilleminault C. Sleep and endothelium activation in patients with UARS and severe OSA, preliminary report. Sleep. 2005;20:A196*

65. *Parish J, Shepard J. Cardiovascular effects of sleep disorders. Chest. 1990;97(5):1220-6.*

66. *Morgenthaler T, Lerman A. Endothelial dysfunction assessed by peripheral arterial tonometry in obstructive sleep apnea patients improves with CPAP therapy. Sleep. 2005;20(suppl):A177.*

67. *Alchanatis M, Tourkohoriti G, Kakouros S, Kosmas E, Podaras S. Daytime pulmonary hypertension in patients with obstructive sleep apnea: the effect of continuous positive airway pressure on pulmonary hemodynamics. Respiration 2001; 68:566-572*

68. *Sajkov D Wang T, Saunders NA, Bune AJ, McEvoy RD. Continuous positive airway pressure treatment improves pulmonary hemodynamics in patients with obstructive sleep apnea. Am J Respir Crit Care Med 2002; 165:152-158*

69. *Arias MA Garcia-Rio F, Alonso-Fernandez A, Martinez I, Villamor J. Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure: a randomized, controlled cross-over study. Eur Heart J 2006; 27:1106-1113*

70. *Fletcher EC, Schaaf JW, Miller J, et al. Long-term cardiopulmonary sequelae in patients with sleep apnea and chronic lung disease. Am Rev Respir Dis 1987;135:525-33.*

71. *Krieger J, Sforza E, Apprill M, et al. Pulmonary hypertension, hypoxemia, and hypercapnia in obstructive sleep apnea patients. Chest 1989;96:729-37.*

72. *Shinozaki T, Tatsumi K, Sakuma T, et al. Daytime pulmonary hypertension in the obstructive sleep apnea syndrome. Nihon Kyobu Shikkan GakkaiZasshi 1995;33:1073-9*

73. *Laks L, Lehrhaft B, Grunstein RR, et al. Pulmonary hypertension in obstructive sleep apnoea. Eur Respir J 1995;8:537-41.*

74. *Bady E, Achkar A, Pascal S, et al. Pulmonary arterial hypertension in patients with sleep apnoea syndrome. Thorax 2000;55:934-9.*