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Sleep, death, and the heart

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Mansukhani MP, Wang S, Somers VK. Sleep, death, and the heart. Am J Physiol Heart Circ Physiol 309: H739–H749, 2015. First published July 17, 2015; doi:10.1152/ajpheart.00285.2015.—Obstructive and central sleep apnea have been associated with increased risk of adverse cardiovascular events and mortality. Sympathetic dysregulation occurring as a result of the respiratory disturbance is thought to play a role in this increased risk. Sleep apnea increases the risk of arrhythmias, myocardial ischemia/infarction, stroke, and heart failure, all of which may increase mortality risk. A higher incidence of nocturnal arrhythmias, cardiac ischemia, and sudden death has been noted in subjects with sleep-disordered breathing (SDB). In this review, the association between SDB and each of these conditions is discussed, as well as the potential mechanisms underlying these risks and the effects of treatment of SDB. Particular emphasis is placed on the relationship between SDB and nocturnal atrial and ventricular arrhythmias, myocardial ischemia/infarction and sudden death.

Obstructive sleep apnea (OSA) is characterized by repeated upper-airway occlusion and hypoxemia in sleep. OSA is common in the general adult population and occurs primarily as a result of an anatomically narrow upper airway due to obesity, bony and soft tissue structures, although several other factors, including neural control of the airway, may be important contributors (149). Central sleep apnea (CSA), on the other hand, is most commonly seen in the context of heart failure, where cessation of breathing occurs because of a reduced central drive to breathe (149). In normal sleep, changes in respiration, heart rate (HR), and blood pressure (BP) are sleep-stage dependent (118, 145), whereas in obstructive and CSA, they correlate with severity and duration of apnea (67, 87).

Both types of sleep-disordered breathing (SDB), OSA and CSA, have been shown to be associated with sympathetic dysregulation in sleep and during wakefulness as well (28, 78, 88, 107, 142, 144). The peripheral chemoreflex is thought to play an important role in this dysregulation (23, 30, 60, 87, 108, 146–148, 155, 175). The response to hypoxemia in OSA appears exaggerated compared with that in subjects of similar weight without OSA, who are exposed to similar levels of hypoxemia (106, 142). The chemoreflex-induced sympathetic response to a combination of apnea, hypoxemia, as well as hypercapnia could explain the increased risk of adverse cardiovascular events and death in patients with OSA (87, 88).

In this review, the association between SDB and sudden death in adults is discussed. The relationship between SDB and nocturnal arrhythmias, nocturnal myocardial ischemia/infarction, heart failure, and stroke, all of which could potentially increase mortality risk in this group of patients, is reviewed. While periodic limb movements of sleep (69) and sleep deprivation (41) could potentially be associated with increased risk of adverse cardiovascular events and mortality, these subjects are outside the scope of this review. Medications have not been found to help significantly in the treatment of OSA (101). There is limited evidence supporting the role of medication in the treatment of CSA in the context of heart failure when positive airway pressure (PAP) is not tolerated, especially after optimization of medical therapy (6). The effects of continuous PAP (CPAP), oral appliances, and surgical treatment of SDB, where applicable, are discussed.

Systemic Hypertension

OSA is very closely associated with pulmonary (62) and systemic hypertension (15, 51, 89, 170). Approximately half of patients with systemic hypertension have coexisting OSA (113). The risk of both baseline and future hypertension is increased in OSA (15, 51, 89, 170) in a dose-response fashion. Thus the higher the severity of untreated OSA, the greater the incidence of hypertension (89, 115). In addition, OSA has been noted to be the most common secondary etiology in patients with resistant hypertension (113). A recent study

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showed that rapid eye movement (REM)-predominant OSA is also significantly associated with current and future risk of hypertension (97).

It is possible that sympathetic dysregulation induced by OSA may play a role in the development of hypertension. There are data from a number of animal studies demonstrating increases in BP in response to airway occlusion (14) and intermittent hypoxia (23, 27, 31, 77, 152). One study of human subjects with OSA showed that the sympathetic response to hypoxia was related to apnea-hypopnea index (AHI) and daytime/nighttime BP (39). Recent experiments conducted in a rat model of sleep apnea have suggested that the changes in sympathetic control induced by chronic, intermittent hypoxia might actually precede the development of hypertension (59).

Furthermore, treatment of OSA with continuous PAP (CPAP) (56, 105, 144), oral appliances (117), tracheostomy (28), and maxillo-mandibular advancement surgery (58) has been shown to decrease BP. Maximum reduction appears to occur in patients with coexisting diabetes mellitus (104) and in those with severe OSA (120) and resistant hypertension (55, 161). Modest beneficial effects of long-term CPAP treatment on BP have been reported not just in subjects with a current diagnosis of hypertension but also in subjects who are prehypertensive (24, 169). The effects of CPAP use on the risk of incident or new hypertension, on the other hand, are mixed (7, 89). Interestingly, the beneficial effects of CPAP on BP appear to be more pronounced in OSA subjects with excessive daytime sleepiness (116) and are absent in those without sleepiness (7, 8, 128) in some studies.

Nondipper BP pattern. Nondipping of BP at night has been noted to be an adverse prognostic factor for cardiovascular morbidity and mortality (163). Undiagnosed SDB could be responsible in part for these surges in BP at night (25, 121). Recurrent episodes of apnea and hypoxemia increase sympathetic activation, increasing cardiac output and peripheral vasconstriction (145). Once breathing restarts at the termination of an apnea, the increased cardiac output is delivered into constricted blood vessels, resulting in striking BP surges at night (111, 126). The severity of respiratory disturbance appears to be related to a nondipping BP profile in younger subjects, whereas in older subjects, severity of sleep disturbance appears to have more of an influence on nondipping status (133). Increased inflammation (57) and white matter changes in the brain (76) have been postulated as possible mechanisms conferring an increased risk of adverse events in patients with OSA and a nondipping BP profile.

CPAP treatment could alleviate the detrimental effects of SDB on nocturnal BP. A study conducted in patients with resistant hypertension demonstrated that a higher proportion of OSA patients treated with CPAP after 12 wk had a nocturnal dipping BP pattern compared with those not on CPAP (91). Another recent study suggested that evening dosing of antihypertensive medication may result in a decrease in nighttime BP and attenuate nondipper status in nonsleepy patients with OSA and nondipping BP, irrespective of CPAP use (68).

Arrhythmias

Atrial fibrillation. SDB has been found to be more common in patients with atrial fibrillation (AF) than in other high-risk patients with multiple other comorbidities (37), as well as in patients with multiple other comorbidities (37), as well as in patients with atrial fibrillation (AF) than in other high-risk patients with multiple other comorbidities (37), as well as in patients with atrial fibrillation (AF) than in other high-risk patients with multiple other comorbidities (37), as well as in patients with atrial fibrillation (AF) than in other high-risk patients with multiple other comorbidities (37), as well as in patients with atrial fibrillation (AF) than in other high-risk patients with multiple other comorbidities (37), as well as.
due to an increase in events between midnight and 6:00 AM, but without OSA (OR 1.43, 95%; CI 1.12–1.82). While an increase in OSA severity was associated with complex ventricular ectopy but not with AF, CSA was found to be more strongly associated with AF, suggesting that different types of sleep apnea-related stresses may be linked to different types of arrhythmias.

The effects of treatment of OSA on reducing ventricular arrhythmias are mixed in the medical literature. In one study of 400 patients with SDB undergoing polysomnography, about half were found to have arrhythmias, including nonsustained VT, sinus arrest, second-degree atrioventricular block, and ventricular premature contractions. After tracheostomy was performed as a treatment for OSA in the 55 patients who had significant arrhythmias, no arrhythmias were noted other than ventricular premature contractions (49). Some studies have shown that CPAP has a favorable effect in reducing ventricular arrhythmias (1, 129, 131), whereas others have not (21); in particular, the impact on the risk of VT is unclear.

**Brugada syndrome.** Brugada syndrome is an uncommon condition of uncertain prevalence that is associated with sudden death in otherwise healthy individuals, usually occurring in the fourth decade of life. It was first described in 1992 in patients with recurrent VT/VF, with characteristic ST elevation in leads V1–V3, and right bundle branch block (16). Some patients have a proven sodium channel SCN5A gene mutation, but other ion channel mutations have also been described (17).

Sudden unexplained nocturnal death syndrome (SUNDS) has been described in Laos, Japan, and Philippines in healthy young men, as a condition characterized by night terrors, vocalizations, tachycardia, sweating, sympathetic activation, breathing irregularities, and VF (96, 156). Brugada syndrome and SUNDS are thought to be closely linked (40, 80, 162).

An increased frequency of VF between midnight and 6:00 AM has been demonstrated in patients with Brugada syndrome (92), and a high prevalence of OSA has also been found in patients with Brugada syndrome (82). Macedo et al. (82) demonstrated that despite a normal body mass index of 24.7 kg/m², SDB, mainly OSA (AHI, 17.2 ± 14/h), was present in 45% of patients with Brugada syndrome versus in 27% of matched controls (P ≤ 0.01). In the nine subjects with Brugada syndrome who were treated for high risk of fatal arrhythmias, defined as Brugada syndrome type 1 EKG with syncope or resuscitated sudden cardiac death (SCD), two-thirds had SDB. In a recent study, Brugada syndrome was not found to be associated with autonomic dysfunction unless there was coexisting SDB (153). Thus there is a possibility that the presence of OSA in patients with Brugada syndrome may contribute to the increased mortality in this group of patients through sympathetic dysregulation, but further studies are needed to confirm these hypotheses.

**Nocturnal Myocardial Ischemia/Infarction**

The association between nocturnal hypoxemia and nocturnal myocardial ischemia and arrhythmias was initially demonstrated in a study of 19 consecutive patients with acute myocardial infarction (MI) (32). Subjects were monitored continuously with Holter monitor and pulse oximetry for at least two nights, for 8 h or longer each night, between 2 and 6 days following MI. Episodic and constant hypoxemia were common; the former was found to occur simultaneously with episodic tachycardia, ST segment changes, and other arrhythmias in more than half the patients after the first night. In a series of patients with nocturnal ischemia, Franklin et al. (29) described a patient awakened by angina at 4:46 AM, preceded by a clear episode of apnea and hypoxemia. More recent studies have shown an increased risk of MI in patients with SDB (38, 73). A Danish study of 33,274 individuals with SDB demonstrated heightened risk of MI, particularly in those below 50 years of age (73). Another study showed that OSA was an independent predictor of MI with an OR of 4.9 (95%; and CI, 2.9–8.3; P = 0.017) (38).

Sympathetic nerve activity is lower, and there is less fluctuation in respiratory and BP measures in normal awake subjects compared with those with OSA. Sympathetic activity, HR, and BP changes are more marked in sleep, especially in REM sleep, in patients with OSA, and these changes appear to be ameliorated by the use of CPAP (144). These autonomic and hemodynamic changes resulting from hypoxemia and/or apnea in patients with OSA may induce cardiac ischemia. A study conducted in 226 patients undergoing coronary angiography for angina pectoris, who had a sleep study and Holter monitoring performed simultaneously, showed ST-segment depression in 56% of the patients and nocturnal ST-segment depression in 31% (100). ST-segment depression occurring...
within 2 min following an apnea, hypopnea, or desaturation was seen in 19% of those with nocturnal ST-segment depression, particularly in men (P < 0.01) and in those with more severe SDB (P < 0.001). In most of these subjects (70%), there was a series of three or more breathing events (apnea, hypopnea, or desaturation) preceding the ST-segment depression.

Sympathetic activation (88), as well as changes in endothelial (9) and platelet (10) function at night, could increase the risk of adverse nocturnal coronary events and thus may account for the reversed day-night variation of acute MI seen in patients with OSA (72). In this study, 92 patients with acute MI in whom the time of onset of chest pain was clearly known underwent polysomnography. MI occurred in 32% of patients with OSA between midnight and 6:00 AM compared with 7% of those without OSA (Fig. 2) and was in contrast to the usual diurnal occurrence in the general population. Among those who had an MI between midnight and 6:00 AM, 91% had OSA, a sixfold higher odds (95%; CI, 1.3–27.3, P = 0.01) compared with those in whom MI occurred during the other 12 h of the day.

CPAP treatment has recently been shown to decrease the risk of repeat revascularization after percutaneous coronary intervention (167). However, the beneficial effects of CPAP on reducing risk of MI have been observed in some (38) but not in other studies (73).

Stroke

OSA has been demonstrated to be an independent risk factor for stroke and death in prospective longitudinal cohorts (5, 73, 90, 103, 123, 159, 168). Additionally, an increased risk of mortality has been noted in patients with OSA who have suffered an acute ischemic stroke (85).

Both OSA and CSA can be seen after an acute ischemic stroke, and in many patients, SDB is seen to persist for months following a stroke. Whether this persistent SDB reflects the presence of preexisting undiagnosed SDB preceding the onset of stroke is unclear at this time (86).

Recently, severe OSA was associated with ischemic stroke, with symptoms noted soon after waking from sleep, the so-called “wake-up stroke” (54). In this subcategory of stroke patients, symptoms are thought to commence during sleep, and since the exact time of onset of symptoms is not known, they are generally excluded from revascularization therapy (164).

Possible mechanisms through which OSA may increase the risk of incident stroke include AF (86) or increased thrombogenicity by increasing fibrinogen levels, platelet adhesiveness, and blood viscosity (138, 158). One recent study indicated significantly increased morning fibrinogen levels in patients with severe OSA compared with controls (P = 0.003) and those with mild OSA (P = 0.02), after adjusting for age, body mass index, BP, smoking, and alcohol consumption (138).

Additionally, increased risk of a right to left shunt across a patent foramen ovale (PFO) and increased risk of deep venous thromboembolism in patients with OSA as discussed below are potential contributory factors that could increase overall risk of stroke in these patients.

Patent foramen ovale. PFO is a congenital defect of the atrial septum that frequently persists into adulthood (53, 166). The vast majority of patients are asymptomatic. However, the most dreaded potential complication of a PFO is cryptogenic stroke through paradoxical embolism (74, 95). PFO may be more common in patients with OSA (48, 66), and patients with OSA may have larger, more clinically significant shunts across a PFO (137).

In a recent study of 10 patients (8 male), aged 55 ± 11 years, undergoing right heart catheterization, simulated OSA via the Mueller maneuver resulted in an increased right-left pressure gradient across the atrial septum, higher than that recorded during the valsala maneuver (70). This was thought to be secondary to greater blood return to the right atrium from extrathoracic veins. These preliminary results provide a possible hemodynamic basis for increased risk of stroke across a PFO in patients with OSA.

Both OSA and PFO have been shown to be associated with reduced fibrinolytic activity during sleep; thus it is possible that a combination of both of these conditions results in a greater prothrombotic state in sleep that can predispose to stroke, compared with either condition alone (125).

One case report described disappearance of right to left shunting across a PFO in a patient with OSA treated with CPAP for 1 wk (119). Further studies are needed to ascertain the effects of treatment of SDB in the context of PFO.

The effects of PFO closure on symptoms and oxygen desaturation in patients with OSA is mixed in the literature, with one study showing no change (137) and others showing beneficial effects on these measures (2, 164).

Deep venous thrombosis. Deep venous thrombosis (DVT) can lead to pulmonary embolism in 50% of untreated individuals, usually within days or weeks (22, 45). Also, paradoxical embolism from DVT can result in stroke in the setting of a PFO as noted above, and both of these complications, namely pulmonary embolism and stroke, can be fatal.

OSA is a state of hypercoagulability, and several reports have indicated a higher prevalence of DVT in patients with OSA (3, 4, 18, 114). A recent large prospective study evaluated 5,680 subjects with newly diagnosed sleep apnea and 4,505 controls over an average follow-up period of 3.6 years (18). A total of 30 subjects (0.53%) with sleep apnea developed a DVT versus 10 (0.22%) from the
control group ($P = 0.002$) (Fig. 3). This effect was independent of confounders, demonstrating that sleep apnea may be an independent risk factor for DVT. The risk of DVT was noted to be even higher in those needing CPAP treatment (HR, 9.58 beats/min, 95%; and CI, 3.18–28.82, $P < 0.001$). Another recent study (114) showed an up to fourfold increase in the risk of DVT and pulmonary emboli (PE) in patients with OSA, and one study (4) suggested that the association between SDB and DVT/PE was significant in female but not in male subjects. Patients with OSA also appear to need a higher dose of warfarin for anticoagulation than those without OSA (64).

The effects of CPAP treatment on the risk and outcomes of DVT are unknown at this time.

Heart Failure

Patients with heart failure can have both OSA and CSA, with the latter often manifesting as a crescendo-decrescendo breathing pattern called Cheyne-Stokes respiration (CSR) (63, 141). CSA and CSR are thought to arise as a result of increased responsiveness to arterial carbon dioxide levels noted in patients with heart failure (61).

High sympathetic drive is evident in subjects with systolic and diastolic heart failure, and in those with CSA, levels of sympathetic activity increase even further (125a, 143, 154, 160). This increased sympathetic activity may explain the higher mortality risk noted in patients with CHF and CSA (79). However, some data suggest that in patients with CHF, increased sympathetic activity may be related to heart failure severity and not to CSA severity (83). In a study of 55 patients with CHF, mean pulmonary artery pressure, but not measures of sleep apnea severity, independently correlated with total and cardiac norepinephrine spillover. Autonomic dysfunction, evidenced by decreased HR variability, has also been reported in patients with CSA (75). CPAP treatment has been shown to decrease cardiac sympathetic activity and alleviate autonomic dysfunction in patients with CHF (44, 52).

In a study designed to elucidate the mechanisms underlying SCD in 216 patients with stable advanced heart failure, 21 (9%) patients experienced cardiac arrest over a 4-year follow-up period. The most common electrocardiographic rhythms preceding SCD included severe bradycardia in nine patients, VT/VF in eight patients, electromechanical dissociation in two patients, and AV block in two patients (81). All of these arrhythmias, including bradyarrhythmias, are commonly noted in patients with severe SDB.

Severe CSA has been associated with increased risk of AF in patients with systolic heart failure (46). CSA has also been associated with ventricular arrhythmias in CHF, and VT/VF is the most common cause of sudden nocturnal death in patients with CHF (47). Thus there may be a link between nocturnal arrhythmias and sudden nocturnal death in patients with CHF.

One study in patients with CHF demonstrated that SDB induced electrical instability in the form of increased nighttime T-wave alternans, a risk marker of lethal arrhythmias and sudden death at night (151). Further studies are required to demonstrate conclusively increased mortality in CHF patients as a result of SDB, both CSA and OSA.

CPAP treatment has been shown to increase ejection fraction in almost all patients with OSA and in 50% of those with CSA (71). A meta-analysis showed that the ejection fraction improved by about 5% after CPAP treatment in patients with OSA and heart failure (150). Observational studies have indicated improved survival rates in patients with CHF who are effectively treated with PAP (5, 71). It should be noted, however, that preliminary results from the not-yet published SERVE-HF randomized controlled trial have indicated increased cardiovascular mortality risk in patients with moderate-severe CSA and chronic symptomatic heart failure (New York Heart Association, classes II–IV) with an estimated ejection fraction of $\leq 45\%$ using an adaptive servoventilator form of PAP treatment. The reasons for these findings are unclear, and further analyses will need to be undertaken to clarify this issue (125a).

Exercise Tolerance

A decrease in functional capacity on exercise testing has been noted in patients with OSA (84, 127), and one study showed that decrease in functional capacity in patients with

![Fig. 3. Freedom from deep vein thrombosis in subjects with and without sleep apnea. Reproduced from Chou et al. (18) with permission.](http://wjxph.ajpheart.org/ by 10.220.33.5 on April 6, 2017 www.ajpheart.org)
OSA was associated with increased mortality risk (110). A recent study showed that exercise training reduced sympathetic nerve activity in patients with CHF. Exercise training was seen to improve SDB and increase duration of deep sleep in those with OSA but not in those with CSA (157). Further studies are needed to clarify the association between reduced exercise capacity and increased mortality in patients with SDB.

Sudden Death

An increased risk of nocturnal sudden death has been demonstrated in patients with OSA (35, 36). In a study spanning 16 years and involving 112 adult subjects with SCD who had undergone prior polysomnography, rates of SCD during four different intervals of the day were compared between those with and without OSA (35). In contrast to the general population, where the risk of SCD peaks during the day with a nadir between midnight and 6:00 AM, in this study, SCD occurred between midnight and 6:00 AM in 46% of subjects with OSA versus 21% of those without OSA ($P = 0.01$) (Fig. 4). In addition, the AHI directly correlated with the relative risk of SCD between midnight and 6:00 AM. Similar results were seen when data were analyzed by usual sleep-wake cycles, i.e., rates of SCD were higher during sleep (10:00 PM to 6:00 AM) in those with OSA (54% of total sudden deaths) versus those without OSA (24%).

While OSA increased the probability of SCD occurring at night, it may also increase the overall risk of SCD per se. The incidence of SCD in OSA was assessed in 10,701 adults who underwent first polysomnography between 1987 and 2003 and were followed for up to 15 years (36). A total of 142 subjects had resuscitated/fatal SCD during a mean follow-up period of 5.3 years, which was an annual rate of 0.27%. An AHI $>20$/h (HR, 1.14 beats/min, $P = 0.029$) (Fig. 5B).

The mechanisms underlying increased risk of SCD in SDB are unclear. An autopsy study of 25 subjects with OSA and sudden death revealed cardiomyopathy in 11 cases, sudden unexpected death without morphologic findings in 6 cases, and other cardiovascular diseases not related to OSA in the remainder (173).

Conclusions

Sleep disordered breathing, both OSA and CSA, has been associated with increased risk of death. Apnea, hypoxemia, and hypercapnia act synergistically to elicit sympathetic activation, which is thought to be a major mechanism underlying elevated risk of adverse cardiovascular consequences and mortality. Vagal responses to apnea are also of importance, especially in bradyarrhythmias and in triggering AF. OSA has been shown to increase the risk of SCD at night. An increase in potentially lethal nocturnal arrhythmias, including AF and VT/VF, may confer higher nighttime mortality risk in patients with OSA. In addition, OSA is being recognized as a risk factor for nocturnal myocardial ischemia and MI and may raise the risk of ischemic stroke occurring in sleep as well. While the risk of stroke could be mediated through AF in patients with OSA, PFO and DVT, both of which are seen in association with OSA, may be additional mechanisms conferring increased stroke and mortality risk in this population. Finally, OSA and CSA are closely linked to heart failure, another potential mechanism that may contribute to an elevated mortality risk in patients with SDB. Other factors such as impaired exercise capacity, increased periodic limb movements of sleep, and sleep deprivation, seen...
more frequently in patients with SDB than in the general population, may also play a role in increasing mortality. Large-scale, prospective, randomized trials are required to definitively demonstrate a causal association between SDB and each of the above cardiovascular conditions and death and to clarify the effects of treatment of SDB. Identification of the exact mechanisms underlying these relationships may provide potential new avenues for individualized screening, prevention, and treatment of the adverse cardiovascular consequences.

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AUTHOR CONTRIBUTIONS
M.P.M. and V.K.S. conception and design of research; M.P.M. analyzed data; M.P.M. prepared figures; M.P.M. and V.K.S. interpreted results of experiments; M.P.M. and V.K.S. approved final version of manuscript; M.P.M. and V.K.S. wrote manuscript; M.P.M., S.W., and V.K.S. edited and revised manuscript; M.P.M., S.W., and V.K.S. approved final version of manuscript.

REFERENCES


Review

H748
SLEEP APNEA AND DEATH

111. O’Donnell CP, Ayuse T, King ED, Schwartz AR, Smith PL, Robot-
ham JL. Airway obstruction during sleep increases blood pressure

112. Otto ME, Belohlavek M, Romero-Corral A, Gami AS, Gilman G,
Svatikova A, Lopez-Jimenez F, Khandheria BK, Somers
VK. Comparison of cardiac structural and functional changes in obe-
seous otherwise healthy adults with versus without obstructive sleep apnea. Am

113. Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK,
Romano AC, Amodeo C, Bortolotto LA, Krieger EM, Bradley TD,
Locrenzi-Filho G. Obstructive sleep apnea: the most common secondary
cause of hypertension associated with resistant hypertension. Hyperten-

Association between obstructive sleep apnea and severe sleep throbosiss / pul-
monary embolism: a population-based retrospective cohort study. Thromb

115. Peppard PE, Young T, Palta M, Skatrud J. Association between
obstructive sleep apnea and deep vein thrombosis / pul-
monary embolism: a population-based retrospective cohort study. Stroke

116. Phillipson EA, McClean PA, Sullivan CE, Zamel N. Interaction of
metabolic and behavioral respiratory control during hypercapnia and

117. Pinet C, Orehek J. CPAP suppression of awake right-to-left shunting
through patent foramen ovale in a patient with obstructive sleep apnea. J Appl

118. Pinto P, Barbara C, Montserrat JM, Pataraos RS, Guarino MP,
Carmo MM, Macedo MP, Martinho C, Dias R, Gomes MJ. Effects of
CPAP on nitrative and norepinephrine levels in severe and mild-moderate

R, Fersini C, Lugaresi E. Undiagnosed sleep-disordered breathing among

120. Raghuam A, Clay R, Kumbam A, Tereshchenko LG, Khan A. A
systematic review of the association between obstructive sleep apnea and

121. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O’Connor GT,
Resnick HE, Diener-West M, Sanders MH, Wolf PA, Geraghty EM,
Ali T, Lebowitz M, Punjabi NM. Impact of sleep apnea on sympathetic nervous
system activity in heart failure patients with obstructive sleep apnea. Thorax

122. Redolfi S, Arnulf I, Pottier M, Lajou J, Cosimi G, Redolfi S, Arnulf I,
Pottier M, Lajou J, Cosimi G. Interaction of obstructive sleep apnea with

123. Rizzi CF, Cintra F, Mello-Fujita L, Rios LF, Mendonca ET, Feres
MC, Tufik S, Poyares D. Does obstructive sleep apnea impair the

124. Rigatoni GV, Smith DM, Langford BA, Davies RJ, Bradley T. Ob-

125. Ross VA, Stoewsas HC, Camen G, Steffel J, Bloch KE, Stradling JR,
Kohler M. The effects of continuous positive airway pressure therapy
withdrawal on cardiac repolarization: data from a randomized controlled trial.

126. Rupprecht S, Hutschenreuther J, Brehm B, Figgula HR, Witte OW,
Schwab M. Causality in the relationship between central sleep apnea and

127. Ryan CM, Usui K, Floras JS, Bradley TD. Effect of continuous
positive airway pressure on ventricular ectopy in heart failure patients

128. Sano K, Watanabe E, Hayano J, Mieno Y, Sobue Y, Yamamoto M,
Ichikawa T, Sakakibara H, Imaizumi K, Ozaki Y. Central sleep
apnea and inflammation are independently associated with arrhythmia

129. Sasaki N, Osono R, Yamauchi R, Teramani K, Munenori M,
differences in the mechanism of nondipping among patients with ob-

130. Schultz HD, Marcus NJ, Del Rio R. Role of the carotid body in the

131. Shah RV, Abbasi SA, Heydari B, Farhad H, Dodson JA, Bakker JP,
John RM, Yves A, Malhotra A, Blankstein R, Jerosch-Herold M,
Kwong R, Neilan TG. Obesity and sleep apnea are independently
associated with adverse left ventricular remodeling and clinical outcome
in patients with atrial fibrillation and preserved ventricular function. Am

132. Shaikh ZF, Jafy J, Ward N, Malhotra A, de Villa M, Polkey MI,
Mullen MJ, Morrell MJ. Patent foramen ovale in severe obstructive
sleep apnea: clinical features and effects of closure. Chest 143: 56–63,
2013.

133. Shamsuzzaman A, Amin RS, Calvin AD, Davison D, Somers VK.
Severity of obstructive sleep apnea is associated with elevated plasma

134. Shamsuzzaman AS, Winnicki M, Lanfranchi P, Wolk R, Kara T,
Accuro V, Somers VK. Elevated C-reactive protein in patients with obstructive

135. Shimizu T, Guillonmiant C, Stools R, Schigger I. Leftward shift of
the interventricular septum and pulsus paradoxus in obstructive sleep

136. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD.
Risk factors for central and obstructive sleep apnea in 450 men and

137. Smith ML, Niedermaier ON, Hardy SM, Decker MJ, Strohl KP. Role

Impact of sleep apnea on sympathetic nervous system activity in heart

139. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural

140. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve

141. Somers VK, Mark AL, Abboud FM. Potentiation of sympathetic nerve
responses to hypoxia in borderland hypertensive subjects. Hypertension

142. Somers VK, Mark AL, Zavala DC, Abboud FM. Contrasting effects of
hypoxia and hypercapnea on ventilation and sympathetic activity in

143. Somers VK, Mark AL, Zavala DC, Abboud FM. Influence of venti-
lation and hypocapnea on sympathetic nerve responses to hypoxia in

144. Somers VK, White DP, Amin R, Abraham WT, Costa F, Calebras A,
Daniels S, Floras JS, Hunt CE, Olson LJ, Pickering TG, Russell R,
Woo M, Young T. Sleep apnea and cardiovascular disease: an American
Heart Association/American College of Cardiology Foundation Scien-
tific Statement from the American Heart Association Council for High
Blood Pressure Research Professional Education Committee. Council on
Clinical Cardiology, Stroke Council, and Council on Cardiovascular

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