THE LINDE GROUP

Linde

Recent publications.

Sleep apnoea and cardiovascular disease.

With an introduction by
Winfried J. Randerath, MD

Contents.

Sleep apnoea and cardiovascular disease.

Abstracts.

Sleep apnoea and cardiovascular disease. Introduction.

Sleep-related breathing disorders (SRBD) present in the phenotypes of obstructive sleep apnoea syndrome (OSAS), central sleep apnoea including Cheyne-Stokes respiration and hypoventilation/hypoxemic syndromes. Whilst most patients suffer from combinations of obstructive and central breathing disturbances, they will be classified according to the predominant type.

Winfried J. Randerath, MD

Specialist in Internal Medicine, Pneumology, Allergology, Environmental Medicine, Sleep Medicine, Infectiology (DGI)

Institute of Pneumology at the University Witten/Herdecke, Clinic for Pneumology and Allergology, Center of Sleep Medicine and Respiratory Care, Bethanien Hospital, Solingen, Germany

All types of respiratory disturbances have been related to heart diseases. Obstructive sleep apnoea (OSA) has widely been accepted to be one of the major cardiovascular risk factors. Conversely, about 50 % of heart failure patients present with obstructive or central breathing disturbances. Cardiovascular diseases substantially contribute to the mortality and morbidity of sleep apnoea patients. For these reasons, there is major interest in the coherence of the sleep apnoea syndromes and cardiovascular disorders.

Most recently, Gil Martin et al. pointed out the role of chronic intermittent hypoxia in the development of cardiovascular sequelae. These authors exposed healthy persons to nocturnal intermittent hypoxia for 28 consecutive nights and found significant impairment of cardiovascular and hemodynamic parameters. Muscle sympathetic nerve activity, diastolic blood pressure and forearm vascular resistance all increased. The authors concluded that there is a correlation between increases of blood pressure and sympathetic activity and vascular resistance in chronic intermittent hypoxia [1].

The important role of oxygen desaturation during sleep in the pathophysiology of cardiovascular disorders has also been underlined by a recent study of Baguet et al. [2]. They studied patients newly diagnosed with OSA without known cardiovascular diseases; 22.7 % of these patients presented with left ventricular diastolic dysfunction and 13 % showed left ventricular hypertrophy. The only respiratory parameter associated with diastolic dysfunction and left ventricular hypertrophy was mean nocturnal oxygen saturation.

OSA is associated with a frequent change between repetitive hypoxia and reoxygenation, which induces sympathetic nerve activity, oxidative stress and insulin resistance. Endothelial dysfunction is the consequence. Therefore, atherosclerosis is induced by sleep apnoea. Additional long-term effects are ventricular hypertrophia, systolic and diastolic heart failure and myocardial ischemia. Chan and Wilcox [3] have reviewed the current data on cardiac arrhythmias and sleep apnoea, finding that hypoxemia, excessive negative intrathoracic pressures and repeated arousals may promote the development of cardiac arrhythmias.

Despite conflicting results on the prevalence of bradyarrhythmias, that CPAP appears to abolish bradyarrhythmias in the majority of OSA patients [4-6]. Both, cross-sectional and longitudinal studies have reported that OSAS is associated with atrial fibrillation. Additionally, it has been shown that the risk of developing atrial fibrillation in OSA patients under 65 years of age is increased by 2.2fold. There is a direct temporal link between OSA-related events and the devel-

Winfried J. Randerath, MD

opment of paroxysmal atrial fibrillation. Several studies have proposed that OSAS is associated with an increased risk of sudden cardiac death, especially at night. This effect might be due to increased sympathetic nerve activity, the proinflammatory and procoagulant states.

The Sleep Heart Health Study proved a higher prevalence of sustained ventricular tachycardia and complex ventricular ectopy in obstructive sleep apnoea patients compared to non-OSA patients. These results were confirmed more recently by an odds ratio of 17.4 for non-sustained ventricular tachycardias after an apnoeic episode compared with normal breathing.

Logan and Bradley's [7] recently pointed out that the overall frequency of sleep apnoea in patients with ischemic heart diseases, systolic heart failure or stroke is relevantly increased compared to the general population. A prevalence of obstructive sleep apnoea in patients with severe systolic heart failure has been shown to be 37 % and the prevalence of central sleep apnoea 23 % [8]. Diastolic dysfunction proves more prevalent than systolic dysfunction in sleep apnoea. The Sleep Heart Health Study showed that an AHI > 11/h was associated with increased prevalence of cardiovascular disorders, especially heart failure. It was associated with increased left ventricular mass and reduced ejection fraction. Moreover, coronary artery disease can be negatively influenced by sleep apnoea. Major adverse cardiac events, restenosis of coronary vessels and mortality are associated with higher respiratory disturbances during sleep [9–16].

Obstructive sleep apnoea also effects severely cerebral circulation. Lee et al. compared the extent of atherosclerotic changes of the carotid and femoral arteries. They demonstrated a 10.5fold increase in heavy versus mild snorers. Interestingly, they only found an independent risk for arterial sclerotic changes at the carotids.

This suggests that the mechanical influence of snoring, e.g. by vibration, influences cerebral vessels [17]. Redline et al. studied the prevalence of cerebral ischemic events in the Sleep Heart Health Study. Over a period of 8.7 years, they found a 2.86fold risk elevation in men (AHI > 20/h) and women (AHI > 25/h). Cerebral infarction may be the endpoint of a development which begins with the detrimental influence of snoring on the carotids. On the other hand, cerebral vascular alterations seem to induce sleep apnoea [18]. Rupprecht et al. studied 59 patients with asymptomatic extra- and intracranial stenosis using polysomnography and analysed heart rate variability. They found central breathing disturbances in 39 % of the patients with extracranial stenosis. Moreover, the sensitivity of the chemoreceptors was increased, a state which can substantially contribute to the pathogenesis of central sleep apnoea [19].

Optimal treatment is still under discussion. While CPAP is currently the treatment of choice, the CanPAP trial failed to show a significant improvement of mortality in heart failure patients with sleep related breathing disorders. Oxygen supplementation as well as CPAP reduced respiratory disturbances by 50 % on average. However, optimal suppression of respiratory disturbances seems to be crucial [20].

Therefore, adaptive servoventilation is the focus of ongoing intensive studies on the treatment of heart failure patients with sleep-related breathing disorders, especially Cheyne-Stokes respiration. Adaptive servoventilation has been shown to improve respiratory disturbances, left ventricular function and daytime performance. To date, however, evidence on mortality and long-term outcome is still lacking [21–23].

References.

1. Gilmartin GS, Lynch M, Tamisier R, Weiss JW. Chronic intermittent Hypoxia in Humans during 28 nights results in blood pressure elevation and increased muscle sympathetic nerve activity. Am J Physiol Heart Circ Physiol. 2010 Jun 25.

2. Baguet JP, Barone-Rochette G, Levy P, Vautrin E, Pierre H, Ormezzano O, et al. Left ventricular diastolic dysfunction is linked to severity of obstructive sleep apnoea. Eur Respir J. 2010 Jun 18.

3. Chan KH, Wilcox I. Obstructive sleep apnea: novel trigger and potential therapeutic target for cardiac arrhythmias. Expert Rev Cardiovasc Ther. 2010 Jul;8(7):981–94.

4. Gami AS, Hodge DO, Herges RM, Olson EJ, Nykodym J, Kara T, et al. Obstructive sleep apnea, obesity, and the risk of incident atrial fibrillation. J Am Coll Cardiol. 2007 Feb 6;49(5):565–71.

5. Mehra R, Benjamin EJ, Shahar E, Gottlieb DJ, Nawabit R, Kirchner HL, et al. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. Am J Respir Crit Care Med. 2006 Apr 15;173(8):910–6.

6. Monahan K, Storfer-Isser A, Mehra R, Shahar E, Mittleman M, Rottman J, et al. Triggering of nocturnal arrhythmias by sleep-disordered breathing events. J Am Coll Cardiol. 2009 Nov 3;54(19):1797–804.

7. Logan AG, Bradley TD. Sleep apnea and cardiovascular disease. Curr Hypertens Rep. 2010 Jun;12(3):182–8.

8. Yumino D, Wang H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, et al. Prevalence and physiological predictors of sleep apnea in patients with heart failure and systolic dysfunction. J Card Fail. 2009 May;15(4):279–85.

9. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993 Apr 29;328(17):1230–5.

10. Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med. 2001 Mar;163 (3 Pt 1):685–9.

11. Owan TE, Redfield MM. Epidemiology of diastolic heart failure. Prog Cardiovasc Dis. 2005 Mar-Apr;47(5):320–32.

12. Arias MA, Garcia-Rio F, Alonso-Fernandez A, Mediano O, Martinez I, Villamor J. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. Circulation. 2005 Jul 19;112(3):375–83.

13. Peker Y, Hedner J, Kraiczi H, Loth S. Respiratory disturbance index: an independent predictor of mortality in coronary artery disease. Am J Respir Crit Care Med. 2000 Jul;162(1):81–6.

14. Yumino D, Tsurumi Y, Takagi A, Suzuki K, Kasanuki H. Impact of obstructive sleep apnea on clinical and angiographic outcomes following percutaneous coronary intervention in patients with acute coronary syndrome. Am J Cardiol. 2007 Jan 1;99(1):26–30.

15. Wang H, Parker JD, Newton GE, Floras JS, Mak S, Chiu KL, et al. Influence of obstructive sleep apnea on mortality in patients with heart failure. J Am Coll Cardiol. 2007 Apr 17;49(15):1625–31.

16. Yumino D, Wang H, Floras JS, Newton GE, Mak S, Ruttanaumpawan P, et al. Relationship between sleep apnoea and mortality in patients with ischaemic heart failure. Heart. 2009 May;95(10):819–24.

17. Lee SA, Amis TC, Byth K, Larcos G, Kairaitis K, Robinson TD, et al. Heavy snoring as a cause of carotid artery atherosclerosis. Sleep. 2008 Sep 1;31(9):1207–13.

18. Redline S, Yenokyan G, Gottlieb DJ, Shahar E, O'Connor GT, Resnick HE, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med. 2010 Jul 15;182(2):269–77.

19. Rupprecht S, Hoyer D, Hagemann G, Witte OW, Schwab M. Central sleep apnea indicates autonomic dysfunction in asymptomatic carotid stenosis: a potential marker of cerebrovascular and cardiovascular risk. Sleep. 2010 Mar 1;33(3):327–33.

20. Arzt M, Floras JS, Logan AG, Kimoff RJ, Series F, Morrison D, et al. Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: a post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). Circulation. 2007 Jun 26;115(25):3173–80.

21. Bitter T, Westerheide N, Faber L, Hering D, Prinz C, Langer C, et al. Adaptive servo-ventilation in diastolic heart failure and Cheyne-Stokes respiration. Eur Respir J. 2010 Aug;36(2):385–92.

22. Teschler H, Dohring J, Wang YM, Berthon-Jones M. Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. Am J Respir Crit Care Med. 2001 Aug 15;164(4):614–9.

23. Pepperell JC, Maskell NA, Jones DR, Langford-Wiley BA, Crosthwaite N, Stradling JR, et al. A randomized controlled trial of adaptive ventilationforCheyne-Stokesbreathinginheart failure. Am J Respir Crit Care Med. 2003 Nov 1;168(9):1109–14.

Abstract. Chronic intermittent hypoxia in humans during 28 nights results in blood pressure elevation and increased muscle sympathetic nerve activity.

Gilmartin GS, Lynch M, Tamisier R, Weiss JW.

Beth Israel Deaconess Medical Center

Am J Physiol Heart Circ Physiol.
2010 Jun 25.
[Epub ahead of print]

Chronic intermittent hypoxia (CIH) is thought to be responsible for the cardiovascular disease associated with obstructive sleep apnea (OSA). Increased sympathetic activation, altered vascular function and inflammation are all putative mechanisms.

We have recently reported a new model of CIH in healthy humans which is associated with both increases in blood pressure and augmented peripheral chemosensitivity(31). We tested the hypothesis that exposure to CIH would also result in augmented muscle sympathetic nerve activity (MSNA) and altered vascular reactivity contributing to blood pressure elevation.

We therefore exposed healthy subjects between the ages of 20 and 34 (n = 7) to 9 hours of nocturnal intermittent hypoxia for 28 consecutive nights. Cardiovascular and hemodynamic variables were recorded at three time points; MSNA was collected prior to and following exposure.

Diastolic blood pressure
(71 ± 1.3 vs. 74 ± 1.7 mmHg, $p < 0.01$),

MSNA
(9.94 ± 2.0 to 14.63 ± 1.5 B/min, $p < 0.05$;
16.89 ± 3.2 to 26.97 ± 3.3 B/100hb, $p = 0.01$),

and forearm vascular resistance (FVR)
(35.3 ± 5.8 vs. 55.3 ± 6.5 mmHg · ml^{-1} · min · 100 g $tissue^{-1}$, $p = 0.01$)

all increased significantly after 4 weeks of exposure. Forearm blood flow (FBF) response following ischemia of 15 minutes (reactive hyperemia) fell below baseline values after 4 weeks, following an initial increase after 2 weeks of exposure.

From these results we conclude that the increased blood pressure following prolonged exposure to CIH in healthy humans is associated with sympathetic activation and augmented FVR.

PMID: 20581089
[PubMed – as supplied by publisher]

Abstract. Left ventricular diastolic dysfunction is linked to severity of obstructive sleep apnoea.

Baguet JP, Barone-Rochette G, Lévy P, Vautrin E, Pierre H, Ormezzano O, Pépin JL.

University Hospital Grenoble France

Eur Respir J.
2010 Jun 18.
[Epub ahead of print]

Obstructive sleep apnoea has been related to increased cardiovascular risk. The present study examined the relationships between respiratory parameters and left ventricular abnormalities in obstructive sleep apnoea. One hundred and fifty newly diagnosed OSA patients without any known cardiovascular disease were included (age = 49 ± 11 years, BMI = 27.1 ± 3.3 kg/m2, respiratory disturbance index = 41 ± 18/h). Haemodynamic, biological, respiratory, cardiac and arterial parameters were assessed at inclusion.

Thirty-four patients (22.7 %) had a grade 1 left ventricular diastolic dysfunction. Patients with an abnormal diastole were older ($p < 0.001$) and 81 % of them were hypertensive. The only respiratory parameter independently associated with the E/A ratio was mean nocturnal oxygen saturation. Seventeen patients (13 %) had left ventricular hypertrophy.

A multivariate analysis showed that clinic systolic blood pressure and mean nocturnal oxygen saturation were independently associated with left ventricular hypertrophy. In a logistic regression model, an age > 58 years (OR 3.29, 95 % CI 1.78–5.64) and mean nocturnal oxygen saturation < 92 % (OR 2.76, 95 % CI 1.45–4.91) were associated with left ventricular diastolic dysfunction. Our findings demonstrate that left ventricular diastolic dysfunction frequently occurs in patients with obstructive sleep apnoea and that it is related to the severity of oxygen desaturation.

[PubMed – as supplied by publisher]

Abstract. Obstructive sleep apnea: novel trigger and potential therapeutic target for cardiac arrhythmias.

Chan KH, Wilcox I.

Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia

Expert Rev Cardiovasc Ther.
2010 Jul;8(7):981–94.

Obstructive sleep apnea (OSA), the most common form of sleep-disordered breathing, is prevalent and frequently underdiagnosed in our community.

Although presenting with predominantly respiratory symptoms, the most serious complications from OSA are cardiovascular, including arrhythmias, disease of the sinus node and conducting system, and sudden cardiac death.

The acute and chronic effects of OSA on the cardiovascular system, which include major effects on autonomic function during sleep and wakefulness, are potent contributors to the development and persistence of cardiac arrhythmias.

Although large randomized studies are currently lacking, treatment of OSA may be an important primary or additional therapy to supplement the use of drugs or devices in the treatment of cardiac arrhythmias.

PMID: 20602559
[PubMed – in process]

Abstract. Sleep apnea and cardiovascular disease.

Logan AG, Bradley TD.

Mount Sinai Hospital, 435-600 University Avenue, Toronto, ON, M5G 1X5, Canada

Curr Hypertens Rep.
2010 Jun;12(3):182–8.

Cardiovascular disease is still the leading cause of death in North America. To improve outcomes, it will likely be necessary to identify new potentially treatable conditions.

Sleep apnea affects approximately 50% of patients with cardiovascular disease and is associated with increased cardiovascular risk. Continuous positive airway pressure is currently the treatment of choice and has many short-term favorable effects. The long-term benefits, however, remain elusive.

Further, it may not be the ideal treatment for central sleep apnea, and the benefits of alternatives such adaptive servo-ventilation are currently being tested.

Randomized controlled trials are now needed to determine whether treating sleep apnea will improve survival and reduce cardiovascular disease risk.

Until better evidence becomes available, testing for sleep apnea cannot be recommended as part of the routine cardiovascular disease risk assessment, nor can its treatment be recommended for the prevention or management of cardiovascular disease in asymptomatic patients.

PMID: 20424951
[PubMed – in process]

Abstract. Cardiovascular disease risk reduction with sleep apnea treatment.

Jean-Louis G, Brown CD, Zizi F, Ogedegbe G, Boutin-Foster C, Gorga J, McFarlane SI.

Expert Rev Cardiovasc Ther.
2010 Jul;8(7):995–1005.

Cardiovascular diseases are the leading cause of death among adults in developed countries. An increase in prevalent cardiovascular risk factors (e.g., obesity, hypertension and diabetes) has led to a concerted effort to raise awareness of the need to use evidence-based strategies to help patients at risk of developing cardiovascular disease and to reduce their likelihood of suffering a stroke.

Sleep apnea has emerged as an important risk factor for the development of cardiovascular disease. Epidemiologic and clinical evidence has prompted the American Heart Association to issue a scientific statement describing the need to recognize sleep apnea as an important target for therapy in reducing cardiovascular disease risks.

This article examines evidence supporting associations of sleep apnea with cardiovascular disease and considers evidence suggesting cardiovascular risk reductions through sleep apnea treatment.

Perspectives on emerging therapeutic approaches and promising areas of clinical and experimental research are also discussed.

PMID: 20602560
[PubMed – in process]

Abstract. Cardiovascular consequences of sleep apnea.

Selim B, Won C, Yaggi HK.

Division of Pulmonary and Critical Care Medicine, Yale University School of Medicine, 333 Cedar Street, PO Box 208057,
New Haven, CT 06520-8057, USA

Clin Chest Med.
2010 Jun;31(2):203–20.

Cardiovascular disease has been the leading cause of death since 1900. Strategies for cardiovascular disease and prevention have helped to reduce the burden of disease, but it remains an important public health challenge.

Therefore, understanding the underlying pathophysiology and developing novel therapeutic approaches for cardiovascular disease is of crucial importance.

Recognizing the link between sleep and cardiovascular disease may represent one such novel approach.

Obstructive sleep apnea (OSA), a common form of sleep-disordered breathing, has a high and rising prevalence in the general adult population, attributable in part to the emerging epidemic of obesity and enhanced awareness.

OSA has been independently linked to specific cardiovascular outcomes such as hypertension, stroke, myocardial ischemia, arrhythmias, fatal and nonfatal cardiovascular events, and all-cause mortality. Treatment of OSA may represent a novel target to reduce cardiovascular health outcomes.

PMID: 20488282
[PubMed – in process]

Abstract. Cardiovascular consequences of obese and nonobese obstructive sleep apnea.

Ramar K, Caples SM.

Division of Pulmonary, Sleep and Critical Care Medicine, Center for Sleep Medicine, Mayo Clinic, 200 First Street South West, Rochester, MN 55901, USA

Med Clin North Am.
2010 May;94(3):465–78.

Current evidence suggests a role for obstructive sleep apnea (OSA) in the development of cardiovascular disorders.

However, obesity is an active confounder in this relationship. OSA and obesity share similar pathophysiologic mechanisms potentially leading to cardiovascular disorders. Presence of OSA in obese patients may further contribute to adverse cardiovascular outcomes when compared with each condition in isolation.

In this review the authors explore the complex relationship between OSA and obesity (and nonobese subjects) in the development of cardiovascular disorders.

PMID: 20451027
[PubMed – indexed for MEDLINE]

Abstract. Sleep in congestive heart failure.

Sharma B, Owens R, Malhotra A.

Division of Sleep Medicine, Harvard Medical School, Brigham and Women's Hospital, 75 Francis Street # Asb1, Boston, MA 02115-6106, USA

Med Clin North Am.
2010 May;94(3):447–64.

Breathing disorders during sleep are common in congestive heart failure (CHF).

Sleep-disordered breathing (SDB) in CHF can be broadly classified as 2 types: central sleep apnea with Cheyne-Stokes breathing, and obstructive sleep apnea.

Prevalence of SDB ranges from 47 % to 76 % in systolic CHF.

Treatment of SDB in CHF may include optimization of CHF treatment, positive airway pressure therapy, and other measures such as theophylline, acetazolamide, and cardiac resynchronization therapy. Periodic limb movements are also common in CHF.

PMID: 20451026
[PubMed – indexed for MEDLINE]

Linde AG
Linde Healthcare, Seitnerstrasse 70, 82049 Pullach, Germany
Phone +49.89.7446-0, www.linde-healthcare.com

Lore Ipsum

12345678 1209 - 1 X L 6P