



The interaction between OSA and hypertension—by Dr. Virend Somers

Virend Kristen Somers has a Doctorate in Medicine and a Doctorate of Philosophy in Cardiovascular Physiology. He was appointed Associate Professor with tenure in Cardiovascular Diseases at the University of Iowa and served as Director of the Cardiovascular Neurophysiology Laboratory. He is presently Professor of Medicine in the Divisions of Cardiovascular Diseases and Hypertension at the Mayo Clinic and Mayo Foundation, Director of the GCRC Sleep Core Laboratory, and has been appointed as a Mayo Foundation Clinical Investigator. He is Board Certified in Internal Medicine and Cardiovascular Diseases. He is certified by the American Society of Hypertension as a Consultant in Hypertension.

He also currently serves on the editorial boards of *Circulation*, *Sleep*, and the *Italian Heart Journal*, and is the Consulting Medical Editor for the *American Journal of Physiology—regulatory, integrative, and comparative*. He has been elected to membership of the Association of University Cardiologists.

Introduction

There is increasing recognition of the high and rising prevalence of both obstructive sleep apnea (OSA) and obesity in the general population. While OSA has long been linked to obesity, a strong association between OSA and the initiation and progression of cardiovascular pathophysiology is also emerging. Perhaps the most compelling evidence available to link OSA to a specific cardiovascular disease condition is the interaction between OSA and high blood pressure.

A number of studies have reported a high prevalence of hypertension in OSA patient populations as well as high levels of OSA in hypertensive cohorts. The etiologic association between OSA and hypertension has been somewhat blurred because of the confounding effect of obesity as well as other comorbidities that characterize both patients with hypertension and patients with OSA.

Acute effects of OSA

To understand why patients with OSA may develop cardiovascular disease, it is important to recognize the profound homeostatic disturbances that are evoked by the repetitive episodes of cessation of breathing.

The lack of airflow during OSA causes a “collapse” of the upper airway, in much the same way as a wet paper straw collapses. This collapse occurs during inspiration. Patients then make repeated attempts to breathe in against the occluded airway.

During this period of obstructive apnea, there is a progressive reduction in oxygen saturation, often to levels less than 40%, together with CO₂ retention. During and at the end of apnea, there is significant disturbance of the electroencephalogram and muscle tone, indicating arousals from sleep. The recurrent episodes of often severe nocturnal hypoxemia, CO₂ retention, and apnea elicit chemoreflex activation with consequent increases in peripheral sympathetic traffic, causing vasoconstriction and increased blood pressure. These repetitive vasoconstrictor episodes cause surges in blood pressure to levels as high as 240/140 mmHg. The arousals may also contribute to the increases in blood pressure at the end of apneas.

Potential mechanisms linking OSA to hypertension

There appears to be some carry-over effect of these nocturnal metabolic, pressor, and reflex responses, so that patients with OSA have high levels of sympathetic traffic even during wakefulness and when breathing normally. They also appear to have other characteristics predisposing them to the development of hypertension, including faster heart rates, depressed heart rate variability, and excessive blood pressure variability. These abnormalities are evident even in apparently healthy patients who



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have OSA but are free of any overt cardiovascular disease conditions.

Repetitive nocturnal arousals have a significant effect on daytime wakefulness. These arousals cause substantial sleep disturbance, particularly during REM sleep, resulting in sleep deprivation and daytime somnolence. Sleep deprivation is itself now being understood as an important cause of neural, vascular, and endocrine disruption, leading to increases in blood pressure.

OSA patients are also characterized by other abnormalities that suggest increased risk for hypertension. Acute nocturnal hypoxemia elicits an increase in plasma endothelin levels. Endothelin is a potent endogenous vasoconstrictor, and its pressor effects can persist for several hours.

This may be one mechanism to explain carry-over of pressor effects of OSA into daytime wakefulness.

Another possible mechanism may include endothelial dysfunction. Endothelial dysfunction has usually been linked to disease conditions such as hypertension, hyperlipidemia, diabetes, smoking, and heart failure. However, in the absence of any of these disease conditions, OSA patients have abnormalities in endothelial production of the vasodilator nitric oxide.

Further evidence of this endothelial dysfunction emerges from data suggesting that sleep apnea patients may also have lower levels of nitric oxide in the plasma. Thus, there are a number of mechanisms, acting together or individually, which may predispose to the future development of hypertension in normotensive patients with significant OSA.

Evidence linking OSA to hypertension

The Sleep Heart Health Study is the largest of several studies suggesting that the presence of OSA is independently associated with an increased risk for hypertension. There appears to be a dose–response relationship that associates increasing sleep apnea severity with higher blood pressure levels.

Recent data from the Wisconsin cohort provide further and more compelling evidence of an etiological link between OSA and hypertension. Over a four-year follow-up of individuals studied

from the community, these investigators noted that the likelihood of the development of new hypertension was substantially increased in patients with significant sleep apnea who had received no treatment.

This again appeared to follow a dose–response relationship in that increasing severity of sleep apnea at initial study was associated with a greater likelihood of new hypertension at four-year follow-up. In those patients with the most severe apnea (apnea/hypopnea index >15), the likelihood of new hypertension was increased three-fold, to about 45%.

Thus, the absence of treatment of sleep apnea appears to predispose to the development of what we generally consider to be essential hypertension. Further evidence of the etiologic link between sleep apnea and elevated daytime blood pressure levels is also apparent from studies of effects of treatment. Two recent randomized studies employing therapeutic versus subtherapeutic CPAP showed that blood pressure in those individuals receiving therapeutic CPAP was significantly lower, both at night and during the daytime.

Summary

The epidemic of obesity is probably associated with a prevalence of OSA much greater than earlier estimates. This emphasizes the importance of recognizing the potential cardiovascular pathophysiology of OSA and particularly its role in the development of hypertension. The evidence provides a compelling argument for supposing that, first, untreated sleep apnea leads to increased risk for future hypertension, and second, that treatment of OSA results in significant blood pressure lowering both at night and, importantly, during the daytime. These findings have clear implications for understanding the potential effect not only of OSA, but also of its treatment on the future development of vascular disease, renal failure, stroke, and heart failure.



Dr. Virend Kristen Somers
Associate Professor in
Cardiovascular Diseases



From the Editor



Hypertension is one of the fastest-growing health conditions in the western world. It affects approximately 50 million people in the United States alone and approximately 1 billion people worldwide. Unless effective measures are taken, it will continue to increase as populations age and obesity levels increase.

This edition of ResMedica focuses on the problem of hypertension and the cardiovascular consequences of sleep-disordered breathing (SDB). We summarize some of the key messages from the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7 report), including pertinent facts and figures about hypertension and some suggestions for treatment. Most importantly, this report, for the first time, identifies sleep apnea as a cause of hypertension. We also explain some of the suggestions for lowering blood pressure from the National Heart, Lung, and Blood Institute in the USA.

We explore the cardiovascular consequences of SDB in an interview with Dr Lee Goldberg and an article from Dr Virend Somers. Dr Goldberg is a cardiologist and Assistant Professor of Medicine at the University of Pennsylvania School of Medicine. Dr Goldberg has found that SDB is very common in patients with heart disease and that treating it can improve a patient's response to conventional cardiovascular therapies. Dr Somers is a leading cardiologist and Professor of Medicine in the Divisions of Cardiovascular Diseases and Hypertension at the Mayo Clinic, and we are delighted to include his article, "The interaction between OSA and hypertension."

As well as our regular features, we include a summary of recently published articles, along with an abstract of recent research by Becker et al.

Thank you for your continued support and interest in ResMedica. We trust that you'll find this issue a valuable addition to the series. Please be sure to send us your feedback at clinicalnews@resmed.com.au.



Lisa MacKenzie
Editor

JNC 7—new guidelines for hypertension

The National High Blood Pressure Education Program (NHBPEP), part of the National Heart, Lung, and Blood Institute (NHLBI), has published a new report on the problem of hypertension. Known as JNC 7, it is the seventh report from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. It aims to present findings from many of the latest hypertension studies and trials, to provide up-to-date guidelines for clinicians, and to simplify the classification of blood pressure. Following is a summary of the main features of the report. Please refer to our *Website of interest* segment for further details on how you can obtain the full text of the report.

Key messages

Hypertension is the most common primary diagnosis in the US. Efforts to control hypertension are falling short of the 50% reduction goal set for 2010.

The problem increases with age, with more than two-thirds of people over 65 in the US suffering

hypertension; this group also has the lowest rate of blood pressure (BP) control.

The report finds a clear relationship between blood pressure and cardiovascular disease (CVD), independent of other risk factors. The higher the blood pressure, the greater is the chance of heart attack, heart failure, stroke, and kidney disease.

The report also identifies the following causes of hypertension:

- sleep apnea
- drug-induced or related causes
- chronic kidney disease
- primary aldosteronism
- renovascular disease
- chronic steroid therapy and Cushing's syndrome
- pheochromocytoma
- coarctation of the aorta
- thyroid or parathyroid disease.

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JNC 7 strongly recommends increased education for both healthcare professionals and the public in order to prevent an epidemic of hypertension. The report also stresses the need for a combination of lifestyle modifications and drug therapy in order to reach blood pressure goals.

The benefits of lowering blood pressure are evident: in patients with stage 1 hypertension and additional cardiovascular risk factors, a 12 mmHg reduction in systolic blood pressure (SBP) over ten years will prevent one death for every eleven patients treated.

JNC 7 identifies a series of public health and community approaches that will contribute to reducing blood pressure in the population. It suggests public health strategies including reducing calories, saturated fat, and salt in processed foods and increasing community/school opportunities for physical activity. The committee believes these strategies may interrupt and prevent the continuing costly cycle of managing hypertension and its complications.

Key facts and figures

- For people over the age of 50, SBP is a more important CVD risk factor than diastolic blood pressure (DBP).
- The risk of CVD beginning at 115/75 mmHg doubles with each increment of 20/10 mmHg.
- Patients who are normotensive at age 55 have a 90% lifetime risk of developing hypertension.
- Individuals with an SBP of 120–139 mmHg or a DBP of 80–89 mmHg should be considered as pre-hypertensive. They require health-promoting lifestyle modifications to prevent the onset of CVD.

Blood pressure classification	SBP mmHg*		DBP mmHg*
Normal	<120	and	<80
Prehypertension	120–139	or	80–90
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	>160	or	>100

* SBP = Systolic Blood Pressure
* DBP = Diastolic Blood Pressure



Benefits of lowering blood pressure:

Condition	Average percent reduction
Stroke incidence	35–40%
Myocardial infarction	20–25%
Heart failure	50%

Cardiovascular disease risk factors

- hypertension
- cigarette smoking
- obesity (BMI >30)
- physical inactivity
- dyslipidemia
- diabetes mellitus
- microalbuminuria or estimated Glomerular Filtration Rate (GFR) <60 ml/min
- age (older than 55 for men, 65 for women)
- family history of premature CVD (men under 55, women under 65).

Treating hypertension

Antihypertensive therapy aims to reduce cardiovascular and renal morbidity and mortality. Treating SBP should be the primary focus, as most patients will achieve the desired DBP once SBP reaches goal level.

Clinicians should aim to treat BP <140/90 mmHg or BP <130/80 mmHg in patients with diabetes or chronic kidney disease.

JNC 7 makes a number of observations and recommendations about treating hypertension:

- The majority of hypertensive patients require two or more antihypertensive drugs to reduce hypertension.
- Thiazide-type diuretics should be used as the initial therapy.
- If BP is >20/10 mmHg above goal, therapy should initiate with two agents, one of which should be a thiazide-type diuretic.
- There are some compelling indications for the use of other drug classes such as heart failure, diabetes etc.
- **Changes to lifestyle are an important component.**

Lowering blood pressure— simple steps for your patients



While patients have no control over cardiovascular disease (CVD) and blood pressure risk factors such as their age and family history, they can make a real difference to risk factors such as high blood pressure, abnormal cholesterol, tobacco use, diabetes, obesity, and physical inactivity.

Hypertension can almost always be avoided by following these suggestions:

1. Maintain a healthy weight

Body mass index (BMI) and waist circumference are the important measurements of weight. A BMI of 25–29.9 is considered overweight; BMI of 30 or more qualifies as obesity. A waist measurement of more than 35 inches (89 cm) in women and 40 inches (102 cm) in men is considered high risk. If patients are overweight or obese, they should lose weight. Even a few pounds (kilograms) will make a difference in reducing blood pressure.

2. Keep physically active

Adults should complete 30 minutes of moderate physical activity on most days of the week. Moderate-level activity includes:

- gardening for 30–45 minutes
- climbing stairs for 15 minutes
- pushing a stroller for 30 minutes
- walking for 30 minutes
- bicycling for 30 minutes
- swimming laps for 20 minutes
- running for 15 minutes.

These exercise periods can be divided into 10-minute timeslots.

3. Eat a healthy diet

Adopt a diet rich in fruits, vegetables, and low-fat dairy products while controlling saturated and total fat content. Patients may find that the Dietary Approaches to Stop Hypertension (DASH) eating plan, which was developed to help people understand healthy eating habits, will help them with this goal.

4. Reduce salt

- Buy fresh or “no-salt” canned and frozen vegetables
- Avoid processed meat, poultry, and fish
- Cook without adding salt
- Avoid instant sauces and flavorings
- Choose low-salt convenience foods
- Read the package to find reduced-salt varieties of foods.

5. Reduce alcohol consumption

Moderate alcohol consumption = one drink a day for women, two drinks a day for men.*

6. Take prescribed drugs as directed

Patients should follow the lifestyle changes mentioned above as well as taking their medication, as prescribed by their doctor.

For more detailed information, refer to the patient booklet *Your guide to lowering blood pressure* published by the National Heart, Lung, and Blood Institute, US. Refer to our article *Website of interest* for further information.

Modification	Recommendation	Approximate SBP reduction range
weight reduction	Maintain normal BMI (18.5-24.9)	5–20 mmHg/10 kg weight loss
adopt DASH eating plan	Adopt a balanced diet—increase fruit, vegetable and low-fat dairy products. Reduce saturated and total fat intake	8–14 mmHg
dietary sodium reduction	Reduce dietary sodium intake to < 100 mmol/day	2–8 mmHg
physical activity	Regular aerobic physical activity 30 mins / day.	4–9 mmHg
moderate alcohol consumption	Men: < 2 drinks* per day. Women [†] : < 1 drink per day	2–4 mmHg

* 1 drink = ½ oz or 15 ml ethanol (eg, 12 oz beer, 5 oz wine, 1.5 oz 80-proof whiskey)

[†] and lighter weight persons

Sleep apnea—a cardiologist's perspective

An interview with Dr. Lee Goldberg



Dr. Lee Goldberg
Assistant Professor
of Medicine

Dr. Lee Goldberg is a cardiologist and Assistant Professor of Medicine at the University of Pennsylvania School of Medicine.

He is Medical Director of the University of Pennsylvania Health System's Heart Failure Disease Management Program and Medical Director of the Heart-Lung Transplantation Program at the Hospital of the University of Pennsylvania.

Dr. Goldberg is also a Fellow of the American College of Cardiology (FACC), and a member of the American Heart Association and the International Society of Heart and Lung Transplantation.

He teaches and lectures widely and has published numerous books and papers on aspects of cardiology.

What is sleep-disordered breathing (SDB) and why is it significant to cardiologists?

SDB is defined as a disrupted respiratory pattern that occurs during sleep and manifests by hypopneas and apneas. It is associated with hypoxia, disturbed sleep patterns, increased catecholamines, and an increased incidence of atrial and ventricular arrhythmias. Several clinical syndromes can cause SDB, including obstructive sleep apnea (OSA) and central sleep apnea (CSA).

OSA is by far the most common syndrome and the type that is most familiar to clinicians. It is characterized by obstruction of the upper airway during sleep that leads to a cessation of breathing. During these episodes, there is an intense effort to breathe, resulting in significant negative intra-thoracic pressure. As hypoxia develops, the adrenergic system is activated and an arousal occurs. This disrupts sleep and allows the lax tissue in the upper airway to be mobilized. Patients with OSA are more likely to suffer hypertension and are typically obese. Their partners complain of loud snoring punctuated by episodes of apnea. The patients may be unaware of their arousals but do report daytime somnolence. This sometimes has disastrous consequences, including automobile accidents, decreased productivity at work, and impaired social relationships.

CSA more commonly occurs in patients with heart failure and those with stroke. It is manifested by periodic breathing, including episodes of hyperventilation followed by episodes of apnea. This form of breathing is often referred to as Cheyne–Stokes respiration (CSR). As in OSA, there are wide swings in adrenergic tone as well as frequent arousals and disrupted sleep. The pathophysiological mechanisms of central sleep apnea are complex but most researchers agree that in heart failure a decreased cardiac output, providing feedback to the chemoreceptor areas of the brain, appears to be important. In addition, patients with chronic heart failure tend to hyperventilate, causing a decreased PaCO₂ level. This chronic reduction in CO₂ in the blood can desensitize receptors in the brainstem responsible for the regulation of breathing and enable the cyclic pattern of CSR to begin.

In our experience, many patients suffer from a picture of “mixed” apneas that include some obstructive episodes as well as some central episodes. For this reason, classification of this group of patients is not always black and white. We have also found that SDB is very common in patients with heart disease and that treating it can improve a patient's response to the traditional cardiovascular therapies.

What benefits can a cardiologist expect by treating SDB in the setting of cardiovascular disease?

SDB has many detrimental effects on the cardiovascular system. Increased adrenergic tone is thought to be one major impact of SDB on the heart. In addition, wide swings in intrathoracic pressure have direct negative mechanical effects on the heart via increased afterload. Several studies have shown remarkable improvements in cardiovascular markers and outcomes when SDB is treated. For example, a recent study has shown significantly improved blood pressures in patients with difficult to control hypertension after treatment for SDB. Atrial and ventricular arrhythmias are less common in patients being treated for their SDB, and there is at least a trend towards improved survival. Nearly every study has shown improved quality of life that may translate into improved patient compliance and less depression.

What specific benefits can be expected by treating SDB in the setting of heart failure?

Heart failure is a very common and deadly disorder. In the United States, approximately 4.9 million people suffer from heart failure, with a five-year mortality approaching 50%. SDB can contribute to the development and progression of heart failure. In addition, heart failure itself may lead to the development of SDB.

Heart failure is an elevated catecholamine state that ultimately leads to worsening cardiac function, progression of disease, and ultimately death. In heart failure, ejection fraction, exercise capacity, quality of life, and catecholamines are all improved by the treatment of SDB. In addition, there has been improvement in transplant-free survival despite maximal medical therapy. Several studies are underway to further define the benefits of the treatment of SDB in heart failure.

In our experience, patients have had fewer hospital admissions and report improved stamina, less fatigue, and improved quality of life. In addition, some patients have had improvements in their ejection fractions and obvious increases in exercise capacity. For these reasons, we aggressively screen and treat for SDB in our patients with heart failure. Patients with heart failure typically take several different medications, each with its own side effects and challenges. One advantage of treating SDB in this population of patients is that the therapies are “non-drug” and therefore are often met with more acceptance from patients.



What are some practical screening and diagnostic tools cardiologists can use to identify SDB in their patients?

We typically start with a few screening questions that are incorporated into our new patient questionnaire. We ask about symptoms of fatigue and hypersomnolence and also ask both the patient and their partner about snoring and witnessed apneas. The gold standard for diagnosing SDB is a polysomnogram, which is typically administered in a sleep lab. There are now several more portable diagnostic tools that can be administered at home or in the hospital. These range from special analysis of heart rate variability in holter monitor tracings, to overnight pulse oximetry, to devices such as the Embletta™, which is essentially a portable “holter monitor” for sleep that patients can apply themselves at home. These technologies have made it much easier to screen patients and establish a diagnosis.

Patients with central sleep apnea are often not obese but tend to have advanced heart failure. Men, and those with atrial fibrillation and lower ejection fractions, appear to be at increased risk. In these populations we are more aggressive about screening sleep studies even in the absence of traditional SDB risk factors.

What are the current treatment options for SDB?

The treatment depends somewhat on the type of SDB. For OSA, continuous positive airway pressure (CPAP) can abolish many of the apneic events. This technology involves having the patient wear a mask connected to a device while they sleep. The device applies positive pressure to the airway. This helps to “splint” open the airway in order to avoid obstructive episodes. This therapy has been shown to reduce afterload in patients with obstructive apneas. It has been shown to be safe in nearly all patients with the exception of those who are dehydrated with very low pulmonary capillary wedge pressures. Weight loss, surgery to remove excess tissue in the upper airway, and certain appliances that are used in the mouth are alternative therapies.

Treatment for CSA is somewhat more controversial but includes CPAP and nocturnal oxygen. Autotitrating devices may have an advantage in this setting in that they may help to avoid hyperventilation and at the same time provide support in the prevention of apneas.

How do you treat obstructive sleep apnea?

I recommend some form of CPAP to nearly all my patients with OSA and cardiovascular disease because I am convinced that this will rapidly treat their problem and will lead to improved outcomes and slower progression of their cardiac disease. Many of my patients prefer an autotitrating device as they find this more comfortable. From the clinical perspective, I think of the autotitrating devices as a sort of “pacemaker” for sleep. The device monitors the respiratory pattern and then adjusts itself to maintain a normal respiratory pattern. We know that SDB can vary from night to night, and I feel confident that these newer devices can address this important issue. In this same group of patients, I use the diagnosis of SDB to drive home the importance of weight loss.

How do you treat central sleep apnea?

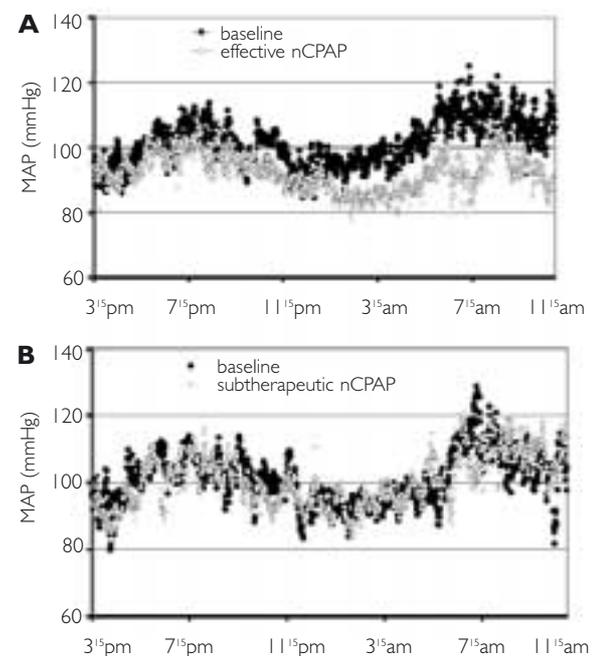
Our center is participating in a clinical trial evaluating the use of an autotitrating device called the AutoSet CS™ in patients with CSA and heart failure. Patients enrolled are randomized to either nocturnal oxygen or the AutoSet™ device. Like its cousin, the AutoSet Spirit™ for OSA, the AutoSet CS device can monitor the respiratory pattern and adjust itself using a special algorithm. The advantage of this device is that it can successfully treat CSA in a single night without the need for titration visits. For patients ineligible for the protocol, we recommend traditional CPAP titrated over several visits in the sleep lab or nocturnal oxygen.

Effect of nasal continuous positive airway pressure (nCPAP) treatment on blood pressure patients with obstructive sleep apnea (OSA)

Becker HF, Jerrentrup A, Ploch T, Grote L, Penzel T, Sullivan CE, Peter JH. *Circulation*. 2003 107(1):68-73

This study builds on increasing evidence that OSA is an independent risk factor for arterial hypertension. The researchers studied the effect of nCPAP on arterial hypertension in 60 patients with OSA over a period of nine weeks.

They found that effective nCPAP treatment in patients with moderate to severe OSA leads to a substantial reduction in both day and night arterial blood pressure. The fact that a 50% reduction in the apnea-hypopnea index did not result in a decrease in blood pressure emphasizes the importance of highly effective treatment. The drop in mean blood pressure by 10 mmHg would be predicted to reduce coronary heart disease event risk by 37% and stroke risk by 56%.

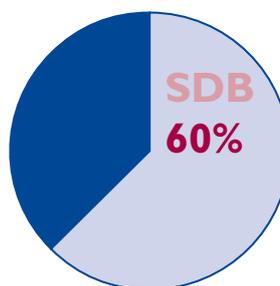
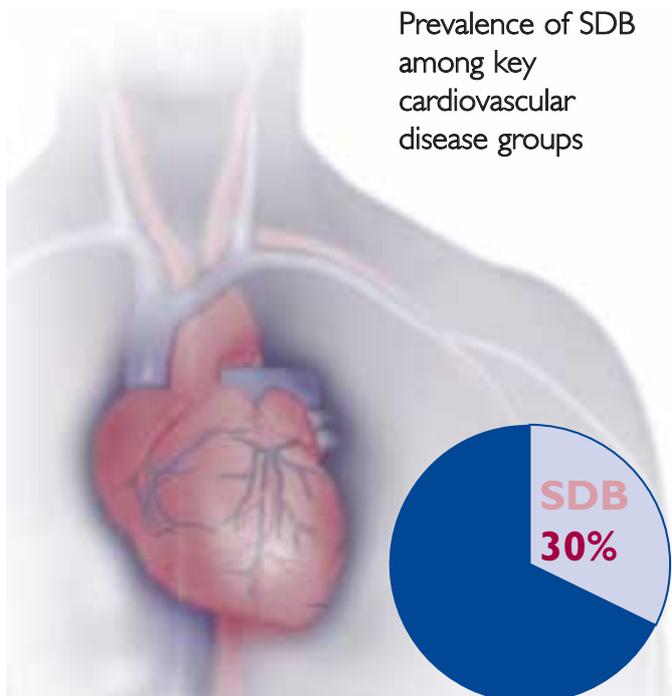


A = Mean arterial blood pressure without treatment (closed circles) and therapeutic nCPAP treatment (open circles)

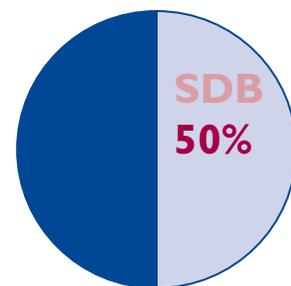
B = Mean arterial blood pressure without treatment (closed circles) and subtherapeutic nCPAP treatment (open circles)

Facts and figures

Prevalence of SDB among key cardiovascular disease groups



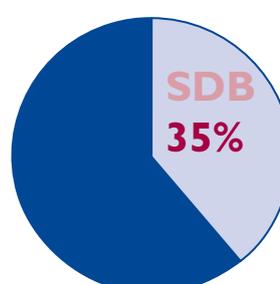
Stroke



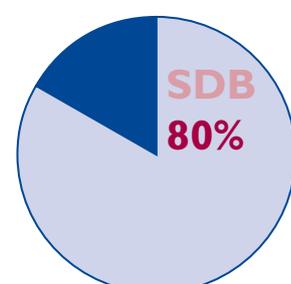
Congestive heart failure



Coronary artery disease



Hypertension

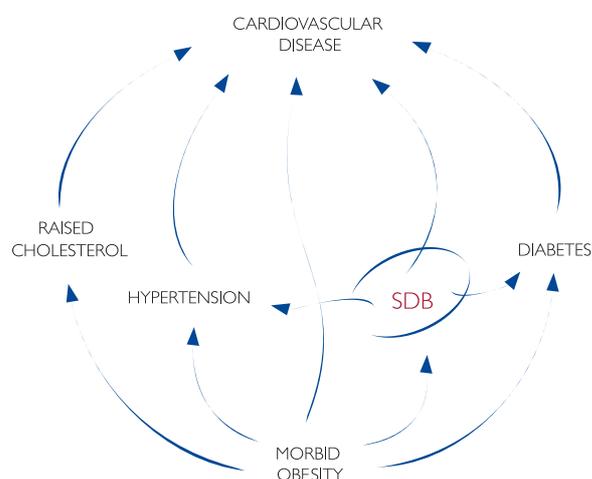


Drug-resistant hypertension

- “Sleep-disordered breathing (SDB) affects 80% of drug-resistant hypertension patients.”¹
- “Evidence...indicates that undiagnosed obstructive sleep apnea...with or without symptoms, is independently associated with increased likelihood of hypertension, cardiovascular disease, stroke...and diminished quality of life.”²
- “SDB has direct, proven links to many chronic diseases. Untreated SDB is known to accelerate the worsening of severe respiratory conditions. Research has revealed that untreated SDB contributes significantly to cardiovascular diseases and may be a causative factor in some cases of hypertension.”²
- “Treating SDB is now a vital part of the treatment and management of these major diseases.”³
- “SDB is recognized as a serious health problem that impacts the cardiovascular system in several ways. The comorbidity of SDB and cardiovascular disease has been well established; SDB has been linked with hypertension, coronary artery disease, congestive heart failure, transient ischemic attack, and stroke.”⁴

- “SDB has a dose-response relationship with hypertension, independent of all known risk factors (age, gender, BMI, smoking, alcohol, others).”⁵

1. Logan et al. *Hypertension* 2001
2. Young et al. *Am J Respir Crit Care Med* 2002
3. Kaneko et al. *N Engl J Med* 2003
4. Bradley TD, Floras JS. *Lung Biology in Health and Disease* 2000
5. Lavie et al. *BMJ* 2000



Obstructive sleep apnea and cardiovascular disease



A strong link between OSA and cardiovascular diseases has been established through several epidemiological studies over the last 10 years.

The largest study of OSA and cardiovascular disease was the Sleep Health Heart Study, which involved over 6000 subjects. This study demonstrated that OSA is an independent risk factor for hypertension, coronary artery disease, and congestive heart failure. Stroke has also been linked with OSA in many studies, and the condition is very prevalent in stroke survivors.

Hypertension is the predominant mechanism by which OSA has been thought to cause cardiovascular diseases. Hypertension is a well known risk factor for all cardiovascular diseases, including stroke, and treatment is an important part of management. However, some recent publications have suggested alternative mechanisms that may lead to cardiovascular disease in patients with OSA.

Endothelial cells line the surfaces of blood vessels and release locally vasoactive substances (endothelin and nitric oxide), which regulate vascular tone. Impaired endothelial function has been demonstrated in patients who smoke, are hypertensive, or have diabetes, and is associated with an increased risk of cardiovascular events. Patients with OSA also demonstrate impaired endothelial function, and there is preliminary evidence that it can be reversed with CPAP treatment. The mechanism is unclear but is probably due to repetitive hypoxia or hypercapnia, or to rapidly changing blood pressure.

Activation of inflammatory pathways and inflammatory cells is another abnormality demonstrated in OSA patients that may cause cardiovascular disease. Inflammation has been shown to be an important factor

in the progression of cardiovascular diseases, particularly heart failure and ischemic heart disease. Patients with OSA have increased levels of inflammatory markers such as C-reactive protein, interleukin 6, and tumor necrosis factor. It is thought that this is due to repetitive hypoxia. Recent studies have shown that levels of these markers can be reduced to normal with several weeks of CPAP therapy.

Adhesion of circulating inflammatory cells to endothelium is one of the initial steps in atherosclerosis. Repetitive hypoxia increases the number of adhesion molecules these cells express and increases their ability to stick to vessel walls. When they adhere to vessel walls they produce oxygen free radicals, which cause damage to the endothelial cells lining the vessel walls. It has recently been demonstrated that patients with OSA have elevated levels of adhesion molecules and superoxides and that these levels are reduced by short-term treatment with CPAP.

Cardiovascular events are generally caused by rupture of atheromatous plaques and occlusion of blood vessels by clots. Patients with OSA may demonstrate increased hematocrit, levels of fibrinogen, blood viscosity, and platelet stickiness, all of which predispose to the formation of clots. The finding that CPAP therapy may improve some of these abnormalities suggests that OSA is the cause and that treatment may be effective at reducing cardiovascular events.

These effects of OSA are independent of hypertension and suggest alternative mechanisms whereby OSA may cause or accelerate cardiovascular disease. They also suggest that CPAP treatment is likely to be an important part of the management of these important diseases.

By Dr: Glenn Richards, Medical Director, ResMed Ltd.

Websites of interest

The National Heart, Lung, and Blood Institute (NHLBI) concentrates on national programs in diseases of the heart, blood vessels, lung, and blood; blood resources; and sleep disorders. Since October 1997, the NHLBI has also had administrative responsibility for the NIH Women's Health Initiative
www.nhlbi.nih.gov

For information on The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), visit
www.nhlbi.nih.gov/guidelines/hypertension

Available information includes:

- JNC 7 Express Guidelines
- Physician Reference Card
- JNC 7 Slide Show.

You will also find information for patients, including *Your guide to lowering blood pressure* and *Facts about the DASH eating plan*.

Recent research articles

1. Refractory hypertension and sleep apnea: effect of CPAP on blood pressure and baroreflex. Logan AG, Tkacova R, Perlikowski SM, Leung RS, Tisler A, Floras JS, Bradley TD. *Eur Respir J*. 2003 Feb;21(2):241-7.

This study was undertaken to determine whether abolition of obstructive sleep apnea (OSA) by continuous positive airway pressure (CPAP) could reduce blood pressure (BP) in patients with refractory hypertension. In 11 refractory hypertensive patients with OSA, the acute effects of CPAP on nocturnal BP were studied during sleep and its longer term effects on 24-h ambulatory BP after 2 months. During a single night's application, CPAP abolished OSA and reduced systolic BP in stage 2 sleep from 138.3 +/- 6.8 to 126.0 +/- 6.3 mmHg. There was also a trend towards a reduction in average diastolic BP (from 77.7 +/- 4.5 to 72.9 +/- 4.5). CPAP usage for 2 months was accompanied by an 11.0 +/- 4.4 mmHg reduction in 24-h systolic BP. In addition, both the nocturnal and daytime components of systolic BP fell significantly by 14.4 +/- 4.4 and 9.3 +/- 3.9 mmHg, respectively. Diastolic BP was reduced significantly at night by 7.8 +/- 3.0 mmHg. In patients with refractory hypertension, acute abolition of obstructive sleep apnea by continuous positive airway pressure reduces nocturnal blood pressure. These data also suggest that continuous positive airway pressure may reduce nocturnal and daytime systolic blood pressure chronically. Randomized trials are needed to confirm the latter results.

2. Hypertension and obstructive sleep apnea. Phillips BG, Somers VK. *Curr Hypertens Rep*. 2003 Oct;5(5):380-5.

Obstructive sleep apnea is a common disorder that is often unrecognized and under appreciated. Emerging evidence suggests that there is a causal link between obstructive sleep apnea and hypertension. This relationship appears to be independent of other comorbidities that have been previously linked to hypertension, such as obesity. The majority of studies support the contention that alleviation of sleep-disordered breathing has a clinically significant beneficial impact on decreasing both night-time and daytime blood pressure. A pathophysiologic basis for patients with sleep apnea having an increased risk for hypertension is not fully elucidated. However, there is consistent evidence that autonomic mechanisms are implicated. Sympathetic activation along with humoral responses to repetitive episodes of hypoxemia and apnea over the longer term

may cause vasoconstriction, endothelial dysfunction, and possibly hypertension. Patients with sleep apnea are often obese and may be predisposed to weight gain. Hence, obesity may further contribute to hypertension in this patient population.

3. Obstructive sleep apnea and cardiovascular disease. Lattimore JD, Celermajer DS, Wilcox I. *J Am Coll Cardiol*. 2003 May 7;41(9):1429-37.

Obstructive sleep apnea (OSA) is a common disorder associated with an increased risk of cardiovascular disease and stroke. As it is strongly associated with known cardiovascular risk factors, including obesity, insulin resistance, and dyslipidemia, OSA is an independent risk factor for hypertension and has also been implicated in the pathogenesis of congestive cardiac failure, pulmonary hypertension, arrhythmias, and atherosclerosis. Obesity is strongly linked to an increased risk of OSA, and weight loss can reduce the severity of OSA. The current standard treatment for OSA—nasal continuous positive airway pressure (CPAP)—eliminates apnea and the ensuing acute hemodynamic changes during sleep. Long-term CPAP treatment studies have shown a reduction in nocturnal cardiac ischemic episodes and improvements in daytime blood pressure levels and left ventricular function. Despite the availability of effective therapy, OSA remains an underdiagnosed and undertreated condition. A lack of physician awareness is one of the primary reasons for this deficit in diagnosis and treatment.

4. Relationship of systolic BP to obstructive sleep apnea in patients with heart failure. Sin DD, Fitzgerald F, Parker JD, Newton GE, Logan AG, Floras JS, Bradley TD. *Chest*. 2003 May;123(5):1536-43.

OBJECTIVES: Obstructive sleep apnea (OSA) is an independent risk factor for hypertension in the general population. Hypertension is, in turn, an important risk factor for the development and progression of congestive heart failure (CHF). Our objective was to determine whether OSA would be associated with elevated daytime BP in medically treated patients with CHF. **DESIGN:** Cross-sectional study. **SETTING:** Tertiary care, university-affiliated sleep disorders and heart failure clinics. **PATIENTS:** 301 consecutive patients with CHF. **MEASUREMENTS AND RESULTS:** We measured daytime BP and performed overnight sleep studies to



assess for the presence of OSA. Among these patients, OSA was present in 121 patients (40%) and their systolic BP was significantly higher than in patients without OSA. Patients with OSA were 2.89 times (95% confidence interval, 1.25 to 6.73) more likely to have systolic hypertension (ie BP \geq 140 mmHg) than those without OSA after controlling for other risk factors, including obesity. The degree of systolic BP elevation was directly related to the frequency of obstructive apneas and hypopneas. CONCLUSIONS: In medically treated patients with CHF, daytime systolic BP and the prevalence of systolic hypertension are significantly increased in patients with OSA, compared to those without OSA, independent of other potentially confounding factors. OSA may therefore have contributed to the presence of systolic hypertension in some of these patients.

5. Sleep apnea and markers of vascular endothelial function in a large community sample of older adults.

Nieto FJ, Harrington DM, Redline S, Benjamin EJ, Robbins JA. *Am J Respir Crit Care Med.* 2003 Oct 9.

Clinical studies have suggested that sleep apnea is associated with impaired brachial artery flow-mediated dilation, a surrogate of endothelial dysfunction. We examined this question among elderly participants in the baseline examination of the Sleep Heart Health/Cardiovascular Health Study cohort ($n=1,037$, age >68 years, 56% female). Indices of sleep apnea, derived from 12-channel home polysomnography were: apnea-hypopnea index (average number of apneas/hypopneas per hour) and hypoxemia index (% time below 90% O₂ saturation). Baseline arterial diameter and flow-mediated dilation (%FMD) were measured by ultrasound. Sleep apnea measures were associated with baseline diameter and %FMD, although these associations were weakened after adjustment for other cardiovascular risk factors, particularly body mass index (BMI). However, a statistically significant linear association between the hypoxemia index and baseline diameter was observed even after adjustment for BMI and other confounders ($p<0.01$). The associations were stronger among participants <80 years and among hypertensives. This study adds to the growing body of evidence linking sleep apnea with vascular dysfunction in older subjects. Whether these relationships are entirely independent of obesity is

unclear. This association might be one of the mechanisms explaining the relation between sleep apnea, hypertension, and cardiovascular disease.

6. Plasma homocysteine levels in obstructive sleep apnea: association with cardiovascular morbidity. Lavie L, Perelman A, Lavie P. *Chest* 2001 Sep;120(3):900-8.

OBJECTIVES: Obstructive sleep apnea (OSA) is associated with cardiovascular morbidity and mortality. Plasma levels of homocysteine are also associated with cardiovascular morbidity and mortality. We therefore investigated homocysteine and conventional cardiovascular risk factors in OSA patients with and without cardiovascular morbidity in comparison with normal control subjects and ischemic heart disease (IHD) patients without OSA. SETTING: Technion Sleep Medicine Center, Haifa, Israel. METHODS AND PARTICIPANTS: Levels of homocysteine, cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, creatinine, vitamins B(12) and B(6), and folic acid were determined in 345 participants after overnight fasting. These included OSA patients with IHD ($n = 49$), with hypertension ($n = 61$), or without any cardiovascular disease ($n = 127$). Two control groups were employed: IHD patients without or with low likelihood for sleep apnea ($n = 35$), and healthy control subjects ($n = 73$). RESULTS: After adjustment for age, body mass index, creatinine, and existence of diabetes mellitus, OSA patients with IHD had significantly higher homocysteine levels (14.6 \pm 6.77 micromol/L) than all other groups including the IHD-only patients. Hypertensive OSA patients had comparable homocysteine levels to IHD patients (11.80 \pm 5.28 micromol/L and 11.92 \pm 5.7 micromol/L, respectively), while patients with OSA only had comparable levels to normal control subjects (9.85 \pm 2.99 micromol/L and 9.78 \pm 3.49 micromol/L, respectively). No differences in conventional cardiovascular risk factors or in vitamin levels were found between groups. CONCLUSIONS: Patients with the combination of IHD and OSA have elevated homocysteine levels. We hypothesize that these results may be explained by endothelial dysfunction combined with excess free-radical formation in OSA patients.



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19–24 March 2004	Sydney, Australia	TSANZ Annual Scientific Meeting (Thoracic Society of Australia and New Zealand)
12–16 May 2004	Vienna, Austria	14th European Congress of Physical Rehabilitation Medicine
21–26 May 2004	Orlando, FL, USA	ATS (American Thoracic Society)
5–10 June 2004	Philadelphia, PA, USA	APSS 18th Annual Meeting (Associated Professional Sleep Society)
12–15 June 2004	Wroclaw, Poland	Heart Failure Update Meeting 2004
23–26 June 2004	Vancouver, Canada	5th World Stroke Congress
28 August–1 Sept 2004	Munich, Germany	European Society of Cardiology Congress 2004
4–8 September 2004	Glasgow, Scotland	14th European Respiratory Society Congress
12–15 September 2004	Toronto, Canada	HFSA (Heart Failure Society of America)
5–9 October 2004	Prague, Czech Republic	17th European Sleep Research Society Congress
15–17 October 2004	Sydney, Australia	ASA (Australasian Sleep Association)
23–28 October 2004	Seattle, WA, USA	CHEST 2004
26–28 October 2004	Orlando, FL, USA	Medtrade 2004
7–12 November 2004	New Orleans, LA, USA	AHA (American Heart Association)

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