Sleep Apnea and Cardiovascular Disease

Anthony R. Dal Nogare

Medical Grand Rounds

January 29, 2004

"What did it matter where you lay once you were dead? In a dirty sump or in a marble tower on top of a high hill? You were dead, you were sleeping the big sleep, you were not bothered by things like that. You just slept the big sleep, not caring about the nastiness of how you died or where you fell."

The Big Sleep by Raymond Chandler

Poins: Falstaff! - fast asleep behind the arras, and snorting like a horse.
Prince Henry: Hark, how hard he fetches breath.

A description of Falstaff asleep, Henry IV by Shakespeare

Introduction

Sleep apnea is a very common condition. Based on large, population-based surveys of mostly asymptomatic adults who have had overnight sleep studies, about 12% of adult males and 5% of females have a significant number of apneas (1-3). About 20% of the US population has essential hypertension with no discernable cause. Obesity, the main risk factor for obstructive sleep apnea (OSA), is becoming an epidemic problem in Western countries. Clinicians have long suspected a link between sleep apnea and hypertension but the connection has been difficult to prove due to a paucity of well designed studies and the confounding influence of obesity, which is a risk factor for both conditions.

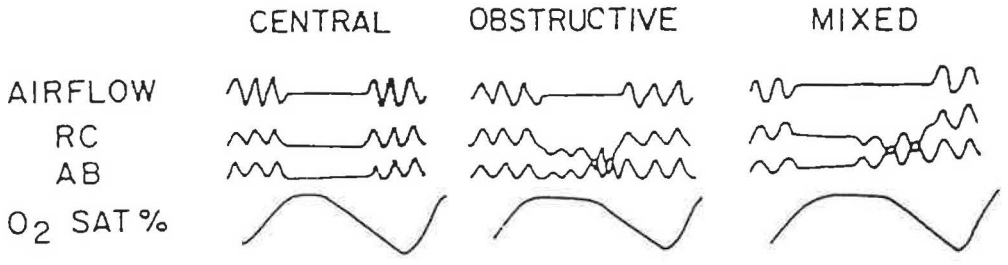
Given the prevalence of sleep apnea and cardiovascular disease, and the attendant morbidity and mortality, establishing a causal connection has important public health implications. Over the past decade there have been good clinical and basic scientific studies which have clarified the connection between sleep disordered breathing and cardiovascular disease. The following three questions will be addressed:

1. Is sleep apnea a risk factor for hypertension and other cardiovascular diseases?
2. How does sleep apnea cause hypertension?
3. Does treatment of sleep apnea benefit cardiovascular disease?

Sleep apnea and sleep apnea syndrome

There are two types of sleep apnea, obstructive and central. Obstructive sleep apnea, or OSA, occurs when upper airway soft tissue collapses during inspiration. The diaphragm and intercostal muscles continue to contract but there is no airflow and the patient eventually wakes up due to a combination of hypoxemia and hypercapnia. The vast majority of patients with sleep disordered breathing have OSA. Central sleep apnea occurs due to failure of central respiratory drive to the diaphragm and is rare, except for a type of central apnea known as Cheyne-Stokes respiration (CSR) which is often affects heart failure patients(4). Mixed apneas start out as central apneas followed by diaphragm/intercostal muscle contraction. All types of apnea cause hypoxemia and hypercapnea, which can be severe depending on apnea duration.

Figure 1. Three types of sleep apnea



Am. Rev. Resp. Dis. 134:791, 1986

Sleep apnea is usually diagnosed with an overnight sleep study during which the number of apneas (> 10 seconds of no airflow) and hypopneas (ten seconds of decreased airflow plus >4% fall in arterial oxygen saturation) are counted. The apnea-hypopnea index (AHI) is the number of apneas and hypopneas per hour averaged over an eight hour sleep period and is the basic measurement used to quantify sleep apnea severity. Since many

normal, healthy males snore and have apneas and hypopneas the distinction between a normal and pathologic AHI is blurry, but most investigators consider an AHI > 30 to be indicative of severe sleep apnea(5).

The diagnosis of sleep apnea syndrome requires both an increased AHI and daytime sleepiness severe enough to interfere with the patients ability to function. This is an important distinction since many people, especially males, have an elevated AHI but are not somnolent. For example, a recent large, population based survey which excluded subjects known to have sleep apnea syndrome found that 6% had an AHI >30(6).Daytime sleepiness is due to repetitive arousals to wakefulness which occur at the end of each apnea, resulting in fragmented, poor quality sleep and REM sleep deprivation.

Abnormal cardiovascular physiology during sleep

Non-REM sleep, which accounts for 85% of total sleep, is a time of rest and relaxation for the cardiovascular system. Sympathetic nervous activity (SNA) decreases, parasympathetic tone rises, and heart rate, systolic and diastolic blood pressure all fall(5). The normal nocturnal blood pressure fall is referred to as "dipping" and occurs both in normals and in essential hypertension patients (7). A very different pattern develops when OSA patients sleep. Elevations, sometimes to extreme levels, in systemic blood pressure, pulmonary arterial pressure, and heart rate occur.

Figure 2. Hemodynamic changes during sleep in OSA

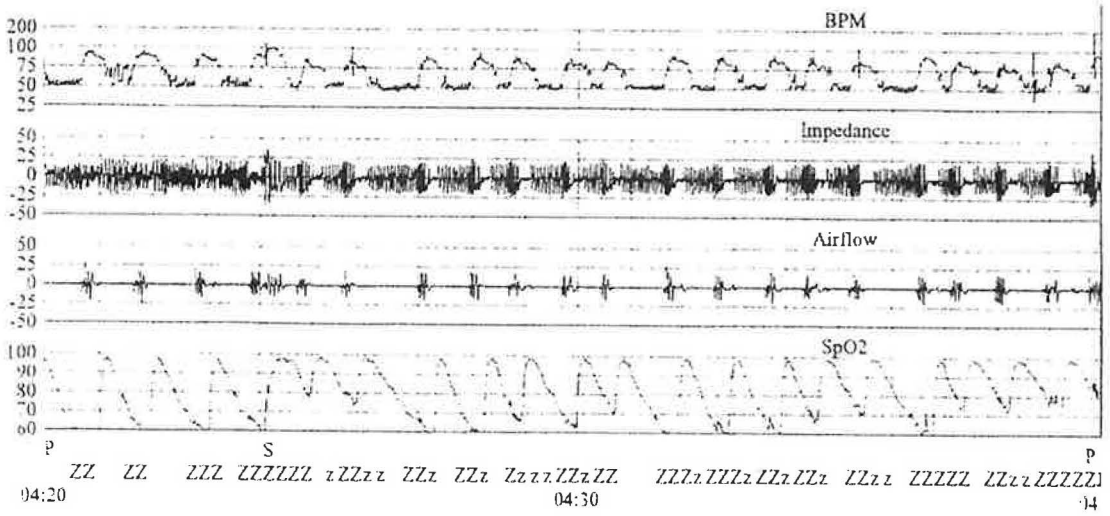
Case No.	Before Tracheostomy			
	Average No. of Apneas per Hour of Sleep	Lowest Recorded Pao_2*	Highest Recorded Pressures†	
			Femoral Artery	Pulmonary Artery
		←	*mm Hg*	→
1	78	34	168/100 (123)	38/24 (27)
2	64	50	160/100 (120)	60/40 (47)
3	60	38	205/134 (158)	70/50 (57)
4	63	36	200/120 (147)	80/54 (63)
5	90	30	194/124 (148)	60/48 (52)
6	80	43	170/110 (130)	38/22 (27)
Mean ± SEM	73 ± 5	38 ± 3	(137 ± 6)	(45 ± 6)

Annals Int. Med. 89:454, 1978

Peak systemic and pulmonary arterial pressures occur at the beginning of each arousal; at that time sympathetic outflow is maximal due to hypoxia and the change from sleep to wakefulness (8). Although apnea-induced systemic hypertension is clearly due to catecholamines, pulmonary hypertension is not, since pulmonary arteries have little sympathetic innervation. The acute rise in pulmonary pressure is due to a direct effect of alveolar hypoxia on pulmonary arterial smooth muscle cells, which rapidly constrict in response to hypoxia (9). Systemic blood pressure falls after each apnea but overnight the inter-apnea baseline blood pressure gradually rises, so that blood pressure in the morning is often higher than it was at sleep onset. Overnight plasma and urine catecholamines are elevated, and catecholamine levels correlate best with the amount of time patients are hypoxemic (10).

Abnormal cardiac rhythms also occur during OSA sleep. Marked sinus arrhythmia is common and when present only during sleep is almost pathognomic of OSA (11).

Figure 3. Sinus arrhythmia during OSA



J. Heart Lung Transplantation 16:394, 1997

Bradycardia occurs at the end of each apneic period when hypoxemia is maximal, and tachycardia occurs during the arousal period when the patient wakes up. In awake, breathing subjects hypoxemia causes tachycardia due to catecholamine release, and OSA patients have increased sympathetic activity during apneas, so bradycardia seems paradoxical. The explanation involves the diving reflex, which is highly developed in diving mammals such as seals and is also present as a vestigial reflex in humans (12). The combination of breath holding and cold water immersion is the most potent stimulus, but apneas, especially if they last > 10 seconds, also elicit it. Bradycardia is vagally mediated and can be blocked by atropine or cardiac denervation (13). Hypoxemia during the apnea is also a stimulus, because nocturnal oxygen administration prevents bradycardias (14). Nocturnal electrocardiographic monitoring to detect sinus arrhythmia has been recommended as a simple OSA screening test (15). In one recent study, detection of large (>20 beats/minute) cyclic variation in sleep heart rate had an 86% positive predictive value for diagnosing significant (AHI >15) OSA (16).

In addition to sinus arrhythmia heart block often occurs. In three separate series totaling 684 patients electrocardiographic monitoring during a sleep study detected sinus pauses of > 2 seconds in 11%, second or third degree heart block in 8%, and ventricular tachycardia in 3% (17-19). The higher levels of block usually occurred in patients with severe OSA (AHI >60). These patients all had normal daytime 12 lead electrocardiograms, were not taking any drugs with negative chronotropic effects, and were asymptomatic from their nocturnal arrhythmias. In most cases effective treatment of OSA with either a tracheostomy or continuous positive airway pressure (CPAP) results in normal sinus rhythm during sleep (20).

Daytime hypertension in OSA

Many observational studies have reported an association between daytime hypertension and OSA but these have been small and often poorly controlled for confounding variables such as obesity, age, and cigarette smoking. Two different animal

models have shown that OSA can cause persistent hypertension. Rats exposed to 35 days of intermittent nocturnal hypoxia (20 seconds/minute while sleeping) develop hypertension and bi-ventricular hypertrophy (21). In an ingenious canine model which reproduces the pathophysiology of OSA, a surgically implanted tracheal balloon was inflated periodically while the dogs slept. During the apnea the animals developed hypoxemia, hypercapnea, and eventually woke up, at which time the balloon was deflated. After five weeks mean blood pressure went up 16 mmHg. Hypertension was not due to frequent arousals, since waking the animals up with a periodic loud noise had no effect on daytime blood pressure. Hypertension resolved one to three weeks after resumption of normal sleep (22).

Two large clinical studies published in 2000 have established OSA as a significant hypertension risk factor. The Sleep Heart Health Study was a large, community based cross sectional study enrolling 6,132 adults, none of whom were known to have a sleep apnea syndrome. Extensive demographic and medical data was collected and an overnight sleep study performed. After multivariate adjustment for weight, age, sex, and smoking hypertension risk was linearly related to the AHI. An AHI >30 gave an adjusted odds ratio for hypertension of 1.37 (confidence interval(CI) 1.03-1.83). The amount of hypoxemic sleep time was also a hypertension risk factor (6). The data from this single time, point prevalence study have been confirmed in a population based longitudinal study which determined that that sleep apnea often precedes hypertension. The Wisconsin Sleep Cohort Study enrolled 709 working adults, none of whom had cardiopulmonary disease or a known sleep apnea syndrome, and followed them for five years after a baseline sleep study. After adjustment for all known hypertension risk factors sleep apnea was a strong predictor for a subsequent diagnosis of hypertension. The adjusted hypertension odds ratio was 2.89 (CI 1.46-5.64) for subjects having an AHI>15 on their baseline sleep study (23). A population based case control study compared 116 hypertensive males to 116 normotensive controls matched for age, BMI, smoking, and physical activity. 12% of the hypertensives had an AHI >30 versus 2% of the controls (24). Extrapolating from these results 12% of hypertensive men have significant OSA, sleep apnea is an independent hypertension risk factor, and risk is greatest for an AHI >15.

Table 1. Wisconsin sleep cohort 4 year followup data

TABLE 3. ADJUSTED ODDS RATIOS FOR HYPERTENSION AT A FOLLOW-UP SLEEP STUDY, ACCORDING TO THE APNEA–HYPOPNEA INDEX AT BASE LINE.*

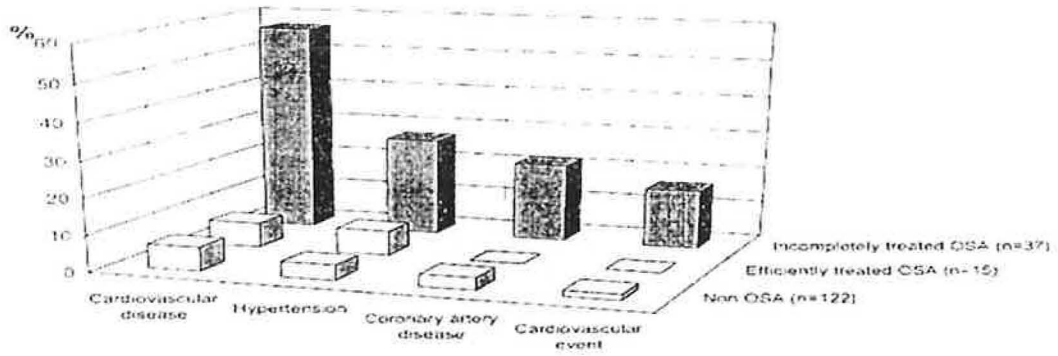
BASE-LINE APNEA–HYPOPNEA INDEX	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS AND NONMODIFIABLE RISK FACTORS (AGE AND SEX)	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS, NONMODIFIABLE RISK FACTORS, AND HABITUS (BMI AND WAIST AND NECK CIRCUMFERENCE)	ODDS RATIO, ADJUSTED FOR BASE-LINE HYPERTENSION STATUS, NONMODIFIABLE RISK FACTORS, HABITUS, AND WEEKLY ALCOHOL AND CIGARETTE USE
		odds ratio (95% confidence interval)		
0 events/hr†	1.0	1.0	1.0	1.0
0.1–4.9 events/hr	1.66 (1.35–2.03)	1.65 (1.33–2.04)	1.42 (1.14–1.78)	1.42 (1.13–1.78)
5.0–14.9 events/hr	2.74 (1.82–4.12)	2.71 (1.78–4.14)	2.03 (1.29–3.19)	2.03 (1.29–3.17)
≥15.0 events/hr	4.54 (2.46–8.36)	4.47 (2.37–8.43)	2.89 (1.47–5.69)	2.89 (1.46–5.64)
P for trend‡	<0.001	<0.001	0.002	0.002

Based on the Sleep Heart Health and Wisconsin data, 6-12% of adults have an AHI >15 without excessive daytime sleepiness, raising the question of how to identify hypertensive patients with OSA. In general, OSA patients with high AHI are overweight males who snore loudly. A history of snoring, followed by a period of silence, followed by loud snorting and sudden arm/leg movements can often be obtained from the bed partner. 24 hour ambulatory blood pressure monitoring may identify the hypertensive OSA patient because 50% do not decrease blood pressure during sleep (nondippers). Lastly OSA may make hypertension difficult to treat. In a series of 41 medically compliant patients with refractory hypertension, defined as poor control despite maximal doses of ≥ 3 drugs, 83% had OSA (25).

Other cardiovascular diseases and OSA

Since hypertension is an important risk factor for many cardiovascular diseases it is not surprising that OSA has been linked to left ventricular hypertrophy, congestive heart failure, ischemic heart disease, and stroke. In general, the data linking OSA to these other conditions is not as good as for hypertension. In a canine model one month of OSA caused a decreased ejection fraction, an increased left ventricular end-systolic volume, and a small increase in left ventricular mass (26). A group of 29 normotensive, newly diagnosed OSA patients were evaluated by radionuclide ventriculography and compared to a control group matched for age, blood pressure, and weight. The OSA patients (average AHI 54) had lower ejection fractions and abnormal diastolic function (reduced left ventricular peak filling rate), suggesting that left ventricular hypertrophy occurs early, even before daytime hypertension (27). An echocardiographic investigation has detected left ventricular hypertrophy in a group of 30 normotensive OSA subjects (AHI 28)(28). Early ventricular hypertrophy might occur due to increased afterload from inspiration against a closed airway (Mueller maneuver) or from apnea-associated blood pressure surges. The Sleep Heart Health Study data show that an AHI >11 is an independent risk factor for ischemic heart disease (OR 1.27), heart failure (OR 2.20), and stroke (OR 1.58). AHI < 11 were not associated with excess cardiovascular disease (29). One small longitudinal study followed 182 healthy males for seven years. 122 had no significant OSA, 60 had OSA (AHI 16), and they were closely matched for age, weight, blood pressure, and smoking. None had cardiac disease at entry.

Figure 4. CV disease over 7 year followup (AJRCCM 166:162, 2002)



Overall OSA patients had an 5 fold elevated risk of suffering one of the cardiac endpoints on figure 4. Effective CPAP (continuous positive airway pressure) therapy

decreased cardiac risk to that of the control subjects, suggesting that CPAP reduces cardiac risk (30).

For patients with established coronary artery disease OSA can make sleep risky rather than restful. Nocturnal subendocardial ischemia, as measured by ST segment depression, occurs in 20 to 60 % of patients during a single night sleep study (31,32). Ischemic ST segment changes usually develop at the end of apneas, when patients are hypoxemic, tachycardic, and hypertensive, and are likely the result of increased oxygen demand coupled with a reduced oxygen supply. Increased platelet aggregability may also contribute to myocardial ischemia, because ST depression clusters around 6 am, when circulating epinephrine levels are highest and platelet aggregability is increased. Epinephrine activates platelets via the platelet $\alpha 2$ receptor (33,34). Sudden nocturnal cardiac death has been reported to occur more frequently in patients with known (35) or suspected (36) OSA.

OSA and pulmonary hypertension

Intermittent hypoxia causes proliferation of pulmonary vascular smooth muscle, raising vascular resistance and pulmonary arterial pressure. As little as 2 hours hypoxia per day, over a one month period, causes pulmonary hypertension and right ventricular hypertrophy in animals (37). A subgroup of 1,001 subjects from the large, population based Sleep Heart Health Study had both an echocardiogram and overnight sleep study. 90 subjects with high AHIs (42 ±15) were matched with 90 similar subjects with AHI <5 and right ventricular dimensions compared. The OSA group had significantly thicker right ventricles (38). Direct measurement of pulmonary artery pressure at the time of OSA diagnosis, in patients free from any other cardiopulmonary disease and with normal daytime arterial blood gases, has shown that 20 – 30% have pulmonary hypertension (39,40).

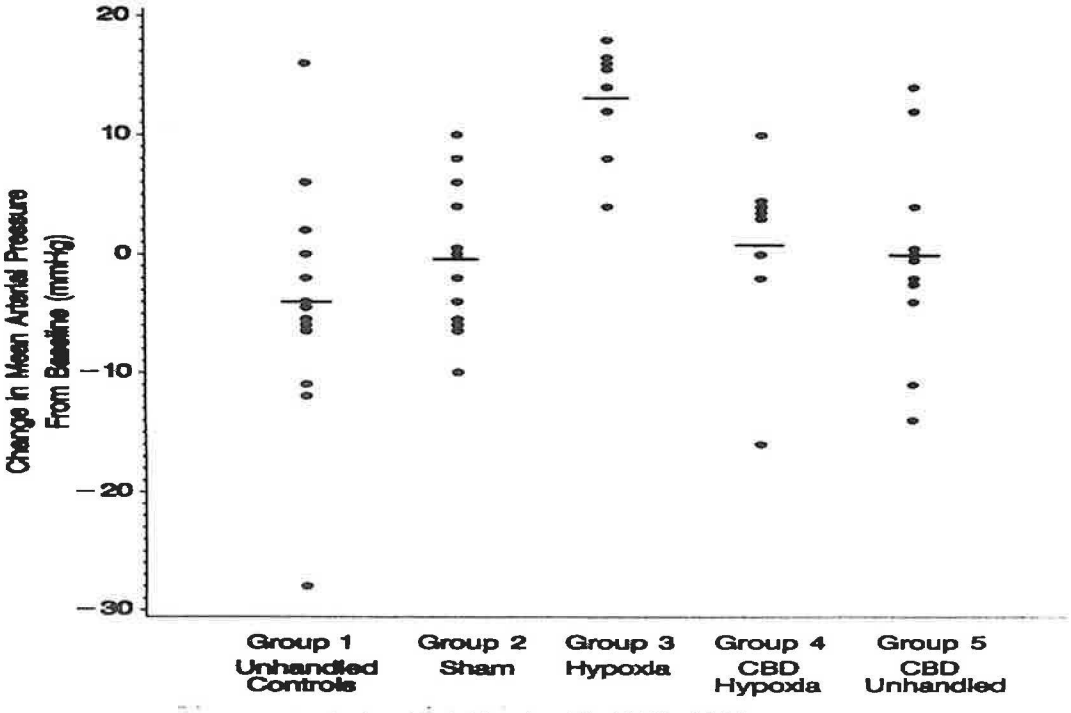
Obesity-hypoventilation syndrome (OHS, Pickwickian syndrome) patients are mobidly obese and have chronic ventilatory failure, defined as an elevated PaCO2 on a daytime arterial blood gas. 90% have OSA, often severe, and 60% have pulmonary hypertension and right heart failure (41). The prognosis for OHS patients is very poor.

Mechanism of OSA induced hypertension

Three interrelated hypoxemic responses cause persistent hypertension in OSA patients. They are chronic sympathetic nervous system activation, mechanical strain on arteries, and activation of HIF-1 (hypoxia inducible factor), a transcription factor which orchestrates many hypoxic responses.

Sympathetic overactivity – A rat OSA model, in which the animals are repeatedly exposed to 20 seconds hypoxemia over 8 hours for 35 days, has demonstrated that sympathetic activation causes daytime hypertension. Intermittently hypoxemic animals are hypertensive, have elevated circulating catecholamines, and have marked augmentation of sympathetic output in response to hypoxemia or hypoxemia/hypercapnea (42-45). Sympathetic denervation with 6-hydroxydopamine prevents hypertension (46). The carotid body is the major peripheral sensor of hypoxemia; carotid body denervation prevents hypertension (figure 5), suggesting that carotid body input causes hypertension by stimulating central sympathetic activation (47).

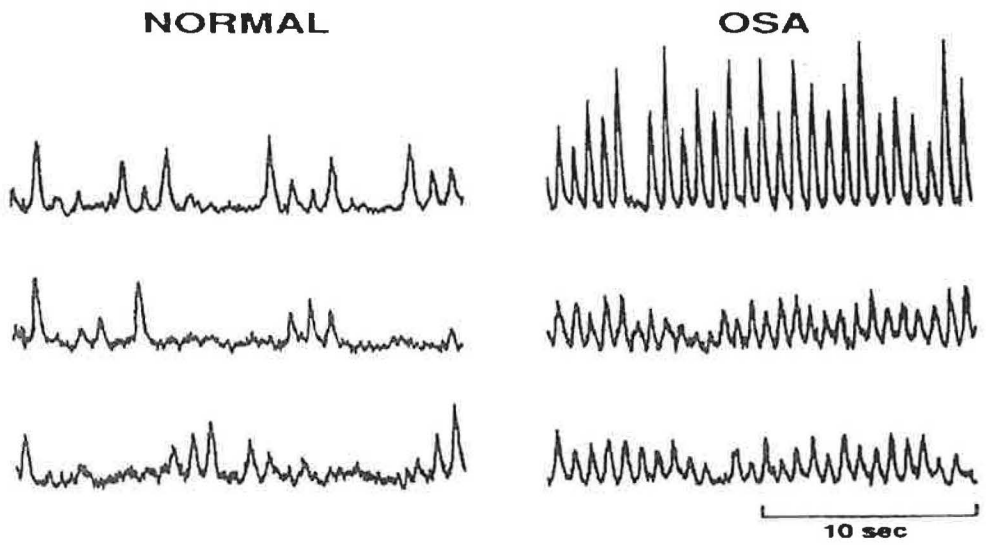
Figure 5. Carotid body denervation (CBD) prevents hypertension



J. Applied Physio. 72:1978, 1992

Clinical studies have detected increased sympathetic neural activity in OSA patients. Data from a population-based sample of 116 hypertensive men, 44 of whom had OSA, showed that hypertensive OSA subjects have high overnight urinary catecholamines compared to weight matched hypertensive patients without OSA (10). Sympathetic output to arteries in limb muscles can be measured with a technique called microneurography (MSNA). MSNA rises to high levels when OSA patients sleep and remains high when they are awake (Figure 6). MSNA is elevated even in normotensive OSA subjects (48,49). Exposure of normal subjects to intermittent hypoxemia over a 20 minute period causes a persistent increase in MSNA lasting for over 20 minutes (50,51). Carotid body afferent activity can be reduced by 100% oxygen; breathing 100% oxygen for 20 minutes reduced blood pressure and MSNA (17% MSNA reduction) in OSA patients but not in normal controls (52). Thus both the rat model and clinical data suggest that hypoxemia signals through carotid body chemoreceptors, causing persistent sympathetic nervous system activation.

Figure 6. MSNA in controls and OSA patients



J. Clin. Invest. 96:1897, 1995

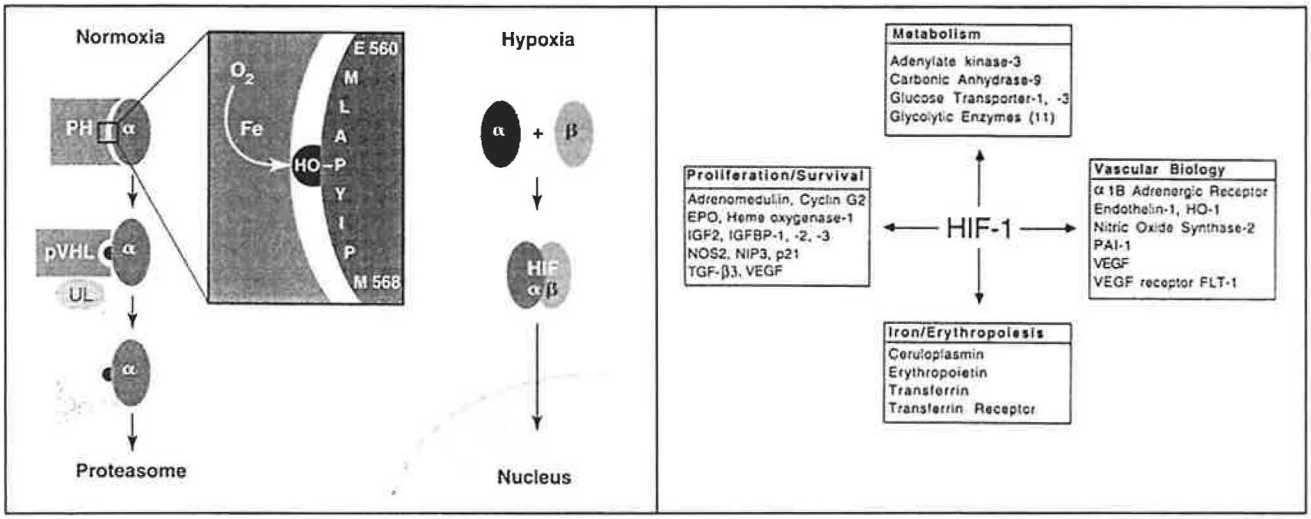
Mechanical strain – Nocturnal apnea-associated hypertension could cause persistent hypertension by activating shear stress response elements (SSRE). Endothelial and smooth muscle genes with SSREs include PDGF- A and B, Tissue Factor, TGF-B, the mitogen-activated protein kinases ERK and JNK, and heme oxygenase-1(53-56). Activation of these genes promotes smooth muscle and fibroblast proliferation and connective tissue deposition in arteries, resulting in thicker, less compliant arteries. Evidence that arterial remodeling occurs comes from measurements of carotid arterial wall thickness. Compared to a group of well-matched controls, OSA patients have a 45% increase in carotid thickness (57).

Mechanical strain and sympathetic activation also increase vascular wall NADPH oxidase, an enzyme which converts oxygen to the superoxide anion. Superoxide is a reactive oxygen radical which can be converted to other oxidizing compounds or combine with nitric oxide to form the highly reactive nitrogen radical peroxynitrite ($ONOO^-$). If superoxide and nitric oxide are in close proximity peroxynitrite formation occurs very rapidly. Peroxynitrite oxidizes tetrahydrobiopterin, an essential cofactor for endothelial nitric oxide synthase (eNOS), and oxidized tetrahydrobiopterin impairs eNOS nitric oxide synthesis. Since nitric oxide tonically relaxes vascular smooth muscle, decreased NO releases results in vasoconstriction and increased blood pressure. The concept that arterial wall oxidants can uncouple NO synthesis is called endothelial dysfunction, has been well documented in animal models of hypertension, and can be measured by administrating acetylcholine to patients; acetylcholine releases endothelial NO, lowering resistance and increasing blood flow (58-60). Endothelial dysfunction is present in OSA patients and is observed even when daytime blood pressure is normal (61).

Hypoxia- inducible factor 1 (HIF-1)- Although there is little direct evidence for HIF-1 activation in OSA, there is little doubt that it plays a central role in the pathophysiology of hypoxemia, and hypoxemia is associated with the increased

sympathetic activity and hypertension of OSA. Figure 7 outlines HIF-1 regulation, and figure 8 shows the large number of genes regulated by HIF-1.

Figure 7. HIF-1 regulation **Figure 8. HIF-1 effects**



Science 292:451, 2001 Cell 107:1, 2001

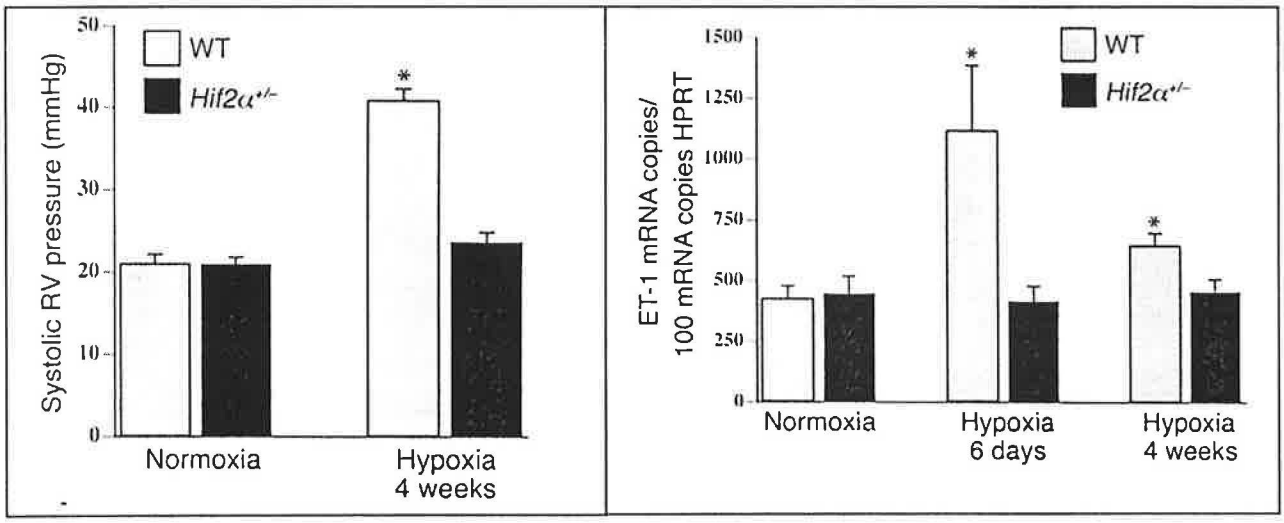
Under normoxic conditions an oxygen sensitive, proline hydroxylase adds an OH group to proline 564 which targets the α subunit for proteasomal destruction. At physiologically relevant (PO2 <50 mmHg) hypoxia the proline hydroxylase is inactive and HIF-1α combines with the β subunit, forming the active heterodimer which moves to the nucleus (62-66). HIF-1 activates genes by binding to hypoxia response elements (HREs) on promoter sequences. Six hours of hypoxia results in high level HIF-1 activity in many organs, with particularly strong expression in lungs, heart, Type 1 carotid body cells, and vascular endothelium (67,68). Of particular relevance for OSA are HIF-1 regulation of sympathetic responses and endothelin-1 (ET-1).

HIF-1 and catecholamines - HIF-1 is essential for normal maturation of the sympathetic nervous system; HIF-1 null mice die in utero from bradycardia (69,70). In adults HIF-1 regulates tyrosine hydroxylase, the rate-limiting enzyme of catecholamine synthesis, as well as vascular α1 adrenergic receptors (71,72). HIF-1 plays a key role in the carotid bodies response to hypoxemia. Brief hypoxic exposures markedly increase HIF-1 in the catecholamine rich, Type 1 carotid body cells which sense hypoxemia. Normally, hypoxemic carotid body stimulation increases blood pressure, central sympathetic outflow, and cardiac norepinephrine content. HIF-1 +/- heterozygote mice, exposed to three days hypoxemia, do not increase carotid body afferent nerve activity and do not develop increased hypoxic ventilatory drive (73). Thus HIF-1 in the carotid body is involved in sensing and signaling hypoxemia to the central nervous system. Compared to hypoxemic, HIF-1+/+ wild-type mice, HIF-1 +/- strains have a 71% reduction in circulating norepinephrine levels (74). These animal data strongly link HIF-1 to hypoxemia-induced sympathetic responses.

HIF-1 and endothelin-1(ET-1) – ET-1 is a 21 amino acid peptide which has an important role in systemic and pulmonary hypertension, vascular wall remodeling, and cardiac hypertrophy. Endothelial and lung cells release ET-1, which causes both acute

vasoconstriction and vascular remodeling through its proliferative effects on smooth muscle cells(75-77). The ET-1 gene is regulated by HIF-1, and HIF-1 antisense oligonucleotides prevent increased myocardial ET-1 activity in heart failure (78,79). Data from animal OSA models shows that circulating ET-1 increases rapidly, within five days of OSA onset, and remains elevated (80). OSA patients have high circulating ET-1 levels at night (81). Convincing data comes from animal experiments investigating the role of HIF-1 and ET-1 in hypoxic pulmonary hypertension. Wild type, HIF-1 +/+ mice exposed to hypoxia develop pulmonary hypertension secondary to remodeling of pulmonary arteioles; there is a marked increase in arterial smooth muscle, pulmonary vascular resistance and pressure rises, and the right ventricle hypertrophies. There is a rapid increase in HIF-1 activity, circulating catecholamines go up, as does ET-1 levels in lung and myocardium. ET-1 does not increase in hypoxemic HIF-1 heterozygotes, circulating norepinephrine levels are 71% lower, and the mice do not develop pulmonary vascular remodeling, pulmonary hypertension, or ventricular hypertrophy. (Figure 8).

Figure 8. Hypoxemic responses in HIF-1 +/+ and +/- mice



J. Clin. Invest. 111:1522, 2003

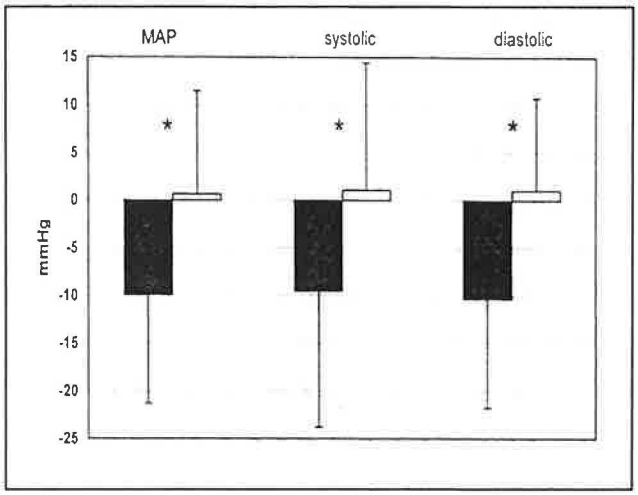
Unfortunately systemic blood pressure and left ventricular hypertrophy was not measured in these experiments (80). The heterozygous HIF-1 +/- mice had only a 50% reduction in HIF-1, raising the possibility that partial HIF-1 inhibition might benefit chronically hypoxemic patients. Although there are no clinical investigations measuring HIF-1 activation in OSA patients plasma levels of three proteins regulated by HIF-1 – erythropoietin, vascular endothelial growth factor, and ET-1 – are elevated and decrease when OSA is treated and the patients are no longer hypoxemic (82-84). HIF-1 is probably the key proximal molecule regulating carotid body hypoxemic responses, sympathetic nervous system activity, and the vascular remodeling (ET-1 mediated) which occurs after intermittent hypoxemia.

Cardiovascular effects of OSA therapy

Standard treatment for OSA is continuous positive airway pressure (CPAP), usually in the range of 10 to 15 cmH2O, delivered by a nasal mask while the patient sleeps. CPAP prevents upper airway collapse, nocturnal hypoxemia, and markedly improves daytime somnolence and functional status of symptomatic, OSA syndrome

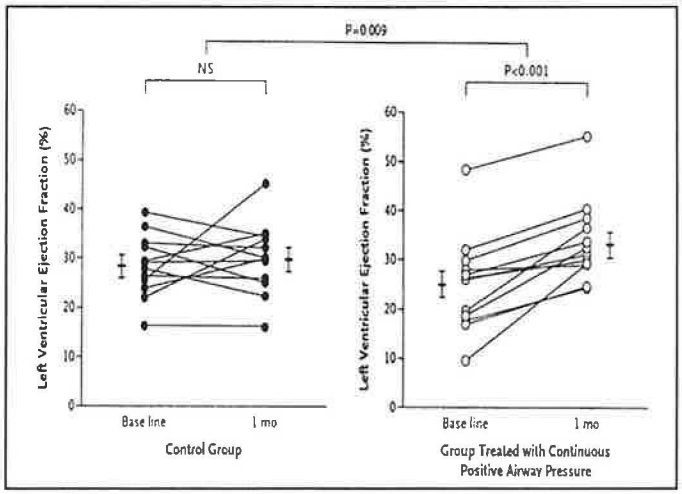
patients. Many clinical studies have also shown cardiac benefits of CPAP, although most of these have been small and uncontrolled. One prospective, randomized and placebo controlled trial was published in 2003. The effect of 60 days CPAP and sham-CPAP on blood pressure was measured in 32 obese, OSA syndrome patients who had severe disease (AHI 63). Twenty four hour blood pressure measurements revealed that CPAP lowered both day and night pressure with a significant 10mmHg fall in average mean blood pressure (Figure 10)(85). Another recent trial investigated the effect of CPAP on cardiac function in a group of heart failure patients with OSA (average AHI 36). The 24 patients in this study were receiving optimal medical heart failure therapy and the effect of one month of randomly assigned CPAP on blood pressure and ejection fraction was measured. CPAP treated patients had a 10 mmHg fall in systolic blood pressure and a 35% increase in ejection fraction (Figure 11)(86).

Figure 10. CPAP (closed bars)effect on blood pressure



Circulation 107:68, 2003

Figure 11. CPAP improves ejection fraction



NEJM 348:1238, 2003

A similar increase in ejection fraction was observed in 8 OSA patients with dilated cardiomyopathies, and the ejection fraction decreased when CPAP was stopped(87). CPAP also decreases MSNA (88), lowers overnight circulating catecholamine levels, prevents apnea-associated bradyarrhythmias and heart block (20), and reduces nocturnal ST segment depression and nocturnal angina (31). In an uncontrolled study of CPAPs effect on pulmonary arterial pressure, 22 OSA patients received 4 months CPAP. Five of the 22 had pulmonary hypertension at baseline evaluation. In all but one patient pulmonary arterial resistance and pressure fell (89).

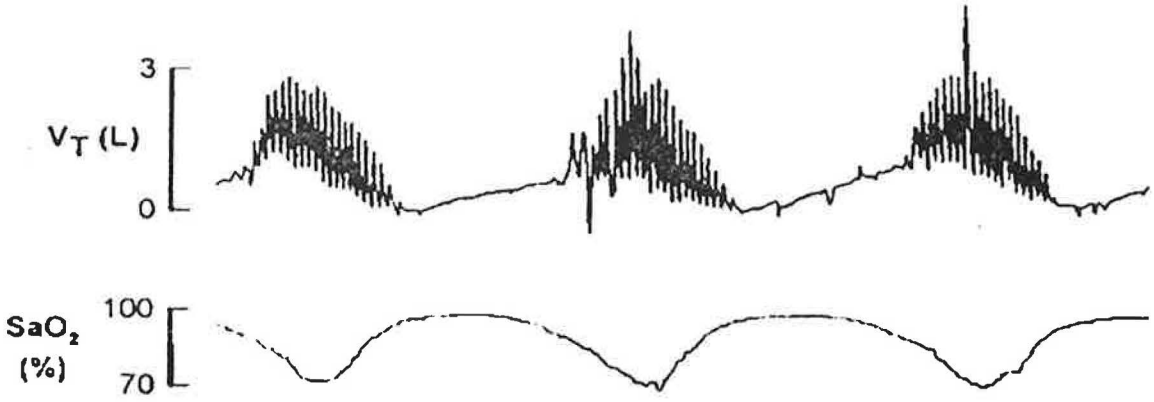
These reports of beneficial CPAP effects are encouraging, but have mostly enrolled a subset of OSA patients having either OSA syndrome or very high AHIs and thus severe disease. It is currently unknown if CPAP will benefit OSA patients with less severe disease. Compliance with chronic CPAP is poor when patients do not have OSA syndrome, because patients don't notice any symptomatic improvement and CPAP is cumbersome, inconvenient, and expensive. Thus asymptomatic OSA patients rarely continue CPAP for more than a few months (90,91). Population-based surveys show that most hypertensive OSA patients, even with AHI of >15, are not excessively sleepy

during the day, and it seems unlikely that such patients would use CPAP as a long term treatment.

Central sleep apnea and congestive heart failure

As previously discussed OSA-induced hypertension may may cause heart failure. Patients with established, usually severe heart failure can develop a different type of sleep-disordered breathing – Cheyne-Stokes breathing, which is a central sleep apnea.

Figure 12. Cheyne-Stokes breathing pattern



AJRCCM 159:1494, 1999

During CSR tidal volumes preceding apneic periods increase and decrease in a rhythmic fashion and, in contrast to OSA, there is no upper airway obstruction or respiratory muscle effort during apneas. Hypoxemia and hypercapnea develop and patients have frequent arousals, although CSR patients rarely complain of severe daytime sleepiness (4). In addition to heart failure, CSR occurs in normal subjects at high altitude and can occur as a complication of severe cerebrovascular disease. . In one large series of 450 CHF patients who were referred to a sleep laboratory, 33% had CSR (92).

The characteristic rhythmic pattern of CSR results from instability, or oscillatory behavior, in the feedback/control system which regulates respiration (93-95). The three elements of this system are shown on Table 2.

Table 2. The respiratory control system

Controller	Plant	Feedback
Medulla	Lungs	PaCO2, PaO2
Carotid bodies	Respiratory muscles	Circulation time

Oscillatory, unstable behavior develops in controlled systems when any of the following exist:

- Increased controller gain – for any incremental change in the sensed variable (PaCO2, PaO2) the controller output is too large.
- Decreased damping – When stores of the sensed variable are too small (total body oxygen and carbon dioxide content).
- Feedback delay – Prolonged circulatory time causes an excessive delay between the plants output (PaCO2, PaO2 in blood leaving the lungs) and the time that output is detected by controllers.

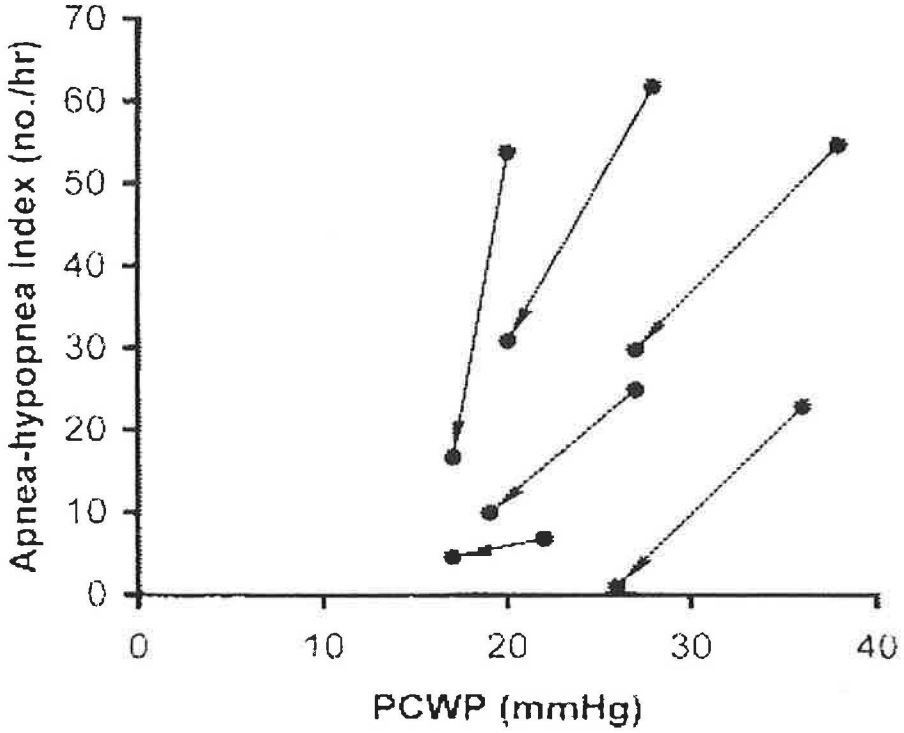
Investigation into the pathophysiology of CSR in CHF patients has shown that it results from both increased controller gain and feedback delay.

Increased controller gain – In normal people respiration is largely regulated by medullary chemoreceptors which sense CSF pH and maintain arterial CO2 closely around 40mmHg. During sleep the medullary CO2 setpoint increases by about 5 mmHg, so PaCO2 normally increases at night. When people are awake respiration is maintained by cortical and chemoreceptor inputs and apneas rarely occur. During sleep cortical and reticular activating formation stimuli disappear and chemoreceptor drive totally controls breathing; if PacCO2 falls below a certain level (the apnea threshold) respiration ceases until the PaCO2 rises above the threshold value.

A striking abnormality of CSR/CHF patients is that they have a low PaCO2, measured while they are awake or asleep. PaCO2 often declines during sleep and goes below 35 mmHg. In one series of 59 CHF patients, 78% of patients with a daytime PaCO2 <35 had CSR, and in a second group of 450 CHF patients an awake PaCO2 <38 increased the odds ratio for CSR by 4.3(96,92). A low sleep PaCO2 destabilizes breathing since controller gain fluctuates from zero (at the apnea threshold) to 2-4 liters ventilation/mmHg PaCO2 above the threshold. The central role low PaCO2 plays in CSR has been convincingly demonstrated by CO2 rebreathing experiments. When ten CSR/CHF patients breathed in small amounts of carbon dioxide, sufficient to raise PaCO2 by only 2 mmHg, CSR was completely abolished in all ten (97).

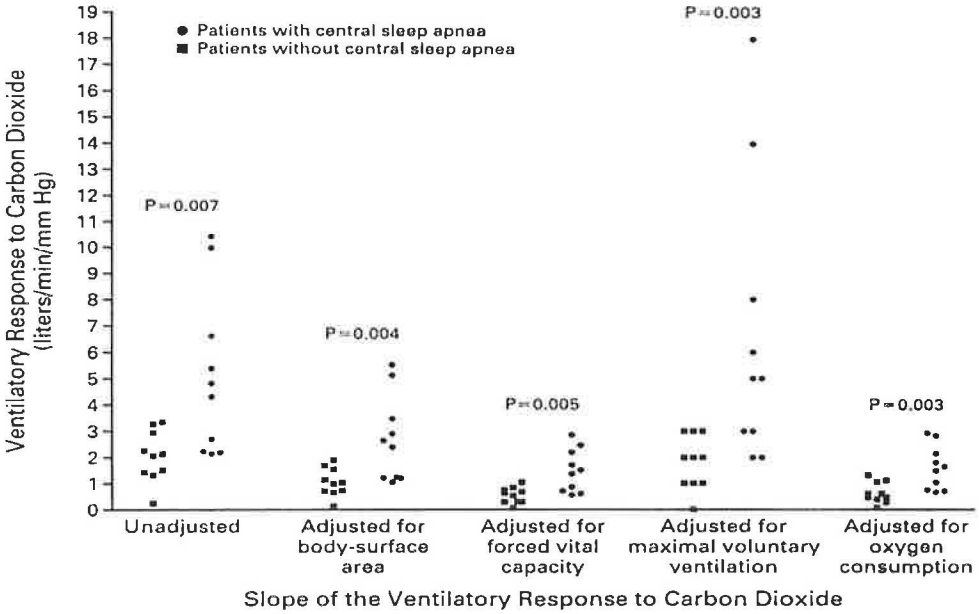
Why do CSR/CHF patients have a chronically low PaCO2? Two possible explanations are pulmonary edema and increased ventilatory drive. Pulmonary edema causes stiff, noncompliant lungs which stimulate pulmonary J receptors; afferent impulses travel through the vagus nerve and increase central respiratory drive. Pulmonary congestion typically increases when patients lie down to sleep, which may explain why PaCO2 of CSR/CHF patients remains low at night. When groups of CSR/CHF patients are compared to CHF patients without CSR, left ventricular function, as measured by ejection fraction, is similar. However CSR patients have higher pulmonary capillary wedge pressures, increased end-diastolic left ventricular volumes, and lower cardiac outputs, findings which support the idea that chronic pulmonary edema predisposes to CSR (98-100). Intensive heart failure therapy, sufficient to lower pulmonary capillary wedge pressure to normal, also decreases CSR frequency (figure 14). Ventilatory drive is assessed by rebreathing CO2 and measuring the increase in minute ventilation per mmHg increase in PaCO2, and there is a large genetic component accounting for much of the variability in ventilatory responses between individuals. CSR/CHF patients, when compared to CHF patients without CSR, have markedly higher ventilatory responses to carbon dioxide (Figure 15). Both central and peripheral chemoreceptor responses to PaCO2 are increased(101-103). Increased ventilatory drive increases controller gain, further destabilizing breathing patterns when PaCO2 is close to the apnea threshold. Whether increased ventilatory drive is congenital or acquired is not known; it may be acquired since hypoxemia, present during CSR apneas, also increases the gain of ventilatory CO2 response. Increased gain in CSR is thus due to a combination of chronic pulmonary edema, augmented ventilatory drive, and hypoxemia.

Figure 14. Relationship between PCWP and CSR



Circulation 99:1574, 1999

Figure 15. Increased ventilatory responses of CSR patients

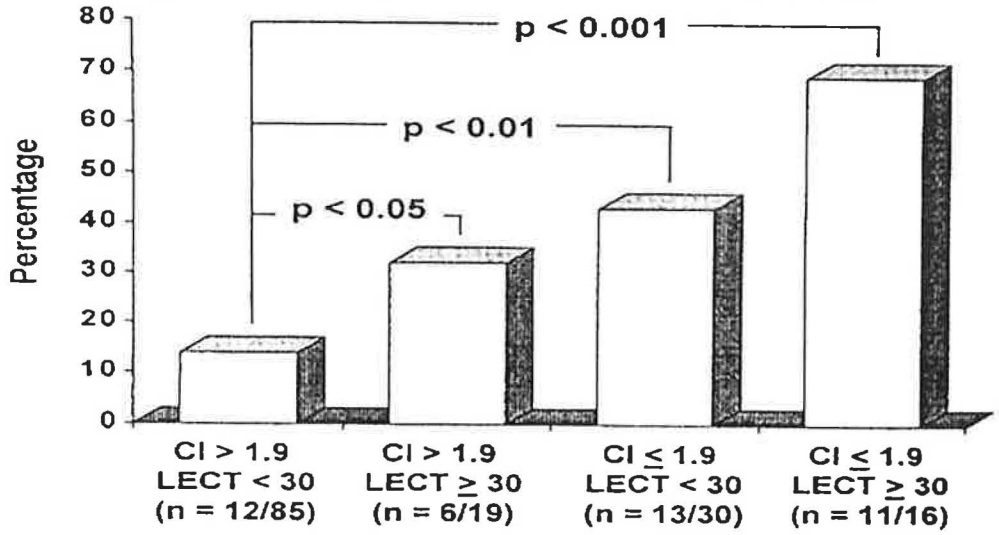


NEJM 341:949, 1999

Feedback delay- In 1956 Arthur Guyton caused CSR in dogs by inserting long pieces of tubing into the animals carotid arteries; when circulation time to the brain was

increased by 1-2 minutes CSR occurred (104). Humans with CHF do not have such markedly prolonged circulation times but investigators have found that CSR patients, compared to CHF patients without CSR, have prolonged lung to ear circulation time (LECT); a normal LECT is 6-10 seconds. Figure 16 illustrates the relationship between cardiac index, circulation time, and CSR prevalence in a group of 150 severe CHF patients who had sleep studies and right heart catheterization performed. The time delay in controller feedback caused by prolonged circulatory time causes large swings in amplitude of the controllers output, resulting in the variable tidal volumes so characteristic of CSR (98,105,106).

Figure 16. CSR prevalence in 150 CHF patients



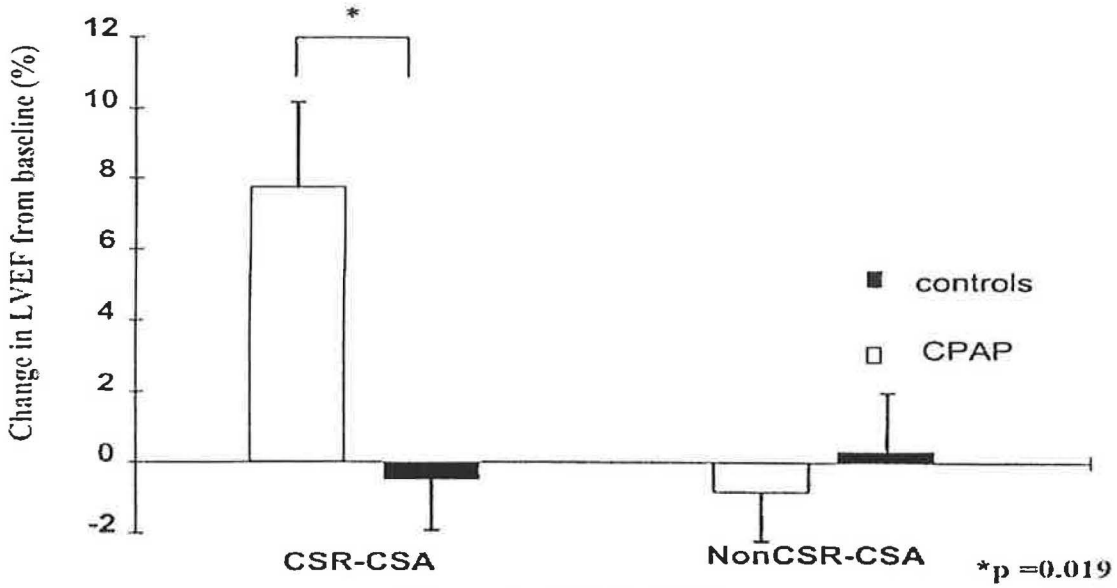
Amer. J. Cardio. 84:900, 1999

What is the clinical significance of CSR in a CHF patient? Because CSR is strongly associated with poor systolic function it is not surprising that patients with CSR have a poor prognosis. In one study of 62 CHF patients followed for 28 months CSR (AHI >30) was an independent predictor of death and was associated with two year mortality of 50% (107). Since overnight urinary norepinephrine levels are higher in CSR patients, compared to CHF patients without CSR, the deleterious effects of catecholamines on afterload and ventricular arrhythmias may account for the excess mortality(108).

CPAP can be used to treat CSR. CPAP reduces apneas and desaturations and it also has a postive inotropic effect. In acute heart failure patients CPAP, by increasing intrathoracic pressure, reduces both preload and afterload and increases cardiac output. In subjects with normal systolic function CPAP has no inotropic effect (109). CPAP ,administered to 18 CSR/CHF patients for one month, resulted in a significant fall in overnight urine norepinephrine and a 7% increase in left ventricular ejection fraction (108). One prospective, long term, randomized CPAP trial has been performed. 66 severe (ejection fraction 20% in the CSR group, 23% in the non-CSR) CHF patients were randomly assigned to CPAP or no CPAP, received optimal medical therapy, and were followed over 2.2 years for endpoints of death or heart transplantation. 29 patients had CSR, and 37 did not. At a 3 month evaluation ejection fraction had increased by 8% in CPAP treated CSR patients but not in the other three groups (Figure 17). Over long term

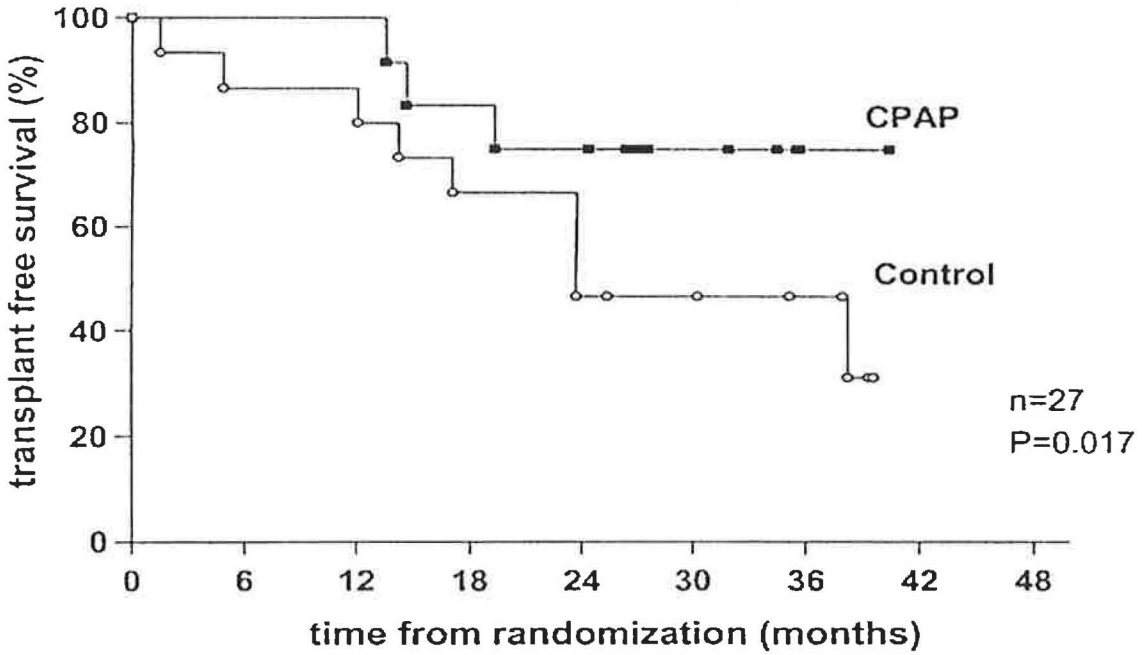
followup CPAP improved survival but only in the CSR/CHF group (Figure 18)(110). A large prospective CPAP trial (the Canadian Positive Airway Pressure Trial for Heart Failure) is now underway to confirm these promising results. CPAP may turn out to be a valuable adjunct therapy for severe CHF.

Figure 17. Effect of CPAP on left ventricular ejection fraction



Circulation 102:61, 2000

Figure 18. Survival of CSR patients



Circulation 102:61, 2000

Two other CSR therapies are theophylline and atrial pacing. In a placebo-controlled trial five days of oral theophylline significantly reduced CSR and improved nocturnal oxygenation. There was no change in daytime arterial blood gases or pulmonary function, and these results were obtained with theophylline levels in the low

therapeutic range (11 ug/ml)(111). There is another report of theophyllines efficacy for life-threatening CSR (112). The mechanism by which theophylline improves nocturnal breathing is unknown but may involve adenosine antagonism and central respiratory drive. CSR/CHF patients with atrial pacemakers benefit from turning up the paced rate while sleeping. In a group of fifteen such patients, increasing the heart rate by 15 beats lead to a 61% decrease in the AHI (113). The mechanism by which pacing affects nocturnal apneas is unclear but may involve decreased circulation time.

1. Young T, Peppard P, Cottlieb D: Epidemiology of Obstructive Sleep Apnea. Am J Respir Crit Care Med 165:1217-1239, 2002.
2. Young T et al: The Occurrence of Sleep-Disordered Breathing Among Middle-aged Adults. New England J of Med 328: 1230-35, 1993.
3. Bradley T, Floras J: Sleep Apnea and Heart Failure. Circulation. 107:1822-1826,2003.
4. Leung, R and Bradley, T: Sleep Apnea and Cardiovascular Disease. Am J Respir Crit Care Med 164:2147-2165, 2001.
5. Bearpark H, etal: Snoring and Sleep Apnea. Am J Respir Crit Care Med 151:1459-1465, 1995.
6. Nieto F, etal: Association of Sleep-Disordered Breathing, Sleep Apnea, and Hypertension in a Large Community-Based Study. JAMA 283:1829-1836, 2000.
7. Suzuki M, Guilleminault C, Otsuka K, Shiomi T: Blood Pressure "Dipping" and "Non-Dipping" in Obstructive Sleep Apnea Syndrome Patients. Sleep19:382-387, 1996.
8. Motta J, etal: Tracheostomy and Hemodynamic Changes in Sleep-Induced Apnea. Annals of Internal Medicine 89:454-458, 1978.
9. Schneider, H. etal: Neural and local effects of hypoxia on cardiovascular responses to obstructive apnea. J Appl Physio. 88:1093-1102, 2000.
10. Elmasry A, etal: Obstructive sleep apnoea and urin catecholamines in hypertensive males: a population-based study. Eur Respir J 19:511-517, 2002.
11. Guilleminault C, Connolly S, Winkle R, Melvin K: Cyclical Variation of the Heart Rate in Sleep Apnea Syndrome. Lancet I: 126, 1984.
12. Qvist J, etal: Hemoglobin concentrations and blood gas tensions of free-diving Weddell seals. J.Applied Physio. 86:1560-1568, 1986.
13. Madden B, etal: Absence of Bradycardic Response to Apnea and Hypoxia in Heart Transplant Recipients with Obstructive Sleep Apnea. J of Heart and Lung Trans 56:394-307, 1997.
14. Zwillich C, Devlin T, White D, etal: Bradycardia during Sleep Apnea. J Clin Invest 69:1286-1292, 1982.
15. Roche F, etal: Screening of Obstructive Sleep Apnea Syndrome by Heart Rate Variability Analysis. Circulation 100: 1411-1415, 1999.
16. Stein P, etal: A Simple Method to Identify Sleep Apnea Using Holter Recordings. J of Cardiovascular Elec 14:467-473, 2003.
17. Guilleminault C, Connolly S, Winkle R: Cardiac Arrhythmia and Conduction Disturbances During the Sleep in 400 Patients with Sleep Apnea Syndrome. Amer J of Cardiology 52:490-494, 1983.
18. Grimm W, etal: Outcome of Patients with Sleep Apnea-Associated Severe Bradyarrhythmias After Continuous Positive Airway Pressure Therapy. Amer J of Cardiology 86:688-692, 2000.
19. Harbison J, O'Reilly P, McNicholas W: Cardiac Rhythm Disturbances in the Obstructive Sleep Apnea Syndrome. Chest 118: 591-595, 2000.
20. Heinrich B, Brandenburg U, Peter Jorg, VonWichert P: Reversal of Sinus Arrest and Atrioventricular Conduction Block in Patients with Sleep Apnea during Nasal Continuous Positive Airway Pressure. Am J Respir Crit Care Med 151:215-218, 1995.
21. Fletcher E, Lesske J, Qian W, Miller III C, Unger T: Repetitive, Episodic Hypoxia Causes Diurnal Elevation of Blood Pressure in Rats. Hypertension 19:555-560, 1992.

22. Brooks D, Horner R, Kozar L, Render-Teixeira C, Phillipson E: Obstructive Sleep Apnea as a Cause of Systemic Hypertension. J Clin Invest 99:106-109, 1997.
23. Peppard P, Young T, Palta M, Skatrud J: Prospective Study of the Association Between Sleep-Disordered Breathing and Hypertension. New England J of Med 342:1378-1384, 2000.
24. Sjöström C, etal: Prevalence of sleep apnoea and snoring in hypertensive men: a population based study. Thorax 57:602-607, 2002.
25. Logan A, etal: High prevalence of unrecognized sleep apnoea in drug-resistant hypertension. J of Hypertension 19: 2271-2276, 2001.
26. Parker J, etal: Acute and Chronic Effects of Airway Obstruction on Canine Left Ventricular Performance. Am J Respir Crit Care Med 160:1888-1896, 1999.
27. Alchanatis M, etal: Evidence for left ventricular dysfunction in patients with obstructive sleep apnoea syndrome. Eur Respir J 20:1239-1245, 2002.
28. Hedner J, Ejnell H, Caidahl K: Left ventricular hypertrophy independent of hypertension in patients with obstructive sleep apnoea. Journal of Hypertension 8:941-946, 1990.
29. Shahar E, etal: Sleep-disordered Breathing and Cardiovascular Disease. Am J Respir Crit Care Med 163:19-25, 2001.
30. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J: Increased Incidence of Cardiovascular Disease in Middle-aged Men with Obstructive Sleep Apnea. Am J Respir Crit Care Med 166:159-165, 2002.
31. Franklin K, Nilsson J, Sahlin C, Näslund U: Sleep apnoea and nocturnal angina. Lancet 345:1085-1087, 1995.
32. Peled N, Abinader E, Pillar G, Sharif D, Lavie P: Nocturnal Ischemic Events in Patients with Obstructive Sleep Apnea Syndrome and Ischemic Heart Disease. Journal of American College of Cardiology 34:1744-1749, 1999.
33. Eisensehr I, etal: Platelet activation, epinephrine, and blood pressure in obstructive sleep apnea syndrome. Neurology 51:188-195, 1998.
34. Sanner B, Konermann M, Tepel M, Groetz J, Mummenhoff C, Zidek W: Platelet function in patients with obstructive sleep apnoea syndrome. Eur Respir J 16:648-652, 2000.
35. Peker Y, Hedner J, Kraiczi H, Lőth S: Respiratory Disturbance Index. Am J Respir Crit Care Med 162:81-86,2000.
36. Seppälä T, etal: Sudden death and sleeping history among Finnish men. Journal of Internal Medicine 229:23-28, 1991.
37. Nattie E., Doble, EA: Threshold of Intermittent Hypoxia-Induced Right Ventricular Hypertrophy. Resp. Physio 56:253-259, 1984.
38. Guidry U, etal: Echocardiographic Features of the Right Heart in Sleep-Disordered Breathing. Am J Respir Crit Care Med 165:933-938, 2001.
39. Sanner B, Doberauer C, Konermann M, Sturm A, Zidek W: pulmonary hypertension in patients with obstructive sleep apnea syndrome. JAMA 157:1997.
40. Sajkov D, etal: Daytime Pulmonary Hemodynamics in Patients with Obstructive Sleep Apnea without Lung Disease. Am J Respir Crit Care Med 159: 1518-1526, 1999.
41. Kessler R, etal: The Obesity-Hypoventilation Syndrome Revisited. Chest 120:369-376, 2001.
42. Fletcher, E: Sympathetic Over Activity in the Etiology of Hypertension of Obstructive Sleep Apnea. Sleep 26:15-19, 2003.

43. Greenberg, H. etal: Chronic intermittent hypoxia increases sympathetic responsiveness to hypoxia and hypercapnia. J. Applied Physio. 86:298-305, 1999.
44. Bao, G etal: Blood pressure response to chronic episodic hypoxia: role of the sympathetic nervouc system. J. Applied Physio. 83:95-101, 1997.
45. Fletcher, E; Bao G, Li, Rena: Renin Activity and Blood Pressure in Response to Chronic Episodic Hypoxia. Hypertension 34: 309-314, 1999.
46. Fletcher E, etal: Sympathetic Denervation Blocks Blood Pressure Elevation in Episodic Hypoxia. Hypertension 20:612-618, 1992.
47. Fletcher, E, etal: Carotid chemoreceptors, systemic blood pressure, and chronic episodic hypoxia mimicking sleep apnea. Journal of Appl. Physiol. 72:1978-1984, 1992.
48. Somers, V etal: Sympathetic Neural Mechanisms in Obstructive Sleep Apnea. J Clin Invest 96:1897-1904, 1995.
49. Narkiewicz K, etal: Sympathetic Activity in Obese Subjects With and Without Obstructive Sleep Apnea. Circulation 98:772-776, 1998.
50. Xie, A etal: Neurocirculatory consequences of intermittent asphyxia in humans. J Appl Physiol 89:1333-1339, 2000.
51. Xie Ailiang, etal: Exposure to hypoxia produces long-lasting sympathetic activation in humans. J Appl Physiol 91:1555-1562, 2001.
52. Narkiewicz K, etal: Contribution of Tonic Chemoreflex Activation to Sympathetic Activity and Blood Pressure in Patients with Obstructive Sleep Apnea. Circulation 97:943-945, 1998.
53. Gimbrone Jr., M; Nagel, T; and Topper, J. N.: Biomechanical Activation: an Emerging Paradigm in Endothelial Adhesion Biology. J Clin. Invest. 99:1809-1813, 1997.
54. Xu, Q etal: Acute Hypertension Activates Mitogen-activated Protein Kinases in Arterial Wall. Journal of Clinical Investigation 97:508-514, 1996.
55. Wagner, C, etal: Hemodynamic Forces Induce the Expression of Heme Oxygenase in Cultured Vascular Smooth Muscle Cells. Journal of Clinical Investigation 100:589-596, 1997.
56. Lin, Ming-Chao, etal: Shear Stress Induction of the Tissue Factor Gene. Journal of Clinical Investigation 99:737-744, 1997.
57. Silvestrini M, etal: Carotid Artery Wall Thickness in Patients with Obstructive Sleep Apnea Syndrome. Stroke 33:1782-1785, 2002.
58. Sowers, J: Hypertension, Angiotensin II, and Oxidative Stress. New England Journal of Medicine 346:1999-2001, 2003.
59. Higashi Y, etal: Endothelial Function and Oxidative Stress in Renovascular Hyptertension. New England Journal of Medicine 346:1954-1962, 2002.
60. Landmesser U, etal: Oxidation of tetrahydrobiopterin leads to uncoupling of endothelial cell nitric oxide synthase in hypertension. Journal of Clinical Investigation 111:1201-1209, 2003.
61. Kato M, etal: Impairment of Endothelium-Dependent Vasocilation of Resistance Vessels in Patients with Obstructive Sleep Apnea. Circulation 102:2607-2610, 2000.
62. Ivan, M. etal: HIFα Targeted for VHL-Mediated Destruction by Proline Hydroxylation: Implications for O_2 Sensing. Science 292:464-468, 2001.
63. Safran, M and Kaelin Jr., W: HIF hydroxylation and the mammalian oxygen-sensing pathway. Journal of Clinical Investigation 111:779-783, 2003.

64. Semenza, G: HIF-1 and mechanisms of hypoxia sensing. Current Opinion in Cell Biology 13:167-171, 2001.
65. Semenza, G: Surviving ischemia: adaptive responses mediated by hypoxia-inducible factor 1. Journal of Clinical Investigation 106:809-812, 2000.
66. Semenza, G: HIF-1, O_2, and the 3 PHDs: How Animal Cells Signal Hypoxia to the Nucleus. Cell 107:1-3, 2001.
67. Wang, G and Semenza, G: General involvement of hypoxia-inducible factor 1 in transcriptional response to hypoxia. Proc. Natl. Acad. Sci. USA 90:4304-4308, 1993.
68. Wiesener, M etal: Widespread hypoxia-inducible expression of HIF-2α in distinct cell populations of different organs. FASEB Journal 17:271-273, 2003.
69. Tian, H etal: The hypoxia-responsive transcription factor EPAS1 is essential for catecholamine homeostasis and protection against heart failure during embryonic development. Genes Development 12:3320-3324, 1998.
70. Peng, J; Zhang, L.; Drysdale, L. and Fong, Guo-Hua: The transcription factor EPAS-1 / hypoxia-inducible factor 2α plays an important role in vascular remodeling. PNAS 97:8386-8391, 2000.
71. Norris, Melanie L and Millhorn, David E.: Hypoxia-induced Protein Binding to O_2-responsive Sequences on the Tyrosine Hydroxylase Gene. Journal of Biological Chemistry 270:23774-23779, 1995.
72. Eckhart A, Yang N, Xin, X and Faber, J: Characterization of the α_{1B}-adrenergic receptor gene promoter region and hypoxia regulatory elements in vascular smooth muscle. Proc. Natl. Acad. Sci. USA 94:9487-9492, 1997.
73. Kline D, etal: Defective carotid body function and impaired ventilatory responses to chronic 1α. PNAS 99:821-826, 2002.
74. Yu, A etal: Impaired physiological responses to chronic hypoxia in mice partially deficient for hypoxia-inducible factor 1α. Journal of Clinical Investigation 103:691-696, 1999.
75. Schiffrin E: Role of Endothelin-1 in Hypertension and Vascular Disease. American Journal of Hypertension 14:835-895, 2001.
76. Kanagy N; Walker B, Nelin L: Role of Endothelin in Intermittent Hypoxia-Induced Hypertension. Hypertension 37:511-515, 2001.
77. Wort S, Woods M, Warner T; Evans T, and Mitchell J: Endogenously Released Endothelin-1 from Human Pulmonary Artery Smooth Muscle Promotes Cellular Proliferation. Am. J. Respir. Cell Mol. Biol. 25:104-110, 2001.
78. Yamashita, K. etal: Molecular Regulation of the Endothelin-1 Gene by Hypoxia. Journal of Biological Chemistry 276:12645-12653, 2001.
79. Kakinuma, Y. etal: Novel Molecular Mechanism of Increased Myocardial Endothelin-1 Expression in the Failing Heart Involving the Transcriptional Factor Hypoxia-Inducible Factor-1α Induced for Impaired Myocardial Energy Metabolism. Circulation 103:2387-2394, 2001.
80. Brusselmans, K etal: Heterozygous deficiency of hypoxia-inducible factor - 2α protects mice against pulmonary hypertension and right ventricular dysfunction during prolonged hypoxia. Journal of Clinical Investigation 111:1519-1527, 2003.
81. Phillips B etal: Effects of obstructive sleep apnea on endothelin-1 and blood pressure. Journal of Hypertension 17:61-66, 1999.
82. Cahan C etal: Erythropoietin levels with treatment of obstructive sleep apnea. J Appl. Physiol. 79:1278-1285, 1995.

83. Schulz R etal: Serum Levels of Vascular Endothelial Growth Factor Are Elevated in Patients with Obstructive Sleep Apnea and Severe Nighttime Hypoxia. Am J Respir Crit Care Med 165:67-70, 2002.
84. Lavie L etal: Plasma Vascular Endothelial Growth Fqactor in Sleep Apnea Syndrome. Am J Respir Crit Care Med 165:1624-1628, 2002.
85. Becker H, etal: Effect of Nasal Continuous Positive Airway Pressure Treatment on Blood Pressure in Patients with Obstructive Sleep Apnea. Circulation 107:68-73, 2003.
86. Kaneko Y, etal: Cardiovascular Effects of Continuous Positive Airway Pressure in Patients with Heart Failure and Obstructive Sleep Apnea. New England Journal of Medicine 348:1233-1241, 2003.
87. Malone S, etal: Obstructive sleep apnoea in patients with dilated cardiomyopathy: effects of continuous positive airway pressure. Lancet 338: 1480-1483, 1991.
88. Narkiewicz K, etal: Nocturnal Continuous Positive Airway Pressure Decreases Daytime Sympathetic Traffic in Obstructive Sleep Apnea. Circulation 100:2332-2335, 1999.
89. Sajkov D, etal: Continuous Positive Airway Pressure Treatment Improves Pulmonary Hemodynamics in Patients with Obstructive Sleep Apnea. Am J Respir Crit Care Med 165:152-158, 2002.
90. Rolfe I., Olson L: Long-Term Acceptance of Continuous Positive Airway Pressure in Obstructive Sleep Apnea. Amer. Rev. Resp. Dis 144:1130-1133, 1991.
91. Barbé F, etal: Treatment with Continuous Positive Airway Pressure Is Not Effective in Patients with Sleep Apnea but No Daytime Sleepiness. Annals of Internal Medicine 134:1015-1023, 2001.
92. Sin D, etal: Risk Factors for Central and Obstructive Sleep Apnea in 450 Men and Women with Congestive Heart Failure. Am J Respir Crit Care Med 160:1101-1106, 1999.
93. Bradley T, and Floras J: Sleep Apnea and Heart Failure Part II: Central Sleep Apnea. Circulation 107:1822-1826, 2003.
94. Cherniack N and Longobardo G: Cheyne-Stokes Breathing. New England Journal of Medicine 288:952-957, 1973.
95. Cherniack N: Respiratory Dysrhythmias During Sleep. New England Journal of Medicine. 305:325-330, 1981.
96. Javaheri S and Corbett WS: Association of Low PaCO2 with Central Sleep Apnea and Ventricular Arrhythmias in Ambulatory Patients with Stable Heart Failure. Annals of Internal Medicine 128:204-207, 1998.
97. Lorenzi-Filho G, etal: Effects of Inhaled Carbon Dioxide and Oxygen on Cheyne-Stokes Respiration in Patients with Heart Failure. Am J Respir Crit Care Med: 159:1490-1498, 1999.
98. Mortara A, etal: Association Between Hemodynamic Impairment and Cheyne-Stokes Respiration and Periodic Breathing in Chronic Stable Congestive Heart Failure Secondary to Ischemic or Idiopathic Dilated Cardiomyopathy. The American Journal of Cardiology 84:900-904, 1999.
99. Tkacova R, etal: Left Ventricular Volume in Patients with Heart Failure and Cheyne-Stokes Respiration during Sleep. Am J Respir Crit Care Med 156:1549-1555, 1997.
100. Solin P, etal: Influence of Pulmonary Capillary Wedge Pressure on Central Apnea in Heart Failure. Circulation 99:1574-1579, 1999.

101. Javaheri, Shahrokh: A Mechanism of Central Sleep Apnea in Patients with Heart Failure. New England Journal of Medicine 341:949-954, 1999.
102. Solin P, Roebuck T, Johns D, Walters E. and Naughton M: Peripheral and Central Ventilatory Responses in Central Sleep Apnea with and without Congestive Heart Failure. Am J Respir Crit Care Med 162:2194-2200, 2000.
103. Xie A, Rutherford R, Rankin F, Wong B, and Bradley T.Douglas: Hypocapnia and Increased Ventilatory Responsiveness in Patients with Idiopathic Central Sleep Apnea. Am J Respir Crit Care Med 152:1950-1955, 1995.
104. Guyton A, Crowell J and Moore J: Basic Oscillating Mechanism of Cheyne-Stokes Breathing. American Journal of Physiology 187:395-398, 1956.
105. Cherniack, Neil S.: Apnea and Periodic Breathing During Sleep. New England Journal of Medicine 341:985-987,1999.
106. Tkacova R, etal: Overnight Shift From Obstructive to Central Apneas in Patients with Heart Failure Role of PCO2 and Circulatory Delay. Circulation 103:238-243, 2001.
107. Lanfranchi P, etal: Prognostic Value of Nocturnal Cheyne-Stokes Respiration in Chronic Heart Failure. Circulation 99:1435-1440, 1999.
108. Naughton M, etal: Effects of Nasal CPAP on Sympathetic Activity in Patients with Heart Failure and Central Sleep Apnea. Am J Respir Crit Care Med 152:473-479, 1995.
109. Bradley, T etal: Cardiac Output Response to Continuous Positive Airway Pressure in Congestive Heart Failure. Am Rev Respir Dis 145:377-382, 1992.
110. Sin D, etal: Effects of Continuous Airway Pressure on Cardiovascular Outcomes in Heart Failure Patients With and Without Cheyne-Stokes Respiration. Circulation 102:61-66, 2000.
111. Javaheri S, etal: Effect of Theophylline on Sleep Disordered Breathing in Heart Failure. New England Journal of Medicine 335:562-566, 1996.
112. Pesek C, etal: Theophylline Therapy for Near-Fatal Cheyne-Stokes Respiration. Annals of Internal Medicine 130:427-430, 1999.
113. Garrigue S, etal: Benefit of Atrial Pacing in Sleep Apnea Syndrome. New England Journal of Medicine 346:404-412, 2002.