# Obstructive Sleep Apnea as a Cause of Systemic Hypertension

## Evidence from a Canine Model

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## Abstract

**Several epidemiological studies have identified obstructive sleep apnea (OSA) as a risk factor for systemic hypertension, but a direct etiologic link between the two disorders has not been established definitively. Furthermore, the specific physiological mechanisms underlying the association between OSA and systemic hypertension have not been identified. The purpose of this study was to systematically examine the effects of OSA on daytime and nighttime blood pressure (BP). We induced OSA in four dogs by intermittent airway occlusion during nocturnal sleep. Daytime and nighttime BP were measured before, during, and after a 1–3-mo long period of OSA. OSA resulted in acute transient increases in nighttime BP to a maximum of 13.0±2.0 mmHg (mean±SEM), and eventually produced sustained daytime hypertension to a maximum of 15.7±4.3 mmHg. In a subsequent protocol, recurrent arousal from sleep without airway occlusion did not result in daytime hypertension. The demonstration that OSA can lead to the development of sustained hypertension has considerable importance, given the high prevalence of both disorders in the population. (*J. Clin. Invest.* 1997. 99:106–109.) Key words: cardiovascular system • blood pressure • arousal • hemodynamics • sleep disorders**

## Introduction

The National Commission on Sleep Disorders Research has identified sleep disorders as a major public health burden affecting the lives of millions of Americans (1). One of the most common and serious of these disorders is obstructive sleep apnea (OSA),[1] which is characterized by repetitive episodes of upper airway collapse during sleep, resulting in interruption of airflow despite persisting respiratory efforts (2). Obstructive apneas are typically associated with progressively increasing asphyxia until termination by a brief arousal from sleep and restoration of upper airway patency (2). Population studies have estimated that 2% of women and 4% of men who are between 30 and 60 yr old suffer from a clinically important degree of sleep apnea (3).

Several epidemiological studies have identified OSA as an important risk factor for systemic hypertension, myocardial infarction, stroke, and sudden death (4–6). Given the high prevalence of sleep-disordered breathing, the potential importance of OSA in contributing to cardiovascular morbidity and mortality is considerable. The strongest association demonstrated to date is between OSA and hypertension, but a direct etiologic link between the two disorders has not been established definitively. Furthermore, epidemiological and clinical studies are limited in this regard since by the time patients with OSA come to clinical attention, the disorder and its possible long-term sequelae have often been present for several years. In addition, patients with OSA typically present with other risk factors for hypertension, notably obesity. Sleep apnea, however, appears to be an independent risk factor for hypertension even when confounding variables (i.e., obesity, gender, and age) are controlled statistically (6).

Given these considerations, the aims of this study were to use a canine model of OSA to determine whether OSA per se leads to sustained systemic hypertension. Since each animal served as its own control, we were able to examine the specific effects of OSA on blood pressure (BP) in the absence of other confounding variables. We also investigated the effects on BP of recurrent arousals from sleep without airway occlusion.

## Methods

*Animal preparation.* OSA was produced in four dogs (three female, one male, 23–31 kg) using a modification of a model developed in our laboratory (7). All surgical and experimental procedures were approved by the Animal Care Committee of the University of Toronto. The dogs were trained to sleep in the laboratory and then underwent two surgical procedures at least 2 mo before initiation of studies. The first was to create a permanent side-hole tracheostomy, and the second was to implant a three-channel telemetry unit (TLM11M3D70-CCP; Data Sciences, St. Paul, MN) for monitoring of arterial BP, the electroencephalogram (EEG) from implanted skull electrodes, and nuchal electromyogram (EMG; 7, 8). Surgery was performed under general anesthesia and aseptic conditions. Before surgery, each dog was premedicated with atropine (0.02–0.05 mg/kg i.m.). Anesthesia was induced with a short-acting barbiturate (thiamyl sodium, 10–20 mg/kg i.v.) and maintained either with halothane (titrated to effect, typically 0.5–2%) or a long-acting barbiturate (pentobarbitone, titrated to effect, typically 30 mg/kg i.v.). Long-acting penicillin (15,000–20,000 U/kg i.m.) and an analgesic (buprenorphine, 0.01–0.02 mg/kg, i.m.) were administered postoperatively. The wires from the EEG and EMG electrodes were tunneled subcutaneously to a pouch created in the lower abdominal wall, where the body of the telemetry transmitter was placed. The fluid-filled arterial BP catheter, which was connected to a sensor in the body of the transmitter, was tunneled subcutaneously from the abdominal pouch to the femoral triangle, inserted into the deep femoral artery, and advanced through the external iliac artery to the bifurcation of the aorta.

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*Received for publication 15 July 1996 and accepted in revised form 23 October 1996.*

1. *Abbreviations used in this paper:* EEG, electroencephalogram; EMG, electromyogram; OSA, obstructive sleep apnea.

J. Clin. Invest.
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0021-9738/97/01/0106/04 $2.00
Volume 99, Number 1, January 1997, 106–109

*Induction of OSA.* A schematic of the OSA model is shown in Fig. 1. The radiofrequency signals of the EEG, EMG, and BP emitted by the telemetry unit were detected by water-resistant receivers (RL2000; Data Sciences) that were positioned around the pen in which the dog was housed. The EEG and EMG signals were converted to analogue signals, amplified, filtered, and relayed to a microcomputer through an analogue-to-digital board. The computer produced a judgment of sleep–wake state every 6 s, based on the frequencies in the EEG signal and the amplitude of the averaged EMG signal (7). Whenever a period of sleep of predetermined length (generally 18 s) was identified by the computer, it generated a radio signal that was detected by a receiver controller unit housed in a jacket worn by the dog. The signal activated a quiet custom-designed occlusion valve attached to the endotracheal tube (9-mm internal diameter, 12.3-mm external diameter, Aire-Cuf; Bivona, Gary, IN) through which the dog breathed, resulting in an obstructive apnea. When the dog awoke, the computer generated a signal to release the occlusion. Thus, the model closely simulated human OSA by producing repeated episodes of airway occlusion and arousal from sleep. A second computer received and stored the cardiovascular variables from the dog (8). Because the model used biotelemetry and computer technology, there were no physical attachments between the dog and the recording equipment, allowing it to move about freely, and the system required no human intervention (except for routine monitoring and maintenance).

OSA was produced in each dog during a 1–3-mo period. The severity of the disorder, defined by the number of apneas per hour of sleep (i.e., apnea index), was allowed to increase by changing the duration of sleep that was required to generate the signal to close the occlusion valve. As a result, the apnea index increased progressively from 10–30 events per hour of sleep on nights 1–7 to 50–60 events per hour of sleep after 14 nights.

*Sleep fragmentation without airway occlusion.* In a separate protocol, the same four dogs were restudied at least 6 mo after completion of the OSA protocol to determine the effects on BP of sleep fragmentation without airway occlusion. For this purpose, we again used the telemetry system and computer algorithm to detect sleep. Whenever a sleep period of predetermined length was identified by the computer, it generated a signal to activate an acoustic alarm that produced a sound at a frequency of 17–30 kHz. When the dog was aroused from sleep, the alarm ceased. If the dog failed to wake up, the frequency of the sound increased progressively along a variable ramp of 10–30 s, which minimized habituation to the acoustic stimulus. In addition, the sleep records were reviewed on a daily basis, and if $> 10\%$ of the acoustic stimuli failed to induce arousal, the amplitude of the sound was increased on the subsequent nights. In practice, the dogs aroused to $> 85\%$ of the acoustic stimuli on a nightly basis, resulting in sleep fragmentation, but without the changes in blood gases and intrathoracic pressure that are associated with obstructive apneas. As in the OSA protocol, the arousal index (i.e., number of arousals per hour of sleep) was allowed to increase by changing the number of consecutive epochs of sleep required to activate the acoustic alarm. Thus, in each dog, we were able to create a degree of sleep disruption similar to that produced during OSA. In fact, the arousal index during the early and later stages of sleep fragmentation did not differ from the apnea index during the corresponding phases of the OSA protocol ($P \geq 0.2$).

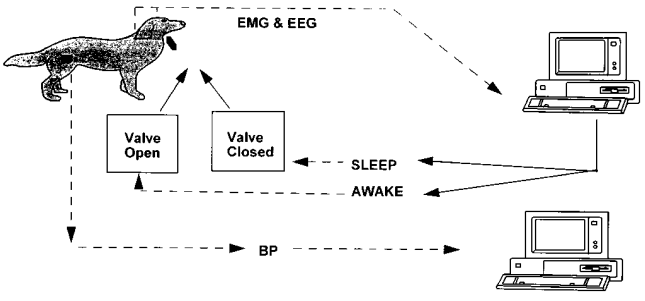


*Figure 1.* Schematic of the OSA model in the dog. Each dog had an implanted telemetry system with three channels: EEG, EMG, and BP. Signals were sent by telemetry to two computers, one for the detection of sleep–wake state and the other for analysis of hemodynamic data.

*Experimental protocol.* Each animal was studied during a control period of 1–2 mo before induction of OSA, during 1–3 mo of OSA, and during a recovery period of 1 mo after cessation of OSA. During the period of OSA, the dogs were generally under direct observation during the day and were kept awake with human companionship. Whenever they displayed presleep behavior (nodding of the head, closing of the eyes) or were left unattended, however, the monitoring–occlusion system was activated. On average, the monitoring–occlusion system was activated for 14–16 h/d. After completion of the OSA experiments, the dogs were restudied on the sleep fragmentation protocol for 1–2 mo before, 1–2 mo during, and up to 1 mo after cessation of sleep fragmentation. Throughout both protocols, the experimental conditions, diet, weight, and daily routine of the dogs remained constant.

The duration of OSA and sleep fragmentation varied among the four dogs because of the limited life of the battery in the telemetry unit and the variable duration of time that was required to obtain stable baseline measurements during the control period. However, both OSA and sleep fragmentation were continued until changes in daytime BP had reached a plateau, which occurred within 4 wk in all dogs.

*Analysis of nighttime and daytime BP.* Arterial BP was recorded for 12 h every night, and the mean BP was calculated by the computer on a minute-by-minute basis. Mean nighttime BP (the average of the minute-by-minute values) was calculated for four nights in the control period, two nights of early OSA or sleep fragmentation (apnea or arousal index $< 30$ per hour of sleep), four nights in the later stages of OSA or sleep fragmentation (apnea or arousal index $> 45$ per hour of sleep), and the first night after cessation of OSA or sleep fragmentation. The four consecutive nights in the later stages of OSA or sleep fragmentation were selected arbitrarily once the degree of sleep apnea or sleep fragmentation had been stable for at least 4 wk. Measurements of daytime mean arterial BP during wakefulness were made every 7–14 d during the control, OSA or sleep fragmentation, and recovery periods. Mean daytime BP was calculated by averaging the mean BP of $>$ 6,000 cardiac cycles at a standardized time period during the day, with a stable laboratory temperature. For these measurements, the dogs lay recumbent and were in a state of relaxed wakefulness, according to standard EEG criteria (9). Mean arterial BP was calculated by the data acquisition system using a moving time average. The implanted catheter was validated periodically as described previously (8).

*Data analysis.* The data were analyzed to answer three separate statistical questions: (*a*) Did OSA result in a change in nighttime or daytime BP? (*b*) Did sleep fragmentation result in a change in nighttime or daytime BP? (*c*) Were the changes in BP with OSA the same as with sleep fragmentation? Questions *a* and *b* were addressed with a one-way ANOVA with repeated measures using commercially available software (Sigmastat; Jandel Scientific, San Rafael, CA). Question *c* was analyzed using a paired *t* test, comparing the changes in BP during OSA with those during sleep fragmentation. All analyses included a single mean value for each dog at each time period (i.e., $n = 4$), thereby ensuring that no dog was overrepresented in any analysis. For all tests, differences were considered statistically significant if the null hypothesis was rejected at a level of $P < 0.05$ using a two-tailed test.

## Results

OSA resulted in progressive increases in nighttime mean arterial BP (Fig. 2) to a maximum of 13.0±2.0 mmHg

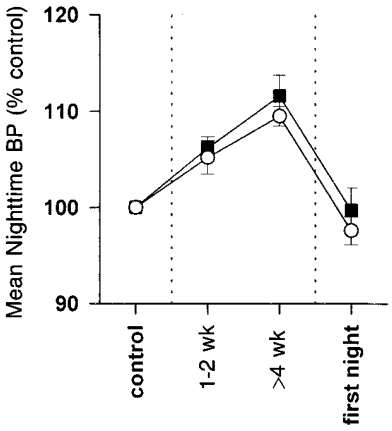


*Figure 2.* Mean nighttime arterial blood pressure in four dogs during OSA (*filled squares*) and sleep fragmentation (*open circles*). The dashed lines indicate the beginning and end, respectively, of the OSA or sleep fragmentation phase. The post-OSA or –sleep fragmentation values represent the first recovery night. The error bars represent the SEM of the mean. The duration of the OSA and sleep fragmentation phases ranged from 5 to 14 wk and 5 to 7.5 wk, respectively. Data points are joined for ease of interpretation; note, however, that the time periods between points on the *x* axis are unequal.

(mean±SEM; one-way ANOVA with repeated measures, $P = 0.005$) and in daytime mean arterial BP (Fig. 3) to a maximum of 15.7±4.3 mmHg (ANOVA, $P = 0.004$). This response was present within 4 wk in each of the four dogs (range for nighttime BP increase = 9.4–18.5 mmHg; range for daytime BP increase = 6.0–26.8 mmHg). Immediately after cessation of OSA, nighttime mean arterial BP returned to control values, whereas daytime hypertension resolved slowly during a 1–3 wk period. The immediate return of nighttime BP to the control value was probably related to the fact that on the first night after cessation of OSA, the dogs' sleep was considerably more consolidated than in the pre-OSA control period (10).

Sleep fragmentation without airway occlusion resulted in an increase in nighttime mean arterial BP (Fig. 2) of 11.2±1.0 mmHg (ANOVA, $P = 0.04$). In contrast, sleep fragmentation produced only a small increase in daytime mean arterial BP

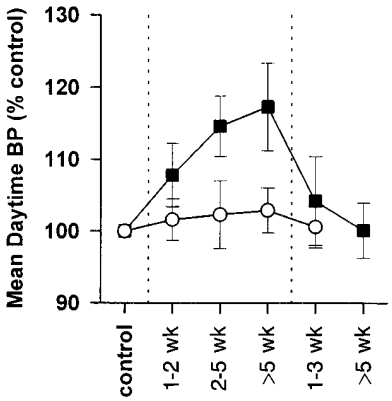


*Figure 3.* Mean daytime arterial BP in four dogs during OSA (*filled squares*) and sleep fragmentation (*open circles*). The format of the data points is the same as in Fig. 2.

(Fig. 3) of 4.0±4.0 mmHg (ANOVA, $P = 0.72$). These responses were observed in each of the four dogs (range for nighttime BP increase = 8.8–13.7 mmHg; range for daytime BP increase = −4.5–14.3 mmHg). There was no difference between the change in nighttime BP produced by sleep fragmentation and that produced by OSA (paired *t* test, $P = 0.4$). In contrast, the change in daytime BP during sleep fragmentation was significantly less than the change during OSA (paired *t* test, $P < 0.001$). There were no changes in nighttime or daytime heart rates during either OSA or sleep fragmentation.

## Discussion

There are two major findings from this study: (*a*) OSA per se produces sustained daytime hypertension; and (*b*) recurrent arousals from sleep alone cannot account for the daytime hypertension observed in OSA. These data provide the first direct evidence of a cause and effect relationship between OSA and the development of systemic hypertension.

Spontaneous sleep-disordered breathing has been described in brachycephalic dogs such as the English bulldog (11), but unlike apneas in humans, apneas in the bulldog occur only during rapid eye movement sleep. Short-term (≤ 24 h) models of OSA have been produced in adult pigs (12) and dogs (13), but these models are not suitable for the study of the long-term consequences of the disorder. The present study represents the first report of the long-term application of an induced model of repetitive upper airway occlusion during sleep. Our findings extend those of the short-term studies, which showed that periods of upper airway obstruction result in acute transient increases in arterial BP (12, 13) by demonstrating that during a period of weeks, OSA results in sustained daytime hypertension, even during relaxed wakefulness.

Several authors have reported a remarkably high prevalence of OSA in hypertensive compared to normotensive patients (14, 15), although this finding has not been consistent (16). Other studies have demonstrated that the prevalence of hypertension among patients with OSA is higher than in the general population (6, 17, 18). A major problem with this type of epidemiological evidence is the presence of confounding variables, particularly obesity, that predispose to both OSA and hypertension. Nevertheless, even in studies in which obesity, gender, and age were statistically controlled, sleep apnea continued to be an independent risk factor for hypertension (6, 18). A few clinical studies have described a decrease in blood pressure after effective treatment of OSA (19, 20), but interpretation of these studies is complicated by concurrent changes in body mass, alcohol consumption, and antihypertensive medications as well as the direct effects of treatment on the cardiovascular system, such as continuous positive airway pressure (20).

In contrast to these epidemiological and clinical studies, the present study in dogs has demonstrated a direct link between OSA and hypertension in the absence of confounding variables. Despite the species differences, our findings are likely to be relevant to OSA in humans, given the similarities between this canine model of OSA and the human condition (7). It is theoretically possible, however, that bypassing of the upper airway in our dogs somehow altered the BP responses to airway occlusion. Several stimuli that characterize OSA may contribute to the relationship between OSA and hypertension, including repetitive episodes of hypoxia and hypercapnea,

disruption of sleep architecture, and fluctuations in intrathoracic pressure during the occluded respiratory efforts (6). The results of our study indicate, however, that disruption of sleep architecture by recurrent arousals is not the underlying stimulus, suggesting that hypoxia and/or fluctuations in intrathoracic pressure are of critical importance. Support for the role of hypoxia can be derived from the observation that rats subjected to chronic intermittent hypoxia patterned after the hypoxia of sleep apnea develop sustained elevations of BP after 20 d of exposure (21).

In contrast to daytime BP, we found that recurrent arousals from sleep resulted in the same degree of nighttime hypertension as did OSA (Fig. 2). It is not clear whether the arousals produced by the acoustic stimuli are physiologically equivalent in all respects to those produced by OSA. Nevertheless, since the arousal and apnea indices in the two protocols were matched and stable after 2 wk, the findings suggest that the transient BP increases associated with apneic events may be the result of arousal from sleep. This interpretation concurs with studies in humans demonstrating that supplemental oxygen or manipulations of ventilation and intrathoracic pressure have little effect on postocclusion increases in BP (22, 23). In contrast, graded arousals from sleep produce BP increases that vary with the degree of arousal (24). Taken together, these studies support the interpretation that BP elevations at the end of obstructive apneas may be largely attributable to arousal from sleep. As demonstrated in the present study, however, these nighttime surges in BP do not necessarily translate into daytime hypertension in the absence of additional stimuli.

In conclusion, we have used a canine model of recurrent upper airway occlusion during sleep to demonstrate that OSA causes systemic hypertension. The development of hypertension could not be attributed to the recurrent arousals from sleep that characterize the OSA syndrome. Given the high prevalence of hypertension and OSA in the general population, these findings suggest that the possibility of OSA should be considered in all patients with essential hypertension.

## Acknowledgments

This work was supported by the Medical Research Council (MRC) of Canada (operating grant MT-4606). D. Brooks was supported by an award from the Ontario Ministry of Health, and R.L. Horner was supported by an MRC of Canada postdoctoral fellowship.

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